CENTER FOR DRUG EVALUATION AND RESEARCH

APPLICATION NUMBER:

761258Orig1s000

ADMINISTRATIVE and CORRESPONDENCE DOCUMENTS

CDER Breakthrough Therapy Designation Determination Review Template (BTDDRT)

IND/NDA/BLA #	138576
Request Receipt Date	Jan 28, 2021
Product	Penupulimab (AK105) Injection
Indication	Treatment of patients with metastatic non-keratinizing nasopharyngeal carcinoma (NPC) who have disease progression after two or more prior lines of therapy including platinum-containing chemotherapy
Drug Class/Mechanism of Action	PD-1 inhibitor
Sponsor	Akeso Biopharma Co., Ltd
ODE/Division	Division of Oncology 2
Breakthrough Therapy Request (BTDR) Goal Date (within 60 days of receipt)	March 28, 2021

Note: This document must be uploaded into CDER's electronic document archival system as a ***clinical review: REV-CLINICAL-24 (Breakthough Therapy Designation Determination) even if the review is attached to the MPC meeting minutes and*** *will serve as the official primary Clinical Review for the Breakthrough Therapy Designation Request (BTDR).* ***Link this review to the incoming BTDR.*** *Note: Signatory Authority is the Division Director.*

Section I: Provide the following information to determine if the BTDR can be denied without Medical Policy Council (MPC) review.

1. **Briefly describe the indication for which the product is intended (Describe clearly and concisely since the wording will be used in the designation decision letter):**

Penpulimab (AK105) is indicated for the treatment of patients with metastatic non-keratinizing nasopharyngeal carcinoma (NPC) with disease progression after two or more prior lines of therapy including platinum-containing chemotherapy.

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

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

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

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

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

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

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

b. Are the clinical data used to support preliminary clinical evidence that the drug may demonstrate substantial improvement over existing therapies on 1 or more clinically significant endpoints adequate and sufficiently complete to permit a substantive review?

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

i. Only animal/nonclinical data submitted as evidence ☐
ii. Insufficient clinical data provided to evaluate the BTDR (e.g. only high-level summary of data provided, insufficient information about the protocol[s]) ☐
iii. Uncontrolled clinical trial not interpretable because endpoints are not well-defined and the natural history of the disease is not relentlessly progressive (e.g. multiple sclerosis, depression) ☐
iv. Endpoint does not assess or is not plausibly related to a serious aspect of the disease (e.g., alopecia in cancer patients, erythema chronicum migrans in Lyme disease) ☐
v. No or minimal clinically meaningful improvement as compared to available therapy[2]/ historical experience (e.g., <5% improvement in FEV1 in cystic fibrosis, best available therapy changed by recent approval) ☐

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

If 4b is checked "No", BTDR can be denied without MPC review. Skip to number 6 for clearance and sign-off (Note: The Division always has the option of taking the request to the MPC for review if the MPC's input is desired. If this is the case, proceed with BTDR review and complete Section II). If the division feels MPC review is not required, send the completed BTDDRT to Miranda Raggio for review. Once reviewed, Miranda will notify the MPC Coordinator to remove the BTDR from the MPC calendar. If the BTDR is denied at the Division level without MPC review, the BTD Denial letter still must be cleared by Miranda Raggio, after division director and office director clearance.

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

6. Clearance and Sign-Off (no MPC review)

Deny Breakthrough Therapy Designation ☐

Reviewer Signature: {See appended electronic signature page}
Team Leader Signature: {See appended electronic signature page}
Division Director Signature: {See appended electronic signature page}

Section II: If the BTDR cannot be denied without MPC review in accordance with numbers 1-3 above, or if the Division is recommending that the BTDR be granted, provide the following additional information needed by the MPC to evaluate the BTDR.

7. A brief description of the drug, the drug's mechanism of action (if known), the drug's relation to existing therapy(ies), and any relevant regulatory history. Consider the following in your response.

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

[2] For a definition of available therapy refer to Guidance for Industry: "Expedited Programs for Serious Conditions—Drugs and Biologics" http://www.fda.gov/downloads/Drugs/GuidanceComplianceRegulatoryInformation/Guidances/UCM358301.pdf

Drug Description
Penpulimab is a humanized IgG1 monoclonal antibody directed against programmed death receptor-1 (PD-1).

Information regarding NPC and the intended population for the proposed indication
NPC, comprised of keratinizing, non-keratinizing differentiated, and non-keratinizing undifferentiated subtypes, is a relatively rare disease with 129,000 new cases of NPC worldwide in 2018, with the US accounting for approximately 2% of the worldwide cases. Non-keratinizing NPC, for which Epstein Barr virus (EBV) is an etiologic factor, is endemic in East and Southeast Asia, where 95% of NPC is of the non-keratinizing subtype. While the keratinizing squamous cell subtype is more common in the US (25%) compared to Southern China (2%), non-keratinizing undifferentiated NPC is still the most common subtype even in the US (63% of NPC in the US)**.** Recurrent NPC is a serious and life-threatening condition, and median OS for patients with recurrent metastatic NPC with disease progression on or after platinum-containing chemotherapy is approximately 5-11 months.

The drug's relation to existing therapy(ies)
There are currently no FDA-approved therapies for the treatment of recurrent or metastatic NPC. Per NCCN guidelines, standard first-line treatment in the US for patients with recurrent/metastatic NPC without the option for surgery or radiation therapy includes platinum-based combination or single agent chemotherapy; the preferred first-line regimen is cisplatin in combination with gemcitabine. Options in the NCCN guidelines (not FDA-approved) for subsequent-line regimens include combination or single agent chemotherapy; nivolumab (category 2B recommendation - based upon lower-level evidence, consensus that the intervention is appropriate) for patients with previously treated recurrent or metastatic non-keratinizing disease; and pembrolizumab (category 2B) for patients with PD-L1-positive, recurrent or metastatic disease.

Relevant regulatory history
Penpulimab is not approved in the US or any other country/region for any indication.

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.

The BTDR is supported by overall response rate (ORR) by independent radiology review committee (IRRC) (primary endpoint) and duration of response (DoR) (secondary endpoint) from Study AK 105-202, an open-label, single arm study conducted in China. The sponsor plans to conduct a multi-center, global, double-blind, randomized trial of penpulimab in combination with cisplatin and gemcitabine versus cisplatin and gemcitabine, as first-line treatment for patients with NPC with a primary endpoint of progression-free survival (PFS).

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

- *A clinical endpoint that directly measures the clinical benefit of a drug (supporting traditional approval).*

- *A surrogate/established endpoint that is known to predict clinical benefit of a drug (i.e., a validated surrogate endpoint that can be used to support traditional approval).*

- *An endpoint that is reasonably likely to predict clinical benefit of a drug (supporting accelerated approval), and the endpoint used in a confirmatory trial or trials to verify the predicted clinical benefit.*

The Division considers overall response rate (ORR), when large in magnitude and/or associated with durable responses, an endpoint that is reasonably likely to predict clinical benefit for patients with metastatic solid tumor malignancies, including NPC. Progression-free survival, depending upon magnitude, and overall survival are considered by the Division to be clinical endpoints that would support traditional approval.

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

None.

9. A brief description of available therapies, if any, including a table of the available Rx names, endpoint(s) used to establish efficacy, the magnitude of the treatment effects (including hazard ratio, if applicable), and the specific intended population. Consider the following in your response:

- *If the available therapies were approved under accelerated approval, provide the information for the endpoint used to support accelerated approval and the endpoint used to verify the predicted clinical benefit.*

There are currently no therapies with FDA approval for the treatment of patients with recurrent or metastatic NPC.

- *In addition to drugs that have been approved by FDA for the indication, also identify those treatments that may be used off-label for that indication.*

Options in the NCCN guidelines for the treatment of NPC following progression on platinum based chemotherapy include combination or single agent chemotherapy; nivolumab (category 2B recommendation) for patients with previously treated recurrent or metastatic non-keratinizing disease; and pembrolizumab (category 2B recommendation) for patients with PD-L1-positive, recurrent or metastatic disease.

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

Toripalimab (TAB001), a anti-PD-1 antibody, is being studied for a similar indication and was granted BTD in August 2020 for the treatment of patients with recurrent or metastatic non-keratinizing nasopharyngeal carcinoma (NPC) with disease progression on or after platinum-containing chemotherapy.

