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RESEARCH**

APPLICATION NUMBER:

761258Orig1s000

MULTI-DISCIPLINE REVIEW

Summary Review

Clinical Review

Non-Clinical Review

Statistical Review

Clinical Pharmacology Review

NDA/BLA Multi-disciplinary Review and Evaluation

Disclaimer: In this document, the sections labeled as “Data” and “The Applicant’s Position” are completed by the Applicant, which do not necessarily reflect the positions of the FDA.

Application Type	BLA, Class 2 Resubmission
Application Number(s)	761258
Priority or Standard	Standard
Submit Date(s)	October 2, 2024
Received Date(s)	October 2, 2024
PDUFA Goal Date	April 2, 2025
Division/Office	Division of Oncology 2
Review Completion Date	April 23, 2025
Established Name	Penpulimab-kcqx
(Proposed) Trade Name	N/A
Pharmacologic Class	Programmed death receptor-1 (PD-1) blocking antibody
Code name	N/A
Applicant	Akeso Biopharma Co., Ltd.
Formulation(s)	10 mg/mL, 10 mL
Dosing Regimen	In combination with either cisplatin or carboplatin and gemcitabine for the first-line treatment of non-keratinizing nasopharyngeal carcinoma (NPC): 200 mg as an intravenous infusion every 3 weeks. As a single agent for non-keratinizing NPC with disease progression on or after platinum-based chemotherapy and at least one other prior line of therapy: 200 mg as an intravenous infusion every 2 weeks.
Applicant Proposed Indication(s)/Population(s)	Penpulimab-kcqx, in combination with gemcitabine and cisplatin or carboplatin, is indicated as first-line treatment of patients with recurrent or metastatic nasopharyngeal carcinoma (NPC). Penpulimab-kcqx, as a single agent, is indicated for the treatment of adults with metastatic non-keratinizing NPC with disease progression on or after platinum-based chemotherapy and at least one other prior line of therapy.
Recommendation on Regulatory Action	Traditional Approval

Disclaimer: In this document, the sections labeled as “Data” and “The Applicant’s Position” are completed by the Applicant and do not necessarily reflect the positions of the FDA.

Penpulimab

Recommended Indication(s)/Population(s) (if applicable)	Penpulimab-kcqx, in combination with either cisplatin or carboplatin and gemcitabine, is indicated for the first-line treatment of adults with recurrent or metastatic non-keratinizing nasopharyngeal carcinoma (NPC). Penpulimab-kcqx, as a single agent, is indicated for the treatment of adults with metastatic non-keratinizing NPC and disease progression on or after platinum-based chemotherapy and at least one other prior line of therapy.

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Abbreviations: DHOT, Division of Hematology Oncology Toxicology; OB, Office of Biostatistics; OCP, Office of Clinical Pharmacology; OOD, Office of Oncologic Diseases

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Abbreviations: DEPI, Division of Epidemiology; DMEPA, Division of Medication Error Prevention and Analysis; DRISK, Division of Risk Management; OPDP, Office of Prescription Drug Promotion; OPQ, Office of Pharmaceutical Quality; OSE, Office of Surveillance and Epidemiology; OSI, Office of Scientific Investigations

Glossary

AC	Advisory Committee
ADA	Anti-Drug Antibody
ADCC	Antibody-Dependent Cell-Mediated Cytotoxicity
ADCP	Antibody Dependent Cellular Phagocytosis
ADCR	Antibody Dependent Cytokine Release
ADME	Absorption, Distribution, Metabolism, Excretion
AE	Adverse Event
ALT	Alanine Aminotransferase
ALP	Alkaline Phosphatase
ALB	Serum Albumin
AST	Aspartate Aminotransferase
BLA	Biologics License Application
BTB	Breakthrough Therapy Designation
CDC	Complement Dependent Cytotoxicity
CDER	Center For Drug Evaluation And Research
CFR	Code Of Federal Regulations
CMC	Chemistry, Manufacturing, And Controls
CNS	Central Nervous System
COSTART	Coding Symbols For Thesaurus Of Adverse Reaction Terms
CRF	Case Report Form
CSR	Clinical Study Report
CTLA-4	Cytotoxic T-Lymphocyte Associated Protein 4
CL	Clearance
CLCr	Creatinine Clearance
CYP	Cytochrome P450
DCR	Disease Control Rate
DoR	Duration Of Response
ECG	Electrocardiogram
ECOG	Eastern Cooperative Oncology Group
FDA	Food And Drug Administration
GCP	Good Clinical Practice
GLP	Good Laboratory Practice
ICH	International Conference On Harmonization
IL	Interleukin
IND	Investigational New Drug
irAEs	Immune-Related Adverse Events
ISS	Integrated Summary Of Safety
IV	Intravenous Infusion
LDH	Lactic Dehydrogenase

NDA/BLA Multi-disciplinary Review and Evaluation- BLA 761258

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MedDRA	Medical Dictionary For Regulatory Activities
NCI-CTCAE	National Cancer Institute-Common Terminology Criteria For Adverse Event
NDA	New Drug Application
NME	New Molecular Entity
NOAEL	No Observed Adverse Effect Level
NPC	Nasopharyngeal Carcinoma
OPQ	Office Of Pharmaceutical Quality
ORR	Overall Response Rate
OSI	Office Of Scientific Investigation
PBMC	Peripheral Blood Mononuclear Cell
PFS	Progression-Free Survival
PD	Pharmacodynamics
PD-1	Programmed Death Receptor-1
PD-L1	Programmed Death Ligand-1
PI	Prescribing Information
PK	Pharmacokinetics
PPI	Patient Package Insert
PPQ	Process Performance Qualification
PREA	Pediatric Research Equity Act
PRO	Patient Reported Outcome
Q2W	Every 2 Weeks
REMS	Risk Evaluation And Mitigation Strategy
RTOR	Real-Time Oncology Review
SAE	Serious Adverse Event
SAP	Statistical Analysis Plan
SOC	Standard Of Care
TBIL	Total Bilirubin
TCR	Tissue Cross-Reactivity
TEAE	Treatment Emergent Adverse Event
TK	Toxicokinetics
TNF	Tumor Necrosis Factor
TTR	Time To Response

1. Executive Summary

1.1. Product Introduction and Regulatory Background

Penpulimab-kcqx (hereafter referred to as penpulimab) is a human IgG1 monoclonal antibody directed against programmed death receptor-1 (PD-1), thereby blocking the immunosuppressive interaction between PD-1 and programmed cell death ligand 1 (PD-L1) and programmed cell death ligand 2 (PD-L2). It is not approved for any indication in the U.S.

An initial Biologics Licensing Application (BLA) was submitted for penpulimab as a single-agent for patients with previously treated nasopharyngeal carcinoma (NPC) on July 16, 2021, based on the results of the single-arm trial, Study AK105-202. FDA issued a Complete Response on January 19, 2024, as penpulimab did not demonstrate a clear advantage over currently available therapeutic options due to changes in the treatment landscape for NPC, to grant accelerated approval. Additionally, deficiencies were identified in CGMP operations in the penpulimab drug substance and drug product manufacturing facility, and in the manufacture of penpulimab.

On February 27, 2024, the Applicant requested a Type B meeting under IND 138576 to discuss whether an interim analysis of the randomized trial, Study AK105-304, could be conducted to support a BLA for penpulimab in combination with either cisplatin or carboplatin and gemcitabine for the first-line treatment of patients with recurrent or metastatic NPC. The Applicant also wanted to discuss plans to address the chemistry, manufacturing, and controls deficiencies identified in the Complete Response Letter. The meeting was granted with preliminary comments from the FDA issued to the Applicant on April 12, 2024. After additional email communications between the Applicant and FDA on April 17, 2024, and April 19, 2024, agreement was reached to cancel the Type B meeting.

In the current Class 2 BLA resubmission, the Applicant is seeking two indications in NPC with two different dosing regimens. For the Applicant's proposed indication for use "in combination with gemcitabine and cisplatin or carboplatin, as first-line treatment of patients with recurrent or metastatic nasopharyngeal carcinoma", the proposed dosage regimen is penpulimab 200 mg intravenously (IV) once every three weeks (Q3W).

The Applicant's proposed indication for penpulimab as a single agent is for "the treatment of adults with metastatic non-keratinizing NPC with disease progression on or after platinum-based chemotherapy and at least one other prior line of therapy". The Applicant proposed dosage regimen is penpulimab 200 mg IV once every two weeks (Q2W).

1.2. Conclusions on the Substantial Evidence of Effectiveness

The Applicant intends for this marketing application to support approval of penpulimab for two indications: 1) in combination with either cisplatin or carboplatin and gemcitabine for the first-line treatment of patients with metastatic or recurrent NPC and 2) as a single agent for the treatment of adult patients with metastatic non-keratinizing NPC with disease progression on or after platinum-containing chemotherapy and at least one other prior line of therapy.

The primary study providing evidence in support of the first-line indication is Study AK105-304. In Study AK105-304, 291 adult patients with metastatic or recurrent WNPC who had not received previous systemic chemotherapy for recurrent or metastatic disease were randomized (1:1) to receive either penpulimab in combination with cisplatin or carboplatin and gemcitabine Q3W for up to 6 cycles followed by single-agent penpulimab Q3W or placebo Q3W in combination with cisplatin or carboplatin and gemcitabine Q3W for up to 6 cycles followed by single-agent placebo Q3W. Treatment was administered until disease progression, unacceptable toxicity, or a maximum of 24 months. The primary efficacy endpoint was progression free survival (PFS) by blinded independent review committee (BICR) per RECIST v.1.1, with a key secondary endpoint of overall survival (OS). At an interim analysis of PFS based on 189 events (85% information fraction [IF]), the trial demonstrated a statistically significant and clinically meaningful improvement in BICR-assessed PFS favoring the penpulimab arm, with a hazard ratio (HR) of 0.45 (95% CI 0.33, 0.62, p-value <0.0001), corresponding to a median PFS of 9.6 months (95% CI 7.1, 12.5) in the penpulimab arm and 7.0 months (95% CI 6.9, 7.3) in the placebo arm. Although the observed 2.6-month improvement in median PFS is modest for an add-on therapy, the treatment effect, as measured by the HR, was consistent across subgroups and withstood rigorous sensitivity analyses, highlighting the robustness and reliability of the results. These results are also supported by a longer median DOR in the penpulimab arm of 9.8 months (95% CI: 7, 17.4) compared to 5.7 months (95% CI: 5.5, 6.7) in the placebo arm. While a statistically significant improvement in OS has not been demonstrated in Study AK105-304, the OS results at the first formal interim analysis (70% IF) indicate no detrimental effect of penpulimab on OS. At this interim analysis, the OS HR was 0.91 (95% CI: 0.64, 1.31), with median OS not reached in the penpulimab arm and 31.3 months (95% CI: 27.4, NE) in the placebo arm. Notably, 80% of patients receiving placebo either crossed over to open-label treatment with penpulimab or received another anti-PD-(L)1 antibody as the next subsequent therapy upon confirmed disease progression, which may impact interpretability of the OS results. OS will be tested again at a second prespecified interim analysis (80% IF) and a final analysis.

Study AK105-202 provides the primary efficacy data in support of the indication for the treatment of patients with non-keratinizing NPC with disease progression on or after platinum-containing chemotherapy and at least one other prior line of therapy. In Study AK105-202, 125 patients with metastatic non-keratinizing NPC received penpulimab 200 mg IV Q2W until disease progression, unacceptable toxicity, or a maximum of 24 months. The major efficacy

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outcome measures were objective response rate (ORR) and duration of response (DOR) according to RECIST v1.1 as assessed by an Independent Radiology Review Committee (IRRC). The IRRC-assessed ORR was 28% (95% CI: 20, 37) and the median duration of response (DOR) was not reached (95% CI: 9.2, not evaluable). Among the 35 patients with an objective response, 46% had an observed DOR of ≥ 12 months. The Study AK105-202 results are considered clinically meaningful for the evaluated patient population, and the results of the randomized Study AK105-304 provide further confidence in the benefit of penpulimab for the treatment of patients with advanced NPC.

A major limitation of this application was that Study AK105-304 was conducted mostly in China (96% of randomized patients) and Study AK105-202 was conducted exclusively in China. Section 21 CFR 314.106(b) outlines three requirements to establish the acceptability of foreign data as the sole basis for marketing approval:

1. The foreign data are applicable to the U.S. population and U.S. medical practice.
2. The studies have been performed by clinical investigators of recognized competence.
3. FDA is able to validate the data through an onsite inspection or other appropriate means.

FDA will apply this policy in a flexible manner according to the nature of the drug and data being considered.

A flexible regulatory approach is warranted given the high unmet need for effective treatment options for NPC. These trials were initiated prior to the approval of regimens with toripalimab, the only other anti-PD-(L)1 antibody approved for NPC in the U.S. Cisplatin or carboplatin plus gemcitabine was considered an appropriate control arm in Study AK105-304 when the trial was designed, making the study results relevant to U.S. medical practice. Cisplatin plus gemcitabine was considered standard of care for the first-line treatment of recurrent or metastatic NPC in the U.S., and carboplatin plus gemcitabine was considered an appropriate option for patients who may be unable to tolerate or who have contraindications to cisplatin. The incidence of NPC is much higher in East Asia relative to the U.S., where NPC is a relatively rare disease, making enrollment to clinical trials more feasible in that region of the world. Clinical site inspections were conducted by FDA to validate the data supporting this application. To further address the issue of applicability to the U.S. population, the Applicant will be collecting additional clinical data to further characterize the safety and efficacy of penpulimab in combination with either cisplatin or carboplatin and gemcitabine for the treatment of non-keratinizing NPC in a study population whose demographic and disease characteristics are more representative of the population of U.S. patients with NPC (see Postmarketing Commitments later in this review for details).

Although patients with both non-keratinizing and keratinizing NPC were eligible for enrollment into Study AK105-304, only one patient (0.7%) with keratinizing histology was enrolled to the penpulimab plus chemotherapy arm. While this patient had a confirmed response to the

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investigational therapy, the contribution of penpulimab to the overall treatment effect cannot be isolated as it was administered in combination with chemotherapy. Only patients with non-keratinizing NPC were eligible for enrollment into Study AK105-202. No additional data are available outside of these two trials evaluating the anti-tumor activity of penpulimab as a single agent in patients with keratinizing NPC. Given almost no clinical data available for penpulimab in patients with keratinizing NPC, FDA recommends that the indications are limited to patients with non-keratinizing histology.

The clinical data demonstrate substantial evidence of effectiveness and a positive risk-benefit assessment, which are supportive of traditional approval for penpulimab for the following indications:

- Penpulimab, in combination with either cisplatin or carboplatin and gemcitabine for the first-line treatment of adults with recurrent or metastatic non-keratinizing NPC.
- Penpulimab, as a single agent, for the treatment of adults with metastatic non-keratinizing NPC and disease progression on or after platinum-based chemotherapy and at least one other prior line of therapy.

1.3. Benefit-Risk Assessment (BRA)

Benefit-Risk Summary and Assessment

There were 133,354 new cases of NPC diagnosed globally in 2020, and approximately 80,000 people died from NPC in 2020. More than 75% of the global cases of NPC develop in South and East Asia, compared with 1.6% in Northern America. NPC is rare in the U.S., with <1 case per 100,000 people each year. The World Health Organization classifies NPC in three major subtypes: non-keratinizing undifferentiated, non-keratinizing differentiated, and keratinizing squamous cell carcinoma. While the non-keratinizing undifferentiated subtype of NPC is the predominant subtype in both Southern China (95%) and the U.S. (63%), the keratinizing subtype of NPC is uncommon in Southern China (2%) relative to the US (25%).

The prognosis for patients with recurrent, unresectable, or metastatic NPC is poor. On October 27, 2023, FDA approved toripalimab (a monoclonal antibody targeting programmed cell death protein 1 [PD-1]) with cisplatin and gemcitabine for the first-line treatment of adults with metastatic or recurrent, locally advanced NPC, based on the randomized, double-blind JUPITER-02 trial. In the JUPITER-02 trial, toripalimab with cisplatin and gemcitabine demonstrated a median PFS of 11.7 months and a median OS not yet reached. Patients who received placebo with cisplatin and gemcitabine had a median PFS of 8.0 months and median OS of 33.7 months. On the same day, FDA also approved toripalimab as a single agent for adult patients with recurrent unresectable or metastatic NPC with disease progression on or after a platinum-containing therapy based on the results of the open-label, multicohort POLARIS-02 trial, which demonstrated an ORR as assessed by BICR of 21% and a median DOR of 14.9 months. Despite these recent approvals, metastatic NPC remains a fatal, incurable disease, and an unmet need exists for patients with advanced NPC.

Penpulimab is a monoclonal antibody targeting PD-1, an immune checkpoint inhibitor with an established pharmacological class of PD-1 blocking antibody. The proposed dosage regimen for penpulimab in combination with cisplatin or carboplatin and gemcitabine is 200 mg intravenously (IV) once every 3 weeks (Q3W). The Applicant's proposed dosage regimen for penpulimab when administered as a single agent is 200 mg IV Q2W. The Applicant's proposed indications for penpulimab are: 1) penpulimab, in combination with either cisplatin or carboplatin and gemcitabine, for the first-line treatment of adults with recurrent or metastatic NPC, and 2) penpulimab, as a single agent, for the treatment

of adults with metastatic non-keratinizing NPC and disease progression on or after platinum-based chemotherapy and at least one other prior line of therapy.

The primary study supporting the first-line indication is Study AK105-304, in which 291 patients with recurrent or metastatic NPC were randomized 1:1 to receive either penpulimab 200 mg IV Q3W in combination with 6 cycles of cisplatin or carboplatin and gemcitabine (n=144) or placebo with cisplatin or carboplatin and gemcitabine (n=147). The primary efficacy endpoint was PFS by BICR per RECIST v1.1, with a key secondary endpoint of OS. An interim analysis of PFS was initially proposed at 155 events (70% IF) but was conducted at 189 events (85% IF) instead. This overrun was a result of a change in the analysis population that stemmed from difficulty enrolling patients outside of Asia, due to the rarity of NPC in other parts of the world, and the approval of toripalimab plus cisplatin and gemcitabine during the conduct of the trial. These changes in the analysis plan were deemed acceptable to the FDA review team for this particular application. At the interim analysis of PFS based on 189 events, the trial demonstrated a statistically significant and clinically meaningful improvement in BICR-assessed PFS favoring the penpulimab arm, with a HR of 0.45 (95% CI 0.33, 0.62, p-value <0.0001), corresponding to a median PFS of 9.6 months (95% CI 7.1, 12.5) in the penpulimab arm and 7.0 months (95% CI 6.9, 7.3) in the placebo arm. In total, 31% and 11% of patients were alive and progression free after 12 months of follow-up in the penpulimab and placebo arms, respectively. The presence of a tail in the Kaplan-Meier PFS curves, which begin to separate at approximately 7 months, suggests that some patients may derive prolonged PFS benefit or that there is potentially late treatment effect with penpulimab, which are not captured by median PFS alone. The PFS treatment effect, as measured by the HR, was consistent across subgroups and withstood rigorous sensitivity analyses, highlighting the robustness and reliability of the results. The ORR was 68% (95% CI: 60, 76) for the penpulimab arm and 64% (95% CI: 56, 72) for the placebo arm. There was a longer median DOR in the penpulimab arm of 9.8 months (95% CI: 7, 17.4) compared to 5.7 months (95% CI: 5.5, 6.7) in the placebo arm.

While a statistically significant improvement in OS has not been demonstrated in Study AK105-304, the OS results at the first formal interim analysis (70% IF) indicate no detrimental effect of penpulimab on OS. At this interim analysis, the OS HR was 0.91 (95% CI: 0.64, 1.31), with median OS not reached in the penpulimab arm and 31.3 months (95% CI: 27.4, NE) in the placebo arm. Notably, 49% of patients receiving placebo crossed over to open-label treatment with penpulimab upon confirmed disease progression, and an additional 31% of patients on the placebo arm received an anti-PD-(L)1 antibody as the next subsequent therapy outside of Study AK105-304, which may impact interpretability of the OS results. OS will be tested again at a second prespecified interim analysis (80% IF) and a final analysis.

Regarding the indication for penpulimab as a single agent, Study AK105-202 provides the primary efficacy data which evaluated patients with metastatic, non-keratinizing NPC with disease progression on or after platinum-containing chemotherapy and at least one other prior line of

therapy. In Study AK105-202, 125 patients with metastatic, non-keratinizing NPC received penpulimab 200 mg IV Q2W until disease progression, unacceptable toxicity, or a maximum of 24 months. The major efficacy outcome measures were ORR and DOR according to RECIST v1.1 as assessed by an IRRC. The IRRC-assessed ORR was 28% (95% CI 20, 37) and the median DOR was not reached (95% CI 9.2, not evaluable). Among the 35 patients with an objective response, 46% had a DOR of ≥ 12 months. These results are considered clinically meaningful when considering the intended patient population, and the results of Study AK105-304 provide further confidence in the benefit of penpulimab for the treatment of advanced NPC. Given the recent approval of toripalimab plus cisplatin and gemcitabine, and the results of Study AK105-304 for penpulimab, it is expected that the majority of U.S. patients with NPC will receive an anti-PD-(L)1 antibody in combination with chemotherapy as first-line treatment; however, there will be patients with NPC who may have already received first-line treatment with chemotherapy alone and a subsequent line of therapy who would be eligible to receive and may benefit from penpulimab as a single agent.

Among the 146 patients who received penpulimab in combination with cisplatin or carboplatin and gemcitabine in Study AK105-304, the most common ($\geq 20\%$) adverse reactions were nausea (58%), vomiting (55%), hypothyroidism (45%), constipation (41%), decreased appetite (36%), decreased weight (26%), cough (25%), COVID-19 infection (25%), fatigue (25%), rash (24%), and pyrexia (21%). Serious adverse reactions occurred in 51% of patients. The most frequent serious adverse reactions ($\geq 2\%$) were thrombocytopenia (19%), decreased neutrophils (14%), decreased white blood cells (12%), anemia (8%), myelosuppression (3.4%), decreased sodium (2.7%), pneumonia (2.1%), and nausea (2.1%). There was one fatal adverse reaction (0.7%) due to syndrome of inappropriate antidiuretic hormone secretion (SIADH). Permanent discontinuation of penpulimab due to an adverse reaction occurred in 3.4% of patients. Adverse reactions which resulted in permanent discontinuation of penpulimab were acute myocardial infarction, acute kidney injury, brain edema, diabetic ketoacidosis, increased potassium, increased lipase, and thrombocytopenia (0.7% each).

The evaluation of safety for penpulimab as a single agent included analyses of safety data for 130 patients with NPC treated with penpulimab 200 mg IV Q2W as a single agent in Study AK105-202 and a monotherapy pooled population of 372 patients with advanced solid tumors (including the 130 patients with NPC) or classical Hodgkin lymphoma treated with penpulimab 200 mg IV Q2W. Among the 372 patients who received single agent penpulimab, the most common ($\geq 20\%$) adverse reactions were anemia (25%) and hypothyroidism (23%). Among the 130 patients with NPC treated with penpulimab 200 mg IV Q2W as a single agent in Study AK105-202, the most common ($\geq 20\%$) adverse reactions were hypothyroidism (39%) and musculoskeletal pain (25%). Serious adverse reactions occurred in 22% of these 130 patients. Serious adverse reactions in $\geq 1\%$ were pneumonia (3.8%), pneumonitis (1.5%), respiratory failure (1.5%), and rash (1.5%). Fatal adverse reactions occurred in 1% of patients with NPC treated with single-agent penpulimab, including a case each of pneumonitis, septic shock, colitis, and hepatitis. Permanent discontinuation of penpulimab due to an adverse reaction occurred in 3.8% of patients with NPC. Adverse reactions which resulted

in permanent discontinuation of penpulimab in $\geq 1\%$ of patients with NPC were rash, hepatitis, herpes zoster, spinal cord compression and pleural effusion (0.8% each).

Immune-related adverse events (irAEs) occurred in 31% of patients (including Grade 3 to 4 irAEs in 4.1% of patients) in Study AK105-304 and 22% of patients (including Grade 3 to 4 irAEs in 10% of patients) in Study AK105-202. In Study AK105-304, the most common ($\geq 2\%$) irAEs included hypothyroidism and dermatologic toxicity. There were no fatal immune-related adverse reactions. In the monotherapy pool, irAEs occurring at an incidence $\geq 2\%$ included hypothyroidism and dermatologic toxicity. Infusion related reactions occurred in 3.4% and 10% of patients in Study AK105-304 and Study AK105-202, respectively.

The overall safety profile of penpulimab was similar to that observed with other PD-1 blocking antibodies. Safety issues identified as significant and serious during the BLA review were immune-related adverse events and infusion-related reactions, which are adequately addressed by the information in the Warnings and Precautions section included in product labeling. There were no significant safety concerns identified during BLA review requiring risk management beyond labeling or warranting consideration for Risk Evaluation and Mitigation Strategy (REMS). Penpulimab appears to have an acceptable safety profile when assessed in the context of a life-threatening disease with unmet medical need.

A major limitation of the data is that the two primary trials supporting this marketing application were conducted predominantly or entirely in China. Of the 291 randomized patients in Study AK105-304, only 11 patients were enrolled from outside of China, specifically from the U.S., Canada, and Brazil. Study AK105-202 trial was conducted exclusively in China. Therefore, the patient populations in the trials are not reflective of the racial and ethnic demographics of patients with NPC in the U.S. While both Studies AK105-304 and AK105-202 were conducted predominantly in China, a flexible regulatory approach is warranted given the high unmet need for treatment options for patients with NPC. These trials were initiated prior to the approval of regimens with toripalimab, the only other FDA-approved anti-PD-(L)1 antibody for U.S. patients with NPC. Cisplatin or carboplatin plus gemcitabine was considered an appropriate control arm in Study AK105-304 when the trial was designed, making the study results relevant to U.S. medical practice. Cisplatin plus gemcitabine was considered standard of care for the first-line treatment of recurrent or metastatic NPC in the U.S., and carboplatin plus gemcitabine was considered an appropriate option for patients who may be unable to tolerate or who have contraindications to cisplatin. The incidence of NPC is much higher in East Asia relative to the U.S., where NPC is a relatively rare disease, making enrollment to clinical trials more feasible in that region of the world. Clinical site inspections were conducted by FDA to validate the data supporting this application. To further address the issue of applicability to the U.S. population, the Applicant will be collecting additional clinical data to further characterize the safety and efficacy of penpulimab in combination with either cisplatin or carboplatin and gemcitabine for the treatment of non-keratinizing NPC in a study population whose demographic and disease

characteristics are more representative of the population of U.S. patients with NPC (see Postmarketing Commitments later in this review for details).

Although patients with both non-keratinizing and keratinizing NPC were eligible for enrollment into Study AK105-304, only one patient (0.7%) with keratinizing histology was enrolled to the penpulimab plus chemotherapy arm. While this patient had a confirmed response to the investigational therapy, the contribution of penpulimab to the overall treatment effect cannot be isolated as it was administered in combination with chemotherapy. Only patients with non-keratinizing NPC were eligible for enrollment into Study AK105-202. No additional data are available outside of these two trials evaluating the anti-tumor activity of penpulimab as a single agent in patients with keratinizing NPC. The available data do not provide sufficient evidence to support the efficacy and safety of penpulimab in patients with keratinizing NPC. Keratinizing and non-keratinizing NPC are biologically distinct subtypes with different etiologies, molecular profiles, and responses to treatment. Non-keratinizing NPC is strongly associated with Epstein-Barr virus (EBV) infection and typically demonstrates higher sensitivity to immunotherapy and chemotherapeutic agents. In contrast, keratinizing NPC is more frequently linked to environmental factors such as smoking and exhibits different treatment response patterns. Given almost no clinical data available for penpulimab in patients with keratinizing NPC, FDA recommends that the indications are limited to patients with non-keratinizing histology.

The results of Study AK105-304 and Study AK105-202 support a positive risk-benefit assessment and are supportive of traditional approval of penpulimab for the following indications:

- Penpulimab, in combination with either cisplatin or carboplatin and gemcitabine for the first-line treatment of adults with recurrent or metastatic non-keratinizing NPC.
- Penpulimab, as a single agent, for the treatment of adults with metastatic non-keratinizing NPC and disease progression on or after platinum-based chemotherapy and at least one other prior line of therapy.

Dimension	Evidence and Uncertainties	Conclusions and Reasons
Analysis of Condition	- Nasopharyngeal carcinoma originates in the nasopharynx from the base of the skull to the palate. - There were 133,354 cases worldwide in 2020 with the majority of cases (>75%) in South and East Asia and 1.6% in Northern America, and approximately 80,000 people died from NPC in 2020. NPC is rare in the United States, with <1 case per 100,000 people each year. - There are three major histologic subtypes of NPC based on the WHO classification, with differences in subtype distribution between North America and China: Type 1 keratinizing squamous cell carcinoma (25% vs 2%), Type 2 non-keratinizing differentiated carcinoma (12 vs 3%), and Type 3 non-keratinizing undifferentiated carcinoma (63% vs 95%). - For metastatic NPC, the median OS is 29.1 months with first-line platinum-based chemotherapy alone. A statistically significant OS improvement was also observed with median OS not reached (95% CI: 38.7 months, not estimable) for toripalimab-tpzi in combination with platinum-based chemotherapy (based on the POLARIS-02 trial).	The incidence of NPC is substantially higher in Southeast Asia relative to the U.S. A higher proportion of patients with NPC in North America develop the keratinizing squamous subtype compared with China, where the vast majority of patients develop the non-keratinizing undifferentiated subtype. The prognosis for metastatic NPC remains poor with limited therapeutic options.

Dimension	Evidence and Uncertainties	Conclusions and Reasons
Current Treatment Options	- Toripalimab-tpzi, in combination with cisplatin and gemcitabine, is approved for the first-line treatment of metastatic or recurrent NPC based on results from the JUPITER-02 trial. The trial demonstrated a median PFS of 11.7 months with toripalimab-tpzi versus 8.0 months with placebo, both in combination with cisplatin and gemcitabine (HR 0.52; 95% CI: 0.36–0.74; p=0.0003). A statistically significant OS improvement was also observed with median OS not reached (95% CI: 38.7 months, not estimable) for the toripalimab-tpzi-containing regimen and 33.7 months (95% CI: 27.0, 44.2) for the placebo-containing regimen (HR 0.63 [95% CI: 0.45, 0.89], p-value=0.0083). - Toripalimab-tpzi is also approved for NPC with disease progression on or after a platinum-containing chemotherapy based on an ORR of 21% (95% CI 15, 28) and median DOR of 14.9 months (95% CI: 10.3, not estimable) in the POLARIS-02 trial. - Prior to the approval of toripalimab-tpzi, in the metastatic setting, standard of care treatment for first line therapy was cisplatin plus gemcitabine, with a reported median PFS of 7.0 months and median OS of 29.1 months.	Metastatic NPC represents a life-threatening disease. For patients with metastatic or recurrent NPC, FDA approved toripalimab-tpzi in combination with cisplatin and gemcitabine in the first line setting and toripalimab-tpzi as a single agent with disease progression on or after a platinum-containing therapy.
Benefit	- The primary trials supporting this BLA are Study AK105-304 and Study AK105-202. - The efficacy of penpulimab combined with cisplatin or carboplatin and gemcitabine was assessed in Study AK105-304, a randomized, double-blind, multi-center trial. A total of 291 patients with recurrent or metastatic NPC received either penpulimab or a placebo alongside cisplatin or carboplatin and gemcitabine every three weeks for up to six cycles. This was followed by single agent penpulimab or placebo every	The trial demonstrated a statistically robust improvement in the primary endpoint of BICR-assessed PFS. Efficacy is further demonstrated with a longer median DOR in the penpulimab plus chemotherapy arm vs the placebo plus chemotherapy arm. While not statistically significant, the results for

Dimension	Evidence and Uncertainties	Conclusions and Reasons
	three weeks until disease progression, unacceptable toxicity, or a maximum duration of 24 months. - Study AK105-304 met its primary endpoint of BICR-assessed PFS at an interim analysis of PFS (85% IF). Median PFS was 9.6 (95% CI: 7.1, 12.5) in the penpulimab arm versus 7.0 (95% CI: 6.9, 7.3) in the placebo arm, with a PFS HR of 0.45 (95% CI: 0.33, 0.66) and $p < 0.0001$. - In Study AK105-304, the ORR was 68% in the penpulimab arm and 64% in the placebo arm. The secondary endpoint of DOR demonstrated that penpulimab with cisplatin or carboplatin and gemcitabine had a longer median DOR at 9.8 months (95% CI: 7.0, 17.4) compared to cisplatin or carboplatin and gemcitabine alone at 5.7 months (95% CI: 5.5, 6.7). - In Study AK105-304, OS results were not statistically significant at the first formal interim analysis, with 70% of pre-specified OS events having occurred in the overall population. At this interim analysis, the OS HR was 0.91 (95% CI: 0.64, 1.31), with median OS not reached in the penpulimab arm and 31.3 months (95% CI: 27.4, NE) in the placebo arm. In total, 80% of patients on the placebo arm received penpulimab or another anti-PD-(L)1 antibody following confirmed disease progression, which may impact interpretability of OS results.	OS at the first formal interim analysis (70% IF) indicate there is no evidence of a detrimental effect on OS with penpulimab. These results provide substantial evidence of effectiveness for penpulimab, in combination with cisplatin or carboplatin and gemcitabine, for the first-line treatment of adults with recurrent or metastatic non-keratinizing NPC. Regarding an indication for the treatment of adults with metastatic non-keratinizing NPC after disease progression on platinum-containing chemotherapy and at least one additional line of therapy, the ORR of 28% with 46% of responders having a response ≥ 12 months, demonstrated in Study AK105-202, is considered clinically meaningful for the intended patient population. Furthermore, the results of Study AK105-304 provide further confidence in the benefit of penpulimab for advanced NPC.

Dimension	Evidence and Uncertainties	Conclusions and Reasons
	The efficacy of single-agent penpulimab was evaluated in Study AK105-202, an open-label, multicenter, single-arm trial conducted in a single country (China). A total of 125 patients with unresectable or metastatic non-keratinizing NPC, who had disease progression after platinum-based chemotherapy and at least one other line of therapy, received single-agent penpulimab 200 mg IV Q2W until disease progression or unacceptable toxicity, or a maximum of 24 months. The ORR per BICR was 28% (95% CI: 20, 37) with a median DOR not reached (95% CI: 9.2, not estimable). Among the 35 patients with an objective response, 83% had an observed DOR ≥ 6 months and 46% had an observed DOR ≥ 12 months.	
Risk and Risk Management	- FDA's safety analyses for penpulimab 200 mg Q3W in combination with cisplatin or carboplatin and gemcitabine was assessed in 146 patients treated in Study AK105-304. - FDA's evaluation of safety for penpulimab as a single agent focused on analyses of safety data for 125 patients with NPC treated with penpulimab 200 mg Q2W as a single agent in Study AK105-202 and a pooled population of 372 patients with advanced solid tumors or classical Hodgkin lymphoma who were treated with penpulimab 200 mg Q2W (monotherapy pool). - Serious adverse reactions occurred in 51% of patients in Study AK105-304; the most common serious adverse reactions ($\geq 2\%$) were thrombocytopenia (19%), decreased neutrophils (14%), decreased white blood cells (12%), anemia (8%), myelosuppression (3.4%), decreased sodium (2.7%), pneumonia (2.1%), and nausea (2.1%). There was one (0.7%) fatal adverse reaction due to SIADH.	The overall safety profile of penpulimab is similar to other PD-1 blocking antibodies. Safety issues identified as significant and serious during the BLA review were immune-related adverse events and infusion-related reactions, which are adequately addressed by the information in the Warnings and Precautions section included in product labeling. There were no significant safety concerns identified during BLA review requiring risk management beyond labeling or warranting consideration for Risk Evaluation and Mitigation Strategy (REMS).

Dimension	Evidence and Uncertainties	Conclusions and Reasons
	- Permanent discontinuation of penpulimab due to an adverse reaction occurred in 3.4% of patients in Study AK105-304. Adverse reactions which resulted in permanent discontinuation of penpulimab were acute myocardial infarction, acute kidney injury, brain edema, diabetic ketoacidosis, increased potassium, increased lipase, and thrombocytopenia (0.7% each). - Serious adverse reactions occurred in 22% in Study AK105-202. Serious adverse reactions in $\geq 1\%$ in Study AK105-202 were pneumonia (3.8%), pneumonitis (1.5%), respiratory failure (1.5%), and rash (1.5%). Fatal adverse reactions occurred in 1% of patients treated with penpulimab, including a case each of pneumonitis, septic shock, colitis, and hepatitis. - Permanent discontinuation of penpulimab due to an adverse reaction occurred in 3.8% of patients in AK105-202. Adverse reactions which resulted in permanent discontinuation of penpulimab in $\geq 1\%$ in Study AK105-202 were rash, hepatitis, herpes zoster, spinal cord compression and pleural effusion (0.8% each). - Immune-related adverse events (irAEs) occurred in 31% of patients (Grade 3 to 4, 4.1%) in Study AK105-304 and 22% of patients (Grade 3 to 4, 10%) in Study AK105-202. - In Study AK105-304, the most common irAEs $\geq 2\%$ were hypothyroidism and dermatologic toxicity. There were no fatal immune-related adverse reactions. In Study AK105-202, irAEs occurring at an incidence $\geq 2\%$ were hypothyroidism and dermatologic toxicity. - Infusion-related reactions occurred in 3.4% and 10% of patients in AK105-202 and the pooled safety dataset, respectively.	Penpulimab appears to have an acceptable safety profile when assessed in the context of a life-threatening disease with unmet medical need. The clinical data supports a positive risk-benefit assessment and is supportive of traditional approval penpulimab for the following indications: - Penpulimab in combination with either cisplatin or carboplatin and gemcitabine for the first-line treatment of adults with recurrent or metastatic non-keratinizing nasopharyngeal carcinoma (NPC) - Penpulimab as a single agent for the treatment of adults with metastatic non-keratinizing NPC with disease progression on or after platinum-based chemotherapy and at least one other prior line of therapy.

1.4. Patient Experience Data

Patient Experience Data Relevant to this Application (check all that apply)

☒	The patient experience data that was submitted as part of the application, include:	Section where discussed, if applicable
☒	Clinical outcome assessment (COA) data, such as	
☒	Patient reported outcome (PRO)	Section 8.1.2
☐	Observer reported outcome (ObsRO)	
☐	Clinician reported outcome (ClinRO)	
☐	Performance outcome (PerfO)	
☐	Qualitative studies (e.g., individual patient/caregiver interviews, focus group interviews, expert interviews, Delphi Panel, etc.)	
☐	Patient-focused drug development or other stakeholder meeting summary reports	
☐	Observational survey studies designed to capture patient experience data	
☐	Natural history studies	
☐	Patient preference studies (e.g., submitted studies or scientific publications)	
☐	Other: (Please specify)	
☐	Patient experience data that was not submitted in the application, but was considered in this review.	

X

Cross-Disciplinary Team Leader

2. Therapeutic Context

2.1. Analysis of Condition

NPC is a rare malignancy in most parts of the world but is endemic in Southeast Asia, Eastern Asia (especially Southern China) and North Africa (Chen YP, et al. 2019). According to the International Agency for Research on Cancer, in 2018, there were about 129,000 new cases of NPC and >70% of new cases are in Eastern and Southeast Asia, with an age-standardized rate of 3.0 per 100,000 in China to 0.4 per 100,000 in populations that are mainly Caucasian (Bray F, et al. 2018). Among the U.S. population, Chinese American accounted for approximately 36% of new cases of NPC according to the U.S. SEER 18 registries. NPC remains an important cause of cancer-related death worldwide with an incidence of approximately 50,000 deaths annually (Carioli G, et al. 2017; Tang LL, et al. 2016).

NPC is currently classified by the World Health Organization (WHO) into 3 major histological subtypes: keratinizing squamous cell carcinoma (WHO type 1), differentiated nonkeratinizing carcinoma (WHO type 2), and undifferentiated carcinoma (WHO type 3) (Ou SI, et al. 2007). Nonkeratinizing NPC, for which Epstein Barr virus (EBV) is an etiologic factor, constitutes most cases in endemic areas (>95%), including Southeast Asia, Eastern Asia and North Africa. The keratinizing subtype is more closely associated with cigarette smoking/alcohol consumption and accounts for a higher proportion of cases in nonendemic regions including the U.S (Wang Y, et al. 2013; Argirion I, et al. 2020). It has been noted that the incidence of the nonkeratinizing subtype is increasing in North America (Argirion I, et al. 2020), and similarly, findings of nonkeratinizing carcinoma being the predominant histology have been reported among white populations living in Europe (Svajdler Jr M, et al. 2016; Ruuskanen M, et al. 2019; Slevin F, et al. 2020). Despite differences in etiology and histology, current clinical management of NPC is consistent across the histologic subtypes.

The FDA's Assessment:

There were approximately 133,354 cases of NPC diagnosed worldwide in 2020 with the majority of cases (>75%) in South and East Asia and 1.6% in Northern America, and approximately 80,000 people died from NPC in 2020 (Globocan, 2020). NPC is rare in the United States, with <1 case per 100,000 people each year (Cancer.Net, 2022). A review of data from the Surveillance, Epidemiology, and End Results (SEER) registry reported by Sun et al (2017) identified 3919 patients with histologically confirmed NPC between 2004 and 2013. Among the 3919 patients, median age was 54 years (range 44, 63) and 71% of patients were male. Information on race was included for 3672 patients with 49% White, 12% Black, and 39% Asian (including 18% Chinese ethnicity). Information on histology was included for 1087 patients; of these patients, 83% had non-keratinizing and 17% had keratinizing NPC.

2.2. Analysis of Current Treatment Options

The Applicant's Position:

Guidelines for RM-NPC are consistent between the U.S. and China. Before the approval of PD-1 inhibitors in RM-NPC, the NCCN Head and Neck Cancer Clinical Practice Guidelines® recommend platinum-based chemotherapy regimens for first-line treatment of RM-NPC, with gemcitabine-cisplatin (GC) representing the preferred platinum-based regimen (category 1 recommendation). Other recommended regimens of first-line include cisplatin/5-FU, cisplatin or carboplatin/ docetaxel or paclitaxel, carboplatin/ cetuximab or gemcitabine/ carboplatin (*NCCN Head and Neck Cancer Clinical Practice Guidelines®, V4, 2024*). Although a high percentage of patients with NPC initially respond to chemotherapy, the duration of response is usually short (<6 months on average); median PFS for first-line GP treatment is only 7 months (*Zhang L, 2016*).

PD-1 inhibitors (toripalimab, camrelizumab and tislelizumab) combined with chemotherapy were firstly approved by the NMPA in China in the first-line treatment of RM-NPC, while in October 2023 FDA also approved toripalimab in combination with chemotherapy in the same indication. The recommendations on RM-NPC from clinical guidelines have converged again in the U.S. and China.

The FDA's Assessment:

FDA agrees with the Applicant that on October 27, 2023, FDA granted traditional approval to toripalimab-tpzi in combination with cisplatin and gemcitabine for the first-line treatment of adults with metastatic or recurrent, locally advanced NPC based on the results of the JUPITER-02 trial. The median PFS was 11.7 months for patients treated with toripalimab-tpzi with cisplatin and gemcitabine versus 8.0 months for patients treated with placebo with cisplatin and gemcitabine (PFS HR 0.52; 95% CI 0.36, 0.74; p=0.0003). A statistically significant OS improvement was also observed with median OS not reached (95% CI: 38.7 months, not estimable) for the toripalimab-tpzi-containing regimen and 33.7 months (95% CI: 27.0, 44.2) for the placebo-containing regimen (HR 0.63 [95% CI: 0.45, 0.89], p-value=0.0083). On October 27, 2023, FDA also granted traditional approval to toripalimab-tpzi as a single agent for the treatment of adults with recurrent unresectable or metastatic NPC with disease progression on or after a platinum-containing chemotherapy based on results of the POLARIS-02 trial. In 172 patients, the ORR by BICR was 21% (95% CI: 15, 28) and median DOR was 14.9 months (95% CI: 10.3, not estimable).

3. Regulatory Background

3.1. U.S. Regulatory Actions and Marketing History

The Applicant's Position:

Penpulimab has been approved for marketing in three oncology indications in China, including second or later lines of classic Hodgkin lymphoma (cHL), second or later lines of nasopharyngeal carcinoma (NPC) and first-line non-small cell lung cancer (NSCLC). Penpulimab is not currently approved or marketed in the US. The clinical development program for penpulimab is being conducted under Investigational New Drug (IND) 138576 with Division of Regulatory Operations -Oncologic Diseases for DO2, and the relevant regulatory history is included in [Section 3.2](#).

The FDA's Assessment:

FDA agrees with the Applicant's position.

3.2. Summary of Presubmission/Submission Regulatory Activity

The Applicant's Position:

Penpulimab is a Anti-PD-1 monoclonal antibody which received the Phase I Study May Proceed letter on Apr 11, 2018, under IND 138576, for the treatment of advanced solid tumors.

The FDA granted penpulimab Fast Track designation (FTD) on October 13, 2020, for the development of penpulimab, as systemic monotherapy for metastatic NPC patients who had progressed after two or more prior lines of therapy including platinum-containing chemotherapy. Orphan Drug Designation was granted by the FDA on February 23, 2021, for the treatment of nasopharyngeal carcinoma. Breakthrough Therapy Designation (BTD) was granted on March 24, 2021.

The penpulimab BLA (# 761258) was submitted in July 2021 for an accelerated approval for the treatment of patients with metastatic NPC who have progressed after two or more prior lines of therapy including platinum-containing chemotherapy. The PDUFA date was July 16, 2022.

During the BLA review period, the phase III protocol AK105-304 was submitted to the IND 138576 in August 2021, which intended to confirm the clinical benefit and to support full approval of penpulimab for the treatment of patients with metastatic or recurrent NPC. FDA completed four rounds of comments on the protocol and SAP, and both FDA and Sponsor reached agreement on the protocol and the SAP. No issues were outstanding.

During the BLA review period, FDA stated that the submission on May 30, 2022, constituted a major amendment and therefore the PDUFA date was extended to October 16, 2022.

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On October 14, 2022, FDA stated that due to restrictions on travel, FDA was unable to complete an inspection during the current review cycle for the application. Therefore, FDA was deferring action on the application until the inspection can be completed.

On January 19, 2024, FDA issued a Complete Response letter (CRL), due to the changing treatment landscape for NPC and product quality deficiencies.

On February 27, 2024, in light of the statement that the initial BLA was unable to be approved based on the results of the Phase II trial (AK105-202) and in order to address the deficiencies outlined in the CRL, Akeso requested a type B meeting to seek FDA's advice whether an interim analysis of the Phase III trial, AK105-304, was able to be conducted to support a BLA if the primary endpoint was met and if the plans to address the product quality deficiencies listed in the CRL were acceptable. The meeting was granted and the Sponsor presented its position and plans in a briefing document submitted to FDA on March 23, 2024. The FDA generally agreed with the applicant's position and plans, and also provided specific suggestions and comments.

A brief teleconference between Akeso and FDA was held on May 22, 2024. FDA confirmed that a BLA submission based on the results of Study AK105-304 would be considered a resubmission to BLA 761258, for the treatment of patients with recurrent or metastatic NPC and if the BLA was approved, the approval would be for the first-line treatment of patients with NPC as evaluated in Study AK105-304.

A summary of the key activities and Agency advice are provided in [\[Applicant – Table 1\]](#).

Applicant – Table 1 Key Regulatory Activities

Date	Milestone events	Outcome
2018.4.11	IND approved	Penpulimab received the Phase I Study May Proceed letter under IND 138576 for the treatment of advanced solid tumors.
2020.10.13 2021.02.23 2021.03.24	Fast Track Designation (FTD) Orphan Drug Designation (ODD) Breakthrough Designation (BTD)	The FDA granted penpulimab FTD on October 13, 2020; ODD on Feb 23, 2021; BTD on March 24, 2021
2021.01	Pre-BLA meeting	Reached an agreement for the BLA submission for accelerated approval based on AK105-202
2021.04	Pre-BLA meeting for CMC only	Reached an agreement for the applicant's proposed CMC strategy for a BLA submission.

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Date	Milestone events	Outcome
2021.04~2021.08	Type F iPSP meeting (WRO) & Agreed iPSP	FDA recommended (b) (4) Initial pediatric study plan agreement- (COR-PSP-04) iPSP-1 was received.
2021.07.16	Initial BLA submission	The BLA was submitted under the RTOR program between May and July, 2021.
2021.8.27	AK105-304 protocol submission(V 2.0, Aug. 25, 2021)	As required at the AK105-202 pre BLA meeting, AK105-304 full protocol was submitted to the IND for FDA review.
2021.09.08	Application Orientation Meeting (AOM)	Addressed technical aspects of the BLA
2021.09.28	Filing Communication - Filing Review Issues Identified	FDA completed the filing review and determined that the application was sufficiently complete to permit a substantive review. The PDUFA date was July 16, 2022.
2021.11	Bioresearch Monitoring (BIMO) inspection	FDA conducted the BIMO (GCP) inspection for BLA at (b) (4) from (b) (4)
2021.12.14	Mid-cycle meeting	Discussed review issues identified by the FDA by then.
2022.04.11	Late-cycle meeting	1. Discussion of Substantive Review Issues 2. Postmarketing Requirements/Postmarketing Commitments 3. Review Plans on Multi-disciplinary review and labeling discussions
2022.04.25	Phase III enrollment plan (ex-China)	As committed at the late-cycle meeting, the sponsor submitted the Phase III enrollment plan (ex-China) to the FDA.
2022.06.14	Review Extension – Major Amendment	FDA stated that the submission on May 30, 2022 constituted a major amendment and therefore the PDUFA date was extended to October 16, 2022.
2022.03~2023.03	Multiple rounds of labeling negotiations	FDA communicated with the Sponsor regarding the labeling on March 3, 2022, April 28,2022, May 14,2022, July 22, 2022, and March 20,2023.
2022.07	PMR-PMC language	FDA communicated with the sponsor regarding PMR-PMC language in July, 2022.

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Date	Milestone events	Outcome
2022.08.02	Teleconference with promotional regulatory reviewer	Discussion with FDA on the preparation of promotional materials and timeline of submission.
2022.09~11	Promotional materials submission and TC	Promotional materials were submitted to the FDA OPDP on September 29, 2022, and then promotional materials were revised per FDA' comments and resubmitted. A teleconference between OPDP and the Sponsor was held on December 5, 2022.
2022.10.14	General Advice Letter	FDA stated that due to restrictions on travel, FDA was unable to complete an inspection during the current review cycle for the application. Therefore, FDA was deferring action on the application until the inspection can be completed.
2022.12.09	Mature duration of response (DOR) results from Trial AK105-202	As committed in the PMR/PMC Memo, the Sponsor submitted the mature DoR results from AK105-202 to the BLA.
2023.7.25~08.07	Pre-License Inspection (GMP)	A pre-license inspection of a drug substance (DS) and drug product (DP) manufacturing facility at Akeso Biopharma Co., Ltd was conducted from July 25 to August 7, 2023. An eight-item Form FDA 483 was issued to the firm for the observations. A written response to the inspectional observations was provided to the FDA on August 28, 2023.
2023.09~2023.11	BIMO inspections (GCP)	FDA conducted the BIMO (GCP) inspections for BLA 761258 between Sep, 2023 and Nov, 2023 at 3 clinical sites. No complete response issues related to the BIMO (GCP) inspections.
2023.11.08	Update on the status of Study AK105-304	A request was received from FDA to update the enrollment status of Study AK105-304 and a response was submitted to FDA on November 8, 2023.
2023.12.21	Teleconference to discuss manufacturing inspection results and the status of the BLA	FDA informed the Sponsor: 1. Given the changing treatment landscape for NPC, current results of Study AK105-202 in patients with metastatic non-keratinizing NPC with disease progression on or after platinum-based chemotherapy and at least one other prior line of therapy treated with penpulimab-kcqx did not provide a meaningful advantage over currently available therapy. 2. CMC deficiencies would be provided in the complete response letter.

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Date	Milestone events	Outcome
2024.01.19	Complete Response Letter	FDA completed the review of the application and determined that they were unable to approve this application in its present form.
2024.02.27	Type B meeting request	Akeso requested a type B meeting to seek FDA's advice whether an interim analysis of the Phase III trial, AK105-304, was able to be conducted to support a BLA if the primary endpoint was met and if the plans to address the product quality deficiencies listed in the CRL were acceptable.
2024.04.12	Meeting minutes	The FDA generally agreed with the applicant's position and plans, and also provided specific suggestions and comments.
2024.05.22	A brief teleconference	FDA confirmed that a BLA submission based on the results of Study AK105-304 would be considered a resubmission to BLA 761258, for the treatment of patients with recurrent or metastatic nasopharyngeal carcinoma (NPC) and if the BLA is approved, the approval would be for the first-line treatment of patients with NPC as evaluated in Study AK105-304.
2024.10.02	BLA resubmission	The BLA was resubmitted on October 2, 2024.

The FDA's Assessment:

FDA agrees with the Applicant's position with the following additions. On July 16, 2021, the Applicant submitted BLA 761258 for the proposed indication for penpulimab-kcqx for the treatment of adult (b) (4) with metastatic non-keratinizing nasopharyngeal carcinoma with disease progression on or after platinum-based chemotherapy and at least one other prior line of therapy. Data from Study AK105-202, a single arm, open label study of penpulimab in patients with metastatic non-keratinizing NPC who had received prior therapy, conducted entirely in China, was provided as the primary evidence in support of the proposed indication. Amongst the 111 patients in the primary efficacy population, the ORR was 30% (95% CI 21, 39) (data cutoff date of February 3, 2021). The median DOR was not reached (range 3.8, 17.1+); a total of 39% of the 33 responding patients had a DOR $\geq$ 9 months.

During FDA's review of this BLA, FDA toripalimab-tpzi, an anti-PD-1 antibody, in combination with cisplatin and gemcitabine was granted traditional approval for the first-line treatment of adult patients with metastatic or recurrent, locally advanced NPC based on a randomized trial which demonstrated a 3.7-month improvement in progression-free survival (PFS) with the addition of toripalimab-tpzi to cisplatin and gemcitabine. This approval changed the standard of

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care for patients with metastatic or recurrent, locally advanced NPC with the inclusion of anti-PD-1-based therapy in the first-line treatment setting. At the time of this approval, toripalimab-tpzi was also approved as a single agent for patients with unresectable or metastatic NPC with disease progression on or after a platinum-containing chemotherapy based on ORR and DOR results from a single arm study of patients with metastatic NPC (ORR 21% (95% CI 15, 28); median DOR 14.9 months (95% CI 10.3, not estimable). Given the approvals of toripalimab-tpzi for patients with NPC, the efficacy of penpulimab, based on the results of Study AK105-202, did not demonstrate a clear advantage over currently available therapeutic options for patients with metastatic, non-keratinizing NPC to grant an accelerated approval. In addition, following the pre-license inspection (PLI) of Akeso Biopharma, Co., Ltd., Guangdong, China (FEI 3017057933), deficiencies in CGMP operations were identified in the penpulimab drug substance and drug product manufacturing facility. FDA reviewed the responses from the facility and concluded that not all deficiencies had been satisfactorily resolved. Further, the Office of Pharmaceutical Quality (OPQ) identified various deficiencies related to the cell bank system used to manufacture penpulimab, process control strategy, validation of analytical procedures and drug product filling operation. After reviewing the Applicant's responses, OPQ concluded that the data were not sufficient to support a conclusion that the manufacture of penpulimab-kcqx was well-controlled and would lead to a product that is pure and potent. On January 19, 2024, the FDA issued a complete response (CR) letter stating that given the changing treatment landscape for NPC, the results of Study AK105-202 in patients with metastatic non-keratinizing NPC with disease progression on or after platinum-based chemotherapy and at least one other prior line of therapy treated with penpulimab did not demonstrate a meaningful advantage over available therapy, as required by Section 21 of the Code of Federal Regulations (CFR) 601.41 Subpart E for accelerated approval.

On February 27, 2024, FDA received a Type B meeting request under IND 138576 from the Applicant to seek advice on whether a BLA could be submitted for penpulimab for NPC if there was a statistically significant difference in PFS at an interim analysis of Study AK105-304, and if the plans to address the chemistry, manufacturing, and controls deficiencies listed in the aforementioned CR letter were acceptable. On April 12, 2024, FDA issued preliminary meeting comments indicating that the PFS results of an interim analysis for Study AK105-304 may be acceptable to support re-submission of the BLA; however, FDA sought further clarification regarding the Applicant's proposal to conduct an interim analysis of PFS that was not consistent with the one pre-specified in the statistical analysis plan. In a follow-up email communication on April 17, 2024, the Applicant indicated that while an interim analysis of PFS was initially proposed at 155 events (70% information fraction [IF]), there was an overrun of PFS events due to a change in the analysis population that stemmed from difficulties enrolling patients from outside of Asia. On April 19, 2024, FDA sent an email communication indicating that an interim PFS analysis based on 190 events (86% IF) may be acceptable for this particular application but that additional sensitivity analyses of PFS should be provided by the Applicant. Agreement was reached between the Applicant and FDA to cancel the Type B meeting.

4. Significant Issues From Other Review Disciplines Pertinent to Clinical Conclusions on Efficacy and Safety

4.1. Office of Scientific Investigations (OSI)

For Study AK105-304, three clinical investigators (Cis), Drs. Feng Liu (Site # 1004), Chuanben Chen (Site # 1007), and Song Qu (site # 1023); the Applicant; and the imaging Contract Research Organization (CRO), (b) (4) were inspected. Inspections of Drs. Liu, Dr. Chen and Dr. Qu, the Applicant, and (b) (4) did not identify significant concerns about study conduct, data discrepancies, issues with Good Clinical Practice (GCP), or regulatory compliance.

Inspection of Dr. Liu (Site # 1004) did identify that one MRI tumor assessment was not submitted for central review. The patient was found to have stable disease on this omitted scan as well as two previous scans that were reviewed by blinded independent central review (BICR) per protocol. Therefore, it was judged that this omitted scan would not materially change the results of the primary progression free survival (PFS) endpoint. For Study AK105-202, earlier inspections were delayed due to the Covid-19 pandemic and not further pursued due to the initial issuance of a complete response letter.

During the sponsor inspection, an Applicant representative reported 42 protocol deviations that had not been previously submitted to the BLA. The Applicant stated that the deviations were identified after the study data cutoff date of April 29, 2024. These deviations have been since submitted to the review division via electronic mail on March 28, 2025, and to the BLA 761258 on April 17, 2025. Please refer to the Addendum to Clinical Inspection Summary dated March 27, 2025, outlining the protocol deviations summaries in a total of 29 patients. Overall, the protocol deviations did not appear to impact patient safety or data integrity.

4.2. Product Quality

An initial Biologics Licensing Application (BLA) was submitted for penpulimab as a single-agent for patients with previously treated NPC on July 16, 2021, based on the results of the single-arm trial, Study AK105-202. During the review of that application, a pre-license inspection was performed on July 25, 2023, to August 07, 2023, of the drug substance (DS) and drug product (DP) manufacturing facility at Akeso Biopharma Co., Ltd., Shennong Road No. 6, Zhongshan City, Guangdong Province, China. An eight-item Form FDA 483 was issued to the firm at the end of the inspection on August 07, 2023, for the following observations: (1) The firm had not adequately validated its manufacturing processes for AK105 DS and DP in its manufacturing facility located in (b) (4). Additionally, the firm failed to establish process controls to ensure that the drug products it manufactures have the identity, strength, quality, and purity they purport or are represented to possess; (2) Procedures designed to prevent microbiological

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contamination of drug products purporting to be sterile had not been established or followed; (3) The firm's manufacturing control strategy did not adequately control for the potential introduction of adventitious agents from other products manufactured in the facility; (4) The firm's manufacturing control strategy and procedures were inadequate to prevent cross-contamination and product mix-up from all products manufactured in the multiproduct manufacturing facility in (b) (4) (5) Written records of investigations into unexplained discrepancies, or the failure of a batch or any of its components to meet specifications, did not always include appropriate documentation, conclusions, and follow-up; (6) The firm's quality unit's oversight of its GMP manufacturing operations was inadequate; (7) There were discrepancies between the current DS and DP manufacturing processes at the facility and the manufacturing processes described in the BLA 761258; and (8) Standard Operating procedures or work instructions were not followed, or did not contain sufficient details.

As a result, the Office of Pharmaceutical Quality (OPQ) recommended a Complete Response for the previously submitted BLA. A Complete Response Letter was issued to Akeso on January 19, 2024, citing deficiencies in CGMP operations identified in the penpulimab drug substance and drug product manufacturing facility listed in the application.

Additional deficiencies identified during the CMC review included the lack of a working cell bank for product manufacture, unacceptable method performance for the PD-1 Reporter Gene Assay, reduced and non-reduced capillary electrophoresis sodium dodecyl sulfate (CE-SDS) methods used for routine testing, and inadequate validation of the visual inspection process.

For this resubmission of the BLA, a second pre-license inspection was performed from February 21, 2025, to March 04, 2025, of the DS and DP manufacturing facility at Akeso Biopharma Co., Ltd., Shennong Road No. 6, Zhongshan City, Guangdong Province, China. A six-item Form FDA 483 was issued to the firm at the end of the inspection on March 04, 2025. The 483 observations and firm's written FDA-483 response dated March 10, 2025, and response to the request for additional information (RAI) dated March 20, 2025, were reviewed. The firm's responses and corrective actions to the FDA Form 483 observations and RAI are adequate. Consequently, OPMA/DPMA recommends approval of the BLA resubmission for penpulimab.

Based on the totality of information provided in the original BLA submission and the Class 2 resubmission, OPQ has determined that the data submitted in this application are sufficient to support a conclusion that the manufacture of penpulimab-kcqx is well-controlled and will lead to a product that is pure and potent. It is recommended that this product be approved for human use under conditions specified in the package insert. Refer to the OPQ Executive Summary and Primary assessment memos of this application for detailed information.

4.3. Clinical Microbiology

Clinical Microbiology not applicable for this application.

4.4. Devices and Companion Diagnostic Issues

There was no device or companion diagnostic test reviewed as part of this application.

5. Nonclinical Pharmacology/Toxicology

5.1. Executive Summary

Penpulimab is a human IgG1 monoclonal antibody that targets programmed cell death protein 1 (PD-1); its established pharmacologic class is PD-1-blocking antibody. PD-1 is expressed on activated T and B cells, natural killer cells, and myeloid lineage cells. Binding of PD-1 to its ligands, programmed death-ligand 1 (PD-L1) and PD-L2, inhibits T-cell activity, T-cell proliferation, and cytokine production. In the tumor microenvironment, PD-1 signaling contributes to the inhibition of T cell-mediated immune surveillance of tumors. Thus, blockade of PD-1 signaling in the tumor microenvironment is intended to enhance tumor immunosurveillance and anti-tumor immune responses.

In in vitro studies, penpulimab bound to human and cynomolgus monkey PD-1 but did not bind rodent PD-1, supporting the use of cynomolgus monkeys as the single pharmacologically relevant species for toxicity assessment. In cellular assays, penpulimab blocked the binding of human PD-1 to human PD-L1 and PD-L2 and also competitively bound to PD-1 expressed on the surface of human PD-1-transfected 293T cells. Additionally, penpulimab induced the secretion of interleukin-2 (IL-2) and interferon-gamma (IFN- γ) in a mixed culture of peripheral blood mononuclear cells (PBMCs) and dendritic cells (DCs) and in a mixed culture of PBMCs, DCs, and Raji Burkitt lymphoma cells. Penpulimab also enhanced IFN- γ secretion by cytomegalovirus (CMV)-responsive human PBMCs during the recall response to CMV antigen.

Given that penpulimab does not bind mouse PD-1, the Applicant investigated the in vivo antitumor activity of penpulimab in a human PD-1 knock-in genetically engineered mouse model (HuGEMM) implanted subcutaneously with MC38 mouse colon adenocarcinoma cells. Intraperitoneal administration of penpulimab at doses of 0.8 and 8 mg/kg twice a week for a total of 5 doses resulted in tumor growth inhibition (TGI) compared to the isotype control. The Applicant also evaluated the antitumor activity of penpulimab in immunodeficient mice implanted subcutaneously with Raji cells expressing PD-L1 or a Raji-PD-L1/PBMC mixture. Intravenous (IV) administration of penpulimab (10 mg/kg) on Days 7, 13, and 21 resulted in greater TGI compared to the isotype control.

The Applicant evaluated the safety of penpulimab in cynomolgus monkeys in GLP-compliant repeat-dose toxicology studies of up to 13 weeks duration. In the 6- and 13-week studies, monkeys received IV infusion of penpulimab at doses up to 60 mg/kg once every 2 weeks. There were no mortalities or penpulimab-related findings of toxicological significance. Target

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organs of toxicity in the 6-week study were the kidney (increased cortical tubular pigment or pigmented interstitial macrophages), spleen (increased cellularity), adrenal gland (cortical hypertrophy), parotid salivary gland (acinar cell atrophy), thymus (increased weight); and in the 13-week study was lymph nodes (erythrophagocytosis and increased cellularity). The incidence of anti-drug antibody formation was 63.33% in the 6-week study and 93.33% in the 13-week study, which may explain the limited findings noted in the 13-week study. In clinical trials done to support the approval of penpulimab in the proposed patient population, toxicities associated with penpulimab were primarily immune-mediated adverse reactions that are predicted by its mechanism of action. At the recommended clinical dose of 200 mg, the human AUC₀₋₃₃₆ was 26200 µg*h/mL.

Based on its mechanism of action and data from the literature, there is potential for enhanced immune responses to infection following treatment with penpulimab. *Mycobacterium tuberculosis* (Mtb)-infected PD-1 knockout mice exhibited decreased survival compared to wild-type mice, which correlated with increased bacterial proliferation and inflammatory responses in these animals. It is unclear whether decreased survival resulted from an inability to mount an appropriate antibacterial response or a failure to control the immune response leading to normal tissue destruction and organ failure (Lazar-Molnar, et al. 2010). Furthermore, in mouse models of lymphocytic choriomeningitis virus (LCMV) infection, the absence of PD-1 pathway signaling led to fatal CD8+ T cell-mediated killing of virally infected vascular endothelial cells, systemic vascular leakage, and ultimately cardiovascular collapse (Frebel et al. 2012; Mueller et al. 2010). Similarly, PD-L1-deficient mice died early after chronic systemic LCMV infection (Barber et al. 2006). In addition, blockade of PD-1 with an anti-PD-1 antibody in Mtb infection in monkeys can exacerbate the infection and lead to death and severe pulmonary stress in infected monkeys (Kauffman et al. 2021). A brief description of these data was included in Section 13.2 of the label to convey these potential risks to prescribers.

No reproductive or embryo-fetal developmental toxicology studies were conducted with penpulimab. Rather, the Applicant provided a literature-based assessment of the potential reproductive toxicity of penpulimab, consistent with the alternative approach described in the FDA Guidance for Industry Oncology Pharmaceuticals: Reproductive Toxicity Testing and Labeling Recommendations. Data from the literature demonstrate that the PD-1/PD-L1 pathway plays a critical role in maintaining maternal immunological tolerance to the fetus during pregnancy. Blockade of PD-1/PD-L1 signaling in murine models of pregnancy resulted in an increased incidence of fetal loss but no fetal malformations; however, late onset autoimmunity can occur in PD-1-deficient mice. Based on these findings, the potential risks of administering penpulimab during pregnancy include increased rates of abortion or stillbirth and an increased risk in offspring of developing immune-related disorders or altering the normal immune response. As a result, the pharmacology/toxicology team recommends a warning for embryo-fetal toxicity in the prescribing information. Based on a half-life of penpulimab of 23.9 days, females of reproductive potential are advised to use effective contraception during treatment with PENPULIMAB-KCQX and for 4 months after the last dose. The Applicant did not

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evaluate transfer of penpulimab to the fetus or milk, but IgG antibodies can be present in milk. Because of the potential adverse effects of PENPULIMAB-KCQX on a breastfeeding child, the review team included recommendations in the label not to breastfeed during treatment with PENPULIMAB-KCQX and for 4 months after the last dose. Neither genetic toxicology or carcinogenicity studies were conducted or required to support the use of an antibody in the currently proposed indication.

Recommendation:

There are no outstanding issues from a pharmacology/toxicology perspective that would prevent the approval of penpulimab (either in combination with gemcitabine and cisplatin or carboplatin, or as a single agent) for the treatment of adult patients with non-keratinizing NPC.

5.2. Referenced NDAs, BLAs, DMFs

The Applicant's Position:

N/A

5.3. Pharmacology

Primary Pharmacology

The FDA's Assessment (all data presented by FDA):

Primary pharmacology studies NCS105-0001 through NCS105-00010 were reviewed by the FDA under the original IND. All other pharmacology studies were reviewed under the current BLA.

A. In Vitro Studies

The Applicant determined the binding affinities of penpulimab for human (Study NCS105-0001), cynomolgus monkey (Study NCS105-0005), mouse (Study NCS105-0006), and rat PD-1 (Study NCS105-0007) using the enzyme-linked immunoassay (ELISA). Penpulimab (0.0014–1 µg/mL) bound to human PD-1-mFc fusion protein (human PD-1 extracellular domain fused to murine IgG Fc domain) and monkey PD-1-hFc fusion protein (monkey PD-1 extracellular domain fused to human IgG1 Fc domain) with EC₅₀ values of 0.053 and 0.215 nM, respectively, but did not bind to mouse or rat PD-1, supporting the use of cynomolgus monkeys as a pharmacologically relevant species for toxicity assessment.

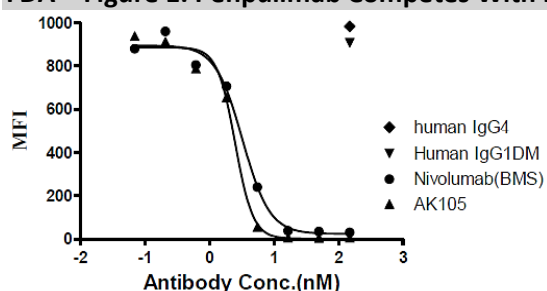
The Applicant determined the binding activity of penpulimab to PD-1 expressed on the surface of human PD-1-transfected 293T cells (293T-PD-1 cells) by fluorescence activated cell sorting (FACS) analysis (Study NCS105-0008). Penpulimab (0.1–20 nM) bound to human PD-1 in a dose-

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dependent manner, with an EC_{50} of 2.53 nM. As assessed by surface plasmon resonance, penpulimab (1.56–50 nM) exhibited high binding affinity for human PD-1, with a K_D of 0.588 nM (Study NCS105-0002), which was similar to the K_D of the anti-PD-1 comparator antibody nivolumab.

The Applicant used competitive ELISA to evaluate the activity of penpulimab in competing with PD-L1 (Study NCS105-0003) and PD-L2 (Study NCS105-0004) for binding to PD-1. Penpulimab (0.002–3 μ g/mL) blocked the binding of immobilized human PD-1-hFc to human PD-L1-mFc and human PD-L2-His fusion proteins in a dose-dependent manner, with EC_{50} values of 0.878 and 1.483 nM, respectively. The Applicant used FACS to evaluate the activity of penpulimab in competing with PD-L1 for binding to 293T-PD-1 cells (Study NCS105-0009). Penpulimab (0.07–150 nM) competitively bound to PD-1 on 293T-PD-1 cells in a dose-dependent manner, with an EC_{50} of 2.526 nM (FDA – Figure). Binding of penpulimab was comparable to the positive control, nivolumab, which competitively bound to PD-1 with an EC_{50} of 3.281 nM.

FDA – Figure 1. Penpulimab Competes With PD-L1 for Binding to Cell Surface PD-1

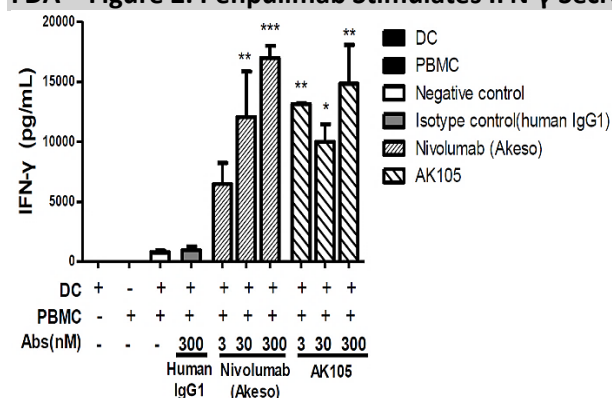


Source: Excerpted from the Applicant's submission: Study NCS105-0009

Abbreviations: BMS, Bristol Myers Squibb; IgG, immunoglobulin G; PD-1, programmed cell death protein 1; PD-L1, programmed cell death ligand 1

To evaluate the effect of penpulimab on the secretion of IFN- γ and IL-2 from lymphocytes, the Applicant conducted an allogeneic mixed lymph reaction (MLR) experiment (Study NCS105-00010). In this MLR, investigators incubated in vitro-differentiated DCs of one donor (stimulator) with allogeneic PBMCs of another donor (responder) at a ratio of 10:1, followed by the addition of penpulimab (3, 30, 300 nM). Nivolumab Akeso (synthesized by the Applicant) was used as a positive control. IFN- γ and IL-2 levels were measured by ELISA. Compared with the isotype and negative controls, penpulimab significantly enhanced the secretion of IFN- γ (FDA – Figure) and IL-2 (FDA – Figure) in the mixed culture of PBMCs and DCs in a dose-independent manner.

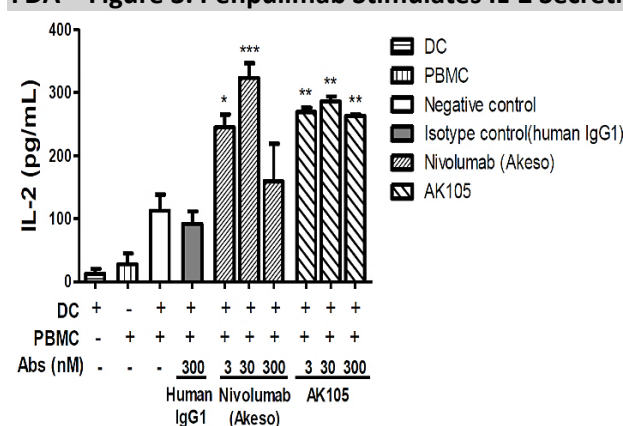
FDA – Figure 2. Penpulimab Stimulates IFN-γ Secretion in a Mixed Culture of PBMCs and DCs



Source: Excerpted from the Applicant's submission: Study NCS105-00010

Abbreviations: DC, dendritic cell; IFN-γ, interferon-gamma; IgG, immunoglobulin G; PBMC, peripheral blood mononuclear cell

FDA – Figure 3. Penpulimab Stimulates IL-2 Secretion in a Mixed Culture of PBMCs and DCs

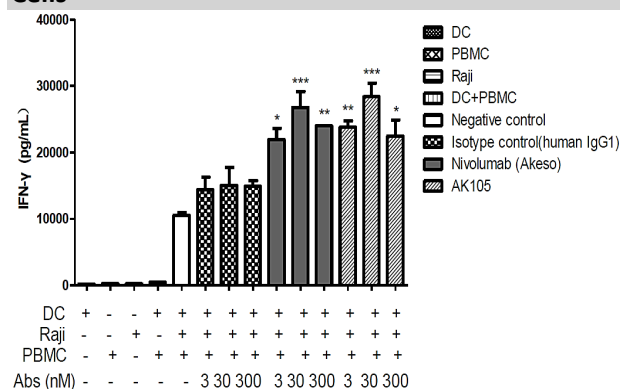


Source: Excerpted from the Applicant's submission: Study NCS105-00010

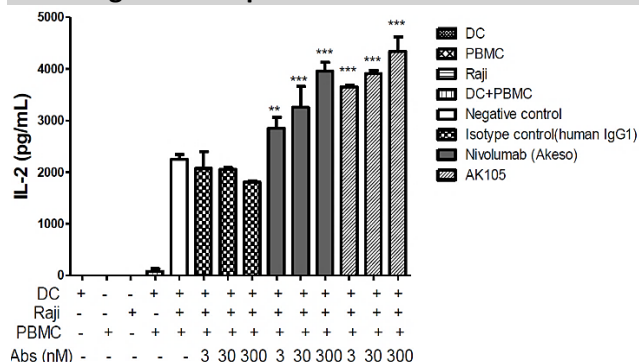
Abbreviations: DC, dendritic cell; IgG, immunoglobulin G; IL, interleukin; PBMC, peripheral blood mononuclear cell

The Applicant further studied the effects of penpulimab on IFN-γ and IL-2 secretion in a mixed culture of human PBMCs, DCs, and the Raji B-cell lymphoma line (Study NCS105-0021). In this MLR assay, penpulimab (3, 30, 300 nM) significantly enhanced the secretion of IFN-γ (FDA – Figure) and IL-2 (FDA – Figure) in the mixed culture of PBMCs, DCs, and Raji cells in a dose-dependent manner.