11. Information related to the preliminary clinical evidence:

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

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

Study ID	Trial Design	Treatment Group	Patient Group	Results to support BTDR
AK 105-202	Single arm Planned N=130 Stg IVB non-keratinizing NPC	Penpulimab 200mg Q2wk	Previously treated with disease progression after two or more prior therapies, including platinum-based chemotherapy N=112	• ORR 26% (95% CI: 18, 35) • Median DOR 13.3 mos (range 2.3+, 17+) • 48% of responders with DOR ≥6 months*

*As of Jan 2021 data cut-off date, only 4 responders (14%) had progressed or stopped study for other reason; the remaining 11 responders were still on study but had not yet reached 6 months past onset of response.

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

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

AK 105-202 is an open label, single arm study of penpulimab being conducted in China. Data provided to support the BTDR is based on a total of 112 patients with non-keratinizing NPC with disease progression after two or more lines of therapy, including platinum-based chemotherapy. Prelimianry results demonstrate an ORR of 26% (95% CI 18, 25), along with durable responses (median DOR 13.3 months with 48% of responders having DOR ≥6 months) in a refractory population of previously treated patients with NPC for whom there is no FDA-approved therapy.

Penpulimab demonstrates a toxicity profile consistent with other anti-PD(L)1 antibodies, with the identified risk of immune-mediated toxicities.

The sponsor plans to conduct a randomized, placebo-controlled trial of penpulimab in combination with cisplatin and gemcitabine versus cisplatin and gemcitabine, as first-line treatment for patients with NPC with a primary endpoint of progression-free survival (PFS).

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

☒ GRANT:

Provide brief summary of rationale for granting:

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

The Division considers the observed response rate for patients with non-keratinizing NPC with disease progression after two or more prior therapies, including platinum-containing chemotherapy. in association with durable responses (median DOR 13.3 months) indicates that penpulimab may demonstrate substantial improvement on a clinically significant endpoint(s), in a setting where no FDA-approved therapy exists.

Note, if the substantial improvement is not obvious, or is based on surrogate/pharmacodynamic endpoint data rather than clinical data, explain further.

☐ DENY:

Provide brief summary of rationale for denial:

Note that not looking as promising as other IND drugs is not a reason for denial; the relevant comparison is with available (generally FDA-approved) therapy. If the Division does not accept the biomarker/endpoint used as a basis for traditional approval or accelerated approval or as a basis for providing early clinical evidence of a substantial improvement over available therapy, explain why:

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

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

The Sponsor plans to submit a marketing application seeking accelerated approval for penpulimab based on the results of Study AK 105-202. The sponsor proposes to use the results of a randomized, placebo-controlled trial of penpulimab, in combination with cisplatin and gemcitabine, , as first-line treatment for patients with NPC to verify the clinical benefit of penpulimab for the treatment of patients with NPC.

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:

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

16. Clearance and Sign-Off (after MPC review):

Grant Breakthrough Therapy Designation ☐
Deny Breakthrough Therapy Designation ☐

Reviewer Signature: {See appended electronic signature page}
Team Leader Signature: {See appended electronic signature page}
Division Director Signature: {See appended electronic signature page}

Revised 10/13/20 /M. Raggio

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

/s/

SATINDER K CHOUDHARY
04/07/2021 04:59:52 PM

ERIN A LARKINS
04/07/2021 05:02:05 PM

B HARPREET SINGH
04/12/2021 08:42:59 AM

IND 138576

MEETING MINUTES

Akeso Biopharma, Inc.
Attention: Liang Liu
81 Belhaven Ave.
Daly City, CA 94015

Dear Ms. Liu:[1]

Please refer to your investigational new drug application (IND) submitted under section 505(i) of the Federal Food, Drug, and Cosmetic Act for AK105.

We also refer to the teleconference between representatives of your firm and the FDA on January 15, 2021. The purpose of the meeting was to discuss and reach an agreement on a marketing application for penpulimab for the treatment of metastatic nasopharyngeal carcinoma (NPC) in patients with progression of disease after two or more lines of therapy including platinum-based chemotherapy.

A copy of the official minutes of the meeting/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 Kwadwo Korsah, Pharm.D., Regulatory Health Project Manager, at (301) 796-6630.

Sincerely,

{See appended electronic signature page}

Harpreet Singh, M.D.
Director
Division of Oncology 2 (DO 2)
Office of Oncologic Diseases (OOD)
Center for Drug Evaluation and Research

Enclosure:

- Meeting Minutes
- Sponsor's Presentation Slides

[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:	Type B
Meeting Category:	Pre-BLA
Meeting Date and Time:	January 15, 2020; 10:00 – 11:00am EST.
Meeting Location:	Teleconference
Application Number:	IND 138576
Product Name:	AK105
Indication:	Metastatic NPC with disease progression after two or more prior lines of therapy including platinum-containing chemotherapy
Sponsor Name:	Akeso Biopharma, Inc.
Regulatory Pathway:	351(a) of the Public Health Service Act
Meeting Chair:	Erin Larkins
Meeting Recorder:	Kwadwo Korsah

FDA ATTENDEES

Harpreet Singh, Director, DO2
Erin Larkins, Clinical Team Leader
Nicole Drezner, Clinical Team Leader (acting)
Satinder Choudhary, Clinical Reviewer
Shaily Arora, Associate Director for Safety, OOD
Kwadwo Korsah, Regulatory Health Project Manager (RHPM)
Liza Stapleford, Clinical Reviewer
Erica Nakajima, Clinical Reviewer
Katie Chon, Clinical Reviewer
Pallavi Mishra-Kalyani, Statistics Team Leader
Yi Ren, Statistics Team Leader
Jeanne Fourie Zirkelbach, Clinical Pharmacology Team Leader
Whitney Helms, Nonclinical Team Leader
Melissa Pegues, Nonclinical Reviewer
Wendy Weinberg, Product Quality Team Leader
Kathryn King, Product Quality Reviewer
Opeyemi Udoka, RHPM
Raniya Al-matari, RHPM
Ashley Lane, RHPM
Emily Pak, RHPM

SPONSOR ATTENDEES
Michelle Xia, President and CEO
Xiaoping Jin, Senior Vice-president, Clinical Development
Dennis Xia, Senior Vice-President, Regulatory Affairs
Max Wang, Senior Vice-President, Clinical Operations
Baiyong Li, Chief Scientific Officer
Jiacheng Yang, Medical Manager
(b) (4), Akeso Consultant
Jason Ni, Senior Vice-President Clinical Development and PV
Charlie Zhang, Senior Vice-President CMC and Process Development
Mengying Xia, Senior Manager, Clinical Operations
Yunying Huang, Manager, Regulatory Affairs

BACKGROUND

Chemistry Manufacturing and Controls (CMC)

Penpulimab (AK105) is a humanized recombinant IgG1 kappa antibody engineered to lack Fc effector function that binds to human programmed cell death 1 (PD-1). It is produced in CHO cells and is purified using standard bioprocessing techniques. Both drug substance and drug product are manufactured at Akeso Biopharma, Guangdong, China.

Nonclinical

Penpulimab is an antibody targeting PD-1; targeting PD-1 can lead to an enhanced immune response, including the anti-tumor immune response. Akeso states that they have conducted pharmacology studies demonstrating the binding of penpulimab to human PD-1, enhancement of immune activation, anti-tumor activity, and the lack of complement-dependent cytotoxicity, antibody-dependent cellular phagocytosis, and antibody-dependent cell-medicated cytotoxicity. Akeso also conducted toxicology studies of up to 13 weeks in Cynomolgus monkeys.

Clinical

Standard first-line treatment in the US for patients with recurrent/metastatic NPC without the option for surgery or radiation therapy includes platinum-based combination or single agent chemotherapy; the preferred first-line regimen is cisplatin in combination with gemcitabine. There are no FDA-approved or preferred regimens for subsequent lines of therapy; however, options in the NCCN guidelines for subsequent-line regimens include combination or single agent chemotherapy; nivolumab (category 2B recommendation) for patients with previously treated recurrent or metastatic non-keratinizing disease; and pembrolizumab (category 2B recommendation) for patients with PD-L1-positive, recurrent or metastatic disease.

Although NPC, comprised of keratinizing, non-keratinizing differentiated, and non-keratinizing undifferentiated subtypes, is endemic in Southeast Asia, it is rare in the US population (1-2 cases per 100,000). The keratinizing squamous cell subtype is more common in the US (25% vs. 2% of NPC cases) and has a poorer prognosis, while the non-keratinizing undifferentiated subtype is more common in Southeast Asia (95% vs. 63% of NPC cases).

Akeso Biopharma (Akeso) proposes to submit an original Biologics Licensing Application (BLA) for penpulimab based on the results of Study AK105-202 for the treatment of patients with metastatic NPC with disease progression after two or more prior lines of therapy including platinum-containing chemotherapy.

Study AK105-202 – Single arm trial
Study AK105-202 is a multi-center, open label, single arm study, conducted in China, of penpulimab 200 mg once every 2 weeks (Q2W) in patients with metastatic (stage IVB) non-keratinizing NPC with disease progression after two or more prior lines of therapy including platinum-containing chemotherapy. The primary endpoint is overall response rate (ORR) based on RECIST v1.1 as assessed by independent radiology review committee (IRRC). An interim analysis was planned to occur after at least 110 patients had completed at least 16 weeks of follow-up.

At the data cut-off date of September 18, 2020, a total of 130 patients were enrolled, including 111 patients with follow-up of at least 16 weeks from first dose. Efficacy results are presented in the meeting package for the 111 patients with ≥16 weeks of follow-up. The confirmed ORR per IRRC was 27% (95%CI 19%, 36%). Median duration of response (DOR) had not been reached (range: 1.0+, 11.4+ months); Kaplan-Meier estimate of the percentage of patients with DOR ≥6 months was 86%. For the subgroup of patients with PD-L1 tumor proportion score ≥50% ORR was 40% (95% CI 25, 56), while ORR was 20% (95% CI 11, 31) for the subgroup with PD-L1 TPS <50%. The most common (≥10%) treatment-related adverse events (TRAEs) among the 130 patients treated in Study AK105-202 were hypothyroidism (28%), anemia (25%), aspartate aminotransferase increased (12%) and white blood cell decreased (11%). Treatment-related serious adverse events occurred in 11% of patients, with TRAEs leading to treatment-discontinuation in 3% of patients.

Akeso proposes to provide the efficacy data from the September 18, 2020 data cut-off date (primary efficacy analysis population of 111 patients with at least 16 weeks of follow up) in the initial BLA submission. Follow-up efficacy data for all treated patients who have had at least 24 weeks follow-up since start of treatment will be submitted at the time of the 90-day safety update.

The primary safety population will include 130 patients from Study AK105-202. As of the data cut-off date of September 18, 2020, approximately 465 patients had received at least one dose of penpulimab across six clinical trials, including 372 patients (83 Australian, 289 Chinese) treated with penpulimab 200 mg Q2W as a single agent.

Based on the proposed table of contents included in the meeting package, it is unclear if Akeso plans to submit an Integrated Summary of Safety (ISS) and Integrated Summary of Efficacy (ISE). For the analysis of immune-related adverse events (irAE), medical review will be performed to confirm whether a “suspicious” irAE is confirmed to be an irAE. Akeso states, “Suspicious irAEs will be identified, defined, and may require the use of steroid hormones or other immunosuppressive agents, and/or physiological hormone replacement therapy (adverse reactions associated with endocrine disease). A confirmed irAE will be defined as a suspected irAE that has been medically reviewed and considered as an immune-mediated mechanism of action, with no clear alternative etiology.”

FDA sent Preliminary Comments to Akeso on January 13, 2021.

DISCUSSION OF FDA RESPONSES TO SPONSOR QUESTIONS

1. Does the Agency agree that the efficacy and safety data from the pivotal study (AK105-202) would be sufficient to support the registration of penpulimab, in patients with metastatic NPC who had progressed after two or more prior lines of therapy including platinum-containing chemotherapy, under an accelerated approval path?

   FDA Response: We agree that with additional follow-up the results from Study AK105-202 proposed for inclusion in a BLA submitted under the provisions of 21 CFR 314 Subpart H (accelerated approval) may provide sufficient clinical evidence to characterize the benefits and risks of penpulimab. Due to limited duration of follow-up, the results presented in your meeting package based on a data cut-off date of September 18, 2020 would not be sufficient to support filing of a marketing application. In general, in order to provide an adequate assessment of durability of response in a marketing application, all responders should have follow-up of at least 6 months past onset of response.

   Given that only patients with non-keratinizing NPC were enrolled, the indication may be limited to patients with non-keratinizing NPC. A final determination on the adequacy of data provided to support your proposed indication will be made after review of all the data submitted with your BLA.
   In addition, in a future BLA submission, justification will need to be made that the patients enrolled in Study AK105-202 adequately represent the US population in terms of disease characteristics, sex, race/ethnicity, age, and standards of care, as described in 21 CFR 312.33(a)(2) and 21 CFR 314.50(d)(5)(v). Further information is provided in the FDA Guidance for Industry entitled “Collection of Race and Ethnicity Date in Clinical Trials,” found at: https://www.fda.gov/media/75453/download.

   Regarding the dosage regimen for penpulimab, per in vitro pharmacology study results, the EC_{50} for competitive binding to PD-1 for penpulimab (7.87 nM) is lower than that of nivolumab (12.73 nM) with similar dosing regimens for a patient with an average weight of 70 kg (i.e., 200 mg Q2W penpulimab and 210 mg Q2W nivolumab). In a response to the current meeting, provide additional justification to support the proposed penpulimab dosing regimen of 200 mg Q2W that includes PD target engagement, and exposure-response (E-R) relationships for efficacy and safety (with a summary of efficacy and safety by dosage level). In your response, provide adequate justification for the proposed flat dosing regimen of penpulimab that includes the effect of body weight on penpulimab exposure, and provide immunogenicity (ADA) data from all completed trials with penpulimab.

Finally, FDA expects that the BLA will contain adequate justification for the following:

a) The penpulimab dosing regimen of 200 mg Q2W as a single agent for the treatment of patients with metastatic nasopharyngeal carcinoma who progressed after two or more prior lines of therapy.
b) The proposed flat dosing approach of penpulimab given that the population pharmacokinetic (PopPK) analysis suggested body weight as a significant covariate on the PK of penpulimab.

Sponsor's response received via email on January 14, 2021

Question 1a: The Agency has agreed that with additional follow-up the results from Study AK105-202 proposed for inclusion in a BLA submitted under the provisions of 21 CFR 314 Subpart H (accelerated approval) may provide sufficient clinical evidence to characterize the benefits and risks of penpulimab.

The Sponsor will provide the efficacy data from a new DCO date (primary efficacy analysis population of 111 patients with at least 24 weeks of follow up for confirmed responders past onset of the response) in the initial BLA submission. Does the Agency concur with the plan?

Sponsor response:
The sponsor will set a new DCO for BLA submission to ensure that all the responders have follow-up of at least 24 weeks past onset of response. Since the tumor assessment for this study was performed every 8 weeks, 24 weeks post first dosing corresponds to the third post-baseline assessments and the subsequent post-baseline assessment was performed at Week 32.
As of data cutoff date of Jan 13, information for durability of response was presented below.

Table 1: Summary of duration of response

	IRC-assessed N=111 (DCO 9/18/2020)	Investigator-assessed N=112[a] (DCO 9/18/2020)	Investigator-assessed N=112[a] (DCO 1/13/2021)
Confirmed ORR, % (95% CI)	27.0 (19.0, 36.3)	25.0% （17.3, 34.1）	25.9% (18.1, 35.0)
Responders, n	30	28	29
Actual proportion of responders with DOR ≥6 months, %	33.3% (n=10)	42.9% (n=12)	48.3% (n=14)
Ongoing response has reached 24 weeks (5.5 months) but has not yet reached 6 months past onset of	3.3% (n=1)	0	31.0% (n=9)

response[b] , %			
Ongoing response has not yet reached 24 weeks (5.5 months) past onset of response[b] , %	53.3% (n=16)	50% (n=14)	6.9% (n=2)
Proportion of responders with PD prior to 6 months past onset of response or censored due to stopping study for another reason, %	10.0% (n=3)[c]	7.1% (n=2)[c]	13.8% (n=4)[c]

a. 1 patient had no measurable lesions at baseline assessed by IRC, but had a measurable lesion assessed by investigator.
b. Tumor assessment is performed every 8 weeks for the first year. 24-weeks post first dosing corresponds to the third post-baseline assessments and the subsequent post-baseline assessment was performed at Week 32. Ongoing response is defined as the patient with confirmed resoponse still remains for receiving the study treatment.
c. All subjects discontinued study treatment due to radiographic disease progression.