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FDA – Figure 4. Penpulimab Stimulates IFN- γ Secretion in a Mixed Culture of PBMCs, DCs, and Raji Cells

Source: Excerpted from the Applicant's submission: Study NCS105-00021

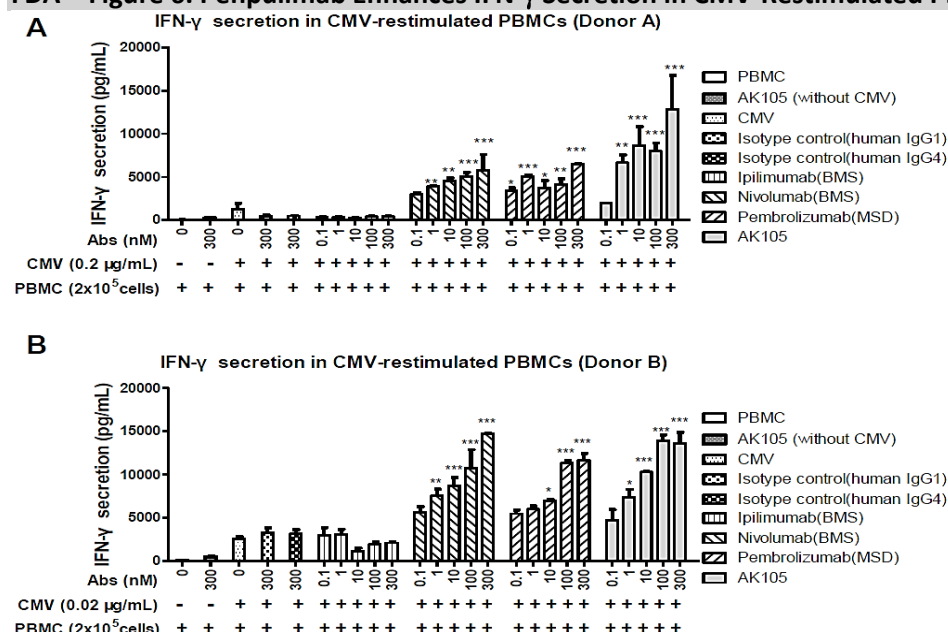
Abbreviations: DC, dendritic cell; IFN- γ , interferon-gamma; PBMC, peripheral blood mononuclear cell**FDA – Figure 5. Penpulimab Stimulates IL-2 Secretion in a Mixed Culture of PBMCs, DCs, and Raji Cells**

Source: Excerpted from the Applicant's submission: Study NCS105-00021

Abbreviations: DC, dendritic cell; IL, interleukin; PBMC, peripheral blood mononuclear cell

The Applicant conducted a cellular assay to evaluate the effect of penpulimab on IFN- γ secretion by CMV-responsive human PBMCs during the recall response to CMV antigen (Study NCS105-0024). PBMCs from two donors were prescreened for a CMV recall response using a serially diluted CMV peptide pool. As assessed by ELISA on Day 4, the CMV peptide pool effectively induced the secretion of IFN- γ in a dose-dependent manner, demonstrating that the PBMCs were previously infected by CMV and could re-respond to CMV antigen. The CMV-responsive PBMCs were stimulated with CMV antigen in the absence or presence of penpulimab (0.1–300 nM). Pembrolizumab and nivolumab were assessed as positive controls, and ipilimumab (anti-cytotoxic T lymphocyte antigen-4 antibody) served as a negative control. After a 4-day incubation, the antigen-induced IFN- γ response was measured by ELISA. Compared with the isotype and negative controls, penpulimab significantly enhanced the secretion of IFN- γ in a dose-dependent manner by CMV-responsive human PBMCs during the recall response to CMV antigen, showing comparable activity with nivolumab and pembrolizumab (FDA – Figure).

FDA – Figure 6. Penpulimab Enhances IFN-γ Secretion in CMV-Restimulated PBMCs



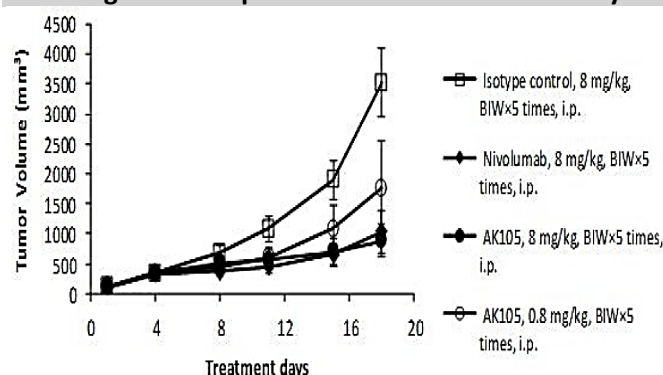
Source: Excerpted from the Applicant's submission: Study NCS105-00024

Abbreviations: CMV, cytomegalovirus; IFN-γ, interferon-gamma; IgG, immunoglobulin G; PBMC, peripheral blood mononuclear cell

B. In Vivo Studies

Because penpulimab does not bind to mouse PD-1, male C57BL/6 mice were genetically engineered to express a chimeric human/mouse PD-1 gene; these mice have a functional human PD-1 with expression regulated by the mouse PD-1 promoter. The Applicant investigated the in vivo antitumor activity of penpulimab in this human PD-1 knock-in genetically engineered mouse model (HuGEMM) implanted subcutaneously with MC38 mouse colon adenocarcinoma cells (Study E3174-B1701). Nivolumab (manufactured by Bristol-Myers) was used as a comparator control. Intraperitoneal administration of 0.8 and 8 mg/kg penpulimab twice a week for a total of 5 doses resulted in 74.1% and 54.5% TGI, respectively, compared to the isotype control (FDA – Figure). Penpulimab exhibited similar in vivo antitumor activity as nivolumab. There were no mortalities, and body weights remained stable during treatment.

FDA – Figure 7. Penpulimab has Antitumor Activity in PD-1 HuGEMM MC38-Bearing Mice

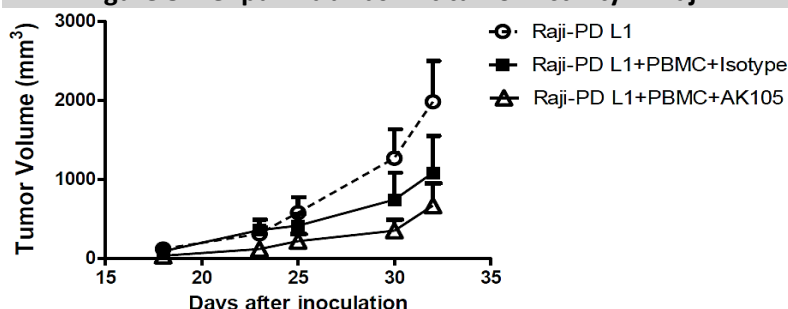


Source: Excerpted from the Applicant's submission: Study E3174-B1701

Abbreviations: HuGEMM, humanized genetically modified mouse model; PD-1, programmed cell death protein 1

The Applicant also evaluated the antitumor activity of penpulimab in female SCID/Beige mice implanted subcutaneously with Raji cells expressing PD-L1 (Raji-PD-L1 cells) or a Raji-PD-L1/PBMC mixture, in order to provide an immune component that is responsive to anti-PD-1 antibody and can generate an antitumor immune response (Study NCS105-0014). Intravenous administration of penpulimab (10 mg/kg) on Days 7, 13, and 21 resulted in greater TGI compared to the isotype control (FDA – Figure), without inducing significant toxicity based on body weight loss.

FDA – Figure 8. Penpulimab has Antitumor Activity in Raji-PD-L1-Bearing Mice



Source: Excerpted from the Applicant's submission: Study NCS105-00014

Abbreviations: PBMC, peripheral blood mononuclear cell; PD-1, programmed cell death protein 1

Secondary Pharmacology

The Applicant's Position:

In the Fc domain of penpulimab, point mutations were introduced to eliminate a series of Fc receptor mediated effects, including antibody-dependent cell-mediated cytotoxicity (ADCC), antibody dependent cellular phagocytosis (ADCP), complement dependent cytotoxicity (CDC) and Fc receptor mediated cytokine release. The affinity of penpulimab to Fc-receptor FcγRIIIa, FcγRI and C1q were evaluated by Fortebio Octet molecular interaction assay and confirmed lack

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of binding. Cellular assays were further conducted to evaluate the ADCC, ADCP, CDC and antibody dependent cytokine release (ADCR) activity of penpulimab, and penpulimab shows no ADCC, ADCP, CDC activity or ADCR of IL-6 and IL-8 from human macrophages. In binding selectivity assay, penpulimab binds to human PD-1 but not to human CTLA-4, which is a homologous protein of PD-1. Penpulimab also does not bind to human lymphocyte-activation gene 3 (LAG3) or human T cell immunoglobulin and ITIM domain (TIGIT), which are co-inhibitory receptors like PD-1. The activity of penpulimab to elicit cytokine IL-1 β , IL-6 and TNF- α release from peripheral blood mononuclear cells (PBMCs) was also tested and penpulimab does not elicit cytokine release of these cytokines from PBMC, suggesting the low risk of triggering cytokine release syndrome.

The FDA's Assessment:

FDA agrees with the Applicant's conclusions.

Safety PharmacologyThe Applicant's Position:

Safety pharmacology studies were conducted during cynomolgus monkey toxicity studies, and effect of penpulimab on vital functions in cardiovascular system, central nervous system (CNS) and respiratory system were investigated. The evaluation of safety pharmacology endpoints including body temperature, respiratory rate, blood oxygen saturation, electrocardiograms, and blood pressure upon treatment with penpulimab was incorporated into the repeat-dose toxicology study in cynomolgus monkey conducted under GLP condition. There were no treatment-related effects on body temperature, respiratory rate, blood oxygen saturation, electrocardiograms, or blood pressure found in the repeat dose toxicology study. Thus no specific concerns were observed on vital functions in cardiovascular system, CNS and respiratory system.

The FDA's Assessment:

FDA agrees with the Applicant's conclusions. In vivo, cardiovascular parameters were assessed pre-treatment; 2 to 5 hours after dosing on Days 1, 15, 29, and 43; and 1 day prior to recovery necropsy (Day 84) in the 13-week repeat-dose monkey study. Findings were reviewed under the General Toxicology section below. There were no toxicologically significant changes observed at doses up to 60 mg/kg/day.

5.4. ADME/PK

The Applicant's Position:

Single dose pharmacokinetics (PK) and repeat-dose toxicokinetics (TK) evaluation of penpulimab were performed in cynomolgus monkey which is the specie showing cross-reactivity to penpulimab. In single dose PK study, systemic exposure of penpulimab (AUC and Cmax) was approximately dose-proportional in cynomolgus monkeys from 1 mg/kg to 10 mg/kg. No significant differences in systemic exposure were noted. A high incidence of anti-drug antibody (ADA) formation was observed, which was related to the accelerated elimination of penpulimab in ADA-positive animals at the end of the elimination phase. Repeat dose PK (TK) of penpulimab was investigated in the 6-week and 13-week toxicity study. Dose-dependent increase in systemic exposure of penpulimab (AUC and Cmax) was noted following repeat intravenous dosing. Decreases in systemic exposure levels were noted in a few animals (Day 29 or 71, respectively), which is due to the formation of ADAs. There was no significant systemic accumulation after repeat dosing of penpulimab once every two weeks for 6 weeks or 13 weeks.

The FDA's Assessment:

FDA agrees with the Applicant's summary of the nonclinical ADME/PK data. Traditional distribution, metabolism, and excretion studies were not conducted with penpulimab because it is a monoclonal antibody.

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FDA – Table 1. ADME/PK

Type of Study	Major Findings
Absorption	Cynomolgus monkeys received penpulimab at a single IV dose of 1, 3, or 10 mg/kg.
Study P16-048-YD (reviewed by Dr. Manheng): Pharmacokinetic Study of a Monoclonal Antibody AK105 by Intravenous Infusion to Cynomolgus Monkeys	- Exposure increased dose proportionally. - There were no significant sex-related differences in exposure. - On Day 8, anti-drug antibodies (ADAs) were detected in 1/3 animals in each dose group. On Days 15, 22, and 29, ADAs were detected in all animals except one female at 3 mg/kg and one female at 10 mg/kg.

Mean Toxicokinetic Parameters in Monkeys Following Single IV Administration of Penpulimab

Dosage	Sex		$t_{1/2}$ h	C_{max} μg/ml	AUC_{0-672h} h*μg/ml	AUC_{INF} h*μg/ml	V_z ml/kg	Cl ml/h/kg	MRT h
1 mg/kg	Male	mean	122.80	26.10	2894.87	3078.22	57.40	0.33	144.75
		SD	28.67	3.28	276.07	277.60	11.04	0.03	30.60
	Female	mean	140.31	23.37	2592.18	3141.56	63.69	0.32	121.24
		SD	39.99	2.53	512.74	472.24	9.90	0.05	40.56
3 mg/kg	Male	mean	121.65	76.71	9080.55	9616.25	54.73	0.32	145.43
		SD	29.05	4.28	1508.91	1537.93	9.19	0.05	34.86
	Female	mean	166.94	67.87	10557.56	11383.25	62.54	0.27	180.40
		SD	54.70	4.09	1699.32	2425.98	9.99	0.05	32.25
10 mg/kg	Male	mean	64.03	340.18	42364.40	42756.89	22.04	0.25	151.15
		SD	60.00	94.71	12599.87	12627.73	19.36	0.08	24.32
	Female	mean	167.16	280.71	50391.10	55254.51	44.01	0.20	201.21
		SD	57.55	12.32	14572.59	17963.73	7.68	0.08	43.33

Source: Excerpted from the Applicant's submission: Study P16-048-YD

Abbreviations: AUC_{INF} , area under the plasma concentration-time curve extrapolated to infinity; AUC_{0-672h} , area under the plasma concentration-time curve from 0 to 672 hours; Cl, clearance; C_{max} , maximum plasma concentration; IV, intravenous; MRT, mean residence time; SD, standard deviation; $t_{1/2}$, half-life; V_z , apparently volume of distribution during the terminal phase

5.5. Toxicology

5.5.1. General Toxicology

The Applicant's Position:

In 6-week repeat-dose toxicity study, no apparent toxicity was observed in cynomolgus monkeys following intravenous infusion of penpulimab at 4, 15, or 60 mg/kg once every two weeks for 6 weeks. Treatment-related histopathological change of kidneys (increased cortical tubular pigment or pigmented interstitial macrophages) was noted in some animals but no impact on kidney functions. Pigment in the cortical tubular epithelium of the kidneys is not reported as a common background finding in cynomolgus monkeys. In this study, there were no apparent changes in clinical chemistry, urinalysis, or organ weights which would indicate an impact of treatment on kidney function. There were also no other histopathological changes associated with the pigment which were indicative of damage to the kidneys. These changes were therefore considered not to be adverse. The no observed adverse effect level (NOAEL) was considered to be 60 mg/kg.

In 13-week repeat-dose toxicity study, no apparent toxicity and histopathological change of kidney was observed in cynomolgus monkeys following intravenous infusion of penpulimab at 4, 15, or 60 mg/kg once every two weeks for 13 weeks, the NOAEL was considered to be 60 mg/kg.

The FDA's Assessment:

In general, FDA agrees with the Applicant's assessment of the toxicology data. In the 6-week repeat-dose toxicology study, clinical chemistry findings included a dose-dependent decrease in total bilirubin and increase in creatine kinase levels at all dose levels in males, which were present at the end of the recovery period. In addition to the kidney, as noted by the Applicant, other target organs of toxicity in the 6-week study were the spleen (increased cellularity of the red and white pulp), adrenal gland (cortical hypertrophy), parotid salivary gland (acinar cell atrophy), and thymus (increased weight). Changes in the adrenal gland, spleen, and thymus (females) were present at the end of the recovery period. Of the 30 monkey serum samples tested, 19 were ADA-positive with an incidence of 63.33%.

In the 13-week toxicity study, histological findings included erythrophagocytosis and increased cellularity in the lymph nodes (inguinal, mandibular, mesenteric), which were present at the end of the recovery period. Limited findings may be reflective of ADA formation. Of the 30 monkey serum samples tested, 28 were ADA-positive with an incidence of 93.33%.

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Study title/number: A 13-Week Intravenous Infusion Toxicity Study of AK105 Injection With a 6-Week Recovery Period in Cynomolgus Monkeys**Key Study Findings**

- There were no mortalities or penpulimab-related findings of toxicological significance.
- Histological findings included increased cellularity and erythrophagocytosis in the inguinal, mandibular, and mesenteric lymph nodes.
- The NOAEL was 60 mg/kg.

GLP compliance: Yes

FDA – Table 2. Methods (13-Week Study; Monkeys)

Methods	
Dose and frequency of dosing:	0, 4, 15, and 60 mg/kg Once every 2 weeks for 13 weeks
Route of administration:	Intravenous
Formulation/Vehicle:	Sodium chloride injection
Species/Strain:	Monkey/Cynomolgus
Number/Sex/Group:	Main: 3 monkeys/sex/group Recovery: 2 monkeys/sex/group; 6-week recovery period
Age:	3.5 to 4 years old
Satellite groups/unique design:	Toxicokinetic: 5 monkeys per sex per group/lymphocyte subsets, cytokine assay, immunogenicity, immunoglobulin assay, complement assay, body temperature, blood pressure
Deviation from study protocol affecting interpretation of results:	No

FDA – Table 3. Observations and Results: Changes From Control (13-Week Study; Monkeys)

Parameters	Major Findings
Mortality	None
Clinical Signs	No penpulimab-related findings; signs noted were also present in the controls, were infrequent, had no dose-response relationship, and/or were common spontaneous changes in monkeys.
Body Weight	Unremarkable
Feed Consumption	Unremarkable
Body Temperature	Unremarkable

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Parameters	Major Findings
ECG	No penpulimab-related findings; the changes observed in QTcB, QTcB, and Q-T were considered individual variations due to lack of a dose-relationship and small magnitude.
Blood Pressure	Unremarkable
Ophthalmoscopy	Unremarkable
Hematology	Unremarkable
Coagulation	Unremarkable
Clinical Chemistry	Unremarkable
Urinalysis	Unremarkable
Gross Pathology	No penpulimab-related lesions
Organ Weights	No penpulimab-related findings; although there were statistically significant increases in brain weight at 4 and 60 mg/kg, ovary weight at 15 mg/kg, and thymus weight at 60 mg/kg in females, due to the lack of a clear dose-relationship and corresponding microscopic findings, the Applicant considered the increases to be incidental.
Histopathology (Adequate battery: Yes)	Treatment-related histopathology findings were limited to the lymph nodes (FDA – Table 4).
Lymphocyte Subsets	No penpulimab-related changes in CD3+, CD4+, CD8+, CD20+, or CD4+/CD8+ ratios
Cytokine Assay	No penpulimab-related changes in TNF- α , IFN- γ , IL-2, IL-4, IL-5, or IL-6
Immunoglobulin Assay	No penpulimab-related changes in IgA, IgG, or IgM
Complement Assay	No penpulimab-related changes in C3 or C4
Immunogenicity	At the end of the 13-week treatment period, ADAs were detected in 10/10, 9/10, and 10/10 monkeys dosed with 4, 15, and 60 mg/kg penpulimab, respectively. Neutralization activities were detected in 28/30 of the ADA-positive serum samples. All recovery animals (4 per group) were ADA-positive at the end of the recovery period. ADAs resulted in lower penpulimab concentrations in several animals (5, 5, and 2 animals in the 4, 15, and 60 mg/kg groups, respectively).
Toxicokinetics	• C_{max} and AUC_{last} generally increased dose proportionally on Day 1. In females, C_{max} and AUC_{last} increased in a greater than dose-proportional manner on Day 71; in males, the C_{max} increased dose proportionally and the AUC_{last} increased in a less than dose-proportional manner. • The only sex-related differences were lower exposure in males than females at 15 mg/kg on Day 71 due to ADA. • There was no significant accumulation of penpulimab.

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Parameters	Major Findings					
Toxicokinetic Parameters for Penpulimab						
	Males			Females		
mg/kg	4	15	60	4	15	60
Day 1						
C _{max} (ng/mL)	0.08	0.36	1.30	0.09	0.31	1.23
AUC _{last} (h*mg/mL)	9.86	39.94	153.24	10.32	37.30	142.19
Day 71						
C _{max} (ng/mL)	0.10	0.23	1.56	0.09	0.38	1.74
AUC _{last} (h*mg/mL)	13.84	11.40	156.33	8.90	42.94	194.11

On Day 71, TK parameters were not calculated in 3 monkeys (2 in 4 mg/kg group and 1 in 15 mg/kg group) due to severe ADA effects

Abbreviations: AUC_{last}, AUC from the time of dosing to the time the last serum drug was detected (up to 336 hours); C_{max}, maximum plasma concentration; h, hours; TK, toxicokinetic

Abbreviations: ADA, antidrug antibody; AUC_{last}, area under the concentration-time curve from time zero to the time of the last measurable concentration; C_{max}, maximum plasma concentration; IFN-γ, interferon-gamma; IgA, immunoglobulin A; IgG, immunoglobulin G; IgM, immunoglobulin M; IL-6, interleukin-6; TNF-α, tumor necrosis factor alpha

FDA – Table 4. Selected Histopathology Findings (13-Week Study; Monkeys)

Organ/Tissue	Finding	Result Modifier	Dose (mg/kg)	Male				Female			
				0	4	15	60	0	4	15	60
			# of monkeys examined	3/2R	3/2R	3/0R	3/2R	3/2R	3/2R	3/0R	3/2R
LYMPH NODE	Cellularity, increased	Inguinal; mandibular; mesenteric	Slight		1		2/2R	1			2/2R
	Erythrophagocytosis	Inguinal; mandibular; mesenteric	Min	1	1	2	1/2R	1	3	1	2R
		Inguinal	Slight		1		1				1
			Mar		2/1R	1	1				

Abbreviations: Mar, Marked; Min, Minimal; Mod, Moderate; R, Recovery

5.5.2. Genetic Toxicology

The Applicant's Position:

Genetic toxicology studies were not conducted with penpulimab. As described in ICH Guidance S6, the range and type of genotoxicity studies routinely conducted for pharmaceuticals are not applicable to biotechnology-derived pharmaceuticals.

The FDA's Assessment:

FDA agrees that genetic toxicology studies are not needed to support the use of penpulimab per ICH S6.

5.5.3. Carcinogenicity

The Applicant's Position:

Carcinogenicity studies were not conducted with penpulimab, which is consistent with its use in patients with advanced malignancies (see the ICH Guidance S9). If penpulimab is developed for use in other indications, an assessment of its carcinogenic potential may be warranted; however rodent bioassays are inappropriate, as penpulimab does not appear to be active in rodents.

The FDA's Assessment:

FDA agrees that carcinogenicity studies are not needed to support the use of penpulimab in the currently proposed indication per ICH S9.

5.5.4. Reproductive and Developmental Toxicology

The Applicant's Position:

Fertility, embryonic fetal development or pre- and postnatal developmental toxicity studies were not conducted with penpulimab. As described in ICH Guidance S9, fertility and early embryonic developmental toxicity study is not warranted for marketing of pharmaceuticals for the treatment of patients with advanced cancer. Information available from general toxicology studies on the pharmaceutical's effect on reproductive organs were used as the basis of the assessment of impairment of fertility. In the 6-week and 13-week repeat-dose toxicity studies, there were no notable effects in the male and female reproductive organs.

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Embryo-fetal development toxicity studies were not conducted with penpulimab. Literature data shows that a central function of the PD-1/PD-L1 pathway is to preserve pregnancy by maintaining maternal immune tolerance to the fetus. Blockade of PD-L1 signaling has been shown in murine models of pregnancy to disrupt tolerance to the fetus and to increase fetal loss. There are potential reproductive risks when giving penpulimab during pregnancy, including increased rates of miscarriage or stillbirth. Penpulimab is an IgG1 antibody drug with high affinity to human FcRn, thus it is expected to cross the placenta during third-trimester pregnancy in human, though the exposure of penpulimab in fetus under treatment dose level is undetermined. Based on its mechanism of action, fetal exposure to penpulimab may increase the risk of developing immune-mediated disorders or altering the normal immune response and immune-mediated disorders have been reported in PD-1 knockout mice.

Pre- and postnatal toxicity studies were not conducted with penpulimab. As described in ICH Guidance S9, pre- and postnatal toxicity study is not warranted for marketing of pharmaceuticals for the treatment of patients with advanced cancer.

The FDA's Assessment:

FDA agrees that dedicated reproductive and developmental toxicity studies are not needed to support this BLA submission. To address the potential effects of penpulimab on embryo-fetal development, the Applicant submitted an assessment of the potential reproductive toxicity of penpulimab using a weight-of-evidence approach. FDA agreed in January 2021 that this approach appeared reasonable.

The PD-1/PD-L1 pathway plays a critical role in maintaining maternal immunological tolerance to the fetus during pregnancy (Guleria et al. 2005). PD-L1 is expressed in the human placenta throughout pregnancy and at the maternal-fetal interface in fetal villous syncytiotrophoblasts and extravillous cytotrophoblasts (Petroff et al. 2003). Blockade of PD-L1 signaling in murine models of pregnancy disrupts tolerance to the fetus, resulting in increased fetal loss (Guleria et al. 2005).

Penpulimab is a humanized IgG1 antibody, and human IgG is known to cross the placenta; thus, penpulimab may be transmitted from the mother to the fetus. Based on its mechanism of action and findings from murine models of pregnancy (Guleria et al. 2005), administration of penpulimab is likely to disrupt the maintenance of normal pregnancy. Potential risks associated with administration of penpulimab during pregnancy include increased rates of abortion and stillbirth. In addition, as PD-1 knockout mice develop late onset autoimmune phenotypes (Okazaki and Honjo 2007), fetal exposure to penpulimab may alter the normal immune response or increase the risk of developing immune-related disorders. As inhibition of the PD-1/PD-L1 pathway can lead to increased risk of immune-mediated rejection of the developing fetus, resulting in fetal death, a warning for embryofetal toxicity is recommended for PENPULIMAB-KCQX. Based on a half-life of approximately 24 days, females of reproductive

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potential are advised to use effective contraception during treatment with PENPULIMAB-KCQX and for 4 months after the last dose of PENPULIMAB-KCQX.

Fertility studies have not been conducted with penpulimab and are not needed to support a BLA for the proposed indication. In 6- and 13-week repeat-dose toxicity studies in monkeys, there were no notable effects on male and female reproductive organs up to the highest dose tested of 60 mg/kg (approximately ≥ 4.7 times the human exposure based on AUC at the 200 mg clinical dose); however, most animals in these studies were not sexually mature.

5.5.5. Other Toxicology Studies

The Applicant's Position:

The investigation of tissue cross-reactivity of penpulimab with normal human and normal cynomolgus monkey frozen tissues revealed that penpulimab reacted with normal human spleen and lymph nodes and normal cynomolgus monkey spleen, mesenteric lymph node, thymus, jejunum and colon. PD-1 is expressed on the surface of activated T cells, B cells, and macrophages, and as the results of penpulimab tissue cross-reactivity (TCR) studies showed no unexpected binding of penpulimab to human or cynomolgus monkey tissues was found. In hemolysis study, penpulimab at the concentration of 10 mg/mL had no hemolytic or aggregation effect on human red blood cells.

The FDA's Assessment:

FDA agrees with the Applicant's conclusions. Standard positive controls confirmed the sensitivity and validity of these GLP-compliant studies.

Literature Based Assessment of Potential for Effects of Infection

(Previously reviewed by FDA)

While loss of PD-1 function enhances clearance of some tumors and viral infections, it increases susceptibility to certain other pathogens such as tuberculosis in some animal models. PD-1-deficient mice (C57BL/6) infected with *Mycobacterium tuberculosis* (Mtb) exhibited a decrease in survival, which correlated with uncontrolled bacterial proliferation and a larger inflammatory response in the lungs of PD-1-deficient mice compared with wild-type controls. Thus, PD-1 appears to be required to control infection and the inflammatory responses in the lungs of mice infected with Mtb (Lazar-Molnar, et al. 2010); however, the pathogenesis of this observation has not been clearly defined. In particular, it is unclear whether the decreased survival reflects rampant bacterial growth resulting from an inability to mount appropriate antibacterial responses and/or whether it is a failure to downregulate the immune reaction that leads to massive tissue destruction and organ failure.

In a recent publication, Kauffman et al. (2021) evaluated the role of PD-1 during Mtb infection of rhesus macaques. Monkeys (~2 years old; males) were infected with 30-50 colony forming units of fluorescently labeled Mtb into the right lower lung lobe. Tissue from Mtb-infected monkeys was harvested 15–16 weeks post-infection and assessed for PD-1 expression using flow cytometry. Additional Mtb-infected monkeys were intravenously infused with 10 mg/kg of isotype control (DSPR4) or a primatized anti-PD-1 monoclonal antibody (n=6/group) at 2, 4, 6, 8, 10, and 13 weeks post-infection to determine the role of PD-1 during an Mtb infection. PET scans and 18FDG (18F-fluoro-2-deoxy-D-glucose) uptake, granuloma size and number, and colony forming units per granuloma were used to evaluate infection. Monkeys in both studies were necropsied at 15–16 weeks post-infection. Treatment of Mtb-infected monkeys with an anti-PD-1 antibody led to early euthanasia in one monkey due to severe pulmonary stress and another monkey developed cachexia and showed elevated 18FDG uptake in the lungs but survived until study termination. PD-1 expression in Mtb-infected monkeys occurred more frequently on antigen specific CD4 and CD8 T cells in lung granulomas compared to other tissues. Mtb-infected monkeys treated with an anti-PD-1 showed similar numbers of granulomas compared to controls, but these were characterized as larger granulomas, with increased 18FDG uptake and a higher bacterial load. The increased bacterial loads noted with PD-1 blockade occurred primarily within the site of infection (pulmonary lymph nodes and granulomas), suggesting it did not result in disseminated infection. The mechanism underlying the increased bacterial loads after PD-1 blockade in Mtb infection are not clear, but IFN- γ and TNF have been previously implicated. Evaluation of cytokines in granulomas of isotype and anti-PD-1-treated monkeys indicated that IFN- γ , TNF, and IL-18 were the most dysregulated cytokines and positively correlated with bacterial loads after PD-1 blockade. Data from Kauffman et al. (2021) indicate that blockade of PD-1 with an anti-PD-1 antibody can exacerbate Mtb infection in monkeys, consistent with previous findings noted in PD-1 knockout mice infected with Mtb (Lazar-Molnar et al. 2010).

X

X

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6. Clinical Pharmacology

6.1. Executive Summary

The FDA's Assessment:

The Applicant seeks approval of penpulimab for the treatment of the following indications at the following proposed recommended dosages:

- In combination with either cisplatin or carboplatin and gemcitabine for the first-line treatment of nasopharyngeal carcinoma (NPC). The recommended dosage is penpulimab 200 mg administered via intravenous (IV) infusion every three weeks (Q3W).
- As a single agent for the treatment of non-keratinizing NPC with diseases progression on or after platinum-based chemotherapy and at least one prior line of therapy. The recommended dosage is penpulimab 200 mg administered via IV infusion every two weeks (Q2W).

The recommended dosage of penpulimab 200 mg IV Q2W as a single agent was selected from the pivotal Study AK105-202, which was previously reviewed during the initial BLA review cycle. The proposed dosage 200 mg Q2W was supported by the clinical benefit and safety profile from Study AK105-202. The clinical pharmacology review found the proposed dosage acceptable based on population PK (PPK), exposure response (E-R) and immunogenicity analyses. (Reference ID: 5313694).

The recommended dosage of 200 mg IV Q3W in combination with chemotherapy (either cisplatin or carboplatin and gemcitabine) was reviewed in this submission. The primary evidence of efficacy and safety was obtained from the pivotal study AK105-304, in which patients were randomized (1:1) to receive either penpulimab 200 mg Q3W by IV infusion in combination with chemotherapy or placebo in combination with chemotherapy.

The clinical pharmacology review addressed the following two key review issues:

ISSUE #1 – Is the proposed dosage acceptable?: The proposed dosage of penpulimab 200 mg Q3W is acceptable for patients with NPC given the following considerations from Study AK105-304:

- The dosages of penpulimab 200 mg Q2W as a single agent and penpulimab 200 mg Q3W in combination with chemotherapy showed comparable exposures based on PPK analysis. No dosage adjustment is recommended for patients based on age, sex, race, body weight, serum albumin, baseline LDH, baseline C-reactive protein, baseline ECOG score,

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immunogenicity status, tumor type, co-administration with chemotherapy, mild or moderate renal impairment, and mild or moderate hepatic impairment. The effect of severe renal impairment or severe hepatic impairment on penpulimab PK is unknown.

- The E-R analysis for efficacy showed a flat relationship but is considered exploratory due to a limited exposure range from one dose level in Study AK105-304. Any relationship between exposure and efficacy endpoints should be interpreted with caution.
- The E-R analysis for safety did not show a relationship with overall treatment-emergent adverse events (TEAEs). However, there is a positive correlation between exposure and immune-related adverse events (irAEs) and specific adverse events (AEs) including decreased white blood cells, hypothyroidism, rash, and upper respiratory tract infections. These AEs are not clinically significant due to comparable dose interruptions and discontinuations between treatment arms in Study AK105-304.

ISSUE #2 – Is the observed immunogenicity acceptable?: The incidence of treatment emergent anti-drug antibodies (ADAs) and neutralizing antibodies (NAbs) against penpulimab were 8.8% (12/137) and 33% (4/12), respectively in the penpulimab arm of Study AK105-304. Although observed trough concentrations (C_{trough}) decreased by 47% in ADA positive patients enrolled in Study AK105-304, ADAs or NAbs did not have a clinically significant effect on penpulimab pharmacokinetics (PK). The PPK analysis showed <20% differences in the Geometric Mean Ratios (GMRs) for clearance (CL), area under the curve at steady-state (AUC_{ss}), maximum concentration at steady state ($C_{max,ss}$) and minimum concentration at steady state ($C_{min,ss}$). The observed 47% decrease in C_{trough} in Study AK105-304 is attributable to patient factors such as weight and albumin, as the patients who tested positive and negative for ADA are not randomized. The effect of ADAs on safety and efficacy cannot be determined due to low numbers of ADA positive patients in Study AK105-304.

Recommendations: The Office of Clinical Pharmacology has reviewed the information submitted in BLA 761258 and determined it is approvable from a clinical pharmacology perspective. The key review issues with specific recommendations and comments are summarized in the table below:

FDA – Table 5. Key Clinical Pharmacology Review Issues

Review Issue	Recommendations and Comments
Pivotal and supportive evidence of effectiveness	The primary evidence of effectiveness is derived from 144 adult patients with metastatic NPC enrolled in Study AK105-304 who received penpulimab 200 mg IV Q3W plus chemotherapy. In Study AK105-304, the primary endpoint of PFS showed a statistically significant and clinically meaningful improvement favoring penpulimab in combination with chemotherapy versus placebo with chemotherapy. Refer to the FDA's assessment in Section 8.2 for details. The E-R analysis for efficacy is considered exploratory due to a limited exposure range from one dose level (See Section 19.4.3.1).

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Review Issue	Recommendations and Comments
General dosing instructions	The proposed recommended dosage is 200 mg IV Q3W in combination with either cisplatin or carboplatin and gemcitabine. The proposed dosing regimen is supported by the statistically significant and clinically meaningful improvement in BIRC-assessed PFS and the safety profile of penpulimab plus chemotherapy vs placebo plus chemotherapy in Study AK105-304. The PPK, E-R, and immunogenicity data from Study AK105-304 provide supportive evidence that the proposed recommended dosage of 200 mg IV Q3W is acceptable.
Dosing in patient subgroups	No dosage adjustment is recommended for age (18-91 years), sex, race (White and Asian), body weight (32-113 kg), serum albumin (22 to 54.5 g/L), baseline LDH (111 to 4,450 IU/L), baseline C-reactive protein (0 to 328 mg/L), baseline ECOG score (0 and 1), immunogenicity status, tumor type (NPC and other tumors), co-administration with chemotherapy, mild or moderate renal impairment (creatinine clearance [CL _{cr}] ≥ 30 mL/min), mild (total bilirubin ≤ ULN and AST > ULN or total bilirubin > 1 to 1.5 times ULN and any AST) or moderate hepatic impairment (total bilirubin > 1.5 to 3 times ULN and any AST) according to the results of PPK analyses.
Immunogenicity	Of the 137 evaluable patients in Study AK 105-304 with NPC who received penpulimab 200 mg IV Q3W, 8.8% (12/137) of patients tested positive for treatment emergent ADAs and 33% (4/12) of patients for treatment emergent NABs. The PPK analysis indicates that treatment emergent ADA had no significant impact on penpulimab PK, with <20% differences in the GMRs for CL, AUC _{ss} , C _{max,ss} , and C _{min,ss} . Although observed PK data showed a 47% decrease in C _{trough} in ADA positive patients, this is attributable to patient factors such as weight and albumin, as the patients who tested positive and negative for ADA are not randomized. There is insufficient information to characterize the effects of anti-penpulimab antibodies on the safety and efficacy of penpulimab due to low number of ADA positive patients in Study AK105-304.
Labeling	The proposed labeling is acceptable upon the Applicant's agreement to FDA revisions to the draft labeling.

Abbreviations: ADA, anti-drug antibody; AST, aspartate aminotransferase; AUC_{ss}, area under the plasma concentration-time curve at steady state; CL, clearance; C_{max,ss}, maximum plasma concentration at steady state; C_{min,ss}, minimum plasma concentration at steady state; C_{trough}, trough concentration; ECOG, Eastern Cooperative Oncology Group; E-R, exposure-response; GMR, geometric mean ratio; IV, intravenous; LDH, lactic dehydrogenase; NAb, neutralizing antibody; NPC, nasopharyngeal carcinoma; PFS, progression-free survival; PK, pharmacokinetic(s); PPK, population pharmacokinetics; Q3W, every 3 weeks; ULN, upper limit of normal

6.2. Summary of Clinical Pharmacology Assessment

6.2.1. Pharmacology and Clinical Pharmacokinetics

Data:

Penpulimab is a humanized immunoglobulin G1 (IgG1) monoclonal antibody targeting programmed cell death-1 (PD-1). Penpulimab binds specifically to human PD-1 with high affinity

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and competitively blocks the binding of PD-1 to its ligand programmed cell death-1 (PD-L1) and programmed cell death ligand-2 (PD-L2), thereby relieving immunosuppression of T lymphocytes, promoting the proliferation of lymphocytes and the secretion of related cytokines, and ultimately recovering cytotoxic activities of T cells to block tumor growth.

Pharmacokinetic (PK) data of penpulimab were derived from 8 clinical studies. A total of 771 patients were included in the population PK analysis (PopPK), and 31 patients who underwent intensive sampling were included in the non-compartmental PK analysis. The patients received penpulimab at 1.0, 3.0 or 10.0 mg/kg Q2W, 200 mg Q2W or 200 mg Q3W. According to the non-compartmental analysis (NCA), the C_{max} and AUC_{0-14d} increased relatively proportional within the dose range of 1.0 mg/kg to 10.0 mg/kg.

Penpulimab is administered via IV infusion. Based on population PK (PopPK) model ($n=771$), after single dose IV infusion of 200 mg, the terminal elimination half-life ($t_{1/2}$) of penpulimab is 32.4 days. The mean (CV%) of volume of distribution was 10.2 L (43.5%). The mean (CV%) of CL was 0.229 L/day (32.7%).

Steady state concentrations of penpulimab were reached by week 15 following 200 mg Q3W, with accumulation ratios for C_{max} and AUC of 1.53 and 2.10, respectively. The mode-predicted means of $C_{max,ss}$, $C_{avg,ss}$ and $C_{min,ss}$ are 87.6 $\mu\text{g/mL}$, 45.5 $\mu\text{g/mL}$ and 30.1 $\mu\text{g/mL}$, respectively. The effective half-lives ($t_{1/2eff}$) calculated based on C_{max} and AUC were 13.6 days and 22.4 days, respectively.

Receptor occupancy (RO) is an important measure of the in vivo biological activity of penpulimab and also an important parameter underlying the determination of the recommended dose in clinical studies. In the Phase Ia clinical study conducted in Australia (AK105-101 study), patients with advanced solid tumors received penpulimab therapy (1, 3 and 10 mg/kg Q2W). PD-1 RO reached 80% to 100% starting from two days post-dose for all these cohorts. No apparent correlation between RO value and dose level was noted.

The Applicant's Position:

Penpulimab exhibited linear PK characteristics in patients who received penpulimab by IV administration within the dose range of 1.0 mg/kg to 10.0 mg/kg. PopPK analysis indicated that distribution of penpulimab was limited to the central vascular compartment, and with an effective half-life of 22.4 days and mild accumulation upon repeat dosing.

The FDA's Assessment:

FDA agrees with the Applicant's position that the exposure to penpulimab increased dose proportionally over the range of 1 mg/kg to 10 mg/kg after a single dose.

6.2.2. General Dosing and Therapeutic Individualization

6.2.2.1. General Dosing

Data:

In the Phase Ia dose-escalation trial, no DLT occurred at the highest dose cohort of 10.0 mg/kg Q2W and no maximum tolerated dose (MTD) was explored, therefore the maximum administered dose (MAD) for this study was 10.0 mg/kg Q2W. Phase Ia PK data showed a linear relationship between exposure of penpulimab and dose over the dose range of 1.0 mg/kg Q2W to 10.0 mg/kg Q2W. Receptor occupancy analysis showed 80% to 100% PD-1 receptor occupancy starting on day 2 after administration. There was no significant difference in receptor occupancy between 1.0, 3.0 and 10.0 mg/kg doses level. The efficacy results showed anti-tumor activities at doses ranging from 1.0 mg/kg to 10.0 mg/kg Q2W. Since higher drug concentrations can be obtained with the 3 mg/kg dosing regimen than with the 1 mg/kg dosing regimen, this may ensure to achieve more stable blood concentrations after multiple doses for better sustained receptor occupancy.

Results of study AK105-101 showed that, following IV administration of penpulimab 1.0, 3.0 and 10.0 mg/kg, C_{max} and $AUC_{(0-14d)}$ increased proportionally with dose; the 90% confidence interval (CI) of β values of $AUC_{(0-14d)}$ and C_{max} was 0.676-1.15 and 0.844-1.13, respectively.

Based on population PK (PopPK) model (n=771), the PK parameters following single-dose IV infusion of penpulimab 200 mg are as follows: the mean C_{max} (CV%) was 57.6 $\mu\text{g/mL}$ (19.5%), the mean $AUC_{(0-inf)}$ (CV%) was 955 $\mu\text{g}\cdot\text{day/mL}$ (29.6%), the mean CL (CV%) was 0.229 L/day(32.7%), the mean V_z (CV%) was 10.2 L(43.5%), and the mean terminal elimination half-life ($t_{1/2}$) (CV%) was 32.4 days(43.5%).

Following multi-dose administration of penpulimab 200 mg Q3W, the steady state was reached by Week 15; the mode-predicted mean of $C_{max,ss}$, $C_{avg,ss}$ and $C_{min,ss}$ (CV%) are 87.6 $\mu\text{g/mL}$ (21.1%), 45.5 $\mu\text{g/mL}$ (29.1%) and 30.1 $\mu\text{g/mL}$ (38.1%), respectively; the mean (CV%) accumulation ratios for C_{max} and AUC were 1.53 (12.6%) and 2.10 (19.4%), respectively. The effective half-lives($t_{1/2eff}$) calculated based on C_{max} and AUC were 13.6 days and 22.4 days, respectively.

The steady-state drug concentrations following administration of penpulimab 200 mg Q3W in 771 patients are simulated. *In vitro* studies indicated 0.5 $\mu\text{g/mL}$ penpulimab was associated with a receptor occupancy close to 90%. PopPK analysis showed that, with a penpulimab dose of 200 mg Q3W, the steady-state trough concentration in more than 95% of patients was >10 $\mu\text{g/mL}$, which is 100-fold higher than those at which 80% of the receptors (0.1 $\mu\text{g/mL}$) could be occupied or 20-fold higher than those at which 90%~100% of the receptors (0.5 $\mu\text{g/mL}$) could be occupied.

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A logistic regression analysis was performed to explore the exposure-efficacy (E-E) and exposure-safety (E-S) relationships. E-E analysis suggested a relative flat exposure-response (ORR/DCR) curve and no apparent difference in exposure between responders and non-responders. E-R safety analysis indicated that no apparent correlation between exposure and incidence of TEAE/TRAE (Grade 3+) in the wide dose range (1-10 mg/kg Q2W) with either monotherapy or in combination therapy.

In NPC population, penpulimab (200 mg Q3W) in combination with chemotherapy, was safe and tolerable.

The Applicant's Position:

The recommended dosage of penpulimab was 200 mg Q3W administered with intravenous infusion (IV). Dose selection is based on the following considerations:

Safety:

- In phase 1 dose-escalation phase, Penpulimab was well tolerated up to 10 mg/kg Q2W, no DLT was observed.
- In NPC population, Penpulimab (200 mg Q3W) in combination with chemotherapy, was safe and tolerable.
- E-R safety analysis indicated that no apparent correlation between exposure and incidence of TEAE/TRAE (Grade 3+) in the wide dose range (1 - 10 mg/kg Q2W) with either monotherapy or in combination therapy.

Efficacy:

- Penpulimab 200 mg Q3W demonstrated notable clinical benefits in NPC population: the median PFS was 9.6 months (95% CI: 7.1, 12.5), compared to placebo of 7.0 months (95% CI: 6.9, 7.3).
- E-R analysis suggested a relative flat exposure-response (ORR/DCR) curve and no apparent difference in exposure between responders and non-responders.

PK/PD:

- Penpulimab exhibited linear PK characteristics over large dose range (1-10 mg/kg Q2W) with terminal half-life of 32.4 day.
- No intrinsic/extrinsic factor had clinically meaningful effect on PK and exposures were similar between Caucasian and Asian patients.

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- At 200 mg Q3W dose, observed mean trough concentrations in NPC patients ranged from 27.9 – 43.7 µg/mL, which was much higher than the exposure (0.5 µg/mL) achieving 90% receptor occupancy (RO) in vitro.

The FDA's Assessment:

FDA generally agrees that the proposed recommended dosage of 200 mg IV Q3W is supported by the observed clinical safety, efficacy, and PK/PD data from Study AK105-304.

FDA disagrees that the E-R analysis for efficacy is relatively flat and concludes that the E-R analysis for efficacy is inconclusive given that the analysis only included one dose level.

FDA generally agrees that there appears to be no apparent correlation between the incidence of most TEAEs and penpulimab exposure, but there is a positive correlation between exposure and immune-related adverse events (irAEs) and some specific adverse events (AEs) including decrease in white blood cells (WBC), hypothyroidism, rash, and upper respiratory tract infections (Refer to Section [19.4.3.3](#)). However, there were comparable dose interruptions (77% penpulimab arm vs 71% placebo arm) and discontinuations (12% penpulimab arm vs 9% placebo arm), and the relationship between exposure and irAEs and other AEs is likely not clinically significant.

6.2.2.2. Therapeutic Individualization

Data:

Intrinsic factors that might have an impact on penpulimab PK were subjected to covariate analysis by the PopPK model to identify main contributors to the PK variability.

Covariates investigated for their potential to influence penpulimab PK included age, body weight (WT), creatinine clearance (CLcr), creatinine concentration (CR), total bilirubin (TBIL), aspartate transaminase (AST), alkaline phosphatase (ALP), alanine aminotransferase (ALT), lactic dehydrogenase (LDH), albumin (ALB), tumor size (TSIZEB), Eastern Cooperative Oncology Group (ECOG) score, C-reactive protein (CRP) at baseline, tumor type (DIAG), sex, race, co-administration (COMBO) and total anti-drug antibody (TADA).

A two-compartment model with zero-order IV infusion and first-order elimination adequately described penpulimab PK. The typical subject is a male Asian patient with NPC and negative TADA, WT of 62.0 kg, ALB of 41.9 g/L, CRP of 9.55 mg/L, LDH of 214 IU/L, age of 55 years old, and receiving penpulimab plus chemotherapy.

The final model included the effects of (i) WT, age, ALB, LDH, race, sex, and TADA on clearance (CL); (ii) WT, ALB, SEX, COMBO and DIAG on volume of the central compartment (V_1); (iii) CRP, COMBO and DIAG on volume of the peripheral compartment (V_2). None of the other covariates

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tested had statistically significant effect on the PK parameters.

The parameter estimates for the final PopPK model are shown in [Applicant – Table 2](#).

Applicant – Table 2 Population PK Parameter Estimates From the Final Model for Penpulimab

Parameter	Estimate	RSE (%)	95% CI (bootstrap)	Shrinkage (%)
Fixed Effects				
CL (L/day)	0.217	2.21	0.200 — 0.229	/
V1 (L)	4.05	1.40	3.94 — 4.16	/
Q (L/day)	0.492	15.1	0.245 — 0.745	/
V2 (L)	7.51	4.98	6.77 — 8.51	/
CL-AGE	0.192	18.6	0.109 — 0.264	/
CL-ALB	-0.690	16.7	-0.913 — -0.454	/
CL-LDH	0.110	25.6	0.0523 — 0.167	/
CL-RACE	-0.231	17.8	-0.305 — -0.138	/
CL-SEX	-0.111	22.9	-0.158 — -0.0607	/
CL-TADA	0.168	21.2	0.104 — 0.239	/
CL-WT	0.405	18.1	0.258 — 0.556	/
V1-ALB	-0.305	20.3	-0.431 — -0.183	/
V1-COMBO	-0.0904	16.4	-0.118 — -0.0591	/
V1-DIAG	-0.0981	14.7	-0.125 — -0.0701	/
V1-SEX	-0.128	13.8	-0.158 — -0.0943	/
V1WT	0.479	9.56	0.379 — 0.562	/
V2-COMBO	-0.548	5.15	-0.600 — -0.494	/
V2-CRP	0.0844	25.0	0.0448 — 0.133	/
V2-DIAG	-0.212	29.1	-0.369 — -0.106	/
Between-Subject Variability				
CL	27.2%	4.65	23.6% — 29.7%	12.9
V1	16.3%	5.95	14.3% — 18.2%	24.5
V2	45.5%	11.2	33.5% — 57.0%	38.0
Residual Variability				
Proportional (%)	18.1	3.65	16.8 — 19.5	11.4
Additive (µg/mL)	2.11	9.00	1.71 — 2.46	11.4

Abbreviations: CL: clearance ;V1: volume of the central compartment ;V2: volume of the peripheral compartment ;Q: inter-compartment clearance;AGE: baseline age (years);ALB: baseline albumin (g/L);LDH: baseline lactate dehydrogenase (IU/L) ;WT: baseline body weight (kg) ;CRP: baseline C-reactive protein (mg/L);RACE: race;SEX: [REDACTED];TADA: Total anti-drug antibody/immunogenicity;COMBO: co-administration; DIAG: Diagnosis of Tumor type;NPC: nasopharyngeal carcinoma; CI values are taken from bootstrap calculations (923 of 1000 successful runs).

Data source: [Module 5.3.3.5 Penpulimab PopPK and ER report Appendix 2-Table 7 and Table 10](#).

To evaluate the clinical relevance of the identified statistically significant covariates, the relationships between the identified covariates and steady-state exposures were assessed. Impacts of covariates retained in the final model on the area under concentration-time curve within the dosing interval in steady state (AUC_{SS}), $C_{max,SS}$ and $C_{min,SS}$ are described in [Applicant – Table 3](#). Based on these results, it showed that while these covariates had statistically significant effects on PK parameters, they did not have clinically significant effects on steady-state exposure ($\leq 30\%$).

Applicant – Table 3 Population PK Parameter Estimates from the Final Model for Penpulimab

	AUC _{ss}		C _{max,ss}		C _{min,ss}	
	GMR	95% CI	GMR	95% CI	GMR	95%CI
10% of AGE vs typical subject	1.09	1.06-1.12	1.05	1.04-1.07	1.12	1.09-1.16
10% of ALB vs typical subject	0.863	0.843-0.884	0.898	0.884-0.911	0.827	0.800-0.854
10% of CRP vs typical subject	0.995	0.972-1.02	0.991	0.977-1.01	0.987	0.956-1.02
10% of LDH vs typical subject	1.03	1.01-1.06	1.02	1.00-1.03	1.04	1.01-1.08
10% of WT vs typical subject	1.11	1.09-1.14	1.13	1.11-1.15	1.13	1.09-1.17
90% of AGE vs typical subject	0.954	0.932-0.977	0.970	0.956-0.985	0.940	0.911-0.971
90% of ALB vs typical subject	1.08	1.06-1.11	1.07	1.05-1.08	1.10	1.06-1.14
90% of CRP vs typical subject	0.984	0.961-1.01	0.994	0.980-1.01	0.984	0.953-1.02
90% of LDH vs typical subject	0.913	0.891-0.935	0.955	0.941-0.969	0.882	0.854-0.912
90% of WT vs typical subject	0.904	0.884-0.925	0.894	0.882-0.907	0.892	0.864-0.920
Monotherapy vs Combination for COMBO	1.13	1.11-1.16	1.15	1.13-1.17	1.16	1.12-1.19
Female vs Male for SEX	1.01	0.983-1.03	1.04	1.03-1.06	0.941	0.909-0.973
Non-Asian vs Asian for RACE	1.30	1.27-1.33	1.16	1.14-1.18	1.41	1.36-1.45
Others vs NPC for DIAG	0.989	0.966-1.01	1.05	1.03-1.06	0.956	0.925-0.987
Positive vs Negative for TADA	0.856	0.836-0.877	0.926	0.912-0.939	0.809	0.783-0.836

Abbreviations: AGE: baseline age (years); ALB: baseline albumin (g/L); LDH: baseline lactate dehydrogenase (IU/L); WT: baseline body weight (kg); CRP: baseline C-reactive protein (mg/L); RACE: race; SEX: ; TADA: Total anti-drug antibody/immunogenicity; COMBO: co-administration; DIAG: Diagnosis of Tumor type; NPC: nasopharyngeal carcinoma; AUC_{ss}: area under the serum concentration-time curve during the dosing interval at steady state; C_{max,ss}: maximum concentration at steady state; C_{min,ss}: trough concentration at steady state; GMR: geometric mean ratio;

Data source: [Module 5.3.3.5 Penpulimab PopPK and ER report Appendix 2-Table 12](#).

Age:

Among the 771 patients included in the PopPK analysis, the median age was 55 years (range: 18-91 years). The results of the stepwise covariate model (SCM) indicated that age had a statistically significant effect on CL of penpulimab. CL of penpulimab increased with age. This increase in penpulimab CL ranged from -8.82% to +4.74% of the median CL estimate when age increased from the 10% (34.0 years) to the 90% (70.0 years). However, comparison of model-predicted steady state exposures (C_{max,ss}, C_{min,ss}, AUC_{ss}) indicated exposure ratios of less than 30%, suggesting that age has no clinically meaningful impact on penpulimab exposures.

Sex:

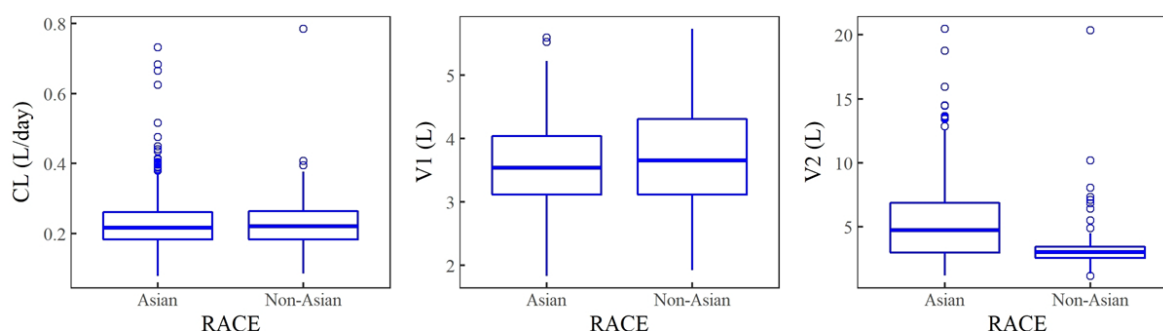
Females accounted for 25.6% (n=197), and males accounted for 74.4% (n=574). The CL and apparent volume of distribution of central compartment V₁ of penpulimab were 11.1% and 12.8% lower in females than in males with the same weight and conditions, indicating sex had a statistically significant impact on CL and V₁. However, comparison of model-predicted steady-state exposures (C_{max,ss}, C_{min,ss}, AUC_{ss}) indicated exposure ratios of less than 30%. Overall, the impact of sex on PK exposure was not clinically significant.

Race:

There were 679 (88.1 %) Asians, and 92 (11.9 %) non-Asian patients. The non-Asians included 85 Caucasians (11.0%) and 7 patients of other races (0.908%). The results of the SCM indicated that race had a statistically significant effect on CL. The relationships between race and PK parameters are depicted in [Applicant – Figure 1](#).

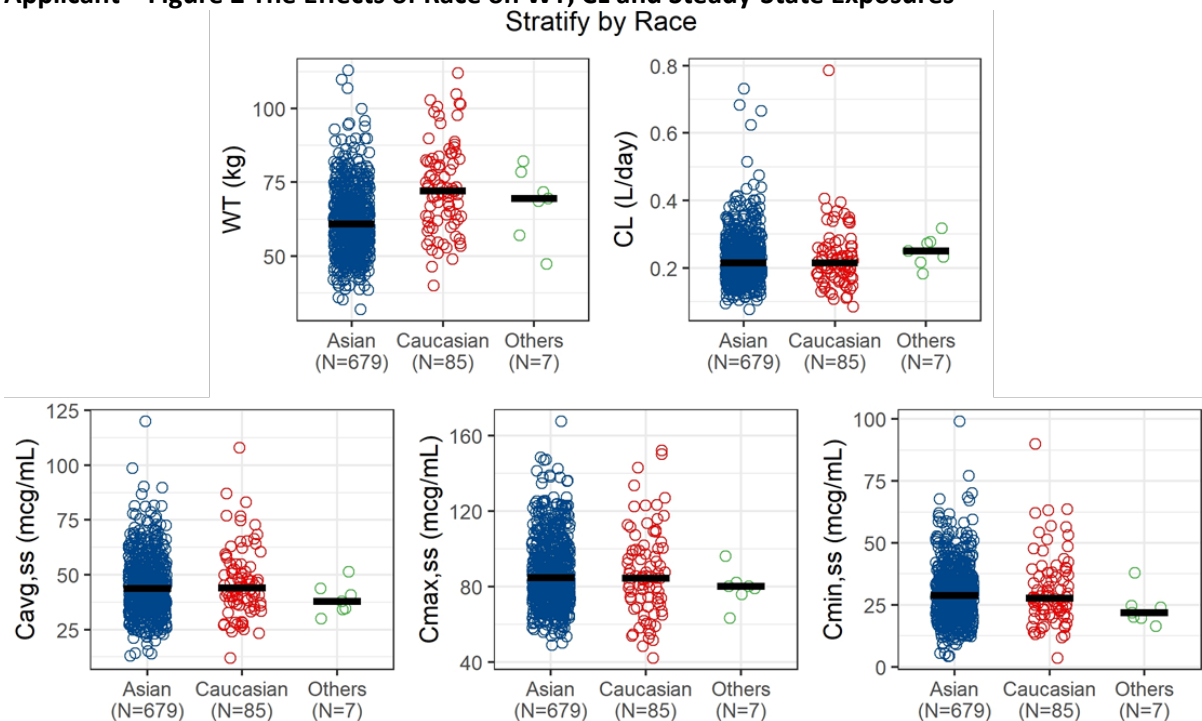
Compared to Asians, the CL of non-Asians was 23.1% lower. Under the same body weight and other conditions, changes in AUC_{ss} and $C_{max,ss}$ due to race were not clinically significant but were marginally significant in $C_{min,ss}$. However, compared to Asians, non-Asians have a higher body weight, particularly Caucasians. The median body weights of Asians, Caucasians, and other patients were 61.0, 72.1, and 69.5 kg, respectively. CL and V_1 of penpulimab increased with body weight. Based on PopPK model simulations following 200mg Q3W, the predicted median values of $C_{min,ss}$ were 28.9 and 27.8 $\mu\text{g/mL}$ for Asians and Caucasians, respectively; $C_{max,ss}$ were 84.9 and 84.7 $\mu\text{g/mL}$ for Asians and Caucasians, respectively; and $C_{avg,ss}$ were 43.8 and 44.0 $\mu\text{g/mL}$ for Asians and Caucasians, respectively. Therefore, the individual PK parameters and steady-state exposures were no significant differences between Asians and non-Asians, especially between Asians and Caucasians. The details are shown in [Applicant – Figure 2](#) and [Applicant – Table 4](#).

Applicant – Figure 1 The Effects of Race on PK Parameters



Data source: [Module 5.3.3.5 Penpulimab PopPK and ER report Appendix 2-Figure 7](#).

Applicant – Figure 2 The Effects of Race on WT, CL and Steady-State Exposures
Stratify by Race



Data source: [Module 5.3.3.5 Penpulimab PopPK and ER report Appendix 2-Figure 30.](#)

Applicant – Table 4 Summary of CL and Exposure (200mg Q3W) Stratified by Race

Parameter	Race	n	Median	P5	P95
WT (kg)	Asian	679	61.0	45.0	80.5
	Caucasian	85	72.1	52.1	102
	Others	7	69.5	47.4	82.2
CL (L/day)	Asian	679	0.216	0.137	0.357
	Caucasian	85	0.216	0.123	0.369
	Others	7	0.251	0.184	0.318
C _{avg,ss} (µg/mL)	Asian	679	43.8	26.6	67.8
	Caucasian	85	44.0	25.8	76.8
	Others	7	37.9	30.0	51.6
C _{max,ss} (µg/mL)	Asian	679	84.9	63.0	121
	Caucasian	85	84.7	54.0	127
	Others	7	80.4	63.6	96.2
C _{min,ss} (µg/mL)	Asian	679	28.9	14.1	51.1
	Caucasian	85	27.8	13.8	57.0
	Others	7	22.0	16.4	38.1

Data source: [Module 5.3.3.5 Penpulimab PopPK and ER report Appendix 2-Table 18.](#)

Body weight:

The median weight was 62.0 kg (range: 32.0-113 kg). The SCM results showed that penpulimab Volume of distribution of central compartment (V_1) increased with CL and body weight. In a patient with an extremely low weight (48.0 kg, 10% quantile) comparing to the patient with median weight (62 kg), V_1 and CL was 11.5% and 9.85% lower, respectively; In a patient with an extremely high weight (79.4 kg, 90% quantile) comparing to the patient with median weight (62 kg), V_1 and CL was 12.6% and 10.5% higher, respectively. Weight had a statistically significant impact on CL and V_1 . However, comparison of model-predicted steady state exposures ($C_{max,ss}$, $C_{min,ss}$, AUC_{ss}) indicated exposure ratios of less than 30%. Hence, it is considered that the impact of weight on AUC_{ss} , $C_{max,ss}$ and $C_{min,ss}$ was not clinically significant.

Renal impairment:

In accordance with the Guidance on Pharmacokinetics in Patients with Impaired Renal Function released by FDA in 2024, renal impairment in the 771 patients included into the population PK analysis set was graded by creatinine clearance (CLcr). The grading criteria and included patients are summarized as follows. Normal renal function, CLcr $\geq$ 90 mL/min (n=405); mild renal impairment: CLcr < 90 mL/min and CLcr $\geq$ 60 mL/min (n=301); moderate renal impairment: CLcr < 60 mL/min and CLcr $\geq$ 30 mL/min (n=64); 1 patient with severe renal impairment (CLcr < 30 mL/min) has been included.

Through PopPK covariate screening, it was found that the renal function related factor (CLcr) did not have a statistically significant impact on population PK parameters of penpulimab. The results showed that there was no significant difference in clearance between patients with mild or moderate renal impairment and patients with normal renal function.

Data of penpulimab in patients with severe renal impairment are not adequate.

Hepatic impairment:

Hepatic impairment of the 771 patients included in PopPK analysis was graded by TBIL and AST. Grading criteria and included patients are summarized as follows. Normal hepatic function: TBIL < upper limit of normal (ULN) and AST < ULN (n=652); mild hepatic impairment: TBIL $\leq$ ULN and AST > ULN or TBIL = 1.0 to 1.5 $\times$ ULN, regardless of AST (n=113); moderate hepatic impairment: TBIL = 1.5 to 3.0 $\times$ ULN, regardless of AST (n=6); no patient with severe hepatic impairment (TBIL > 3.0 $\times$ ULN, regardless of AST) has been included.

Through PopPK analysis covariate screening, it was found that the hepatic function related factors (TBIL, AST) did not have a statistically significant impact on population PK parameters of penpulimab. The results showed that there was no significant difference in clearance between

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patients with mild or moderate hepatic impairment and patients with normal hepatic function. Data of penpulimab in patients with severe hepatic impairment are not adequate.

Tumor type:

Among the 771 patients included in PopPK analysis, there were 302 (39.2%) patients with nasopharyngeal carcinoma and 469 (60.8%) patients with other tumor types. The SCM results indicated that tumor type had a statistically significant effect on V_1 and V_2 . Compared to NPC patients, the V_1 and V_2 of other solid tumor patients were 9.81% and 21.2% lower, respectively. However, comparison of model-predicted steady-state exposures ($C_{max,ss}$, $C_{min,ss}$, AUC_{ss}) indicated exposure ratios of less than 30%, suggesting that tumor type has no clinically meaningful impact on penpulimab exposures.

Eastern Cooperative Oncology Group (ECOG) score:

Among the 771 patients included in PopPK analysis, there were 243 (31.5%) patients with a baseline Eastern Cooperative Oncology Group (ECOG) score of 0 and 528 (68.5%) patients with an ECOG score of 1. Population PK covariate screening results showed that ECOG score did not have a statistically significant impact on PK parameters of penpulimab.

Serum albumin (ALB):

Among the 771 patients included in PopPK analysis, the median albumin (ALB) was 41.9 g/L (range: 22.0 - 67.7 g/L). Population PK covariate screening results showed that penpulimab CL and V_1 decreased with increase of ALB; Clearance (CL) of the patient with ALB at the 10% quantile level (34.7 g/L) was 13.9% higher than CL of the patient with ALB at the median level; CL of the patient with ALB at the 90% quantile (47.4 g/L) was 8.16% lower than CL of the patient with ALB at the median level. the central compartment (V_1) of the patient with ALB at the 10% quantile level (34.7 g/L) was 5.92% higher than V_1 of the patient with ALB at the median level; V_1 of the patient with ALB at the 90% quantile (47.4 g/L) was 3.69% lower than V_1 of the patient with ALB at the median level. Therefore, ALB had a statistically significant impact on CL and V_1 . The geometric mean ratios of PK parameters (AUC_{ss} , $C_{max,ss}$, $C_{min,ss}$) in patients with ALB at 10% or 90% quantile levels versus the typical patient were between 0.8 and 1.1; namely, the differences were less than 30%. Hence, the impact of ALB on AUC_{ss} , $C_{max,ss}$ and $C_{min,ss}$ was not clinically significant.

Lactic dehydrogenase (LDH):

Among the 771 patients included in PopPK analysis, the median LDH was 214 IU/L (range: 111 - 4450 IU/L). SCM results showed that penpulimab CL increased with increase of LDH; CL of the patient with LDH at the 10% quantile level (154 IU/L) was 13.9 % lower than CL of the patient with LDH at the median level; CL of the patient with LDH at the 90% quantile (447 IU/L) was

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8.44% higher than CL of the patient with LDH at the median level. Therefore, LDH had a statistically significant impact on CL. The geometric mean ratios of PK parameters (AUC_{SS} , $C_{max,SS}$, $C_{min,SS}$) in patients with LDH at 10% or 90% quantile levels versus the typical patient were between 0.8 and 1.1; namely, the differences were less than 30%. Hence, the impact of LDH on AUC_{SS} , $C_{max,SS}$ and $C_{min,SS}$ was not clinically significant.

C-reactive protein (CRP):

Among the 771 patients included in PopPK analysis, the median baseline CRP was 9.55 mg/L (range: 0 - 328 mg/L). SCM results showed that CRP did not have a statistically significant impact on CL of penpulimab, but indicated that the V_2 increased with increase of ALB; the V_2 of the patient with CRP at the 10% quantile level (1.10 mg/L) was 16.7% lower than V_2 of the patient with CRP at the median level; V_2 of the patient with CRP at the 90% quantile (70.9 mg/L) was 18.4% higher than V_2 of the patient with CRP at the median level. Therefore, CRP had a statistically significant impact on V_2 . The geometric mean ratios of PK parameters (AUC_{SS} , $C_{max,SS}$, $C_{min,SS}$) in patients with CRP at 10% or 90% quantile levels versus the typical patient were between 0.8 and 1.1; namely, the differences were less than 30%. Hence, the impact of CRP on AUC_{SS} , $C_{max,SS}$ and $C_{min,SS}$ was not clinically significant.

Impacts of extrinsic factors on PK:

Impacts of extrinsic factors (e.g., food, alcohol or smoking) on penpulimab PK have not been assessed in this study.

Impacts of immunogenicity on PK:

If ADA to penpulimab were detected at any visit, the patient was classified as TADA-positive immune response, otherwise as a TADA-negative immune response. Impacts of TADA on PK parameters were analyzed by a PopPK analysis.

Among the 771 patients included in PopPK analysis, 235 patients (30.5%) were TADA positive, and 536 patients (69.5%) were TADA negative. The SCM results indicated that TADA had a statistically significant effect on CL of penpulimab.

Compared to TADA-negative patients, the CL of TADA-positive patients was 16.8% higher. However, comparison of model-predicted steady state exposures ($C_{max,ss}$, $C_{min,ss}$, AUC_{ss}) indicated exposure ratios of less than 30%, suggesting that TADA has no clinically meaningful impact on penpulimab exposures.

Impacts of Combination Therapy (Co-administration) PK:

Among the 771 patients included in PopPK analysis, 380 patients (49.3%) received penpulimab

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monotherapy, and 391 patients (50.7%) received penpulimab plus chemotherapy. The results of SCM indicated that co-administration had a statistically significant effect on V_1 and V_2 .

Compared to penpulimab monotherapy patients, the V_1 and V_2 of penpulimab plus chemotherapy patients were 9.04% and 54.8% lower, respectively. However, comparison of model-predicted steady state exposures ($C_{max,ss}$, $C_{min,ss}$, AUC_{ss}) indicated exposure ratios of less than 30%, suggesting that co-administration has no clinically meaningful impact on penpulimab exposures.

The Applicant's Position:

The PK profiles of penpulimab could be described using a two-compartment model with zero-order IV infusion and first-order elimination. Covariate analysis showed that the impacts of age, body weight, ALB, LDH, race, TADA and sex on CL and impacts of body weight, ALB, combination therapy, tumor type and sex on V_1 were statistically significant, impacts of CRP, combination therapy and tumor type on V_2 were statistically significant, but these factors were not clinically significant.

According to PopPK analysis, body weight (32.0 to 113 kg), age (18 to 91 years), sex, race (White and Asian), ADA, albumin (22.0 to 67.7g/L), C-reactive protein (0 to 328 mg/L), lactate dehydrogenase (111 to 4450 IU/L), tumor types (NPC vs. other tumors) and co-administration (monotherapy vs. combination therapy) were identified as significant covariates affecting PK of Penpulimab. However, these covariates did not have clinically meaningful effects on the steady-state exposures, thus no dose adjustment is required. Mild to moderate hepatic impairment or mild to moderate renal impairment did not have significant impact on the CL and steady-state exposures of Penpulimab, therefore no dose adjustment is required. There's no sufficient data on patients with severe hepatic impairment or severe renal impairment.

The FDA's Assessment:

FDA agrees with the Applicant's position that no dosage adjustment is recommended based on age (18 to 91 years), sex, race (White [3%] and Asian [97%]), body weight (32 to 113 kg), serum albumin (22 to 54.5 g/L), baseline LDH (111 to 4,450 IU/L), baseline C-reactive protein (0 to 328 mg/L), baseline ECOG score (0 and 1), immunogenicity status, tumor type (NPC and other tumors), co-administration with chemotherapy, mild or moderate renal impairment (creatinine clearance [CL_{Cr}] ≥ 30 mL/min), mild (total bilirubin $\leq$ ULN and AST $>$ ULN or total bilirubin > 1 to 1.5 times ULN and any AST) or moderate hepatic impairment (total bilirubin > 1.5 to 3 times ULN and any AST) according to the results of the PPK analyses.

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6.2.2.3. Outstanding Issues

Data:

[N/A]

The Applicant's Position:

[N/A]

The FDA's Assessment:

There are no outstanding issues.

6.3. Comprehensive Clinical Pharmacology Review

6.3.1. General Pharmacology and Pharmacokinetic Characteristics

Data:

The clinical pharmacology of Penpulimab has been studied in patients with malignant solid tumors such as NPC or non-solid tumours such as cHL who received penpulimab by intravenous infusion administration at dose range of 1 - 10 mg/kg every 2 weeks, or 200 mg every 2 or 3 weeks. Levels of serum penpulimab were measured using validated methods and the results were used to evaluate PK parameters.

PK data of penpulimab were derived from 8 clinical studies. A total of 771 patients were included into population PK analysis, and 31 patients who underwent intensive sampling into non-compartmental PK analysis. The PK profile is outlined as follows:

Absorption

Penpulimab is administered via IV infusion, and the drug directly enters blood circulation.

Distribution

According to PopPK analysis, following administration of penpulimab 200 mg as a single IV infusion, the mean (CV%) of volume of distribution was 10.2 L (43.5%).

Elimination

According to PopPK analysis, the mean (CV%) of CL was 0.229 L/day (32.7%). The effective half-

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life ($t_{1/2eff}$) was 22.4 days (27.4%), following IV infusion of 200 mg every 3 weeks.

Linearity/non-linearity

The exposure of penpulimab increase dose proportionally in the dose range of 1 to 10 mg/kg.

Steady state

According to PopPK analysis, the penpulimab concentration was approximate to the steady state at Week 15 following IV infusion of penpulimab 200 mg Q3W, and the accumulation ratios for C_{max} and AUC were 1.53 and 2.10, respectively. The mean steady-state trough concentration (CV%) was 30.1 µg/mL (38.1%).

Other PopPK analysis Results

A two-compartment model with zero-order IV infusion and first-order elimination adequately described penpulimab PK. The typical subject is a male Asian patient with NPC and negative TADA, WT of 62.0 kg, ALB of 41.9 g/L, CRP of 9.55 mg/L, LDH of 214 IU/L, age of 55 years old, and receiving penpulimab plus chemotherapy.

According to PopPK analysis, body weight (32.0 to 113 kg), age (18 to 91 years), sex, race (White and Asian), ADA, albumin (22.0 to 67.7g/L), C-reactive protein (0 to 328 mg/L), lactate dehydrogenase (111 to 4450 IU/L), tumor types (NPC vs. other tumors) and co-administration (monotherapy vs. combination therapy) were identified as significant covariates affecting PK of Penpulimab. However, these covariates did not have clinically meaningful effects on the steady-state exposures, thus no dose adjustment is required. Mild to moderate hepatic impairment or mild to moderate renal impairment did not have significant impact on the CL and steady-state exposures of Penpulimab, therefore no dose adjustment is required. There's no sufficient data on patients with severe hepatic impairment or severe renal impairment.

Immunogenicity results

Total of 720 patients included in the immunogenicity evaluation were treated with penpulimab of 1, 3 and 10 mg/kg Q2W, or 200mg Q2W/Q3W (either monotherapy or combination therapy). 26.8% of patients developed treatment-emergent ADA (TEADA), and 7.9% of patients had positive neutralizing antibody (Nab).

- 349 patients were treated with penpulimab monotherapy at 1, 3 and 10mg/kg Q2W, or 200mg Q2W/Q3W, 30.1% of patients developed treatment-emergent ADA (TEADA), and 5.2% patients had positive Nab.

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- 371 patients were treated with penpulimab of combination therapy at 200mg Q3W, 23.7% of patients developed treatment-emergent ADA (TEADA), and 10.5% of patients had positive Nab.
- For NPC patients who received penpulimab in combination with chemotherapy, Proportion of patients with ADA positive at baseline and post-baseline was 3.6%, and 10.9%, respectively. 8.8% of patients developed TEADA, and 2.9% of those patients had positive Nab.

The overall incidence rates of TEAEs and immune-related adverse events(irAEs) between TEADA and ADA-negative patients were comparable. ADA has no clinically meaningful impact on penpulimab efficacy and safety.

The Applicant's Position:

The information from clinical studies contributing to the clinical pharmacology evaluation of penpulimab was included in the submitted reports ([Module 2.7.2 Summary of Clinical Pharmacology](#), [Module 5.3.3.5 Penpulimab PopPK and ER report](#)). Penpulimab exhibited linear PK(from dose 1.0 mg/kg to 10.0 mg/kg) with an effective half-life ($t_{1/2\text{eff}}$) of 22.4 days and the mean of CL was 0.229 L/day.

No dedicated clinical drug-drug interaction studies have been conducted in humans. Penpulimab is a humanized monoclonal antibody, PK interactions with other drugs have not been studied. As monoclonal antibodies are not metabolized by cytochrome P450 (CYP) or other drug metabolizing enzymes, inhibition or induction of these enzymes by co-administered medicinal products is not anticipated to affect the pharmacokinetics of penpulimab.

Overall, penpulimab administered by intravenous infusion at fixed 200mg Q3W regimen, demonstrated a favorable benefit-risk profile for patients in the target population of recurrent or metastatic nasopharyngeal carcinoma.

The FDA's Assessment:

FDA agrees with the Applicant's summary of the PK characteristics of penpulimab. Of the 137 evaluable patients in Study AK 105-304 with NPC who received penpulimab 200 mg IV Q3W, 8.8% (12/137) of patients tested positive for treatment emergent ADAs and 33% (4/12) of patients for treatment emergent NAb. The PPK analysis indicates that treatment emergent ADA had no significant impact on penpulimab PK, with <20% differences in the GMRs for CL, AUC_{ss}, C_{max,ss}, and C_{min,ss}. Although observed PK data showed a 47% decrease in C_{trough} in ADA positive patients, this is attributable to patient factors such as weight and albumin, as the patients who tested positive and negative for ADA are not randomized.