The time to response and duration of response assessed by IRC and Investigator were presented in

Figure 1, Figure 2 and Figure 3.

Figure 1: Time to Response and Duration of Response Based on RECIST 1.1 per Investigator -DCO as of 13 Jan 2021

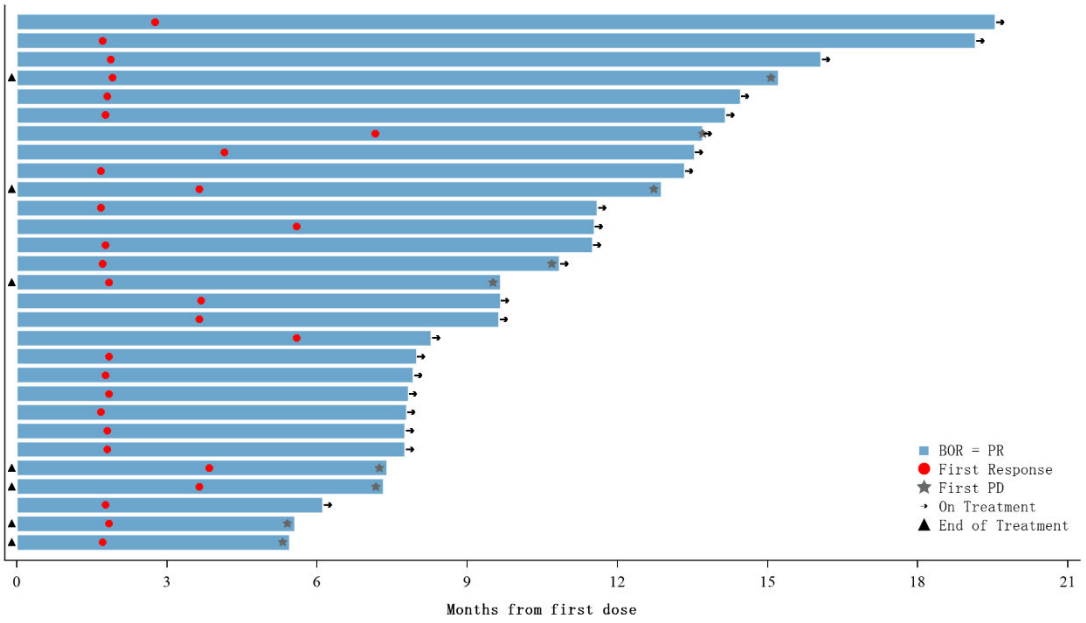


Figure 2: Time to Response and Duration of Response Based on RECIST 1.1 per Investigator - DCO as of 18 Sep 2020

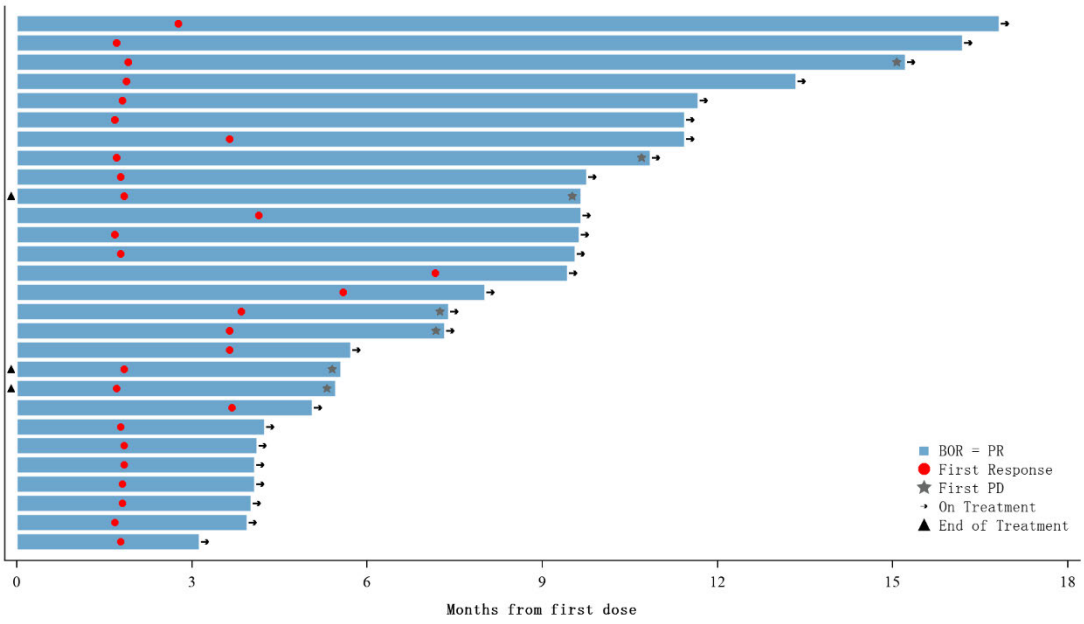
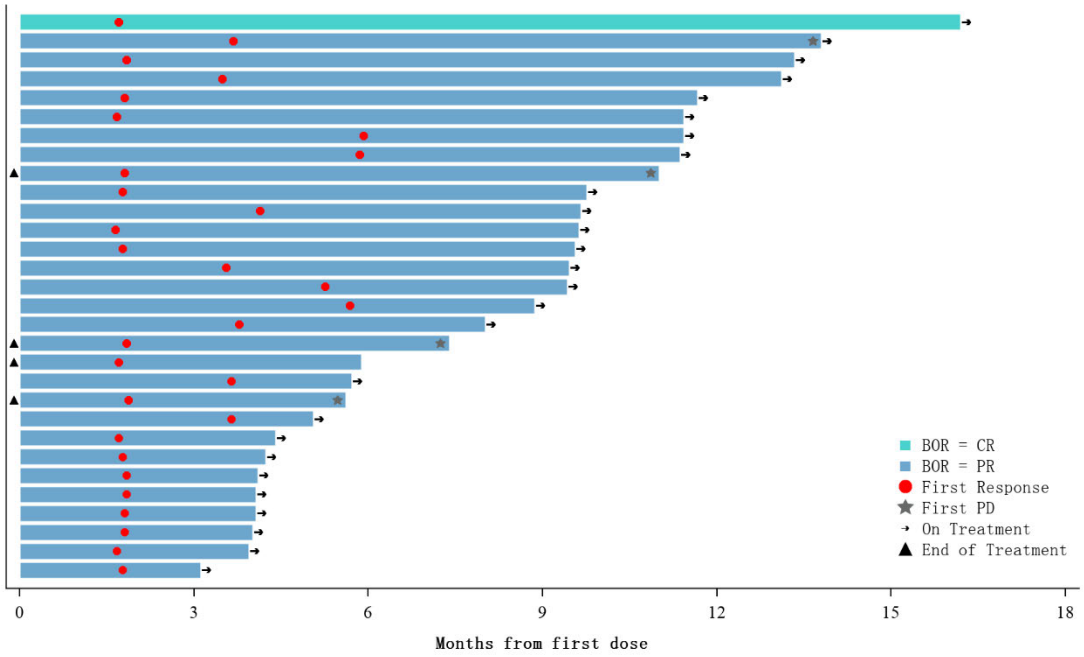


Figure 3: Time to Response and Duration of Response Based on RECIST 1.1 per IRRC - DCO as of 18 Sep 2020



Discussion during meeting: FDA stated that given the refractory population, the proposal to submit data based on a January 2021 cutoff date which will result in approximately 50% of responders in the primary efficacy analysis population (N=111) having follow up of at least 6 months past onset of response is acceptable to support filing of the BLA.

Question 1b: The Agency requests that in a future BLA submission, justification will need to be made that the patients enrolled in Study AK105-202 adequately represent the US population in terms of disease characteristics, sex, race/ ethnicity, age, and standards of care, as described in 21 CFR 312.33(a)(2) and 21 CFR 314.50(d)(5)(v).

The Sponsor has conducted the detailed analyses for summary of baseline characteristics and prior therapy for primary efficacy analysis population of 111 patients. Does the Agency concur with the justification that was made that the patients enrolled in Study AK105-202 adequately represent the US population?

Sponsor response:
Guidelines for treating metastatic NPC in the United States are consistent with those in China. The recommended first-line regimen for metastatic NPC is platinum-based combination chemotherapy without the option for surgery or radiation therapy. There are no FDA-approved or preferred regimens for

subsequent lines of therapy; however, options for subsequent-line regimens include combination or single agent chemotherapy.
The proposed indication would be metastatic non-keratinizing NPC with disease progression after two or more prior lines of therapy including platinum- containing chemotherapy. It is rare in the US population (1-2 cases per 100,000) for non-keratinizing NPC.
Summary of baseline characteristics and prior therapy is presented below:

Table 2: Summary of baseline characteristics

		FAS (N=111)
Median age, years(range)		49.6 (20.8-65.7)
[redacted] n(%)	Male	84 (75.7%)
	Female	27 (24.3%)
ECOG PS, n(%)	0	34 (30.6%)
	1	77 (69.4%)
PD-L1, n(%) (Shuwen SAB-028)	Positive (TPS≥50%)	43 (38.7%)
	Negative (TPS < 50%)	66 (59.5%)
	NA[a]	2 (1.8%)
Histology, n(%)	Nonkeratinizing differentiated	36 (32.4%)
	Nonkeratinizing undifferentiated	71 (64.0%)
	Nonkeratinizing differentiated status unknown	4 (3.6%)
Stage at Study entry, n(%)	IVb	111(100%)

Table 3: Summary of prior therapy

			FAS (N= 111)
first line	Platinum combination therapy	GP	25 (22.5%)
		TP+DP	27+56 (74.8%)
		Other platinum-containing regimen	9 (8.1%)
	Platinum monotherapy therapy		3 (2.7%)
Lines of Prior chemotherapy, n(%)		2L	69 (62.2%)
		≥3L	42 (37.8%)
Prior Radiotherapy for primary lesion n(%)		Yes	94 (84.7%)
		No	16 (14.4%)
Types of Prior Chemotherapy, n(%)		Platinum	111 (100.0%)
		Taxanes	97 (87.4%)
		Gemcitabine	51 (45.9%)
		Fluorouracil	97 (87.4%)

Discussion during meeting: FDA stated that the justification appears reasonable; however, this justification will need to be included in the marketing application and will be a review issue.

Question 1c: The agency request the sponsor could provide additional justification to support the proposed penpulimab dosing regimen of 200 mg Q2W that includes PD target engagement, and exposure-response (E-R) relationships for efficacy and safety (with a summary of efficacy and safety by dosage level). In your response, provide adequate justification for the proposed flat dosing regimen of penpulimab that includes the effect of body weight on penpulimab exposure, and provide immunogenicity (ADA) data from all completed trials with penpulimab.

Does the Agency concur with the dosing regimen of 200mg Q2W and other information listed below?

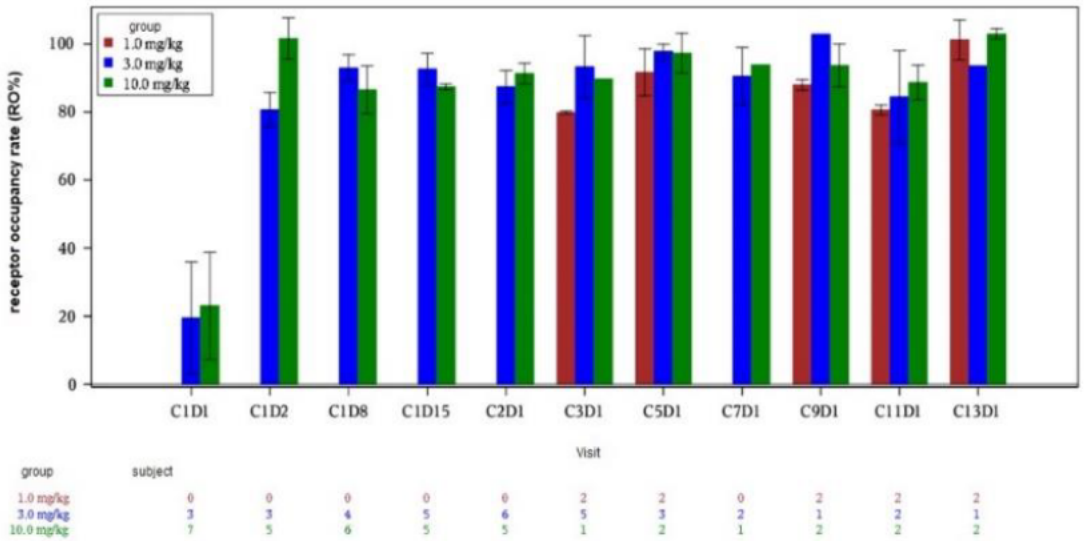
Sponsor response:

1. PD target engagement

A receptor occupancy assay used to examine target engagement in the PBMC demonstrated that at around or above 1mg/kg Q2W, receptor occupancy has reached saturation. While 200 mg Q2W has similar exposure level to 3mg/kg

Q2W, the 200 mg Q2W dosing regimen is expected to offer sufficient target engagement.

Figure 4: PD-1 receptor occupancy rate (RO) after administration of different dose groups



2. E-R relationships of efficacy and safety with dosage level summary

There was no significant difference in the incidence of TEAE and TRAE, or in the incidence of TRAE grade 3 or above at different dose levels. Due to the small cohort size at lower dose levels, the association between ORR and dose levels cannot be adequately evaluated.

Table 4: Safety data from AK105-101 study (Phase 1a/1b) in advanced solid tumors

safety	1.0mg/kg (N=3)	3.0mg/kg (N=6)	10.0mg/kg (N=7)	200mg Q2W (N=83)	Total (N=99)
TEAE	3 (100.0%)	6 (100.0%)	7 (100.0%)	81 (97.6%)	97 (98.0%)
TRAE	2 (66.7%)	5 (83.3%)	4 (57.1%)	33 (39.8%)	44 (44.4%)
≥Grade 3 TEAE	2 (66.7%)	3 (50.0%)	5 (71.4%)	39 (47.0%)	49 (49.5%)
≥Grade 3 TRAE	0	1 (16.7%)	2 (28.6%)	3 (3.6%)	6 (6.1%)
SAE	2 (66.7%)	3 (50.0%)	4 (57.1%)	29 (34.9%)	38 (38.4%)
Drug-related SAE	0	0	2 (28.6%)	4 (4.8%)	6 (6.1%)
TEAE leading to death	0	0	0	2 (2.4%)	2 (2.0%)
TRAE leading to death	0	0	0	0	0
TEAE leading to drug discontinuation	0	0	0	5 (6.0%)	5 (5.1%)
TRAE leading to drug discontinuation	0	0	0	1 (1.2%)	1 (1.0%)

Table 5: Efficacy data from AK105-101 study (Phase 1a/1b) in advanced solid tumors

Response	1.0mg/kg	3.0mg/kg	10.0mg/kg	200mg Q2W	Total

	(N=3)	(N=6)	(N=5)	(N=61)	(N=75)
ORR (%)	66.7%	0	40%	14.8%	17.3%
DCR (%)	100%	33.3%	60%	44.3%	46.7%
CR(n)	0	0	0	0	0
PR(n)	2	0	2	9	13
SD(n)	1	2	1	18	22
PD(n)	0	4	2	34	40

3. Effect of body weight on penpulimab exposure

The covariate of body weight has statistically significant influence on V1 (PK parameter central compartment volume). The influence of body weight on V1 does not appear to result in an influence on drug exposure. Clinical data shows that there is no significant impact of body weight on PK parameters such as AUC_{SS}, $C_{max,SS}$, $C_{trough,SS}$, as shown in the table below.