6.3.2. Clinical Pharmacology Questions

6.3.2.1. Does the clinical pharmacology program provide supportive evidence of effectiveness?

Yes, the clinical pharmacology program provides supportive evidence of penpulimab effectiveness in patients in the target population of recurrent or metastatic nasopharyngeal carcinoma.

Data:

For AK105-304 study, patients with recurrent or metastatic NPC were enrolled in the study. Among the 286 patients included in the primary efficacy population, per the primary analysis of BICR-assessed PFS based on RECIST v1.1, 80 (55.6%) subjects in AK105 group and 109 (74.1%) subjects in placebo group had PD or died, median PFS of the two groups was 9.6 (95% CI: 7.1, 12.5) and 7.0 (95% CI: 6.9, 7.3) months, respectively. Compared with placebo group, median PFS in AK105 group was 2.6 months longer, the risk of PD or death was reduced by 55%, HR=0.45 (95% CI: 0.33, 0.62; P<0.0001). Per BICR's assessment, the confirmed ORR or DCR for AK105 group was 68.1% (95% CI: 59.8%, 75.6%) and 91.0% (95% CI: 85.1%, 95.1%), respectively.

To support the clinical efficacy observed with penpulimab dosed at 200mg Q3W regimen, exposure-efficacy relationship was evaluated in NPC population (AK105-304 study), see [Module 2.7.2, Section 3.3.1 and 3.3.2]. Univariate logistic regression analysis was conducted to assess the relationship between penpulimab PK exposures and model-predicted ORR response (CR/PR) or DOR response (CR/PR/SD). Results of E-R analysis suggested a relative flat exposure-response (ORR/DCR) curve and no apparent difference in exposure between responders and non-responders.

A total of 380 patients received penpulimab monotherapy at 1, 3, 10 mg/kg Q2W, or 200 mg Q2W. There's no significant dose or exposure-dependent increase in the incidence of TEAEs, TRAEs or CTCAE Grade3+ AEs, and drug-related SAEs. A total of 391 patients received penpulimab 200 mg Q3W in combination therapy. Similar to monotherapy, there was no significant increase in TEAE/TRAE (Grade 3+) with increasing of PK exposure, while association with irAE was found to be statistically significant. For AEs with incidence rate of 10% or higher, white blood cell count decrease, hypothyroidism, rash and upper respiratory tract infection were associated with higher exposure, consistent with common adverse events observed in this population.

Overall, E-R safety analysis suggested a flat exposure-response relationships between penpulimab exposure and most AEs in both monotherapy and combination therapy groups. However, higher exposure levels may be associated with a slightly increased risk of irAEs and some specific AEs.

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The Applicant's Position:

Penpulimab 200 mg Q3W showed notable clinical benefits in patients with NPC, and E-R analysis suggested a relative flat exposure-response (ORR/DCR) curve and no apparent difference in exposure between responders and non-responders. In NPC population, Penpulimab (200 mg Q3W) in combination with chemotherapy was safe and tolerable. E-R safety analysis indicated that no apparent correlation between exposure and incidence of TEAE/TRAЕ (Grade 3+) in the wide dose range (1-10 mg/kg Q2W) with either monotherapy or in combination therapy.

In conclusion, the interim analysis results of AK105-304 showed that the Phase 3 trial of penpulimab combined with gemcitabine and cisplatin/carboplatin as the first-line treatment for R/M NPC patients, met the preset primary endpoint of BICR-assessed PFS, and there was no evidence of a detrimental effect on the long survival follow up. Compared with the current standard chemotherapy regimen, penpulimab combined with gemcitabine and cisplatin/carboplatin did not increase the toxicity of chemotherapy. Compared with similar studies of other PD-1 inhibitors combined with chemotherapy as first-line treatment for R/M NPC, the efficacy and safety were generally consistent, no new safety signal was identified. Therefore, penpulimab combined with gemcitabine and cisplatin/carboplatin has a relatively significant benefit-risk ratio in R/M NPC patients globally.

The FDA's Assessment:

FDA does not agree that there is a flat E-R relationship for efficacy. FDA notes that as in the penpulimab monotherapy analysis during the original BLA submission, the E-R analysis for efficacy of penpulimab in combination with chemotherapy is inconclusive due to the limited exposure range of penpulimab at one dose level.

6.3.2.2. Is the proposed dosing regimen appropriate for the general patient population for which the indication is being sought?

Yes, penpulimab administered by intravenous infusion at 200mg Q3W regimen is appropriate for the first-line treatment for R/M NPC patients when combined with gemcitabine and cisplatin/carboplatin. The proposed dosing regimen is supported by the observed efficacy, safety, and PK/PD data.

Data:

In the Phase Ia dose-escalation trial, no DLT occurred at the highest dose cohort of 10.0 mg/kg Q2W and no MTD was explored, therefore the maximum administered dose(MAD) for this study was 10.0 mg/kg Q2W. Phase Ia PK data showed a linear relationship between exposure of penpulimab and dose over the dose range of 1.0 mg/kg Q2W to 10.0 mg/kg Q2W; receptor

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occupancy analysis showed 80% to 100% PD-1 receptor occupancy starting on day 2 after dosing. There was no significant difference in receptor occupancy between the 1.0, 3.0 and 10.0 mg/kg doses. According to the non-compartmental analysis, the drug exposure, expressed as C_{max} and $AUC_{(0-14d)}$, increased proportionally with dose within the dose range of 1.0 mg/kg to 10.0 mg/kg following single-dose IV infusion of penpulimab.

Simulation of steady-state concentrations with sparse sampling following Q2W administration in the 771 patients in the population PK analysis set who received penpulimab 200 mg showed that in more than 95% of patients the steady-state trough concentrations could reach over steady state trough concentrations > 10 µg/mL, which is 100-fold higher than those at which 80% of the receptors (0.1 µg/mL) or 20-fold higher than those at which 90%~100% of the receptors (0.5 µg/mL) could be occupied in vitro.

The population PK profile of penpulimab could be described using a two-compartment model with zero-order IV infusion and first-order elimination. Covariate analysis showed that the impacts of age, body weight, ALB, LDH, race, TADA and sex on CL and impacts of body weight, ALB, combination therapy, tumor type and sex on V_1 were statistically significant, impacts of CRP, combination therapy and tumor type on V_2 were statistically significant, but these factors were not clinically significant.

Based on the final PopPK model, serum concentrations were simulated for 771 patients after IV infusion of 200 mg penpulimab, and PK parameters were calculated by non-compartmental modeling. Simulated PK parameters following single-dose IV infusion of penpulimab 200 mg are as follows: the mean C_{max} (CV%) was 57.6 µg/mL (19.5%), the mean $AUC_{(0-inf)}$ (CV%) was 955 µg*day/mL (29.6%), the mean CL (CV%) was 0.229 L/d (32.7%), the mean V_z (CV%) was 10.2 L (43.5%), the mean terminal elimination half-life ($t_{1/2}$) (CV%) was 32.4 d (43.5%).

Based on the final population PK model, serum penpulimab concentrations at each time point within 42 weeks following multi-dose (200 mg Q3W) IV infusion in 771 patients were simulated. Following multi-dose administration of penpulimab 200 mg Q3W, the steady state was reached at about Week 15; the model-predicted mean of $C_{max,ss}$, $C_{avg,ss}$ and $C_{min,ss}$ (CV%) are 87.6 µg/mL (21.1%), 45.5 µg/mL (29.1%) and 30.1 µg/mL (38.1%), respectively; the mean accumulation ratios for C_{max} and AUC (CV%) were 1.53 (12.6%) and 2.10 (19.4%), respectively. The effective half-lives ($t_{1/2eff}$) calculated based on C_{max} and AUC were 13.6 days and 22.4 days, respectively.

According to PopPK analysis, body weight (32.0 to 113 kg), age (18 to 91 years), sex, race (White and Asian), ADA, albumin (22.0 to 67.7g/L), C-reactive protein (0 to 328 mg/L), lactate dehydrogenase (111 to 4450 IU/L), tumor types (NPC vs. other tumors) and co-administration (monotherapy vs. combination therapy) were identified as significant covariates affecting PK of Penpulimab. However, these covariates did not have clinically meaningful effects on the steady-state exposures, thus no dose adjustment is required. Mild to moderate hepatic impairment or

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mild to moderate renal impairment did not have significant impact on the CL and steady-state exposures of Penpulimab, therefore no dose adjustment is required. There's no sufficient data on patients with severe hepatic impairment or severe renal impairment.

The Applicant's Position:

The recommended dosage of penpulimab was 200 mg Q3W administered intravenous (IV) infusion, based on available safety, efficacy and PK/PD results from Phase 1 to 3 trials, and for details, see section 6.2.2.1 General Dosing.

The FDA's Assessment:

FDA agrees that a dosage of 200 mg Q3W in combination with chemotherapy is acceptable based on the results of the PPK, E-R, and immunogenicity analyses, in addition to the clinical benefit and safety profile observed from Study AK105-304 (Refer to Section 6.2.2).

6.3.2.3. Is an alternative dosing regimen or management strategy required for subpopulations based on intrinsic patient factors?

No, penpulimab administered by intravenous infusion at 200mg Q3W regimen is appropriate for the first-line treatment for R/M NPC patients when combined with gemcitabine and cisplatin/carboplatin.

Data:

The population PK profile of penpulimab could be described using a two-compartment model with zero-order IV infusion and first-order elimination. Covariate analysis showed that the impacts of age, body weight, ALB, LDH, race, TADA and sex on CL and impacts of body weight, ALB, combination therapy, tumor type and sex on V_1 were statistically significant, impacts of CRP, combination therapy and tumor type on V_2 were statistically significant, but these factors were not clinically significant.

According to PopPK analysis, body weight (32.0 to 113 kg), age (18 to 91 years), sex, race (White and Asian), ADA, albumin (22.0 to 67.7g/L), C-reactive protein (0 to 328 mg/L), lactate dehydrogenase (111 to 4450 IU/L), tumor types (NPC vs. other tumors) and co-administration (monotherapy vs. combination therapy) were identified as significant covariates affecting PK of Penpulimab. However, these covariates did not have clinically meaningful effects on the steady-state exposures, thus no dose adjustment is required. Mild to moderate hepatic impairment or mild to moderate renal impairment did not have significant impact on the CL and steady-state exposures of Penpulimab, therefore no dose adjustment is required. There's no sufficient data on patients with severe hepatic impairment or severe renal impairment.

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The Applicant's Position:

No dose adjustment is required based on age, race, body weight or sex. No dose adjustment is required in patients with mild, moderate (b) (4) renal impairment, data of penpulimab in patients with severe renal impairment are not adequate. No dose adjustment is required in patients with mild or moderate hepatic impairment. There's no sufficient data on patients with severe hepatic impairment or severe renal impairment.

The FDA's Assessment:

FDA generally agrees with the Applicant's position that no dosage adjustment is currently required based on intrinsic patient factors evaluated in the PPK analysis and that there are insufficient data in patients with severe renal and hepatic impairment. (b) (4)

6.3.2.4. Are there clinically relevant food-drug or drug-drug interactions, and what is the appropriate management strategy?

No, penpulimab is intended for intravenous infusion administration; therefore, food-drug interactions are not expected.

The Applicant's Position:

Penpulimab is intended for intravenous infusion administration; therefore, food-drug interactions are not expected.

Penpulimab is a humanized monoclonal antibody, and PK interactions with other drugs have not been studied. As monoclonal antibodies are not metabolized by cytochrome P450 (CYP) or other drug metabolizing enzymes, inhibition or induction of these enzymes by co-administered medicinal products is not anticipated to affect the pharmacokinetics of penpulimab.

Penpulimab belongs to a class of drugs called immune checkpoint inhibitors. Because the mechanism of action of this class of drugs is to block inhibitory signal that prevents activation of T cells there is a potential that these drugs may cause immune mediated adverse drug reaction. Withhold or permanently discontinue penpulimab depending on severity. In general, if penpulimab requires interruption or discontinuation, administer systemic corticosteroid therapy (1 mg to 2 mg/kg/day prednisone or equivalent) until improvement to Grade 1 or less. Upon improvement to Grade 1 or less, initiate corticosteroid taper and continue to taper over at least 1 month. Consider administration of other systemic immunosuppressants in patients whose immune-mediated adverse reactions are not controlled by corticosteroid therapy.

The FDA's Assessment:

FDA agrees with the Applicant's position that no food-drug or drug-drug interactions for penpulimab are expected.

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X

Primary Reviewer Francis Green

Team Leader Jeanne Fourie-Zirkelbach

Pharmacometrics Ye Xiong

Team Leader Youwei Bi

7. Sources of Clinical Data

7.1. Table of Clinical Studies

Data:

The penpulimab is being studied in clinical trials across different tumor types. This application is based primarily on the efficacy and safety data from patients in the target population of recurrent or metastatic nasopharyngeal carcinoma in Study AK105-304 and AK105-202 (please refer to the AK105-202 Assessment Aid in BLA sequence 0004 submitted in June 2021). Further supportive safety data for penpulimab are also included from 8 studies in patients of multiple tumor types ([Applicant – Table 5](#)).

Applicant – Table 5 Listing of Clinical Trials Relevant to this BLA

Study number	Study design	Patient population	Penpulimab dosing regimen	Number of patients in safety set
AK105-101	multicenter, open-label, dose escalation and dose expansion Phase Ia/Ib study	advanced solid tumors refractory/relapsed to standard therapies	Phase Ia: penpulimab 1.0, 3.0, and 10.0 mg/kg Q2W (n=3, 6 and 7, respectively) Phase Ib: penpulimab 200mg Q2W	99 (phase 1a 16; phase 1b 83)
AK105-201	a multicenter, open-label, single-arm clinical study	relapsed or refractory classical Hodgkin lymphoma (cHL)	Penpulimab 200 mg Q2W	94

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Study number	Study design	Patient population	Penpulimab dosing regimen	Number of patients in safety set
AK105-202	a multicenter, open-label, single-arm clinical study	metastatic nasopharyngeal carcinoma	Penpulimab 200 mg Q2W	130
AK105-204	a multicenter, open-label, single-arm, basket-designed clinical study	advanced solid tumors refractory/relapsed to standard therapies	Penpulimab 200 mg Q2W	65
AK105-205	multicenter, open-label, phase II study	first line metastatic nasopharyngeal carcinoma (NPC)	Arm A (n=8): penpulimab 200mg Q3W + cisplatin 80mg/m ² , D1, Q3W + gemcitabine 1000mg/m ² , D1, D8, Q3W + anlotinib 12mg QD, D1-D14, Q3W; Arm B (n=6): Penpulimab 200mg + cisplatin 80mg/m ² , D1, Q3W + gemcitabine, 1000mg/m ² , D1, D8, Q3W; Arm C (n=14): penpulimab 200mg + gemcitabine 1000mg/m ² , D1, D8 + anlotinib 12mg QD, D1-D14, Q3W	28
AK105-301(Part I)	multicenter, randomized, double-blind phase III study	first line advanced or metastatic non-squamous, non-small cell lung cancer (nsq-NSCLC)	penpulimab/placebo 200mg Q3W + carboplatin AUC5 Q3W + pemetrexed 500mg/m ² Q3W, up to 4 cycles, followed by penpulimab/placebo 200mg Q3W + pemetrexed 500mg/m ² Q3W	46 (penpulimab arm)
AK105-302	multicenter, randomized, double-blind phase III study	treatment naive locally advanced squamous non-small cell lung cancer (sq-NSCLC)	penpulimab/placebo 200mg Q3W + paclitaxel 175 mg/m ² + carboplatin AUC5 Q3W, up to 4 cycles, followed by penpulimab/placebo 200mg Q3W; patients in the placebo arm could cross over to receive penpulimab 200mg Q3W monotherapy after PD	275 (penpulimab arm: 173; placebo arm cross-over: 102)
AK105-304	multicenter, randomized, double-blind phase III study	First line recurrent or metastatic nasopharyngeal carcinoma (NPC)	penpulimab/placebo 200mg Q3W + cisplatin 80mg/m ² , D1/ Carboplatin AUC5, D1, Q3W ^a + gemcitabine, 1000mg/m ² , D1, D8, Q3W, up to 6 cycles, Q3W followed by penpulimab/placebo 200mg Q3W monotherapy;	288 (penpulimab arm: 146; placebo arm: 142; placebo arm cross-over: 68)

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Study number	Study design	Patient population	Penpulimab dosing regimen	Number of patients in safety set
			patients in the placebo arm could cross over to receive penpulimab 200mg Q3W monotherapy after PD	

^a Carboplatin (AUC5 Q3W) may be selected as a replacement of cisplatin at the discretion of investigators in ex-Asia regions in AK105-304.

The Applicant's Position:

All studies listed above are pertinent to the evaluation of safety penpulimab to support the proposed indication.

- In combination with chemotherapy for the first-line NPC
Proposed indication: Penpulimab is indicated, in combination with gemcitabine and cisplatin or carboplatin as first-line treatment of patients with recurrent or metastatic nasopharyngeal carcinoma (RM-NPC).
- As a monotherapy for metastatic NPC (please refer the AK105-202 Assessment Aid in BLA sequence 0004 submitted in June 2021)
Proposed indication: Penpulimab is indicated, as a monotherapy, for the treatment of patients with metastatic nonkeratinizing NPC progressed on or after platinum-based chemotherapy and at least one other prior line of therapy.

The FDA's Assessment:

FDA agrees with the Applicant's position that the primary efficacy and safety data supporting the two indications are from Studies AK105-304 (penpulimab in combination with chemotherapy) and AK-105-202 (penpulimab monotherapy). Pooled safety data from 372 patients enrolled in Studies AK105-202, AK105-101, AK105-201, and AK105-204 were used to further define the safety profile of penpulimab. Study AK105-304 is reviewed in the main body of this Assessment Aid. See the Assessment Aid Addendum for review of the Efficacy Data for Study AK105-202.

8. Statistical and Clinical Evaluation

8.1. Review of Relevant Individual Trials Used to Support Efficacy

8.1.1. Study AK105-304

Trial Design

The Applicant's Description:

AK105-304 is a randomized, double-blind, multi-center phase III clinical study to compare the efficacy and safety of penpulimab combined with chemotherapy and placebo combined with chemotherapy in the first-line treatment of R/M NPC.

Approximately 278 subjects were planned to be enrolled in this study. The subjects were randomized in a 1:1 ratio to the 2 treatment groups, stratified by stages of disease (primary metastases vs. recurrent), ECOG (0 vs. 1), and liver metastasis (present vs. absent):

Arm A (experimental arm): Penpulimab+ gemcitabine + cisplatin/carboplatin, every 3 weeks (Q3W) for up to 6 cycles, followed by penpulimab monotherapy Q3W.

Arm B (control arm): Placebo+ gemcitabine + cisplatin/carboplatin, Q3W for up to 6 cycles, followed by placebo monotherapy Q3W.

In each arm, carboplatin was selected as a replacement of cisplatin at the discretion of investigator prior to randomization. After randomization, change of chemotherapy regimen was not allowed during the treatment period. Subjects received up to 6 cycles of penpulimab or placebo combined with chemotherapy, followed by penpulimab or placebo monotherapy Q3W as maintenance treatment until lack of clinical benefit as judged by the investigator (comprehensive judgment by the investigator based on RECIST v1.1 imaging assessment and clinical condition), intolerable toxicity, completion of 24 months of treatment, or other criteria for discontinuation outlined in the protocol, whichever occurred first.

The study consisted of a screening period (up to 28 days from the signing of the informed consent form to the first dose of study treatment), a treatment period (including on-treatment visits and an end-of-treatment visit), and a follow-up period (including a safety follow-up visit, a disease progression follow-up visit, and survival follow-up visits). Subjects underwent a screening evaluation within 28 days before the first dose to confirm eligibility. Tumor specimens (tumor tissue samples either archived or freshly obtained) were collected from subjects during the screening period.

Regular tumor response assessments were performed for all subjects, with PFS evaluated by BICR based on RECIST v1.1 as the primary response variable. Subjects underwent a tumor assessment every 6 weeks (± 7 days) for the first 54 weeks after the first dose of study

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treatment, and every 9 weeks (± 7 days) thereafter until radiographic progression or loss of clinical benefit (whichever occurs later), or the start of new antitumor therapy, or lost to follow-up, or death, or withdrawal of consent, or study closure, whichever occurred first.

If any radiographic disease progression was confirmed by BICR (based on RECIST v1.1), the treatment assignment was unblinded for the subject. The subjects could receive open-label penpulimab monotherapy (200 mg, administered on Day 1 of each cycle, Q3W) until intolerable toxicity, lack of clinical benefit as judged by the investigator, or completion of 24 months of treatment, or study termination by the sponsor, whichever occurred first.

Subjects in Arm A were allowed to continue open-label treatment with penpulimab monotherapy beyond radiographic disease progression if, in the opinion of the investigator, the subject would benefit from continued treatment and if other criteria are met as outlined in the protocol.

Subjects in Arm B had the opportunity to crossover to open-label treatment with penpulimab monotherapy after radiographic disease progression (confirmed by BICR) if, in the opinion of the investigator, the subject would benefit from treatment with penpulimab and if other criteria were met as outlined in the protocol.

Adverse events (AEs) of each subject were recorded until 30 days after the last dose of study treatment (either penpulimab/placebo or chemotherapy) or the initiation of other antitumor therapy, whichever occurred first. Serious adverse events (SAEs) were recorded until 90 days after the last dose of study treatment (including chemotherapy) or the initiation of other antitumor therapy, whichever occurred first. Immune-related AEs (irAEs) were recorded until 90 days after the last dose of penpulimab (regardless of initiation of other antitumor therapy). Survival assessment was performed every 3 months (± 7 days) after the last dose to collect survival and subsequent antitumor therapy information.

The FDA's Assessment:

In general, FDA agrees with the Applicant's description of Study AK105-304. FDA clarifies that, in protocol version 2.1, dated August 31, 2022, based on FDA's recommendation for a multiregional clinical trial, the Applicant had proposed to enroll 218 (78%) of the patients in China and the remaining 60 (22%) patients from outside Asia. This update to the patient enrollment strategy was added after study initiation but prior to the conduct of any efficacy analysis. Despite these enrollment goals, as of the data cut-off date of April 29, 2024, the study had enrolled 291 patients, of whom only 11 (3.8%) were enrolled outside of Asia. The Applicant clarified that the study had enrolled 280 patients in China to adhere to Chinese regulatory requirements; however, due to enrollment difficulties outside of Asia, the study was only able to enroll 11 patients outside Asia. This change in enrollment was deemed acceptable for this particular application by the FDA review team and was communicated to the Applicant during preliminary meeting minutes issued April 12, 2024, for a pre-BLA meeting, and in subsequent email communications on April 17, 2024, and April 19, 2024. See FDA's assessment under

section “Statistical Analysis Plan and Amendments” for additional details.

Study Endpoints

The Applicant’s Description:

- Primary Efficacy Endpoint: progression-free survival (PFS) assessed by blinded independent center review (BICR) based on Response Evaluation Criteria in Solid Tumor, version 1.1 (RECIST v1.1).
- Key Secondary Efficacy Endpoints: overall survival (OS)
- Other Secondary Endpoints:
 - 1) BICR-assessed ORR, DoR, and DCR based on RECIST v1.1.
 - 2) Investigator-assessed PFS, ORR, DoR, and DCR based on RECIST v1.1.
 - 3) Safety assessment: incidence and severity of adverse events (AEs) and serious adverse events (SAEs), and clinically significant laboratory abnormalities.
 - 4) PK profile: serum drug concentrations of penpulimab in individual subjects at different time points after penpulimab administration.
 - 5) Immunogenicity: number and percentage of subjects with detectable anti-drug antibody (ADA).
 - 6) Health-related quality of life (HRQoL): the European Organization for Research and Treatment of Cancer Quality of Life Questionnaire-Core 30 (EORTC QLQ-C30) and EORTC QLQ-H&N43.
 - 7) PD-L1 expression in tumor samples, and the correlation between PD-L1 expression and efficacy.
 - 8) Blood EBV level at baseline and changes from baseline after administration of study drugs, and correlation between blood EBV level and efficacy.

The FDA’s Assessment:

In general, FDA agrees with the Applicant’s description of the study endpoints with the exception that DCR was considered to be an exploratory endpoint.

Statistical Analysis Plan and Amendments

The Applicant’s Description:

The sample size calculation was based on the primary endpoint of BICR-assessed PFS. At a two-sided alpha level of 0.05, a sample size of 278 patients (218 patients from China and 60 patients from ex-Asia countries) with 222 PFS events would provide 89% power for the trial to detect a hazard ratio (HR) of 0.65. Due to extreme enrollment challenges in ex-Asia countries which had

been discussed with FDA, all 280 patients enrolled in China and 11 patients enrolled from ex-Asia countries at the time of data cutoff were included for the global analysis.

Based on the FDA's agreement to the population change, it's documented in the statistical analysis plan that an interim efficacy analysis of PFS is planned to be performed by an independent external statistician overseen by Independent Data Monitoring Committee (IDMC) when over 190 PFS events have been observed. As of the data cutoff date of April 29, 2024, there were 189 BICR-assessed PFS events in the ITT population.

Applicant – Table 6 Listing of Statistical Analysis Plan amendment

Version No.	Effective Date	Major changes to the statistical analysis plan
V1.0	31Aug2022	First version
V1.1	16Sep2022	1) Removed ORR from key secondary endpoints; and removed ORR from the sequential testing procedure. 2) Updated dropout rate as 5% per 12 months for PFS for sample size estimation. Updated analysis timing, event number, stopping boundaries (p-value and Z-score) and approximate hazard ratio (HR) thresholds for interim and final analyses of PFS.
V1.2	05Sep2023	1) Included the investigator's choice of platinum chemotherapy as a stratification factor in the stratified analysis of PFS and OS endpoints. 2) Added the subgroup analysis based on the investigator's choice of platinum-chemotherapy
V2.0	24Apr2024	1) Due to reasons described in the FDA briefing document for a Type B meeting scheduled for April 22, 2024, the primary analysis population was adjusted to include all 280 patients enrolled in China and all patients from ex-Asia countries . 2) Per FDA request, a sensitivity analysis as added using the first 218 patients enrolled in China and all patients from ex-Asia countries 3) The PFS interim analysis was delayed from 155 events to over 190 events due to extremely slow ex-China enrollment but the PFS final analysis remained at 222 events. 4) No amendment to the current protocol (version 3.0, 24Mar2023) was made for these changes that were relected only in SAP V2.0
V2.1	17Jun2024	1) Added a new BIRC-assessed PFS sensitivity analysis: For the stratified analysis, the stratification factors were stage of disease at study entry (primary metastases vs. recurrent), ECOG score (0 vs. 1), liver metastases (present vs absent) and investigator's choice of chemotherapy regimens (carboplatin vs. cisplatin), all obtained from the EDC. 2) Added a consistency analysis between BIRC-assessed and investigator-assessed results. 3) Modified the specific description of subgroup analysis, such as adjusting the age group to 50 as the boundary. 4) Modified the imputation rules of the date of AE and concomitant medication. 5) Added the analysis of baseline and safety based on the crossover treatment set (CTS). 6) The efficacy and safety sections were more accurately described without modifying the analysis logic established in the previous version

Definition of Key Analysis Sets

- Intention-to-treat (ITT) set:

ITT set included all randomized subjects. Subjects were analyzed according to the treatment to which they were randomized. The ITT set was used for the disposition of subjects, demographics, baseline characteristics and primary efficacy analysis.

- Safety Set (SS)

SS included all randomized subjects who received at least one dose of the study drug. Subjects were analyzed according to the treatment that they actually received. The SS was used for drug exposure and safety analysis.

- Pharmacokinetics Set (PKS)

PKS included all randomized subjects who received at least one dose of penpulimab and had at least one valid post-dose serum concentration data.

- Immunogenicity Set (IMS)

For the penpulimab plus chemotherapy group, IMS included all randomized subjects who received at least one dose of the penpulimab and had at least one pre-dose immunogenicity assessment and one post-dose immunogenicity assessment. For the placebo plus chemotherapy group, it included all subjects who entered the crossover treatment phase and received at least one dose of penpulimab, and had at least one pre-dose immunogenicity assessment before the crossover treatment and one post-dose immunogenicity assessment.

- Crossover Treatment Set (CTS)

CTS included subjects of the control group who received AK105 at least once during the crossover treatment phase.

The FDA's Assessment:

The proposed sample size of 278 for Study AK105-304 was based on PFS. As of protocol version 2.1, dated August 31, 2022, the Applicant had proposed to enroll 218 (78%) patients in China and 60 (22%) from outside of Asia. As of the data cut-off date of April 29, 2024, the study had enrolled 291 patients of whom only 11 (3.8%) patients were enrolled outside of Asia. Based on version 2.1 of the statistical analysis plan, dated June 17, 2024, assuming a median PFS of 7 months in the placebo arm and 10.8 months in the penpulimab arm, 222 events would provide 89% power to detect a hazard ratio of 0.65 at a 2-sided level of significance of 0.05. The accrual duration for the study was 28 months with a follow-up of an additional 6 months. The annual dropout rate was assumed to be 5%. The primary analysis was a stratified log-rank test based on the ITT population.

In protocol version 2.2 and in statistical analysis plan version 1.1, submitted to the FDA on September 16, 2022, one interim analysis for PFS was proposed at 155 (70%) events for efficacy, which was considered reasonable at that time by the review team. However, in the

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briefing document for the pre-BLA meeting, the Applicant stated that according to a data transfer from an imaging vendor, 172 PFS events had been observed at that time across the treatment and placebo arms and that the Applicant projected an immediate data cutoff date would result in 190 (86%) PFS events for the interim analysis. In an email communication dated April 17, 2024, the Applicant clarified that the study had enrolled 280 patients in China to adhere to Chinese regulatory requirements and that the Applicant had planned to include the first 218 patients from China in the efficacy population for the marketing application in the US and that the projected 155 PFS events would be based on those 218 patients from China, along with 60 patients from outside of Asia. The Applicant stated that substantial challenges were experienced during patient enrollment outside of Asia due to the approval of toripalimab, the conduct of the trial during the COVID-19 epidemic period, and the rarity of NPC outside of Asia. The Applicant also stated that patients with NPC in the U.S in the first-line setting could be prescribed immunotherapies, which would make patients less willing to participate in a randomized clinical trial with a 50% chance of receiving chemotherapy only in the first line treatment setting. Hence, the Applicant proposed to include all 280 patients from China in the efficacy population for the marketing application in the US. The Applicant further stated that this proposed change in the efficacy population required FDA's concurrence prior to the conduct of a formal analysis and therefore, the Applicant did not conduct the PFS interim analysis based on 155 events and the number of events had overrun the prespecified number of events at the time of the pre-BLA meeting. The Applicant also stated that the 222 events prespecified for the final analysis of PFS was expected to be reached on January 10, 2025. The review team informed the Applicant that a PFS interim analysis based on 190 events could be acceptable for a marketing application in the US. Consequently, the statistical analysis plan for Study AK105-304 was updated and version 2.1 dated June 17, 2024, reflected these proposed changes to the PFS interim analysis at 190 (86%) events. In this version, the Applicant stated that the efficacy boundaries at the interim and final analysis of PFS would be calculated based on the O'Brien-Fleming boundaries using the observed information fraction. The actual PFS interim analysis, based on the data cut-off date of April 29, 2024, was conducted based on 189 (85%) events. Based on O'Brien-Fleming boundaries, the 2-sided p-value boundary at the interim analysis of PFS was 0.030.

The study was also designed to test OS. Assuming a median OS of 29 months in the placebo arm and 44.6 months in the penpulimab arm, 172 deaths would provide 80% power to detect a hazard ratio of 0.65 at a 2-sided level of significance of 0.05. Two formal interim analyses were proposed, at 103 (60%) deaths and at 138 (80%) deaths. Additionally, if PFS was statistically significant at the interim analysis, the Applicant proposed to spend a 2-sided nominal alpha of 0.0001 for a descriptive analysis of OS at the time of the primary PFS analysis. Efficacy boundaries would be calculated based on the observed information fraction using the O'Brien-Fleming boundary method. The Applicant proposed a hierarchical testing strategy where PFS would be tested first at a 2-sided alpha of 0.05, and OS would be tested only if PFS was statistically significant.

Protocol AmendmentsThe Applicant's Description:

[Applicant – Table 7](#) lists major modifications to Study AK105-32024 protocol with each amendment.

Applicant – Table 7 Protocol Amendments

Version	Effective date	Major changes to the protocol
V1.0	25 May 2021	First version
V2.0	24 Dec 2021	- Added a sub-study in adolescent population. - Inclusion criteria 8, added "If tumor tissue sample is unavailable, the requirement may be waived after discussion with the Sponsor." - Exclusion criteria 9, added the requirement of a washout period after hormone use, "have received systemic corticosteroids (>10 mg daily doses of prednisone or equivalent) or other immunosuppressive medications within 14 days prior to the first dose of study treatment" - Exclusion criteria 14, clarified the definition of hepatitis B and C infection. - Exclusion Criteria 25 and 26, deleted psychiatric disorders in exclusion 25 and refined the definition of psychiatric disorders, "Subjects with serious neurological or psychiatric disorders, including dementia and epileptic seizure." in exclusion 26. - Added ORR and OS analysis plan. - The timing of IDMC safety review was adjusted to "approximately every 6 months". - Action to be taken with penpulimab for grade 2 myocarditis was revised to permanent discontinuation. - Erratum to Table 4 Dose modification of chemotherapy drugs based on chemotherapy-related hematological toxicity observed in the previous cycle. - Clarified that relevant tests that meet the requirements of this study, which are available before signing the ICF, can be used as the basis for screening and do not need to be repeated. - Clarified that dosing on the nearest feasible date is allowed if scheduled dosing is not possible due to procedural reasons such as holidays, weekends.
V2.1	31 Aug 2022	- ORR and OS were included as key secondary endpoints - Corrected that platelet count $\geq 100 \times 10^9/L$ as inclusion criterion.

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Version	Effective date	Major changes to the protocol
		- Section 6 (study procedures) - Deleted the requirement for obtaining PD-L1 expression status prior enrolment. - Clarified the schedule for HRQoL assessment. - Clarified the frequency of ECG, coagulation tests and thyroid function tests at crossover phase. - Clarified that some C1D1 tests may not be performed if an acceptable test is performed within the specified timeframe at crossover phase. - Deleted the requirement for dosing interval between last dose of chemotherapy and IP dosing at crossover phase. - Section 9.5 (pregnancy reporting): text was added to clarify that local guidance will be followed for contraception and pregnancy reporting timeframe post last dose of chemotherapy drugs. - Synopsis and section 11 (statistical methods): - Updated estimate enrolment period and sample size justification. - Text was added to indicate that a descriptive analysis of OS will be conducted and a nominal α of 0.0001 (two-sided) will be spent.
V2.2	16 Sep 2022	ORR was removed from key secondary endpoints and form the sequential testing procedure.updated dropout rate as 5% per 12 months for PFS for sample size estimation, and updated analysis timing, event number, stopping boundaries (p-value and Z-score) and approximate hazard ratio (HR) thresholds for interim and final analyses of PFS.
V3.0	24 Mar 2023	- Carboplatin was added to the combination regimen. - The renal criteria of CrCl were modified to "Calculated creatinine clearance* (CrCl) $\geq$ 50 mL/min; if cisplatin is selected, (CrCl) $\geq$ 60 mL/min." - Exclusion criteria 9 was clarified further in terms of use of corticosteroids and its timing before subject's first study dose.

The FDA's Assessment:

FDA agrees with the Applicant's position.

8.1.2. Study Results (the Analysis Data Cutoff Date is April 29, 2024)

Compliance with Good Clinical Practices

Data:

The study protocols and informed consent documents were reviewed by local IRB/IEC as required by regulations prior to implementation at participating institutions.

The Applicant's Position:

The study was conducted and monitored in compliance with the protocol, the ethical principles that have their origin in the Declaration of Helsinki and the ICH consolidated Guideline E6 for GCP and applicable regulatory requirement(s).

The FDA's Assessment:

FDA agrees with the Applicant's position.

Financial Disclosure

Data:

N/A

The Applicant's Position:

Appropriate financial disclosure was collected during the course of Study AK105-304, and no financial arrangements with the Investigator impacted the validity of the study. Additional information regarding financial disclosures can be found in [\[Section 19.2\]](#).

The FDA's Assessment:

FDA agrees with the Applicant's position.

Patient DispositionData:

The study was conducted from August 16, 2021 (the first subject signed the ICF) to April 29, 2024 (data cutoff) across 36 sites in China and 10 sites in ex-Asia countries, including 2 in U.S., 1 in Canada and 7 in Brazil.

As shown in [Applicant – Table 8](#), a total of 410 subjects were screened, and 291 subjects were randomized, including 144 in AK105 group and 147 in placebo group. Of these, 11 were ex-Asia patients from U.S., Canada, and Brazil. All except 3 subjects received study drugs.

Among all the subjects enrolled in the study, by the data cutoff date, 259 (89.0%) subjects discontinued from the assigned treatment, with 124 (86.1%) in AK105 group and 135 (91.8%) in placebo group. In placebo group, 68 (46.3%) subjects crossed over to receive AK105 monotherapy after progressed on the initially assigned treatment. One hundred and four (35.7%) subjects had completed the study (49 [34.0%] in AK105 group, 55 [37.4%] in placebo group).

Applicant – Table 8 Subject Disposition (all subjects screened)

	AK105 + Chemotherapy n (%)	Placebo + Chemotherapy n (%)	Total n (%)
Screened			410
Enrolled			292
Randomized	144 (100)	147 (100)	291 (100)
Received AK105/placebo at least once	144 (100)	144 (98.0)	288 (99.0)
Treatment ongoing at DCO-AK105/placebo	20 (13.9)	12 (8.2)	32 (11.0)
End of treatment-AK105/placebo	124 (86.1)	135 (91.8)	259 (89.0)
Radiographic disease progression	62 (43.1)	104 (70.7)	166 (57.0)
Subject request	18 (12.5)	9 (6.1)	27 (9.3)
Subjects complete study treatment per protocol (up to 24 months of treatment)	14 (9.7)	3 (2.0)	17 (5.8)
Initiation of new anti-tumor therapy	8 (5.6)	1 (0.7)	9 (3.1)
Investigator decision	3 (2.1)	6 (4.1)	9 (3.1)
Adverse event	5 (3.5)	2 (1.4)	7 (2.4)
Death	5 (3.5)	2 (1.4)	7 (2.4)
Clinical disease progression without radiographic confirmation	2 (1.4)	3 (2.0)	5 (1.7)
Withdrawal of consent	0	1 (0.7)	1 (0.3)
Other*	7 (4.9)	4 (2.7)	11 (3.8)
Study ongoing at DCO	95 (66.0)	92 (62.6)	187 (64.3)
End of study	49 (34.0)	55 (37.4)	104 (35.7)
Death	48 (33.3)	49 (33.3)	97 (33.3)
Withdrawal of consent	1 (0.7)	2 (1.4)	3 (1.0)

	AK105 + Chemotherapy n (%)	Placebo + Chemotherapy n (%)	Total n (%)
Other [#]	0	4 (2.7)	4 (1.4)

*Other reasons for end of treatment-AK105/placebo: AK105 group (n=7): dose interruption for more than 12 weeks (n=5); subject request (n=2). Placebo group (n=4): dose interruption for more than 12 weeks (n=2); planned to initiate new anti-tumor therapy (n=2)
#Other reason for end of study: 4 subjects in placebo group refused survival follow-up.
Source Data: ADSL.xpt Module 5.3.5.1, Study AK105-304 CSR [Table 14.1.1.1.1 in Section 14](#)

The Applicant’s Position:

AK105-304 was first initiated in China in August 2021. To reflect the global distribution of NPC, especially to represent the NPC population in the U.S. in line with FDA’s recommendation, Akeso originally planned to enroll 60 patients outside of China. However, despite tremendous efforts Akeso has made to complete enrollment outside of China, we have been experiencing extreme challenges during the enrollment period. Among the three-year arduous efforts, we contacted a total of 234 ex-Asia sites and only initiated 19 sites in the US, Canada, Brazil and Australia. Up until September 18, 2024, we have enrolled a total of 16 patients outside of China, including 3 in the US, 6 in Canada, and 7 in Brazil. 11 subjects from ex-Asia countries were included in this analysis (as of April 29, 2024).

As of 29 April 2024, compared with AK105 group, more subjects in placebo group had completed the study treatment assigned at randomization (86.1% vs 91.8%). The most common reason for discontinuation of study treatment in both groups was PD. 68 (34.5%) in placebo group crossed over to receive AK105 monotherapy after BICR confirmed radiographic PD.

The FDA’s Assessment:

FDA agrees with the Applicant’s description of patient disposition for Study AK105-304. Substantially more patients in the placebo arm (71%) discontinued treatment due to radiographic disease progression, as compared to the penpulimab arm (43%).

Protocol Violations/Deviations

Data:

As shown in [Applicant – Table 9](#), a total of 63 (21.6%) subjects had at least one critical protocol deviation. 25 (8.6%) failed to report SAE within 24 hours; 15 (5.2%) related to study drug compliance, except for one subject who wasn’t assigned the right drug code according to the IWRS, the others were failure to interrupt/permanently discontinue study medication after reaching the criteria for interruption/discontinuation of study medication specified in the

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protocol, mainly due to drug interruption beyond 6 weeks because of COVID-19 pandemic; 12 (4.1%) related to visit delay (out-of-window visit >42 days for non-AE reasons); 7 (2.4%) related to tumor assessments, failure to perform at least 2 consecutive times of the planned tumor imaging assessments, or missing one or more areas in the imaging assessment at screening; 6 (2.1%) related to concomitant medications, short-term use of traditional Chinese medicinal products with anti-tumor effects; 5 (1.7%) were related to study procedures; 1 (0.3%) related to inclusion/exclusion criteria, use of glucocorticoids within 10 days before the first study dose, which did not meet the 2-week washout period; and 1 (0.3%) related to laboratory assessment.

Applicant – Table 9 Critical protocol deviations (ITT)

	AK105 + Chemotherapy (N = 144) n (%)	Placebo + Chemotherapy (N = 147) n (%)	Total (N = 291) n (%)
Subjects with at least one critical protocol deviation	37 (25.7)	26 (17.7)	63 (21.6)
Safety Report	13 (9.0)	12 (8.2)	25 (8.6)
Study Drug Compliance	8 (5.6)	7 (4.8)	15 (5.2)
Visit Schedule	8 (5.6)	4 (2.7)	12 (4.1)
Efficacy Criteria	4 (2.8)	3 (2.0)	7 (2.4)
Concomitant Medications	3 (2.1)	3 (2.0)	6 (2.1)
Study Procedures	4 (2.8)	1 (0.7)	5 (1.7)
Inclusion/Exclusion Criteria	1 (0.7)	0	1 (0.3)
Laboratory Assessment	1 (0.7)	0	1 (0.3)

Source Data: ADDV.xpt Module 5.3.5.1, AK105-304 CSR [Table 14.1.2 in Section 14](#)

The Applicant's Position:

No notable safety or efficacy issues were observed through the follow up of subjects involved in those critical protocol deviations. No deviations were identified that would substantially impact the study results or conclusion of the efficacy and safety data. Thus, no subjects were excluded from statistical analysis in this report due to protocol deviations.

The FDA's Assessment:

FDA acknowledges the protocol deviations noted by the Applicant and agrees that these deviations do not impact the integrity of Study AK105-304 or interpretation of the study results. Furthermore, in the primary efficacy population for Study AK105-202, there were 6 major violations in 6 patients (5%) and no critical protocol deviations were identified.

Table of Demographic CharacteristicsData:

Of the 291 subjects in ITT set, 284 (97.6%) were Asians, 6 (2.1%) were white, 1 (0.3%) was black or African American. The median age was 51.0 years old (range: 23-75), mostly male (81.8%), 48.8% never smoker, and 67.7% never alcohol drinker ([Applicant – Table 10](#)).

Applicant – Table 10 Patient demographics (ITT)

	AK105 + Chemotherapy (N = 144)	Placebo + Chemotherapy (N = 147)	Total (N = 291)
Age (years)			
n	144	147	291
Mean (SD)	51.3 (9.50)	49.0 (9.88)	50.1 (9.75)
Median	51.0	50.0	51.0
Min, Max	31, 75	23, 68	23, 75
Age category, n (%)			
≤50 years	66 (45.8)	77 (52.4)	143 (49.1)
>50 years	78 (54.2)	70 (47.6)	148 (50.9)
Gender, n (%)			
Male	119 (82.6)	119 (81.0)	238 (81.8)
Female	25 (17.4)	28 (19.0)	53 (18.2)
Ethnicity, n (%)			
Hispanic or Latino	2 (1.4)	2 (1.4)	4 (1.4)
Non-Hispanic and non-Latino	142 (98.6)	145 (98.6)	287 (98.6)
Race, n (%)			
Asian	140 (97.2)	144 (98.0)	284 (97.6)
Black or African American	0	1 (0.7)	1 (0.3)
White	4 (2.8)	2 (1.4)	6 (2.1)
Baseline weight (kg)			
Mean (SD)	60.69 (10.790)	59.60 (10.584)	60.14 (10.682)
Median	60.00	59.60	60.00
Min, Max	32.0, 101.6	38.5, 90.0	32.0, 101.6
Baseline BMI (kg/m ²)			
Mean (SD)	22.21 (3.212)	21.90 (3.257)	22.05 (3.233)
Median	21.60	21.48	21.58
Min, Max	14.8, 31.6	15.6, 31.5	14.8, 31.6
Smoking status, n (%)			
Never	65 (45.1)	77 (52.4)	142 (48.8)
Current	17 (11.8)	16 (10.9)	33 (11.3)
Former	62 (43.1)	54 (36.7)	116 (39.9)
Drinking status, n (%)			
Never	94 (65.3)	103 (70.1)	197 (67.7)
Current	13 (9.0)	7 (4.8)	20 (6.9)
Former	37 (25.7)	37 (25.2)	74 (25.4)
Region, n (%)			

	AK105 + Chemotherapy (N = 144)	Placebo + Chemotherapy (N = 147)	Total (N = 291)
Asian countries	138 (95.8)	142 (96.6)	280 (96.2)
Ex-Asia countries	6 (4.2)	5 (3.4)	11 (3.8)

Source Data: ADSL.xpt Module 5.3.5.1, AK105-304 CSR Table 14.1.3.1.1, 14.1.3.2.1 in Section14

The Applicant's Position:

The baseline demographic characteristics were well-balanced between AK105 group and placebo group. The racial distribution in AK105-304 is similar to that in the KEYNOTE-122 study and probably represents a reasonable racial characteristic of a global trial in NPC. On the other hand, JUPITER-02, the study used for FDA approval of toripalimab, exclusively enrolled patients from Asia countries.

The FDA's Assessment:

In general, FDA agrees with the Applicant's description of patient demographics for Study AK105-304. In the penpulimab arm, 10% of patients were 65 years or older, as compared to 3.4% of patients in the placebo arm. Otherwise, the demographics were well-balanced between the treatment arms. As of the data cut-off date of April 29, 2024, the study had enrolled 291 patients of whom only 11 (3.8%) patients were enrolled outside of Asia, specifically in the US, Canada, and Brazil. Otherwise, the demographics appear to be comparable between the treatment arms.

Since Study AK105-304 was conducted primarily in China, with 96% of the patients enrolled in China, the patient population may not be representative of the US population of patients with NPC. A postmarketing commitment (PMC) will be issued to better characterize the safety and efficacy of penpulimab plus chemotherapy in a patient population whose demographic and disease characteristics are more representative of the population of U.S. patients with NPC. See Section 13 on Postmarketing Commitments for additional details.

Other Baseline Characteristics (e.g., disease characteristics, important concomitant drugs)

Data:

The disease stage at enrollment was mainly recurrent NPC (67.7%), and 32.3% was primary metastasis. The majority of subjects had distant metastases (80.1%), of which liver metastases was most common (45.6%). The histological type was mostly non-keratinizing undifferentiated squamous cell carcinoma (76.6%), followed by non-keratinizing differentiated squamous cell carcinoma (19.2%). More than half of the subjects had ECOG score of 1 at enrollment (63.9%). PD-L1 expression TPS $\geq$ 50% accounted for 37.5%, and EBV DNA $\geq$ 500 copies/mL accounted for 63.6%.

A total of 198 (68.0%) subjects received previous radiotherapy, including 100 (69.4%) in AK105 group and 98 (66.7%) in placebo group. Except one subject with bone metastasis in AK105 group who received local palliative radiotherapy, the rest received radical radiotherapy. A total of 195 (67.0%) subjects received previous systemic therapy, including 98 (68.1%) in AK105 group and 97 (66.0%) in placebo group. (Applicant – Table 11).

Applicant – Table 11 Baseline disease characteristics (ITT)

	AK105 + Chemotherapy (N = 144)	Placebo + Chemotherapy (N = 147)	Total (N = 291)
Stage of disease at study entry (EDC)*, n (%)			
Primary metastases	45 (31.3)	49 (33.3)	94 (32.3)
Recurrent	99 (68.8)	98 (66.7)	197 (67.7)
Only local recurrent	27 (18.8)	31 (21.1)	58 (19.9)
Metastases	72 (50.0)	67 (45.6)	139 (47.8)
ECOG score (EDC), n (%)			
0	51 (35.4)	54 (36.7)	105 (36.1)
1	93 (64.6)	93 (63.3)	186 (63.9)
Liver metastases (EDC), n (%)			
Present	58 (40.3)	60 (40.8)	118 (40.5)
Absent	86 (59.7)	87 (59.2)	173 (59.5)
Investigator's choice of chemotherapy regimens, n (%)			
Carboplatin	3 (2.1)	4 (2.7)	7 (2.4)
Cisplatin	141 (97.9)	143 (97.3)	284 (97.6)
Region, n (%)			
Asian countries	138 (95.8)	142 (96.6)	280 (96.2)
Ex-Asia countries	6 (4.2)	5 (3.4)	11 (3.8)
Disease duration (months)			
Mean (SD)	29.67 (29.085)	25.12 (24.435)	27.38 (26.887)
Median	24.67	18.73	21.62
Min, Max	0.2, 166.3	0.2, 133.4	0.2, 166.3
Pathological classification#, n (%)			
Non-keratinizing squamous cell carcinoma, undifferentiated	112 (77.8)	111 (75.5)	223 (76.6)
Non-keratinizing squamous cell carcinoma, differentiated	25 (17.4)	31 (21.1)	56 (19.2)
Keratinizing squamous cell carcinoma	1 (0.7)	1 (0.7)	2 (0.7)
Other	6 (4.2)	4 (2.7)	10 (3.4)
Cancer stage at initial diagnosis, n (%)			
II	6 (4.2)	7 (4.8)	13 (4.5)
III	44 (30.6)	35 (23.8)	79 (27.1)
IVA	48 (33.3)	55 (37.4)	103 (35.4)
IVB	45 (31.3)	50 (34.0)	95 (32.6)
IVC	1 (0.7)	0	1 (0.3)

	AK105 + Chemotherapy (N = 144)	Placebo + Chemotherapy (N = 147)	Total (N = 291)
Distant metastases site, n (%)			
Bone/bone marrow	58 (40.3)	63 (42.9)	121 (41.6)
Liver [■]	57 (39.6)	59 (40.1)	116 (39.9)
Lung	48 (33.3)	47 (32.0)	95 (32.6)
Lymph node	42 (29.2)	37 (25.2)	79 (27.1)
Other	13 (9.0)	19 (12.9)	32 (11.0)
Baseline PD-L1 expression level, n (%)			
Positive (TPS≥50%)	55 (38.2)	54 (36.7)	109 (37.5)
Negative (TPS<50% or NA)	83 (57.6)	86 (58.5)	169 (58.1)
Missing	6 (4.2)	7 (4.8)	13 (4.5)
Baseline EBV DNA level, n (%)			
< 500 copies/mL	54 (37.5)	46 (31.3)	100 (34.4)
≥500 copies/mL	87 (60.4)	98 (66.7)	185 (63.6)
Missing	3 (2.1)	3 (2.0)	6 (2.1)
Prior anti-cancer therapies	100 (69.4)	98 (66.7)	198 (68.0)
Radiotherapy	100 (69.4)	98 (66.7)	198 (68.0)
Systemic therapy	98 (68.1)	97 (66.0)	195 (67.0)

#Other in pathological classification: 5 subjects of non-keratinizing (differentiation/undifferentiated unknown), 3 subjects of non-keratinizing (differentiated/undifferentiated mixed), and 2 subjects of poorly differentiated squamous cell carcinoma (keratinized/non-keratinized unknown).

■The liver lesion information for 2 subjects with liver metastasis was inaccurately entered in the EDC, leading to the misclassification as non-liver metastasis.

Source Data: ADSL.xpt Module 5.3.5.1, Study AK105-304 CSR [Table 14.1.3.1.1](#), [14.1.3.2.1](#), [Table 14.1.4 in Section14](#)

The Applicant's Position:

The population treated in AK105-304 were managed according to the standard of care for patients with NPC in the US. In ITT population, the majority of patients had metastatic disease (80.1%); 45.6% had liver metastases. The histological type was mostly non-keratinizing undifferentiated squamous cell carcinoma (76.6%), followed by non-keratinizing differentiated squamous cell carcinoma (19.2%). Of the 11 subjects enrolled from ex-Asia countries, the disease stage at enrollment was mainly recurrent NPC (72.7%), and 27.3% was primary metastasis. The majority of subjects had distant metastases (63.6%), of which lung metastases was most common (45.5%). The histological type was mostly non-keratinizing differentiated squamous cell carcinoma (54.5%), followed by non-keratinizing undifferentiated squamous cell carcinoma (45.5%). Prior to study entry, radiotherapy or concurrent chemoradiation was administered to all of those with recurrent disease.

The FDA's Assessment:

In general, FDA agrees with the Applicant's description of baseline characteristics for Study AK105-304. One patient was randomized to the placebo arm per IWRS with an ECOG score of 1, whereas the correct ECOG score for that patient was 0 per electronic data capture (EDC).

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Additionally, six patients (four in the penpulimab arm and two in the placebo arm) were randomized per IWRS with stage of disease as "primary metastases," when the correct stage per EDC was "recurrent." Lastly, one patient was randomized to the penpulimab arm per IWRS with liver metastases status as "present", whereas the correct liver metastases status for that patient was "absent" per the EDC.

Treatment Compliance, Concomitant Medications, and Rescue Medication Use

Data:

Treatment Compliance

Penpulimab was administered intravenously, and each infusion was documented. Subjects who had AK105 interruption or permanently discontinued due to AEs were discussed in Section 8.2.4.3 and 8.2.4.4.

Concomitant Medications

A total of 144 (100.0%) subjects in AK105 group and 144 (98.0%) subjects in placebo group had at least one concomitant medication. The most commonly used ($\geq 50\%$) drug types were antiemetics and antinauseants, immunostimulants, drugs for acid related disorders, blood substitutes and perfusion solutions, corticosteroids for systemic use, antianemic preparations, bile and liver therapy, vitamins, and diuretics. Those frequently used concomitant medications were mainly used for pre-treatment of chemotherapy, as well as for the management of common chemotherapy complications such as nausea, vomiting, and hematological toxicity.

The Applicant's Position:

The use of concomitant medications did not affect the efficacy or safety of penpulimab.

The FDA's Assessment:

FDA agrees with Applicant's position.

Efficacy Results – Primary Endpoint (Including Sensitivity Analyses)

Data:

As of April 29, 2024, the median duration of follow-up was 19.1 months (range: 0, 31.5), with a 6-month follow-up rate of 93.1% and a 12-month follow-up rate of 81.8%

In the ITT population, per BICR's assessment based on RECIST v1.1, 80 (55.6%) subjects in

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AK105 group and 109 (74.1%) subjects in placebo group had PD or died ([Applicant – Table 12](#)). The median PFS was 9.6 months (95% CI: 7.1, 12.5) in AK105 group and 7.0 months (95% CI: 6.9, 7.3) in placebo group. Compared with placebo group, AK105 group reduced the risk of PD or death by 55% (HR=0.45, 95% CI: 0.33, 0.62, P<0.0001) based on stratified Log-rank test ([Applicant – Figure 3](#)). The study crossed the O'Brien-Fleming boundary for this preset interim analysis (2-sided P-value boundary is 0.030 based on 189 PFS events).

Applicant – Table 12 Primary analysis of BICR-assessed PFS (ITT)

	AK105 + Chemotherapy (N = 144)	Placebo + Chemotherapy (N = 147)
PFS events, n (%)	80 (55.6)	109 (74.1)
Disease progression, n (%)	76 (52.8)	108 (73.5)
Death, n (%)	4 (2.8)	1 (0.7)
PFS (months) [a]		
25th percentile (95% CI)	5.72 (5.36, 6.93)	5.52 (4.37, 5.75)
Median (95% CI)	9.63 (7.13, 12.45)	7.00 (6.90, 7.29)
75th percentile (95% CI)	23.98 (18.79, NR)	9.59 (8.41, 11.17)
Min, Max	0.0, 29.1+	0.0, 31.3+
Progression-free survival rate (%) (95% CI)		
At 6 months	70.9 (62.0, 78.1)	66.4 (57.3, 73.9)
At 12 months	44.2 (34.9, 53.0)	15.4 (9.4, 22.7)
At 18 months	35.9 (27.0, 44.9)	8.2 (4.0, 14.5)
At 24 months	22.8 (13.1, 34.0)	5.5 (1.6, 13.0)
Stratified log-rank 2-sided P value [b]	<0.0001	
Stratified Cox proportional hazards regression model [c]		
HR (95% CI)	0.45 (0.33, 0.62)	

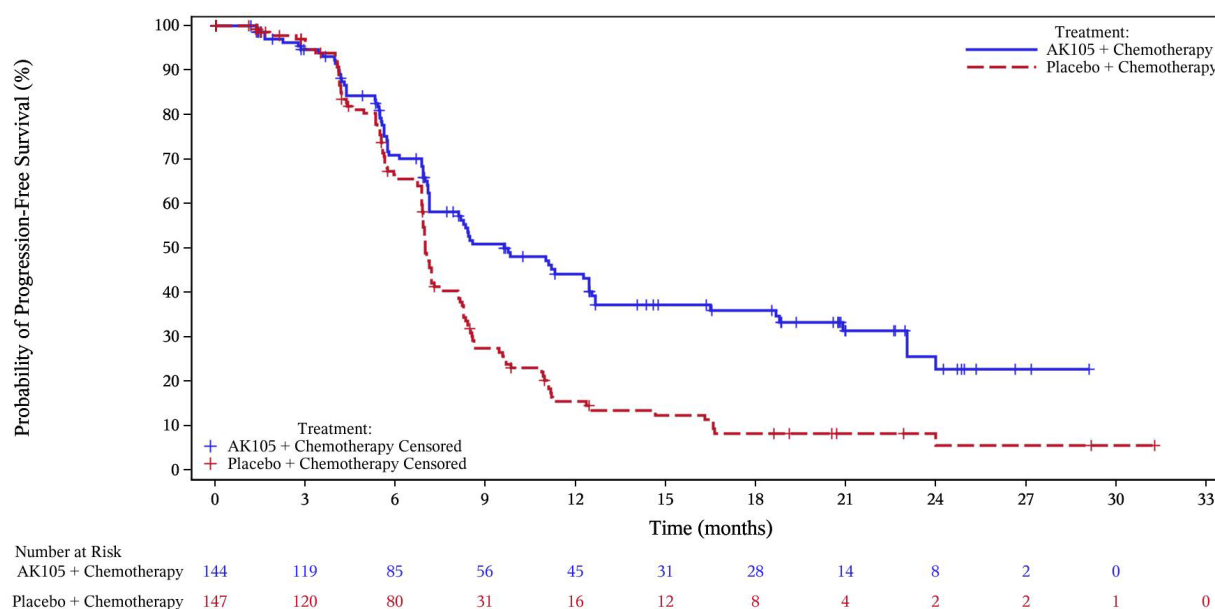
[a] Based on Kaplan-Meier method. +: censored

[b] For the stratified analysis, the stratification factors are stage of disease at study entry (primary metastases vs. recurrent), ECOG score (0 vs. 1), liver metastases (present vs absent) obtained from the IWRS and investigator's choice of chemotherapy regimens (carboplatin vs. cisplatin) obtained from the EDC.

[c] A stratified Cox proportional hazard regression model with tied events handled by the Efron's method is used. For the stratified analysis, the stratification factors are the same as above.

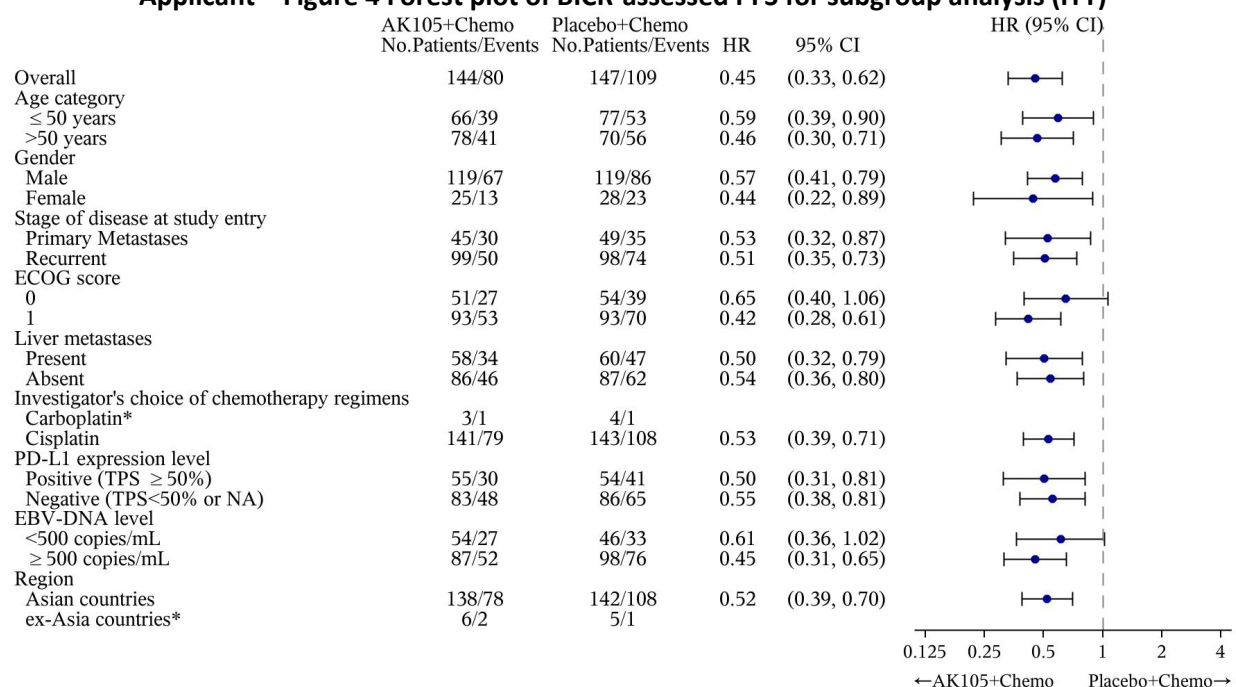
Source Data: ADRS.xpt Module 5.3.5.1 AK105-304 CSR [Table 14.2.1.1.1 in Section 14](#)

Applicant – Figure 3 Kaplan-Meier plot of BICR-assessed PFS (ITT)



Source Data: ADRS.xpt Module 5.3.5.1 AK105-304 CSR [Figure 14.2.1.1.1 in Section 14](#).

Forest plots for subgroup analyses of BICR assessed PFS were presented in [Applicant – Figure 4](#). The results showed that penpulimab combined with chemotherapy demonstrated robust PFS benefits over chemotherapy alone across all pre-specified subgroups.

Applicant – Figure 4 Forest plot of BICR-assessed PFS for subgroup analysis (ITT)

Subgroup analyses are performed based on an unstratified Cox proportional hazards regression model with tied events handled by the Efron's method.

Overall analysis is performed based on a stratified Cox proportional hazards regression model with tied events handled by the Efron's method.

*: The subgroup has less than 10 PFS events and HR is not reported.

Source Data: ADRS.xpt Module 5.3.5.1 AK105-304 CSR [Figure 14.2.1.1.2 in Section 14](#)

To assess the robustness of the primary endpoint of this study, the following sensitivity analyses were conducted for BICR-assessed PFS:

Sensitivity analysis 1: The unstratified log-rank test and unstratified Cox proportional hazards regression model was performed to compare PFS time between two groups, HR=0.53 (95% CI: 0.40, 0.71), P<0.0001. The results were consistent with the primary analysis.

Sensitivity analysis 2: For the stratified analysis, the stratification factors were stage of disease at study entry (primary metastases vs. recurrent), ECOG score (0 vs. 1), liver metastases (present vs. absent) and investigator's choice of chemotherapy regimens (carboplatin vs. cisplatin) all obtained from the EDC instead of randomization system (IWRS). The results (HR=0.45; 95% CI: 0.33, 0.63; P<0.0001) were consistent with the primary analysis.

Sensitivity analysis 3: Subject who has experienced radiological PD or death right after missing two or more consecutive tumor assessments were considered as progressed at the time of PD or death, whichever occurs first. The results of this analysis (HR=0.47; 95% CI: 0.34, 0.64; P<0.0001) were similar to those of the primary analysis.

Sensitivity analysis 4: Subject who had initiated a new anticancer therapy before radiological PD or death were considered as progression at the time of starting the new anticancer therapy.

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The results of this analysis (HR=0.48; 95% CI: 0.35, 0.65; P<0.0001) were similar to those of the primary analysis.

Sensitivity analysis 5: Per FDA request, included only the first 218 subjects enrolled in China and all 11 subjects enrolled in ex-Asia countries, using the same statistical methods as in the primary analysis. 65 (56.5%) subjects in AK105 group and 83 (72.8%) subjects in placebo group had PD or died, the median PFS was 8.4 (95% CI: 7.1, 12.5) and 7.0 (95% CI: 6.9, 7.2) months, respectively. Compared with placebo group, the risk of PD or death was reduced by 52%, HR=0.48 (95% CI: 0.33, 0.68; P<0.0001). The results of this sensitivity analysis were similar to those of the primary analysis.

The Applicant's Position:

As of DCO date for this interim analysis, compared with placebo group, a significant benefit in terms of PFS was demonstrated in AK105 group (P<0.0001), which reduced the risk of PD or death by 55% (HR=0.45, 95% CI: 0.33, 0.62), which is numerically better than the other PD-1 inhibitors (with the caveats of cross-study comparison). The PFS results assessed by BICR and investigator were consistent. In the subgroup analysis, PFS benefits of AK105 were observed across all subgroups (Age, [REDACTED], Stage of disease at study entry, ECOG score, Liver metastases, Investigator's choice of chemotherapy regimens, PD-L1 expression levels, EBV-DNA level, Region). In addition, the sensitivity analyses of PFS showed similar efficacy.

The FDA's Assessment:

FDA's stratified analysis of PFS did not include the stratification factor of investigator's choice of chemotherapy (cisplatin vs. carboplatin) as it was not a stratification factor originally [REDACTED] considered at the time of randomization. Additionally, only 2.4% of all randomized patients received carboplatin which in turn resulted in sparse strata. FDA's analysis based on the data cut-off date of April 29, 2024, without using the above-mentioned stratification factor yielded results that were numerically identical to that of the Applicant's. This also indicated that the stratification factor of investigator's choice of chemotherapy had minimal effect on the primary analysis of PFS. FDA's sensitivity analyses that excluded the stratification factor of investigator's choice of chemotherapy also yielded results that were numerically identical to the Applicant's analysis.

Although the difference in median PFS was only approximately 2.6 months (median PFS was 9.6 months [95% CI: 7.1, 12.5]) in the penpulimab-kcqx arm and 7.0 months [95% CI: 6.9, 7.3] in the placebo arm), the PFS Hazard ratio was 0.45 (95% CI: 0.33, 0.62, two-sided p-value <0.0001). There is a clear separation of the Kaplan-Meier curves at around 7 months which indicates a treatment effect favoring the penpulimab arm based on the Kaplan-Meier plot for PFS as [REDACTED] assessed by BICR. At 12 months, 31% patients in the penpulimab arm and 11% patients in the

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placebo arm were alive and progression free, which is supportive of a PFS benefit favoring the penpulimab arm.

In general, FDA agrees with the exploratory subgroup analyses provided by the Applicant. In the subgroup of patients with age below 65 years, the median PFS in the penpulimab arm was 9.8 months (95% CI: 8.1, 12.7) and 7.0 months (95% CI: 6.9, 7.3) in the placebo arm, with a hazard ratio of 0.49 (95% CI: 0.36, 0.67). In the subgroup of patients with age 65 years or older, the median PFS in the penpulimab arm was 5.6 months (95% CI: 2.8, NE) and 5.8 months (95% CI: 5.4, NE) in the placebo arm, with a hazard ratio of 1.60 (95% CI: 0.32, 7.99). The results of this exploratory subgroup analysis should be interpreted with caution since there were only 20 patients (15 in the penpulimab arm and 5 in placebo arm) with age 65 years or older in the study, based on the data cut-off date of April 29, 2024.

Data Quality and Integrity

Data:

All the required components of the electronic Common Technical Document (eCTD) were included in this submission. AK105-304 and other studies included in the resubmission were conducted according to Good Clinical Practice.

The Applicant's Position:

The submission contained all the required components of the electronic Common Technical Document (eCTD) and was of adequate quality and integrity to allow for review of the clinical trial data supporting the proposed indication.

The quality assurance procedures were implemented during the conduct of the study including but not limited to regular site monitoring, investigator meetings and training sessions for clinical research associates, and site initiation visits to review the clinical protocol, CRF, and study procedures. Additionally, independent Quality Assurance audits were conducted for selected sites, and no concerns on data integrity were reported following site inspections by the independent Quality Assurance audits.

The FDA's Assessment:

FDA agrees with the Applicant's position.

Efficacy Results – Secondary and other relevant endpointsData:**Key secondary endpoint: Overall survival (OS)**

Since PFS reached statistical significance, according to the statistical analysis plan, a descriptive analysis for OS was performed with the allocated nominal α of 0.0001. As shown in [Applicant – Table 13](#), [Applicant – Figure 5](#), 48 (33.3%) and 49 (33.3%) subjects died in AK105 group and placebo group, respectively. The median OS for two groups was not reached (HR=0.94, 95%CI: 0.63, 1.40). 24-month survival rate was 66.3% in AK105 group and 61.9% in placebo group, respectively.

Applicant – Table 13 OS-Primary analysis (ITT)

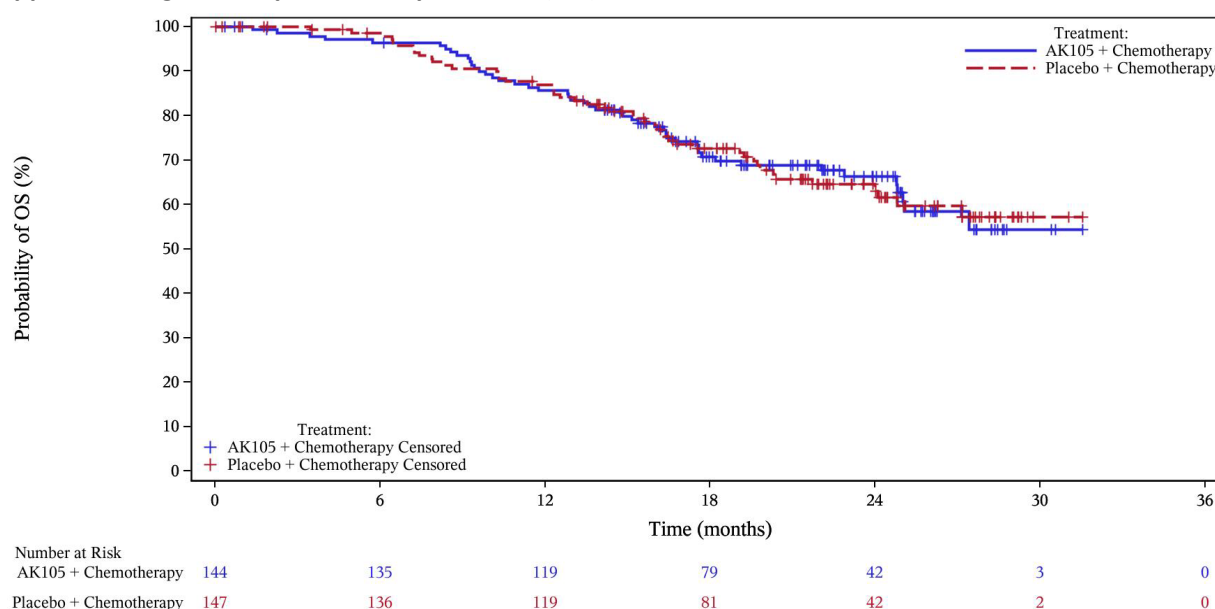
	AK105 + Chemotherapy (N = 144)	Placebo + Chemotherapy (N = 147)
Death, n (%)	48 (33.3)	49 (33.3)
OS (months) [a]		
25th percentile (95% CI)	16.72 (13.60, 22.87)	16.49 (14.09, 20.30)
Median (95% CI)	NR (25.00, NR)	NR (24.80, NR)
75th percentile (95% CI)	NR (NR, NR)	NR (NR, NR)
Min, Max	0.4, 31.5+	0.0, 31.5+
Overall survival rate (%) (95% CI)		
At 6 months	96.4 (91.6, 98.5)	98.6 (94.4, 99.6)
At 12 months	85.6 (78.6, 90.5)	87.0 (80.1, 91.6)
At 24 months	66.3 (57.1, 74.0)	61.9 (52.2, 70.2)
Stratified Cox proportional hazards regression model [b]		
HR (95% CI)	0.94 (0.63, 1.40)	
Unstratified Cox proportional hazards regression model [c]		
HR (95% CI)	0.97 (0.65, 1.45)	

[a] Based on Kaplan-Meier method. +: censored.

[b] A stratified Cox proportional hazard regression model with tied events handled by the Efron's method is used. For the stratified analysis, the stratification factors are the same as above.

[c] Sensitivity analysis 1 is based on an unstratified Cox proportional hazards regression model with tied events handled by the Efron's method.

Source Data: ADTTE.xpt Module 5.3.5.1 AK105-304 CSR [Table 14.2.3.1 in Section 14](#)

Applicant – Figure 5 Kaplan-Meier plot of OS (ITT)

Source Data: ADTTE.xpt Module 5.3.5.1 AK105-304 CSR [Figure 14.2.3.1 in Section 14](#)

68 (46.3%) subjects in placebo group had crossed over to receive AK105 monotherapy after PD, which was explicitly allowed by design. An analysis based on the ITT principle will lead to a biased estimate of the true treatment effect and will likely underestimate the AK105 group's true survival benefit. Therefore, to investigate the impact of the existence of such a high percentage of crossover and to correct for the potential bias in the primary analysis, three commonly used statistical methods for correcting treatment-switching are considered as sensitivity analyses: Rank Preserving Structural Failure Time (RPSFT) model, Inverse Probability of Censoring Weighting (IPCW) method and two-stage Accelerated Failure Time (AFT) model. After adjusting for potential bias in OS caused by the crossovers, the trend of OS benefit became more evident, with an HR of 0.62 (0.41, 0.94) by RPSFT model, 0.75 (0.43, 1.30) by IPCW method, and 0.78 (0.52, 1.17) by two-stage AFT model ([Applicant – Table 14](#)).

Applicant – Table 14 OS -Sensitivity Analysis (ITT)

	AK105 + Chemotherapy (N=144)	Placebo + Chemotherapy (N=147)
Rank Preserving Structural Failure Time (RPSFT) Model [a]		
Events, n (%)	48 (33.3)	51 (34.7)
Censored, n (%) [b]	96 (66.7)	96 (65.3)
Stratified Hazard Ratio (95% CI) [c]	0.62 (0.41, 0.94)	
Inverse Probability of Censoring Weighting (IPCW) [d]		
Events, n (%)	48 (33.3)	29 (19.7)
Censored, n (%) [e]	96 (66.7)	118(80.3)
Stratified Hazard Ratio (95% CI) [c]	0.75 (0.43, 1.30)	
Two-stage Accelerated Failure Time (AFT) Model [f]		

	AK105 + Chemotherapy (N=144)	Placebo + Chemotherapy (N=147)
Events, n (%)	48 (33.3)	49 (33.3)
Censored, n (%) [b]	96 (66.7)	98 (66.7)
Stratified Hazard Ratio (95% CI) [c]	0.78 (0.52, 1.17)	

[a] The RPSFT model with the addition of an interaction term between the treatment and the time-to-crossover is considered.

[b] Based on OS status after re-censoring.

[c] The stratification factors are stage of disease at study entry (primary metastases vs. recurrent), ECOG score (0 vs. 1), liver metastases (present vs absent) obtained from the IWRS and investigator's choice of chemotherapy regimens (carboplatin vs. cisplatin) obtained from the EDC.

[d] Baseline confounders considered for the calculation of the (stabilized) weight in IPCW model include [REDACTED], age group (≤50 years, >50 years), baseline disease stage (primary metastatic, recurrent), baseline liver metastasis (present, absent), baseline ECOG score (0, 1) and investigator's choice of chemotherapy regimens (carboplatin vs. cisplatin), while the only time-dependent confounder considered is the occurrence of PD (no, yes).

[e] Subjects are censored at the onset of crossover if applicable.

[f] The covariates included in the AFT model are [REDACTED], age group (≤50 years, >50 years), baseline disease stage (primary metastatic, recurrent), baseline liver metastasis (present, absent), baseline ECOG score (0, 1), and investigator's choice of chemotherapy regimens (carboplatin vs. cisplatin).

Source Data: ADTTE.xpt Module 5.3.5.1 AK105-304 CSR [Table 14.2.3.2 in Section 14](#)

Other secondary endpoints

Investigator-assessed PFS

Per investigator assessment, 78 (54.2%) subjects in AK105 group and 112 (76.2%) subjects in placebo group had PD or died, the median PFS was 12.3 (95% CI: 9.7, 14.6) and 7.2 (95% CI: 7.0, 8.3) months in the two groups, respectively. Compared with placebo group, AK105 group reduced the risk of progression or death by 56% (HR=0.44, 95% CI: 0.32, 0.60; P<0.0001) based on the stratified log-rank test. These results were consistent with those of BICR-assessed PFS.

BICR-assessed ORR/DCR

Per BICR assessment, 26 (18.1%) subjects in AK105 group and 13 (8.8%) subjects in placebo group had confirmed CR; 72 (50.0%) subjects in AK105 group and 81 (55.1%) in placebo group had confirmed PR. The ORR for the two groups was 68.1% (95% CI: 59.8%, 75.6%) and 63.9% (95% CI: 55.6%, 71.7%), respectively. The DCR for the two groups was 91.0% (95% CI: 85.1%, 95.1%) and 91.8% (95% CI: 86.2%, 95.7%), respectively.

Investigator-assessed ORR/DCR

Per investigator assessment, 11 (7.6%) subjects in AK105 group and 4 (2.7%) subjects in placebo group had confirmed CR, and 84 (58.3%) subjects in AK105 group and 80 (54.4%) subjects in placebo group had confirmed PR. The ORRs for the two groups were 66.0% (95% CI: 57.6%, 73.7%) and 57.1% (95% CI: 48.7%, 65.3%), respectively. The DCR for the two groups was 91.0% (95% CI: 85.1%, 95.1%) and 91.2% (95% CI: 85.4%, 95.2%), respectively.

The Applicant's Position:

Median OS has not yet been reached for either group, and the OS data is immature. Since this study began on August 25, 2021, the therapeutic landscape for advanced NPC has changed considerably, especially with the approval of immune checkpoint inhibitors. To maximize patients' clinical benefits, by design, this study allows patients in placebo group to receive AK105 treatment after PD. 73 (50.7%) subjects in AK105 group and 107 (72.8%) subjects in placebo group received subsequent anti-tumor therapies. Specifically, 68 (46.3%) subjects in placebo group crossed over to receive the same treatment as AK105 group after PD, and 42 (28.6%) subjects received other anti-PD-1 therapies. Furthermore, more subjects in placebo group (60 [40.8%]) received two or more types of systemic anti-tumor treatment sequences or combinations (e.g., targeted therapy, chemotherapy, and other immunotherapy) compared to AK105 group (39 [27.1%]). After adjusting for potential bias in OS caused by the crossovers, the sensitivity analyses showed that the HR adjusted for crossover effects ranged from 0.62 to 0.78. The lowest corrected HR, 0.62, was comparable to the HR observed for toripalimab in the JUPITER-02 study.

The FDA's Assessment:

At the time of the BLA submission, the Applicant provided an analysis of OS based on the data cut-off date of April 29, 2024, when 97 (56%) deaths were observed in 291 enrolled patients. This was a descriptive analysis of OS conducted at the time of the PFS interim analysis. According to the SAP, the first formal interim analysis for OS (OS IA1) was expected to be conducted at 103 deaths (60% information fraction of pre-specified OS events for the final analysis). On January 23, 2025, FDA requested that the Applicant provide the results of OS IA1, and the results was submitted to the FDA based on a data cut-off date of January 24, 2025. At the time of the first OS interim analysis, the study had enrolled 296 patients, with the additional five patients being enrolled outside of China. Of these five additional patients, three were already under screening at the time of the pre-BLA meeting. The first interim analysis was conducted at 121 (70%) events, instead of the prespecified 103 (60%) events. Based on the pre-BLA meeting documents, the Applicant had projected that 103 deaths would be observed by January 10, 2025. It appears that deaths accrued faster than the Applicant's projection. Additionally, the Applicant also stated that an analysis at 60% information fraction would not be very informative, given that a descriptive OS analysis was conducted at 56% information fraction. FDA's analysis of OS did not include investigator's choice of chemotherapy as a stratification factor for analysis. The following table provides FDA's analysis of OS at 70% information fraction, based on the data cut-off date of January 24, 2025. OS was not statistically significant at the first interim analysis.

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FDA – Table 6. First Formal Interim Analysis of OS

Efficacy Parameter	Penpulimab + Chemotherapy (N=146)	Placebo + Chemotherapy (N=150)
OS events, n (%)	58 (40%)	63 (42%)
Median OS (months), (95% CI)	NR (27.4, NE)	31.3 (27.2, NE)
Hazard Ratio (95% CI) ¹	0.91 (0.64, 1.31)	
p-value ^{1,2}	0.615	

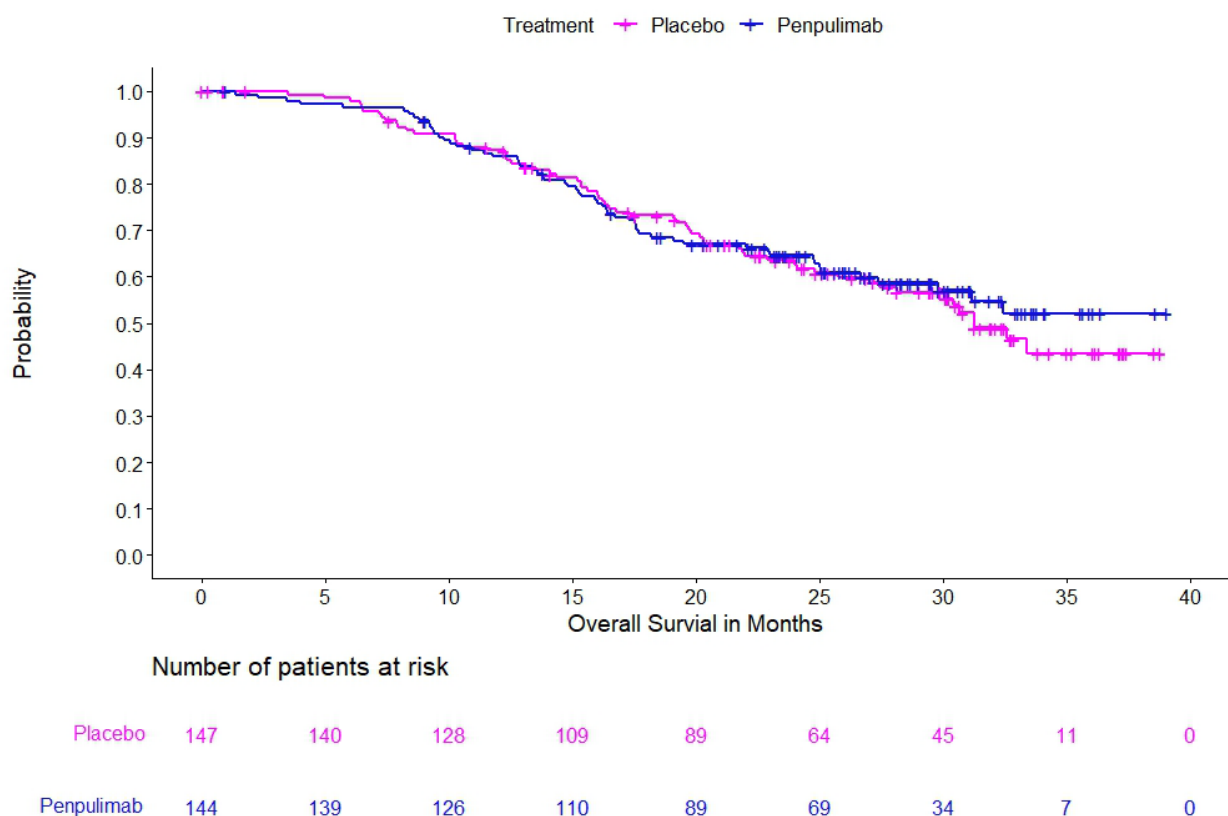
Source: FDA analysis based on Applicant-provided analysis dataset adsl.xpt and adtte.xpt. DCO: January 24, 2025

¹ Stratified by stage of disease (primary metastases vs. recurrent), ECOG score (0 vs. 1), and liver metastasis (present vs absent) based on the IWRS.

² Compared to the p-value boundary of 0.0150 based on 70% information fraction.

Abbreviations: CI, confidence interval; DCO, data cutoff; ECOG, Eastern Cooperative Oncology Group; IWRS, Interactive Web Response System; NE, not evaluable; NR, not reached; OS, overall survival

The Kaplan-Meier plot for OS based on the data cut-off date of January 24, 2025, is provided below.

FDA – Figure 9. Kaplan-Meier Plot for OS

Source: FDA analysis based on Applicant-provided analysis dataset adsl.xpt and adtte.xpt. DCO: January 24, 2025

Abbreviations: DCO, data cutoff; OS, overall survival

Crossover is allowed in Study AK105-304. At the time of the first formal OS interim analysis, 74 (49%) patients in the placebo arm crossed over to receive open-label treatment with penpulimab monotherapy after BICR assessed disease progression. Due to the high crossover rate, the Applicant conducted three supportive analyses to adjust for treatment crossover, including the rank preserving structural failure time (RPSFT) model, the inverse probability of censoring weighting (IPCW) model, and the two-stage accelerated failure time (AFT) model. The following table shows the Applicant-provided sensitivity analyses.

FDA – Table 7. Supportive Analyses of OS to Adjust for Crossover Based on Updated OS Data

Analytical Method	HR (95% CI)
RPSFT model (interaction)	0.76 (0.53, 1.09)
IPCW model	0.85 (0.53, 1.39)
Two-stage AFT model	0.79 (0.55, 1.14)

Source: Applicant-provided updated OS interim analysis report, page 8, submitted February 3, 2025. DCO: January 24, 2025
Abbreviations: AFT, Accelerated Failure Time; CI, confidence interval; DCO, data cutoff; HR, hazard ratio; IPCW, Inverse Probability of Censoring Weighting; OS, overall survival; RPSFT, Rank Preserving Structural Failure Time

FDA also conducted a sensitivity analysis based on the 291 patients who were originally included in the BLA submission but based on the first interim analysis data cut-off date of January 24, 2025. The results of this sensitivity analysis provided results that were numerically the same as those presented in [FDA – Table 7](#).

The Applicant provided analysis based on DCR, an endpoint that FDA considers exploratory in nature because it includes stable disease, which may reflect the natural history of disease and is not a direct measurement of how treatment benefit is sustained. FDA did not verify the results based on an analysis of DCR.

Dose/Dose Response

Data:

N/A

The Applicant's Position:

Please refer to Section [6.2.2.1](#) on general dosing summary.

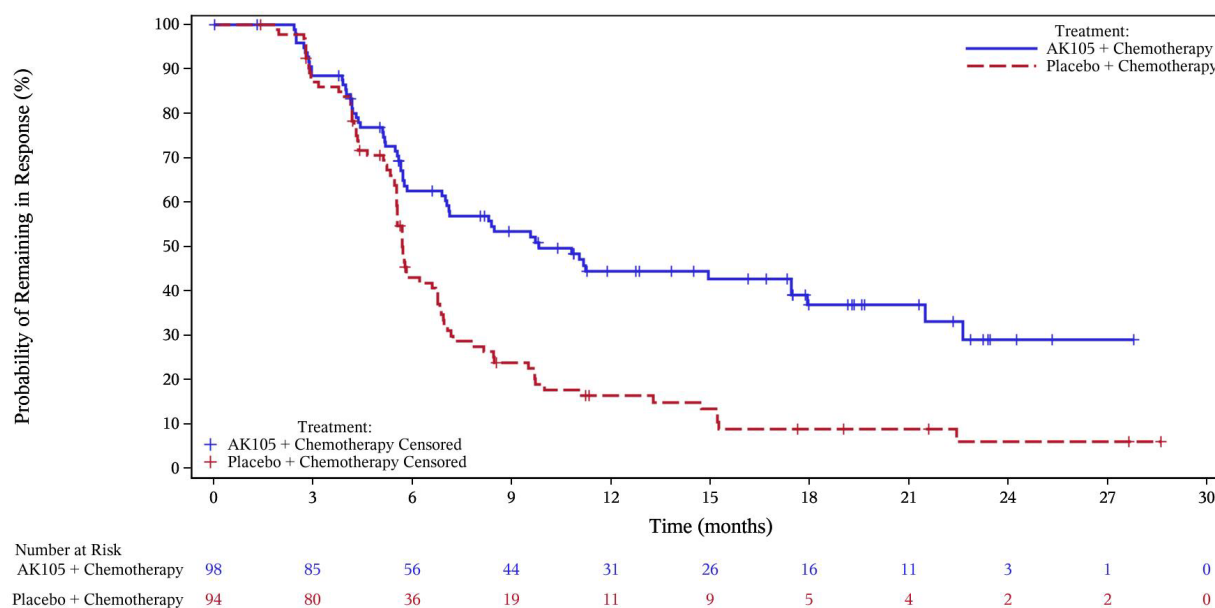
The FDA's Assessment:

FDA agrees with the Applicant's position.

Durability of ResponseData:

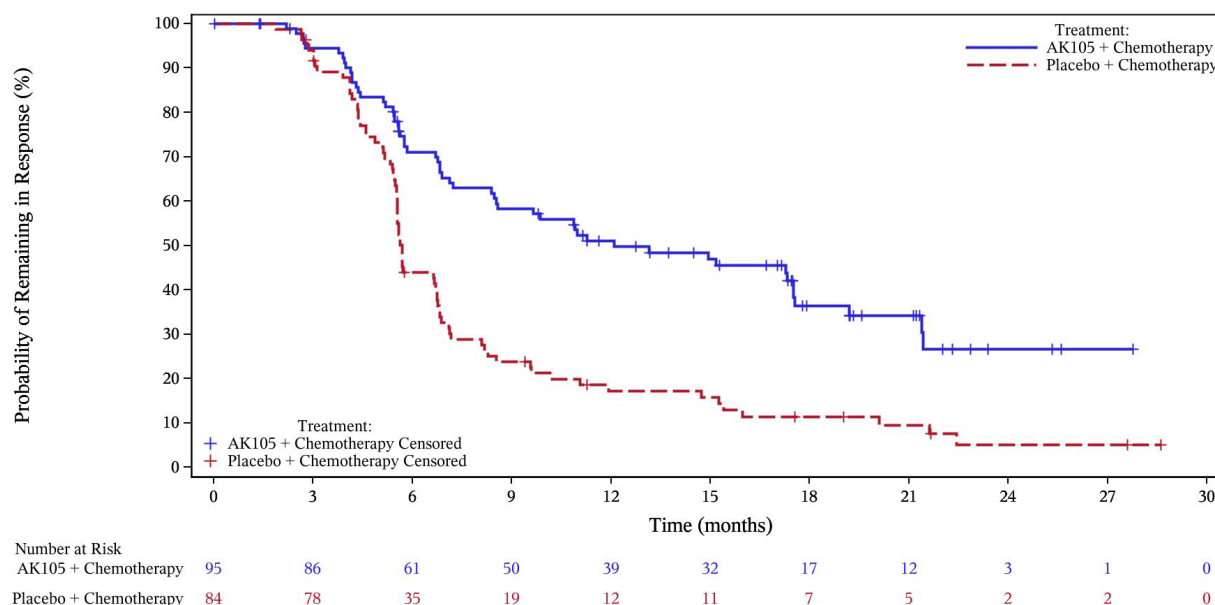
Per BICR assessment, the median TTR for the two groups was 1.5 (range: 1.2, 5.5) months and 1.5 (range: 1.2, 7.3) months, respectively. The median DoR for the two groups was 9.8 (95% CI: 7.0, 17.5) and 5.7 (95% CI: 5.5, 6.7) months, respectively, with AK105 group showing a longer DoR than placebo group with an HR of 0.40 (95%CI: 0.27, 0.59) ([Applicant – Figure 6](#)).

Per investigator assessment, the median TTRs for the two groups were 1.5 (range: 1.2, 11.6) months and 1.5 (range: 1.2, 5.8) months, respectively. The median DoR was also longer in AK105 group (12.1 months, 95% CI: 8.5, 17.5) compared to placebo group (5.7 months, 95% CI: 5.5, 6.7) with an HR of 0.35 (95%CI: 0.23, 0.52) ([Applicant – Figure 7](#)).

Applicant – Figure 6 Kaplan-Meier plot of BICR-assessed DoR

Source Data: ADTTE.xpt Module 5.3.5.1 AK105-304 CSR [Figure 14.2.4.1.1 in Section 14](#)

Applicant – Figure 7 Kaplan-Meier plot of investigator-assessed DoR



Source Data: ADTTE.xpt Module 5.3.5.1 AK105-304 CSR [Figure 14.2.4.2.1 in Section 14](#)

The Applicant's Position:

For both the BICR-assessed and investigator-assessed responses, DoR in AK105 group was longer than in placebo group with HRs of 0.4 (95%CI: 0.27, 0.59) and 0.35 (95%CI: 0.23, 0.52), respectively.

The FDA's Assessment:

In general, FDA agrees with the Applicant's position. The median DOR in the penpulimab arm was 9.8 months (95% CI: 7.0, 17.4). The observed 6-month landmark rates of DOR were 57% in penpulimab arm, as compared to 38% in the placebo arm. The analysis of DOR is restricted to responders and thus the Applicant-provided analysis of DOR based on hazard ratio is not considered a valid comparison as it is not based on the ITT population. The results of ORR and DOR in Study AK105-304 are consistent with that of Study AK105-202. The median duration of response was not reached in Study AK105-202. See the Assessment Aid Addendum for additional efficacy information for Study AK105-202.

Persistence of Effect

Data:

See the section on DoR, PFS, and OS above.

The Applicant's Position:

Significant benefits in PFS were observed in the AK105 group compared to placebo group, as assessed by both BICR and investigators. PFS benefits of AK105 were consistent across all examined subgroups. Furthermore, DoR in AK105 group was also much longer than that in the placebo group. Although the overall survival (OS) data is still immature, after adjusting for potential bias due to crossovers, there also appears an OS benefit. These findings indicate that NPC patients may derive sustained benefits from AK105 treatment.

The FDA's Assessment:

Refer to FDA's Assessment on Durability of Response and Key secondary endpoint: Overall survival (OS) above.

Efficacy Results – Secondary or exploratory COA (PRO) endpoints

Data:

Health-related Quality of Life (HRQoL) Analysis

EORTC QLQ-C30 global health status/QoL and each functional scale score at baseline and each visit, as well as the change in score from baseline to the last assessment in the study are summarized in [Table 14.2.6.1 in Section 14 of 5.3.5.1 AK105-304 CSR](#). The two groups had similar global health status/QoL scores at baseline, and the scores in both groups showed a downward trend after the start of treatment, followed by a slight increase with disease progression. There was no notable difference in the trend of score changes between the two groups.

The changes in EORTC QLQ-H&N43 up to the last assessment in the study are summarized in [Table 14.2.6.2 in Section 14 of 5.3.5.1 AK105-304 CSR](#). No notable differences were found between the two groups.

The Applicant's Position:

The study is not intended to study quality of life. The overall PRO data from EORTC QLQ-C30 and QLQ-H&N43 demonstrated some improvements in symptoms and functioning after treatment in AK105 group and placebo group.

The FDA's Assessment:

There was no formal testing plan proposed for patient-reported outcome (PRO) endpoints. FDA considers these analyses of PRO endpoints to be exploratory in nature and limited by the

sample size of the trial. FDA agrees there were no notable differences observed between arms in terms of patient-reported symptoms and function.

Additional Analyses Conducted on the Individual Trial

Data:

N/A

The Applicant's Position:

N/A

The FDA's Assessment:

No additional analyses were conducted.

8.1.3. Integrated Review of Effectiveness

The FDA's Assessment:

The clinical and statistical review teams conclude that the Applicant provided substantial evidence of effectiveness for penpulimab in combination with either cisplatin or carboplatin and gemcitabine as first-line treatment in adult patients with metastatic or recurrent, locally advanced nasopharyngeal carcinoma and for penpulimab, as a single agent, in adult patients with recurrent unresectable or metastatic NPC with disease progression on or after a platinum-containing chemotherapy and at least one other line of treatment. See FDA's Assessment in Section [8.1.5](#) for additional discussion.

8.1.4. Assessment of Efficacy Across Trials

This section is not applicable because the application is supported by one pivotal trial (AK105-304).

Primary Endpoints

Data:

N/A

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The Applicant's Position:

N/A

The FDA's Assessment:

FDA disagrees with the Applicant's position since both Studies AK105-304 and AK105-202 support this marketing application for two separate indications. However, Studies AK105-304 and AK105-202 were conducted in different patient populations and were not pooled. Although the trial results were not pooled, the results of the two trials of penpulimab in patients receiving first-line treatment or later-line treatment for NPC are supportive of each other. See the Assessment Aid Addendum for the efficacy review of Study AK105-202.

Secondary and Other Endpoints

Data:

N/A

The Applicant's Position:

N/A

The FDA's Assessment:

FDA agrees with the Applicant's position.

Subpopulations

Data:

N/A

The Applicant's Position:

N/A

The FDA's Assessment:

FDA agrees with the Applicant's position.

Additional Efficacy Considerations

The FDA's Assessment:

N/A.

8.1.5. Integrated Assessment of Effectiveness

Data:

As of data cutoff date for this interim analysis, the median follow-up time was 19.1 months (range: 0.0, 31.5), penpulimab combined with gemcitabine and cisplatin/carboplatin significantly improved PFS in the first-line treatment of R/M NPC, as compared to gemcitabine and cisplatin/carboplatin alone. The key efficacy outcomes are summarized as follows:

- Primary Endpoint BICR-assessed PFS:
 - Primary analysis: 80 (55.6%) subjects in AK105 group and 109 (74.1%) subjects in placebo group had PD or died, and the median PFS was 9.6 (95% CI: 7.1, 12.5) and 7.0 (95% CI: 6.9, 7.3) months, respectively. Compared with placebo group, AK105 group reduced the risk of PD or death by 55% (HR=0.45, 95% CI: 0.33, 0.62; P<0.0001). The study crossed the O'Brien-Fleming boundary for this PFS interim analysis (2-sided P-value boundary is 0.030 based on 189 PFS events).
 - Sensitivity analysis per FDA request: Included only the first 218 Asian subjects and all 11 ex-Asia subjects, 65 (56.5%) subjects in AK105 group and 83 (72.8%) subjects in placebo group had PD or died, and the median PFS was 8.4 (95% CI: 7.0, 12.5) and 7.0 (95% CI: 6.9, 7.2) months, respectively. Compared with placebo group, AK105 group reduced the risk of PD or death by 52%, HR=0.48 (95% CI: 0.33, 0.68; P<0.0001). The results of this sensitivity analysis and the primary analysis were consistent.
- Key Secondary Endpoint OS:
 - Since PFS reached statistical significance, as planned in the SAP, a descriptive analysis of OS was conducted with a nominal α of 0.0001. A total of 97 OS events were observed, with 48 from AK105 group and 49 from placebo group with an HR of 0.94 (95% CI: 0.63, 1.40). 24-month survival rate was 66.3% in AK105 group and 61.9% in placebo group. Median OS has not yet been reached for either group, and the OS data is immature.
 - 68 (46.3%) subjects in placebo group had crossed over to receive AK105 monotherapy after PD, which was explicitly allowed by design. Three sensitivity analyses were conducted via the commonly used methods for correcting crossover effects: Rank Preserving Structural Failure Time (RPSFT) model, Inverse Probability of Censoring Weighting (IPCW) method and two-stage Accelerated Failure Time (AFT) model. After

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adjusting for potential bias in OS caused by the crossovers, the trend of OS benefit became more evident, with an HR of 0.62 (0.41, 0.94) by RPSFT model, 0.75 (0.43, 1.30) by IPCW method, and 0.78 (0.52, 1.17) by two-stage AFT model.

- Other Secondary Endpoints:

- Investigator-assessed PFS: 78 (54.2%) subjects in AK105 group and 112 (76.2%) subjects in placebo group had PD or died, and the median PFS was 12.3 (95% CI: 9.7, 14.6) and 7.2 (95% CI: 7.0, 8.3) months, respectively. Compared with placebo group, AK105 group reduced the risk of progression or death by 56% (HR=0.44, 95% CI: 0.32, 0.60; P<0.0001).
- BICR-assessed response: the confirmed ORR for AK105 group and placebo group was 68.1% (95% CI: 59.8%, 75.6%) and 63.9% (95% CI: 55.6%, 71.7%), respectively. The median DoR for the two groups was 9.8 (95% CI: 7.0, 17.5) and 5.7 (95% CI: 5.5, 6.7) months, respectively, with AK105 group showing a longer DoR than placebo group with an HR of 0.4 (95%CI: 0.27, 0.59).
- Investigator-assessed response: the confirmed ORR for AK105 group and placebo group was 66.0% (95% CI: 57.6%, 73.7%) and 57.1% (95% CI: 48.7%, 65.3%), respectively. The median DoR was also longer in AK105 group (12.1 months, 95% CI: 8.5, 17.5) compared to placebo group (5.7 months, 95% CI: 5.5, 6.7) with an HR of 0.35 (95%CI: 0.23, 0.52).

The Applicant's Position:

The interim analysis results of AK105-304 showed that the Phase 3 trial of penpulimab combined with gemcitabine and cisplatin/carboplatin as the first-line treatment for R/M NPC patients, demonstrated large and robust treatment effect in terms of both BICR-assessed PFS (the primary endpoint) and investigator-assessed PFS. However, the study design allowing crossover after PD substantially affects the OS results. After correcting the confounding effect of crossovers via common statistical methods, the OS effect becomes evident and similar to those shown in other phase 3 studies on other anti-PD-1 agents. Compared with similar studies of other PD-1 inhibitors combined with chemotherapy as first-line treatment for R/M NPC, the efficacy was generally comparable. Furthermore, the sensitivity analysis of PFS including 218 Asian and 11 ex-Asia subjects showed similar efficacy. Therefore, penpulimab combined with gemcitabine and cisplatin/carboplatin has a favorable efficacy and provides a new beneficial treatment option for R/M NPC patients globally.

The FDA's Assessment:

Based on the results from Studies AK105-304 and AK105-202, the review team concluded that the Applicant provided substantial evidence of effectiveness for penpulimab in combination with cisplatin or carboplatin and gemcitabine, for the first-line treatment of adult patients with metastatic or recurrent, locally advanced nonkeratinizing NPC and for penpulimab as monotherapy, in adult patients with recurrent unresectable or metastatic NPC of

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nonkeratinizing histology with disease progression on or after platinum-based chemotherapy and at least one other line of therapy.

Study AK105-304 demonstrated a statistically significant improvement in BICR-assessed PFS favoring the penpulimab arm, with a HR of 0.45 (95% CI 0.33, 0.62; $p < 0.0001$), corresponding to a median PFS of 9.6 months (95% CI: 7.1, 12.5) in the penpulimab arm and 7.0 months (95% CI: 6.3, 7.3) in the placebo arm. The proportions of patients with observed PFS of at least 12 months was 31% in the penpulimab arm and 11% in the control arm. The PFS HR of 0.45 and a 2.6-month improvement in median PFS, along with a 20 percent-point difference in observed PFS rate at 12 months are considered clinically meaningful in this disease setting. In Study AK105-304, while the numerical difference in median PFS between the two arms was less than 3 months (median PFS was 9.6 months (95% CI: 7.1, 12.5) in the penpulimab-kcqx arm and 7.0 months (95% CI: 6.9, 7.3) in the placebo arm), the substantial reduction in the risk of disease progression or death in the penpulimab plus chemotherapy arm as compared to chemotherapy alone, as indicated by the hazard ratio, underscores a clinically meaningful benefit. The Kaplan-Meier curves begin to separate at approximately around 7 months, which suggests that some patients may derive prolonged PFS benefit, or that there may be a potential late treatment effect, which was not captured by median PFS alone. The ORR was 68% in the penpulimab arm and 64% in the placebo arm. The secondary endpoint of DOR demonstrated that penpulimab with cisplatin or carboplatin and gemcitabine had a longer median DOR at 9.8 months (95% CI: 7.0, 17.4) compared to cisplatin or carboplatin and gemcitabine alone at 5.7 months (95% CI: 5.5, 6.7).

These results provide substantial evidence of effectiveness for penpulimab in combination with cisplatin (or carboplatin) and gemcitabine, for the first-line treatment of adults with metastatic or with recurrent, locally advanced nonkeratinizing NPC. OS was not statistically significant at the first formal interim analysis, conducted at 70% information fraction. The HR was 0.91 (95% CI: 0.64, 1.31, $p = 0.615$). Median OS was not reached in the penpulimab arm (95% CI: 27.4, NE), while the median OS in the placebo arm was 31.3 months (95% CI: 27.2, NE). However, the interpretation of these results is challenging due to several reasons. Notably, a high rate of crossover from the placebo arm to the penpulimab arm (49%) may have impacted any potential OS difference between the treatment arms. Additionally, a substantial proportion of patients (31%) in the placebo arm received another anti-PD-(L)1 antibody upon disease progression. In total 80% of patients in the placebo arm received either penpulimab or another anti-PD-(L)1 antibody as subsequent treatment. This may have influenced survival outcomes and further complicated the assessment of treatment effect. Consequently, while no apparent OS detriment was observed at the time of the first formal OS analysis (DCO date: January 24, 2025), the impact of these post-progression treatments will be considered in future analyses when mature OS data are available.

Among 125 patients with recurrent unresectable or metastatic NPC of nonkeratinizing histology with disease progression on or after platinum-based chemotherapy and at least one other line

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of therapy, treated with penpulimab monotherapy in Study AK105-202, the ORR was 27% (95% CI: 20, 35). The median DOR was not reached (95% CI: 9.2, NE). Among the 35 patients with a complete or partial response, 83% had a DOR $\geq$ 6 months and 46% had a DOR $\geq$ 12 months. These results are considered clinically meaningful when considering the intended patient population. Furthermore, the results of Study AK105-304 provide further confidence in the benefit of single-agent penpulimab in advanced NPC.

A major limitation of the data is that Study AK105-304 enrolled 96% of the patients in China (based on a data cut-off date of April 29, 2024), and Study AK105-202 was conducted exclusively in China. While both Studies AK105-304 and AK105-202 were conducted predominantly in China, a flexible regulatory approach is warranted given the high unmet need for treatment options for patients with NPC. These trials were initiated prior to the approval of regimens with toripalimab, the only other FDA-approved anti-PD-(L)1 antibody for U.S. patients with NPC. Cisplatin or carboplatin plus gemcitabine was considered an appropriate control arm in Study AK105-304 when the trial was designed, making the study results relevant to U.S. medical practice. Cisplatin plus gemcitabine was considered standard of care for the first-line treatment of recurrent or metastatic NPC in the U.S., and carboplatin plus gemcitabine was considered an appropriate option for patients who may be unable to tolerate or who have contraindications to cisplatin. The incidence of NPC is much higher in East Asia relative to the U.S., where NPC is a relatively rare disease, making enrollment to clinical trials more feasible in that region of the world. Clinical site inspections were conducted by FDA to validate the data supporting this application. To further address the issue of applicability to the U.S. population, the Applicant will be collecting additional clinical data to further characterize the safety and efficacy of penpulimab in combination with either cisplatin or carboplatin and gemcitabine for the treatment of non-keratinizing NPC in a study population whose demographic and disease characteristics are more representative of the population of U.S. patients with NPC (see Postmarketing Commitments later in this review for details).

8.2. Review of Safety

Data:

The penpulimab is being studied in clinical trials across different tumor types. The primary evidence to support the safety of penpulimab is generated from 8 clinical studies of penpulimab as monotherapy or in combination therapy (including AK105-101, AK105-201, AK105-202, AK105-204, AK105-205, AK105-301 (Part I), AK105-302 and AK105-304) and presented in two separate parts, Monotherapy Part (n=558) and Combination Therapy Part (n=393).

The Applicant's Position:

Monotherapy Part

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Monotherapy Part includes pooled safety data from 558 patients with a variety of tumor types across 6 studies who have been exposed to penpulimab monotherapy at any dose levels. In the monotherapy part, safety data is presented for NPC 200mg Q2W population (n=130), Penpulimab 200mg Q2W (n=372) and Overall Population (n=558). In addition, safety data generated from different regions is also presented separately as Asia vs ex-Asia in population receiving penpulimab 200mg Q2W.

- ***NPC 200mg Q2W population (n=130)***
 - NPC 200mg Q2W data was generated from AK105-202;
- ***Penpulimab 200mg Q2W (n=372)***
 - Ex-Asian data was generated from AK105-101 Phase Ib
 - Asian data was generated from AK105-201, AK105-202, and AK105-204;
 - Total data of all tumor types at 200mg Q2W were generated from AK105-101 Phase Ib, AK105-201, AK105-202, and AK105-204;
- ***Overall Population (n=558)***
 - All dose data were pooled from all patients with various tumor types who received penpulimab monotherapy at any dose in the above 6 studies.

Combination Therapy Part

Combination Therapy Part includes patients who have been exposed to penpulimab in combination with chemotherapy or other regimens from 4 studies. Since penpulimab was administered in patients with different tumor types in combination with different chemotherapies, safety data from different studies were not pooled. Instead, data from each study were presented and summarized separately:

- AK105-304 in which penpulimab 200mg Q3W was administered in combination with cisplatin or carboplatin and gemcitabine to 146 patients with NPC
- AK105-302 in which penpulimab 200mg Q3W was administered in combination with paclitaxel and carboplatin to 173 patients with sq-NSCLC
- AK105-301 in which penpulimab 200mg Q3W was administered in combination with carboplatin and pemetrexed to 46 patients with nsq-NSCLC
- AK105-205 in which penpulimab 200mg Q3W was administered in combination with chemotherapy with or without anlotinib to 28 patients with NPC (Arm A: penpulimab + gemcitabine + cisplatin + anlotinib, n=8; Arm B: penpulimab + gemcitabine + cisplatin, n=6; Arm C: penpulimab + gemcitabine + anlotinib, n=14)

The FDA's Assessment:

FDA's review of the safety profile of penpulimab 200 mg Q3W in combination with cisplatin or carboplatin and gemcitabine was based on data from 146 patients with NPC who received at least one dose of penpulimab on Study AK105-304. FDA did not agree with pooling data from trials incorporating other combination regimens (such as from Studies AK105-302, AK105-301, and AK105-205), given differences in safety profiles and challenges in isolating toxicities specifically associated with penpulimab.

FDA's review of the safety profile of penpulimab 200 mg Q2W was based on data from 130 patients with NPC who received at least one dose of penpulimab on Study AK105-202 supported by pooled data (n=372) from Studies AK105-202 (n=130), AK105-101 (n=83), AK105-201 (n=94), and AK1050-204 (n=65) of penpulimab 200 mg Q2W as a single agent for patients with advanced solid tumors and classic Hodgkin lymphoma. FDA did not pool safety data for penpulimab as a single agent with alternative dosing schedules.

8.2.1. Safety Review Approach

Data:

N/A

The Applicant's Position:

The safety evaluation performed as part of the penpulimab clinical development program was consistent with ICH guidelines.

The safety analyses supporting this application were comprehensive and included all Serious TEAEs (SAEs,) all TEAEs, especially Grade ≥ 3 all-causality and treatment-emergent AEs, AEs leading to drug discontinuations, AEs leading to drug interruption, laboratory abnormalities.

A consistent approach for the categorization of an AE as immune-related AE (irAE) was also applied following a prespecified case definition consisting of both programmatic checks and medical review (see [Module 5.3.5.1 AK105-304 CSR](#), [appendices 16.1.9, irAEs Characterization Charter](#))

The FDA's Assessment:

FDA agrees that the safety data permitted an adequate assessment of penpulimab's safety profile. FDA utilized the safety datasets generated for Study AK105-304 and Study AK105-202 and pooled safety population to review the safety profile of penpulimab (described in [Section 8.2](#)). Throughout the review of safety data, FDA sent multiple information requests (IRs)

soliciting additional clinical information about medical causes of death when the patient narratives were unclear or did not provide sufficient information.

8.2.2. Review of the Safety Database

Overall Exposure

Data:

The summary of clinical safety includes safety data from 951 patients who have been exposed to one or more doses of penpulimab monotherapy or in combination with other regimens. The safety data was generated in two separate parts, Monotherapy Part (n=558) and Combination Therapy Part (n=393).

Monotherapy Part

558 patients were included in the monotherapy part with a variety of tumor types who have been exposed to penpulimab monotherapy at any dose levels, including 372 patients treated with penpulimab at 200mg Q2W and 186 patients treated with penpulimab at other doses (1, 3, 10 mg/kg Q2W and 200mg Q3W).

Regarding the tumor types, monotherapy safety population including 198 patients with NPC (AK105-202 and AK105-304 control arm cross-over), 112 patients with non-small-cell lung cancer (NSCLC) (AK105-302 control arm cross-over), 94 patients with classic Hodgkin's lymphoma (cHL) (AK105-201) and 154 patients with various other solid tumors (AK105-101 phase Ib and AK105-204).

NPC 200mg Q2W population

A total of 130 NPC patients have been treated with penpulimab 200mg Q2W. The median total duration of exposure was 139.5 days (range: 14-878 days), median number of penpulimab doses was 9.5 (range: 1-59), median relative dose intensity was 98.13% (range: 52.6 - 121.7). Approximately 68.5% of patients were treated for more than 3 months, 44.6% for more than 6 months, 30.0% of patients received treatment for at least 12 months.

Penpulimab 200mg Q2W population

A total of 372 patients have been treated with penpulimab 200mg Q2W. The median duration of exposure was 168.5 days (range: 13 to 878 days). The median number of doses received was 12.0 (range: 1-59), median relative dose intensity was 98.25% (range: 52.6 - 121.7). Approximately 66.1% of patients were treated for more than 3 months, 49.2% for more than 6 months, 33.6% of patients received treatment for at least 12 months.

Overall Monotherapy Population

A total of 558 patients with various tumor types have been treated with penpulimab at any dose level. The median duration of exposure was 126 days (range: 8 to 1022 days). The median number

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of doses received was 8 (range: 1-71), median relative dose intensity was 100.0% (range: 52.6% - 131.3%). Approximately 60.9% of patients were treated for more than 3 months, 42.5% for more than 6 months, 25.6% of patients received treatment for at least 12 months.

Combination Therapy Part

Combination Therapy Part includes 393 patients who have been exposed to penpulimab 200mg Q3W in combination with chemotherapy or other regimens, including 146 patients with NPC treated with penpulimab in combination with cisplatin and gemcitabine; 173 nsq-NSCLC patients treated with penpulimab in combination with paclitaxel and carboplatin, 46 sq-NSCLC patients treated with penpulimab in combination with carboplatin and pemetrexed and 28 NPC patients treated with penpulimab in combination with chemotherapy with or without anlotinib (Arm A: penpulimab + gemcitabine + cisplatin + anlotinib, n=8; Arm B: penpulimab + gemcitabine + cisplatin, n=6; Arm C: penpulimab + gemcitabine + anlotinib, n=14).

AK105-304

A total of 146 patients with NPC have been treated with penpulimab 200mg Q3W in combination with cisplatin/carboplatin and gemcitabine in AK105-304. The median total duration of exposure was 259.0 days (range: 13-753 days), median number of penpulimab doses was 11 (range: 1-35), median relative dose intensity was 100.0% (range: 60.0% - 100.0%). Approximately 82.9% of patients were treated for more than 3 months, 71.2% for more than 6 months, 38.4% of patients received treatment for at least 12 months.

AK105-302

A total of 173 patients with sq-NSCLC have been treated with penpulimab 200mg Q3W in combination with carboplatin and paclitaxel in AK105-302. The median total duration of exposure was 294.0 days (range: 11-763 days), median number of penpulimab doses was 14 (range: 1-35), median relative dose intensity was 97.14% (range: 50.2%-190.9%). Approximately 86.7% of patients were treated for more than 3 months, 68.8% for more than 6 months, 41.0% of patients received treatment for at least 12 months.

AK105-301

A total of 46 patients with nsq-NSCLC have been treated with penpulimab 200mg Q3W in combination with carboplatin and paclitaxel in AK105-301. The median total duration of exposure was 229.5 days (range: 16-784 days), median number of penpulimab doses was 9 (range: 1-35), median relative dose intensity was 90.81% (range: 59.7%-131.3%). Approximately 82.6% of patients were treated for more than 3 months, 60.9% for more than 6 months, 30.4% of patients received treatment for at least 12 months.

AK105-205

A total of 28 patients with metastatic NPC have been treated with penpulimab 200mg Q3W in combination with chemotherapy and with or without anlotinib in AK105-205. The median total duration of exposure was 459.0 days (range: 21-756 days), median number of penpulimab

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doses was 18 (range: 1-35), median relative dose intensity was 97.28% (range: 69.4%-100.0%). Approximately 89.3% of patients were treated for more than 3 months, 64.3% for more than 6 months, 50.0% of patients received treatment for at least 12 months.

Applicant – Table 15 Safety Population, Size, and Denominators

Safety Database for the Penpulimab Monotherapy N=558				
Clinical Trial Groups	Penpulimab 200mg Q2W (N=372)	Penpulimab Other Doses (N=186)	Total (N=558)	
AK105-202	130	0	130	
AK105-101 Phase Ib	83	0	83	
AK105-201	94	0	94	
AK105-204	65	0	65	
AK105-304 control arm cross-over	0	68	68	
AK105-302 control arm cross-over	0	102	102	
AK105-101 phase Ia	0	16	16	
Safety Database for the Penpulimab Combination Therapy N=393				
Clinical Trial Groups	Penpulimab 200mg Q3W + GP (N=146)	Penpulimab 200mg Q3W + TC (N=173)	Penpulimab 200mg Q3W + PC (N=46)	Penpulimab 200mg Q3W +Chemo±Anlotinib* (N=28)
AK105-304	146	0	0	0
AK105-302	0	173	0	0
AK105-301	0	0	46	0
AK105-205	0	0	0	28

GP: gemcitabine plus cisplatin/carboplatin; TC: paclitaxel plus carboplatin; PC: pemetrexed plus carboplatin.

*: included 3 treatment arms, penpulimab+GP+anlotinib, penpulimab+GP, penpulimab+gemcitabine + anlotinib

The Applicant's Position:

The eligibility criteria in the pivotal study were clinically relevant for the target population who would receive penpulimab following regulatory approval in the proposed indication.

The exposure to study drug was considered adequate to support characterization of the safety profile of penpulimab and allow for a comprehensive assessment of safety in all patients treated with penpulimab.

The FDA's Assessment:

FDA reviewed the extent of exposure to penpulimab in Study AK105-304, Study AK105-202, and the pooled safety dataset. [FDA – Table 8](#) presents drug exposure in Study AK105-202 and the pooled safety dataset.

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FDA – Table 8. Drug Exposure in the AK105-202 Trial and Pooled Safety for Penpulimab Monotherapy 200 mg IV Q2W (N=372)

	AK105-202 N=130	Pooled Safety Set N=372
Relative intensity (%)		
Mean (SD)	94.93 (8.7)	95.0 (8.0)
Median	98.1	98.2
Range	52.6 to 121.7	52.6 to 121.7
Duration (day)		
Mean (SD)	255.3 (228.8)	287.5 (253.4)
Median	139.5	168.5
Range	14.0 to 878.0	13.0 to 878.0
Total exposure time (month)		
Duration ≥3 months	89 (68.5)	246 (66.1)
Duration ≥6 months	58 (44.6)	183 (49.2)
Duration ≥12 months	39 (30.0)	125 (33.6)

Source: ADSL Dataset

Abbreviations: IV, intravenous; Q2Wk, every 2 weeks; SD, standard deviation

In Study AK105-304, the median number of penpulimab treatment cycles (13 vs. 12) and treatment duration in days (259 vs. 236) were comparable between the experimental and control arms.

In AK105-304, 71% of patients were exposed to penpulimab in combination with either cisplatin or carboplatin and gemcitabine for 6 months or more and 38% were exposed 12 months or more.

In AK105-202, 45% of patients were exposed to penpulimab for 6 months or more and 30% were exposed 12 months or more. In the pooled safety monotherapy dataset, 49% of patients received treatment for at least six months, and 34% for at least 12 months.

The FDA notes that drug exposure data from AK105-304 suggest that the addition of penpulimab did not impact the administration of cisplatin and gemcitabine. However, in AK105-202 and the pooled safety dataset, penpulimab exposure was relatively short, with a median duration of 140 days (4.7 months) and 169 days (5.6 months), respectively.

Relevant characteristics of the safety population:

Data:

Monotherapy Part

NPC 200mg Q2W population

The median age was 49.5 years (range: 20 to 66 years), 76.2% of whom were male, 23.8% were female. Patients with an ECOG score of 0 and 1 were 30.8% and 69.2%, respectively. The median BMI was 21.5 kg/m² (range:13-31).

Penpulimab 200mg Q2W population

The median age was 51.0 years (range: 18 to 91 years), 64.0% of whom were male, 36.0% were female. All patients had an ECOG score of 0 (41.9%) or 1 (58.1%). The median BMI was 22.8 kg/m² (range:13-43).

Overall Monotherapy Population

In patients with various tumor types who were treated with penpulimab at any dose level, the median age was 54.2 years (range: 18 to 91 years), 69.7% of whom were male, 30.3% were female. All patients had an ECOG score of 0 (39.6%) or 1 (60.4%). The median BMI was 22.3 kg/m² (range:13-43).

Combination Therapy Part

In patients treated with penpulimab 200mg Q3W in combination with cisplatin/carboplatin and gemcitabine in AK105-304, the median age was 51.0 years (range: 23 to 75 years), 82.2% of whom were male, 17.8% were female. All patients had an ECOG score of 0 (36.3%) or 1 (63.7%). The median BMI was 21.6 kg/m² (range:15-32).

The Applicant's Position:

The demographic characteristics were generally comparable across NPC safety population and all other studies where penpulimab was used as monotherapy or in combination therapy.

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The FDA's Assessment:

FDA – Table 9 presents the baseline demographic and disease characteristics of the safety analysis populations from Studies AK105-304, AK105-202, and the pooled safety dataset.

FDA – Table 9. Patient Characteristics in AK105-304, AK105-202, and the Pooled Safety Dataset

Characteristic	AK105-304 N=291		Penpulimab Monotherapy	
	Penpulimab+ Chemotherapy N=144	Placebo+ Chemotherapy N=147	AK105-202 N=130	Pooled Safety N=372
Median age, years (range)	51 (31 to 75)	50 (23 to 68)	49.5 (20 to 66)	51 (18 to 91)
≥ Age 65 years (%)	10	3.5	1.5	18.5
Sex (%)				
Male	83	81	76	64
Female	17	19	24	36
Race (%)				
Asian	97	98	100	81
ECOG performance status (%)				
0	35	36	31	42
1	65	64	69	58
Histology (%)				
Non-keratinizing undifferentiated	78	76	67	NA
Non-keratinizing differentiated	17	21	29	NA
Keratinizing	0.7	0.7	NA	NA
Other	4.2	2.7	3.8	NA
Prior lines of therapy (%)				
2	NA	NA	63	NA
≥3	NA	NA	36	NA
Tumor type (%)				
NPC	100	100	100	35
NSCLC	NA	NA	NA	2.7
cHL	NA	NA	NA	25
HCC	NA	NA	NA	6
Gastric	NA	NA	NA	6
Ovarian	NA	NA	NA	5
BTC	NA	NA	NA	3.0
Esophageal squamous cell	NA	NA	NA	3.0
Other	NA	NA	NA	15

Source: ADSL Dataset

Other includes Pancreatic Adenocarcinoma, Colorectal, Endometrial, SCLC, Cervical, Squamous Cell of the Head & Neck, Breast, Kidney, Mesothelioma, Neuroendocrine Neoplasm, Melanoma, Gallbladder, Skin squamous cell, and Urothelial Cancer. Source: IR from Applicant.

Abbreviations: BTC, biliary tract cancer; cHL, classical Hodgkin lymphoma; ECOG, Eastern Cooperative Oncology Group; HCC, hepatocellular carcinoma; NPC, nasopharyngeal carcinoma; NSCLC, non-small cell lung cancer

Disclaimer: In this document, the sections labeled as “Data” and “The Applicant’s Position” are completed by the Applicant and do not necessarily reflect the positions of the FDA.

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FDA agrees that regarding male predominance, this is consistent with what is expected in the US patient population with NPC. However, the median age of patients in AK105-304 (51 years) and AK105-202 (50 years) is slightly younger than the median age for US patients with NPC (53 or 54 years). Furthermore, given that nearly all patients in the efficacy populations for both studies were of Chinese ethnicity, the efficacy populations do not reflect the racial and ethnic diversity of the US patient population with NPC. Patients with keratinizing histology were permitted to enroll to Study AK105-304; however, only very few patients with keratinizing histology were included in this trial and were therefore greatly underrepresented relative to the incidence of this histology in the US population with NPC. In total, only 0.7% of patients in each arm of AK105-304 had keratinizing histology compared to 35% of patients in the US with NPC expected to have keratinizing histology. Only patients with non-keratinizing histology were eligible for enrollment into Study AK105-202. There were no additional patients with non-keratinizing NPC in the pooled dataset.

Despite the differences noted above, FDA agrees that the safety data from AK105-304, AK105-202, and the pooled safety dataset provide sufficient data for evaluations of the safety profile of penpulimab in combination with cisplatin or carboplatin and gemcitabine and as a single agent.

Adequacy of the safety database:

Data:

Integrated penpulimab Monotherapy Part includes pooled safety data from 558 patients with a variety of tumor types across 6 studies who have been exposed to penpulimab monotherapy at any dose levels. Of those patients, 372 patients with penpulimab 200mg Q2W were included for overall safety evaluation.

Integrated penpulimab Combination Therapy Part includes 393 patients who have been exposed to penpulimab 200mg Q3W in combination with chemotherapy or other regimens. Of those patients, 146 patients with NPC treated with penpulimab in combination with cisplatin and gemcitabine were included for overall safety evaluation.

The Applicant's Position:

The safety database was considered adequate to support the characterization of the safety profile of penpulimab in the proposed patient population.

The FDA's Assessment:

FDA did not independently verify data from the AK105-302 or AK105-301 trials because these patients received chemotherapy regimens other than cisplatin or carboplatin and gemcitabine.

FDA did not independently verify the data for the pooled monotherapy dataset of 558 patients because they received penpulimab at varying doses and schedules, ranging from 1 mg/kg Q2W to 10 mg/kg Q2W and 200 mg Q3W.

FDA focused its safety analysis of penpulimab monotherapy on a subset of the pooled dataset, including 372 patients treated with penpulimab 200 mg IV Q2W, including 130 patients from Study AK105-202. FDA agrees that the size and quality of the safety data provide a sufficient basis for assessing the safety profile of penpulimab both in combination with cisplatin or carboplatin and gemcitabine, and as a single agent.

8.2.3. Adequacy of Applicant's Clinical Safety Assessments

Issues Regarding Data Integrity and Submission Quality

Data:

All clinical trials in this package were conducted according to Good Clinical Practice. Monitors were responsible for ensuring adherence to the protocol; compliance with GCP. The study team and site personnel collaborated closely to ensure the completeness, accuracy, and consistency of the study data. Direct access to medical and laboratory records of all subjects was permitted to verify entries on the study-specific eCRFs.

Central laboratories were preferred in the studies. Where local laboratories were used, their qualification was strictly evaluated by the study monitors.

All safety evaluation procedures including monitoring for AEs, reporting SAEs, physical examinations, vital sign measurements, clinical laboratory tests, and ECGs were standard (i.e., widely used and generally recognized as reliable, accurate, and relevant).

The Applicant's Position:

Although there were several cases of untimely reporting of SAEs as described in critical protocol deviation, no issues were identified that could affect the quality and integrity of the submitted datasets and individual case narratives.

The FDA's Assessment:

FDA agrees with the Applicant's position.

Categorization of Adverse EventData:

The data collection of AEs from the 8 clinical studies is provided in [Applicant – Table 16](#).

Applicant – Table 16 Summary of Reporting of AEs Across the Studies

Study No.	AE data collected during treatment
AK105-101	AEs that occurred from the first dosing date through 90 days after the last dose of penpulimab; or reemerged during treatment, having been present at baseline but stopped prior to treatment; or worsened in severity since treatment relative to the pretreatment state when the AE was continuous.
AK105-201	
AK105-202	
AK105-204	AEs that occurred from the first dosing date through 30 days after the last dose of penpulimab or until initiation of subsequent anticancer therapy; or reemerges during treatment, having been present at baseline but stopped prior to treatment; or worsened in severity since treatment relative to the pretreatment state when the AE was continuous. irAEs that occurred within 90 days after the last dose, regardless of whether the patient had started a new anti-tumor therapy or not.
AK105-205	AEs that occurred from the first dosing date through 30 day (for non-SAE) or 90 days (for SAE) after the last dose of penpulimab/anlotinib or until initiation of subsequent anticancer therapy, whichever occurs first.
AK105-301	AEs that occurred from the first dose of study treatment through 30 days (for non-SAE) or 90 days (for SAE) after the last dose of study treatment.
AK105-302	
AK105-304	AEs that occurred from the first dose of study treatment through 30 days (for non-SAE) or 90 days (for SAE) after the last dose of study treatment, or started new anti-cancer therapy, whichever occurs first. irAEs that occurred within 90 days after the last dose, regardless of whether the patient had started a new anti-tumor therapy or not.

AEs were coded using MedDRA by System Organ Class (SOC) and Preferred Term (PT). AEs were coded using MedDRA 24.0 (AK105-304, AK105-205, AK105-301) and MedDRA 22.0 (other studies), respectively.

AEs in AK105-204, AK105-205, AK105-301 (Part 1), AK105-302 and AK105-304 studies were graded according to NCI-CTCAE version 5.0, and AEs in AK105-101, AK105-201, and AK105-202 studies were graded according to NCI-CTCAE version 4.03.

The Applicant's Position:

The safety of penpulimab was evaluated on the basis of the:

- Frequency, type, severity, and causal relationship of AEs to study treatment.
- Frequency of deaths, SAEs, and other clinically significant AEs (including AEs leading to drug discontinuation and AEs requiring dose interruption)

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- Frequency and type of AEs in key demographic and baseline characteristics subgroups.
- Changes in laboratory variables.

The approach to the analysis of AEs was appropriate in evaluating the safety data.

The FDA's Assessment:

FDA agrees with the Applicant's position.

Routine Clinical Tests

Data:

Clinical laboratory data were collected routinely throughout the study.

Clinical laboratory values were graded according to CTCAE 4.03 (AK105-101, AK105-201, AK105-202) or CTCAE 5.0 (AK105-204, AK105-205, AK105-301, AK105-302, and AK105-304).

Clinical laboratory tests included hematology, blood chemistry, coagulation function tests, thyroid function tests, urinalysis, virological tests, and pregnancy tests. The schedule of main laboratory tests for each study is presented in [Module 2.7.4, Table 3](#).

The Applicant's Position:

The laboratory evaluation (laboratory tests and timepoints) as described in the protocols was reasonable and adequate to monitor the safety of the penpulimab.

The FDA's Assessment:

FDA agrees with the Applicant's position.

8.2.4. Safety Results

8.2.4.1. Deaths

Data:

Monotherapy Part

NPC 200mg Q2W population

A total of 58 (44.6%) deaths occurred in NPC 200mg Q2W population. A total of 2 (1.5%) deaths occurred within 30 days after the last dose. Deaths between 30 and 90 days after the last dose occurred in 16 subjects (12.3%). Deaths more than 90 days after the last dose occurred in 40

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subjects (30.8%).

18 (13.8%) patients had AEs that resulted in death, regardless of causality. Excluding disease progression, AEs with an outcome of death were reported in 7 (5.4%) patients: unexplained death in 3 patients (PID (b) (6), PID (b) (6), PID (b) (6)), respiratory failure in 2 patients, septic shock in 1 patient, and sudden death (PID (b) (6)) in 1 patient.

Drug-related AE leading to death occurred in 2 patients (PID (b) (6), “death” as PT, died 73 days after the last dose, causality unable to be assessed; PID (b) (6), “death” as PT, died 35 days after the last dose, causality unable to be assessed).

Penpulimab 200mg Q2W population

A total of 143 (38.4%) deaths occurred in penpulimab 200mg Q2W population. A total of 12 (3.2%) deaths occurred within 30 days after the last dose. Deaths between 30 and 90 days after the last dose occurred in 47 subjects (12.6%). Deaths more than 90 days after the last dose occurred in 84 subjects (22.6%).

34 (9.1%) patients had AEs that resulted in death, regardless of causality. Excluding disease progression, AEs with an outcome of death were reported in 12 (3.2%) patients: unexplained death in 3 patients (PID (b) (6), PID (b) (6), PID (b) (6)), respiratory failure in 3 patients, and pneumonia, septic shock, gastrointestinal haemorrhage, haemophagocytic lymphohistiocytosis, cerebral infarction or sudden death (PID (b) (6)) in 1 patient each.

Drug-related AE leading to death occurred in 3 patients (PID (b) (6), “death” as PT, died 73 days after the last dose, causality unable to be assessed; PID (b) (6), “death” as PT, died 35 days after the last dose, causality unable to be assessed; PID (b) (6), “gastrointestinal haemorrhage” as PT, died 20 days after the last dose, causality unable to be assessed).

Overall Monotherapy Population

A total of 225 (40.3%) deaths occurred in overall monotherapy population. A total of 20 (3.6%) deaths occurred within 30 days after the last dose. Deaths between 30 and 90 days after the last dose occurred in 55 subjects (9.9%). Deaths more than 90 days after the last dose occurred in 150 subjects (26.9%).

46 (8.2%) patients had AEs that resulted in death, regardless of causality. Excluding disease progression, AEs with an outcome of death were reported in 19 (3.5%) patients: unexplained death in 7 patients (PID (b) (6), PID (b) (6), PID (b) (6), PID (b) (6), PID (b) (6), PID (b) (6), PID (b) (6)), respiratory failure in 5 patients, pneumonia in 1 patient, septic shock in 1 patient, gastrointestinal haemorrhage in 1 patient, haemophagocytic lymphohistiocytosis in 1 patient, malignant neoplasm progression in 1 patient, cerebral infarction in 1 patient, and sudden death (PID (b) (6)) in 1 patient.

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Drug-related AE leading to death occurred in 6 patients (PID (b) (6), “death” as PT, died 73 days after the last dose, causality unable to be assessed; PID (b) (6), “death” as PT, died 35 days after the last dose, causality unable to be assessed; PID (b) (6), “death” as PT, died 19 days after the last dose, possibly related to penpulimab; PID (b) (6), “gastrointestinal haemorrhage” as PT, died 20 days after the last dose, causality unable to be assessed; PID (b) (6), “respiratory failure” as PT, died 60 days after the last dose, possibly related to penpulimab; PID (b) (6), “death” as PT, died 37 days after the last dose, possibly related to penpulimab).

Deaths occurred in patients receiving penpulimab monotherapy are summarized in [Applicant – Table 17](#).

Applicant – Table 17 Summary of Deaths in Trials with Penpulimab Monotherapy

	NPC 200mg Q2W (N=130)	All Tumor Types 200mg Q2W Ex-Asia (N=83)	Asia (N=289)	Total (N=372)	All Doses Total (N=558)
Number of Death	58 (44.6)	42 (50.6)	101 (34.9)	143 (38.4)	225 (40.3)
Reason for Death					
Adverse Event	2 (1.5)	1 (1.2)	5 (1.7)	6 (1.6)	10 (1.8)
Disease Progression	52 (40.0)	37 (44.6)	77 (26.6)	114 (30.6)	177 (31.7)
Unknown	0	3 (3.6)	15 (5.2)	18 (4.8)	19 (3.4)
Other	4 (3.1)	1 (1.2)	4 (1.4)	5 (1.3)	19 (3.4)
Deaths within 30 days after the last dose	2 (1.5)	5 (6.0)	7 (2.4)	12 (3.2)	20 (3.6)
Adverse Event	0	0	2 (0.7)	2 (0.5)	4 (0.7)
Disease Progression	1 (0.8)	4 (4.8)	4 (1.4)	8 (2.2)	13 (2.3)
Other	1 (0.8)	1 (1.2)	1 (0.3)	2 (0.5)	3 (0.5)
Deaths within 30 to 90 days after the last dose	16 (12.3)	21 (25.3)	26 (9.0)	47 (12.6)	55 (9.9)
Adverse Event	2 (1.5)	1 (1.2)	3 (1.0)	4 (1.1)	5 (0.9)
Disease Progression	12 (9.2)	19 (22.9)	20 (6.9)	39 (10.5)	44 (7.9)
Unknown	0	1 (1.2)	1 (0.3)	2 (0.5)	2 (0.4)
Other	2 (1.5)	0	2 (0.7)	2 (0.5)	4 (0.7)
Death after the last dose +90 days	40 (30.8)	16 (19.3)	68 (23.5)	84 (22.6)	150 (26.9)
Adverse Event	0	0	0	0	1 (0.2)
Disease Progression	39 (30.0)	14 (16.9)	53 (18.3)	67 (18.0)	120 (21.5)
Unknown	0	2 (2.4)	14 (4.8)	16 (4.3)	17 (3.0)
Other	1 (0.8)	0	1 (0.3)	1 (0.3)	12 (2.2)

Source: ISS Combined Supplementary Tables, [Table 10.1.1](#).

TEAEs leading to death are summarized by SOC and PT in [Applicant – Table 18](#).

Applicant – Table 18 TEAEs Leading to Death by SOC and PT with Penpulimab Monotherapy

System Organ Class Preferred Term	NPC 200mg Q2W (N=130)	All Tumor Types 200mg Q2W Ex-Asia (N=83)	Asia (N=289)	Total (N=372)	All Doses Total (N=558)
Number of Subjects with at Least One TEAE Leading to death	18 (13.8)	2 (2.4)	32 (11.1)	34 (9.1)	46 (8.2)
General disorders and administration site conditions	15 (11.5)	0	26 (9.0)	26 (7.0)	35 (6.3)
Disease progression	11 (8.5)	0	22 (7.6)	22 (5.9)	27 (4.8)
Death	3 (2.3)	0	3 (1.0)	3 (0.8)	7 (1.3)
Sudden death	1 (0.8)	0	1 (0.3)	1 (0.3)	1 (0.2)
Respiratory, thoracic and mediastinal disorders	2 (1.5)	0	3 (1.0)	3 (0.8)	5 (0.9)

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System Organ Class Preferred Term	NPC 200mg Q2W (N=130)	All Tumor Types 200mg Q2W		All Doses	
		Ex-Asia (N=83)	Asia (N=289)	Total (N=372)	Total (N=558)
Respiratory failure	2 (1.5)	0	3 (1.0)	3 (0.8)	5 (0.9)
Infections and infestations	1 (0.8)	1 (1.2)	1 (0.3)	2 (0.5)	2 (0.4)
Pneumonia	0	1 (1.2)	0	1 (0.3)	1 (0.2)
Septic shock	1 (0.8)	0	1 (0.3)	1 (0.3)	1 (0.2)
Gastrointestinal disorders	0	0	1 (0.3)	1 (0.3)	1 (0.2)
Gastrointestinal haemorrhage	0	0	1 (0.3)	1 (0.3)	1 (0.2)
Immune system disorders	0	0	1 (0.3)	1 (0.3)	1 (0.2)
Haemophagocytic lymphohistiocytosis	0	0	1 (0.3)	1 (0.3)	1 (0.2)
Neoplasms benign, malignant and unspecified (incl cysts and polyps)	0	0	0	0	1 (0.2)
Malignant neoplasm progression*	0	0	0	0	1 (0.2)
Nervous system disorders	0	1 (1.2)	0	1 (0.3)	1 (0.2)
Cerebral infarction	0	1 (1.2)	0	1 (0.3)	1 (0.2)

Source: ISS Combined Supplementary Tables, Table 4.15.1.

Combination Therapy Part

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48 (32.9%) subjects in penpulimab group and 48 (33.8%) subjects in placebo group died. 2 (1.4%) and 3 (2.1%) subjects died within 30 days after the last dose; 6 (4.1%) and 3 (2.1%) subjects died within 31 to 90 days after the last dose; 40 (27.4%) and 42 (29.6%) subjects died more than 90 days after the last dose in penpulimab group and placebo group, respectively.

In penpulimab group, 7 (4.8%) patients had AEs that resulted in death, regardless of causality. Excluding disease progression, AEs with an outcome of death were reported in 3 (2.1%) patients: death in 1 patient; COVID-19 pneumonia in 1 patient; cardiac failure in 1 patient.

In penpulimab group, drug-related AE leading to death occurred in 2 patients: PID (b) (6), "disease progression" as PT, died 47 days after the last dose, possibly related to penpulimab; PID (b) (6), "cardiac failure" as PT, died 24 days after the last dose, possibly related to penpulimab.

Deaths occurred in patients receiving penpulimab in combination with other regimens are summarized in Applicant – Table 19.

Applicant – Table 19 Summary of Deaths in Trials with Penpulimab Combination Therapy

	AK105-304		AK105-302	AK105-301	AK105-205
	Penpulimab + GP (N=146)	Placebo + GP (N=142)	Penpulimab + TC (N=173)	Penpulimab + PC (N=46)	Penpulimab+ Chemo±Anlotinib (N=28)
Death Number	48 (32.9)	48 (33.8)	68 (39.3)	24 (52.2)	8 (28.6)
Reason for Death					
Adverse Event	2 (1.4)	1 (0.7)	6 (3.5)	2 (4.3)	2 (7.1)
Disease Progression	29 (19.9)	30 (21.1)	44 (25.4)	17 (37.0)	3 (10.7)
Unknown	2 (1.4)	2 (1.4)	0	0	1 (3.6)
Other	15 (10.3)	15 (10.6)	18 (10.4)	5 (10.9)	2 (7.1)
Deaths within 30 days after the last dose	2 (1.4)	3 (2.1)	5 (2.9)	2 (4.3)	1 (3.6)
Adverse Event	1 (0.7)	1 (0.7)	4 (2.3)	1 (2.2)	1 (3.6)

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	AK105-304		AK105-302	AK105-301	AK105-205
	Penpulimab + GP (N=146)	Placebo + GP (N=142)	Penpulimab + TC (N=173)	Penpulimab + PC (N=46)	Penpulimab+ Chemo±Anlotinib (N=28)
Unknown	1 (0.7)	0	0	0	0
Other	0	2 (1.4)	1 (0.6)	1 (2.2)	0
Deaths within 30 to 90 days after the last dose	6 (4.1)	3 (2.1)	13 (7.5)	6 (13.0)	1 (3.6)
Adverse Event	1 (0.7)	0	1 (0.6)	1 (2.2)	1 (3.6)
Disease Progression	4 (2.7)	1 (0.7)	8 (4.6)	3 (6.5)	0
Other	1 (0.7)	2 (1.4)	4 (2.3)	2 (4.3)	0
Death after the last dose +90 days	40 (27.4)	42 (29.6)	50 (28.9)	16 (34.8)	6 (21.4)
Adverse Event	0	0	1 (0.6)	0	0
Disease Progression	25 (17.1)	29 (20.4)	36 (20.8)	14 (30.4)	3 (10.7)
Unknown	1 (0.7)	2 (1.4)	0	0	1 (3.6)
Other	14 (9.6)	11 (7.7)	13 (7.5)	2 (4.3)	2 (7.1)

Source: ADSL.xpt Module 5.3.5.3, Appendix 3.5, Table 10.1.2.

TEAEs leading to death are summarized by SOC and PT in Applicant – Table 20.

Applicant – Table 20 TEAEs Leading to Death by SOC and PT with Penpulimab Combination Therapy

	AK105-304		AK105-302	AK105-301	AK105-205
System Organ Class Preferred Term	Penpulimab + GP (N=146)	Placebo + GP (N=142)	Penpulimab + TC (N=173)	Penpulimab + PC (N=46)	Penpulimab+ Chemo±Anlotinib (N=28)
Number of Subjects with at Least One TEAE Leading to death	7 (4.8)	4 (2.8)	18 (10.4)	6 (13.0)	2 (7.1)
General disorders and administration site conditions	5 (3.4)	3 (2.1)	11 (6.4)	4 (8.7)	0
Disease progression	4 (2.7)	2 (1.4)	6 (3.5)	1 (2.2)	0
Death	1 (0.7)	1 (0.7)	5 (2.9)	2 (4.3)	0
Sudden death	0	0	0	1 (2.2)	0
Infections and infestations	1 (0.7)	0	2 (1.2)	0	1 (3.6)
COVID-19 pneumonia	1 (0.7)	0	0	0	0
Pneumonia	0	0	0	0	1 (3.6)
Sepsis	0	0	1 (0.6)	0	0
Septic shock	0	0	1 (0.6)	0	0
Neoplasms benign, malignant and unspecified (incl cysts and polyps)	0	1 (0.7)	2 (1.2)	0	0
Malignant neoplasm progression	0	0	2 (1.2)	0	0
Tumour haemorrhage	0	1 (0.7)	0	0	0
Respiratory, thoracic and mediastinal disorders	0	0	1 (0.6)	1 (2.2)	1 (3.6)
Haemoptysis	0	0	1 (0.6)	0	0
Pharyngeal haemorrhage	0	0	0	0	1 (3.6)
Respiratory failure	0	0	0	1 (2.2)	0
Cardiac disorders	1 (0.7)	0	1 (0.6)	0	0
Cardiac failure	1 (0.7)	0	0	0	0
Cardiopulmonary failure	0	0	1 (0.6)	0	0
Injury, poisoning and procedural complications	0	0	1 (0.6)	0	0
Fall	0	0	1 (0.6)	0	0
Nervous system disorders	0	0	0	1 (2.2)	0
Cerebrovascular accident	0	0	0	1 (2.2)	0

Disclaimer: In this document, the sections labeled as “Data” and “The Applicant’s Position” are completed by the Applicant and do not necessarily reflect the positions of the FDA.

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Source: [Module 5.3.5.3, ISS, Appendix 3.5, Table 4.15.2.](#)

The Applicant's Position:

Most death cases in the clinical studies were related to disease progression. This is consistent with patients' underlying medical conditions, and possibly concomitant medications. SAE Narratives are available for all patients and include all TEAEs leading to death.

The FDA's Assessment:

FDA reviewed all fatal adverse events in patients from the primary safety population in Studies AK105-304 and AK105-202. Based on this review, one patient (0.7%) in the investigational arm of Study AK105-304 experienced a Grade 5 adverse event that could be at least potentially related to penpulimab (due to syndrome of inappropriate antidiuretic hormone secretion).

Additionally, in the AK105-202 trial of penpulimab monotherapy, four patients (1%) had Grade 5 adverse events that were at least potentially related to penpulimab. Fatal adverse reactions included a case each of pneumonitis, septic shock, colitis, and hepatitis.

A summary of FDA's review of fatal adverse events in Study AK105-304 and Study AK105-202 is provided in the tables below.

FDA – Table 10. Assessment of Causality for Fatal Adverse Events Not Clearly Attributable to Disease Progression in Primary Safety Population in AK105-304

Patient ID	Brief Narrative	FDA/s Assessment of Causality	Included in USPI
(b) (6)	A 56-year-old Chinese man with recurrent NPC and metastases to the liver, lungs, and bone died 47 days after his last dose of penpulimab. Disease progression was noted on Day 288, but treatment continued due to perceived clinical benefit. The final dose was given on Day 321. On Day 478, he developed Grade 3 hyponatremia from SIADH and was hospitalized on Day 482. He was discharged at his request on Day 485 and died suddenly at home the next day. No autopsy was performed.	SIADH FDA considers this event as possibly related to penpulimab given the temporal relationship between the development of SIADH and study treatment.	Yes
(b) (6)	A 51-year-old Chinese man with recurrent NPC and bone metastases died on Day 247 of study therapy, 24 days after his last dose of penpulimab. He developed shortness of	Covid-19 pneumonia FDA considers the event unlikely to be related to	No

Patient ID	Brief Narrative	FDA/s Assessment of Causality	Included in USPI
	breath and fatigue on Day 226, which worsened with activity. A chest CT on Day 237 showed bilateral lung inflammation, pleural and pericardial effusions, and pleural thickening with adhesions. A total of 700 mL of pleural fluid was drained. He tested positive for COVID-19 on Day 244. Echocardiography showed reduced left ventricular motion, systolic dysfunction (EF 32%), restrictive diastolic dysfunction, and severe tricuspid and pulmonary regurgitation. He also had liver and kidney dysfunction, electrolyte imbalances, and coagulopathy. His condition deteriorated, and at the family's request, medical care was withdrawn on Day 247. He died at home that evening. No autopsy was performed. The investigator attributed the death to heart failure.	penpulimab and possibly related to heart failure and COVID-19 pneumonia.	
(b) (6)	A 67-year-old Chinese man with recurrent NPC and metastases to the liver, pelvic bone, and ribs died on Day 68 of treatment, 47 days after his last dose of penpulimab. He was hospitalized on Day 51 after being found unconscious and tested positive for COVID-19. Following supportive care, he regained consciousness. Chest CT revealed diffuse ground-glass opacities and consolidation in both lower lobes, suggestive of viral pneumonia. His condition worsened despite treatment, and he died on Day 68.	Covid-19 Pneumonia FDA considers this event unlikely related to penpulimab and likely related to Covid-19 infection.	No
(b) (6)	A 50-year-old Chinese man died at home on Day 104 of study therapy with penpulimab, 21 days after his last dose. Radiographic assessments at Weeks 6 and 12 showed stable disease. He was found deceased by his family, who expressed concern that the cause of death may have been suicide.	Death NOS FDA considers this event unlikely related to penpulimab.	No

FDA – Table 11. Assessment of Causality for Fatal Adverse Events Not Clearly Attributable to Disease Progression in Primary Safety Population in AK105-202

Patient ID	Brief Narrative	FDA/s Assessment of Causality	Included in USPI
(b) (6)	65-year-old female who on Day 598 of treatment fell on the floor at home and was bedridden. The patient was unable to stand and showed no response to voice. The patient died 73 days after the last dose of penpulimab. No autopsy was performed.	Fall The death occurred due to complications of the fall and is unlikely related to penpulimab.	No
(b) (6)	48-year-old male who was hospitalized 14 days after last dose of penpulimab with shortness of breath, hypoxia and imaging revealed pneumonitis. He was treated with steroids and antibiotics but died 41 days after last dose of penpulimab.	Pneumonitis The death occurred due to complications of pneumonitis and is likely related to penpulimab.	Yes
(b) (6)	A 31-year-old man was found to have Grade 2–3 pneumonitis with CT showing patchy lesions in the right upper and left lower lobes. A fungal smear revealed yeast-like organisms and Candida albicans. He was treated with antifungals, antibiotics, and glucocorticoids. Follow-up imaging showed new inflammation in the left lung, worsening right-sided pleural effusion, and recurrent pleural effusions. Subsequent CT scans revealed new infectious lesions, narrowing of the trachea and bronchi, and increased pericardial effusion. He was discharged with a diagnosis of septic shock and superior vena cava syndrome. The patient died 82 days after his last treatment dose.	Septic shock Penpulimab may have possibly contributed to the death.	Yes
(b) (6)	A 61-year-old patient died four days after receiving the fourth and final dose of penpulimab. On Day 3 post-dose, the patient was found deceased after a fall in the bathroom. No autopsy was performed. The investigator considered trauma as the likely cause of death.	Fall Given the lack of details around patient's death, penpulimab's contribution to death cannot be ruled out.	No

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Patient ID	Brief Narrative	FDA/s Assessment of Causality	Included in USPI
(b) (6)	A 52-year-old man died 43 days after his last dose of treatment following a car accident that resulted in multiple rib fractures and a ruptured spleen. He was discharged from the hospital but was found unconscious at home four days later. He was brought to the ER but died suddenly that same day. No autopsy was performed.	Trauma FDA considers this event unlikely due to penpulimab given the recent car accident.	No
(b) (6)	A 62-year-old man died 75 days after his last dose of penpulimab. He developed worsening diarrhea on Day 15 of treatment, chose to withdraw from the study, and declined further hospital follow-up.	Colitis FDA considers this event possibly related to penpulimab given the temporal relationship between colitis and death.	Yes
(b) (6)	A 60-year-old man died 48 days after his last dose of penpulimab. He experienced worsening Grade 2 hepatic dysfunction and was hospitalized for abnormal liver function tests. After discharge, he declined further treatment and follow-up. No autopsy was performed.	Hepatitis. FDA considers this event possibly related to penpulimab given the temporal relationship between hepatitis and death.	Yes

FDA – Table 12 below summarizes the fatal AEs and FDA’s determination of death causality.