Table 6: Effect of body weight on penpulimab exposure

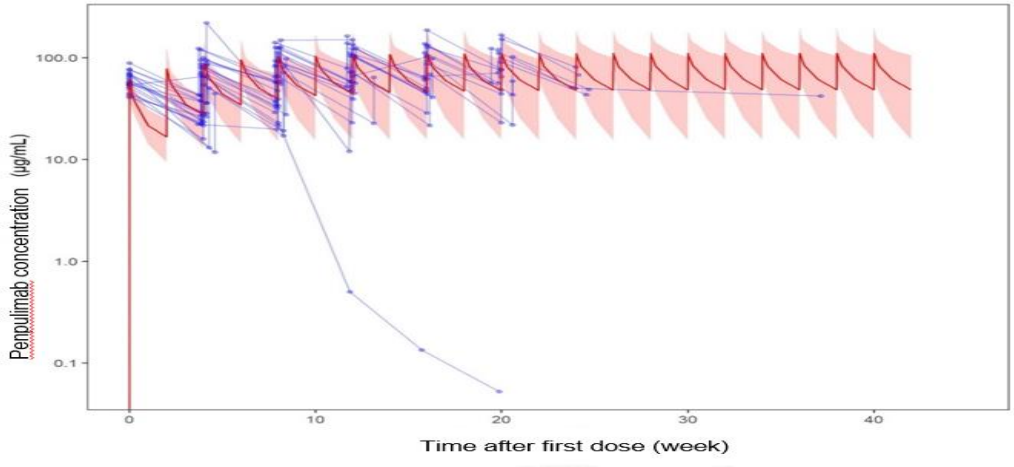
	AUC_{SS}		$C_{max,SS}$		$C_{trough,SS}$	
	GEOM ratio	95%CI	GEOM ratio	95%CI	GEOM ratio	95%CI
10% quantile of body weight vs typical value	0.988	0.969 – 1.007	1.051	1.039 – 1.064	0.968	0.944 – 0.992
90% quantile of body weight vs typical value	1.005	0.986 – 1.024	0.935	0.924 – 0.946	1.028	1.003 – 1.054

4. Immunogenicity (ADA) summary and ADA effect on exposure

Among 260 subjects from study AK105-201, AK105-202, and AK105-204, 10.8% subjects tested positive for ADA post baseline, 8.5% tested positive for NAB.

The results showed that ADA status had no significant effect on drug exposure, and there was no trend of significant decrease in serum drug concentration among ADA positive subjects. Among all subjects tested, only one subject showed significant drop of drug exposure (as shown in the Figure below), which corresponds to an ADA positive subject with the highest level of ADA titer.

Figure 5: Plasma concentration time curve of ADA positive subjects after penpulimab administration at 200 mg Q2W



Discussion during meeting: FDA stated that, overall, the additional rationale appears acceptable to justify a dosage regimen of 200 mg Q2W. A final determination on the adequacy of the data to support the dosage will be a review issue. Akeso stated that the additional justification requested by the FDA for the 200 mg Q3W dosage regimen to be used in combination with chemotherapy will be provided for discussion at a future meeting.

FDA stated that Akeso should ensure that in the BLA submission the analysis on body weight is applicable to the US population where body weight may be higher (b) (4)

2. Does the Agency agree that the proposed randomized controlled Phase 3 study in the first line setting for metastatic or recurrent NPC can be used to confirm the clinical benefit observed in those single-arm monotherapy studies to support accelerated approval of penpulimab for the treatment of patients with metastatic NPC who have progressed after two or more prior lines of therapy including platinum-containing chemotherapy?

FDA Response: Possibly. In order to potentially support a marketing application based on an improvement in PFS alone, the treatment effect should be large in magnitude and statistically robust, with no evidence of detrimental effect on OS. (b) (4) Whether this would be considered clinically meaningful would depend on

the overall risk-benefit profile; this includes additive toxicity of penpulimab to chemotherapy.

(b) (4)

Sponsor's response received via email on January 14, 2021

Sponsor intends (b) (4)

Discussion during meeting: FDA reiterated (b) (4) for the confirmatory, randomized trial (b) (4)

FDA requested clarification regarding Akeso's intent to conduct the randomized study globally based on FDA feedback. Akeso confirmed that the study will be conducted globally.

3. Does the Agency concur that the proposed overall safety plan is sufficient to support the potential early registration of penpulimab monotherapy in 3L+ NPC?

FDA Response: We agree that in general the safety data proposed for inclusion in the BLA appear sufficient to support the filing of a BLA for the proposed indication. In addition to the proposed safety narratives, provide narratives for any adverse events of special interest (AESI). Additional narratives may be requested during the review process.

In the Integrated Summary of Safety (ISS) Datasets ("overall database"), include easily identifiable flags for the different dosing schedules and studies.

Regarding your proposed analysis of immune-related adverse events (irAE), "suspicious irAE" should be categorized as immune-related if it occurred in a patient receiving penpulimab if no alternative etiology is identified, even if steroids, other immunosuppressive drugs, and/or hormone replacement therapy are not administered, as not all patients experiencing immune-mediated AEs may be treated with these therapies, especially for low-grade AEs.

The proposed programmatic identification of suspected irAE may not capture uncommon irAEs not included in Table 12-1 in the meeting background package that were treated with steroids or low-grade irAEs that did not require steroids. You should provide a process describing how such AEs were captured in the trial.

Sponsor's response received via email on January 14, 2021

Question 3a: The Agency requests providing narratives for any adverse events of special interest (AESI). Per the protocol definition for AESI, those irAEs with grade ≥3, infusion reaction with grade ≥3 and systemic hypersensitivity or severe type 1 hypersensitivity would be considered as AESI. The Sponsor plans to provide the manual narratives for those defined AESIs observed in the pivotal study and supportive studies included in the ISS.

Does the Agency concur with the plan regarding the narratives for AESI?

Sponsor response:
For the pivotal study and supportive studies included in the ISS, the Sponsor only capture detailed information for those AESI defined according to the protocol. There is no detailed information captured in the pharmacovigilance database for those irAE with grade 1 or 2.

Discussion during meeting: FDA agreed.

Question 3b: The Sponsor plan to submit an Integrated Summary of Safety in Module 5.3.5.3. The studies planned to be included into ISS are from studies on AK-105 monotherapies (AK105-201, AK105-202, AK105-204, AK105-101), and NOT to be included into ISS from combo studies or blinded studies.

Does the Agency concur with the plan regarding the studies included for ISS?

Sponsor response:
Studies planned to be included into ISS are from studies on AK105 monotherapies (AK105-201, AK105-202, AK105-204, AK105-101)

- Total N=388 with N=372 for proposed dosing regiemn of 200 mg Q2W

Studies planned NOT to be included into ISS are from combo studies

- AK105-203: AK105+ anlotinib in 1L HCC, N=31
- AK105-301 part 1: AK105+ chemotherpay in 1L NSCLC, N=46
- AK105-301 part 2: AK105+ chemotherpay in 1L nonsq-NSCLC, still blinded
- AK105-302: AK105+ chemotherpay in 1L sqNSCLC, still blinded

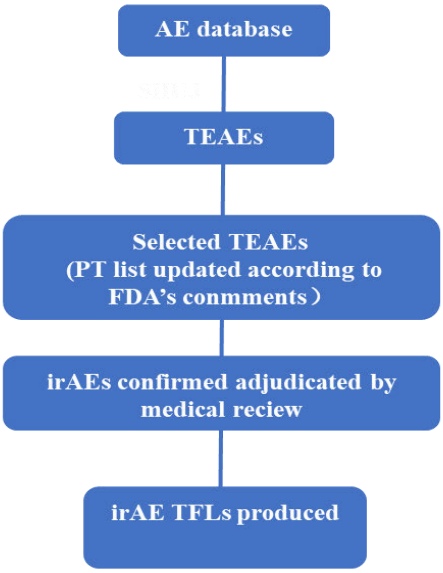
The sponsor proposes to present ISS as following

	200mg Q2W			
NPC 200mg Q2W (N=130)	Australian phase Ib (N=83)	Chinease including NPC (N=289)	Total (N=372)	200mg and other doses Total (N=388)

Discussion during meeting: FDA agreed.

Question 3c: The Sponsor proposed the below process for characterizing irAEs used for the analysis of irAEs included in the drug label?

Process of irAE determination used for the analysis:



Does the Agency concur with the plan regarding irAE determination?

Sponsor response:

The prespecified PT list for irAE will be continually evaluated and updated as the development program proceeds and new data become available from the individual drug or the drug class. We will follow the Agency's suggestion with respect to additional preferred terms (PTs) to be included in the irAE list.

Suspected irAE identified based on the pre-specified PT list for irAE will be confirmed and adjudicated by the Sponsor medical review accord to the rules listed below. "suspicious irAE" would be categorized as immune-related if it occurred in a patient receiving penpulimab if no alternative etiology is identified, even if steroids, other immunosuppressive drugs, and/or hormone replacement therapy are not administered, as not all patients experiencing immune-mediated AEs may be treated with these therapies, especially for low-grade AEs.

Confirmed irAEs will be used for the analysis included in the drug label.

Rules of medical review

A - Definitely	B - Likely	C - Not Attributed
Any of the below bullets are met: 1. Evidence of inflammation by biopsy and/or imaging * 2. Presence of lymphocytic infiltrate **For Diarrhoea or Colitis AESIs ONLY:** 3. Evidence of inflammation by endoscopy or biopsy * **For Endocrinopathy AESIs ONLY:** 4. Hypopituitarism with pituitary enlargement*	**Con Meds criteria:** 1. Use of steroids 2. Use of thyroid therapy 3. Use of other immunosuppressives **Timings/Other AESI Criteria:** 4. Subject has at least one other AE reported within any AESI grouping of interest[b] **For Diarrhoea, Colitis or Dermatitis/Rash AESIs ONLY** 5. AE persists for ≥ 7 days or worsens (ie CTC Grade increase) **Other Criteria:** **For Diarrhoea or Colitis AESIs ONLY:** 6. Concomitant to AE, evidence of bowel wall inflammation by abdominal imaging* **For Endocrinopathy AESI ONLY:** 7. Hypopituitarism without evidence of pituitary enlargement* **For Diarrhoea or Colitis AESIs ONLY:** 8. Presence of concomitant faecal leukocytes, calprotectin*	**For cases not identified by columns 1 and 2 consider the following:** **Con Meds criteria** 1. Concomitant medications known to cause the AE **For Dermatitis/Rash AESIs ONLY:** **2.** Evidence that AE likely due to radiation (i.e. palliative radiation) **Other Criteria:** **3.** AE present in Medical History **4.** Evidence that AE likely due to infection, metabolic disorder (where applicable), concomitant medication, or other documented medical aetiology **5.** Short term duration of event **For all AESIs with exception of Dermatitis/Rash:** 6. Documented tumor progression at site of event* **For Hepatitis AESIs ONLY:** 7. Documented bile duct obstruction at site of event*

* Available from the safety database only i.e. available within the manual patient narratives. Note if a patient narrative has text describing results of either biopsy, imaging or endoscopy it will be assumed that a biopsy, imaging or endoscopy, respectively has been performed

a - Note only treatment-emergent AESIs are to be reviewed. Treatment emergent defined as events present at baseline that worsen in intensity after first dose of IP or events absent at baseline that emerge after first dose of IP. According to the SAPs the primary safety outputs include TEAEs that occur whilst on study drug and either up to 90 days after the last dose of IP, or the start of subsequent anticancer therapy. A subset of tables or listings are also available to show events reported start the post of subsequent anti-cancer therapy. If relevant such AESIs will also be reviewed.

b - The other event can be any grade (even grade 1) and can occur before or after the AESI of interest (ie regardless of timing)

Discussion during meeting: FDA asked Akeso to clarify if Grade 1-2 iRAE from the single arm trial would be characterized and captured in the programmatic analysis of adverse events. Akeso confirmed this would be done.

4. Does the Agency agree with the Proposed Table of Contents for the Penpulimab Monotherapy BLA?

FDA Response: Yes, the proposed outline of the Table of Contents appears acceptable; however, the adequacy of the contents of the BLA will be a review issue. Please confirm that you plan to submit an Integrated Summary of Efficacy and an Integrated Summary of Safety in Module 5.3.5.3. Please also see FDA Additional Comments 6-8.

All narratives and documents are translated into English by organization with experience in medical translation and by trained personnel with medical knowledge.

Sponsor's response received via email on January 14, 2021

The Sponsor has no further comment for clarification. The Sponsor confirm that we plan to submit an Integrated Summary of Safety but not for an Integrated Summary of Efficacy in Module 5.3.5.3.

Discussion during meeting: FDA acknowledged Akeso's plan. FDA stated that if the BLA does not include an ISE, then in addition to a presentation of the results of Study AK105-202, the Summary of Clinical Efficacy (in Module 2) should include a brief summary of topline efficacy results from other sponsor-conducted studies of penpulimab.

5. Does the Agency agree with the application for Real-Time Oncology Review (RTOR) for the initial BLA application for penpulimab?

FDA Response: At this time, we do not have enough information to determine if RTOR would be appropriate. For future questions regarding potential use of the RTOR program, include a proposed timeline for submission of the components of the proposed BLA.

Sponsor's response received via email on January 14, 2021

The Sponsor has no further comment for clarification.

ADDITIONAL COMMENTS

CMC

6. We note that the meeting package did not include questions directly addressing the chemistry, manufacturing and controls (CMC) aspects of AK105. We recommend that you request a CMC-only meeting to address any questions regarding the adequacy of your CMC strategies to support a BLA. Refer to "Guidance for Industry IND Meetings for Human Drugs and Biologics Chemistry, Manufacturing, and Controls Information" by the Food and Drug Administration Center for Drug Evaluation and Research (CDER) Center for Biologics Evaluation and Research (CBER) published in May 2001, available at: https://www.fda.gov/regulatory-information/search-fda-guidance-documents/ind-meetings-human-drugs-and-biologics-chemistry-manufacturing-and-controls-information.

Sponsor's response received via email on January 14, 2021

The Sponsor has no further comment for clarification.

Nonclinical

7. In addition to the studies described in the meeting package, include any pharmacology data on the ability of penpulimab to generate immune memory/recall responses.

Sponsor's response received via email on January 14, 2021

The Sponsor has no further comment for clarification.

8. Clarify the GLP status of the toxicology studies. GLP-compliant studies must conform to US GLP regulations as described in 21 CFR part 58.

Sponsor's response received via email on January 14, 2021

The Sponsor has no further comment for clarification.

9. While an embryofetal development study is unlikely to be necessary to support a product targeting the PD-1 pathway, include an assessment of the potential for reproductive toxicity based on a weight of evidence approach in any future original BLA submission.

Sponsor's response received via email on January 14, 2021

The Sponsor has no further comment for clarification.

Clinical

10. For Study (b) (4), the primary analysis population should be all randomized patients and should be analyzed as randomized (without regard to treatment received).

Sponsor's response received via email on January 14, 2021

The Sponsor has no further comment for clarification.

11. For Study (b) (4), provide a plan to control the overall Type I error rate for testing of any secondary endpoints for which you intend to make labeling claims.

Sponsor's response received via email on January 14, 2021

The Sponsor has no further comment for clarification, and will provide a plan to control error rate in the protocol and SAP.

12. Your prespecified list of irAE should be continually evaluated and updated as the development program proceeds and new data become available from the individual drug or the drug class. Listed below are additional preferred terms (PTs) to be included in the irAE list:

- Lung toxicity: diffuse alveolar damage
- Hepatic toxicity: hepatic failure
- GI toxicity: acute hemorrhagic ulcerative colitis, necrotizing colitis, gastritis, duodenitis
- Renal toxicity: renal impairment, renal disorder, renal tubular disorder, renal tubular acidosis, renal tubular dysfunction, renal tubular atrophy, renal tubular injury, nephropathy toxic, oliguria, anuria, azotemia, creatinine renal clearance decreased
- Endocrine toxicity: tertiary hypothyroidism, autoimmune hypothyroidism, autoimmune thyroiditis, adrenal insufficiency
- Dermatologic toxicity: skin toxicity, immune-mediated dermatitis, seborrheic dermatitis. Also include all PT with term “rash” e.g. mucocutaneous rash, nodular rash, rash papulosquamous, rash maculovesicular, rash macular, etc.
- Nervous system toxicity: myelitis and demyelination, nerve paresis, optic neuritis
- Ocular toxicity: visual impairment, blindness
- Rheumatoid/ skeletal muscle toxicity: polymyalgia rheumatica
- Pancreatic toxicity: Pancreatitis hemorrhagic
- Add another category for other rare/miscellaneous events such as: hemophagocytic lymphohistiocytosis, systemic inflammatory response syndrome, histiocytic necrotizing lymphadenitis, lymphadenitis, solid organ transplant rejection, vasculitis, vasculitis cerebral, vitiligo, keratitis etc.