FDA – Table 12. Summary of Study Deaths, Study AK105-304

	AK105-304	
	Penpulimab + Chemotherapy N=146 N (%)	Placebo + Chemotherapy N=142 N (%)
Total deaths	48 (33)	48 (34)
Death not due to an AE		
Disease progression	45 (31)	47 (33)
Death due to an AE	1 (0.7)	1(0.7)

Source: ADAE

Abbreviations: AE, adverse event

FDA – Table 13. Summary of Study Deaths for Penpulimab as a Single Agent, Study AK105-202 and Pooled Safety Dataset

	AK105-202 N=130 N (%)	Safety Pool N=372 N (%)
Total deaths	47 (36)	143 (38)
Cause of death		
Disease progression	40 (31)	132 (35)
Adverse event	7 (5.3)	11 (3.0)

Source: ADAE

8.2.4.2. Serious Adverse EventsData:***Monotherapy Part******NPC 200mg Q2W population***

31 patients (23.8%) experienced at least one SAE. Excluding death and disease progression, the most commonly (the incidence of PT $\geq$ 1%) reported SAEs included pneumonia, lung infection, respiratory failure, pneumonitis, hepatic function abnormal, and rash.

10 patients (7.7%) had SAEs that were deemed to be drug-related by the investigator. Excluding death and disease progression, pneumonitis and rash occurred in 2 patients each, while other PTs were reported in one patient each, including pneumonia, abdominal infection, herpes zoster disseminated, transaminases increased, pleural effusion, hepatic function abnormal and pemphigoid.

Penpulimab 200mg Q2W population

100 patients (26.9%) experienced at least one SAE. Excluding death and disease progression, the most commonly (the incidence of PT $\geq$ 1%) reported SAEs included pneumonia, lung infection and diarrhoea.

28 patients (7.5%) had SAEs that were deemed to be drug-related by the investigator. Excluding death and disease progression, pneumonia, alanine aminotransferase increased, transaminases increased, immune-mediated pneumonitis, pneumonitis, hepatic function abnormal and rash occurred in 2 patients each; other PTs were reported in one patient each, including lung infection, abdominal infection, herpes zoster, herpes zoster disseminated, aspartate aminotransferase increased, blood bilirubin increased, pleural effusion, pain, gastrointestinal haemorrhage, intestinal obstruction, pemphigoid, hypersensitivity, infusion related reaction, mesangioproliferative glomerulonephritis, renal injury and hypertension.

Overall Monotherapy Population

142 patients (25.4%) experienced at least one SAE. Excluding death and disease progression, the

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most commonly (the incidence of PT $\geq 1\%$) reported SAEs included pneumonia and lung infection.

42 patients (7.5%) had SAEs that were deemed to be drug-related by the investigator. Excluding death and disease progression, pneumonia, alanine aminotransferase increased, immune-mediated pneumonitis and hepatic function abnormal occurred in 3 patients each; other PTs were reported in one patient each, including abdominal infection, herpes zoster, herpes zoster disseminated, blood bilirubin increased, blood creatinine increased, platelet count decreased, pleural effusion, respiratory failure, Pain, immune-mediated hepatitis, gastrointestinal haemorrhage, intestinal obstruction, upper gastrointestinal haemorrhage, pemphigoid, anaphylactic shock, hypersensitivity, heart injury, infusion related reaction, diabetes mellitus, hyponatraemia, mesangioproliferative glomerulonephritis, renal injury, anaemia, hypophyinitis and hypertension.

SAEs in penpulimab monotherapy are summarized by SOC and PT in [Applicant – Table 21](#).

Applicant – Table 21 SAEs in Penpulimab Monotherapy (frequency $\geq 1\%$ in any population)

System Organ Class Preferred Term	NPC 200mg Q2W (N=130)	All Tumor Types 200mg Q2W			All Doses Total (N=558)
		Ex-Asia (N=83)	Asia (N=289)	Total (N=372)	
Number of Subjects with at Least One Serious TEAE	31 (23.8)	29 (34.9)	71 (24.6)	100 (26.9)	142 (25.4)
General disorders and administration site conditions	15 (11.5)	3 (3.6)	27 (9.3)	30 (8.1)	40 (7.2)
Disease progression	11 (8.5)	0	22 (7.6)	22 (5.9)	27 (4.8)
Death	3 (2.3)	0	3 (1.0)	3 (0.8)	7 (1.3)
Complication associated with device	0	1 (1.2)	0	1 (0.3)	1 (0.2)
Non-cardiac chest pain	0	1 (1.2)	0	1 (0.3)	1 (0.2)
Pyrexia	0	1 (1.2)	0	1 (0.3)	1 (0.2)
Infections and infestations	11 (8.5)	11 (13.3)	19 (6.6)	30 (8.1)	39 (7.0)
Pneumonia	2 (1.5)	1 (1.2)	5 (1.7)	6 (1.6)	9 (1.6)
Lung infection	3 (2.3)	0	5 (1.7)	5 (1.3)	6 (1.1)
Lower respiratory tract infection	0	3 (3.6)	0	3 (0.8)	4 (0.7)
Sepsis	0	2 (2.4)	1 (0.3)	3 (0.8)	3 (0.5)
Urinary tract infection	0	1 (1.2)	2 (0.7)	3 (0.8)	3 (0.5)
Bacteraemia	0	1 (1.2)	0	1 (0.3)	1 (0.2)
Biliary sepsis	0	1 (1.2)	0	1 (0.3)	1 (0.2)
Diverticulitis	0	1 (1.2)	0	1 (0.3)	1 (0.2)
Pelvic infection	0	1 (1.2)	0	1 (0.3)	1 (0.2)
Pneumocystis jirovecii pneumonia	0	1 (1.2)	0	1 (0.3)	1 (0.2)
Staphylococcal skin infection	0	1 (1.2)	0	1 (0.3)	1 (0.2)
Gastrointestinal disorders	1 (0.8)	14 (16.9)	7 (2.4)	21 (5.6)	24 (4.3)
Diarrhoea	0	4 (4.8)	0	4 (1.1)	5 (0.9)
Abdominal pain	0	3 (3.6)	0	3 (0.8)	4 (0.7)
Gastrointestinal haemorrhage	0	0	3 (1.0)	3 (0.8)	3 (0.5)
Vomiting	0	3 (3.6)	0	3 (0.8)	3 (0.5)
Ascites	0	1 (1.2)	1 (0.3)	2 (0.5)	2 (0.4)
Intestinal obstruction	0	1 (1.2)	0	1 (0.3)	2 (0.4)
Small intestinal obstruction	0	2 (2.4)	0	2 (0.5)	2 (0.4)
Abdominal pain lower	0	1 (1.2)	0	1 (0.3)	1 (0.2)
Colitis	0	1 (1.2)	0	1 (0.3)	1 (0.2)
Nausea	0	1 (1.2)	0	1 (0.3)	1 (0.2)
Obstruction gastric	0	1 (1.2)	0	1 (0.3)	1 (0.2)
Pancreatitis	0	1 (1.2)	0	1 (0.3)	1 (0.2)
Respiratory, thoracic and mediastinal disorders	4 (3.1)	2 (2.4)	10 (3.5)	12 (3.2)	18 (3.2)

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System Organ Class Preferred Term	NPC 200mg Q2W (N=130)	All Tumor Types 200mg Q2W			All Doses Total (N=558)
		Ex-Asia (N=83)	Asia (N=289)	Total (N=372)	
Respiratory failure	2 (1.5)	0	3 (1.0)	3 (0.8)	5 (0.9)
Pleural effusion	1 (0.8)	0	3 (1.0)	3 (0.8)	3 (0.5)
Pneumonitis	2 (1.5)	0	2 (0.7)	2 (0.5)	3 (0.5)
Asthma	0	1 (1.2)	0	1 (0.3)	1 (0.2)
Chronic obstructive pulmonary disease	0	1 (1.2)	0	1 (0.3)	1 (0.2)
Hepatobiliary disorders	4 (3.1)	2 (2.4)	6 (2.1)	8 (2.2)	12 (2.2)
Hepatic function abnormal	2 (1.5)	0	3 (1.0)	3 (0.8)	4 (0.7)
Cholangitis	0	1 (1.2)	0	1 (0.3)	1 (0.2)
Cholestasis	0	1 (1.2)	0	1 (0.3)	1 (0.2)
Injury, poisoning and procedural complications	3 (2.3)	1 (1.2)	5 (1.7)	6 (1.6)	8 (1.4)
Infusion related reaction	0	1 (1.2)	0	1 (0.3)	1 (0.2)
Metabolism and nutrition disorders	1 (0.8)	1 (1.2)	3 (1.0)	4 (1.1)	8 (1.4)
Dehydration	0	1 (1.2)	0	1 (0.3)	1 (0.2)
Nervous system disorders	1 (0.8)	3 (3.6)	3 (1.0)	6 (1.6)	8 (1.4)
Epilepsy	0	1 (1.2)	1 (0.3)	2 (0.5)	2 (0.4)
Cerebral infarction	0	1 (1.2)	0	1 (0.3)	1 (0.2)
Hemiparesis	0	1 (1.2)	0	1 (0.3)	1 (0.2)
Vascular disorders	1 (0.8)	2 (2.4)	2 (0.7)	4 (1.1)	5 (0.9)
Hypotension	0	1 (1.2)	0	1 (0.3)	2 (0.4)
Hypertension	0	1 (1.2)	0	1 (0.3)	1 (0.2)
Musculoskeletal and connective tissue disorders	1 (0.8)	2 (2.4)	2 (0.7)	4 (1.1)	4 (0.7)
Musculoskeletal pain	0	1 (1.2)	0	1 (0.3)	1 (0.2)
Pain in extremity	0	1 (1.2)	0	1 (0.3)	1 (0.2)
Renal and urinary disorders	0	1 (1.2)	3 (1.0)	4 (1.1)	4 (0.7)
Acute kidney injury	0	1 (1.2)	0	1 (0.3)	1 (0.2)
Skin and subcutaneous tissue disorders	3 (2.3)	0	3 (1.0)	3 (0.8)	4 (0.7)
Rash	2 (1.5)	0	2 (0.7)	2 (0.5)	2 (0.4)
Blood and lymphatic system disorders	1 (0.8)	1 (1.2)	1 (0.3)	2 (0.5)	3 (0.5)
Anaemia	0	1 (1.2)	0	1 (0.3)	2 (0.4)
Immune system disorders	0	1 (1.2)	1 (0.3)	2 (0.5)	3 (0.5)
Hypersensitivity	0	1 (1.2)	0	1 (0.3)	1 (0.2)
Psychiatric disorders	0	2 (2.4)	0	2 (0.5)	2 (0.4)
Delirium	0	1 (1.2)	0	1 (0.3)	1 (0.2)
Psychotic disorder	0	1 (1.2)	0	1 (0.3)	1 (0.2)

Source: ISS Combined Supplementary Tables, Table 4.11.1.

Combination Therapy Part

AK105-304

In patients treated with penpulimab 200mg Q3W in combination with cisplatin/carboplatin and gemcitabine in AK105-304, 74 patients (50.7%) experienced at least one SAE. Excluding disease progression, 73 patients (50.0%) experienced at least one SAE. The most commonly (the incidence of PT $\geq$ 1%) reported SAEs (excluding disease progression) included platelet count decreased, white blood cell count decreased, neutrophil count decreased, blood creatinine increased, anaemia, febrile neutropenia, myelosuppression, pneumonia, upper respiratory tract infection, COVID-19 pneumonia, urinary tract infection, asthenia, epistaxis, hyponatraemia, diabetic ketoacidosis, arrhythmia and nausea.

43 patients (29.5%) had SAEs that were deemed to be drug-related by the investigator, included:

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platelet count decreased occurred in 15 patients; neutrophil count decreased occurred in 11 patients; white blood cell count decreased occurred in 9 patients; anaemia occurred in 8 patients; pneumonia occurred in 3 patients; blood creatinine increased, arrhythmia, diabetic ketoacidosis, hyponatraemia and nausea occurred in 2 patients each. Other PTs were reported in one patient each, included creatinine renal clearance decreased, lipase increased, febrile neutropenia, myelosuppression, COVID-19 pneumonia, pulmonary tuberculosis, urinary tract infection, asthenia, disease progression, oedema peripheral, dyspnoea, organising pneumonia, pleural effusion, cardiac failure, acute myocardial infarction, palpitations, hypochloraemia, hypercalcaemia, hyperkalaemia, hypocalcaemia, hypokalaemia, pancreatitis, hepatic function abnormal, brain oedema, coma, dermatitis acneiform, arthritis, synovitis and hypersensitivity.

For the detailed description of each SAE, see [Module 5.3.5.3, ISS, Appendix 3.4, SAE Narratives for AK105](#).

SAEs in penpulimab combination therapy are summarized by SOC and PT in [Applicant – Table 22](#).

Applicant – Table 22 SAEs in Penpulimab Combination Therapy (frequency ≥ 1% in any population)

System Organ Class Preferred Term	AK105-304		AK105-302	AK105-301	AK105-205
	Penpulimab + GP (N=146)	Placebo + GP (N=142)	Penpulimab + TC (N=173)	Penpulimab + PC (N=46)	Penpulimab+ Chemo±Anlotinib (N=28)
Number of Subjects with at Least One Serious TEAE	74 (50.7)	69 (48.6)	57 (32.9)	18 (39.1)	10 (35.7)
Investigations	40 (27.4)	41 (28.9)	8 (4.6)	3 (6.5)	2 (7.1)
Platelet count decreased	28 (19.2)	30 (21.1)	1 (0.6)	3 (6.5)	1 (3.6)
White blood cell count decreased	18 (12.3)	16 (11.3)	1 (0.6)	0	1 (3.6)
Neutrophil count decreased	20 (13.7)	12 (8.5)	2 (1.2)	0	1 (3.6)
Alanine aminotransferase increased	1 (0.7)	3 (2.1)	1 (0.6)	0	0
Aspartate aminotransferase increased	0	2 (1.4)	2 (1.2)	0	0
Blood creatinine increased	2 (1.4)	0	0	0	0
Blood pressure increased	0	0	0	0	1 (3.6)
Blood and lymphatic system disorders	18 (12.3)	18 (12.7)	8 (4.6)	3 (6.5)	3 (10.7)
Anaemia	12 (8.2)	14 (9.9)	0	3 (6.5)	1 (3.6)
Febrile neutropenia	2 (1.4)	1 (0.7)	5 (2.9)	0	0
Myelosuppression	5 (3.4)	2 (1.4)	0	0	1 (3.6)
Bone marrow failure	0	0	2 (1.2)	0	0
Leukopenia	0	1 (0.7)	0	0	1 (3.6)
Infections and infestations	16 (11.0)	9 (6.3)	11 (6.4)	5 (10.9)	3 (10.7)
Pneumonia	3 (2.1)	4 (2.8)	4 (2.3)	0	2 (7.1)
Upper respiratory tract infection	2 (1.4)	2 (1.4)	0	1 (2.2)	0
COVID-19 pneumonia	4 (2.7)	0	0	0	0
Lung infection	0	0	2 (1.2)	2 (4.3)	0
COVID-19	1 (0.7)	2 (1.4)	0	0	0
Urinary tract infection	2 (1.4)	0	1 (0.6)	0	0
Infection	0	2 (1.4)	0	0	0
Lung abscess	0	0	0	1 (2.2)	0
Mucosal infection	0	0	0	0	1 (3.6)
Pneumonia bacterial	0	0	0	1 (2.2)	0

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System Organ Class Preferred Term	AK105-304		AK105-302	AK105-301	AK105-205
	Penpulimab + GP	Placebo + GP	Penpulimab + TC	Penpulimab + PC	Penpulimab+ Chemo±Anlotinib
	(N=146)	(N=142)	(N=173)	(N=46)	(N=28)
General disorders and administration site conditions	9 (6.2)	6 (4.2)	14 (8.1)	5 (10.9)	0
Disease progression	4 (2.7)	2 (1.4)	6 (3.5)	1 (2.2)	0
Death	1 (0.7)	1 (0.7)	5 (2.9)	2 (4.3)	0
Asthenia	2 (1.4)	1 (0.7)	2 (1.2)	0	0
Pyrexia	0	2 (1.4)	1 (0.6)	1 (2.2)	0
Sudden death	0	0	0	1 (2.2)	0
Respiratory, thoracic and mediastinal disorders	6 (4.1)	0	14 (8.1)	3 (6.5)	2 (7.1)
Immune-mediated pneumonitis	0	0	4 (2.3)	1 (2.2)	0
Haemoptysis	0	0	4 (2.3)	0	0
Epistaxis	2 (1.4)	0	0	0	0
Pharyngeal haemorrhage	0	0	0	0	2 (7.1)
Pleural effusion	1 (0.7)	0	0	1 (2.2)	0
Pneumonitis	0	0	2 (1.2)	0	0
Respiratory failure	0	0	1 (0.6)	1 (2.2)	0
Metabolism and nutrition disorders	8 (5.5)	2 (1.4)	7 (4.0)	0	1 (3.6)
Hyponatraemia	4 (2.7)	0	0	0	1 (3.6)
Decreased appetite	0	0	4 (2.3)	0	0
Diabetic ketoacidosis	2 (1.4)	0	1 (0.6)	0	0
Hypochloraemia	1 (0.7)	0	0	0	1 (3.6)
Hypophosphataemia	0	0	0	0	1 (3.6)
Cardiac disorders	5 (3.4)	0	4 (2.3)	4 (8.7)	0
Arrhythmia	2 (1.4)	0	1 (0.6)	1 (2.2)	0
Cardiac failure acute	0	0	0	1 (2.2)	0
Myocardial infarction	0	0	0	1 (2.2)	0
Pericardial effusion	0	0	0	1 (2.2)	0
Gastrointestinal disorders	5 (3.4)	3 (2.1)	1 (0.6)	2 (4.3)	1 (3.6)
Vomiting	1 (0.7)	3 (2.1)	0	0	0
Nausea	3 (2.1)	0	0	0	0
Diarrhoea	0	0	0	1 (2.2)	0
Ileus	0	0	0	1 (2.2)	0
Stomatitis	0	0	0	0	1 (3.6)
Nervous system disorders	2 (1.4)	8 (5.6)	1 (0.6)	1 (2.2)	0
Cerebral infarction	0	2 (1.4)	1 (0.6)	0	0
Spinal cord compression	0	2 (1.4)	0	0	0
Cerebrovascular accident	0	0	0	1 (2.2)	0
Hepatobiliary disorders	1 (0.7)	0	4 (2.3)	1 (2.2)	0
Hepatic function abnormal	1 (0.7)	0	3 (1.7)	0	0
Cholecystitis	0	0	0	1 (2.2)	0
Injury, poisoning and procedural complications	2 (1.4)	1 (0.7)	2 (1.2)	0	1 (3.6)
Tracheal haemorrhage	0	0	0	0	1 (3.6)
Neoplasms benign, malignant and unspecified (incl cysts and polyps)	1 (0.7)	2 (1.4)	2 (1.2)	0	0
Malignant neoplasm progression	0	0	2 (1.2)	0	0
Musculoskeletal and connective tissue disorders	1 (0.7)	0	2 (1.2)	0	0
Arthralgia	0	0	2 (1.2)	0	0
Renal and urinary disorders	1 (0.7)	1 (0.7)	0	1 (2.2)	0
Calculus urinary	0	0	0	1 (2.2)	0

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System Organ Class Preferred Term	AK105-304		AK105-302	AK105-301	AK105-205
	Penpulimab + GP (N=146)	Placebo + GP (N=142)	Penpulimab + TC (N=173)	Penpulimab + PC (N=46)	Penpulimab+ Chemo±Anlotinib (N=28)
Endocrine disorders	0	0	0	1 (2.2)	0
Hypophysitis	0	0	0	1 (2.2)	0

Source: [Module 5.3.5.3, ISS, Appendix 3.5, Table 4.11.2.](#)

The Applicant's Position:

The frequency and nature of SAEs were generally similar between the NPC penpulimab 200mg Q2W population, penpulimab 200mg Q2W population and the overall monotherapy population, and there were no clinically meaningful differences between these three monotherapy populations for any SAEs.

In the pivotal AK105-304 study, the incidence of SAEs in the penpulimab group was generally similar to that in the placebo group. No serious unexpected AEs were observed.

The FDA's Assessment:

When reviewing SAEs, FDA's process for grouping preferred terms resulted in slightly different percentages. In addition, the FDA included laboratory abnormalities in the review of SAEs.

In Study AK105-304, 51% of patients experienced an SAE. The most frequent serious adverse reactions ($\geq 2\%$) were thrombocytopenia (19%), decreased neutrophils (14%), decreased white blood cells (12%), anemia (8%), myelosuppression (3.4%), decreased sodium (2.7%), pneumonia (2.1%), and nausea (2.1%).

In Study AK105-202, 22% of patients in the NPC population and 27% of patients in the pooled safety dataset had one or more SAEs. The most frequent SAEs ($\geq 1\%$) included pneumonia, pneumonitis, respiratory failure, and rash.

FDA – Table 14. Serious Adverse Events (SAEs) Occurring in 1% or More Patients Treated With Penpulimab and Chemotherapy, AK105-304 Trial

SAE	Penpulimab + Chemotherapy	
	N=146 n (%)	
	All Grade	Grade 3-4
Any	74 (51)	57 (39)
Platelet count decreased	28 (19)	21 (14)
Neutrophil count decreased	20 (14)	15 (10)
White blood cell count decreased	18 (12)	12 (8)
Blood creatinine increased	2 (1.4)	0
Anemia	12 (8)	11 (8)
Myelosuppression	5 (3.4)	3 (2.1)

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SAE	Penpulimab + Chemotherapy	
	N=146 n (%)	
	All Grade	Grade 3-4
Febrile neutropenia	2 (1.4)	2 (1.4)
COVID-19 pneumonia	4 (2.7)	2 (1.4)
Pneumonia	3 (2.1)	2 (1.4)
Upper respiratory tract infection	2 (1.4)	2 (1.4)
Urinary tract infection	2 (1.4)	1 (0.7)
Disease progression	4 (2.7)	0
Fatigue (GT)	2 (1.4)	2 (1.4)
Hyponatremia	4 (2.7)	4 (2.7)
Diabetic ketoacidosis	2 (1.4)	2 (1.4)
Arrhythmia	2 (1.4)	0
Nausea	3 (2.1)	2 (1.4)
Acute kidney injury (GT)	2 (1.4)	2 (1.4)
Hemorrhage (GT)	2 (1.4)	2 (1.4)

Source: ADAE

Fatigue includes: Fatigue and asthenia.

Acute kidney injury includes: acute kidney injury and Creatinine renal clearance decreased.

Hemorrhage includes: Epistaxis and tumor hemorrhage.

Abbreviations: GT - grouped term

FDA – Table 15. Serious Adverse Events (SAEs) Occurring in 1% or More Patients Treated With Penpulimab Monotherapy, AK105-202 Trial

SAE	AK105-202		Safety Pool
	N=130 n (%)		N=372 n (%)
	Any Grade	Grade 3-4	All Grade
Any	29 (22)	7 (5)	100 (27)
Disease progression	11 (8)	0	22 (6)
Death	3 (2.3)	0	3 (0.8)
Pneumonia (GT)	5 (3.8)	3 (2.3)	11 (3.0)
Pneumonitis	2 (1.5)	1 (0.8)	2 (0.5)
Respiratory failure	2 (1.5)	0	3 (0.8)
Rash	2 (1.5)	2 (1.5)	2 (0.5)
Diarrhea	NA	NA	4 (1.1)

Source: ADAE

Pneumonia includes: Pneumonia and lung infection

8.2.4.3. Dropouts and/or Discontinuations Due to Adverse Effects

Data:

The main reason for treatment discontinuation was radiographic disease progression.

Applicant – Table 23 Summary of Treatment Discontinuation for Single Arm Studies

	AK105-101 (N=100)	AK105-201 (N=94)	AK105-202 (N=130)	AK105-204 (N=65)	AK105-205 (N=28)
Treatment discontinuation, n (%)	80 (78.43)	56 (59.57)	106 (81.54)	65 (100.00)	28 (100.00)
Radiographic disease progression	63 (61.76)	27 (28.72)	74 (56.92)	43 (66.15)	12 (42.86)
Symptomatic deterioration without radiographic evidence	0	0	3 (2.31)	2 (3.08)	0
Maximum treatment cycles reached	0	15 (15.96)	0	0	7 (25.00)
Subject request	8 (7.84)	3 (3.19)	4 (3.08)	7 (10.77)	2 (7.14)
Adverse event	4 (3.92)	4 (4.26)	6 (4.62)	5 (7.69)	0
Death	4 (3.92)	0	4 (3.08)	0	1 (3.57)
Start new cancer therapy	0	1 (1.06)	1 (0.77)	3 (4.62)	1 (3.57)
Lost to follow-up	0	0	2 (1.54)	0	0
Study terminated by sponsor	0	0	0	0	3 (10.71)
Other	1 (0.98)	6 (6.38)	12 (9.23)	5 (7.69)	2 (7.14)

Applicant – Table 24 Summary of Treatment Discontinuation for Controlled Studies

	AK105-304		AK105-301		AK105-302	
	Penpulimab Group (N=144)	Placebo Group (N=147)	Penpulimab Group (N=46)	Placebo Group (N=23)	Penpulimab Group (N=175)	Placebo Group (N=175)
Treatment discontinuation, n (%)	124 (86.11)	135 (91.84)	45 (97.83)	23 (100.00)	153 (87.43)	168 (96.00)
Radiographic disease progression	62 (43.06)	104 (70.75)	20 (43.48)	12 (52.17)	72 (41.14)	69 (39.43)
After radiographic disease progression, can't benefit from therapy evaluated by investigator					11 (6.29)	36 (20.57)
Symptomatic deterioration without radiographic evidence	2 (1.39)	3 (2.04)	0	1 (4.35)	1 (0.57)	0
Maximum treatment cycles reached	14 (9.72)	3 (2.04)	4 (8.70)	0	21 (12.00)	4 (2.29)
Subject request	18 (12.50)	10 (6.80)	4 (8.70)	1 (4.35)	1 (0.57)	2 (1.14)
Adverse event	5 (3.47)	2 (1.36)	2 (4.35)	0	8 (4.57)	9 (5.14)
Death	5 (3.47)	2 (1.36)	5 (10.87)	1 (4.35)	7 (4.00)	11 (6.29)
Start new cancer therapy	8 (5.56)	1 (0.68)	1 (2.17)	2 (8.70)	0	1 (0.57)
Lost to follow-up	0	0	2 (4.35)	1 (4.35)	1 (0.57)	1 (0.57)
Investigator decision	3 (2.08)	6 (4.08)	4 (8.70)	4 (17.39)	18 (10.29)	13 (7.43)
Other	7 (4.86)	4 (2.72)	3 (6.52)	1 (4.35)	13 (7.43)	22 (12.57)

Monotherapy Part**NPC 200mg Q2W population**

5 (3.8%) patients experienced at least one TEAE leading to drug discontinuation. Drug-related AEs leading to drug discontinuation occurred in 4 (3.1%) patients. Drug-related AEs leading to drug discontinuation included pleural effusion, herpes zoster disseminated, pemphigoid and transaminases increased (1 patient each).

Penpulimab 200mg Q2W population

22 (5.9%) patients experienced at least one TEAE leading to drug discontinuation. Drug-related AEs leading to drug discontinuation occurred in 11 (3.0%) patients. Drug-related AEs leading to drug discontinuation included immune-mediated pneumonitis, pleural effusion, hypersensitivity,

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herpes zoster disseminated, mesangioproliferative glomerulonephritis, renal injury, pemphigoid, gastrointestinal haemorrhage and transaminases increased.

Overall Monotherapy Population

32 (5.7%) patients experienced at least one TEAE leading to drug discontinuation. Drug-related AEs leading to drug discontinuation occurred in 20 (3.6%) patients. Drug-related AEs leading to drug discontinuation included immune-mediated pneumonitis (0.7%), dyspnoea (0.4%), pleural effusion (0.2%), hepatic function abnormal (0.2%), immune-mediated hepatitis (0.2%), anaphylactic shock (0.2%), hypersensitivity (0.2%), herpes zoster disseminated (0.2%), lung infection (0.2%), mesangioproliferative glomerulonephritis (0.2%), renal injury (0.2%), immune-mediated dermatitis (0.2%), pemphigoid (0.2%), gastrointestinal haemorrhage (0.2%), heart injury (0.2%) and transaminases increased (0.2%).

Applicant – Table 25 AEs Leading to Permanent Discontinuation in Trials with Penpulimab Monotherapy

System Organ Class Preferred Term	NPC 200mg Q2W (N=130)	All Tumor Types 200mg Q2W Ex-Asia (N=83)	Asia (N=289)	Total (N=372)	All Doses Total (N=558)
Number of Subjects with at Least One TEAE Leading to Drug discontinuation	5 (3.8)	5 (6.0)	17 (5.9)	22 (5.9)	32 (5.7)
Respiratory, thoracic and mediastinal disorders	1 (0.8)	0	5 (1.7)	5 (1.3)	8 (1.4)
Immune-mediated pneumonitis	0	0	3 (1.0)	3 (0.8)	4 (0.7)
Dyspnoea	0	0	0	0	2 (0.4)
Pleural effusion	1 (0.8)	0	2 (0.7)	2 (0.5)	2 (0.4)
Gastrointestinal disorders	0	1 (1.2)	3 (1.0)	4 (1.1)	4 (0.7)
Gastrointestinal haemorrhage	0	0	2 (0.7)	2 (0.5)	2 (0.4)
Ascites	0	0	1 (0.3)	1 (0.3)	1 (0.2)
Colitis	0	1 (1.2)	0	1 (0.3)	1 (0.2)
Infections and infestations	1 (0.8)	1 (1.2)	2 (0.7)	3 (0.8)	4 (0.7)
Herpes zoster disseminated	1 (0.8)	0	1 (0.3)	1 (0.3)	1 (0.2)
Lung infection	0	0	0	0	1 (0.2)
Pelvic infection	0	1 (1.2)	0	1 (0.3)	1 (0.2)
Septic shock	0	0	1 (0.3)	1 (0.3)	1 (0.2)
Hepatobiliary disorders	0	1 (1.2)	0	1 (0.3)	3 (0.5)
Cholangitis	0	1 (1.2)	0	1 (0.3)	1 (0.2)
Hepatic function abnormal	0	0	0	0	1 (0.2)
Immune-mediated hepatitis	0	0	0	0	1 (0.2)
Immune system disorders	0	1 (1.2)	1 (0.3)	2 (0.5)	3 (0.5)
Anaphylactic shock	0	0	0	0	1 (0.2)
Haemophagocytic lymphohistiocytosis	0	0	1 (0.3)	1 (0.3)	1 (0.2)
Hypersensitivity	0	1 (1.2)	0	1 (0.3)	1 (0.2)
Nervous system disorders	1 (0.8)	1 (1.2)	2 (0.7)	3 (0.8)	3 (0.5)
Cerebral infarction	0	1 (1.2)	0	1 (0.3)	1 (0.2)
Epilepsy	0	0	1 (0.3)	1 (0.3)	1 (0.2)
Spinal cord compression	1 (0.8)	0	1 (0.3)	1 (0.3)	1 (0.2)
Renal and urinary disorders	0	0	2 (0.7)	2 (0.5)	2 (0.4)
Mesangioproliferative glomerulonephritis	0	0	1 (0.3)	1 (0.3)	1 (0.2)
Renal injury	0	0	1 (0.3)	1 (0.3)	1 (0.2)
Skin and subcutaneous tissue disorders	1 (0.8)	0	1 (0.3)	1 (0.3)	2 (0.4)
Immune-mediated dermatitis	0	0	0	0	1 (0.2)
Pemphigoid	1 (0.8)	0	1 (0.3)	1 (0.3)	1 (0.2)

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System Organ Class Preferred Term	NPC 200mg Q2W (N=130)	All Tumor Types 200mg Q2W			All Doses Total (N=558)
		Ex-Asia (N=83)	Asia (N=289)	Total (N=372)	
Injury, poisoning and procedural complications	0	0	0	0	1 (0.2)
Heart injury	0	0	0	0	1 (0.2)
Investigations	1 (0.8)	0	1 (0.3)	1 (0.3)	1 (0.2)
Transaminases increased	1 (0.8)	0	1 (0.3)	1 (0.3)	1 (0.2)
Neoplasms benign, malignant and unspecified (incl cysts and polyps)	0	0	0	0	1 (0.2)
Tongue neoplasm malignant stage unspecified	0	0	0	0	1 (0.2)

Source: ISS Combined Supplementary Tables, Table 4.21.1.

Combination Therapy Part

In Combination Therapy Part, the incidence of AEs leading to permanent discontinuation in study drug arms was 3.4% (5/146) in AK105-304, 5.2% (9/173) in AK105-302, 8.7% (4/46) in AK105-301 and 3.6% (1/28) in AK105-205, respectively. Drug-related AE leading to permanent discontinuation occurred in 4 (2.7%), 8 (4.6%), 4 (8.7%) and 0 patients in the above 4 studies, respectively.

Applicant – Table 26 AEs Leading to Permanent Discontinuation in Trials with Penpulimab Combination Therapy

System Organ Class Preferred Term	AK105-304		AK105-302	AK105-301	AK105-205
	Penpulimab + GP (N=146)	Placebo + GP (N=142)	Penpulimab + TC (N=173)	Penpulimab + PC (N=46)	Penpulimab+ Chemo±Anlotinib (N=28)
Number of Subjects with at Least One TEAE Leading to Drug discontinuation	5 (3.4)	2 (1.4)	9 (5.2)	4 (8.7)	1 (3.6)
Respiratory, thoracic and mediastinal disorders	0	0	3 (1.7)	1 (2.2)	1 (3.6)
Immune-mediated pneumonitis	0	0	2 (1.2)	1 (2.2)	0
Interstitial lung disease	0	0	1 (0.6)	0	0
Pharyngeal haemorrhage	0	0	0	0	1 (3.6)
Hepatobiliary disorders	0	0	3 (1.7)	0	0
Hepatic function abnormal	0	0	2 (1.2)	0	0
Immune-mediated hepatitis	0	0	1 (0.6)	0	0
Investigations	2 (1.4)	0	0	0	0
Lipase increased	1 (0.7)	0	0	0	0
Platelet count decreased	1 (0.7)	0	0	0	0
Metabolism and nutrition disorders	1 (0.7)	0	0	1 (2.2)	0
Decreased appetite	0	0	0	1 (2.2)	0
Diabetic ketoacidosis	1 (0.7)	0	0	0	0
Hyperkalaemia	1 (0.7)	0	0	0	0
Nervous system disorders	1 (0.7)	1 (0.7)	0	0	0
Brain oedema	1 (0.7)	0	0	0	0
Cerebral infarction	0	1 (0.7)	0	0	0
Blood and lymphatic system disorders	0	0	1 (0.6)	0	0
Bone marrow failure	0	0	1 (0.6)	0	0
Cardiac disorders	1 (0.7)	0	0	0	0
Acute myocardial infarction	1 (0.7)	0	0	0	0
Gastrointestinal disorders	0	0	0	1 (2.2)	0
Diarrhoea	0	0	0	1 (2.2)	0
General disorders and administration site conditions	0	0	0	1 (2.2)	0

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System Organ Class Preferred Term	AK105-304		AK105-302	AK105-301	AK105-205
	Penpulimab + GP	Placebo + GP	Penpulimab + TC	Penpulimab + PC	Penpulimab+ Chemo±Anlotinib
	(N=146)	(N=142)	(N=173)	(N=46)	(N=28)
Death	0	0	0	1 (2.2)	0
Musculoskeletal and connective tissue disorders	0	0	1 (0.6)	0	0
Pain in extremity	0	0	1 (0.6)	0	0
Neoplasms benign, malignant and unspecified (incl cysts and polyps)	0	1 (0.7)	0	0	0
Lung neoplasm malignant	0	1 (0.7)	0	0	0
Renal and urinary disorders	1 (0.7)	0	0	0	0
Acute kidney injury	1 (0.7)	0	0	0	0
Skin and subcutaneous tissue disorders	0	0	1 (0.6)	0	0
Pruritus	0	0	1 (0.6)	0	0
Vascular disorders	0	0	1 (0.6)	0	0
Aortic dissection	0	0	1 (0.6)	0	0

Source: [Module 5.3.5.3, ISS, Appendix 3.5, Table 4.21.2.](#)

The Applicant's Position:

The incidence of AEs resulting in permanent discontinuation of penpulimab was low and similar between the NPC penpulimab 200mg Q2W population, penpulimab 200mg Q2W population and the overall monotherapy population. There were no appreciable differences between the three populations for any of the SOC or PTs.

In the pivotal AK105-304 study, the incidence of AEs resulting in permanent discontinuation of penpulimab/placebo in the penpulimab group was slightly higher than that in the placebo group.

AEs resulting in discontinuation of penpulimab were distributed across a broad range of PTs, with no specific SOC or PT accounting for most of the events (occurred in ≤1% of patients).

The FDA's Assessment:

In Study AK105-304, 3.4% of patients discontinued penpulimab due to AEs. Rates of discontinuation were similar between the penpulimab and placebo arms.

In Study AK105-202, 3.8% of patients discontinued penpulimab due to AEs. The FDA estimates of penpulimab discontinuation due to AEs generally aligned with Applicant's estimates.

In the pooled safety dataset, 6% of patients discontinued penpulimab due to AEs.

AEs leading to permanent discontinuation of penpulimab are listed in [FDA – Table 16](#) and [FDA – Table 17](#) below.

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FDA – Table 16. TEAEs Leading to Permanent Discontinuation in Patients Receiving Penpulimab or Placebo + Chemotherapy in Study AK105-304

TEAE	AK105-304			
	Penpulimab + Chemotherapy		Placebo + Chemotherapy	
	N=146 n (%)		N=142 n (%)	
	All Grade	Grade 3-4	All Grade	Grade 3-4
Any TEAE	5 (3.4)	5 (3.4)	2 (1.4)	1 (0.7)
Acute myocardial infarction	1 (0.7)	1 (0.7)	0	0
Acute kidney injury	1 (0.7)	1 (0.7)	0	0
Brain edema	1 (0.7)	1 (0.7)	0	0
Diabetic ketoacidosis	1 (0.7)	1 (0.7)	0	0
Hyperkalemia	1 (0.7)	1 (0.7)	0	0
Lipase increased	1 (0.7)	1 (0.7)	0	0
Platelet count decreased	1 (0.7)	1 (0.7)	0	0
Lung neoplasm malignant	0	0	1 (0.7)	1 (0.7)
Cerebral infarction	0	0	1 (0.7)	0

Source: ADAE

Abbreviations: TEAE, treatment-emergent adverse event

FDA – Table 17. TEAEs Leading to Permanent Discontinuation in Patients Receiving Penpulimab Monotherapy in Study AK105-202 and the Pooled Safety Dataset

TEAE	AK105-202 N=130 n (%)		Pooled Safety Set N=372 n (%)
	All Grade	Grade 3-4	All Grade
Any TEAE	5 (3.8)	5 (3.8)	22 (5.9)
Herpes zoster disseminated	1 (0.8)	1 (0.8)	1 (0.3)
Pleural effusion	1 (0.8)	1 (0.8)	2 (0.5)
Rash	1 (0.8)	1 (0.8)	1 (0.3)
Spinal cord compression	1 (0.8)	1 (0.8)	1 (0.3)
Transaminases increased	1 (0.8)	1 (0.8)	1 (0.3)
Immune-mediated pneumonitis	0	0	3 (0.8)
GI hemorrhage	0	0	2 (0.5)
Ascites	0	0	1 (0.3)
Colitis	0	0	1 (0.3)
Pelvic infection	0	0	1 (0.3)
Septic Shock	0	0	1 (0.3)
Cholangitis	0	0	1 (0.3)
Hemophagocytic lymphohistiocytosis	0	0	1 (0.3)
Hypersensitivity	0	0	1 (0.3)
Cerebral infarction	0	0	1 (0.3)
Epilepsy	0	0	1 (0.3)
Mesangioproliferative glomerulonephritis	0	0	1 (0.3)
Renal injury	0	0	1 (0.3)

Source: ADAE

Abbreviations: TEAE, treatment-emergent adverse event

8.2.4.4. Dose Interruptions, Delays, and/or Reductions Due to Adverse EffectsData:**Monotherapy Part****NPC 200mg Q2W population**

35 (26.9%) patients experienced at least one AE leading to drug interruption. Drug-related AEs leading to drug interruption occurred in 20 (15.4%) patients. Common drug-related AEs leading to drug interruption (with an incidence of $\geq 1\%$) included alanine aminotransferase increased, hypothyroidism, rash, hepatic function abnormal and anaemia.

Penpulimab 200mg Q2W population

95 (25.5%) patients experienced at least one AE leading to drug interruption. Drug-related AEs leading to drug interruption occurred in 55 (14.8%) patients. Common drug-related AEs leading

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to drug interruption (with an incidence of $\geq 1\%$) included alanine aminotransferase increased, hypothyroidism, rash and hepatic function abnormal.

Overall Monotherapy Population

130 (23.3%) patients experienced at least one AE leading to drug interruption. Drug-related AEs leading to drug interruption occurred in 75 (13.4%) patients. Common drug-related AEs leading to drug interruption (with an incidence of $\geq 1\%$) included alanine aminotransferase increased (1.8%), aspartate aminotransferase increased (1.3%), hypothyroidism (1.3%) and hepatic function abnormal (1.1%).

Applicant – Table 27 AEs Leading to Drug Interruption in Trials with Penpulimab Monotherapy (frequency $\geq 1\%$ in any population)

System Organ Class Preferred Term	NPC 200mg Q2W (N=130)	All Tumor Types 200mg Q2W Ex-Asia (N=83)	Asia (N=289)	Total (N=372)	All Doses Total (N=558)
Number of Subjects with at Least One TEAE Leading to Drug interruption	35 (26.9)	20 (24.1)	75 (26.0)	95 (25.5)	130 (23.3)
Investigations	5 (3.8)	4 (4.8)	15 (5.2)	19 (5.1)	28 (5.0)
Alanine aminotransferase increased	2 (1.5)	2 (2.4)	7 (2.4)	9 (2.4)	12 (2.2)
Aspartate aminotransferase increased	0	2 (2.4)	3 (1.0)	5 (1.3)	9 (1.6)
Amylase increased	0	1 (1.2)	0	1 (0.3)	1 (0.2)
Gamma-glutamyltransferase increased	0	1 (1.2)	0	1 (0.3)	1 (0.2)
Liver function test abnormal	0	1 (1.2)	0	1 (0.3)	1 (0.2)
Infections and infestations	6 (4.6)	2 (2.4)	16 (5.5)	18 (4.8)	26 (4.7)
Pneumonia	1 (0.8)	0	3 (1.0)	3 (0.8)	6 (1.1)
Lung infection	3 (2.3)	0	4 (1.4)	4 (1.1)	4 (0.7)
Sepsis	0	1 (1.2)	1 (0.3)	2 (0.5)	2 (0.4)
Diverticulitis	0	1 (1.2)	0	1 (0.3)	1 (0.2)
Gastrointestinal disorders	0	6 (7.2)	5 (1.7)	11 (3.0)	15 (2.7)
Diarrhoea	0	4 (4.8)	2 (0.7)	6 (1.6)	7 (1.3)
Autoimmune colitis	0	1 (1.2)	0	1 (0.3)	1 (0.2)
Intestinal obstruction	0	1 (1.2)	0	1 (0.3)	1 (0.2)
Small intestinal obstruction	0	1 (1.2)	0	1 (0.3)	1 (0.2)
Hepatobiliary disorders	5 (3.8)	0	9 (3.1)	9 (2.4)	13 (2.3)
Hepatic function abnormal	3 (2.3)	0	5 (1.7)	5 (1.3)	7 (1.3)
Liver injury	2 (1.5)	0	3 (1.0)	3 (0.8)	3 (0.5)
Injury, poisoning and procedural complications	5 (3.8)	1 (1.2)	8 (2.8)	9 (2.4)	11 (2.0)
Infusion related reaction	0	1 (1.2)	1 (0.3)	2 (0.5)	2 (0.4)
Blood and lymphatic system disorders	5 (3.8)	1 (1.2)	7 (2.4)	8 (2.2)	10 (1.8)
Anaemia	4 (3.1)	1 (1.2)	4 (1.4)	5 (1.3)	7 (1.3)
Leukopenia	1 (0.8)	0	3 (1.0)	3 (0.8)	3 (0.5)
Endocrine disorders	5 (3.8)	0	9 (3.1)	9 (2.4)	10 (1.8)
Hypothyroidism	4 (3.1)	0	7 (2.4)	7 (1.9)	8 (1.4)
General disorders and administration site conditions	1 (0.8)	3 (3.6)	3 (1.0)	6 (1.6)	10 (1.8)
Fatigue	0	1 (1.2)	1 (0.3)	2 (0.5)	3 (0.5)
Non-cardiac chest pain	0	2 (2.4)	0	2 (0.5)	2 (0.4)
Metabolism and nutrition disorders	3 (2.3)	1 (1.2)	6 (2.1)	7 (1.9)	10 (1.8)
Hypercalcaemia	0	1 (1.2)	0	1 (0.3)	1 (0.2)
Skin and subcutaneous tissue disorders	3 (2.3)	0	8 (2.8)	8 (2.2)	9 (1.6)
Rash	2 (1.5)	0	4 (1.4)	4 (1.1)	4 (0.7)
Respiratory, thoracic and mediastinal disorders	1 (0.8)	2 (2.4)	1 (0.3)	3 (0.8)	7 (1.3)
Dyspnoea	0	1 (1.2)	0	1 (0.3)	2 (0.4)

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System Organ Class Preferred Term	NPC 200mg Q2W (N=130)	All Tumor Types 200mg Q2W			All Doses Total (N=558)
		Ex-Asia (N=83)	Asia (N=289)	Total (N=372)	
Asthma	0	1 (1.2)	0	1 (0.3)	1 (0.2)
Musculoskeletal and connective tissue disorders	3 (2.3)	2 (2.4)	4 (1.4)	6 (1.6)	6 (1.1)
Arthralgia	0	1 (1.2)	0	1 (0.3)	1 (0.2)
Pain in extremity	0	1 (1.2)	0	1 (0.3)	1 (0.2)
Renal and urinary disorders	0	2 (2.4)	2 (0.7)	4 (1.1)	4 (0.7)
Proteinuria	0	1 (1.2)	1 (0.3)	2 (0.5)	2 (0.4)
Acute kidney injury	0	1 (1.2)	0	1 (0.3)	1 (0.2)
Vascular disorders	0	2 (2.4)	0	2 (0.5)	2 (0.4)
Hot flush	0	1 (1.2)	0	1 (0.3)	1 (0.2)
Hypotension	0	1 (1.2)	0	1 (0.3)	1 (0.2)
Psychiatric disorders	0	1 (1.2)	0	1 (0.3)	1 (0.2)
Depression	0	1 (1.2)	0	1 (0.3)	1 (0.2)

Source: ISS Combined Supplementary Tables, Table 4.17.1.

Combination Therapy Part

In Combination Therapy Part, the incidence of AE leading to drug interruption in study drug arms was 64.4% (94/146) in AK105-304, 35.3% (61/173) in AK105-302, 43.5% (20/46) in AK105-301 and 46.4% (13/28) in AK105-205, respectively. Drug-related AE leading to drug interruption occurred in 52 (35.6%), 41 (23.7%), 12 (26.1%) and 2 (7.1%) patients in the above mentioned four trials, respectively.

Applicant – Table 28 AEs Leading to Drug Interruption in Trials with Penpulimab Combination Therapy (frequency ≥ 1% in any population)

System Organ Class Preferred Term	AK105-304		AK105-302	AK105-301	AK105-205
	Penpulimab + GP (N=146)	Placebo + GP (N=142)	Penpulimab + TC (N=173)	Penpulimab + PC (N=46)	Penpulimab+ Chemo±Anlotinib (N=28)
Number of Subjects with at Least One TEAE Leading to Drug interruption	94 (64.4)	84 (59.2)	61 (35.3)	20 (43.5)	13 (46.4)
Investigations	42 (28.8)	47 (33.1)	23 (13.3)	6 (13.0)	8 (28.6)
Platelet count decreased	21 (14.4)	26 (18.3)	11 (6.4)	3 (6.5)	5 (17.9)
White blood cell count decreased	20 (13.7)	18 (12.7)	3 (1.7)	2 (4.3)	5 (17.9)
Neutrophil count decreased	15 (10.3)	22 (15.5)	3 (1.7)	2 (4.3)	3 (10.7)
Alanine aminotransferase increased	5 (3.4)	1 (0.7)	6 (3.5)	0	0
Aspartate aminotransferase increased	4 (2.7)	0	7 (4.0)	0	0
Blood creatinine increased	4 (2.7)	4 (2.8)	1 (0.6)	1 (2.2)	0
Granulocyte count decreased	0	0	1 (0.6)	0	1 (3.6)
Infections and infestations	44 (30.1)	34 (23.9)	10 (5.8)	5 (10.9)	5 (17.9)
COVID-19	24 (16.4)	17 (12.0)	0	0	3 (10.7)
Pneumonia	6 (4.1)	4 (2.8)	5 (2.9)	0	2 (7.1)
Asymptomatic COVID-19	4 (2.7)	7 (4.9)	0	0	0
COVID-19 pneumonia	8 (5.5)	1 (0.7)	0	0	0
Upper respiratory tract infection	3 (2.1)	2 (1.4)	2 (1.2)	1 (2.2)	0
Lung infection	0	0	1 (0.6)	2 (4.3)	0
H1N1 influenza	2 (1.4)	0	0	0	0
Lung abscess	0	0	0	1 (2.2)	0
Mucosal infection	0	0	0	0	1 (3.6)
Nasopharyngitis	0	0	0	1 (2.2)	0

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System Organ Class Preferred Term	AK105-304		AK105-302	AK105-301	AK105-205
	Penpulimab	Placebo +	Penpulimab	Penpulimab	Penpulimab+
	+ GP (N=146)	GP (N=142)	+ TC (N=173)	+ PC (N=46)	Chemo±Anlotinib (N=28)
Blood and lymphatic system disorders	27 (18.5)	29 (20.4)	3 (1.7)	4 (8.7)	1 (3.6)
Anaemia	23 (15.8)	25 (17.6)	2 (1.2)	4 (8.7)	1 (3.6)
Leukopenia	1 (0.7)	3 (2.1)	0	0	0
Myelosuppression	2 (1.4)	1 (0.7)	0	0	0
Neutropenia	2 (1.4)	1 (0.7)	0	0	0
General disorders and administration site conditions	5 (3.4)	7 (4.9)	9 (5.2)	1 (2.2)	1 (3.6)
Pyrexia	3 (2.1)	4 (2.8)	2 (1.2)	0	0
Asthenia	0	1 (0.7)	5 (2.9)	0	1 (3.6)
Chest discomfort	0	1 (0.7)	0	0	1 (3.6)
Malaise	0	0	1 (0.6)	1 (2.2)	0
Respiratory, thoracic and mediastinal disorders	5 (3.4)	2 (1.4)	9 (5.2)	2 (4.3)	1 (3.6)
Immune-mediated pneumonitis	0	0	4 (2.3)	0	0
Epistaxis	2 (1.4)	0	0	0	0
Pleural effusion	1 (0.7)	0	0	1 (2.2)	0
Productive cough	1 (0.7)	0	0	1 (2.2)	0
Pharyngeal haemorrhage	0	0	0	0	1 (3.6)
Gastrointestinal disorders	5 (3.4)	1 (0.7)	1 (0.6)	5 (10.9)	2 (7.1)
Diarrhoea	2 (1.4)	0	0	1 (2.2)	1 (3.6)
Vomiting	1 (0.7)	1 (0.7)	0	1 (2.2)	0
Abdominal pain upper	0	0	0	1 (2.2)	0
Flatulence	0	0	0	1 (2.2)	0
Gastric haemorrhage	0	0	0	1 (2.2)	0
Ileus	0	0	0	1 (2.2)	0
Stomatitis	0	0	0	0	1 (3.6)
Metabolism and nutrition disorders	6 (4.1)	0	7 (4.0)	0	1 (3.6)
Hyponatraemia	4 (2.7)	0	0	0	1 (3.6)
Decreased appetite	0	0	3 (1.7)	0	0
Hypochloraemia	2 (1.4)	0	0	0	1 (3.6)
Hypokalaemia	2 (1.4)	0	0	0	0
Hypophosphataemia	0	0	0	0	1 (3.6)
Cardiac disorders	3 (2.1)	1 (0.7)	5 (2.9)	3 (6.5)	0
Arrhythmia	2 (1.4)	0	1 (0.6)	1 (2.2)	0
Myocardial infarction	0	1 (0.7)	0	1 (2.2)	0
Pericardial effusion	0	0	0	1 (2.2)	0
Nervous system disorders	1 (0.7)	7 (4.9)	2 (1.2)	0	0
Spinal cord compression	0	2 (1.4)	0	0	0
Syncope	0	2 (1.4)	0	0	0
Skin and subcutaneous tissue disorders	3 (2.1)	0	6 (3.5)	0	0
Rash	0	0	2 (1.2)	0	0
Rash generalised	0	0	2 (1.2)	0	0
Endocrine disorders	2 (1.4)	1 (0.7)	1 (0.6)	2 (4.3)	0
Hypothyroidism	1 (0.7)	1 (0.7)	1 (0.6)	1 (2.2)	0
Hypophysitis	0	0	0	1 (2.2)	0
Hepatobiliary disorders	1 (0.7)	1 (0.7)	2 (1.2)	1 (2.2)	0
Hepatic function abnormal	1 (0.7)	1 (0.7)	2 (1.2)	0	0
Cholecystitis	0	0	0	1 (2.2)	0

Source: Module 5.3.5.3, ISS, Appendix 3.5, Table 4.17.2.

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The Applicant's Position:

The overall incidence of AEs resulting in drug interruption were generally similar between the NPC penpulimab 200mg Q2W population, penpulimab 200mg Q2W population and the overall monotherapy population. There were no marked differences between the three populations for any of the SOC's or PTs.

In the pivotal AK105-304 study, the incidence of AEs resulting in drug interruption of penpulimab/placebo in the penpulimab group was similar to that in the placebo group.

The FDA's Assessment:

FDA included laboratory abnormalities in the analysis of AEs leading to dose interruptions, resulting in the report of additional AEs leading to penpulimab dose interruption compared with Applicant's report.

FDA – Table 18. TEAEs Leading to Dose Interruption in Patients Receiving Penpulimab or Placebo + Chemotherapy ≥1% in Study AK105-304

TEAE	AK105-304			
	Penpulimab + Chemotherapy		Placebo + Chemotherapy	
	N=146 n (%)		N=142 n (%)	
	All Grade	Grade 3-4	All Grade	Grade 3-4
Any TEAE	94 (64)	57 (39)	84 (59)	56 (39)
COVID-19	24 (16)	0	17 (12)	0
Anemia	23 (16)	21 (14)	25 (18)	22 (15)
Platelet count decreased	21 (14)	16 (11)	26 (18)	23 (16)
White blood cell count decreased	20 (14)	9 (6)	18 (13)	12 (8)
Neutrophil count decreased	15 (10)	7 (4.8)	22 (15)	16 (11)
COVID-19 pneumonia	8 (5)	4 (2.7)	1 (0.7)	0
Pneumonia (GT)	6 (4.1)	3 (2.1)	4 (2.8)	1 (0.7)
Alanine aminotransferase increased	5 (3.4)	1 (0.7)	1 (0.7)	1 (0.7)
Hyponatremia	4 (2.7)	4 (2.7)	0	0
Aspartate aminotransferase increased	4 (2.7)	1 (0.7)	0	0
Asymptomatic COVID-19	4 (2.7)	0	7 (4.9)	0
Blood creatinine increased	4 (2.7)	0	4 (2.8)	0
Pyrexia (GT)	3 (2.1)	0	4 (2.8)	1 (0.7)
Upper respiratory tract infection	3 (2.1)	0	2 (1.4)	1 (0.7)
Hemorrhage (GT)	2 (1.4)	2 (1.4)	1 (0.7)	1 (0.7)
Myelosuppression	2 (1.4)	2 (1.4)	1 (0.7)	1 (0.7)
Acute kidney injury (GT)	2 (1.4)	2 (1.4)	1 (0.7)	0
Neutropenia	2 (1.4)	2 (1.4)	1 (0.7)	0
Hypochloremia	2 (1.4)	2 (1.4)	0	0
Hypokalemia	2 (1.4)	2 (1.4)	0	0

Disclaimer: In this document, the sections labeled as "Data" and "The Applicant's Position" are completed by the Applicant and do not necessarily reflect the positions of the FDA.

AK105-304				
TEAE	Penpulimab + Chemotherapy		Placebo + Chemotherapy	
	N=146 n (%)		N=142 n (%)	
	All Grade	Grade 3-4	All Grade	Grade 3-4
Musculoskeletal pain (GT)	2 (1.4)	1 (0.7)	1 (0.7)	0
Diarrhea (GT)	2 (1.4)	1 (0.7)	0	0
Rash (GT)	2 (1.4)	0	1 (0.7)	0
Arrhythmia (GT)	2 (1.4)	0	0	0
H1N1 influenza	2 (1.4)	0	0	0
Leukopenia	1 (0.7)	0	3 (2.1)	1 (0.7)
Fatigue (GT)	1 (0.7)	0	2 (1.4)	0
Spinal cord compression	0	0	2 (1.4)	2 (1.4)
Syncope	0	0	2 (1.4)	1 (0.7)

Source: ADAE

Note: Custom grouped terms are designated by '(GT)'.

- Acute kidney injury (GT) includes: Acute kidney injury, Creatinine renal clearance decreased, and Renal impairment.
- Arrhythmia (GT) includes: Arrhythmia.
- Cough (GT) includes: Cough, and Productive cough.
- Diarrhea (GT) includes: Diarrhea.
- Dizziness (GT) includes: Dizziness.
- Fatigue (GT) includes: Asthenia, and Fatigue.
- Hemorrhage (GT) includes: Epistaxis, and Tumour hemorrhage.
- Headache (GT) includes: Headache.
- Hypothyroidism (GT) includes: Hypothyroidism.

Musculoskeletal pain (GT) includes: Arthritis, Myalgia, and Pain in extremity.

- Neuropathy peripheral (GT) includes: Hypoesthesia.
- Oedema (GT) includes: Oedema peripheral.
- Pneumonia (GT) includes: Pneumonia.
- Pneumonitis (GT) includes: Organizing pneumonia, and Pneumonitis.
- Pyrexia (GT) includes: Pyrexia.
- Rash (GT) includes: Dermatitis acneiform, Drug eruption, and Rash pustular.
- Urinary tract infection (GT) includes: Urinary tract infection.
- Vomiting (GT) includes: Vomiting.

FDA – Table 19. TEAEs Leading to Dose Interruption in Patients Receiving Penpulimab Monotherapy ≥1% in Study AK105-202 or the Pooled Safety Dataset

TEAE	AK105-202 N=130 n (%)		Pooled Safety Set N=372 n (%)
	All Grade	Grade 3-4	All Grade
Any TEAE	33 (25)	10 (8)	95 (26)
Pneumonia (GT)	4 (3.1)	3 (2.3)	3 (0.8)
Anemia	4 (3.1)	1 (0.8)	5 (1.3)
Hypothyroidism (GT)	4 (3.1)	0	7 (1.9)
Hepatic function abnormal	3 (2.3)	2 (1.5)	5 (1.3)
Pneumonitis (GT)	2 (1.5)	1 (0.8)	0
Rash (GT)	2 (1.5)	1 (0.8)	4 (1.1)
Alanine aminotransferase increased	2 (1.5)	0	9 (2.4)
Aspartate aminotransferase increased	0	0	5 (1.3)
Lung infection	0	0	4 (1.1)
Diarrhea	0	0	6 (1.6)

Source: ADAE

Note: Custom grouped terms are designated by '(GT)'.

- Hypothyroidism (GT) includes: Hypothyroidism.
- Musculoskeletal pain (GT) includes: Back pain.
- Pneumonia (GT) includes: Lung infection, and Pneumonia.
- Pneumonitis (GT) includes: Immune-mediated pneumonitis, and Pneumonitis.
- Pyrexia (GT) includes: Pyrexia.
- Rash (GT) includes: Dermatitis acneiform, and Rash.

Abbreviations: TEAE, treatment-emergent adverse event

8.2.4.5. Significant Adverse Events

Data:

N/A

The Applicant's Position:

Adverse events of special interest are discussed in [Section 8.2.5].

AEs leading to drug interruption, including withdrawal of treatment are discussed above.

The FDA's Assessment:

N/A

8.2.4.6. Treatment Emergent Adverse Events and Adverse Reactions

Data:

Monotherapy Part

NPC 200mg Q2W population

Excluding disease progression, 123 out of 130 (94.6%) patients had at least one TEAE. Most patients had Grade 1 or 2 AEs; 38 (29.2%) patients had at least one $\geq$ Grade 3 TEAE. The incidence of drug-related TEAEs was 71.5% (93/130), and the incidence of $\geq$ Grade 3 drug-related TEAEs was 8.5% (11/130).

The most commonly (the incidence of PT $\geq$ 20%) reported TEAEs included anemia and hypothyroidism. Common $\geq$ Grade 3 TEAEs (with an incidence of $\geq$ 1%) were anaemia, hepatic function abnormal, liver injury, lung infection, aspartate aminotransferase increased, blood alkaline phosphatase increased, blood magnesium increased, gamma-glutamyltransferase increased, weight decreased, hyperuricaemia, hyponatraemia, respiratory failure, rash, disease progression and death.

Penpulimab 200mg Q2W population

Excluding disease progression, 355 out of 372 (95.4%) patients had at least one TEAE. Most patients had Grade 1 or 2 AEs; 127 (34.1%) patients had at least one $\geq$ Grade 3 TEAE. The incidence of drug-related TEAEs was 71.8% (267/372), and the incidence of $\geq$ Grade 3 drug-related TEAEs was 9.7% (36/372).

The most commonly (the incidence of PT $\geq$ 20%) reported TEAEs included anemia and hypothyroidism. Common $\geq$ Grade 3 TEAEs (with an incidence of $\geq$ 1%) were anaemia, Diarrhoea, Vomiting, Lower respiratory tract infection, lung infection, pneumonia, Urinary tract infection, alanine aminotransferase increased, aspartate aminotransferase increased, gamma-glutamyltransferase increased, platelet count decreased, hyperuricaemia, hyponatraemia, hypertension and disease progression.

Overall Monotherapy Population

Excluding disease progression, 512 out of 558 (91.8%) patients had at least one TEAE. Most patients had Grade 1 or 2 AEs; 172 (30.8%) patients had at least one $\geq$ Grade 3 TEAE. The incidence of drug-related TEAEs was 69.7% (389/558), and the incidence of $\geq$ Grade 3 drug-related TEAEs was 10.8% (60/558).

The most commonly (the incidence of PT $\geq$ 20%) reported TEAEs included anemia. Common $\geq$ Grade 3 TEAEs (with an incidence of $\geq$ 1%) were anaemia, lung infection, pneumonia, urinary tract infection, aspartate aminotransferase increased, gamma-glutamyltransferase increased, hypokalaemia, hyponatraemia, hypertension, disease progression and death.

Penpulimab

Adverse drug reactions (ADRs) with penpulimab have been determined include the known risks associated with the anti-PD-1/PD-L1 drug class and most frequently AEs ($\geq 10\%$ of patients).

The ADR for proposed patient population presented in the prescribing label excluded lab abnormality AE. The lab abnormality by the CTCAE grade derived based on actual value was presented under a separate table included in the prescribing label.

Applicant – Table 29 Summary of TEAEs in Penpulimab Monotherapy - Excluded Disease Progression

	NPC 200mg Q2W (N=130)	Ex-Asia (N=83)	Asia (N=289)	All Tumor Types 200mg Q2W Total (N=372)	All Doses Total (N=558)
All TEAEs	123 (94.6)	80 (96.4)	275 (95.2)	355 (95.4)	512 (91.8)
Study drug-related TEAEs	93 (71.5)	33 (39.8)	234 (81.0)	267 (71.8)	389 (69.7)
TEAEs of CTCAE Grade 3 or higher	38 (29.2)	38 (45.8)	89 (30.8)	127 (34.1)	172 (30.8)
Drug-related TEAEs of CTCAE Grade 3 or higher	11 (8.5)	3 (3.6)	33 (11.4)	36 (9.7)	60 (10.8)
Serious TEAEs	27 (20.8)	29 (34.9)	60 (20.8)	89 (23.9)	124 (22.2)
Serious drug-related TEAEs	10 (7.7)	4 (4.8)	24 (8.3)	28 (7.5)	42 (7.5)
TEAEs leading to death	7 (5.4)	2 (2.4)	10 (3.5)	12 (3.2)	18 (3.2)
Drug-related TEAEs leading to death	2 (1.5)	0	3 (1.0)	3 (0.8)	6 (1.1)
TEAEs leading to drug interruption	35 (26.9)	20 (24.1)	74 (25.6)	94 (25.3)	129 (23.1)
Drug-related TEAEs leading to drug interruption	20 (15.4)	5 (6.0)	50 (17.3)	55 (14.8)	75 (13.4)
TEAEs leading to drug discontinuation	5 (3.8)	5 (6.0)	17 (5.9)	22 (5.9)	31 (5.6)
Drug-related TEAEs leading to drug discontinuation	4 (3.1)	1 (1.2)	10 (3.5)	11 (3.0)	20 (3.6)

Source: ISS Combined Supplementary Tables, Table 4.1.3.

Applicant – Table 30 Summary of TEAEs by SOC and PT in Penpulimab Monotherapy (frequency $\geq 10\%$)

System Organ Class Preferred Term	NPC 200mg Q2W (N=130)	Ex-Asia (N=83)	Asia (N=289)	All Tumor Types 200mg Q2W Total (N=372)	All Doses Total (N=558)
Number of Subjects with at Least One TEAE	123 (94.6)	81 (97.6)	276 (95.5)	357 (96.0)	516 (92.5)
Investigations	88 (67.7)	16 (19.3)	219 (75.8)	235 (63.2)	328 (58.8)
Aspartate aminotransferase increased	22 (16.9)	4 (4.8)	52 (18.0)	56 (15.1)	80 (14.3)
Alanine aminotransferase increased	18 (13.8)	5 (6.0)	53 (18.3)	58 (15.6)	76 (13.6)
White blood cell count decreased	18 (13.8)	0	47 (16.3)	47 (12.6)	61 (10.9)
Weight decreased	25 (19.2)	3 (3.6)	41 (14.2)	44 (11.8)	49 (8.8)
Weight increased	13 (10.0)	0	45 (15.6)	45 (12.1)	47 (8.4)
Neutrophil count decreased	11 (8.5)	0	33 (11.4)	33 (8.9)	42 (7.5)
Blood thyroid stimulating hormone increased	20 (15.4)	0	34 (11.8)	34 (9.1)	39 (7.0)
C-reactive protein increased	13 (10.0)	0	22 (7.6)	22 (5.9)	30 (5.4)
Metabolism and nutrition disorders	54 (41.5)	28 (33.7)	133 (46.0)	161 (43.3)	239 (42.8)
Hyponatraemia	14 (10.8)	2 (2.4)	17 (5.9)	19 (5.1)	48 (8.6)
Decreased appetite	7 (5.4)	11 (13.3)	21 (7.3)	32 (8.6)	43 (7.7)
Hypertriglyceridaemia	8 (6.2)	0	33 (11.4)	33 (8.9)	43 (7.7)
Hyperuricaemia	9 (6.9)	0	36 (12.5)	36 (9.7)	42 (7.5)
Hypoalbuminaemia	13 (10.0)	1 (1.2)	18 (6.2)	19 (5.1)	39 (7.0)
Infections and infestations	42 (32.3)	32 (38.6)	115 (39.8)	147 (39.5)	186 (33.3)
Upper respiratory tract infection	17 (13.1)	3 (3.6)	54 (18.7)	57 (15.3)	62 (11.1)
General disorders and administration site conditions	48 (36.9)	41 (49.4)	108 (37.4)	149 (40.1)	184 (33.0)
Pyrexia	19 (14.6)	9 (10.8)	44 (15.2)	53 (14.2)	63 (11.3)
Fatigue	3 (2.3)	27 (32.5)	9 (3.1)	36 (9.7)	44 (7.9)
Gastrointestinal disorders	35 (26.9)	57 (68.7)	88 (30.4)	145 (39.0)	182 (32.6)
Diarrhoea	4 (3.1)	23 (27.7)	23 (8.0)	46 (12.4)	53 (9.5)

Disclaimer: In this document, the sections labeled as “Data” and “The Applicant’s Position” are completed by the Applicant and do not necessarily reflect the positions of the FDA.

System Organ Class Preferred Term	NPC 200mg Q2W (N=130)	All Tumor Types 200mg Q2W			All Doses Total (N=558)
		Ex-Asia (N=83)	Asia (N=289)	Total (N=372)	
Constipation	8 (6.2)	14 (16.9)	15 (5.2)	29 (7.8)	45 (8.1)
Nausea	4 (3.1)	21 (25.3)	10 (3.5)	31 (8.3)	41 (7.3)
Vomiting	5 (3.8)	12 (14.5)	12 (4.2)	24 (6.5)	29 (5.2)
Abdominal pain	3 (2.3)	11 (13.3)	6 (2.1)	17 (4.6)	22 (3.9)
Blood and lymphatic system disorders	54 (41.5)	8 (9.6)	104 (36.0)	112 (30.1)	169 (30.3)
Anaemia	50 (38.5)	6 (7.2)	87 (30.1)	93 (25.0)	147 (26.3)
Endocrine disorders	45 (34.6)	10 (12.0)	88 (30.4)	98 (26.3)	126 (22.6)
Hypothyroidism	41 (31.5)	8 (9.6)	76 (26.3)	84 (22.6)	104 (18.6)
Skin and subcutaneous tissue disorders	18 (13.8)	35 (42.2)	64 (22.1)	99 (26.6)	119 (21.3)
Rash	10 (7.7)	14 (16.9)	40 (13.8)	54 (14.5)	64 (11.5)
Pruritus	0	10 (12.0)	11 (3.8)	21 (5.6)	24 (4.3)
Musculoskeletal and connective tissue disorders	30 (23.1)	30 (36.1)	65 (22.5)	95 (25.5)	117 (21.0)
Back pain	18 (13.8)	8 (9.6)	33 (11.4)	41 (11.0)	53 (9.5)
Arthralgia	4 (3.1)	10 (12.0)	7 (2.4)	17 (4.6)	20 (3.6)
Respiratory, thoracic and mediastinal disorders	25 (19.2)	18 (21.7)	60 (20.8)	78 (21.0)	110 (19.7)
Cough	12 (9.2)	10 (12.0)	31 (10.7)	41 (11.0)	55 (9.9)
Renal and urinary disorders	14 (10.8)	8 (9.6)	46 (15.9)	54 (14.5)	73 (13.1)
Proteinuria	9 (6.9)	2 (2.4)	36 (12.5)	38 (10.2)	49 (8.8)
Psychiatric disorders	9 (6.9)	19 (22.9)	15 (5.2)	34 (9.1)	43 (7.7)
Insomnia	8 (6.2)	12 (14.5)	14 (4.8)	26 (7.0)	32 (5.7)

Source: ISS Combined Supplementary Tables, Table 4.3.1.

Combination Therapy Part

AK105-304

In patients treated with penpulimab 200mg Q3W in combination with cisplatin/carboplatin and gemcitabine in AK105-304, 146 (100.0%) patients had at least one TEAE. 132 (90.4%) patients had at least one $\geq$ Grade 3 TEAE. The most commonly (the incidence of PT $\geq$ 20%) reported TEAEs with a marginally higher incidence in the penpulimab group included aspartate aminotransferase increased, weight decreased, blood creatinine increased, anaemia, vomiting, hyponatraemia, hypoalbuminaemia, hypokalaemia, hypochloraemia, pyrexia, COVID-19, cough and hypothyroidism. Common $\geq$ Grade 3 TEAEs (with an incidence of $\geq$ 2%) with a marginally higher incidence in the penpulimab group included lymphocyte count decreased, alanine aminotransferase increased, blood creatine phosphokinase increased, anaemia, pneumonia, COVID-19 pneumonia, hypokalaemia, hyponatraemia, hypocalcaemia, hypomagnesaemia, nausea, hypertension and disease progression.

The incidence of drug-related TEAEs was 89.7% (131/146), and the incidence of $\geq$ Grade 3 drug-related TEAEs was 57.5% (84/146). The most commonly (the incidence of PT $\geq$ 10%) reported drug-relates TEAEs with a marginally higher incidence in the penpulimab group included aspartate aminotransferase increased, platelet count decreased, blood creatinine increased, anaemia, hyponatraemia, hypoalbuminaemia, hypokalaemia, hypertriglyceridaemia, hypochloraemia, hypomagnesaemia, vomiting, diarrhoea, constipation, rash and hypothyroidism. Common $\geq$ Grade 3 drug-relates TEAEs (with an incidence of $\geq$ 1%) with a marginally higher incidence in the penpulimab group included white blood cell count decreased, lymphocyte count decreased, anaemia, hypokalaemia, hyponatraemia, hypertriglyceridaemia,

Penpulimab

hypocalcaemia, hypomagnesaemia, diabetic ketoacidosis, pneumonia and nausea.

Regarding COVID-19 infection, the incidence in AK105 group was higher than that in placebo group. Considering the high infection rate of COVID-19, the incidence of COVID-19 infection was similar between the two groups after analyzed using grouped PT term (including COVID-19, COVID-19 pneumonia and asymptomatic COVID-19) under the SS and CTS sets in the study of AK105-304.

Applicant – Table 31 Summary of TEAEs in Penpulimab Combination Therapy - Excluded Disease Progression

	AK105-304		AK105-302	AK105-301	AK105-205
	Penpulimab + GP (N=146)	Placebo + GP (N=142)	Penpulimab + TC (N=173)	Penpulimab + PC (N=46)	Penpulimab+ Chemo±Anlotinib (N=28)
All TEAEs	146 (100.0)	142 (100.0)	171 (98.8)	46 (100.0)	28 (100.0)
Study drug-related TEAEs	131 (89.7)	121 (85.2)	153 (88.4)	40 (87.0)	25 (89.3)
TEAEs of CTCAE Grade 3 or higher	132 (90.4)	128 (90.1)	115 (66.5)	28 (60.9)	24 (85.7)
Drug-related TEAEs of CTCAE Grade 3 or higher	84 (57.5)	74 (52.1)	52 (30.1)	14 (30.4)	9 (32.1)
Serious TEAEs	73 (50.0)	66 (46.5)	49 (28.3)	18 (39.1)	10 (35.7)
Serious drug-related TEAEs	43 (29.5)	32 (22.5)	31 (17.9)	10 (21.7)	5 (17.9)
TEAEs leading to death	3 (2.1)	1 (0.7)	10 (5.8)	5 (10.9)	2 (7.1)
Drug-related TEAEs leading to death	1 (0.7)	0	5 (2.9)	2 (4.3)	0
TEAEs leading to drug interruption	94 (64.4)	83 (58.5)	61 (35.3)	20 (43.5)	13 (46.4)
Drug-related TEAEs leading to drug interruption	52 (35.6)	38 (26.8)	41 (23.7)	12 (26.1)	2 (7.1)
TEAEs leading to drug discontinuation	5 (3.4)	1 (0.7)	9 (5.2)	4 (8.7)	1 (3.6)
Drug-related TEAEs leading to drug discontinuation	4 (2.7)	1 (0.7)	8 (4.6)	4 (8.7)	0

Source: [Module 5.3.5.3, ISS, Appendix 3.5, Table 4.1.4.](#)

Applicant – Table 32 Summary of TEAEs by SOC and PT in Penpulimab Combination Therapy (frequency ≥ 10%)

System Organ Class Preferred Term	AK105-304		AK105-302	AK105-301	AK105-205
	Penpulimab + GP (N=146)	Placebo + GP (N=142)	Penpulimab + TC (N=173)	Penpulimab + PC (N=46)	Penpulimab+ Chemo±Anlotinib (N=28)
Number of Subjects with at Least One TEAE	146 (100.0)	142 (100.0)	172 (99.4)	46 (100.0)	28 (100.0)
Investigations	141 (96.6)	136 (95.8)	157 (90.8)	41 (89.1)	28 (100.0)
Neutrophil count decreased	125 (85.6)	129 (90.8)	119 (68.8)	25 (54.3)	20 (71.4)
White blood cell count decreased	132 (90.4)	130 (91.5)	106 (61.3)	23 (50.0)	24 (85.7)
Platelet count decreased	89 (61.0)	96 (67.6)	50 (28.9)	12 (26.1)	16 (57.1)
Alanine aminotransferase increased	56 (38.4)	45 (31.7)	63 (36.4)	24 (52.2)	6 (21.4)
Aspartate aminotransferase increased	62 (42.5)	42 (29.6)	43 (24.9)	16 (34.8)	5 (17.9)
Weight decreased	36 (24.7)	22 (15.5)	11 (6.4)	3 (6.5)	5 (17.9)
Blood creatinine increased	31 (21.2)	24 (16.9)	15 (8.7)	1 (2.2)	2 (7.1)
Gamma-glutamyltransferase increased	18 (12.3)	10 (7.0)	31 (17.9)	6 (13.0)	4 (14.3)
Lymphocyte count decreased	16 (11.0)	12 (8.5)	15 (8.7)	1 (2.2)	5 (17.9)
C-reactive protein increased	16 (11.0)	14 (9.9)	3 (1.7)	1 (2.2)	3 (10.7)
Blood thyroid stimulating hormone	9 (6.2)	12 (8.5)	9 (5.2)	2 (4.3)	3 (10.7)

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Penpulimab

System Organ Class Preferred Term	AK105-304		AK105-302	AK105-301	AK105-205
	Penpulimab + GP (N=146)	Placebo + GP (N=142)	Penpulimab + TC (N=173)	Penpulimab + PC (N=46)	Penpulimab+ Chemo±Anlotinib (N=28)
increased					
Blood creatine phosphokinase	9 (6.2)	2 (1.4)	4 (2.3)	1 (2.2)	6 (21.4)
increased					
Blood pressure increased	3 (2.1)	2 (1.4)	3 (1.7)	0	4 (14.3)
Protein urine present	1 (0.7)	3 (2.1)	1 (0.6)	0	4 (14.3)
Albumin urine present	0	0	1 (0.6)	0	7 (25.0)
Granulocyte count decreased	0	0	2 (1.2)	0	3 (10.7)
Blood and lymphatic system disorders	141 (96.6)	128 (90.1)	126 (72.8)	37 (80.4)	23 (82.1)
Anaemia	139 (95.2)	127 (89.4)	119 (68.8)	37 (80.4)	23 (82.1)
Leukopenia	8 (5.5)	8 (5.6)	10 (5.8)	10 (21.7)	4 (14.3)
Neutropenia	5 (3.4)	6 (4.2)	6 (3.5)	5 (10.9)	2 (7.1)
Gastrointestinal disorders	117 (80.1)	119 (83.8)	108 (62.4)	28 (60.9)	20 (71.4)
Nausea	85 (58.2)	90 (63.4)	46 (26.6)	13 (28.3)	11 (39.3)
Vomiting	79 (54.1)	76 (53.5)	27 (15.6)	9 (19.6)	8 (28.6)
Constipation	56 (38.4)	60 (42.3)	32 (18.5)	10 (21.7)	10 (35.7)
Diarrhoea	25 (17.1)	17 (12.0)	29 (16.8)	5 (10.9)	6 (21.4)
Abdominal distension	17 (11.6)	8 (5.6)	14 (8.1)	4 (8.7)	1 (3.6)
Dry mouth	9 (6.2)	4 (2.8)	4 (2.3)	0	4 (14.3)
Toothache	5 (3.4)	4 (2.8)	7 (4.0)	0	3 (10.7)
Mouth ulceration	3 (2.1)	0	6 (3.5)	3 (6.5)	6 (21.4)
Stomatitis	3 (2.1)	4 (2.8)	2 (1.2)	1 (2.2)	3 (10.7)
Metabolism and nutrition disorders	113 (77.4)	101 (71.1)	118 (68.2)	24 (52.2)	18 (64.3)
Decreased appetite	52 (35.6)	55 (38.7)	49 (28.3)	15 (32.6)	8 (28.6)
Hyponatraemia	56 (38.4)	46 (32.4)	28 (16.2)	6 (13.0)	5 (17.9)
Hypoalbuminaemia	44 (30.1)	30 (21.1)	35 (20.2)	7 (15.2)	3 (10.7)
Hypokalaemia	47 (32.2)	21 (14.8)	24 (13.9)	10 (21.7)	2 (7.1)
Hypertriglyceridaemia	18 (12.3)	12 (8.5)	45 (26.0)	4 (8.7)	2 (7.1)
Hyperuricaemia	20 (13.7)	17 (12.0)	26 (15.0)	2 (4.3)	1 (3.6)
Hypochloraeaemia	37 (25.3)	14 (9.9)	9 (5.2)	1 (2.2)	4 (14.3)
Hypomagnesaemia	20 (13.7)	17 (12.0)	16 (9.2)	1 (2.2)	2 (7.1)
Hypercholesterolaemia	13 (8.9)	10 (7.0)	24 (13.9)	3 (6.5)	2 (7.1)
Hypocalcaemia	20 (13.7)	6 (4.2)	9 (5.2)	0	2 (7.1)
Hyperglycaemia	9 (6.2)	3 (2.1)	14 (8.1)	2 (4.3)	3 (10.7)
Hyperlipidaemia	6 (4.1)	11 (7.7)	10 (5.8)	0	4 (14.3)
Hypophosphataemia	11 (7.5)	5 (3.5)	7 (4.0)	0	3 (10.7)
General disorders and administration site conditions	82 (56.2)	73 (51.4)	82 (47.4)	27 (58.7)	18 (64.3)
Pyrexia	31 (21.2)	27 (19.0)	22 (12.7)	8 (17.4)	6 (21.4)
Fatigue	23 (15.8)	22 (15.5)	13 (7.5)	2 (4.3)	0
Asthenia	12 (8.2)	8 (5.6)	21 (12.1)	7 (15.2)	9 (32.1)
Malaise	14 (9.6)	11 (7.7)	12 (6.9)	6 (13.0)	2 (7.1)
Chest discomfort	7 (4.8)	6 (4.2)	1 (0.6)	1 (2.2)	5 (17.9)
Skin and subcutaneous tissue disorders	52 (35.6)	42 (29.6)	150 (86.7)	13 (28.3)	12 (42.9)
Alopecia	8 (5.5)	8 (5.6)	141 (81.5)	3 (6.5)	0
Rash	24 (16.4)	18 (12.7)	25 (14.5)	5 (10.9)	5 (17.9)
Pruritus	16 (11.0)	14 (9.9)	11 (6.4)	5 (10.9)	2 (7.1)
Palmar-plantar erythrodysesthesia	0	0	2 (1.2)	0	6 (21.4)
syndrome					
Skin exfoliation	0	0	0	0	4 (14.3)
Nervous system disorders	56 (38.4)	53 (37.3)	112 (64.7)	4 (8.7)	10 (35.7)
Hypoaesthesia	21 (14.4)	22 (15.5)	78 (45.1)	0	1 (3.6)
Dizziness	18 (12.3)	21 (14.8)	9 (5.2)	1 (2.2)	4 (14.3)

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Penpulimab

System Organ Class Preferred Term	AK105-304		AK105-302	AK105-301	AK105-205
	Penpulimab + GP	Placebo + GP	Penpulimab + TC	Penpulimab + PC	Penpulimab+ Chemo±Anlotinib
	(N=146)	(N=142)	(N=173)	(N=46)	(N=28)
Headache	22 (15.1)	13 (9.2)	3 (1.7)	2 (4.3)	4 (14.3)
Infections and infestations	77 (52.7)	71 (50.0)	51 (29.5)	15 (32.6)	16 (57.1)
COVID-19	35 (24.0)	24 (16.9)	0	0	8 (28.6)
Upper respiratory tract infection	11 (7.5)	10 (7.0)	17 (9.8)	2 (4.3)	3 (10.7)
Pneumonia	9 (6.2)	9 (6.3)	14 (8.1)	2 (4.3)	3 (10.7)
Urinary tract infection	11 (7.5)	8 (5.6)	7 (4.0)	3 (6.5)	3 (10.7)
Respiratory, thoracic and mediastinal disorders	60 (41.1)	48 (33.8)	65 (37.6)	19 (41.3)	16 (57.1)
Cough	32 (21.9)	18 (12.7)	8 (4.6)	4 (8.7)	5 (17.9)
Productive cough	15 (10.3)	8 (5.6)	9 (5.2)	5 (10.9)	1 (3.6)
Epistaxis	12 (8.2)	8 (5.6)	2 (1.2)	0	3 (10.7)
Haemoptysis	0	1 (0.7)	19 (11.0)	3 (6.5)	1 (3.6)
Oropharyngeal pain	9 (6.2)	8 (5.6)	1 (0.6)	1 (2.2)	5 (17.9)
Laryngeal pain	3 (2.1)	1 (0.7)	0	0	4 (14.3)
Dysphonia	1 (0.7)	0	1 (0.6)	2 (4.3)	3 (10.7)
Musculoskeletal and connective tissue disorders	23 (15.8)	37 (26.1)	88 (50.9)	7 (15.2)	8 (28.6)
Pain in extremity	6 (4.1)	8 (5.6)	47 (27.2)	1 (2.2)	2 (7.1)
Arthralgia	3 (2.1)	5 (3.5)	26 (15.0)	0	2 (7.1)
Back pain	5 (3.4)	12 (8.5)	12 (6.9)	3 (6.5)	3 (10.7)
Endocrine disorders	57 (39.0)	30 (21.1)	25 (14.5)	7 (15.2)	15 (53.6)
Hypothyroidism	51 (34.9)	25 (17.6)	13 (7.5)	5 (10.9)	15 (53.6)
Renal and urinary disorders	29 (19.9)	22 (15.5)	35 (20.2)	7 (15.2)	6 (21.4)
Proteinuria	19 (13.0)	17 (12.0)	21 (12.1)	5 (10.9)	4 (14.3)
Psychiatric disorders	20 (13.7)	17 (12.0)	17 (9.8)	2 (4.3)	1 (3.6)
Insomnia	17 (11.6)	14 (9.9)	17 (9.8)	2 (4.3)	0
Vascular disorders	21 (14.4)	19 (13.4)	10 (5.8)	0	7 (25.0)
Hypertension	6 (4.1)	3 (2.1)	5 (2.9)	0	5 (17.9)
Hepatobiliary disorders	8 (5.5)	3 (2.1)	12 (6.9)	2 (4.3)	4 (14.3)
Hepatic function abnormal	6 (4.1)	2 (1.4)	5 (2.9)	1 (2.2)	4 (14.3)

Source: [Module 5.3.5.3, ISS, Appendix 3.5, Table 4.3.2.](#)

The Applicant's Position:

The most common AEs (regardless of severity and causality) in monotherapy observed in NPC penpulimab 200mg Q2W population were comparable to penpulimab 200mg Q2W population and the overall monotherapy population. Most of the AEs were Grade 1 or 2, indicating a tolerable safety profile of penpulimab.

In the pivotal AK105-304 study, only a few of TEAEs occurred at a slightly higher rate in the penpulimab group, such as abnormal transaminases, anemia, metabolic and nutritional disorders, electrolyte abnormalities, COVID-19, hypothyroidism, cough, and headache. Except for COVID-19, these are common AEs in cancer patients, and most of the AEs were grades 1 or 2, without affecting the function of important organs or systems.

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The FDA's Assessment:**FDA – Table 20. Adverse Reactions* (≥ 10%) in Patients With Recurrent or Metastatic NPC Who Received Penpulimab-kcqx in Combination With Either Cisplatin or Carboplatin and Gemcitabine in Study AK105-304**

Adverse Reaction	Penpulimab-kcqx Cisplatin or Carboplatin and Gemcitabine N=146		Placebo Cisplatin or Carboplatin and Gemcitabine N=142	
	All Grades ¹ (%)	Grade 3 or 4 ¹ (%)	All Grades ¹ (%)	Grade 3 or 4 ¹ (%)
Gastrointestinal disorders				
Nausea	58	2.1	64	0
Vomiting ²	55	1.4	54	1.4
Constipation	41	0	44	0
Abdominal distension	12	0	6	0
Endocrine disorders				
Hypothyroidism ⁴	45	0	27	0
Metabolism and nutrition disorders				
Decreased appetite	36	0	39	0
Investigations				
Weight decreased	26	1.4	16	0
Respiratory, thoracic and mediastinal disorders				
Cough ⁵	25	0	16	0
Infections and infestations				
COVID-19	25	0	17	0.7
General disorders and administration site conditions				
Fatigue ⁶	25	1.4	22	0
Pyrexia	21	0	20	0.7
Malaise	10	0	8	0
Nervous system disorders				
Headache	15	0.7	10	0.7
Dizziness ⁸	14	0	15	0.7
Skin and subcutaneous tissue disorders				
Rash ⁹	24	1.4	20	0
Pruritus	11	0	11	0
Renal and urinary disorders				
Proteinuria	14	0	13	0
Acute kidney injury ¹⁰	13	1.4	4.9	0
Musculoskeletal and connective tissue disorders				
Musculoskeletal pain ¹¹	14	0.7	24	0

Disclaimer: In this document, the sections labeled as “Data” and “The Applicant’s Position” are completed by the Applicant and do not necessarily reflect the positions of the FDA.

Adverse Reaction	Penpulimab- kcqx Cisplatin or Carboplatin and Gemcitabine N=146		Placebo Cisplatin or Carboplatin and Gemcitabine N=142	
	All Grades ¹ (%)	Grade 3 or 4 ¹ (%)	All Grades ¹ (%)	Grade 3 or 4 ¹ (%)
Psychiatric disorders				
Insomnia	12	0	10	0

Source: FDA Label

¹ Graded per NCI CTCAE v5.0

² Includes retching

³ Includes enteritis

⁴ Includes blood thyroid stimulating hormone increased, secondary hypothyroidism

⁵ Includes productive cough, upper-airway cough syndrome

⁶ Includes asthenia

⁷ Includes hypoesthesia

⁸ Includes vertigo

⁹ Includes dermatitis, dermatitis acneiform, drug eruption, eczema, rash maculo-papular, rash papular, rash pustular

¹⁰ Includes acute kidney injury, creatinine renal clearance decreased, glomerular filtration rate decreased, renal failure, renal impairment

¹¹ Includes arthralgia, arthritis, back pain, bone pain, musculoskeletal chest pain, musculoskeletal discomfort, myalgia, neck pain, pain in extremity, spinal pain

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FDA – Table 21. Adverse Reactions (≥ 10%) in Patients With Recurrent Metastatic Non-Keratinizing NPC Who Received Penpulimab-kcq in Study AK105-202

Adverse Reaction	Penpulimab-kcq N=130	
	All Grades ¹ (%)	Grade 3 or 4 ¹ (%)
Endocrine disorders		
Hypothyroidism ²	39	0
Musculoskeletal and connective tissue disorders		
Musculoskeletal pain ³	25	0.8
General disorders and administration site conditions		
Pyrexia	15	0
Investigations		
Weight decreased	19	1.5
Infections and infestations		
Upper respiratory tract infection	13	0.8
Respiratory, thoracic and mediastinal disorders		
Cough ⁴	11	0
Skin and subcutaneous tissue disorders		
Rash ⁵	11	2.3

Source: FDA Label

¹ Graded per NCI CTCAE v5.0² Includes blood thyroid stimulating hormone increased³ Includes arthralgia, back pain, bone pain, musculoskeletal chest pain, neck pain, non-cardiac chest pain, pain in extremity⁴ Includes productive cough⁵ Includes dermatitis acneiform, eczema, pemphigoid**8.2.4.7. Laboratory Findings**Data:**Applicant – Table 33 Summary of Laboratory Abnormalities (≥10%) That Worsend from Baseline in the Study of AK105-304 and Penpulimab Monotherapy 200mg Q2W**

Laboratory abnormalities	Penpulimab + GP (N=146)		Placebo + GP (N=142)		Penpulimab monotherapy 200mg Q2W (N=372)	
	Grades 1-4 n/m (%)	Grades 3-4 n/m (%)	Grades 1-4 n/m (%)	Grades 3-4 n/m (%)	Grades 1-4 n/m (%)	Grades 3-4 n/m (%)
CHEMISTRY						
Alanine aminotransferase increased	60/143 (42.0)	11/143 (7.7)	52/140 (37.1)	3/140 (2.1)	94/364 (25.8)	9/364 (2.5)
Alkaline phosphatase increased	45/143 (31.5)	1/143 (0.7)	41/139 (29.5)	0/139	98/364 (26.9)	14/364 (3.8)
Aspartate aminotransferase increased	74/143 (51.7)	8/143 (5.6)	52/140 (37.1)	4/140 (2.9)	120/364 (33.0)	16/364 (4.4)
Blood bilirubin increased	27/143 (18.9)	3/143 (2.1)	15/140 (10.7)	1/140 (0.7)	62/364 (17.0)	10/364 (2.7)
Cholesterol high	67/138 (48.6)	3/138 (2.2)	64/139 (46.0)	1/139 (0.7)	87/362 (24.0)	0/362
Creatinine increased	69/143 (48.3)	2/143 (1.4)	54/139 (38.8)	1/139 (0.7)	261/364 (71.7)	0/364
GGT increased	52/143 (36.4)	2/143 (1.4)	45/138 (32.6)	1/138 (0.7)	101/364 (27.7)	31/364 (8.5)
Hypercalcemia	25/142 (17.6)	3/142 (2.1)	22/139 (15.8)	2/139 (1.4)	74/363 (20.4)	3/363 (0.8)

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Laboratory abnormalities	Penpulimab + GP (N=146)		Placebo + GP (N=142)		Penpulimab monotherapy 200mg Q2W (N=372)	
	Grades 1-4 n/m (%)	Grades 3-4 n/m (%)	Grades 1-4 n/m (%)	Grades 3-4 n/m (%)	Grades 1-4 n/m (%)	Grades 3-4 n/m (%)
Hyperglycemia	NA	NA	NA	NA	103/299 (34.4)	9/299 (3.0)
Hyperkalemia	19/143 (13.3)	4/143 (2.8)	12/139 (8.6)	0/139	27/364 (7.4)	4/364 (1.1)
Hypermagnesemia	14/143 (9.8)	7/143 (4.9)	10/139 (7.2)	4/139 (2.9)	36/361 (10.0)	12/361 (3.3)
Hypertriglyceridemia	80/138 (58.0)	6/138 (4.3)	73/139 (52.5)	6/139 (4.3)	148/362 (40.9)	10/362 (2.8)
Hypoalbuminemia	67/143 (46.9)	0/143	61/140 (43.6)	2/140 (1.4)	120/364 (33.0)	3/364 (0.8)
Hypocalcemia	28/142 (19.7)	1/142 (0.7)	20/139 (14.4)	3/139 (2.2)	27/363 (7.4)	0/363
Hypoglycemia	31/143 (21.7)	2/143 (1.4)	28/138 (20.3)	1/138 (0.7)	28/362 (7.7)	0/362
Hypokalemia	64/143 (44.8)	20/143 (14.0)	43/139 (30.9)	5/139 (3.6)	50/364 (13.7)	7/364 (1.9)
Hypomagnesemia	99/143 (69.2)	6/143 (4.2)	81/139 (58.3)	5/139 (3.6)	79/361 (21.9)	4/361 (1.1)
Hyponatremia	89/143 (62.2)	10/143 (7.0)	81/139 (58.3)	10/139 (7.2)	127/364 (34.9)	17/364 (4.7)
Hypophosphatemia	NA	NA	NA	NA	95/300 (31.7)	17/300 (5.7)
Lipase increased	29/102 (28.4)	11/102 (10.8)	24/103 (23.3)	4/103 (3.9)	5/58 (8.6)	0/58
Serum amylase increased	32/140 (22.9)	4/140 (2.9)	23/139 (16.5)	1/139 (0.7)	4/71 (5.6)	0/71
COAGULATION FUNCTION						
Activated partial thromboplastin time prolonged	19/132 (14.4)	1/132 (0.8)	8/132 (6.1)	0/132	25/237 (10.5)	0/237
HEMATOLOGY						
Anemia	143/146 (97.9)	71/146 (48.6)	136/141 (96.5)	66/141 (46.8)	120/364 (33.0)	13/364 (3.6)
Lymphocyte count decreased	136/146 (93.2)	102/146 (69.9)	126/141 (89.4)	82/141 (58.2)	136/364 (37.4)	39/364 (10.7)
Neutrophil count decreased	134/146 (91.8)	89/146 (61.0)	134/141 (95.0)	91/141 (64.5)	57/364 (15.7)	4/364 (1.1)
Platelet count decreased	99/146 (67.8)	48/146 (32.9)	102/141 (72.3)	52/141 (36.9)	48/364 (13.2)	9/364 (2.5)
White blood cell decreased	144/146 (98.6)	85/146 (58.2)	136/141 (96.5)	82/141 (58.2)	72/364 (19.8)	3/364 (0.8)

Source: ISS Combined Supplementary Tables, [Table 6.3.3](#).

The Applicant's Position:

Changes in laboratory parameters were predominantly Grade 1 or 2 in severity, and the incidence of any grade worsening to Grade 3 or 4 was generally low, suggesting a well-tolerated safety profile.

The FDA's Assessment:

The FDA's review of laboratory abnormalities with penpulimab administration largely agrees with the Applicant's position and we agree penpulimab has a safety profile that is manageable and consistent with what's known for anti-PD-(L)1 antibodies

Laboratory abnormalities worsening from baseline, occurring in 20% or more of patients regardless of the absolute differences between the placebo and chemotherapy arm, based on FDA's review of the current datasets are presented below in [FDA – Table 22](#) in AK105-304 and in [FDA – Table 23](#) for AK105-202 and the pooled safety set.

FDA – Table 22. Select Laboratory Abnormalities* (≥20%) That Worsened From Baseline in Patients With Recurrent or Metastatic NPC Who Received Penpulimab-kcqx in Combination With Either Cisplatin or Carboplatin and Gemcitabine, Study AK105-304

Laboratory Abnormality	Penpulimab-kcqx Cisplatin or Carboplatin /Gemcitabine ²		Placebo Cisplatin or Carboplatin /Gemcitabine ³	
	All Grades ¹ (%)	Grade 3 or 4 ¹ (%)	All Grades ¹ (%)	Grade 3 or 4 ¹ (%)
Hematology				
White blood cell decreased	99	58	97	58
Hemoglobin decreased	98	49	97	47
Lymphocytes decreased	93	70	89	58
Neutrophils decreased	92	61	95	65
Chemistry				
Magnesium decreased	69	4.2	58	3.6
Sodium decreased	62	7	58	7
Triglycerides increased	58	4.3	53	4.3
Aspartate aminotransferase increased	52	6	37	2.9
Cholesterol increased	49	2.2	46	0.7
Creatinine increased	48	1.4	39	0.7
Albumin decreased	47	0	44	1.4
Potassium decreased	45	14	31	3.6
Alanine aminotransferase increased	42	8	37	2.1
GGT increased	36	1.4	33	0.7
Alkaline phosphatase increased	32	0.7	30	0
Lipase increased	28	11	23	3.9
Chloride decreased	25	1.4	11	0
Serum amylase increased	23	2.9	17	0.7
Glucose decreased	22	1.4	20	0.7
Lipids increased	21	1.4	20	0.7

Source: FDA Label

* Select laboratory abnormalities occurring at a higher incidence than in the placebo arm

¹Toxicity graded according to NCI CTCAE v5.0.

²The denominator used to calculate the rate varied from 102 to 146 based on the number of patients with a baseline value and at least one post-treatment value.

³The denominator used to calculate the rate varied from 103 to 142 based on the number of patients with a baseline value and at least one post-treatment value.

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FDA – Table 23. Select Laboratory Abnormalities* (≥20%) That Worsened From Baseline in Patients With Metastatic Non-Keratinizing NPC Who Received Penpulimab-kcq Monotherapy After Platinum Based Chemotherapy and at Least One Other Line of Therapy, Study AK105-202 and the Integrated Safety Set

Laboratory Abnormality	AK105-202 N=130		Safety Set N=372
	All Grades ¹ (%) ^{2All}	Grades 3 or 4 (%)	All Grades (%)
Chemistry			
Creatinine increased	81	0	72
Phosphate decreased	47	8	32
Sodium decreased	46	6	35
Albumin decreased	45	0	33
Triglycerides increased	38	3.1	41
Alkaline phosphatase increased	35	5	27
Aspartate aminotransferase increased	33	3.9	33
GGT increased	34	8	28
Glucose increased	34	0	34
Magnesium decreased	28	0.8	10
Activated partial thromboplastin time prolonged	22	0	11
Alanine aminotransferase increased	20	3.9	26
Hematology			
Lymphocytes decreased	43	16	37
Hemoglobin decreased	36	4.7	33

Source: FDA Label

¹Toxicity graded according to NCI CTCAE v5.0.²Each test incidence is based on the number of patients who had both baseline and at least one on-study laboratory measurement available: penpulimab-kcq (range of the patient number: 128 to 130).

Abbreviations: GGT, gamma-glutamyl transferase; NCI-CTCAE, National Cancer Institute - Common Terminology Criteria for Adverse Events

8.2.4.8. Vital SignsData:

The changes of vital signs (pulse, systolic/diastolic blood pressure, respiratory rate, and body temperature) from baseline to minimum, maximum value, and the end of treatment visit were summarized in [Module 5.3.5.3, ISS, Appendix 3.5, Table 8.1.1 and Table 8.1.2](#).

Median changes from baseline to minimum or maximum and from baseline to final value were generally small and not considered to be clinically meaningful for any of the vital sign parameters.

The Applicant's Position:

Changes from baseline to minimum or maximum and from baseline to end of treatment visit

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were generally small and not considered to be clinically meaningful for any of the vital parameters.

The FDA's Assessment:

FDA agrees with the Applicant's position.

8.2.4.9. Electrocardiograms (ECGs)

Data:

Electrocardiogram (ECG) assessments are part of routine safety monitoring.

Shift table for ECGs of clinical significance from baseline to worst post-baseline was summarized in [Module 5.3.5.3, ISS, Appendix 3.5, Table 7.1.1 and Table 7.1.2](#).

NPC 200mg Q2W population

No patients had a QTcF value > 500 msec or an increase from baseline > 90 msec. No patients had a QTcF value > 480 msec, 3 (2.5%) patients had an increase from baseline > 60 msec.

Penpulimab 200mg Q2W population

2 (0.6%) patients had a QTcF value > 500 msec and 4 (1.1%) patients had an increase from baseline > 90 msec. 6 (1.7%) patients had a QTcF value > 480 msec and 14 (3.9%) patients had an increase from baseline > 60 msec.

Overall Monotherapy population

6 (1.1%) patients had a QTcF value > 500 msec and 7 (1.3%) patients had an increase from baseline > 90 msec. 11 (2.1%) patients had a QTcF value > 480 msec and 21 (4.0%) patients had an increase from baseline > 60 msec.

Conclusions

Individuals with clinically meaningful QTcF values and changes from baseline were found to have had either cardiac medical history or were receiving potentially cardioactive concomitant medications at the time of abnormality or had single occurrences above the defined threshold. There was no evidence of clinically meaningful cardiac effects associated with penpulimab exposure.

Combination Therapy Part

AK105-304

No patients had a QTcF value > 500 msec, 1 (0.7%) patient had an increase from baseline > 90 msec. No patients had a QTcF value > 480 msec, 11 (8.0%) patients had an increase from baseline > 60 msec.

The Applicant's Position:

Electrocardiogram (ECG) assessments are part of routine safety monitoring. There was no evidence of clinically meaningful cardiac effects associated with penpulimab exposure.

The FDA's Assessment:

FDA agrees with the Applicant's position.

8.2.4.10. Immunogenicity

Data:

NPC 200mg Q2W population

The proportion of patients with ADA positive at baseline and post-baseline was 5.9% and 30.3%, respectively. 27.7% of patients developed treatment-emergent ADA (TEADA), and 6.7 % TEADA patients had positive neutralizing antibody (Nab). Among patients with negative baselines, the incidence of TEADA was 25.2%, and the incidence of positive Nab was 6.7%. Only 3 (2.5%) TEADA patients had positive baselines and none of them had positive Nab.

The incidence rates of TEADA and Nab in NPC population who received Penpulimab monotherapy were comparable to other tumor types.

Penpulimab 200mg Q2W population

349 patients were treated with penpulimab monotherapy at 1mg/kg, 3mg/kg, 10mg/kg, 200mg Q2W.

The proportion of patients with ADA positive at baseline and post-baseline was 3.4% and 31.2%, respectively. 30.1% of patients developed treatment-emergent ADA (TEADA), and 5.2 % of patients with TEADA had positive neutralizing antibody (Nab). Among patients with negative baselines, the incidence of TEADA was 28.4%, and the incidence of positive Nab was 5.2%. Only 5 (1.4%) patients with TEADA had positive baselines and none of them had positive Nab.

Among the patients treated with penpulimab monotherapy (1~10mg/kg Q2W, or 200mg Q2W/Q3W), the incidence of AEs such as TEAE, TRAE (CTCAE Grade 3+), serious TEAEs, serious drug-related TEAEs, TEAEs leading to death, drug-related TEAEs leading to death, drug-related TEAEs leading to drug discontinuation in the patients with TEADA were similar to those from ADA-negative patients, and no special type of AE occurred in patients with TEADA.

For drug-related TEAEs leading to dose interruption, the incidence in patients with TEADA was slightly higher than that in the ADA-negative patients (20.0% vs. 13.8%).

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In ex-Asia patients who received penpulimab monotherapy (200mg Q2W), AE events in the TEADA were slightly higher than the ADA-negative patients, probably due to imbalance of the sample size (only 13 patients in ex-Asia group).

In NPC monotherapy population, the incidence of AEs in patients with TEADA was similar to that in the ADA-negative patients, and no special type of AEs occurred.

In addition, the incidences of most irAE-related events in the patients with TEADA were similar to those from the ADA-negative patients, except for the incidence in irAEs leading to drug interruption in patients with TEADA was higher than ADA-negative patients (11.4% vs. 6.3%).

The Applicant's Position:

In TEADA patients, the incidence and types of AEs were generally similar to those of all patients. Treatment emergent ADA had no significant impact on safety.

The FDA's Assessment:

FDA agrees with the Applicant's position.

8.2.5. Analysis of Submission-Specific Safety Issues

8.2.5.1. Immune-related Adverse Events

Data:

Monotherapy Part

irAEs occurred in patient population receiving penpulimab monotherapy are summarized by irAE Group, Subgroup and PT in [Applicant – Table 34](#).

Applicant – Table 34 irAEs Summarized by irAE Group, Subgroup and PT in Trials with Penpulimab Monotherapy

irAE Group irAE Subgroup PT	NPC 200mg Q2W (N=130)	All Tumor Types 200mg Q2W Ex-Asia (N=83)	Asia (N=289)	Total (N=372)	All Doses Total (N=558)
Number of Subjects with at Least One irAE	42 (32.3)	15 (18.1)	107 (37.0)	122 (32.8)	158 (28.3)
Endocrine toxicity	30 (23.1)	8 (9.6)	72 (24.9)	80 (21.5)	101 (18.1)
Hypothyroidism	28 (21.5)	7 (8.4)	62 (21.5)	69 (18.5)	81 (14.5)
Hypothyroidism	25 (19.2)	7 (8.4)	49 (17.0)	56 (15.1)	67 (12.0)
Blood thyroid stimulating hormone increased	5 (3.8)	0	16 (5.5)	16 (4.3)	18 (3.2)
Thyroxine free decreased	3 (2.3)	0	6 (2.1)	6 (1.6)	6 (1.1)
Thyroxine decreased	0	0	2 (0.7)	2 (0.5)	2 (0.4)
Tri-iodothyronine decreased	0	0	2 (0.7)	2 (0.5)	2 (0.4)

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irAE Group	NPC 200mg	All Tumor Types 200mg Q2W			All Doses
irAE Subgroup	Q2W	Ex-Asia	Asia	Total	Total
PT	(N=130)	(N=83)	(N=289)	(N=372)	(N=558)
Tri-iodothyronine free decreased	2 (1.5)	0	2 (0.7)	2 (0.5)	2 (0.4)
Hyperthyroidism	8 (6.2)	4 (4.8)	20 (6.9)	24 (6.5)	33 (5.9)
Hyperthyroidism	6 (4.6)	4 (4.8)	15 (5.2)	19 (5.1)	28 (5.0)
Blood thyroid stimulating hormone decreased	4 (3.1)	0	6 (2.1)	6 (1.6)	7 (1.3)
Thyroxine free increased	2 (1.5)	0	3 (1.0)	3 (0.8)	3 (0.5)
Tri-iodothyronine free increased	0	0	2 (0.7)	2 (0.5)	2 (0.4)
Tri-iodothyronine increased	0	0	2 (0.7)	2 (0.5)	2 (0.4)
Hyperglycaemia/Type 1 diabetes mellitus	2 (1.5)	0	3 (1.0)	3 (0.8)	5 (0.9)
Hyperglycaemia	2 (1.5)	0	3 (1.0)	3 (0.8)	4 (0.7)
Blood glucose increased	0	0	0	0	1 (0.2)
Other thyroid diseases	2 (1.5)	0	4 (1.4)	4 (1.1)	5 (0.9)
Thyroiditis	1 (0.8)	0	1 (0.3)	1 (0.3)	2 (0.4)
Autoimmune thyroid disorder	1 (0.8)	0	1 (0.3)	1 (0.3)	1 (0.2)
Autoimmune thyroiditis	0	0	1 (0.3)	1 (0.3)	1 (0.2)
Thyroid mass	0	0	1 (0.3)	1 (0.3)	1 (0.2)
Adrenal insufficiency	0	0	0	0	1 (0.2)
Glucocorticoid deficiency	0	0	0	0	1 (0.2)
Hypophysitis	0	0	0	0	1 (0.2)
Hypophysitis	0	0	0	0	1 (0.2)
Dermatologic toxicity	12 (9.2)	9 (10.8)	34 (11.8)	43 (11.6)	53 (9.5)
Rash	9 (6.9)	5 (6.0)	25 (8.7)	30 (8.1)	35 (6.3)
Pruritus	0	3 (3.6)	3 (1.0)	6 (1.6)	7 (1.3)
Rash generalised	1 (0.8)	1 (1.2)	3 (1.0)	4 (1.1)	6 (1.1)
Eczema	0	0	2 (0.7)	2 (0.5)	2 (0.4)
Lichen planus	0	0	1 (0.3)	1 (0.3)	2 (0.4)
Pruritus generalised	0	0	2 (0.7)	2 (0.5)	2 (0.4)
Rash maculo-papular	0	2 (2.4)	0	2 (0.5)	2 (0.4)
Dermatitis	0	0	1 (0.3)	1 (0.3)	1 (0.2)
Dermatitis acneiform	1 (0.8)	0	1 (0.3)	1 (0.3)	1 (0.2)
Dermatitis allergic	0	0	1 (0.3)	1 (0.3)	1 (0.2)
Immune-mediated dermatitis	0	0	0	0	1 (0.2)
Pemphigoid	1 (0.8)	0	1 (0.3)	1 (0.3)	1 (0.2)
Rash macular	0	1 (1.2)	0	1 (0.3)	1 (0.2)
Rash pruritic	0	1 (1.2)	0	1 (0.3)	1 (0.2)
hepatotoxicity	4 (3.1)	0	14 (4.8)	14 (3.8)	18 (3.2)
Aspartate aminotransferase increased	2 (1.5)	0	9 (3.1)	9 (2.4)	10 (1.8)
Alanine aminotransferase increased	2 (1.5)	0	7 (2.4)	7 (1.9)	9 (1.6)
Gamma-glutamyltransferase increased	0	0	3 (1.0)	3 (0.8)	3 (0.5)
Hepatic function abnormal	0	0	1 (0.3)	1 (0.3)	2 (0.4)
Transaminases increased	1 (0.8)	0	2 (0.7)	2 (0.5)	2 (0.4)
Blood bilirubin increased	1 (0.8)	0	1 (0.3)	1 (0.3)	1 (0.2)
Immune-mediated hepatitis	0	0	0	0	1 (0.2)
Lung toxicity	1 (0.8)	0	5 (1.7)	5 (1.3)	7 (1.3)
Immune-mediated pneumonitis	1 (0.8)	0	4 (1.4)	4 (1.1)	5 (0.9)
Immune-mediated lung disease	0	0	0	0	1 (0.2)
Interstitial lung disease	0	0	1 (0.3)	1 (0.3)	1 (0.2)
Gastrointestinal toxicity	0	1 (1.2)	3 (1.0)	4 (1.1)	4 (0.7)
Diarrhoea	0	0	3 (1.0)	3 (0.8)	3 (0.5)

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irAE Group irAE Subgroup PT	NPC 200mg Q2W (N=130)	All Tumor Types 200mg Q2W Ex-Asia (N=83)	Asia (N=289)	Total (N=372)	All Doses Total (N=558)
Autoimmune colitis	0	1 (1.2)	0	1 (0.3)	1 (0.2)
Renal toxicity	0	0	2 (0.7)	2 (0.5)	4 (0.7)
Blood creatinine increased	0	0	0	0	1 (0.2)
Mesangioproliferative glomerulonephritis	0	0	1 (0.3)	1 (0.3)	1 (0.2)
Renal impairment	0	0	0	0	1 (0.2)
Renal injury	0	0	1 (0.3)	1 (0.3)	1 (0.2)
Rheumatoid/Skeletal muscle toxicity	1 (0.8)	1 (1.2)	1 (0.3)	2 (0.5)	3 (0.5)
Arthralgia	0	1 (1.2)	0	1 (0.3)	1 (0.2)
Arthritis	1 (0.8)	0	1 (0.3)	1 (0.3)	1 (0.2)
Blood creatine phosphokinase increased	0	0	0	0	1 (0.2)
Hematotoxicity	1 (0.8)	0	1 (0.3)	1 (0.3)	1 (0.2)
Other hematotoxicity	1 (0.8)	0	1 (0.3)	1 (0.3)	1 (0.2)
Lymphocyte count decreased	1 (0.8)	0	1 (0.3)	1 (0.3)	1 (0.2)
Neurotoxicity	0	0	1 (0.3)	1 (0.3)	1 (0.2)
Nerve injury	0	0	1 (0.3)	1 (0.3)	1 (0.2)

Source: ISS Combined Supplementary Tables, Table 5.2.1.

Endocrine Toxicity

Hypothyroidism

Hypothyroidism occurred in 81 (14.5%) patients, including 48 (8.6%) Grade 1 and 33 (5.9%) Grade 2 irAEs. No patient experienced a serious irAE. 7 (1.3%) patients experienced irAEs leading to drug interruption. No patient experienced irAEs leading to drug discontinuation.

Hyperthyroidism

Hyperthyroidism occurred in 33 (5.9%) of patients, including 27 (4.8%) Grade 1 and 6 (1.1%) Grade 2 irAEs. No patient experienced a serious irAE. 2 (0.4%) patients experienced irAEs leading to drug interruption. No patient experienced irAEs leading to drug discontinuation.

Other Thyroid Diseases

Other thyroid diseases occurred in 5 (0.9%) of patients, including 2 (0.4%) Grade 1 and 3 (0.5%) Grade 2 irAEs. No patient experienced a serious irAE. 3 (0.5%) patients experienced irAEs leading to drug interruption. No patient experienced irAEs leading to drug discontinuation.

Hyperglycaemia/Type 1 diabetes mellitus

Hyperglycaemia/type 1 diabetes mellitus occurred in 5 (0.9%) of patients, all Grade 1 irAEs. No patient experienced a serious irAE, irAEs leading to drug interruption, or irAEs leading to drug discontinuation.

Hypophysitis

In overall monotherapy population, only one patient developed immune-mediated hypophysitis,

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which was CTCAE grade 3 and a serious irAE. No irAE leading to interruption or permanent discontinuation of penpulimab.

Adrenal insufficiency

In overall monotherapy population, only one patient developed immune-mediated adrenal insufficiency, which was CTCAE grade 3. There was no serious irAE. No irAE leading to interruption or permanent discontinuation of penpulimab.

Dermatologic Toxicity

Dermatologic toxicity occurred in 53 (9.5%) of patients, including 31 (5.6%) Grade 1, 16 (2.9%) Grade 2 and 6 (1.1%) Grade 3 irAEs. 3 (0.5%) patients experienced a serious irAE. 7 (1.3%) patients experienced irAEs leading to drug interruption. 2 (0.4%) patients experienced irAEs leading to drug discontinuation.

Pulmonary Toxicity

Pulmonary toxicity occurred in 7 (1.3%) patients, including 2 (0.4%) Grade 1, 3 (0.5%) Grade 2 and 2 (0.4%) Grade 3 irAEs. 3 (0.5%) patients experienced a serious irAE. 1 (0.2%) patient experienced irAEs leading to drug interruption. 4 (0.7%) patients experienced irAEs leading to drug discontinuation.

Hepatotoxicity

Hepatotoxicity occurred in 18 (3.2%) patients, including 7 (1.3%) Grade 1, 6 (1.1%) Grade 2 and 5 (0.9%) Grade 3 irAEs. 5 (0.9%) patients experienced a serious irAE. 9 (1.6%) patients experienced irAEs leading to drug interruption. 2 (0.4%) patients experienced irAEs leading to drug discontinuation.

Gastrointestinal Toxicity

Gastrointestinal toxicity occurred in 4 (0.7%) patients, including 1 (0.2%) Grade 1 and 3 (0.5%) Grade 2 irAEs. No patient experienced a serious irAE. 3 (0.5%) patients experienced irAEs leading to drug interruption. No patient experienced irAEs leading to drug discontinuation.

Renal Toxicity

Renal toxicity occurred in 4 (0.7%) patients, including 3 (0.5%) Grade 2 and 1 (0.2%) Grade 3 irAEs. 2 (0.4%) patients experienced a serious irAE. No patient experienced irAEs leading to drug interruption. 2 (0.4%) patients experienced irAEs leading to drug discontinuation.

Musculoskeletal Toxicity

Musculoskeletal toxicity occurred in 3 (0.5%) patients, including 1 (0.2%) Grade 1 and 2 (0.4%) Grade 2 irAEs. No patient experienced a serious irAE. 3 (0.5%) patients experienced irAEs leading to drug interruption. No patient experienced irAEs leading to drug discontinuation.

Hematological Toxicity

In overall monotherapy population, only one patient developed lymphocyte count decreased,

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which was CTCAE grade 2. There was no serious irAE. No irAE leading to interruption or permanent discontinuation of penpulimab.

Nervous System Toxicity

In overall monotherapy population, only one patient developed immune-mediated nerve injury, which was CTCAE grade 2. There was no serious irAE. No irAE leading to interruption or permanent discontinuation of penpulimab.

Combination Therapy Part

irAEs occurred in patient population receiving penpulimab combination therapy are summarized by irAE Group, Subgroup and PT in [Applicant – Table 35](#).

Applicant – Table 35 irAEs Summarized by irAE Group, Subgroup and PT in Trials with Penpulimab Combination Therapy

irAE Group irAE Subgroup PT	AK105-304		AK105-302	AK105-301	AK105-205
	Penpulimab + GP (N=146)	Placebo + GP (N=142)	Penpulimab + TC (N=173)	Penpulimab + PC (N=46)	Penpulimab+ Chemo±Anlotinib (N=28)
Number of Subjects with at Least One irAE	45 (30.8)	12 (8.5)	47 (27.2)	8 (17.4)	8 (28.6)
Endocrine toxicity	29 (19.9)	8 (5.6)	15 (8.7)	4 (8.7)	8 (28.6)
Hypothyroidism	26 (17.8)	6 (4.2)	9 (5.2)	3 (6.5)	8 (28.6)
Hypothyroidism	24 (16.4)	3 (2.1)	9 (5.2)	3 (6.5)	8 (28.6)
Blood thyroid stimulating hormone increased	3 (2.1)	3 (2.1)	0	0	0
Thyroxine free decreased	1 (0.7)	2 (1.4)	0	0	0
Tri-iodothyronine decreased	2 (1.4)	1 (0.7)	0	0	0
Secondary hypothyroidism	1 (0.7)	0	0	0	0
Tri-iodothyronine free decreased	1 (0.7)	0	0	0	0
Hyperthyroidism	3 (2.1)	2 (1.4)	7 (4.0)	1 (2.2)	1 (3.6)
Hyperthyroidism	3 (2.1)	1 (0.7)	7 (4.0)	1 (2.2)	1 (3.6)
Thyroxine increased	0	2 (1.4)	0	0	0
Tri-iodothyronine free increased	0	1 (0.7)	0	0	0
Hyperglycaemia/Type 1 diabetes mellitus	4 (2.7)	0	0	0	0
Diabetic ketoacidosis	2 (1.4)	0	0	0	0
Hyperglycaemia	2 (1.4)	0	0	0	0
Blood glucose increased	1 (0.7)	0	0	0	0
Diabetes mellitus	1 (0.7)	0	0	0	0
Type 1 diabetes mellitus	1 (0.7)	0	0	0	0
Other thyroid diseases	0	1 (0.7)	3 (1.7)	0	0
Thyroid disorder	0	1 (0.7)	1 (0.6)	0	0
Thyroiditis	0	0	2 (1.2)	0	0
Hypophysitis	0	0	1 (0.6)	2 (4.3)	0
Blood corticotrophin decreased	0	0	1 (0.6)	0	0
Cortisol decreased	0	0	0	1 (2.2)	0
Hypophysitis	0	0	0	1 (2.2)	0
Adrenal insufficiency	0	0	1 (0.6)	0	0
Adrenal insufficiency	0	0	1 (0.6)	0	0
Parathyroid disease	0	0	0	0	1 (3.6)
Hypoparathyroidism	0	0	0	0	1 (3.6)

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irAE Group irAE Subgroup PT	AK105-304		AK105-302	AK105-301	AK105-205
	Penpulimab + GP (N=146)	Placebo + GP (N=142)	Penpulimab + TC (N=173)	Penpulimab + PC (N=46)	Penpulimab+ Chemo±Anlotinib (N=28)
Dermatologic toxicity	14 (9.6)	4 (2.8)	22 (12.7)	1 (2.2)	1 (3.6)
Rash	11 (7.5)	4 (2.8)	15 (8.7)	1 (2.2)	0
Pruritus	2 (1.4)	1 (0.7)	5 (2.9)	0	1 (3.6)
Rash generalised	0	0	3 (1.7)	0	0
Dermatitis acneiform	2 (1.4)	0	0	0	0
Dermatitis allergic	1 (0.7)	0	0	0	0
Drug eruption	1 (0.7)	0	0	0	0
Eczema	0	0	1 (0.6)	0	0
Pruritus generalised	0	0	1 (0.6)	0	0
Lung toxicity	1 (0.7)	0	8 (4.6)	1 (2.2)	0
Immune-mediated pneumonitis	0	0	5 (2.9)	1 (2.2)	0
Interstitial lung disease	0	0	2 (1.2)	0	0
Organising pneumonia	1 (0.7)	0	0	0	0
Pneumonitis	0	0	1 (0.6)	0	0
hepatotoxicity	1 (0.7)	0	5 (2.9)	0	0
Alanine aminotransferase	1 (0.7)	0	2 (1.2)	0	0
increased					
Aspartate aminotransferase	1 (0.7)	0	2 (1.2)	0	0
increased					
Hepatic function abnormal	0	0	3 (1.7)	0	0
Gamma-glutamyltransferase	0	0	2 (1.2)	0	0
increased					
Immune-mediated hepatitis	0	0	1 (0.6)	0	0
Pancreatic toxicity	2 (1.4)	0	0	0	1 (3.6)
Lipase increased	1 (0.7)	0	0	0	1 (3.6)
Pancreatitis	1 (0.7)	0	0	0	0
Gastrointestinal toxicity	0	0	1 (0.6)	1 (2.2)	0
Colitis ulcerative	0	0	1 (0.6)	0	0
Diarrhoea	0	0	0	1 (2.2)	0
Rheumatoid/Skeletal muscle toxicity	1 (0.7)	0	1 (0.6)	0	0
Arthralgia	0	0	1 (0.6)	0	0
Arthritis	1 (0.7)	0	0	0	0
Synovitis	1 (0.7)	0	0	0	0
Hematotoxicity	1 (0.7)	0	0	0	0
Thrombocytopenia	1 (0.7)	0	0	0	0
Platelet count decreased	1 (0.7)	0	0	0	0
Renal toxicity	0	0	0	1 (2.2)	0
Blood creatinine increased	0	0	0	1 (2.2)	0

Source: [Module 5.3.5.3, ISS, Appendix 3.5, Table 5.2.2.](#)

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Endocrine Toxicity

Hypothyroidism

In patients treated with penpulimab 200mg Q3W in combination with cisplatin/carboplatin and gemcitabine in AK105-304, hypothyroidism occurred in 26 (17.8%) of patients, including 7 (4.8%) Grade 1 and 19 (13.0%) Grade 2 irAEs. No patient experienced a serious irAE. 1 (0.7%) patient experienced irAEs leading to drug interruption. No patient experienced irAEs leading to drug discontinuation.

Hyperthyroidism

In patients treated with penpulimab 200mg Q3W in combination with cisplatin/carboplatin and gemcitabine in AK105-304, hyperthyroidism occurred in 3 (2.1%) of patients, including 2 (1.4%) Grade 1 and 1 (0.7%) Grade 2 irAEs. There was no serious irAE. No irAE leading to interruption or permanent discontinuation of penpulimab.

Hyperglycaemia/Type 1 diabetes mellitus

In patients treated with penpulimab 200mg Q3W in combination with cisplatin/carboplatin and gemcitabine in AK105-304, hyperglycaemia/type 1 diabetes mellitus occurred in 4 (2.7%) of patients, including 1 (0.7%) Grade 1, 1 (0.7%) Grade 2, 1 (0.7%) Grade 3 and 1 (0.7%) Grade 4 irAEs. 2 (1.4%) patients experienced a serious irAE. 1 (0.7%) patient experienced irAEs leading to drug interruption. 1 (0.7%) patient experienced irAEs leading to drug discontinuation.

Dermatologic Toxicity

In patients treated with penpulimab 200mg Q3W in combination with cisplatin/carboplatin and gemcitabine in AK105-304, dermatologic toxicity occurred in 14 (9.6%) of patients, including 6 (4.1%) Grade 1, 7 (4.8%) Grade 2 and 1 (0.7%) Grade 3 irAEs. 1 (0.7%) patient experienced a serious irAE. 2 (1.4%) patients experienced irAEs leading to drug interruption. No patient experienced irAEs leading to drug discontinuation.

Pulmonary Toxicity

In patients treated with penpulimab 200mg Q3W in combination with cisplatin/carboplatin and gemcitabine in AK105-304, only one patient (0.7%) developed pulmonary toxicity, which was CTCAE grade 2 and a serious irAE. The irAE led to interruption of penpulimab but didn't lead to permanent discontinuation of penpulimab.

Hepatotoxicity

In patients treated with penpulimab 200mg Q3W in combination with cisplatin/carboplatin and gemcitabine in AK105-304, only one patient (0.6%) developed hepatotoxicity, Grade 2. The event was not a serious irAE. The event led to interruption of penpulimab but didn't lead to permanent discontinuation of penpulimab.

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Musculoskeletal Toxicity

In patients treated with penpulimab 200mg Q3W in combination with cisplatin/carboplatin and gemcitabine in AK105-304, only one patient (0.7%) developed musculoskeletal toxicity, which was CTCAE grade 3 and was a serious irAE. The irAE led to interruption of penpulimab but didn't lead to permanent discontinuation of penpulimab.

Hematological Toxicity

In patients treated with penpulimab 200mg Q3W in combination with cisplatin/carboplatin and gemcitabine in AK105-304, only one patient (0.7%) developed thrombocytopenia, which was CTCAE grade 4 and was a serious irAE. The irAE led to interruption of penpulimab but didn't lead to permanent discontinuation of penpulimab.

Pancreatic Toxicity

In patients treated with penpulimab 200mg Q3W in combination with cisplatin/carboplatin and gemcitabine in AK105-304, pancreatic toxicity occurred in 2 (1.4%) of patients, including 1 (0.7%) Grade 2 and 1 (0.7%) Grade 3 irAEs. 2 (1.4%) patients experienced a serious irAE. No patient experienced irAEs leading to drug interruption. 1 (0.7%) patient experienced irAEs leading to drug discontinuation.

The Applicant's Position:

In the overall monotherapy population, the most commonly (the incidence of PT $\geq$ 1%) reported irAEs included hypothyroidism, blood thyroid stimulating hormone increased, thyroxine free decreased, hyperthyroidism, blood thyroid stimulating hormone decreased, rash, pruritus, rash generalised, alanine aminotransferase increased and aspartate aminotransferase increased.

Compared with monotherapy with penpulimab, the combination of penpulimab and chemotherapy did not increase the incidence of irAEs, and the incidence of irAEs in various organs was low. The incidence of hypothyroidism was relatively high, which may also be related to a history of previous radiotherapy. 67.5% of the enrolled patients had recurrent nasopharyngeal carcinoma and had previously received neck radiotherapy, so thyroid damage may have already existed at baseline. Moreover, immune-related endocrine toxicity can be controlled with hormone replacement therapy, and there was no significant safety risk.

The development of irAEs was expected based on the mechanism of action of the drug. The pattern, incidence and severity of irAEs was consistent with other PD-1 inhibitors and was manageable with the use of appropriate dose interruption and immunosuppressants.

The FDA's Assessment:

FDA reviewed the Applicant adjudicated immune-related AEs (irAEs) in AK105-304, AK105-202, and in the pooled safety dataset. Given the potential delayed onset of irAEs, FDA's review includes adverse events that occurred up to 90 days after the last dose of treatment with penpulimab or placebo.

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FDA – Table 24. Immune-Related Adverse Events (irAEs) in the Penpulimab or Placebo +Chemotherapy Arms of AK105-304

irAE	Penpulimab+Chemotherapy (N=146)		Placebo+Chemotherapy (N=142)	
	Grade 1-5 n (%)	Grade 3-4 n (%)	Grade 1-5 n (%)	Grade 3-4 n (%)
Any irAE	45 (30.8)	6 (4.1)	12 (8.5)	0
Endocrine toxicity				
Hypothyroidism	24 (16.4)	0	3 (2.1)	0
Blood thyroid stimulating hormone increased	3 (2.1)	0	3 (2.1)	0
Thyroxine free decreased	1 (0.7)	0	2 (1.4)	0
Tri-iodothyronine decreased	2 (1.4)	0	1 (0.7)	0
Secondary hypothyroidism	1 (0.7)	0	0	0
Tri-iodothyronine free decreased	1 (0.7)	0	0	0
Hyperthyroidism	3 (2.1)	0	1 (0.7)	0
Thyroxine increased	0	0	2 (1.4)	0
Tri-iodothyronine free increased	0	0	1 (0.7)	0
Diabetic ketoacidosis	2 (1.4)	2 (1.4)	0	0
Hyperglycemia	2 (1.4)	0	0	0
Blood glucose increased	1 (0.7)	0	0	0
Diabetes mellitus	1 (0.7)	1 (0.7)	0	0
Type 1 diabetes mellitus	1 (0.7)	1 (0.7)	0	0
Dermatologic toxicity				
Rash	11 (7.5)	0	4 (2.8)	0
Pruritus	2 (1.4)	0	1 (0.7)	0
Dermatitis acneiform	2 (1.4)	1 (0.7)	0	0
Dermatitis allergic	1 (0.7)	0	0	0
Drug eruption	1 (0.7)	0	0	0
Lung toxicity				
Organizing pneumonia	1 (0.7)	0	0	0
Hepatotoxicity				
Alanine aminotransferase increased	1 (0.7)	0	0	0
Aspartate aminotransferase increased	1 (0.7)	0	0	0
Pancreatic toxicity				
Lipase increased	1 (0.7)	1 (0.7)	0	0
Pancreatitis	1 (0.7)	0	0	0
Rheumatoid/Skeletal muscle toxicity				
Arthritis	1 (0.7)	1 (0.7)	0	0
Synovitis	1 (0.7)	1 (0.7)	0	0
Hematotoxicity				
Platelet count decreased	1 (0.7)	1 (0.7)	0	0

Sources: ADAE

FDA – Table 25. Immune-Related Adverse Events (irAEs) in the Penpulimab Monotherapy Trial of AK105-202 or the Safety Set

irAE	NPC 200mg Q2W (N=130)		Safety Set (N=372)	
	All Grades n (%)	Grade 3-4 n (%)	All Grades n (%)	Grade 3-4 n (%)
Any irAE	29 (22.3)	13 (10.0)	76 (20.4)	40 (10.8)
Endocrine toxicity				
Hypothyroidism	17 (13.1)	0	34 (9.1)	0
Thyroxine free decreased	1 (0.8)	0	1 (0.3)	0
Tri-iodothyronine free decreased	1 (0.8)	0	1 (0.3)	0
Dermatologic toxicity				
Rash	7 (5.4)	2 (1.5)	17 (4.6)	5 (1.3)
Eczema	1 (0.8)	0 (0.0)	2 (0.5)	1 (0.3)
Dermatitis acneiform	1 (0.8)	0	1 (0.3)	0
Dermatitis allergic	1 (0.8)	0	1 (0.3)	0
Pemphigoid	1 (0.8)	1 (0.8)	1 (0.3)	1 (0.3)
Pruritus	0	0	2 (0.5)	0
Rash generalized	0	0	2 (0.5)	0
Rash maculo-papular	0	0	2 (0.5)	0
Dermatitis	0	0	1 (0.3)	0
Lichen planus	0	0	1 (0.3)	0
Hyperthyroidism	6 (4.6)	0	19 (5.1)	0
Blood thyroid stimulating hormone decreased	3 (2.3)	0	5 (1.3)	0
Thyroxine free increased	2 (1.5)	0	3 (0.8)	0
Tri-iodothyronine free increased	0	0	2 (0.5)	0
Tri-iodothyronine increased	0	0	1 (0.3)	0
Immune-mediated pneumonitis	1 (0.8)	0	4 (1.1)	2 (0.5)
Other thyroid diseases				
Autoimmune thyroid disorder	1 (0.8)	0	1 (0.3)	0
Thyroiditis	1 (0.8)	0	1 (0.3)	0
Autoimmune thyroiditis	0	0	1 (0.3)	0
Thyroid mass	0	0	1 (0.3)	0
Hepatotoxicity hepatitis				
Alanine aminotransferase increased	0	0	2 (0.5)	2 (0.5)
Aspartate aminotransferase increased	0	0	2 (0.5)	2 (0.5)
Gastrointestinal toxicity diarrhea/colitis				
Diarrhea	0	0	2 (0.5)	2 (0.5)
Autoimmune colitis	0	0	1 (0.3)	0
Neurotoxicity				
Nerve injury	0	0	1 (0.3)	0
Nephritis				
Mesangioproliferative glomerulonephritis	0	0	1 (0.3)	0
Renal injury	0	0	1 (0.3)	1 (0.3)

irAE	NPC 200mg Q2W (N=130)		Safety Set (N=372)	
	All Grades n (%)	Grade 3-4 n (%)	All Grades n (%)	Grade 3-4 n (%)
Rheumatoid / Skeletal muscle toxicity Arthralgia	0	0	1 (0.3)	1 (0.3)

Sources: ADAE

FDA's analysis of irAEs agrees with the Applicant's position. Overall, the most common irAEs were endocrinopathies and dermatitis. There was a very low rate of colitis or pneumonitis amongst populations receiving penpulimab with 2 cases of Grade 3 colitis in the integrated safety set and one case of less than Grade 3 pneumonitis in the penpulimab NPC population in AK105-202. Neither or these irAEs were noted in the first line indication alongside chemotherapy in AK105-304.

8.2.5.2. Infusion-Related Reactions

NPC 200mg Q2W population

5 patients (3.8%) experienced infusion-related reactions, including Grade 1 in 4 patients, Grade 2 in 1 patient. No patient occurred Grade 3-4 infusion-related reactions. No patient experienced serious infusion-related reaction, infusion-related reactions leading to interruption of penpulimab or infusion-related reaction leading to permanent discontinuation of penpulimab. No patient received systemic corticosteroid therapies. All these 5 patients had recovered/resolved.

Penpulimab 200mg Q2W population

38 patients (10.2%) experienced infusion-related reactions, including Grade 1 in 14 patients, Grade 2 in 22 patients. 2 patients occurred Grade 3-4 infusion-related reactions. 3 patients (0.8%) experienced serious infusion-related reaction. Infusion-related reaction led to interruption of penpulimab in 3 patients (0.8%) and 1 patients (0.3%) occurred infusion-related reaction resulted in permanent discontinuation of penpulimab. 8 patients (2.2%) received systemic corticosteroid therapies. All these 38 patients had recovered/resolved.

Overall Monotherapy population

41 patients (7.3%) experienced infusion-related reactions, including Grade 1 in 15 patients, Grade 2 in 23 patients. 3 patients had Grade 3-4 infusion-related reactions. 4 patients (0.7%) experienced serious infusion-related reaction. Infusion-related reaction led to interruption of penpulimab occurred in 3 patients (0.5%) and 2 patients (0.4%) had infusion-related reaction resulted in permanent discontinuation of penpulimab. 9 patients (1.6%) received systemic corticosteroid therapies. All these 41 patients had recovered/resolved.

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5 patients (3.4%) experienced infusion-related reactions, including Grade 1 in 3 patients, Grade

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2 in 2 patients. No Grade 3-4 infusion-related reaction occurred. There was no serious infusion-related reaction, infusion-related reactions leading to interruption of penpulimab or infusion-related reactions leading to permanent discontinuation of penpulimab. 1 patient (0.7%) received systemic corticosteroid therapies. All these 5 patients had recovered/resolved.

The Applicant's Position:

In the overall monotherapy population, The most commonly (the incidence of PT $\geq 1\%$) reported irAEs included hypothyroidism, blood thyroid stimulating hormone increased, thyroxine free decreased, hyperthyroidism, blood thyroid stimulating hormone decreased, rash, pruritus, rash generalised, alanine aminotransferase increased and aspartate aminotransferase increased.

Compared with monotherapy with penpulimab, the combination of penpulimab and chemotherapy did not increase the incidence of irAEs, and the incidence of irAEs in various organs was low. The incidence of hypothyroidism was relatively high, which may also be related to a history of previous radiotherapy. 67.5% of the enrolled patients had recurrent nasopharyngeal carcinoma and had previously received neck radiotherapy, so thyroid damage may have already existed at baseline. Moreover, immune-related endocrine toxicity can be controlled with hormone replacement therapy, and there was no significant safety risk.

The FDA's Assessment:

FDA generally agrees with the Applicant's position. In AK105-304, no patients experienced an infusion-related reaction in the penpulimab arm. Infusion-related reactions occurred in 3.4% and 10% of patients in AK105-202 and the pooled safety dataset, respectively.

8.2.6. Clinical Outcome Assessment (COA) Analyses Informing Safety/Tolerability

Data:

On AK105-304, the EORTC QLQ-C30 global health status/QoL and each functional scale score at baseline and each visit, as well as the change from baseline to the last assessment in the study are summarized in Table 14.2.6.1 in Section 14 of 5.3.5.1 AK105-304 CSR. There was no notable difference in the trend of score changes between the two groups.

The changes in EORTC QLQ-H&N43 up to the last assessment in the study are summarized in Table 14.2.6.2 in Section 14 of 5.3.5.1 AK105-304 CSR. No notable differences were found between the two groups.

No clinical outcome assessments were performed on AK105-202.

The Applicant's Position:

Akeso does not intend to make any claims with respect to the patient reported outcomes.

The FDA's Assessment:

FDA agrees with the Applicant's position.

8.2.7. Safety Analyses by Demographic Subgroups

Data:

This section summarizes the relationship between various intrinsic factors and the safety profile of penpulimab. These data are relevant to patient management based on demographic or other "intrinsic" factors. Only notable differences ($\geq 10\%$) are discussed.

The safety profile of penpulimab was assessed in relation to the following intrinsic factors:

- Age group (< 65 years; ≥ 65 years)
- [REDACTED] (male; female)
- ECOG (0;1)
- Race (Asian; Non-Asian)

All AEs Subgroup Analysis were summarized in [Module 5.3.5.3, ISS, Appendix 3.5, Table 4.2.2, Table 4.5.1.2, Table 4.9.1.2, Table 5.2.4 and ISS Combined Supplementary Tables, Table 4.2.1, Table 4.5.1.1, Table 4.9.1.1, Table 5.2.3.](#)

Age (<65 vs ≥ 65)

In overall penpulimab monotherapy population, there was no appreciable difference between age subgroups for any of the AE categories. The differences between age subgroups in the NPC 200mg Q2W population cannot be assessed due to only 2 patients with age ≥ 65 years enrolled.

Among patients in AK105-302 study, serious TEAEs and TEAEs leading to drug interruption occurred at a higher rate in females than in males.

The differences between age subgroups in other studies of penpulimab combination therapy cannot be assessed due to the small sample size of the patients with age ≥ 65 years (15 patients in AK105-304, 18 patients in AK105-301, and 3 patients in AK105-205).

[REDACTED]

In overall penpulimab monotherapy population, the AE profile of penpulimab was generally similar between females and males.

In NPC 200mg Q2W population, serious TEAEs occurred at a slightly higher rate in females than in males (25.8% vs 23.2%, respectively), as well as TEAEs leading to drug interruption (29.0% vs 26.3%, respectively) and TEAEs leading to drug discontinuation (6.5% vs 3.0%, respectively), this observation should be interpreted in the context of the small sample size of the female subgroup (31 patients).

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Among patients in AK105-304 study, TEAEs of CTCAE grade 3 or higher, serious TEAEs, and TEAEs leading to drug interruption occurred at a higher rate in females than in males, which should be interpreted in the context of the small sample size of the female subgroup (26 females in penpulimab group).

Among patients receiving other penpulimab combination therapy, the number of female patients was too small to assess the differences (13 females in AK105-302, 14 females in AK105-301, and 3 females in AK105-205).

ECOG performance status

In overall penpulimab monotherapy population, the incidence of events was similar in patients with a baseline ECOG performance status of 0 and 1 for most AE categories. However, notable differences were observed for Grade 3 or higher TEAEs (29.9% vs 38.3%) and SAEs (20.4% vs 28.8%), all of which occurred at a higher rate in patients with an ECOG performance status of 1 compared with ECOG performance status of 0.

Among patients in AK105-304 study, the incidence of events was similar in patients with a baseline ECOG performance status of 0 and 1. Among patients in AK105-302 study, TEAEs of CTCAE grade 3 or higher, serious TEAEs, and TEAEs leading to drug interruption occurred at a higher rate in patients with an ECOG performance status of 1 compared with ECOG performance status of 0.

The differences between ECOG subgroups in other studies of penpulimab combination therapy cannot be assessed due to the small sample size.

Race

For penpulimab monotherapy, the safety subgroup analysis revealed no clinically relevant differences in the incidence, nature, or severity of AEs between Asian and non-Asian patients.

The differences between race subgroups in penpulimab combination therapy cannot be assessed due to only 6 non-Asian patients enrolled.

The Applicant's Position:

The AE profile for penpulimab monotherapy population and combination therapy was generally similar across subgroups based on age and sex.

The incidence of AEs of any grade was generally similar between ECOG subgroup, and lower incidence rate of grade 3 or higher TEAEs, SAEs, and TEAEs leading to drug interruption in patients with ECOG performance status of 0 were observed.

The similarity in the safety profiles across ethnic groups suggests that the pharmacological activity and safety profile of penpulimab are not significantly influenced by ethnicity.

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The FDA's Assessment:

FDA reviewed the incidence of AEs by age and sex in the primary and pooled safety populations and agrees with the Applicant's position. A review of safety by race and ethnicity was not possible for the primary safety population given that all patients enrolled in Study AK105-202 were Asian.

8.2.8. Specific Safety Studies/Clinical Trials

Data:

N/A

The Applicant's Position:

N/A

The FDA's Assessment:

N/A

8.2.9. Additional Safety Explorations

Human Carcinogenicity or Tumor Development

Data:

N/A

The Applicant's Position:

No assessment of human carcinogenicity or tumor development was performed.

The FDA's Assessment:

FDA agrees with the Applicant's position.

Human Reproduction and Pregnancy

Data:

N/A

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The Applicant's Position:

Penpulimab has not been studied in pregnant or breastfeeding women. As of the DCO dates for studies on dosing regimen of penpulimab 200 mg Q2W, there were no reports of pregnancies or pregnancy-related events in either study. Based on its mechanism of action, penpulimab has the potential to impact maintenance of pregnancy and may cause fetal harm when administered to a pregnant woman. Human IgG1 is known to cross the placental barrier; therefore, penpulimab has the potential to be transmitted from the mother to the developing fetus. penpulimab is not recommended during pregnancy and in women of childbearing potential not using effective contraception during treatment and for at least 3 months after the last dose.

There is no information regarding the presence of penpulimab in human milk, the absorption and effects on the breastfed infant, or the effects on milk production. Human IgG is excreted in human milk. Because of the potential for adverse reactions in breastfed infants from penpulimab, advise a lactating women not to breastfeed during treatment and for at least 5 months after the last dose.

The FDA's Assessment:

See FDA's Assessment in Section 5.5.4 (Reproductive and Developmental Toxicity) of this review.

Pediatrics and Assessment of Effects on Growth

Data:

The Sponsor planned to recruit adolescents with NPC aged ≤ 12 years in the study of AK105-304. However, due to the low incidence, no patient in this age group was enrolled.

The Applicant's Position:

Pediatric data is not available.

The FDA's Assessment:

FDA agrees with Applicant's position that the safety and effectiveness of penpulimab has not been established in pediatric patients under 12 years of age.

Overdose, Drug Abuse Potential, Withdrawal, and Rebound

Data:

There are no available safety data for penpulimab overdose.

The Applicant's Position:

There is no specific treatment in the event of penpulimab overdose and possible symptoms have not been established.

As a result of its use, mode of action, physiological and pharmacological activity, and lack of stimulant properties, penpulimab monotherapy is unlikely to be abused. Because penpulimab has no known potential for dependence and is not continuously dosed, withdrawal or rebound events are not relevant to penpulimab dosing.

The FDA's Assessment:

FDA agrees with the Applicant's position.

8.2.10. Safety in the Postmarket Setting

Safety Concerns Identified Through Postmarket Experience

Data:

Cumulatively, 866 post-marketing adverse events were received from IBD by 29 Apr 2024, including 430 serious adverse events and 436 non-serious adverse events. Serious adverse events with the highest number of reports (≥ 8 events) included white blood cell count decreased, neutrophil count decreased, platelet count decreased, myelosuppression, rash, immune-mediated lung disease, dyspnoea, chest discomfort, drug-induced liver injury, hepatic function abnormal, hypothyroidism, immune-mediated myocarditis, anaphylactic shock.

The Applicant's Position:

The first indication of penpulimab (Approval Number: GYZZ S20210033) was conditionally approved for marketing in China on 3 Aug 2021 (International Birth Date, IBD). Penpulimab is indicated, as a single agent, for the treatment of adult patients with relapsed or refractory classical Hodgkin lymphoma who have failed at least two lines of systemic chemotherapy. For classical Hodgkin lymphoma, the recommended dosage is administered by intravenous infusion at a recommended dose of 200mg every 2 weeks until disease progression or unacceptable

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toxicity. The second indication was approved for marketing in China on 10 Jan 2024. Penpulimab is indicated, in combination with paclitaxel and carboplatin for the first-line treatment of locally advanced or metastatic squamous non-small cell lung cancer (NSCLC). For locally advanced or metastatic squamous NSCLC, the recommended dosage is 200mg every 3 weeks administered by intravenous infusion until disease progression or unacceptable toxicity. The third indication was approved in China on 24 Apr 2024. Penpulimab is indicated, as a single agent, for the treatment of adult patients with recurrent/metastatic nasopharyngeal cancer who have previously failed at least two lines of systemic therapy. For nasopharyngeal cancer, the recommended dosage is 200mg every 2 weeks administered by intravenous infusion until disease progression or unacceptable toxicity.

Estimated Post-marketing Exposure: cumulative sales was (b) (4) vials from IBD of penpulimab by 29 Apr 2024. The dose administered per patient was 2 vials each cycle; referring to the clinical trial data included in the approved package insert, the median duration of administration of single agent and in combination with chemotherapy was 113 days and 168 days, respectively, and so the median duration of administration of single agent and in combination with chemotherapy was about 8 cycles. Under these assumption, it is estimated that the cumulative number of patients treated with penpulimab in the post-marketing setting was (b) (4). However, considering medication compliance, the actual number of cycles should be fewer than 8 and the actual number of treated patients was more than (b) (4).

Based on the analysis of the post-marketing safety data, mechanism of action of the drug or adverse reaction profile of same class drugs, Marketing Authorization Holder applied to Center for Drug Evaluation, NMPA for revising the package insert of penpulimab to add the adverse reactions of exfoliative dermatitis, myocarditis and immune-mediated myocarditis on 12 Jul 2023 and was approved for revising the package insert on 30 Aug 2023. For other post-marketing reports, no sufficient evidence to prove that there was a definite causality relationship between the adverse events and penpulimab due to limited information or confounding factors. Lack of information on concomitant diseases, concomitant medication, diagnosis evidence of adverse events or medical history and limited follow-up information are prevalent in post marketing reports. Confounding factors such as different medication populations, different combined anti-tumor treatment regimens and differences in the patients' own conditions also existed during the assessment of adverse events.

Overall, the analysis of the post-marketing safety data supports the good tolerability of penpulimab and adequacy of the risk management plan. Benefit-risk profile continues to support further development of penpulimab.

The FDA's Assessment:

FDA agrees with the Applicant's position.

Expectations on Safety in the Postmarket Setting

Data:

New immune-related AEs may be identified in the postmarketing environment.

The Applicant's Position:

Akeso will continue to monitor the safety data of penpulimab and assess the benefit-risk balance of penpulimab. The immune-related AEs can be minimized by routine risk minimisation activities. According to the available safety and efficacy data, treatment with penpulimab is relatively safe and the benefit outweighs the risk.

The FDA's Assessment:

FDA agrees with the Applicant's position.

8.2.11. Integrated Assessment of Safety

Data:

N/A

The Applicant's Position:

In monotherapy part, the safety profile of penpulimab 200mg Q2W in NPC population is consistent with the well-characterized safety profile in the penpulimab 200mg Q2W population and overall monotherapy population. These observations indicate penpulimab being a well-tolerated drug as monotherapy. For penpulimab combination therapy, in the pivotal study AK105-304, the incidence of TEAEs and SAEs were found to be generally similar between the penpulimab group and placebo group. The overall safety profile of penpulimab was tolerable, manageable, and consistent with other marketed PD-1 inhibitors.

The demographic and disease characteristics of patients in the NPC 200mg Q2W monotherapy population and AK105-304 study were representative of the intended population to be treated in clinical practice.

NPC 200mg Q2W population in Monotherapy Part

Excluding disease progression, 123 out of 130 (94.6%) patients had at least one TEAE. Most patients had Grade 1 or 2 AEs; 38 (29.2%) patients had at least one $\geq$ Grade 3 TEAE. 35 (26.9%) patients experienced at least one AE leading to drug interruption. 5 (3.8%) patients experienced at least one TEAE leading to drug discontinuation. A total of 18 (13.8%) patients died due to AE,

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11 of these deaths were due to disease progression.

A total of 58 (44.6%) deaths occurred in NPC 200mg Q2W population. A total of 2 (1.5%) deaths occurred within 30 days after the last dose. Deaths between 30 and 90 days after the last dose occurred in 16 subjects (12.3%). Deaths more than 90 days after the last dose occurred in 40 subjects (30.8%).

18 (13.8%) patients had AEs that resulted in death, regardless of causality. Excluding disease progression, AEs with an outcome of death were reported in 7 (5.4%) patients: unexplained death in 3 patients (PID (b) (6), PID (b) (6), PID (b) (6)), respiratory failure in 2 patients, septic shock in 1 patient, and sudden death (PID (b) (6)) in 1 patient.

31 patients (23.8%) experienced at least one SAE. Excluding death and disease progression, the most commonly (the incidence of PT $\geq$ 1%) reported SAEs included pneumonia, lung infection, respiratory failure, pneumonitis, hepatic function abnormal, and rash.

5 (3.8%) patients experienced at least one TEAE leading to drug discontinuation. Drug-related AEs leading to drug discontinuation occurred in 4 (3.1%) patients.

The incidence of irAEs was 32.3% (42/130). The most commonly (the incidence of PT $\geq$ 1%) reported irAEs included hypothyroidism, blood thyroid stimulating hormone increased, thyroxine free decreased, tri-iodothyronine free decreased, hyperthyroidism, blood thyroid stimulating hormone decreased, thyroxine free increased, hyperglycaemia, rash, alanine aminotransferase increased and aspartate aminotransferase increased.

NPC population in Combination Part: AK105-304

In patients treated with penpulimab 200mg Q3W in combination with cisplatin/carboplatin and gemcitabine in AK105-304, 146 (100.0%) patients had at least one TEAE. 132 (90.4%) patients had at least one $\geq$ Grade 3 TEAE. The most commonly (the incidence of PT $\geq$ 20%) reported TEAEs with a marginally higher incidence in the penpulimab group included aspartate aminotransferase increased, weight decreased, blood creatinine increased, anaemia, vomiting, hyponatraemia, hypoalbuminaemia, hypokalaemia, hypochloraemia, pyrexia, COVID-19, cough and hypothyroidism. Common $\geq$ Grade 3 TEAEs (with an incidence of $\geq$ 2%) with a marginally higher incidence in the penpulimab group included lymphocyte count decreased, alanine aminotransferase increased, blood creatine phosphokinase increased, anaemia, pneumonia, COVID-19 pneumonia, hypokalaemia, hyponatraemia, hypocalcaemia, hypomagnesaemia, nausea, hypertension and disease progression.

In patients treated with penpulimab 200mg Q3W in combination with cisplatin/carboplatin and gemcitabine in AK105-304, 48 (32.9%) subjects in penpulimab group and 48 (33.8%) subjects in placebo group died. 2 (1.4%) and 3 (2.1%) subjects died within 30 days after the last dose; 6 (4.1%) and 3 (2.1%) subjects died within 31 to 90 days after the last dose; 40 (27.4%) and 42 (29.6%) subjects died more than 90 days after the last dose in penpulimab group and placebo group, respectively.

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In penpulimab group, 7 (4.8%) patients had AEs that resulted in death, regardless of causality. Excluding disease progression, AEs with an outcome of death were reported in 3 (2.1%) patients: death in 1 patient; COVID-19 pneumonia in 1 patient; cardiac failure in 1 patient.

In penpulimab group, 74 patients (50.7%) experienced at least one SAE. The most commonly (the incidence of PT $\geq$ 1%) reported SAEs (excluding disease progression) included platelet count decreased, white blood cell count decreased, neutrophil count decreased, blood creatinine increased, anaemia, febrile neutropenia, myelosuppression, pneumonia, upper respiratory tract infection, COVID-19 pneumonia, urinary tract infection, asthenia, epistaxis, hyponatraemia, diabetic ketoacidosis, arrhythmia and nausea.