Sponsor’s response received via email on January 14, 2021

The Sponsor has no further comment for clarification, and will include those additional items.

13. We recommend you submit an updated listing to the FDA for concurrence prior to initiation of your proposed randomized trial. Please see the information provided in the sections on PREA and FDARA requirements below. (b) (4)

Sponsor's response received via email on January 14, 2021

Sponsor intends [redacted] (b) (4)

Discussion during meeting: FDA reiterated [redacted] (b) (4)

14. The Oncology Center for Excellence has developed the Assessment Aid to facilitate FDA's assessment of NDA/BLA applications (including supplements). The Assessment Aid is based on the FDA Multidisciplinary Review template with most sections divided into two parts, clearly delineated to emphasize ownership of each position as either the Applicant's position or the FDA's position. The Applicant fills in their positions in the relevant sections; these should be concise and only include critical information (e.g., should generally be no longer than 100 pages for original BLAs). If the Assessment Aid is offered, FDA would expect receipt of the completed Assessment Aid at the time of submission.

Sponsor's response received via email on January 14, 2021

Penpulimab was granted Fast Track designation on 13 October 2020 as systemic monotherapy for metastatic NPC who had progressed after two or more prior lines of therapy including platinum-containing chemotherapy. The Sponsor would like to clarify whether the Assessment Aid can be offered to facilitate FDA's assessment of BLA application.

Discussion during meeting: FDA stated the use of Assessment Aid would be appropriate.

Clinical Pharmacology

Sponsor's response received via email on January 14, 2021

The sponsor has no further comment for clarification comments 15 to 17.

15. Optimize the dosing regimen before starting trials intended to demonstrate safety and efficacy in support of a marketing application. Pool clinical PK, pharmacodynamic (PD), activity and safety data, as well as nonclinical pharmacology data, to conduct integrated dose-response and exposure-response analyses for dose optimization.

16. Characterize the development of anti-drug antibodies (ADA) to penpulimab, including rate, titer, neutralizing capacity, duration, and effect on the PK, PD, efficacy and safety of penpulimab.

17. Address the following recommendations in support of filing a BLA:

a) 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" (available at: https://www.fda.gov/media/74346/download). 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.

b) Address the following questions in the Summary of Clinical Pharmacology:
   i. 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.
   ii. What are the exposure-response relationships for efficacy, safety and biomarkers?
   iii. 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 penpulimab? What dose modifications are recommended?
   iv. What is the impact of immunogenicity on exposure, efficacy and safety?

c) Apply the following advice in preparing the clinical pharmacology sections of the original submission:
   i. Submit bioanalytical methods and validation reports for all clinical pharmacology and biopharmaceutics trials.
   ii. Provide final study report for each clinical pharmacology trial. Present the pharmacokinetic parameter data as geometric mean with coefficient of variation (and mean ± standard deviation) and median with range as appropriate.
   iii. Provide complete datasets for clinical pharmacology and biopharmaceutics trials. The subjects' unique ID number in the pharmacokinetic datasets should be consistent with the numbers used in the clinical datasets.
      - Provide all concentration-time and derived pharmacokinetic parameter datasets as SAS transport files (*.xpt). A description of each data item should be provided in a define.pdf file. Any concentrations or subjects

that have been excluded from the analysis should be flagged and maintained in the datasets.
- Identify individual subjects with dose modifications; the time to the first dose reduction, interruption or discontinuation; the reasons for dose modifications in the datasets.

iv. Submit the following for the population pharmacokinetic analysis reports:
- Standard model diagnostic plots.
- Individual plots for a representative number of subjects. Each individual plot should include observed concentrations, the individual prediction line and the population prediction line.
- Model parameter names and units in tables.
- Summary of the report describing the clinical application of modeling results.
  Refer to the following pharmacometric data and models submission guidelines
  http://www.fda.gov/AboutFDA/CentersOffices/OfficeofMedicalProductsandTobacco/CDER/ucm180482.htm.

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

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

DISCUSSION OF THE CONTENT OF A COMPLETE APPLICATION

- The content of a complete application was discussed. Refer to discussions above. FDA indicated that while it is appropriate to include in the BLA safety data for each of the safety populations delineated in the tables in Appendix 3 (Presentation of safety data) of the meeting package, the safety data presented in the Assessment Aid should focus primarily on the population of patients with NPC treated with penpulimab 200 mg Q2W (n=130), which will be used to inform Section 6 of the US Prescribing Information (USPI), and the pooled population of all patients treated with a starting dose of 200 mg Q2W (n=372), which will be used to inform Section 5 of the USPI.

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

- Major components of the application are expected to be submitted with the original application and are not subject to agreement for late submission. You stated you intend to submit a complete application and therefore, there are no agreements for late submission of application components.

- FDA recommended that Akeso submit a CMC only meeting. Akeso acknowledged the request.

PREA REQUIREMENTS

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

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

required, regarding dosing, safety, and preliminary efficacy to inform potential pediatric labeling" (section 505B(a)(3)). Applications for drugs or biological products for which orphan designation has been granted and which are subject to the requirements of section 505B(a)(1)(B), however, will not be exempt from PREA (see section 505B(k)(2)) and will be required to include plans to conduct the molecularly targeted pediatric investigations as required, unless such investigations are waived or deferred.

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

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

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

FDARA REQUIREMENTS

Sponsors may request a meeting with the Oncology Center of Excellence Pediatric Oncology Program to discuss preparation of the sponsor's initial pediatric study plan (iPSP) for a drug/biologic that is intended to treat a serious or life-threatening disease/ condition which includes addressing the amendments to PREA (Sec. 505B of the FD &C Act) for early evaluation in the pediatric population of new drugs directed at a target that the FDA deems substantively relevant to the growth or progression of one or more types of cancer in children. The purpose of these meetings will be to discuss the Agency's current thinking about the relevance of a specific target and the specific expectations for early assessment in the pediatric population unless substantive justification for a waiver or deferral can be provided.

Meeting requests should be sent to the appropriate review division with the cover letter clearly stating "**MEETING REQUEST FOR PREPARATION OF iPSP MEETING**

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

UNDER FDARA." These meetings will be scheduled within 30 days of meeting request receipt. The Agency strongly advises the complete meeting package be submitted at the same time as the meeting request. Sponsors should consult the guidance for industry, *Formal Meetings Between the FDA and Sponsors or Applicants*, to ensure open lines of dialogue before and during their drug development process.

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

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[4] and Pregnancy and Lactation Labeling Final Rule[5] websites, which include:

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

Pursuant to the PLLR, you should include the following information with your application

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

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.[6]

The FDA Electronic Submissions Gateway (ESG) is the central transmission point for sending information electronically to the FDA and enables the secure submission of regulatory information for review. Submissions less than 10 GB must be submitted via the ESG. For submissions that are greater than 10 GB, refer to the FDA technical specification *Specification for Transmitting Electronic Submissions using eCTD Specifications*. For additional information, see FDA.gov.[7]

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

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

Bioresearch Monitoring Technical Conformance Guide Containing Technical Specifications.[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-sNDA/sBLA meeting. Those applicants who do not wish to participate in the pilot programs will follow the usual submission process with no impact on review timelines or benefit-risk decisions. More information on these pilot programs, including eligibility criteria and timelines, can be found at the following FDA websites:

- RTOR[9]: In general, the data submission should be fully CDISC-compliant to facilitate efficient review.
- Assessment Aid[10]

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

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

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.

ISSUES REQUIRING FURTHER DISCUSSION

No issues.

ACTION ITEMS

No action items.

ATTACHMENTS AND HANDOUTS

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

/s/

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