In penpulimab group, the incidence of AEs leading to permanent discontinuation was 3.4% (5/146). Drug-related AE leading to permanent discontinuation occurred in 4 (2.7%) patients, including platelet count decreased, lipase increased, brain oedema, acute myocardial infarction, diabetic ketoacidosis, and hyperkalaemia.

45 of 146 (30.8%) patients had at least one irAE. The most commonly (the incidence of PT $\geq$ 1%) reported irAEs included hypothyroidism, blood thyroid stimulating hormone increased, tri-iodothyronine free decreased, hyperthyroidism, diabetic ketoacidosis, hyperglycaemia, rash, pruritus and dermatitis acneiform.

In addition, compared to penpulimab monotherapy, penpulimab combined with chemotherapy did not increase the incidence of irAEs.

Changes in laboratory parameters were predominantly Grade 1 or 2 in severity, and the incidence of any grade worsening to Grade 3 or 4 was generally low. Laboratory abnormalities reported as AEs infrequently resulted in discontinuation of penpulimab, suggesting a tolerable safety profile.

The safety profile was generally not affected by age, [REDACTED] and other factors (eg, ECOG performance status).

The FDA's Assessment:

FDA conducted the safety review of penpulimab in combination with cisplatin or carboplatin and gemcitabine in 146 patients with locally recurrent, unresectable or metastatic NPC who received penpulimab 200 mg Q3W in combination with cisplatin or carboplatin and gemcitabine in the AK105-304 trial. For penpulimab monotherapy, FDA conducted the safety review in 130 patients with locally recurrent or metastatic NPC whose disease progressed on or after platinum-containing chemotherapy and an additional line of therapy who received penpulimab 200 mg Q2W as a single agent in the AK105-202 trial and in a pooled dataset of 372 patients with various solid tumors or cHL who received penpulimab 200 mg Q2W as a single agent. FDA's review of deaths due to AEs in AK105-304, AK105-202, and the pooled safety dataset did not identify unexpected safety signals relative to other anti-PD-(L)1 antibodies.

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Discontinuation of penpulimab due to AEs occurred in 3.4% of patients in AK105-304, and in 3.8% and 5.9% of patients in the AK105-202 trial and the safety pooled dataset, respectively. In AK105-304, AK105-202, and the safety pooled dataset there were no AEs leading to discontinuation that were $\geq 1\%$. In AK105-304 one patient each discontinued penpulimab as a result of Grade 3-4 acute myocardial infarction, AKI, brain edema, DKA, lipase increased, and platelet count decreased. In AK105-202 one patient each discontinued penpulimab due to Grade 3-4 herpes zoster disseminated, pleural effusion, rash, spinal cord compression, and transaminases increased. For the pooled safety population 3 patients discontinued for any grade pneumonitis, 2 for pleural effusion, 2 for GI hemorrhage, and one each for herpes zoster disseminated, rash, spinal cord compression, transaminases increased, ascites, colitis, pelvic infection, septic shock, cholangitis, hemophagocytic lymphohistiocytosis, hypersensitivity, cerebral infarction, epilepsy, mesangioproliferative glomerulonephritis, and renal injury.

Adverse events leading to penpulimab dose interruptions occurred in 64%, 25%, and 26% of patients in AK105-304, AK105-202, and the pooled safety dataset, respectively. In AK105-304, the most frequent AEs leading to dose interruptions ($\geq 2\%$) were Covid19, anemia, thrombocytopenia, white blood cell count decreased, neutrophil count decreased, COVID 19 pneumonia, pneumonia, ALT increased, hyponatremia, AST increased, asymptomatic COVID 19, creatinine increased, pyrexia, and URI. In AK105-202, the most frequent AEs leading to dose interruptions ($\geq 1\%$) were pneumonia, anemia, hypothyroidism, hepatic function abnormal, pneumonitis, rash, and ALT increased. Amongst the pooled safety set these plus AST increased, lung infection, and diarrhea occurred in $\geq 1\%$.

Serious adverse reactions events (SAEs) occurred in 51%, 22%, and 27% of patients in AK105-304, AK105-202, and the pooled safety dataset, respectively. In AK105-304, the most frequent SAEs ($\geq 2\%$) were platelet count decreased, neutrophil count decreased, wbc count decreased, anemia, myelosuppression, COVID19 pneumonia, pneumonia, hyponatremia, and nausea. In AK105-202, the most frequent SAEs ($\geq 2\%$) was only pneumonia while in the pooled safety set no SAE was $\geq 2\%$.

In AK105-304, the most frequent irAEs ($\geq 2\%$) were hypothyroidism, TSH increased, hyperthyroidism, and rash. For AK105-202 and the pooled safety set the most frequent irAEs ($\geq 2\%$) were hypothyroidism, rash, hyperthyroidism, and TSH increased. On FDA review one patient in AK105-304 may have died from SIADH while on AK105-202 one patient may have died from pneumonitis, one from hepatitis, one from colitis, and one from septic shock.

Infusion-related reactions (IRRs) occurred in 3.4% and 10.2% of patients in AK105-304 and the pooled safety dataset, respectively. All IRRs were Grades 1 or 2, except for 2 grade 3-4 IRR in the pooled safety dataset. In AK105-304, the most frequent AEs ($\geq 20\%$) were nausea, vomiting, constipation, hypothyroidism, decreased appetite, weight decreased, cough, Covid19, fatigue, pyrexia, and rash. In AK105-202 the most frequent AEs ($\geq 20\%$) were hypothyroidism and musculoskeletal pain.

In AK105-304, the most frequent Grade 3 to 4 laboratory abnormalities ($\geq 2\%$) were wbc count decreased, hemoglobin decreased, lymphocyte count decreased, neutrophil count decreased, magnesium decreased, sodium decreased, triglycerides increased, AST increased, cholesterol increased, potassium increased, ALT increased, lipase increased, and serum amylase increased. In AK105-202 the most frequent Grade 3 to 4 laboratory abnormalities ($\geq 2\%$) were phosphate decreased, sodium decreased, triglycerides increased, alkaline phosphatase increased, AST increased, GGT increased, ALT increased, and hemoglobin decreased.

The safety profile of penpulimab was similar to other PD-(L)1 blocking antibodies when combined with platinum-based chemotherapy or administered as a monotherapy. The most significant adverse reactions include immune-related adverse events, which are adequately addressed by the information in the Warnings and Precautions section included in product labeling. There were no significant safety concerns identified during BLA review requiring risk management beyond labeling or warranting consideration for Risk Evaluation and Mitigation Strategy (REMS). Penpulimab, in combination with cisplatin or gemcitabine or as a monotherapy, appears to have an acceptable safety profile when assessed in the context of a life-threatening disease with unmet medical need.

8.3. Statistical Issues

The FDA's Assessment:

There were no major statistical issues identified during review of the application. The marketing application was based on results from two studies, Study AK105-304 and Study AK105-202. Study AK105-202 was conducted entirely in China, while 96% of patients enrolled in Study AK105-304 were from China. FDA was not able to examine the consistency of the treatment benefit by geographical location, race and ethnicity, or in a patient population that are more representative of the population of U.S. patients with NPC. As described in Section 1 and Section 8.1.5, given the high unmet need and the fact that only one other FDA-approved immunotherapy exists for NPC in the U.S., a flexible regulatory approach is applied in this case.

For Study AK105-304, as of the data cut-off date of April 29, 2024, the primary endpoint of PFS per BICR was statistically significant at the PFS interim analysis based on 85% information fraction. Of note, as the interim analysis of PFS was originally proposed at 70% information fraction, this interim analysis at 85% information fraction was based on an additional 34 PFS events. The review team considered the overrun of PFS events and the lower-than-expected patient accrual outside of Asia to be acceptable for this particular marketing application as the overrun is mainly due to the difficulties of enrollment outside of Asia. See FDA's assessment under Section 1.3 and 8.1 for "Statistical Analysis Plan and Amendments" for additional details. Similar to PFS, the first interim analysis of OS was conducted at 70% information fraction,

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instead of the prespecified 60% information fraction, resulting in an additional 18 OS events. OS was not statistically significant at the first interim analysis, and thus OS will be formally tested at the second interim analysis at 80% information fraction and, if necessary, at the final analysis when 172 deaths are observed.

There were no major statistical issues identified during the review of Study Ak105-202. Due to the single arm design, no statistical inferential procedures were applied, and the efficacy decision was based on the lower limit of a 95% confidence interval of the response rate in the trial to exceed a clinically relevant response rate with adequate duration of response. The ORR in this pre-treated patient population was clinically relevant, and the responses were durable. In general, the treatment benefit appeared to be consistent across all relevant subgroups. For this study, the time-to-event endpoints of PFS and OS were considered to be descriptive due to a lack of comparator, while the endpoint of DCR was considered to be exploratory in nature.

8.4. Conclusions and Recommendations

The FDA's Assessment:

The demonstration of a statistically significant and clinically meaningful improvement in PFS favoring the penpulimab plus chemotherapy arm in AK105-304, along with a longer median DOR in the penpulimab plus chemotherapy arm vs the placebo plus chemotherapy arm and no evidence of a detrimental effect on OS, provides substantial evidence of effectiveness for penpulimab, at 200 mg IV Q3W in combination with cisplatin or carboplatin and gemcitabine, for the first-line treatment of adults with metastatic or with recurrent, locally advanced nasopharyngeal carcinoma (NPC). The indication for the treatment of adult patients with metastatic NPC of nonkeratinizing histology with disease progression on or after platinum containing chemotherapy and at least one other line of therapy is supported by Study AK105-202. The ORR was 28% (95% CI: 20, 37) and median DOR was not reached. The proportion of patients with observed DOR of at least 12 months was 46%. The results of AK105-202 are considered clinically meaningful for the intended patient population, and the results of the AK105-304 study provide further confidence in the benefit of penpulimab for the treatment of advanced NPC.

The overall safety profile of penpulimab was similar to that observed with other PD-(L)1 blocking antibodies. Safety issues identified as significant and serious during the BLA review were immune-related adverse events and infusion-related reactions, which are adequately addressed by the information in the Warnings and Precautions section included in product labeling. There were no significant safety concerns identified during BLA review requiring risk management beyond labeling or warranting consideration for Risk Evaluation and Mitigation Strategy (REMS). Penpulimab appears to have an acceptable safety profile when assessed in the context of a life-threatening disease with unmet medical need.

Section 21 CFR 314.106(b) outlines three requirements to establish the acceptability of foreign data as the sole basis for marketing approval:

1. The foreign data are applicable to the U.S. population and U.S. medical practice.
2. The studies have been performed by clinical investigators of recognized competence.
3. FDA is able to validate the data through an onsite inspection or other appropriate means.

FDA will apply this policy in a flexible manner according to the nature of the drug and data being considered.

While both AK105-304 and AK105-202 were conducted nearly or entirely exclusively in Asia, a flexible regulatory approach is warranted given the high unmet need and lack of available therapies for US patients with NPC. The comparator arm of cisplatin or carboplatin plus gemcitabine used in the AK105-304 study is considered standard of care for the first-line treatment of NPC in the US and is therefore applicable to US medical practice. The incidence of NPC is much higher in Southeast Asia relative to the United States, where NPC is a relatively rare disease, making enrollment to clinical trials more feasible in that region of the world. While a higher proportion of patients with NPC in the US have keratinizing histology compared to patients in China (25% vs 2%), the majority of patients with NPC even in the US have non-keratinizing histology. The company attempted to enroll patients in the US but with little success and thus had only 2 cases in AK105-304 (one on the interventional and one on the placebo arm). Due to this very limited number of patients evaluated with keratinizing histology, and an absence of data for penpulimab as a single agent for patients with keratinizing NPC, the FDA narrowed the indication to locally advanced, unresectable or metastatic non-keratinizing NPC. AK105-202 enrolled only patients with non-keratinizing NPC.

To further address the issue of applicability to the US population, the Applicant should collect additional clinical data to further characterize the safety and efficacy of penpulimab in combination with cisplatin and gemcitabine for the treatment of NPC in a study population whose demographic and disease characteristics are more representative of the population of U.S. patients with NPC (refer to Section 13).

In addition, clinical site inspections were completed and Study AK105-304 appears to have been conducted adequately and the data generated by the inspected clinical investigators and the imaging CRO and submitted by the Applicant appear acceptable in support of the proposed indication.

The clinical data supports a positive risk-benefit assessment and is supportive of regular approval to penpulimab for the following indications:

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- Penpulimab is indicated, in combination with cisplatin and gemcitabine, for the first-line treatment of adults with metastatic or with recurrent, locally advanced non-keratinizing nasopharyngeal carcinoma (NPC).
- Penpulimab is indicated, as a single agent, for the treatment of adults with recurrent unresectable or metastatic NPC with disease progression on or after a platinum-containing chemotherapy and one additional line of therapy who have not received prior therapy with an anti-PD-(L)1 antibody.

X

X

Primary Statistical Reviewer

Statistical Team Leader

X

X

Primary Clinical Reviewer

Clinical Team Leader

9. Advisory Committee Meeting and Other External Consultations

The FDA's Assessment:

FDA did not refer this application to an advisory committee as no significant efficacy or safety issues were identified during the review that required external input for the proposed indication.

10. Pediatrics

The Applicant's Position:

N/A

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The FDA's Assessment:

FDA agrees with the Applicant's position.

11. Labeling Recommendations

Data:

This is an original application. Please see annotated label in Module 1.14.1.2 for proposed labeling.

The Applicant's Position:

N/A

The FDA's Assessment:

The format, language, and content of the proposed labeling was evaluated and revised for consistency with 21 Code of Federal Regulations (CFR), labeling guidances and current labeling practices of the Office of Oncologic Diseases. The table below summarizes key changes.

FDA – Table 26. Key Labeling Changes

Label Section	Major Changes and Rationale
1 INDICATIONS AND USAGE	Text revised for consistency across oncology labeling.
2 DOSAGE AND ADMINISTRATION	FDA added <i>Table 1 Order of Administration and Regimen for Penpulimab-kcqx in Combination with Either Cisplatin or Carboplatin and Gemcitabine</i> to provide the dose and dosage for each drug in the recommended regimen for the treatment of first-line treatment of adults with recurrent or metastatic non-keratinizing nasopharyngeal carcinoma (NPC) for safety and clarity. FDA revised <i>Table 2 Recommended Dosage Modification for Adverse Reactions</i> for consistency across anti-PD-1/PD-L1 labelings.
5 WARNINGS AND PRECAUTIONS	Text revised for clarity, brevity and consistency across anti-PD-1/PD-L1 labelings. Incidences of adverse reactions adjudicated.
6 ADVERSE REACTIONS	FDA separated the proposed safety pool for Section 5 by disease and regimen. The description of safety for each indication was revised for consistency across labelings, and each number was adjudicated. FDA removed the Applicant's proposed (b) (4)
8.5 Geriatric Use	FDA separated the proposed safety pool for Section 8.5 by disease and regimen.
12 CLINICAL PHARMACOLOGY	FDA provided minor revisions for clarity and brevity.
14 CLINICAL STUDIES	FDA revised the text for clarity and brevity. In <i>Table 7 Efficacy Results in AK105-304</i> , (b) (4) and removed from the table.
17 PATIENT COUNSELING INFORMATION	Section revised for consistency with the full prescribing information.
MEDICATION GUIDE	Please see reviews by Patient Labeling, Division of Medication Error Prevention and Analysis (DMEPA), and Office of Prescription Drug Promotion (OPDP).

12. Risk Evaluation and Mitigation Strategies (REMS)

The Applicant's Position:

The risks of penpulimab could be managed by routine pharmacovigilance activities and labeling. REMS is not necessary to ensure that the benefits outweigh the risk for penpulimab for the following reasons:

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- The benefit of penpulimab in the treatment of NPC was demonstrated in the pivotal study of AK105-202 and AK105-304.
- The risks observed with penpulimab will be communicated through labeling. The risks associated with penpulimab are in part due to its inhibitory effects of PD-1. If approved, penpulimab will belong to a class with many other drugs (nivolumab, pembrolizumab, atezolizumab, durvalumab and avelumab, etc.) in which irAEs are labeled in Warnings and Precautions. The prescribers are likely aware of the risks of irAEs and the management with other drugs in this class.
- Sponsor has robust pharmacovigilance system, which includes data intake, case management, regulatory reporting, literature monitoring, signal management and aggregate reporting.
- In the postmarket setting, Akeso continually conducts routine surveillance of the safety profile of penpulimab including all reports of adverse drug experiences and product compliant reports, and revises RMP, RSI, and package insert if an evaluation of the safety data yields significant new information.

The FDA's Assessment:

The clinical review team determined that a risk evaluation and mitigation strategy (REMS) was not required to ensure safe and effective use of penpulimab for the indicated populations. Recommendations for the safe and effective use of penpulimab are made in labeling and a patient package insert. There are no additional risk management strategies required beyond the recommended labeling. Although penpulimab can cause severe/serious toxicity, there are multiple other approved agents in the same class, and it will be prescribed by oncologists who, by training and experience, understand how to monitor and manage such toxicities.

13. Postmarketing Requirements and Commitment

The FDA's Assessment:

Two Post-Marketing Commitments were agreed upon with the Applicant, noted below.

1. PMC

Complete the ongoing clinical trial AK105-304 (NCT04974398) titled "A Randomized, Double-blind, Multi-center Phase III Study of Penpulimab (AK105) combined with Chemotherapy versus Placebo Combined with Chemotherapy as First-Line Treatment for Recurrent or Metastatic Nasopharyngeal Carcinoma," to obtain mature overall survival (OS) data in accordance with the

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pre-specified statistical analysis plan to formally test OS at 80% information fraction and at the final OS analysis when 172 OS events are observed.

Trial Completion:	05/2026

Final Report Submission:	10/2026

2. PMC

Conduct a clinical trial enrolling an adequate number of patients in the United States (U.S.), that includes a sufficient representation of patients in demographic subgroups that are reflective of the U.S. patient population with nasopharyngeal carcinoma (NPC), to further characterize the efficacy and safety of penpulimab in combination with gemcitabine and either cisplatin or carboplatin in these patients. Conduct sparse sampling for supportive population pharmacokinetic and Exposure-Response (E-R) analyses. The E-R analyses may be used as supportive evidence for the efficacy and safety in the intended patient population. In the E-R analyses report, include an analysis of the presence and clinical impact of the neutralizing anti-drug antibodies on pharmacokinetics, efficacy, and safety of penpulimab.

Draft Protocol Submission:	04/2025

Final Protocol Submission:	08/2025

Trial Completion:	06/2029

Final Report Submission:	12/2029

14. Division Director (DHOT) (NME ONLY)

X

15. Division Director (OCP)

X

16. Division Director (OB)

X

17. Division Director (Clinical)

X

18. Office Director (or Designated Signatory Authority)

This application was reviewed by the Oncology Center of Excellence (OCE) per the OCE Intercenter Agreement. My signature below represents an approval recommendation for the clinical portion of this application under the OCE.

X

19. Appendices

19.1. References

The Applicant's References:

N/A

The FDA's References:

Barber DL, Wherry EJ, Masopust D, et al. Restoring function in exhausted CD8T cells during chronic viral infection. *Nature*. 2006;439:682–687.

Frebel H, Nindl V, Schuepbach RA, et al. Programmed death 1 protects from fatal circulatory failure during systemic virus infection of mice. *J Exp Med*. 2012;209(13):2485–2499.

Guleria I, Khosroshahi A, Ansari MJ, et al. A critical role for the programmed death ligand 1 in fetomaternal tolerance. *J Exp Med*. 2005;202(2):231-237.

Kauffman KD, Sakai S, Lora NE, et al. PD-1 blockade exacerbates *Mycobacterium tuberculosis* infection in rhesus macaques. *Sci Immunol*. 2021;6(55):eabf3861.

Okazaki T and Honjo T. PD-1 and PD-1 ligands: from discovery to clinical application. *Int Immunol*. 2007;19(7):813-24.

Lázár-Molnár E, Chen B, Sweeney KA, et al. Programmed death-1 (PD-1)-deficient mice are extraordinarily sensitive to tuberculosis. *Proc Natl Acad Sci*. 2010;107(30):13402–13407.

Mueller SN, VK Vanguri, SJ Ha, EE West, ME Keir, JN Glickman, et al. PD-L1 has distinct functions in hematopoietic and nonhematopoietic cells in regulating T cell responses during chronic infection in mice. *J Clin Invest* 2010;120(7):2508-2515.

Petroff MG, L Chen, TA Phillips, et al. B7 family molecules are favorably positioned at the human maternal-fetal interface. *Biol Reprod* 2003;68(5):1496-14504.

19.2. Financial Disclosure

The Applicant's Position:

All financial disclosures are described in Section [8.1.2](#)

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The FDA's Assessment:

FDA agrees with the Applicant's position.

Covered Clinical Study (Name and/or Number):* AK105-202

Was a list of clinical investigators provided:	Yes ☒	No ☐ (Request list from Applicant)
Total number of investigators identified: <u>176</u>		
Number of investigators who are Sponsor employees (including both full-time and part-time employees): <u>0</u>		
Number of investigators with disclosable financial interests/arrangements (Form FDA 3455): <u>0</u>		
If there are investigators with disclosable financial interests/arrangements, identify the number of investigators with interests/arrangements in each category (as defined in 21 CFR 54.2(a), (b), (c) and (f)): Compensation to the investigator for conducting the study where the value could be influenced by the outcome of the study: <u>N/A</u> Significant payments of other sorts: <u>N/A</u> Proprietary interest in the product tested held by investigator: <u>N/A</u> Significant equity interest held by investigator in study: <u>N/A</u> Sponsor of covered study: <u>N/A</u>		
Is an attachment provided with details of the disclosable financial interests/arrangements:	Yes ☐	No ☒ Not Applicable
Is a description of the steps taken to minimize potential bias provided:	Yes ☐	No ☒ Not Applicable
Number of investigators with certification of due diligence (Form FDA 3454, box 3) <u>0</u>		
Is an attachment provided with the reason: <u>N/A</u>	Yes ☐	No ☒ Not Applicable

*The table above should be filled by the applicant, and confirmed/edited by the FDA.

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Covered Clinical Study (Name and/or Number):* AK105-304

Was a list of clinical investigators provided:	Yes ☒	No ☐ (Request list from Applicant)
Total number of investigators identified: 369 (including 308 in China, 61 in other countries)		
Number of investigators who are Sponsor employees (including both full-time and part-time employees): <u>0</u>		
Number of investigators with disclosable financial interests/arrangements (Form FDA 3455): <u>0</u>		
If there are investigators with disclosable financial interests/arrangements, identify the number of investigators with interests/arrangements in each category (as defined in 21 CFR 54.2(a), (b), (c) and (f)): Compensation to the investigator for conducting the study where the value could be influenced by the outcome of the study: <u>N/A</u> Significant payments of other sorts: <u>N/A</u> Proprietary interest in the product tested held by investigator: <u>N/A</u> Significant equity interest held by investigator in study: <u>N/A</u> Sponsor of covered study: <u>N/A</u>		
Is an attachment provided with details of the disclosable financial interests/arrangements:	Yes ☐	No ☒ Not Applicable
Is a description of the steps taken to minimize potential bias provided:	Yes ☐	No ☒ Not Applicable
Number of investigators with certification of due diligence (Form FDA 3454, box 3) <u>0</u>		
Is an attachment provided with the reason: N/A	Yes ☐	No ☒ Not Applicable

*The table above should be filled by the applicant, and confirmed/edited by the FDA.

19.3. Nonclinical Pharmacology/ToxicologyData:

N/A

The Applicant's Position:

N/A

Disclaimer: In this document, the sections labeled as "Data" and "The Applicant's Position" are completed by the Applicant and do not necessarily reflect the positions of the FDA.

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The FDA's Assessment:

N/A; See Section 5

19.4. OCP Appendices (Technical Documents Supporting OCP Recommendations)

19.4.1. Bioanalytical Review

FDA has determined that the bioanalytical methods used in the current submission are acceptable to support the clinical pharmacology program.

The concentration of penpulimab in human serum was quantitatively determined by enzyme-linked immunosorbent assay (ELISA). Bioanalysis for Study AK105-304 was conducted by (b) (4) for samples collected outside of China whereas samples from all Chinese trials was analyzed by (b) (4). The method was identical and cross-validation was conducted by (b) (4). All methods were fully validated and adequate. All samples were analyzed within the demonstrated stability window, and all analytical runs met acceptance criteria.

19.4.2. Population PK Analysis

19.4.2.1. Executive Summary

The FDA's Assessment:

The PK of penpulimab in the adult population was characterized by a 2-compartment model with first-order elimination. The population PK model described the observed data reasonably well.

The proposed dosages of 200 mg Q2W for monotherapy and 300 mg Q3W for combination therapy is considered acceptable for the respective proposed patient populations.

19.4.2.2. PPK Assessment Summary

The Applicant's Position:

Penpulimab PPK model was based on pooled data from 8 clinical studies in patients with nasopharyngeal carcinoma, NSCLC, and other tumors. Potential covariates that may influence Penpulimab PK and its variability were also evaluated. A total of 5,849 PK concentrations from 771 patients were included in the PPK analysis.

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The final PPK model was a two-compartment with zero-order IV infusion and first-order elimination. The model indicated that baseline characteristics (body weight, C-reactive protein, albumin, lactate dehydrogenase), ADA, tumor type, co-administration, age, sex and race had statistically significant effects on PK parameters. However, these covariates did not have clinically meaningful effects on the steady-state exposure ($\leq 30\%$). Also, mild to moderate hepatic impairment or mild to moderate renal impairment didn't have significant effect on PK of Penpulimab.

Although Race was found to be correlated with clearance, the overall exposures ($C_{max,ss}$, $C_{avg,ss}$ and $C_{min,ss}$) were essentially the same between Caucasian and Asian populations after taking into consideration of body weight.

According to PPK analysis, the mean (CV%) of volume of distribution was 10.2 L (43.5%), following administration of penpulimab 200 mg as a single IV infusion. The effective half-life and steady-state trough concentration were 22.4 days (27.4%) and 30.1 $\mu\text{g/mL}$ (38.1%), respectively, following IV infusion of 200 mg Q3W.

[Highlight the key findings in the white cells.]

General Information		
Objectives of PPK Analysis		- Characterize AK105 PK profiles in patient population - Identify the source of PK variability in patient population - Predict individual exposure for E-R assessment
Study Included		AK105-101, AK105-201, AK105-202, AK105-204, AK105-205, AK105-301, AK105-302, and AK105-304
Dose(s) Included		1, 3, 10 mg/kg Q2W, 200 mg Q2W, and 200 mg Q3W
Population Included		Nasopharyngeal carcinoma, non-small cell lung cancer, and other tumors (gastric cancer, ovarian cancer and esophageal cancer, hematologic malignancy R/R cHL)
Population Characteristics (Applicant – Table 36)	General	Age median (range): 55 yrs (18-91), 21.7% of patients ≥ 65 yrs Weight median (range): 62 kg (32-113) 574 (74.4%) male 679 (88.1%) in Asian, 85 (11.0%) in Caucasian, and 7 (0.9%) in Others
	Organ Impairment	Hepatic function: 652 (84.5%) in normal, 113 (14.7%) in mild, and 6 (0.8%) in moderate Renal function: 405 (52.5%) in normal, 301 (39.0%) in mild, 64 (8.3%) in moderate, and 1 (0.1%) in severe.
	Pediatrics (if any)	Not applicable
No. of Patients, PK Samples, and BLQ		Total 771 patients with 5,849 PK samples and 61 (1.03%) BLQ.

Sampling Schedule	Rich Sampling	AK105-101: <i>PK samples were collected in Phase 1a on Day 1 pre-dose, end of infusion (EOI), 3-hour post-infusion, Day 2, Day 3, Day 8 in Cycle 1 and pre-dose (Day 15) (for Q2W);</i>	
		AK105-201: <i>PK samples were collected in 6 patients after the first dose (C1D1) and 6th dose (C3D15). The sampling schedule was pre-dose, end of infusion (EOI), 3-hour post-infusion, Day 2, Day 3, and Day 8.</i>	
		AK105-202: <i>PK samples were collected in 9 patients on Day 1 pre-dose, end of infusion (EOI), 3 hours post-infusion, Day 2, Day 3, Day 8 in Cycle 1 and pre-dose (Day 15) (for Q2W)</i>	
	In ITT Population	Not applicable	
Covariates Evaluated	Static	<i>Baseline body weight, creatinine, creatinine clearance, total bilirubin, aspartate aminotransferase, alanine aminotransferase, alkaline phosphatase, lactate dehydrogenase, C-reactive protein, albumin, tumor size, ECOG, age, sex, race, ADA, co-administrator and tumor type</i>	
	Time-varying	Not applicable	
Final Model		Summary	Acceptability [FDA’s comments]
Software and Version		NONMEM, v7.4.4 (ICON Development Solutions, Ellicott City, Maryland)	Yes.
Model Structure		Two-compartment model with zero-order IV infusion and first-order elimination	Yes.
Model Parameter Estimates		Applicant – Table 37	Yes.
Uncertainty and Variability (RSE, IIV, Shrinkage, Bootstrap)		RSE of all parameters were less than 30%. The model converged in 923 out of 1000 bootstrap runs, and its 95% confidence intervals contained the parameter estimates of the final model. With the exception of V2, the IIV and shrinkage of CL and V1 were less than 30%, which indicates limited impact of uncertainties and variabilities on PK characteristics.	Yes.

BLQ for Parameter Accuracy	BQL data were excluded from this analysis.	Yes. BLQ data accounted for 1% of the total number of observations.
GOF, VPC	Applicant – Figure 8, Applicant – Figure 9	Yes.
Significant Covariates and Clinical Relevance	Applicant – Figure 10	Yes. None are likely to have clinically meaningful impact on exposure.
Analysis Based on Simulation (optional)	Applicant – Figure 11	Yes.
Labeling Language	Description	Acceptability [FDA's comments]
12.3 PK	<i>Penpulimab-kcqx exposure increased dose proportionally over the dose range of 1 to 10 mg/kg (0.35 to 3.5 times the approved recommended dosage in a 70 kg patient) after the first dose. The mean accumulation ratio was 1.5^(b)₍₄₎ for maximum concentration (C_{max}) and 2.1^(b)₍₄₎ for area under the concentration curve (AUC) following multiple doses of 200 mg every 3 weeks. Steady-state concentrations of penpulimab-kcqx were reached by Week 15, with mean (CV%) steady-state trough and peak concentrations of 30^(b)₍₄₎ µg/mL (38^(b)₍₄₎%) and ^(b)₍₄₎ µg/mL (21^(b)₍₄₎%), respectively.</i> Distribution <i>The mean (CV%) volume of distribution was 10^(b)₍₄₎ L (^(b)₍₄₎ %).</i>	Generally acceptable. Reporting terminal half-life is preferred ^(b)₍₄₎ given two dosages were approved.

	Elimination The mean (CV%) clearance was 0.2 (b) (4) L/day (b) (4) and the mean (CV%) (b) (4) Metabolism Penpulimab-kcqx is expected to be metabolized into small peptides by catabolic pathways. Specific Populations No clinically significant differences in the pharmacokinetics of penpulimab-kcqx were observed based on body weight (32 to 113 kg), age (18 to 91 years), sex, race (White and Asian), serum albumin (22 to (b) (4) g/L), baseline LDH (111 to 4450 IU/L), baseline C-reactive protein (0 to 328 mg/L), ECOG score, immunogenicity status, tumor type, co-administration (with chemotherapy), mild or moderate renal impairment (creatinine clearance [CLcr] ≥ 30 mL/min), mild (total bilirubin [TBIL] ≤ ULN and AST > ULN or TBIL > 1 to 1.5 times ULN and any AST) or moderate hepatic impairment (TBIL > 1.5 to 3 times ULN and any AST). The effect of severe hepatic (TBIL > 3 times ULN and any AST) or renal impairment (CLcr < 30 mL/min) on the pharmacokinetics of penpulimab-kcqx is unknown.	

Applicant – Table 36 Summary of Baseline Characteristics and Laboratory Values Stratified by Study.

	AK105- 101 (n=99)	AK105- 201 (n=91)	AK105- 202 (n=130)	AK105- 204 (n=60)	AK105- 205 (n=28)	AK105- 301 (n=46)	AK105- 302 (n=173)	AK105- 304 (n=144)	Overall (n=771)
SEX, n (%)									
Male	58 (58.6)	54 (59.3)	99 (76.2)	27 (45.0)	25 (89.3)	32 (69.6)	160 (92.5)	119 (82.6)	574 (74.4)
Female	41 (41.4)	37 (40.7)	31 (23.8)	33 (55.0)	3 (10.7)	14 (30.4)	13 (7.5)	25 (17.4)	197 (25.6)
RACE, n (%)									
Asian	11 (11.1)	91 (100)	130 (100)	60 (100)	28 (100)	46 (100)	173 (100)	140 (97.2)	679 (88.1)
Caucasian	81 (81.8)	0 (0)	0 (0)	0 (0)	0 (0)	0 (0)	0 (0)	4 (2.8)	85 (11.0)
Others	7 (7.1)	0 (0)	0 (0)	0 (0)	0 (0)	0 (0)	0 (0)	0 (0)	7 (0.9)
Tumor type, n (%)									
Others	99 (100)	91 (100)	0 (0)	60 (100)	0 (0)	46 (100)	173 (100)	0 (0)	469 (60.8)
NPC	0 (0)	0 (0)	130 (100)	0 (0)	28 (100)	0 (0)	0 (0)	144 (100)	302 (39.2)
Co-administration, n (%)									
Monotherapy	99 (100)	91 (100)	130 (100)	60 (100)	0 (0)	0 (0)	0 (0)	0 (0)	380 (49.3)
Combination	0 (0)	0 (0)	0 (0)	0 (0)	28 (100)	46 (100)	173 (100)	144 (100)	391 (50.7)
ADA, n (%)									
Negative	54 (54.5)	63 (69.2)	93 (71.5)	36 (60.0)	22 (78.6)	23 (50.0)	118 (68.2)	127 (88.2)	536 (69.5)
Positive	45 (45.5)	28 (30.8)	37 (28.5)	24 (40.0)	6 (21.4)	23 (50.0)	55 (31.8)	17 (11.8)	235 (30.5)
Renal function, n (%)									
Normal	41 (41.4)	85 (93.4)	74 (56.9)	20 (33.3)	13 (46.4)	23 (50.0)	84 (48.6)	65 (45.1)	405 (52.5)
Mild	36 (36.4)	6 (6.6)	43 (33.1)	29 (48.3)	15 (53.6)	20 (43.5)	75 (43.4)	77 (53.5)	301 (39.0)
Moderate	21 (21.2)	0 (0)	13 (10.0)	11 (18.3)	0 (0)	3 (6.5)	14 (8.1)	2 (1.4)	64 (8.3)
Severe	1 (1.0)	0 (0)	0 (0)	0 (0)	0 (0)	0 (0)	0 (0)	0 (0)	1 (0.1)
Hepatic function, n (%)									
Normal	67 (67.7)	87 (95.6)	100 (76.9)	47 (78.3)	25 (89.3)	41 (89.1)	166 (96.0)	119 (82.6)	652 (84.6)
Mild	29 (29.3)	4 (4.4)	28 (21.5)	12 (20.0)	3 (10.7)	5 (10.9)	7 (4.0)	25 (17.4)	113 (14.7)
Moderate	3 (3.0)	0 (0)	2 (1.5)	1 (1.7)	0 (0)	0 (0)	0 (0)	0 (0)	6 (0.8)
WT (kg)									
	70.7 [40.0, 112]	65.0 [40.0, 113]	57.0 [35.2, 94.5]	59.0 [42.0, 87.0]	62.3 [40.0, 85.0]	62.0 [40.0, 95.0]	64.0 [38.5, 94.0]	60.0 [32.0, 102]	62.0 [32.0, 113]
AGE (yr)									
	68.0 [30.0, 91.0]	32.0 [18.0, 68.0]	49.0 [20.0, 65.0]	56.5 [30.0, 76.0]	51.0 [29.0, 65.0]	61.0 [37.0, 72.0]	61.0 [38.0, 74.0]	51.0 [31.0, 75.0]	55.0 [18.0, 91.0]

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	AK105-101 (n=99)	AK105-201 (n=91)	AK105-202 (n=130)	AK105-204 (n=60)	AK105-205 (n=28)	AK105-301 (n=46)	AK105-302 (n=173)	AK105-304 (n=144)	Overall (n=771)
CRP (mg/L)	9.00 [0.400, 263]	25.1 [0.500, 277]	7.91 [0, 145]	2.86 [0.200, 66.2]	5.00 [0.210, 112]	9.86 [0.360, 104]	12.5 [0.440, 200]	8.37 [0.210, 328]	9.55 [0, 328]
LDH (IU/L)	237 [121, 2540]	214 [126, 801]	237 [116, 4450]	241 [143, 942]	189 [141, 1860]	200 [127, 676]	209 [117, 1750]	200 [111, 2080]	214 [111, 4450]
ALB (g/L)	36.0 [22.0, 47.0]	43.4 [22.3, 52.1]	43.5 [24.1, 53.3]	44.7 [29.2, 54.5]	42.9 [33.0, 52.0]	40.7 [30.0, 52.1]	41.4 [26.7, 51.0]	42.0 [28.2, 67.7]	41.9 [22.0, 67.7]

AGE: baseline age; ALB: baseline albumin; LDH: baseline lactate dehydrogenase; WT: baseline body weight; CRP: baseline C-reactive protein. A patient initially lacked classification of hepatic and renal function in AK105-301. After imputing with the median value of the covariate, the patient was classified as having normal hepatic function and moderate renal impairment. Data source: [Module 5.3.3.5 Penpulimab PopPK and ER report Appendix 2-Supplemental Table 1-1 and Table 1-2](#).

Applicant – Table 37 Parameter Estimates from Final Population PK Model.

Parameter	Estimate	RSE (%)	95% CI (bootstrap)	Shrinkage (%)
Fixed Effects				
CL (L/day)	0.217	2.21	0.200 — 0.229	/
V1 (L)	4.05	1.40	3.94 — 4.16	/
Q (L/day)	0.492	15.1	0.245 — 0.745	/
V2 (L)	7.51	4.98	6.77 — 8.51	/
CL-AGE	0.192	18.6	0.109 — 0.264	/
CL-ALB	-0.690	16.7	-0.913 — -0.454	/
CL-LDH	0.110	25.6	0.0523 — 0.167	/
CL-RACE	-0.231	17.8	-0.305 — -0.138	/
CL-SEX	-0.111	22.9	-0.158 — -0.0607	/
CL-TADA	0.168	21.2	0.104 — 0.239	/
CL-WT	0.405	18.1	0.258 — 0.556	/
V1-ALB	-0.305	20.3	-0.431 — -0.183	/
V1-COMBO	-0.0904	16.4	-0.118 — -0.0591	/
V1-DIAG	-0.0981	14.7	-0.125 — -0.0701	/
V1-SEX	-0.128	13.8	-0.158 — -0.0943	/
V1WT	0.479	9.56	0.379 — 0.562	/
V2-COMBO	-0.548	5.15	-0.600 — -0.494	/
V2-CRP	0.0844	25.0	0.0448 — 0.133	/
V2-DIAG	-0.212	29.1	-0.369 — -0.106	/
Between-Subject Variability				
CL	27.2%	4.65	23.6% — 29.7%	12.9
V1	16.3%	5.95	14.3% — 18.2%	24.5
V2	45.5%	11.2	33.5% — 57.0%	38.0

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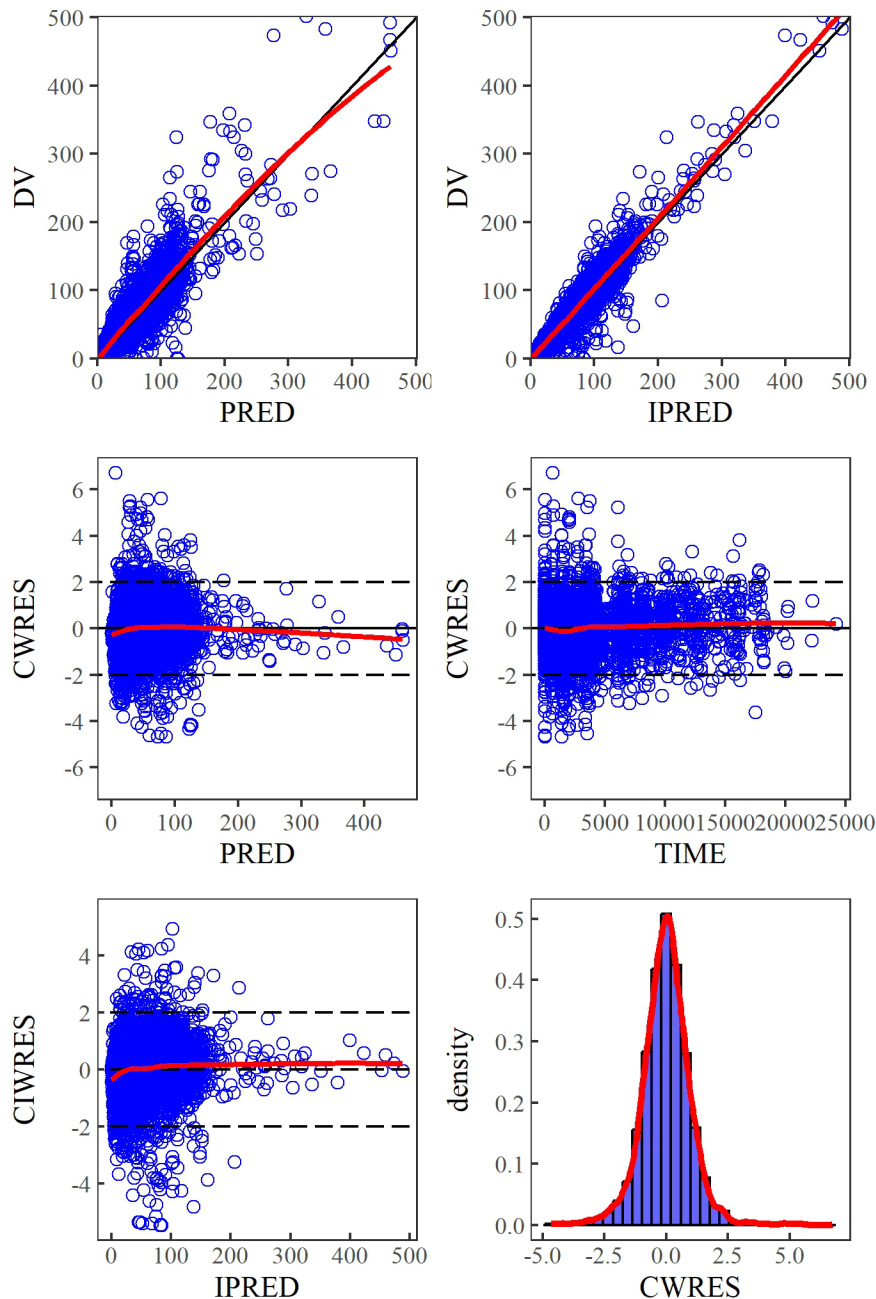
Parameter	Estimate	RSE (%)	95% CI (bootstrap)	Shrinkage (%)
Residual Variability				
Proportional (%)	18.1	3.65	16.8 — 19.5	11.4
Additive (µg/mL)	2.11	9.00	1.71 — 2.46	11.4

Abbreviations: CL: clearance; V1: volume of the central compartment; V2: volume of the peripheral compartment; Q: inter-compartment clearance; AGE: baseline age (years); ALB: baseline albumin (g/L); LDH: baseline lactate dehydrogenase (IU/L); WT: baseline body weight (kg); CRP: baseline C-reactive protein (mg/L); RACE: race; SEX: [REDACTED]; TADA: Total anti-drug antibody; COMBO: co-administration; DIAG: Diagnosis of Tumor type.

CI values are taken from bootstrap calculations (923 of 1000 successful runs).

Data source: [Module 5.3.3.5 Penpulimab PopPK and ER report Appendix 2-Table 7 and Table 10.](#)

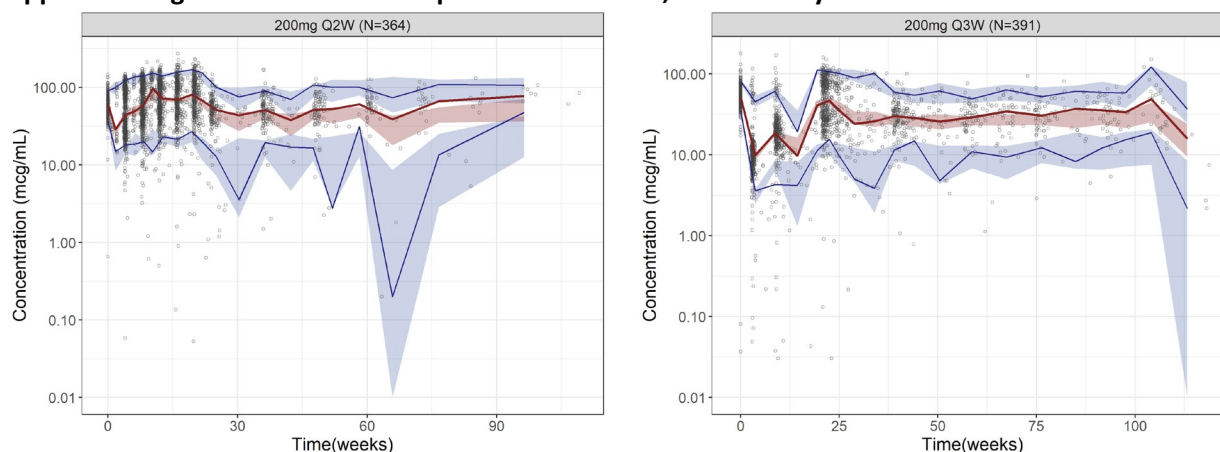
Applicant – Figure 8 Goodness-of-fit Plots for the Final Population PK Model.



The black solid line is the line of identity or the zero line; the red solid line is the loess trend line. CWRES conditional weighted residuals, PRED population prediction, IPRED individual prediction, CIWRES conditional individual weighted residuals, TIME: time after dose in hours.

Data source: [Module 5.3.3.5 Penpulimab PopPK and ER report Appendix 2-Supplemental Figure 13.](#)

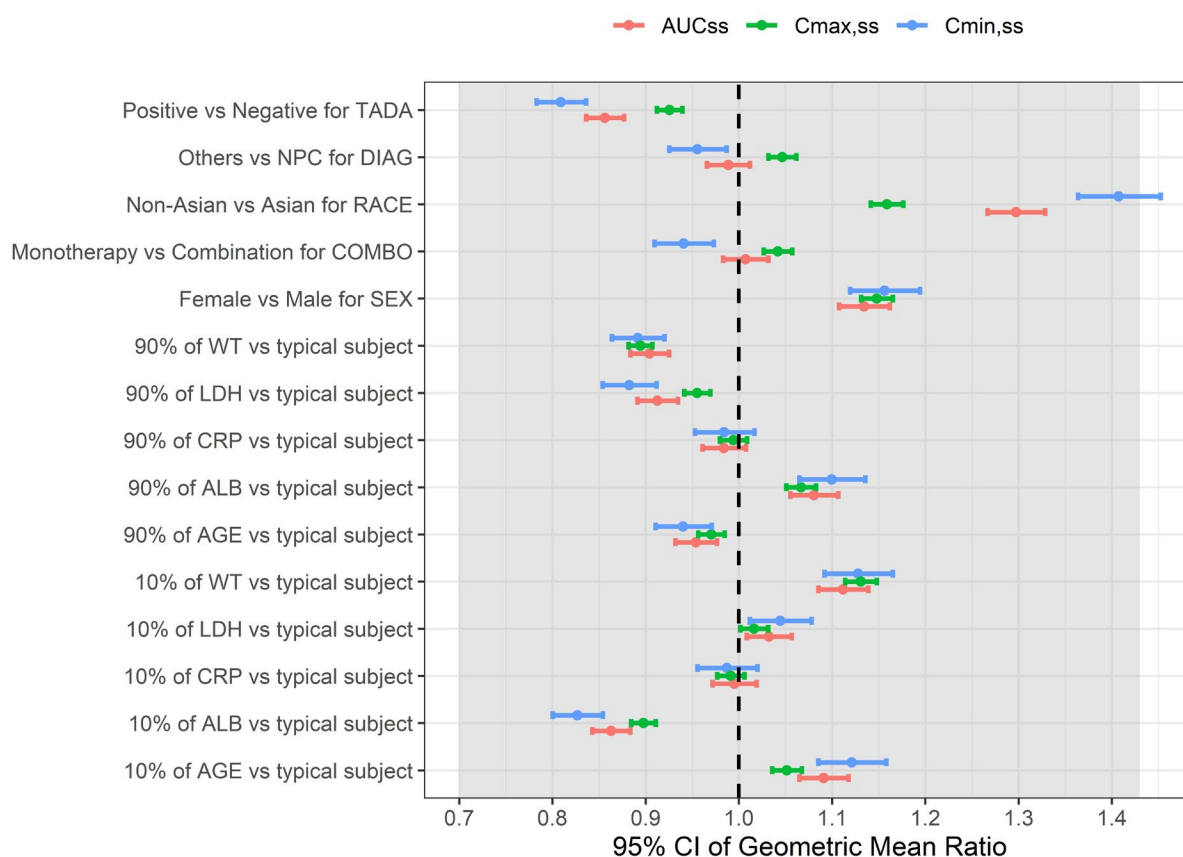
Applicant – Figure 9 VPC of Final Population PK Model, Stratified by Dose.



The gray circles represent observed data, the lines represent observed median (red) and observed 5th/95th percentiles (blue), and the shaded regions represent the 95% confidence intervals of the lines predicted by the final model.

Data source: [Module 5.3.3.5 Penpulimab PopPK and ER report Appendix 2-Supplemental Figure 23](#).

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Applicant – Figure 10 Impact of Significant Covariates on Steady-State Exposures.

Note: The typical subject is a male Asian patient with nasopharyngeal carcinoma and negative TADA, body weight of 62.0 kg, albumin of 41.9 g/L, C-reactive protein of 9.55 mg/L, lactate dehydrogenase of 214 IU/L, age of 55 years old, and receiving Penpulimab plus chemotherapy.

The 10th, 50th and 90th percentile of body weight was 48.0, 62.0 and 79.4 kg, respectively.

The 10th, 50th and 90th percentile of lactate dehydrogenase was 154, 214 and 447 IU/L, respectively.

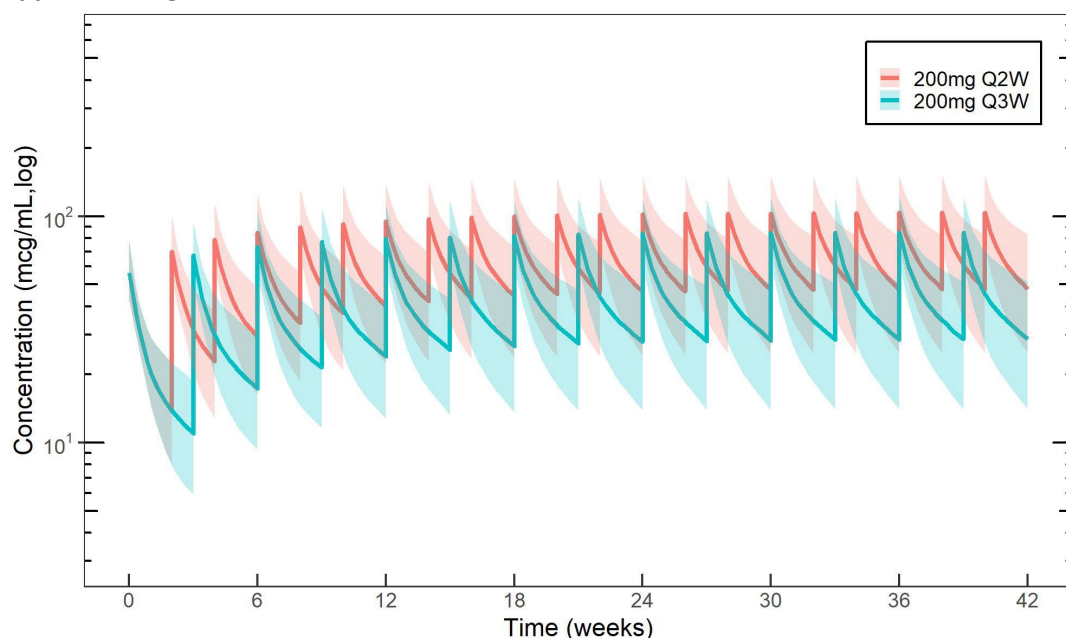
The 10th, 50th and 90th percentile of C-reactive protein was 1.07, 9.55 and 70.9 mg/L, respectively.

The 10th, 50th and 90th percentile of albumin was 34.7, 41.9 and 47.4 g/L, respectively.

The 10th, 50th and 90th percentile of age was 34.0, 55.0 and 70.0 years, respectively.

Data source: [Module 5.3.3.5 Penpulimab PopPK and ER report Appendix 2-Supplemental Figure 25](#).

Applicant – Figure 11 Simulation results



Data source: [Module 5.3.3.5 Penpulimab PopPK and ER report Appendix 2-Supplement Figure 26.](#)

The FDA's Assessment:

The population PK analysis is considered adequate.

19.4.2.3. PPK Review Issues

None.

19.4.2.4. Reviewer's Independent Analysis

None.

19.4.3. Exposure-Response Analysis

19.4.3.1. E-R (Efficacy) Executive Summary

The FDA's Assessment:

Positive E-R trends for ORR and PFS were observed across steady-state exposure with a fixed dosage of 200 mg Q3W, but this analysis is inconclusive due to the limited exposure range of penpulimab at one dose level.

19.4.3.2. E-R (Efficacy) Assessment SummaryThe Applicant's Position:

Target indication: first-line treatment for recurrent or metastatic nasopharyngeal carcinoma (NPC). The E-R analysis included patients from the AK105-304 who received Penpulimab 200 mg Q3W in combination with chemotherapy (n=144). The univariate logistic regression analysis between Penpulimab $C_{avg,ss}$ and ORR/DCR were explored. And Kaplan-Meier survival curve, stratified by quartiles of exposures, was applied to explore the association between exposure and progression-free survival (PFS). E-R analysis suggested a relative flat exposure-response (ORR/DCR) curve and no apparent difference in exposure between responders and non-responders.

[Highlight the key findings in the white cells.]

General Information		
Goal of ER analysis		Characterize the relationships between Penpulimab serum exposures and key efficacy endpoints, including objective response rate (ORR) disease control rate (DCR), progression free survival (PFS), overall survival (OS), duration of response (DOR), and time to response (TTR)
Study Included		AK105-304
Endpoint		ORR, DCR, PFS, DOR TTR
No. of Patients (total, and with individual PK)		144 patients
Population Characteristics (Applicant – Table 38)	General	Age median (range): 51.0 yrs (31 ~75) Weight median (range): 60.0 kg (32.0~101.6) 119 (82.6%) male 140 (97.2%) Asian 4 (2.8%) Caucasian
	Pediatrics (if any)	Not applicable
Dose(s) Included		200mg Q3W
Exposure Metrics Explored (range)		Penpulimab exposure such as $C_{avg,ss}$, $C_{min,ss}$, were derived from PopPK analysis
Covariates Evaluated		The Kaplan-Meier survival curve, stratified by quartile of exposure, was applied to explore the correlation between PK exposure and efficacy endpoint (PFS) in the NPC patients. The effect of the following covariates on PFS was also explored: sex, age, weight, ECOG, C-reactive protein (CPR),

	<i>albumin (ALB), lactate dehydrogenase (LDH), Liver dysfunction groups (LDG), Kidney dysfunction groups (KDG), Anti-drug antibody (ADA), Neutralizing antibodies (NAB), Tumor stage (STAGE), Liver metastasis (LIVERMET).</i>	
Final Model Parameters	Summary	Acceptability [FDA's comments]
Model Structure	ORR and DCR <i>Univariate logistic regression model:</i> $\log i t_i = \theta_1 + \theta_2 (C_{avg,ss_i} - \text{Median}(C_{avg,ss}))$ $P_i = \frac{e^{\text{Logit}_i}}{1 + e^{\text{Logit}_i}}$ PFS, DOR and TTR <i>Kaplan-Meier Method: Plot survival curves for Progression-Free Survival (PFS), Duration of Response (DOR), and Time to Response (TTR) using the Kaplan-Meier method.</i>	Yes.
Model Parameter Estimates	Applicant – Table 39	Yes.
Model Evaluation	<i>Associations were considered significant if the p-value was less than 0.05;</i> Applicant – Table 40 Applicant – Table 41	Yes.
Covariates and Clinical Relevance	<i>The exposure-efficacy response was evaluated by a univariate logistic regression model. ORR/DCR binary response was used as the dependent variable, and model-predicted Penpulimab exposure such as $C_{min,ss}$, $C_{avg,ss}$ were used as independent variables to estimate the regression coefficients, confidence intervals, and significance levels.</i> <i>The Kaplan-Meier survival curve, stratified by quartile of exposure, was applied to explore the correlation between PK exposure and PFS in the NPC patients. Exploratory analysis</i>	Yes.

	<i>showed that covariates such as sex, age, weight, ECOG, CPR, ALB, LDH, LDG, KDG, ADA, NAB, STAGE, LIVERMET, didn't have significant effect on PFS.</i>	
Simulation for Specific Population	<i>Not applicable</i>	
Visualization of E-R relationships	Applicant – Figure 12~Applicant – Figure 14 Applicant – Table 39	Yes.
Overall Clinical Relevance for ER	ORR/DCR: In NPC patients, the logistic regression analysis suggested that there's a positive correlation between Penpulimab $C_{avg,ss}$ and ORR ($p < 0.05$). Quartile analysis also indicated that ORR from Q1 was slightly lower than Q2-4. However, a boxplot of the ORR responder vs. non-responder showed that the PK exposure was comparable between the two groups. The logistic regression analysis also showed a relative flat curve between Penpulimab $C_{avg,ss}$ and DCR. Similar to ORR, the exposure between DCR responder vs. non-responder groups were comparable. Other exposure matrix, such as $C_{max,ss}$ and $C_{min,ss}$ showed the similar trends with ORR/DCR. Since there's only one dose level in the E-E analysis, the relationships between Penpulimab and ORR/DCR may not be conclusive, and will be further evaluated when more data become available. PFS: Kaplan-Meier survival curve, stratified by quartiles of exposures, was applied to explore the association between exposure and progression-free survival (PFS). The K-M curves showed that positive trend of median PFS increasing from 6.93 to 16.5 from Q1 to	Yes. Positive E-R trend for ORR and PFS observed based on one dose level data should be interpreted with caution given the limited exposure range with only one dose level.

	<i>Q3 with median PFS for Q4 not being reached.</i> <i>The $C_{avg,ss}$ cutoff for Q1 was 36.4 $\mu\text{g/mL}$. According to PopPK analysis, only 10% of population's exposure fell below 30.4 $\mu\text{g/mL}$ at 200 mg Q3W, indicating majority of the patients would achieve exposure above lowest quartile (Q2 –Q4), where median PFS are expected to be higher, compared to placebo. Similar trend was also observed in the K-M curve of $C_{min,ss}$ and PFS.</i>	
Labeling Language	Description	Acceptability [FDA's comments]
12.2 Pharmacodynamics	<i>Penpulimab-kcqx exposure-response relationships and the time course of pharmacodynamic response are not fully characterized.</i>	Yes.

Applicant – Table 38 Summary of Baseline Characteristics and Laboratory Values

	Covaraites	AK105-304 200mg Q3W+chemo (n=144)	AK105-304 Placebo+chemo (n=142)
Continuous Covaraites, Median [range]	WTB	60 [32.0, 102]	59 [38.5, 90.0]
	HTB	166 [146, 188]	165 [138, 185]
	BMIB	21.6 [14.8, 31.6]	21.4 [15.6, 31.5]
	AGEB	51 [31.0, 75.0]	50 [23.0, 68.0]
	LDHB	200 [111, 2080]	191 [119, 3840]
	CRPB	8.33 [0.210, 328]	5.37 [0.200, 303]
	ALBB	42 [28.2, 67.7]	42.5 [28.8, 82.1]
	COHORT	144 (100.0%)	142 (100.0%)
	200mg Q3W+chemo	144 (100.0%)	0 (0.0%)
Categorical Variables, n (%)	Placebo+chemo	0 (0.0%)	142 (100.0%)

SEX	144 (100.0%)	142 (100.0%)
Male	119 (82.6%)	115 (81.0%)
Female	25 (17.4%)	27 (19.0%)
RACE	144 (100.0%)	142 (100.0%)
Caucasian	4 (2.8%)	1 (0.7%)
Asian	140 (97.2%)	141 (99.3%)
ECOG	144 (100.0%)	142 (100.0%)
0	51 (35.4%)	50 (35.2%)
1	93 (64.6%)	92 (64.8%)
TADA	137 (95.1%)	0 (0.0%)
Negative	122 (84.7%)	0 (0.0%)
Non-treatment-emergent positive	3 (2.1%)	0 (0.0%)
Treatment-emergent positive	12 (8.3%)	0 (0.0%)
NABB	137 (95.1%)	0 (0.0%)
Negative	137 (95.1%)	0 (0.0%)
TNAB	137 (95.1%)	0 (0.0%)
Negative	133 (92.4%)	0 (0.0%)
Positive	4 (2.8%)	0 (0.0%)
STAGE	144 (100.0%)	142 (100.0%)
Primary metastasis	45 (31.3%)	49 (34.5%)
Recurrent metastasis	99 (68.8%)	93 (65.5%)
LIVERMET	144 (100.0%)	142 (100.0%)
No exist	86 (59.7%)	83 (58.5%)
Exist	58 (40.3%)	59 (41.5%)
CMFL	144 (100.0%)	142 (100.0%)
Yes	144 (100.0%)	142 (100.0%)
LDG	144 (100.0%)	142 (100.0%)
Normal	119 (82.6%)	121 (85.2%)
Mild	25 (17.4%)	21 (14.8%)
KDG	144 (100.0%)	142 (100.0%)
Normal	65 (45.1%)	71 (50.0%)
Mild	77 (53.5%)	71 (50.0%)
Moderate	2 (1.4%)	0 (0.0%)

Note: Descriptive statistics in the table are median [minimum, maximum]; n: Number of subjects included in EES analysis; Abbreviation: WTB (kg): Weight at baseline; HTB (cm): Height at baseline; BMIB (kg/m²): BMI at baseline; AGE_B (years): Age at baseline; LDHB(IU/L): LDH at baseline; CRPB (mg/L): CRP at baseline; ALBB(g/L): ALB at baseline; Data source: [Module 5.3.3.5 Penpulimab PopPK and ER report-Appendix 3-Table B 1-1, Table B 1-2.](#)

Applicant – Table 39 Covariate Distribution of C_{avg,ss} Quartiles for All Subjects Included in the ER Analysis of PFS .

Covaraite	Cavg,ss<=Q1 (n=36)	Q1<Cavg,ss<=Q2 (n=35)	Q2<Cavg,ss<=Q3 (n=37)	Cavg,ss>Q3 (n=36)	total (n=144)
WTB	61 [45.0, 96.0]	57 [46.0, 76.0]	63 [44.0, 84.0]	56 [32.0, 102]	60 [32.0, 102]
HTB	168 [155, 186]	166 [152, 176]	166 [146, 180]	162 [147, 188]	166 [146, 188]

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BMIB	22.3 [16.3, 30.4]	20.9 [18.0, 28.1]	22.8 [17.7, 31.6]	21.1 [14.8, 28.8]	21.6 [14.8, 31.6]
AGEB	51.5 [32.0, 75.0]	53 [32.0, 70.0]	53 [38.0, 72.0]	48.5 [31.0, 66.0]	51 [31.0, 75.0]
LDHB	207 [111, 2080]	211 [125, 1040]	199 [116, 1710]	184 [125, 429]	200 [111, 2080]
CRPB	12.7 [0.500, 164]	11 [1.60, 125]	8.33 [0.210, 328]	4.27 [0.300, 35.5]	8.33 [0.210, 328]
ALBB	39.7 [28.2, 67.7]	40.1 [30.0, 48.8]	43.3 [34.8, 49.1]	43.4 [36.7, 50.1]	42 [28.2, 67.7]
COHORT	36 (100.0%)	35 (100.0%)	37 (100.0%)	36 (100.0%)	144 (100.0%)
200mg	36 (100.0%)	35 (100.0%)	37 (100.0%)	36 (100.0%)	144 (100.0%)
Q3W+chemo					
SEX	36 (100.0%)	35 (100.0%)	37 (100.0%)	36 (100.0%)	144 (100.0%)
Male	31 (86.1%)	29 (82.9%)	35 (94.6%)	24 (66.7%)	119 (82.6%)
Female	5 (13.9%)	6 (17.1%)	2 (5.4%)	12 (33.3%)	25 (17.4%)
RACE	36 (100.0%)	35 (100.0%)	37 (100.0%)	36 (100.0%)	144 (100.0%)
/	/	/	2 (5.4%)	2 (5.6%)	4 (2.8%)
Caucasian					
Asian	36 (100.0%)	35 (100.0%)	35 (94.6%)	34 (94.4%)	140 (97.2%)
ECOG	36 (100.0%)	35 (100.0%)	37 (100.0%)	36 (100.0%)	144 (100.0%)
0 Points	14 (38.9%)	13 (37.1%)	9 (24.3%)	15 (41.7%)	51 (35.4%)
1 Points	22 (61.1%)	22 (62.9%)	28 (75.7%)	21 (58.3%)	93 (64.6%)
TADA	36 (100.0%)	33 (94.3%)	32 (86.5%)	36 (100.0%)	137 (95.1%)
Negative	27 (75.0%)	32 (91.4%)	29 (78.4%)	34 (94.4%)	122 (84.7%)
Non-	2 (5.6%)	/	1 (2.7%)	/	3 (2.1%)
treatment-emergent positive					
	7 (19.4%)	1 (2.9%)	2 (5.4%)	2 (5.6%)	12 (8.3%)
Treatment-emergent positive					
NABB	36 (100.0%)	33 (94.3%)	32 (86.5%)	36 (100.0%)	137 (95.1%)
Negative	36 (100.0%)	33 (94.3%)	32 (86.5%)	36 (100.0%)	137 (95.1%)
TNAB	36 (100.0%)	33 (94.3%)	32 (86.5%)	36 (100.0%)	137 (95.1%)
Negative	33 (91.7%)	33 (94.3%)	31 (83.8%)	36 (100.0%)	133 (92.4%)
Positive	3 (8.3%)	/	1 (2.7%)	/	4 (2.8%)
STAGE	36 (100.0%)	35 (100.0%)	37 (100.0%)	36 (100.0%)	144 (100.0%)
Primary metastasis	18 (50.0%)	16 (45.7%)	7 (18.9%)	4 (11.1%)	45 (31.3%)
	18 (50.0%)	19 (54.3%)	30 (81.1%)	32 (88.9%)	99 (68.8%)
Recurrent metastasis					
LIVERMET	36 (100.0%)	35 (100.0%)	37 (100.0%)	36 (100.0%)	144 (100.0%)
No exist	24 (66.7%)	17 (48.6%)	17 (45.9%)	28 (77.8%)	86 (59.7%)
Exist	12 (33.3%)	18 (51.4%)	20 (54.1%)	8 (22.2%)	58 (40.3%)
CMFL	36 (100.0%)	35 (100.0%)	37 (100.0%)	36 (100.0%)	144 (100.0%)
Yes	36 (100.0%)	35 (100.0%)	37 (100.0%)	36 (100.0%)	144 (100.0%)
LDG	36 (100.0%)	35 (100.0%)	37 (100.0%)	36 (100.0%)	144 (100.0%)

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Normal	26 (72.2%)	29 (82.9%)	33 (89.2%)	31 (86.1%)	119 (82.6%)
Mild	10 (27.8%)	6 (17.1%)	4 (10.8%)	5 (13.9%)	25 (17.4%)
KDG	36 (100.0%)	35 (100.0%)	37 (100.0%)	36 (100.0%)	144 (100.0%)
Normal	20 (55.6%)	14 (40.0%)	16 (43.2%)	15 (41.7%)	65 (45.1%)
Mild	15 (41.7%)	21 (60.0%)	20 (54.1%)	21 (58.3%)	77 (53.5%)
	1 (2.8%)	/	1 (2.7%)	/	2 (1.4%)

Moderate

Abbreviation: COHORT: Cohort; SEX: Sex; RACE: Race; ECOG: ECOG at baseline; TADA: Total ADA (Post-baseline); NABB: Baseline Nab; TNAB: Total NAB (Post-baseline); STAGE: Tumor stage; LIVERMET: Liver metastasis; CMFL: With chemo; LDG: Liver function group; KDG: Kidney function group;

Note: C_{avg,ss} Q1:36.4 µg/mL; C_{avg,ss} Q2: 43.2 µg/mL; C_{avg,ss} Q3: 49.5 µg/mL;

Applicant – Table 40 Parameter Estimates from Final ER Model of ORR/DCR .

ER Model	Variable	Estimate	StdErr	WaldChiSq	ProbChiSq
C _{avg,ss} vs. ORR	Intercept	-0.7907	0.7663	1.0646	0.3022
	C _{avg,ss}	0.0356	0.0175	4.1501	0.0416
C _{avg,ss} vs. DCR	Intercept	1.8368	1.1858	2.3995	0.1214
	C _{avg,ss}	0.0108	0.0266	0.1654	0.6843

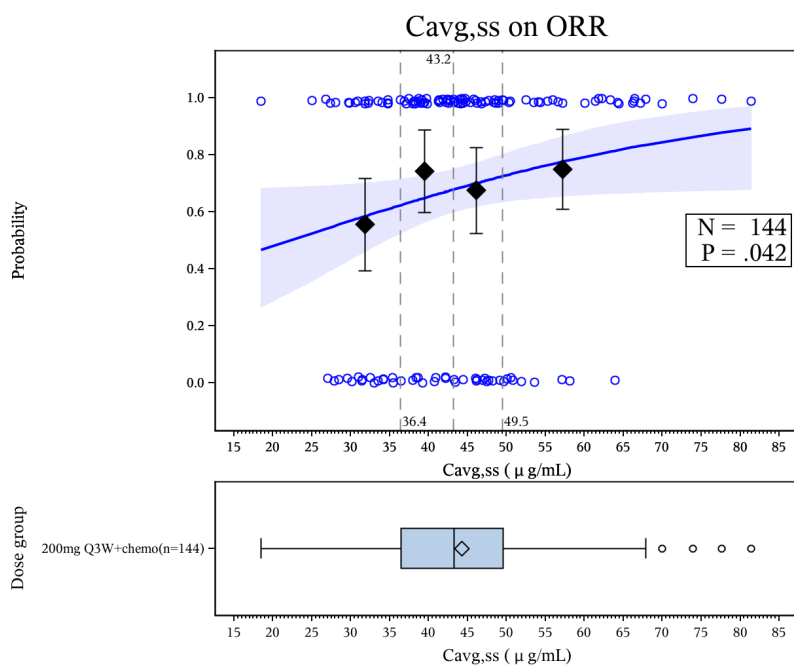
Applicant – Table 41 Median PFS Stratified by Quartiles of C_{avg,ss}

Quartile	N	Median PFS (month)	95% CI Lower	95% CI Upper
C _{avg,ss} Q1	36	6.93	5.52	8.12
C _{avg,ss} Q2	35	8.28	5.75	12.5
C _{avg,ss} Q3	37	16.5	9.63	23.0
C _{avg,ss} Q4	36	NR	8.58	~
AK105 Total	144	9.63	7.13	12.5
Placebo	142	7.00	6.90	7.29

Note: Q1:36.4 µg/mL; Q2: 43.2 µg/mL; Q3: 49.5 µg/mL; NR: Not reached.

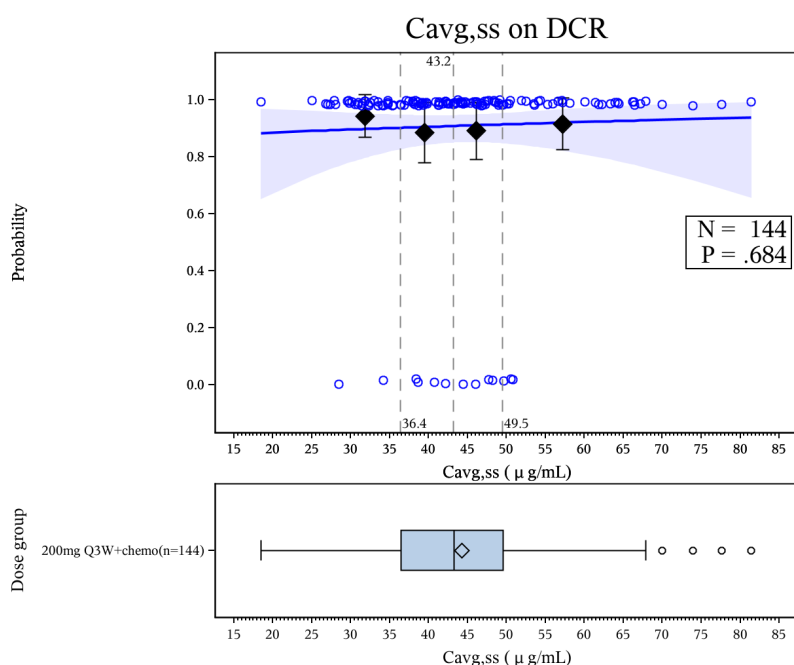
Data Source: [Module 5.3.3.5 Penpulimab PopPK and ER report Appendix 3-Figure B 5-1-4.](#)

Applicant – Figure 12 ER Curves of ORR vs $C_{avg,ss}$ in NPC Patients.



The blue line is the mean probability of response (ORR) simulated with logistic regression models. Shaded region is the 95% confidence intervals of probability. Blue points are the responses (Responder vs non-responder) corresponding to individual's PK exposure. The dotted line is the quartile line of the abscissa variable. Black diamonds and error bars show the median and 95% CI of observed probability of quantiles of concentrations. Sample size and P-value are recorded in the right box.
 Data Source: [Module 5.3.3.5 Penpulimab PopPK and ER report Appendix 3- Figure B 5-1-2.](#)

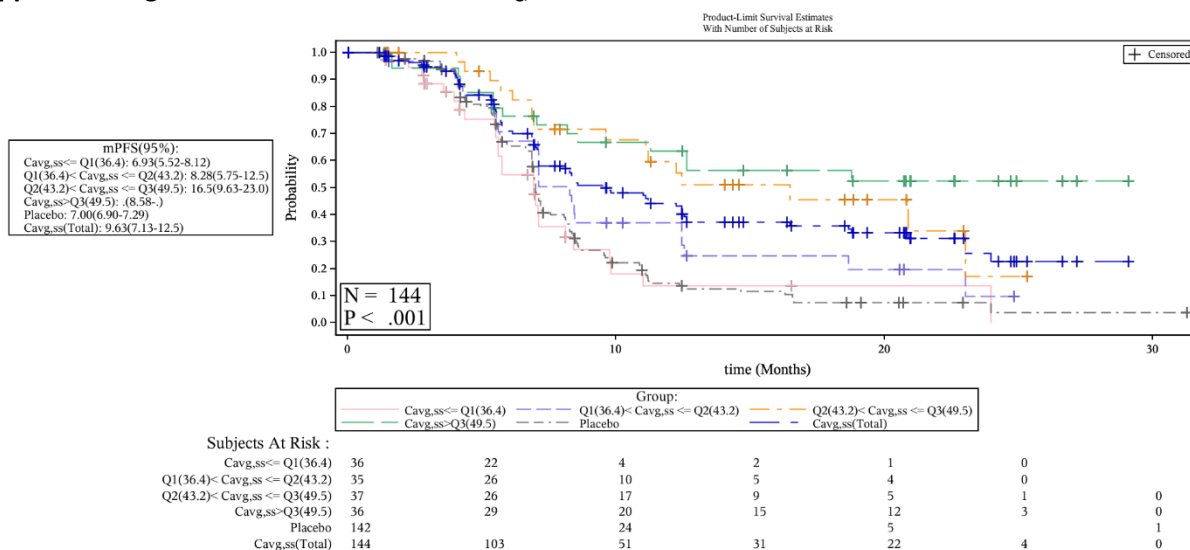
Applicant – Figure 13 ER Curves of DCR vs $C_{avg,ss}$ in NPC Patients.



The blue line is the mean probability of response (DCR) simulated with logistic regression models. Shaded region is the 95% confidence intervals of probability. Blue points are the responses (Responder vs non-responder) corresponding to individual's PK exposure. The dotted line is the quartile line of the abscissa variable. Black diamonds and error bars show the median and 95% CI of observed probability of quantiles of concentrations. Sample size and P-value are recorded in the right box.

Data Source: [Module 5.3.3.5 Penpulimab PopPK and ER report Appendix 3-Figure B 5-1-3.](#)

Applicant – Figure 14 ER Curves of PFS vs $C_{avg,ss}$ in NPC Patients.



Data Source: [Module 5.3.3.5 Penpulimab PopPK and ER report Appendix 3-Figure B 5-1-4.](#)

19.4.3.3. ER (Safety) Executive Summary**The FDA's Assessment:**

Across steady-state exposure over the dosing range from 1 to 10 mg/kg Q2W including 200 mg Q2W and 200 mg Q3W, the risk for Gr $\geq$ 3 TEAEs exhibits a flat trend, whereas the risk for immune related AEs (irAEs) exhibits a positive trend. The positive E-R trend does not appear clinically significant given the low incidences of interruptions (5.7%) and discontinuation (1.8%) due to irAEs.

19.4.3.4. ER (Safety) Assessment Summary**The Applicant's Position:**

The exposure-safety response was evaluated by a univariate logistic regression model. AE responses were used as the dependent variable, and model-predicted Penpulimab exposure such as C_{max,ss}, C_{avg,ss} were used as independent variables to estimate the significance levels. In NPC population, Penpulimab (200 mg Q3W) in combination with chemotherapy, was safe and tolerable. E-R safety analysis indicated that no apparent correlation between exposure and incidence of TEAE/TRAE (Grade 3+) in the wide dose range (1 - 10 mg/kg Q2W) with either monotherapy or in combination therapy.

[Highlight the key findings in the white cells.]

General Information	
Goal of ER analysis	<i>Evaluate the Exposure-Safety (E-S) relationships of Penpulimab in monotherapy patients or all patients.</i>
Study Included	<i>Penpulimab monotherapy: AK105-101, AK105-201, AK105-202, AK105-204 Penpulimab in combination with chemotherapy and others: AK105-205, AK105-301, AK105-302, AK105-304</i>
Population Included	<i>Nasopharyngeal carcinoma, non-small cell lung cancer, solid tumors mainly including gastric cancer, ovarian cancer and esophageal cancer, hematologic malignancy R/R cHL.</i>
Endpoint	● <i>Treatment-Emergent Adverse Event (TEAE):</i> ● <i>Treatment-Related Adverse Event (TRAE):</i> ● <i>CTCAE Grade 3 or Higher TEAE:</i> ● <i>CTCAE Grade 3 or Higher TRAE:</i> ● <i>Time to First Occurrence of TRAE:</i> ● <i>Immune-Related Adverse Event (irAE):</i> ● <i>Infusion-Related Reaction:</i> ● <i>Drug-Related Serious Adverse Event (SAE):</i>

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		TEAE of Special Interest: such as anaemia, WBC decrease, neutrophil count decrease, alanine aminotransferase increase, nausea, aspartate aminotransferase increase, platelet count decrease, hypothyroidism, vomiting, pyrexia, diarrhoea, hyponatraemia, rash, hypokalaemia, hypoaesthesia, hypertriglyceridaemia, weight loss, cough, proteinuria, hyperuricaemia and fatigue.
No. of Patients (total, and with individual PK)		A total of 771 patients received Penpulimab with monotherapy or combination therapy, 380 patients treated with Penpulimab monotherapy at doses of 1, 3, and 10 mg/kg Q2W or 200 mg Q2W. 391 patients were treated with Penpulimab 200 mg Q3W in combination with chemotherapy.
Population Characteristics (Applicant – Table 42)	General	Age median (range):55.0 yrs (18.0 ~ 91.0) Weight median (range) :62.0 kg (32.0 ~ 113.5) 574 (74.4%) male. 679 (88.1%) Asian,85 (11.0%) Caucasian, 7 (0.9%) other;
	Organ impairment	Hepatic - Normal hepatic function (TBIL $\leq$ ULN and AST $\leq$ ULN, n=652(84.6%)), - Mild (TBIL $\leq$ ULN and AST $>$ ULN or TBIL $>$ 1 to 1.5 times ULN and any AST, n=113(14.7%)), - Moderate (TBIL $>$ 1.5 to 3 times ULN and any AST, n=5(0.6%)), and - Severe (TBIL $>$ 3 times ULN and any AST, n=0) hepatic impairment Renal (CrCL) - Normal renal function (CLcr $\geq$ 90 mL/min, n=404 (52.4%)), - Mild (60 mL/min $\leq$ CLcr $<$ 90 mL/min, n=303 (39.3%)), - Moderate (30 mL/min $\leq$ CLcr $<$ 60 mL/min, n=62(8.0%)), and - Severe (CLcr $<$ 30 mL/min, n=1 (0.1%)) renal impairment;
	Pediatrics (if any)	Not applicable
	Geriatrics (if any)	Age median (range):55 yrs (18~91), 21.7% of patients $\geq$65 yr 574 (74.4%) male
Dose(s) Included		1, 3, 10 mg/kg Q2W, 200mg Q2W, and 200mg Q3W
Exposure Metrics Explored (range)		The Penpulimab exposure such as $C_{avg,ss}$, $C_{max,ss}$, were derived from PopPK analysis.

Covariates Evaluated	<i>Not applicable</i>	
Final Model Parameters	Summary	Acceptability [FDA's comments]
Model Structure	Univariate logistic regression model: $\log i t_i = \theta_1 + \theta_2 (C_{avg,ss_i} - \text{Median}(C_{avg,ss}))$ $P_i = \frac{e^{\text{Logit}_i}}{1 + e^{\text{Logit}_i}}$	Yes.
Model Parameter Estimates	Applicant – Table 43	Yes.
Model Evaluation	Associations were considered significant if the p-value was less than 0.05	Yes.
Covariates and Clinical Relevance	The exposure-safety response was evaluated by a univariate logistic regression model. AE responses were used as the dependent variable, and model-predicted Penpulimab exposure such as $C_{max,ss}$, $C_{avg,ss}$ were used as independent variables to estimate the regression coefficients, confidence intervals, and significance levels.	Yes.
Simulation for Specific Population	<i>Not applicable</i>	
Visualization of E-R relationships	Applicant – Figure 15~Applicant – Figure 23	Yes.
Overall Clinical Relevance for ER	<i>Monotherapy</i> A total of 380 patients received Penpulimab monotherapy at 1, 3, 10 mg/kg Q2W, or 200 mg Q2W. There's no significant dose or exposure-dependent increase in the incidence of TEAEs, TRAEs or CTCAE Grade3+ AEs, and drug-related SAEs. However, there's upper ward trend between PK exposure ($C_{avg,ss}$, $C_{max,ss}$) and irAE and the association with $C_{avg,ss}$ being statistically significant.	Yes. Positive E-R trend observed for irAEs does not appear clinically significant given low incidence of interruption (5.7%) and discontinuation

	Combination therapy <i>A total of 391 patients received Penpulimab 200 mg Q3W in combination with chemotherapy.</i> <i>Similar to monotherapy, there was no significant increase in TEAE/TRAЕ (Grade 3+) with increasing of PK exposure, while association with irAE was found to be statistically significant.</i> <i>For AEs with incidence rate of 10% or higher, white blood cell count decrease, hypothyroidism, rash and upper respiratory tract infection were associated with higher exposure, consistent with common adverse events observed in this population.</i> <i>Overall, E-R safety analysis suggested a flat exposure-response relationships between Penpulimab exposure and most AEs in both monotherapy and combination therapy groups. However, higher exposure levels may be associated with a slightly increased risk of irAEs and some specific AEs.</i>	(1.8%) due to irAEs.
Labeling Language	Description	Acceptability [FDA’s comments]
12.2 Pharmacodynamics	<i>Penpulimab-kcqx exposure-response relationships and the time course of pharmacodynamic response are not fully characterized.</i>	Yes.

Applicant – Table 42 Summary of Baseline Characteristics and Laboratory Values

	Variables	Total (n=771)
Continuous variables Median(range)	WTB	62 [32.0, 114]
	HTB	167 [144, 191]
	BMIB	22.7 [13.2, 42.7]
	AGEB	55 [18.0, 91.0]
	LDHB	213 [1.46, 4450]
	CRPB	9.55 [0.00, 328]
	ALBB	41.9 [22.0, 67.7]
	COHORT	771 (100.0%)
	1mg/kg Q2W	3 (0.4%)
	3mg/kg Q2W	6 (0.8%)
	10mg/kg Q2W	7 (0.9%)
	200mg Q2W	364 (47.2%)
	200mg Q3W+chemo	391 (50.7%)
	SEX	771 (100.0%)
Categorical variables n(%)	Male	574 (74.4%)
	Female	197 (25.6%)
	RACE	771 (100.0%)
	Caucasian	85 (11.0%)
	Asian	679 (88.1%)
	Other	7 (0.9%)
	ECOG	771 (100.0%)
	0 Points	286 (37.1%)
	1 Points	485 (62.9%)
	TADA	715 (92.7%)
	Negative	515 (66.8%)
	Non-treatment-emergent positive	8 (1.0%)
	Treatment-emergent positive	192 (24.9%)
	NABB	605 (78.5%)
	Negative	604 (78.3%)
	Positive	1 (0.1%)
	TNAB	605 (78.5%)
	Negative	548 (71.1%)
	Positive	57 (7.4%)
	STAGE	144 (18.7%)
	Primary metastasis	45 (5.8%)
	Recurrent metastasis	99 (12.8%)
	LIVERMET	144 (18.7%)
	No exist	86 (11.2%)

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Exist	58 (7.5%)
CMFL	771 (100.0%)
No	380 (49.3%)
Yes	391 (50.7%)
LDG	770 (99.9%)
Normal	652 (84.6%)
Mild	113 (14.7%)
Moderate	5 (0.6%)
KDG	770 (99.9%)
Normal	404 (52.4%)
Mild	303 (39.3%)
Moderate	62 (8.0%)
Severe	1 (0.1%)

Note: Descriptive statistics in the table are expressed using median [minimum, maximum]; n: Number of subjects included in ESS analysis;

Abbreviation: WTB (kg): Weight at baseline; HTB (cm): Height at baseline; BMIB (kg/m²): BMI at baseline; AGEb (years): Age at baseline; LDHB(IU/L): LDH at baseline; CRPB (mg/L): CRP at baseline; ALBB(g/L): ALB at baseline;

Data source: [Module 5.3.3.5 Penpulimab PopPK and ER report-Appendix 3-Table B 2-1, Table B 2-2:](#)

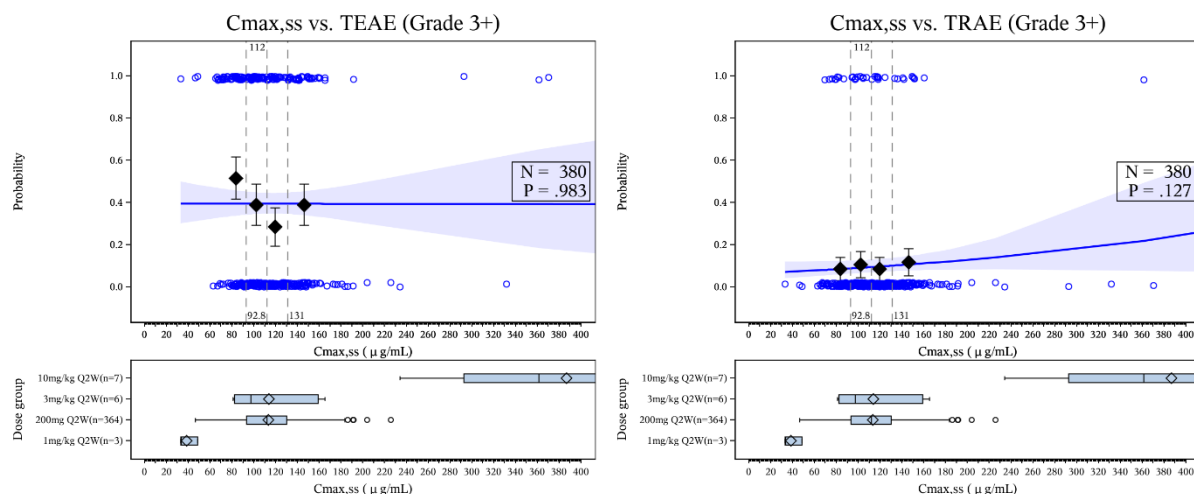
Applicant – Table 43 Parameter Estimates from Final ER Model of (AEs)

	ER Model	Variable	Estimate	StdErr	WaldChiSq	ProbChiSq
Monotherapy	C _{max,ss} vs. TEAE (Grade 3+)	Intercept	-0.422	0.277	2.33	0.127
	C _{max,ss} vs. TEAE (Grade 3+)	C _{max,ss}	-	0.00217	0.0005	0.983
			0.00005			
	C _{max,ss} vs. TRAE (Grade 3+)	Intercept	-2.71	0.371	53.3	<.0001
	C _{max,ss} vs. TRAE (Grade 3+)	C _{max,ss}	0.00396	0.0026	2.32	0.127
	C _{max,ss} vs. irAE	Intercept	-1.14	0.291	15.3	<.0001
	C _{max,ss} vs. irAE	C _{max,ss}	0.00369	0.00227	2.65	0.103
	C _{max,ss} vs. Drug-related SAE	Intercept	-3.11	0.400	60.2	<.0001
	C _{max,ss} vs. Drug-related SAE	C _{max,ss}	0.00467	0.00269	3.01	0.0829
Combination therapy	C _{max,ss} vs. TEAE (Grade 3+)	Intercept	1.31	0.654	4.01	0.0452
	C _{max,ss} vs. TEAE (Grade 3+)	C _{max,ss}	-	0.00772	0.0184	0.892
			0.00105			
	C _{max,ss} vs. TRAE (Grade 3+)	Intercept	-0.173	0.561	0.0949	0.758
	C _{max,ss} vs. TRAE (Grade 3+)	C _{max,ss}	-	0.00665	0.152	0.696
			0.00259			
	C _{max,ss} vs. irAE	Intercept	-2.47	0.616	16.1	<.0001
	C _{max,ss} vs. irAE	C _{max,ss}	0.0177	0.00713	6.19	0.0128
	C _{max,ss} vs. White blood cell count decreased	Intercept	-0.137	0.642	0.0454	0.831
	C _{max,ss} vs. White blood cell count decreased	C _{max,ss}	0.0135	0.00774	3.05	0.0808
	C _{max,ss} vs. Hypothyroidism	Intercept	-3.49	0.674	26.8	<.0001
	C _{max,ss} vs. Hypothyroidism	C _{max,ss}	0.0255	0.00767	11.1	0.0009
	C _{max,ss} vs. Rash	Intercept	-3.96	0.750	27.8	<.0001
	C _{max,ss} vs. Rash	C _{max,ss}	0.0261	0.00842	9.63	0.0019

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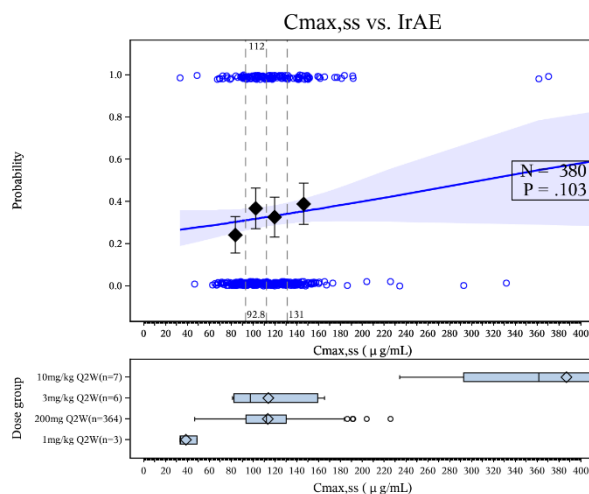
$C_{max,ss}$ vs. Upper respiratory tract infection	Intercept	-4.57	0.934	24.0	<.0001
$C_{max,ss}$ vs. Upper respiratory tract infection	$C_{max,ss}$	0.0255	0.0103	6.01	0.0136

Applicant – Figure 15 ER Curves of Grade 3+TEAE/TRAE vs $C_{max,ss}$ in Monotherapy Patients.



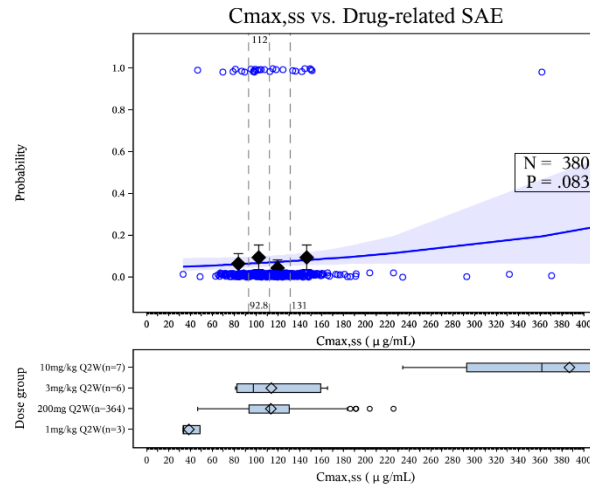
Data source: [Module 5.3.3.5 Penpulimab PopPK and ER report-Appendix 3- Figure B 9-1-1-3, Figure B 9-1-1-4.](#)

Applicant – Figure 16 ER Curves of irAE vs $C_{max,ss}$ in Monotherapy Patients.



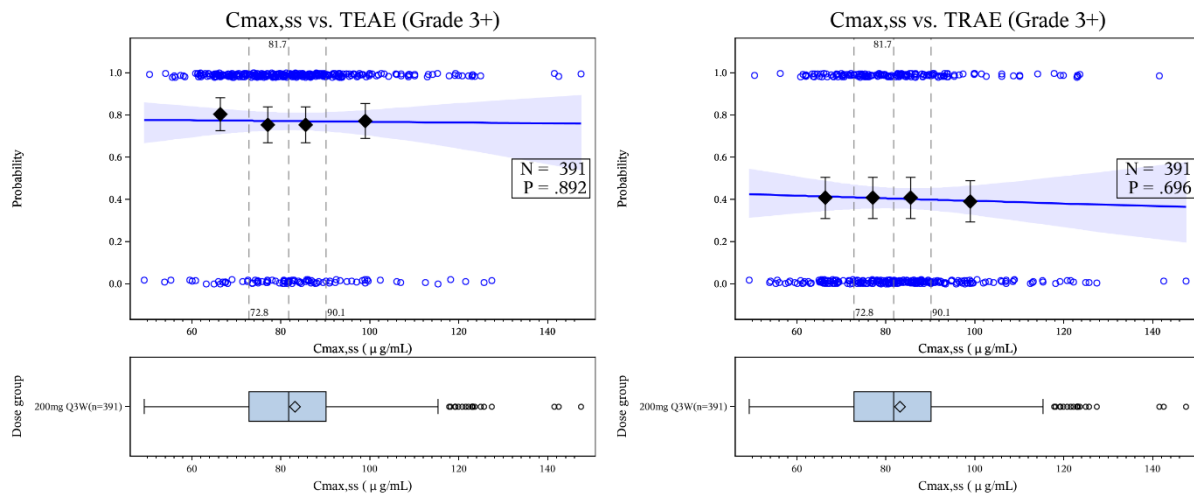
Data source: [Module 5.3.3.5 Penpulimab PopPK and ER report-Appendix 3- Figure B 9-1-1-5.](#)

Applicant – Figure 17 ER Curves of Drug-Related SAE vs $C_{max,ss}$ in Monotherapy Patients.



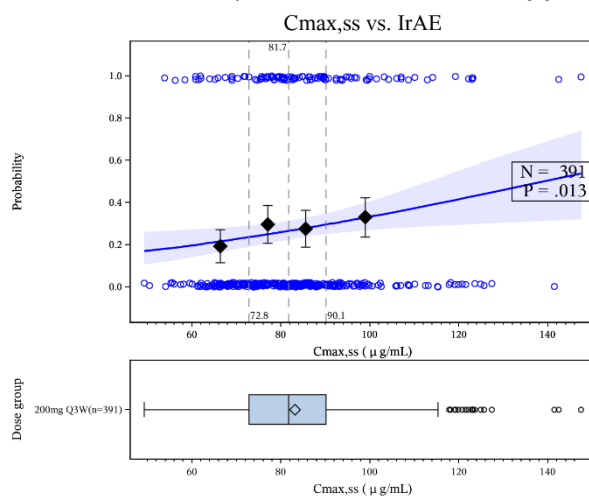
Data source: [Module 5.3.3.5 Penpulimab PopPK and ER report-Appendix 3- Figure B 9-1-1-7.](#)

Applicant – Figure 18 ER Curves of Grade 3+ TEAE/TRAЕ vs $C_{max,ss}$ in Combination Therapy Patients.



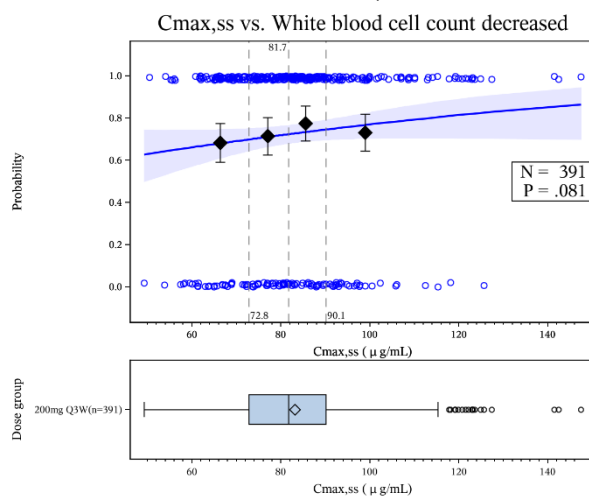
Data source: [Module 5.3.3.5 Penpulimab PopPK and ER report-Appendix 3- Figure B 9-4-1-3, Figure B 9-4-1-4.:](#)

Applicant – Figure 19 ER Curves of irAE vs $C_{max,ss}$ in Combination Therapy Patients.



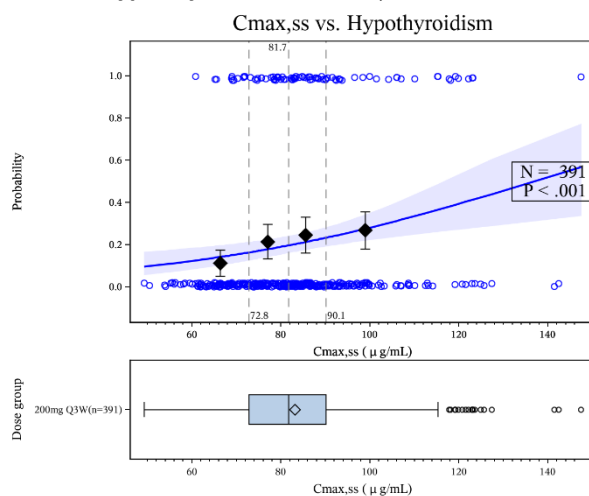
Data source: [Module 5.3.3.5 Penpulimab PopPK and ER report-Appendix 3- Figure B 9-4-1-5.](#)

Applicant – Figure 20 ER Curves of WBC decreased vs $C_{max,ss}$ in Combination Therapy Patients.



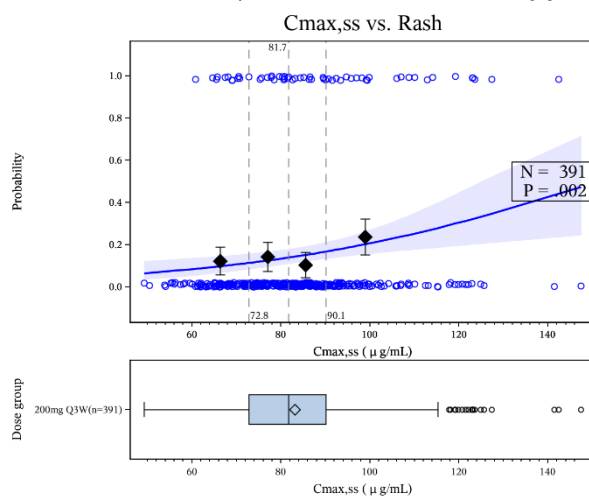
Data source: [Module 5.3.3.5 Penpulimab PopPK and ER report-Appendix 3- Figure B 9-4-2-2.](#)

Applicant – Figure 21 ER Curves of hypothyroidism vs $C_{max,ss}$ in Combination Therapy Patients.



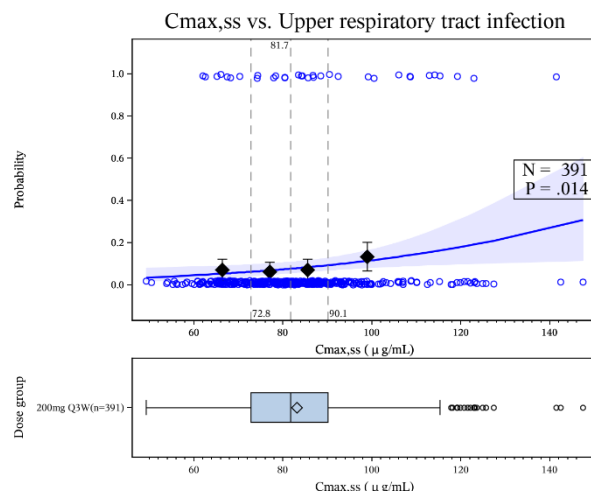
Data source: [Module 5.3.3.5 Penpulimab PopPK and ER report-Appendix 3- Figure B 9-4-2-8.](#)

Applicant – Figure 22 ER Curves of rash vs $C_{max,ss}$ in Combination Therapy Patients.



Data source: [Module 5.3.3.5 Penpulimab PopPK and ER report-Appendix 3- Figure B 9-4-2-16.](#)

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Applicant – Figure 23 ER Curves of Upper respiratory tract infection vs $C_{max,ss}$ in Combination Therapy Patients.

Data source: [Module 5.3.3.5 Penpulimab PopPK and ER report-Appendix 3- Figure B 9-4-2-22.](#)

The FDA's Assessment:

FDA agrees with the E-R analysis conducted by the Applicant.

19.4.3.5. ER Review Issues

None.

19.4.3.6. Reviewer's Independent Analysis

None.

19.4.3.7. Overall Benefit-Risk Evaluation Based on E-R Analyses**The Applicant's Position:**

Penpulimab 200 mg Q3W demonstrated notable clinical benefits and tolerable safety profiles in NPC patients: the median PFS was 9.6 months (95% CI: 7.1, 12.5), compared to placebo of 7.0 months (95% CI: 6.9, 7.3). E-R analysis suggested a relative flat E-R (ORR/DCR) curve and no apparent difference in exposure between responders and non-responders. In NPC patients, Penpulimab (200 mg Q3W) in combination with chemotherapy was safe and tolerable. E-R safety analysis indicated that no apparent correlation between exposure and incidence of TEAE/TRAE (Grade 3+) in the wide dose range (1 - 10 mg/kg Q2W) with either monotherapy or in combination therapy.

The FDA's Assessment:

FDA generally agrees with the Applicant's position. However, ER relationship for efficacy remains inconclusive due to the limited exposure range of penpulimab at one dose level.

19.5. Additional Safety Analyses Conducted by FDA

The FDA's Assessment:

FDA has no additional safety analyses to report.

1. Statistical and Clinical Evaluation

1.1. Review of Relevant Individual Trials Used to Support Efficacy

1.1.1. Studies

1.1.1.1. Study AK105-202

Trial Design

The Applicant's Description:

Study AK105-202 is a single-arm, open-label, multicenter phase II clinical study to evaluate the efficacy and safety of penpulimab in patients with metastatic nonkeratinizing NPC with disease progression on or after platinum-based chemotherapy and at least one other prior line of therapy. Patients were excluded from the study based on history of autoimmune disease, medical conditions requiring systemic immunosuppression, prior organ or allogeneic stem cell transplantation, prior treatment with anti-PD-1, anti-PD-L1 or CTLA-4 antibodies, active central nervous system (CNS) metastases, or ECOG performance score > 2.

Patients received penpulimab 200 mg intravenously every 2 weeks until disease progression as determined by the investigator, or unacceptable toxicity, or a maximum of 24 months, whichever occurred first. Administration of penpulimab was permitted beyond RECIST-defined disease progression if the patients were assessed as clinically beneficial and tolerated to the study drug by the investigator. Tumor measurements were performed every 8 weeks in first year and every 12 weeks thereafter, to determine response by RECIST v1.1 criteria. The primary objective of the study was to evaluate the objective response rate (ORR) assessed by blinded independent radiology review committee (IRRC) per RECIST v1.1. Secondary objectives included duration of response (DoR), progression-free survival (PFS) and overall survival (OS).

The FDA's Assessment:

FDA agrees with the Applicant's description of the trial design for Study AK105-202. FDA clarifies that the study was conducted at multiple sites in China. Since Study AK105-202 is a single arm trial, FDA does not use any inferential procedures to evaluate the trial results. The efficacy decision is based on the lower limit of a 95% confidence interval of the response rate in the trial to exceed a clinically relevant response rate with adequate duration of response. Additionally, time-to-event endpoints such as PFS and OS are not interpretable in a single arm trial due to a lack of comparator and their corresponding analyses are considered as descriptive.

Study Endpoints

The Applicant's Description:

- Primary Efficacy Endpoint: ORR assessed by IRRC per RECIST v1.1 in the Full Analysis Set (FAS).
ORR is defined as the proportion of patients whose best overall response (BOR) is confirmed CR or PR. The confirmation of CR or PR by repeated imaging assessments is performed not less than 28 days (4 weeks) after the first observation of a CR or PR, and there is no evidence of PD between the follow-up of the first observed CR or PR and the follow-up for confirmation of CR or PR.
- Key Secondary Efficacy Endpoints: duration of response (DoR)
- Other Secondary Endpoints:
 - 1) Efficacy: ORR assessed by investigator, Disease control rate (DCR), time to response (TTR), PFS assessed by IRRC and investigator per RECIST v1.1 and OS
 - 2) Pharmacokinetic (PK) and immunogenicity assessment
 - 3) Safety: incidence and severity of adverse events, abnormal laboratory findings with clinical significance.
 - 4) Correlation analysis between the expression of EBV-DNA in blood and the anti-tumor activity of penpulimab.

The FDA's Assessment:

In general, FDA agrees with the Applicant's description of the study endpoints. As noted in the previous section, time-to-event endpoints such as PFS and OS are not interpretable in a single arm study, and their corresponding analyses are considered descriptive.

Statistical Analysis Plan and Amendments

The Applicant's Description:

The sample size calculation was based on the primary endpoint of ORR. A total of 110 patients were needed for an ORR of 15% to be excluded using the lower limit of a two-sided 95% CI. If an ORR of 26% is assumed for penpulimab, there is 82% chance of observing at least 25 responses (an ORR of 22.7%), with the lower limit of the 95% CI excluding a historical response rate of 15%. Considering an attrition rate of 15%, a total sample size of 130 was needed to ensure at least 110 evaluable patients. In this study, an interim analysis was originally planned after at least 110 patients were enrolled and completed at least 16 weeks of follow-up (an interval between the data cutoff date and the date of first dose $\geq$ 16 weeks), and the results of the interim analysis was planned to be used for communicating with the regulatory agencies. There were no plans to stop the trial based on either of these analyses and no formal statistical tests were planned.

An interim analysis of efficacy was conducted after 110 patients treated with penpulimab had an opportunity to be followed for at least 8 months prior to data cutoff date (to allow at least 6

months follow-up past onset of response assuming the response occurs at the first follow-up scan).

The study was completed and the final analysis was conducted at 12 months after the last subject was first dosed were presented below.

Definition of Key Analysis Sets

- Enrollment Analysis Set [ENR]

The ENR includes all patients who have signed the ICF and been enrolled into the study.

- Primary Efficacy Population

The Primary Efficacy Population includes all patients in the ENR who have received at least one dose of penpulimab and meet the following inclusion criteria:

- Patients diagnosed with disease stage of IVb in accordance with Chinese Nasopharyngeal Carcinoma Staging 2017 (2008 Expert Consensus on Nasopharyngeal Cancer Staging Revision) at enrollment.
- Patients who had disease progression on or after platinum-based chemotherapy and at least one other prior line of therapy. Prior neoadjuvant chemotherapy, concurrent chemoradiotherapy, or adjuvant chemotherapy would be considered as the first line of therapy if recurrence/metastasis occurs within 6 months since the last dose of chemotherapy. Switching treatment regimen due to intolerability were not counted as additional lines of therapy.
- Patients with at least one measurable lesion at baseline per RECIST v1.1 as assessed by IRRC if efficacy summary based on IRRC assessment, or at least one measurable lesion at baseline per RECIST v1.1 as assessed by the investigator if efficacy summary based on investigator assessment.
- Patients who had an opportunity to be followed for at least 8 months prior to data cutoff date (to allow at least 6 months follow-up past onset of response assuming the response occurs at the first follow-up scan).

- Safety Analysis Set

The Safety Analysis Set includes all enrolled patients who have received at least one dose of penpulimab.

- Pharmacokinetics Set [PKS]

The PKS includes all enrolled patients in the safety analysis set who have at least one quantifiable concentration data at the scheduled time point and no major and critical protocol violations affecting the concentration data.

- Immunogenicity Set [IMMS]

The IMMS includes all enrolled patients for safety analysis who have received at least one immunogenicity assessment at baseline and post-baseline, respectively.

Applicant – Table 1 shows the amendment history of the the Statistical Analysis Plan (SAP)

Applicant – Table 1 SAP Amendments

Amendment Date	Major changes
11 September, 2020 Version 1.0	• First Version
02 March, 2021 Version 2.0	• Section 7.3.3 & 7.3.4: Added imputation methods for missing or incomplete dates • Section 12.1: Updated sorting of summary tables • Section 13.2: Removed partial description per template • Section 14: Modified algorithm for total treatment cycle • Section 17: Modified ADA positive definition • Section 18.1: Supplemented TEAE judgment conditions • Section 18.1.5: Supplemented explanation of pooled calculation conditions for irAEs • Section 18.3: Removed partial description per template

The FDA’s Assessment:

In general, FDA agrees with the Applicant’s description of the statistical analysis plan. In protocol version 3.0 dated July 6, 2020, the Applicant had stated that the primary analysis of ORR would be conducted once the last enrolled patient had completed at least 24 weeks of follow-up. The primary analysis was conducted based on a data cut-off date of February 3, 2021. An updated analysis of ORR was submitted on January 6, 2025, based on the data cut-off date of September 23, 2021, to provide additional follow-up from onset of response for patients who had a confirmed radiographic response.

Between March 27, 2019 and September 14, 2020, the study had enrolled 130 patients. FDA’s efficacy analysis for Study AK105-202 was based on 125 patients who met the definition of the primary efficacy population, based on the data cut-off date of September 23, 2021. There were five enrolled patients who were not included in the primary efficacy analysis population. One of those patients had only one prior line of systemic therapy, and the other four patients did not have measurable disease at baseline per IRRC assessment.

Protocol Amendments

The Applicant’s Description:

[Applicant – Table 2](#) lists major modifications to Study AK105-202 protocol with each amendment.

Applicant – Table 2 Protocol Amendments

Amendment Date	Major changes to the protocol
4 March, 2019 Version 2.0	- Expanded the enrollment age ≥ 18 years and ≤ 75 years. - Clarified patients with stage IVb metastatic NPC at enrollment. - Removed the requirement of “No more than 3 prior regimens of systemic therapy for recurrent/metastatic nasopharyngeal carcinoma” and clarified the definition of first-line treatment for patients with neoadjuvant chemotherapy, concurrent chemoradiotherapy, or adjuvant chemotherapy. - Modified exclusion criteria “Patients with other active malignancies within 5 years prior to enrollment” to “Patients with other active malignancies within 2 years prior to enrollment” - Deleted ORR assessed by IRRC as the primary endpoint. but ORR assessed by IRRC and investigator will be submitted to the agency for the marketing application. - Add the content of planned interim analysis.
6 July, 2020 Version 3.0	- Deleted the PD-L1 positive analysis set from the study objectives and endpoints, and deleted ORR in the PD-L1 positive population used as a co-primary endpoint for this study. - Clarified that the primary endpoint is ORR assessed by IRRC per RECIST v1.1. - Clarified PD-L1 cut-off value and added definition of PD-L1 positive/negative subgroups. - Redefined treatment discontinuation criteria. - Modified the planned enrollment sample size and adjusted the corresponding statistical analysis plan, including the planned interim analysis. - Clarified whether disease progression required for reporting as SAEs and clarified the reporting requirements for AESIs. - Updated SAE reporting process instructions in accordance with the requirements of Good Clinical Practice (Version 2020).

The FDA’s Assessment:

FDA agrees with the Applicant’s description.

1.1.2. Study Results

1.1.2.1. Study Results of AK105-202

Compliance with Good Clinical Practices

Data:

The study protocols and informed consent documents were reviewed by local IRB/IEC as required by regulations prior to implementation at participating institutions.

The Applicant's Position:

The study was conducted and monitored in compliance with the protocol, the ethical principles that have their origin in the Declaration of Helsinki and the ICH consolidated Guideline E6 for GCP and applicable regulatory requirement(s).

The FDA's Assessment:

The FDA agrees with the Applicant's position.

Financial Disclosure

Data:

N/A

The Applicant's Position:

Appropriate financial disclosure was collected during the course of Study AK105-202, and no financial arrangements with the Investigators impacted the validity of the study. Additional information regarding financial disclosures can be found in [\[Section 19.2 of Assessment Aid for study AK105-304\]](#).

The FDA's Assessment:

The FDA agrees with the Applicant's position.

Patient Disposition

Data:

A total of 171 patients were screened and 130 patients were enrolled. The reason for all screen failure was not meeting eligibility criteria. The first patient was enrolled on March 27, 2019, and the last patient was enrolled on September 14, 2020.

As of September 23, 2021, efficacy analysis included 125 patients who met the definition of primary efficacy population for IRRC assessment (excluding 1 patient, (b) (6) who had only one line of prior therapy; 4 patients, (b) (6) who did not have measurable lesions at baseline assessed by the IRRC) and 128 patients who met the definition of primary efficacy population for Investigator assessment (excluding 1 patient, (b) (6), had only one line of prior therapy; 1 patient, (b) (6), did not have measurable lesion at baseline assessed by the investigator).

The median duration of follow-up was 22.1 months (range: 0.9 to 30.0) for the primary efficacy population for IRRC assessment and 22.0 months (range: 0.9 to 30.0) for the primary efficacy population for Investigator assessment.

[Applicant – Table 3](#) summarizes the reasons for discontinuation. The most common reason for discontinuation was radiographic disease progression (57.6%).

Applicant – Table 3 Patient Disposition - Primary Efficacy Population

Patient distribution	IRRC assessment (N = 125)	Investigator assessment (N=128)
Number of Enrolled Patients ^[a], n	125	128
Number of Patients Treated, n (%)	125 (100.0)	128 (100.0)
Number of Patients still on Treatment, n (%)		
End of Treatment, n (%)	102 (81.6)	104 (81.3)
Adverse Event	5 (4.0)	6 (4.7)
Radiographic Disease Progression	72 (57.6)	72 (56.3)
Symptomatic Deterioration without Radiographic Evidence	3 (2.4)	3 (2.3)
Patient Withdrawal Consent	4 (3.2)	4 (3.1)
Lost to Follow-Up	2 (1.6)	2 (1.6)
Death	4 (3.2)	4 (3.1)
Other	11 (8.8)	12 (9.4)
Number of Patients still under Follow-Up, n (%)	56 (44.8)	57 (44.5)
End of Study, n (%)	69 (55.2)	71 (55.5)
Death	53 (42.4)	55 (43.0)
Lost to Follow-Up	11 (8.8)	11 (8.6)
Withdrawal by Patient	4 (3.2)	4 (3.1)
Other	1 (0.8)	1 (0.8)

Abbreviations: IRRC = Independent Radiology Review Committee.

% = Percentage of patients receiving study treatment as the denominator.

[a] Enrolled patients include all patients who have signed the ICF and been enrolled into the study.

Source Data: ADSL.xpt.

The Applicant's Position:

As of data cutoff date, the median duration of follow-up was 22.1 months (range: 0.9 to 30.0) for the primary efficacy population for IRRC assessment. The final analysis was conducted when the last enrolled subject completed 12-month follow-up and the results are considered mature and were submitted to this BLA.

The FDA's Assessment:

FDA agrees with the Applicant's description of patient disposition. At the data cut-off date of September 23, 2021, out of the 125 patients in the primary efficacy population, 23 (18%) were still under treatment. Patient disposition for the 128 patients in the investigator-assessed population was not independently verified by the FDA.

Table of Demographic Characteristics

Data:

Applicant – Table 4 shows baseline patient demographics.

Applicant – Table 4 Demographic information – Primary Efficacy Population

Characteristic	IRRC assessment (N = 125)	Investigator assessment (N=128)
Age (Years)		
≤65 Years	123 (98.4)	126 (98.4)
>65 Years	2 (1.6)	2 (1.6)
Median	49.6	49.5
Min, Max	21, 66	20, 66
Gender, n (%)		
Male	95 (76.0)	98 (76.6)
Female	30 (24.0)	30 (23.4)
ECOG, n (%)		
0	39 (31.2)	40 (31.3)
1	86 (68.8)	88 (68.8)

Source Data: ADSL.xpt

The Applicant's Position:

The majority of patients were male (76.0%), the median age was 49.6 years (range: 21 to 66 years), and the ECOG performance score was 0 (31.2%) or 1 (68.8%).

The FDA's Assessment:

FDA agrees with the Applicant's description of demographic characteristics based on the 125 patients included in the primary efficacy population.

FDA notes that the male predominance of the study population is consistent with the U.S. patient population with NPC. Given that all patients in the efficacy population were of Chinese ethnicity, the efficacy population do not reflect the racial and ethnic demographics of the U.S. patient population with NPC. FDA was not able to examine the consistency of the treatment benefit by geographical location, race and ethnicity, or in a patient population that is more representative of the population of U.S. patients with NPC. A postmarketing commitment is being issued to obtain more data on penpulimab in patients with NPC in the U.S.

Demographic characteristics for the 128 patients in the investigator-assessed population were not independently verified by the FDA.

Other Baseline Characteristics (e.g., disease characteristics, important concomitant drugs)

Data:

Applicant – Table 5 shows other baseline characteristics.

Applicant – Table 5 Clinical and disease characteristics at baseline – Primary Efficacy Population

Characteristic	IRRC assessment (N = 125)	Investigator assessment (N=128)
PD-L1 (Shuwen SAB-028)		
Positive (TPS≥50%)	46 (36.8)	48 (37.5)
Negative (TPS<50%)	76 (60.8)	77 (60.2)
NA	3 (2.4)	3 (2.3)
Clinical stage at diagnosis, n (%)		
Stage II	4 (3.2)	4 (3.1)
Stage III	32 (25.6)	33 (25.8)
Stage IVA	31 (24.8)	32 (25.0)
Stage IVB	45 (36.0)	46 (35.9)
Unknown	13 (10.4)	13 (10.2)
Neoplasm Histological Type, n (%)		
Non keratinizing differentiated NPC	37 (29.6)	38 (29.7)
Non keratinizing undifferentiated NPC	84 (67.2)	85 (66.4)
Non keratinizing with unknown differentiation NPC	4 (3.2)	5 (3.9)
Location of Metastasis ^[b]		
Liver	60 (48.0)	62 (48.4)
Lymph Node	44 (35.2)	44 (34.4)
Lung	77 (61.6)	77 (60.2)
Bone	62 (49.6)	63 (49.2)
Number of Location of Metastasis		
< 3	84 (67.2)	87 (68.0)
≥ 3	41 (32.8)	41 (32.0)
Prior Line of Therapy, n (%)		
0-1	0	0
2	79 (63.2)	81 (63.3)
≥3	46 (36.8)	47 (36.7)
Median	2.0	2.0
Min, Max	2, 6	2, 6
Peripheral Blood EBV Level at Baseline (IU/mL), n (%)		
≥500 ^[c]	103 (82.4)	105 (82.0)
<500 ^[c]	22 (17.6)	23 (18.0)
LDH at Baseline, n (%)		
≥ ULN ^[d]	61 (48.8)	63 (49.2)
< ULN ^[d]	64 (51.2)	65 (50.8)

Abbreviations: LDH = Lactate dehydrogenase; PD-L1 = programmed cell death - Ligand 1.

Assessment Aid Addendum for Study AK105-202 - BLA 761258

Penpulimab

[a] Time from initial diagnosis to first dose of study drug (months) = (date of first dose of study drug - date of initial diagnosis + 1)/30.4375.

[b] Metastatic sites were derived from the baseline tumor diagnosis form including at the discretion of the investigator, lesions present at baseline and lesions that present previously unequivocally but not indicated at baseline.

[c] The lower limit of detection for EBV DNA level in this study is 500 IU/mL.

[d] ULN: upper limit of normal.

Source Data: ADSL.xpt

The Applicant's Position:

29.6% patients had non-keratinizing differentiated NPC, 67.2% were non-keratinizing undifferentiated NPC, and 3.2% had non-keratinizing NPC with unknown differentiation. 63.2% patients had received 2 prior lines of chemotherapy and 36.8% patients had received 3 or more prior lines of chemotherapy including prior platinum-based chemotherapy. 48.0% patients had liver metastasis.

The FDA's Assessment:

FDA agrees with the Applicant's description of baseline disease characteristics based on the 125 patients included in the primary efficacy population. Baseline disease characteristics for the 128 patients in the investigator-assessed population were not independently verified by the FDA.

Efficacy Results – Primary Endpoint

Data:

Among the 125 patients included in the primary efficacy population for IRRC assessment, 35 patients had a BOR of CR or PR based on IRRC assessment, with a confirmed ORR of 28.0% (95% CI: 20.3%, 36.7%). [Applicant – Table 6](#) provides further details of the responses for the primary efficacy population.

Applicant – Table 6 Summary of best overall response per RECIST 1.1-- Primary Efficacy Population

Response Evaluation	IRRC assessment (N = 125)			Investigator assessment (N=128)		
	n	(%)	95%CI [b]	n	(%)	95%CI [b]
Objective Response (CR+PR) [a]	35	28.0	[20.3, 36.7]	33	25.8	[18.5, 34.3]
Complete Response (CR)	1	0.8	[0.0, 4.4]	0	0.0	[0.0, 2.8]
Partial Response (PR)	34	27.2	[19.6, 35.9]	33	25.8	[18.5, 34.3]
Disease Control (CR+PR+SD)	62	49.6	[40.5, 58.7]	69	53.9	[44.9, 62.8]
Stable Disease (SD)	27	21.6	[14.7, 29.8]	36	28.1	[20.5, 36.8]
Disease Progression (PD)	51	40.8	[32.1, 49.9]	47	36.7	[28.4, 45.7]
No Assessment (NA)	12 [c]	9.6	[5.1, 16.2]	12	9.4	[4.9, 15.8]

% = The total number of patients in the relevant analysis set as the denominator.

[a] ORR is defined as the proportion of patients whose best overall response (BOR) is confirmed complete response (CR) or partial response (PR) based on RECIST 1.1.

[b] Based on binomial exact confidence interval method.

Disclaimer: In this document, the sections labeled as “Data” and “The Applicant's Position” are completed by the Applicant and do not necessarily reflect the positions of the FDA.

Assessment Aid Addendum for Study AK105-202 - BLA 761258 Penpulimab

[c] 12 patients had no data on postbaseline tumor assessment

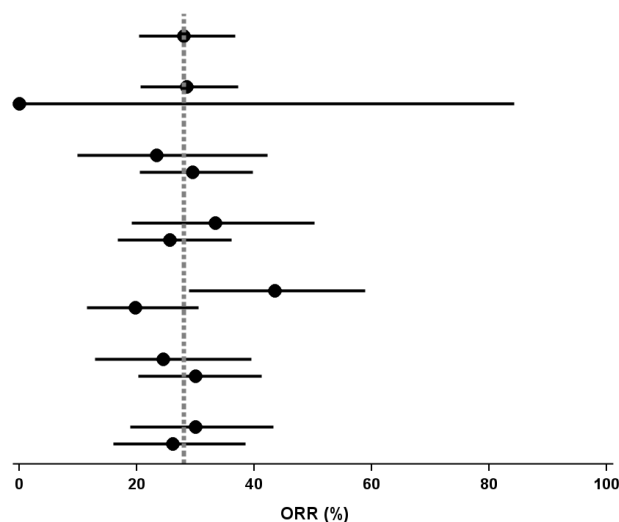
Source Data: ADRS.xpt [module 5.3.5.2 Appendix. AK105-202-final-orr-tfls Table 1.4.2.1.1, Table 14.2.1.2.](#)

Subgroup analyses based on IRRC assessment showed that tumor response was observed across all subgroups (with exception for age > 65 years [n=2]). While numerical differences in point estimates across some subgroups were noted, sample sizes were small and 95% CIs overlapped for most subgroup comparisons. In the subgroups, the patients with positive PD-L1 expression (defined as TPS $\geq$ 50% using Shuwen SAB-028), baseline LDH < ULN or EBV-DNA level in peripheral blood < 500 IU/mL at baseline seems to have a higher response rate. It was also noticed that the ORRs in key subgroups were comparable, such as [REDACTED], prior line of therapy, patients with liver metastasis, disease status (primary or recurrent metastasis).

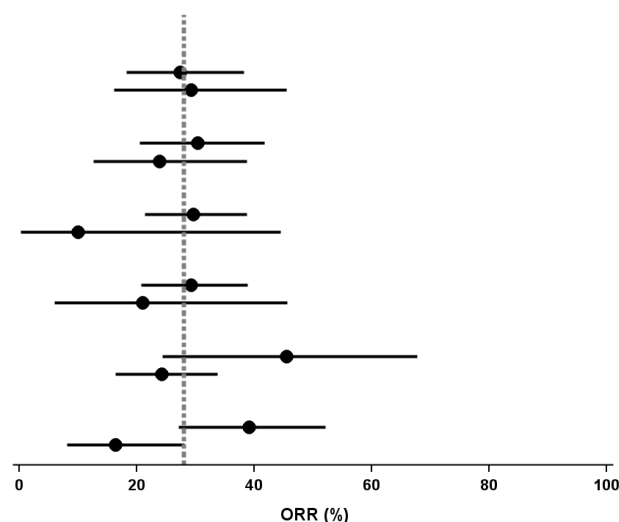
Penpulimab

Applicant – Figure 1 Forest Plot of Objective Response Rate (ORR) Based on RECIST 1.1 per IIRC by Subgroup Factors -- Primary Efficacy Population

Subgroup	N	ORR(%)	95% CI
Overall	125	28.0	(20.3,36.7)
Age			
≤65	123	28.5	(20.7,37.3)
>65	2	0.0	(0.0,84.2)
Gender			
Female	30	23.3	(9.9,42.3)
Male	95	29.5	(20.6,39.7)
ECOG			
0	39	33.3	(19.1,50.2)
1	86	25.6	(16.8,36.1)
PD-L1			
Positive (TPS ≥50%)	46	43.5	(28.9,58.9)
Negative (TPS <50%)	76	19.7	(11.5,30.5)
Cancer Stage at Study Entry			
Primary Metastasis	45	24.4	(12.9,39.5)
Recurrent Metastasis	80	30.0	(20.3,41.3)
Liver metastasis			
Yes	60	30.0	(18.8,43.2)
No	65	26.2	(16.0,38.5)



Subgroup	N	ORR(%)	95% CI
Number of location of metastasis			
<3	84	27.4	(18.2,38.2)
≥3	41	29.3	(16.1,45.5)
Number of location of metastasis			
2	79	30.4	(20.5,41.8)
≥3	46	23.9	(12.6,38.8)
Prior radiotherapy			
Yes	115	29.6	(21.4,38.8)
No	10	10.0	(0.3,44.5)
Prior radiotherapy of primary lesion			
Yes	106	29.2	(20.8,38.9)
No	19	21.1	(6.1,45.6)
EBV Level in Peripheral Blood			
<500	22	45.5	(24.4,67.8)
≥500	103	24.3	(16.4,33.7)
LDH			
LDH<ULN	64	39.1	(27.1,52.1)
LDH≥ULN	61	16.4	(8.2,28.1)



Note: Dashed vertical line-all subjects' ORR(28.0%);Black point-Subgroup subjects' ORR; Black horizontal line- 95% CI of subgroup subjects' ORR.

Source Data: ADRS.xpt

The Applicant's Position:

Results based on an interim analysis of ORR demonstrate substantial evidence of effectiveness of penpulimab monotherapy in patients with metastatic nonkeratinizing NPC with disease progression on or after at least two prior lines of therapy, a serious condition where there is a

Disclaimer: In this document, the sections labeled as "Data" and "The Applicant's Position" are completed by the Applicant and do not necessarily reflect the positions of the FDA.

clear unmet medical need. The primary analysis showed promising ORR by IRRC in the Primary Efficacy Population. The confirmed ORR of 28.0% (95% CI: 20.3%, 36.7%) compares favorably against a historical overall response rate of < 10% reported with chemotherapy agents.

The FDA's Assessment:

In general, FDA agrees with the Applicant's description of the primary efficacy analysis of the 125 patients included in the primary efficacy population for ORR per IRRC. Note that DCR is considered to be an exploratory endpoint and hence, the corresponding analysis was not verified by the FDA. There is a substantial numerical difference in ORR between the TPS $\geq$ 50% (43%, (95% CI: 29, 59)) and the TPS < 50% (20%, (95% CI: 11, 30)) subgroups. Given the exploratory nature of the subgroup analyses, the corresponding results should be interpreted with caution.

Additionally, in "Applicant – Figure 1 Forest Plot of Objective Response Rate (ORR) Based on RECIST 1.1 per IRRC by Subgroup Factors -- Primary Efficacy Population" the Applicant has mislabeled the subgroup analysis by prior lines of therapy, and instead had provided analysis by "Number of location of metastasis" twice. Among the 79 patients who received two prior lines of systemic therapy, ORR per IRRC was 30% (95% CI: 21, 42), whereas among the 46 patients who received at least three prior lines of therapy the ORR per IRRC was 24% (95% CI: 13, 39).

Data Quality and Integrity

Data:

None.

The Applicant's Position:

The submission contained all the required components of the electronic Common Technical Document (eCTD) and was of adequate quality to allow for review of the clinical trial data supporting the proposed indication.

The quality assurance procedures were implemented during the conduct of the study including but not limited to regular site monitoring, conducting investigator meetings and training sessions for clinical research associates, and site initiation visits to review the clinical protocol, CRF, and study procedures. Additionally, independent Quality Assurance audits were conducted for selected sites, and no concerns on data integrity were reported following site inspections by the independent Quality Assurance audits.

The FDA's Assessment: No major data quality or integrity issues were identified during the review of this application.

Efficacy Results – Secondary and other relevant endpoints

Data:

DoR and TTR

The median TTR in the primary efficacy population was 1.84 months (range: 1.6 to 7.4 months). As of the data cutoff date, the longest durable response was 24.9+ months (ongoing), 57.1% of responders remained ongoing, and the median DoR has not reached. The DoR $\geq$ 6 months was 72.7% (24/33) at the data cutoff. The Kaplan-Meier estimate for the percent of patients with a 6-month duration of response is 88.0% (95% CI: 71.2%, 95.3%), and the estimate for the percent of patients with a 9-month duration of response is 69.8% (95% CI: 51.2%, 82.5%).

A summary of DoR and TTR in the primary efficacy population is presented below in [Applicant – Table 7](#).

Applicant – Table 7 DoR and TTR assessment per RECIST v1.1 – Primary Efficacy Population

	IRRC assessment (N = 125)	Investigator assessment (N=128)
Number of Patients with Response (CR + PR) ^[a]	35	33
Time to Response (months) ^{[a] [b]}		
Median (Min - Max)	1.84 (1.6 - 7.4)	1.84 (1.7 - 12.9)
Duration of Response (DoR)(months) ^{[c] [d]}		
Median (Min - Max)	NR (3.8 - 24.9+)	NR (2.7+ - 25.0+)
95% CI	[9.2, -]	[9.3, -]
Number (%) of Patients with Ongoing Response	20 (57.1)	20 (60.6)
3 months DOR Rate (%) [95% CI]	100.0 [100.0, 100.0]	100.0 [100.0, 100.0]
6 months DOR Rate (%) [95% CI]	88.0 [71.2, 95.3]	87.5 [70.0, 95.1]
9 months DOR Rate (%) [95% CI]	69.8 [51.2, 82.5]	75.0 [56.2, 86.6]
12 months DOR Rate (%) [95% CI]	57.7 [39.2, 72.4]	68.8 [49.7, 81.8]
18 months DOR Rate (%) [95% CI]	51.9 [32.3, 68.4]	54.1 [33.0, 71.2]

Abbreviations: CR = complete response; PR = partial response; NR = Not Reached.

% = Percentage of patients with disease response (CR+PR) in the relevant analysis set.

[a] Patients with tumor assessment responses of complete response (CR) and partial response (PR) were included.

[b] Time to Response (TTR) is defined as the time from the first dose of study medication to the first recorded response (CR or PR). It will be calculated only for patients who achieve best overall response of CR or PR.

[c] Duration of response is defined as the time from the patient's first complete or partial response (CR or PR) to the first observation of disease progression or death due to any cause, whichever occurs first.

[d] The Kaplan-Meier method was used.

"+" indicates no progressive disease or death by the time of the last imaging assessment.

Source Data: ADTTE.xpt, ADRS.xpt

PFS

The median PFS based on IRRC assessment in the primary efficacy population was 3.65 months. The 6-month PFS rate was 41.3% (95% CI: 32.2%, 50.2%) and the 12-month PFS rate was 24.2% (95% CI: 16.7%, 32.6%).

A summary of PFS in the primary efficacy population is shown in [Applicant – Table 8](#).

Applicant – Table 8 PFS assessed per RECIST v1.1 – Primary Efficacy Population

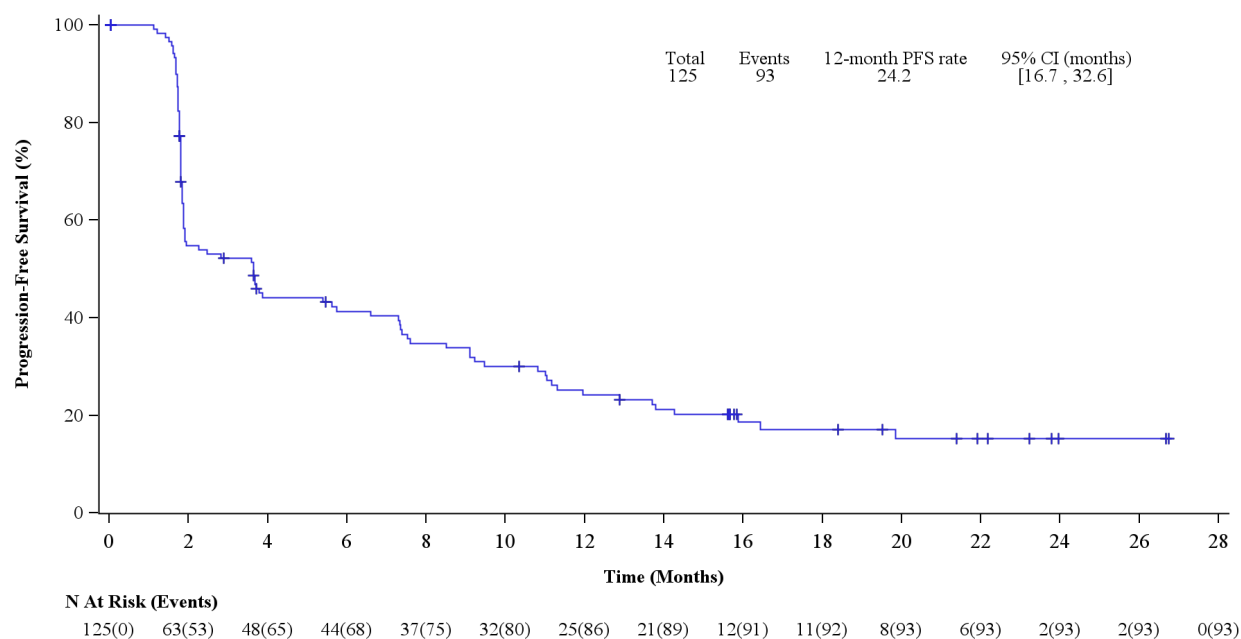
	IRRC assessment (N = 125)	Investigator assessment (N=128)
Number of PFS events, n (%)	93 (74.4)	98 (76.6)
Median PFS (months) ^{[a][b]}	3.65	3.68
95% CI	[1.9, 6.6]	[1.9, 7.2]
PFS rate ^{[a][b]}		
6 months PFS Rate (%) [95% CI]	41.3 [32.2, 50.2]	41.7 [32.8, 50.4]
9 months PFS Rate (%) [95% CI]	33.8 [25.2, 42.6]	34.9 [26.5, 43.5]
12 months PFS Rate (%) [95% CI]	24.2 [16.7, 32.6]	24.7 [17.4, 32.7]

Abbreviations: PFS = progression-free survival; IRRC = Independent Radiology Review Committee.

[a] Progression-free survival (PFS) is defined as the time from the start of the treatment to the date of disease progression (based on RECIST v1.1) or death due to any cause, whichever occurs first.

[b] From product-limit (Kaplan-Meier) method.Source: ADTTE.xpt

Applicant – Figure 2 Kaplan-Meier Plot of Progression-Free Survival (PFS) Based on RECIST 1.1 per IRRC – Primary Analysis Population



Source Data: ADTTE.xpt

Overall survival (OS)

The median OS in the safety analysis set was 22.74 months (95% CI: 17.1, NE). The 6-month OS rate was 80.6% (95% CI: 72.4%, 86.6%), and the 12-month OS rate was 66.4% (95% CI: 57.2%, 74.0%).

A summary of OS in the safety analysis set population is shown in [Applicant – Table 9](#).

Applicant – Table 9 Overall Survival (OS) – Safety Analysis Set

	Total (N = 130)
Number of death events, n (%)	58 (44.6)
Median OS (months) [a][b]	22.74
95% CI	[17.1, -]
OS Rate, n (%) [a][b]	
6 months OS Rate (%) [95% CI]	80.6 [72.4, 86.6]
12 months OS Rate (%) [95% CI]	66.4 [57.2, 74.0]
24 months OS Rate (%) [95% CI]	44.8 [33.2, 55.6]

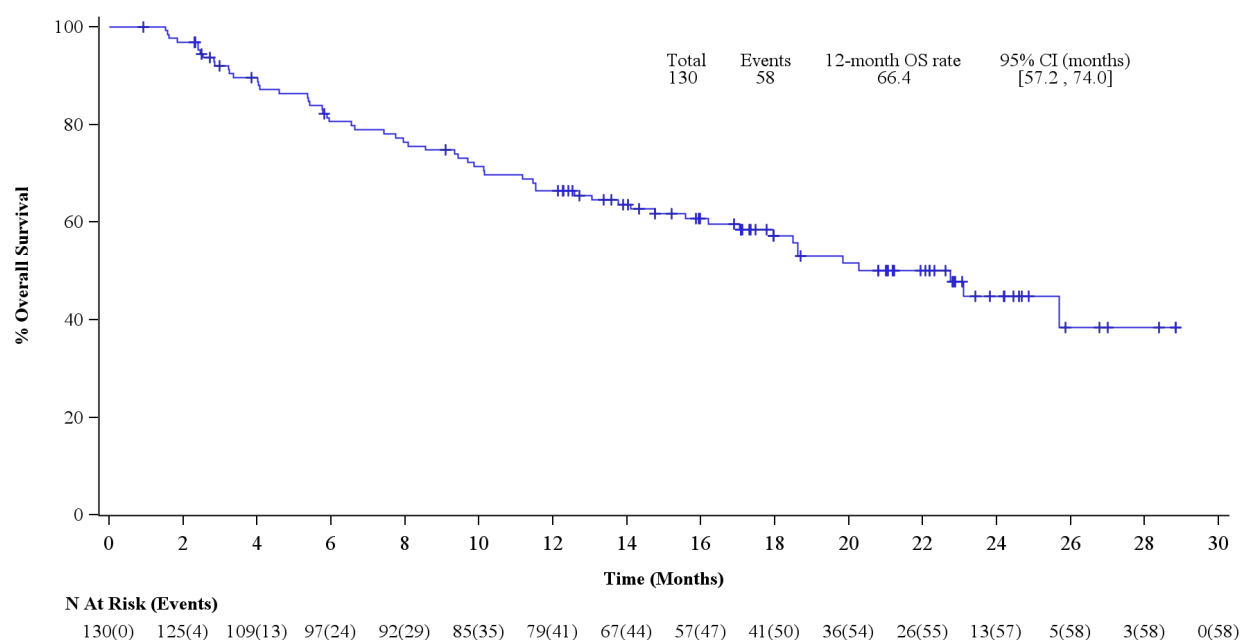
Abbreviation: OS = Overall Survival

[a] Overall survival (OS) is defined as the time from the first dose of study medication until death due to any causes.

[b] From product-limit (Kaplan-Meier) method.

Source Data: ADTTE.xpt

Applicant – Figure 3 Kaplan-Meier Plot of Overall Survival (OS) - Safety Analysis Set



Source Data: ADTTE.xpt

The Applicant's Position:

Results based on the final analysis of additional secondary efficacy variables including DoR, PFS and OS demonstrate substantial evidence of effectiveness of penpulimab monotherapy in patients with metastatic nonkeratinizing NPC with disease progression on or after at least two prior lines of therapy, a serious disease where there is a clear unmet medical need.

The responses were durable. After a median follow-up time of 22.1 months, median DoR has not yet been reached at the time of DCO, and 20 (57.1%) of 35 responders had an ongoing response. The OS results were encouraging in this heavily pretreated NPC population. The median OS was 22.74 months and the 12-month OS rate was 66.4% (95% CI: 57.2%, 74.0%). The percentage of DoR $\geq$ 6 months, median OS, and the 12-month OS rate compare favorably against those seen with chemotherapy agents.

The FDA's Assessment:

FDA's analysis of DOR assessed by IRRC is provided in the table below. The median DOR was not reached. The proportion of patients with observed DOR of at least 6 months was 83%. In addition to the landmark DOR rates provided by the Applicant, that were estimated using the Kaplan-Meier method, FDA calculated the landmark DOR rates based on observed response duration.

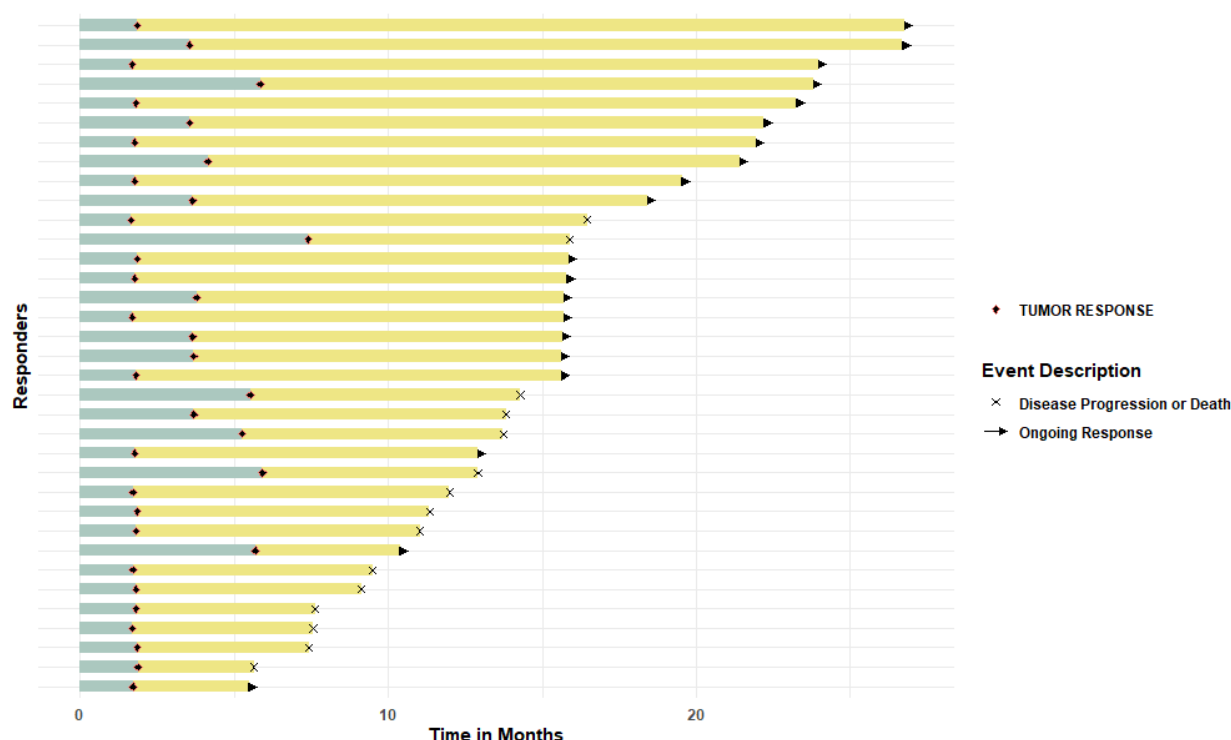
FDA Table 1: Analysis of DOR assessed by IRRC per RECIST 1.1

	Primary Efficacy Population N = 125
Number of responders	35
Median DOR in months (95% CI)	NR (9.2, NE)
Range in months	(3.8, 24.9+)
Observed DOR $\geq$ 6 months, n (%)	29 (83)
Observed DOR $\geq$ 12 months, n (%)	16 (46)

NR = not reached, NE = not evaluable, + indicates an ongoing response; DCO: September 23, 2021
Source: FDA analysis based on Applicant-provided analysis datasets adrs.xpt and adtte.xpt.

The following figure provides the swimmer plot of responders per IRRC in Study AK105-202. Out of the 35 responders, 20 (57%) had an ongoing response as of the data cut-off date of September 23, 2021, while the other 15 (43%) experienced an event (disease progression or death).

FDA Figure 1: Swimmer plot of responders per IRRC



Source: FDA analysis based on Applicant-provided analysis datasets adrs.xpt and adtte.xpt. DCO: September 23, 2021

Note that, in a single arm study such as AK105-202, time-to-event endpoints such as PFS and OS are considered descriptive only due to the absence of a comparator arm. Hence, FDA considers PFS and OS as descriptive endpoints for Study AK105-202. Additionally, the Applicant provided analysis of OS in “Applicant – Table 9” is based on 130 enrolled patients, which is not the efficacy population under consideration.

Dose/Dose Response

Data:

N/A.

The Applicant’s Position:

All patients with NPC in the primary efficacy population received penpulimab 200 mg every two weeks. Therefore, dose response relationships for efficacy could not be evaluated. Univariate logistic regression analyses showed a flat relationship between penpulimab PK exposures and model-predicted ORR (CR/PR).

The FDA’s Assessment:

The FDA agrees that a dose-response relationship is not evaluable given that all patients

received the Q2W dosing regimen of penpulimab.

Durability of Response

Data and Applicant's Position:

A summary of DoR in the primary efficacy population is presented earlier (see [Applicant – Table 7](#)). Given refractory population with metastatic NPC with disease progression on or after at least two prior lines of therapy, the responses were durable, which compare favorably with those seen with historical commonly used chemotherapy agents.

The FDA's Assessment:

Please refer to the section titled “Efficacy Results – Secondary and other relevant endpoints” for FDA's assessment of durability of response.

Persistence of Effect

The Applicant's Position:

The observed effect of ORR in the primary efficacy population is consistent across pre-specified subgroups as illustrated in [Applicant – Table 7](#). Notably, patients with positive PD-L1 status exhibited substantially higher response rates compared to the overall average. Secondly, as highlighted in the previous section, the responses are durable, with more than half of responders (20 out of 35) maintaining an ongoing response at a median follow-up of 22.1 months. (b) (4)

In summary, patients experienced sustained clinical benefits with penpulimab monotherapy, demonstrating persistent efficacy across key measures.

The FDA's Assessment:

The FDA agrees that there may potentially be persistence of effect based on the DOR data and that higher response rates was observed in the PDL1 $\geq 50\%$ population. However, as above, the (b) (4) secondary endpoints of PFS and OS as this is a single arm study and these results are considered descriptive only.

Efficacy Results – Secondary or exploratory COA (PRO) endpoints

Data:

N/A.

The Applicant's Position:

N/A.

The FDA's Assessment:

Not applicable.

Additional Analyses Conducted on the Individual Trial

Data:

IRRC assessments and investigator assessments were comparable in terms of the efficacy endpoints ORR, DoR, DCR, and PFS ([Applicant – Table 10](#)). The concordance between the IRRC- and investigator-assessed ORR in the primary efficacy population ([Applicant – Table 11](#)) was high (94.4%).

Applicant – Table 10 Comparison between IRRC and investigator assessments of efficacy endpoints per RECIST v1.1 - Primary Efficacy Population

	ORR (%) (95% CI)	Median DoR (months) (95% CI) ^[a]	6 months DOR Rate (%) (95% CI) ^[b]	DCR (%) (95% CI)	Median PFS (months) (95% CI) ^[a]
Per IRRC	28.0% (20.3,36.7)	NR (9.2, -)	88.0 (71.2, 95.3)	49.6 (40.5,58.7)	3.65 (1.9, 6.6)
Per investigator	25.8% (18.5,34.3)	NR (9.3, -)	87.5 (70.0, 95.1)	53.9 (44.9,62.8)	3.68 (1.9, 7.2)

[a] From product-limit (Kaplan-Meier) method.

[b] Frequency was calculated based on descriptive statistics.

Source Data: ADTTE.xpt

Applicant – Table 11 Concordance between IRRC and Investigator Assessments

IRRC (N=125)	Investigator (N=125)	
	Responder	Non-responder
Responder ^[a]	30	5
Non-responder ^[a]	2	88

[a] Responder: confirmed CR or PR; Non-responder: SD, PD, or NA.

Source Data: ADRS.xpt [AK105-202-final-orr-tfls Table 1.4.2.1.2](#).

The Applicant's Position:

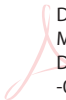
IRRC assessments and investigator assessments were comparable in terms of the efficacy endpoints ORR, DoR, DCR, and PFS per RECIST v1.1.

The FDA's Assessment:

FDA agrees that the results per IRRC assessment and investigator assessments were generally consistent for ORR and DOR. FDA considered comparison based on estimated DOR rate at 6 months, or analyses based on DCR and PFS, as provided by the Applicant in this section, to be exploratory only and did not independently verify these results.

Additionally, FDA agrees with the Applicant's description of concordance and discordance between IRRC and investigator assessed responses. No major discordance is observed between IRRC and investigator assessment.

Signatures

DISCIPLINE	REVIEWER	OFFICE/DIVISION	SECTIONS AUTHORED/ APPROVED	AUTHORED/ APPROVED
Nonclinical Reviewer	Kelie Reece, PhD	CDER/OND/OOD/DHOT	Sections: 5, 19.1, 19.3	Select one: ☒ Authored ☒ Approved
	Signature: Kelie M. Reece -S  Digitally signed by Kelie M. Reece Date: 2025.04.22 12:32:09 -04'00'			
Nonclinical Team Leader	Claudia Miller, PhD	CDER/OND/OOD/DHOT	Sections: 5, 19.1, 19.3	Select one: ☒ Authored ☒ Approved
	Signature: CLAUDIA MILLER -S  Digitally signed by CLAUDIA MILLER -S Date: 2025.04.22 12:12:30 -04'00'			
Clinical Pharmacology Reviewer	Francis Green, PhD	CDER/OTS/OCP/DCPII	Sections: 6, 19.4	Select one: ☒ Authored ☐ Approved
	Signature: JEANNE FOURIE ZIRKELBACH -S  Digitally signed by JEANNE FOURIE ZIRKELBACH -S Date: 2025.04.23 07:14:50 -04'00'			
Clinical Pharmacology Secondary Reviewer	Jeanne Fourie Zirkelbach, PhD	CDER/OTS/OCP/DCPII	Sections: 6, 19.4	Select one: ☒ Authored ☒ Approved
	Signature: JEANNE FOURIE ZIRKELBACH -S  Digitally signed by JEANNE FOURIE ZIRKELBACH -S Date: 2025.04.23 07:15:23 -04'00'			
Nonclinical Division Director	Haleh Saber, PhD	CDER/OND/OOD/DHOT	Sections: 5, 19.1, 19.3	Select one: ☐ Authored ☒ Approved
	Signature: Haleh Saber -S  Digitally signed by Haleh Saber -S Date: 2025.04.22 17:53:35 -04'00'			

DISCIPLINE	REVIEWER	OFFICE/DIVISION	SECTIONS AUTHORED/ APPROVED	AUTHORED/ APPROVED
Clinical Pharmacology / Pharmacometrics Reviewer	Ye Xiong, PhD	CDER/OTS/OCP/DPM	Sections: 19.4	Select one: ☒ Authored ☐ Approved
	Signature: Ye Xiong -S Digitally signed by Ye Xiong -S Date: 2025.04.22 12:59:15 -04'00'			
Clinical Pharmacology / Pharmacometrics Team Leader	Youwei Bi, PhD	CDER/OTS/OCP/DPM	Sections: 19.4	Select one: ☒ Authored ☒ Approved
	Signature: HAO ZHU -S Digitally signed by HAO ZHU -S Date: 2025.04.23 10:22:45 -04'00'			
Clinical Reviewer	Kevin Breen, MD	CDER/OND/OOD/DOII	Sections: 8	Select one: ☒ Authored ☐ Approved
	Signature: KEVIN T. BREEN -S Digitally signed by KEVIN T. BREEN Date: 2025.04.22 15:39:46 -04'00'			

DISCIPLINE	REVIEWER	OFFICE/DIVISION	SECTIONS AUTHORED/ APPROVED	AUTHORED/ APPROVED
Clinical Pharmacology Deputy Division Director	Stacy Shord, PharmD	CDER/OTS/OCP/DCPII	Sections: 6, 19.4	Select one: ☒ Approved
	Signature: Stacy Shord -S Digitally signed by Stacy Shord - Date: 2025.04.23 10:13:14 -04'00'			
Clinical Team Leader	Timil Patel, MD	CDER/OND/OOD/DOII	Sections: All	Select one: ☒ Authored ☒ Approved
	Signature: See signature in DARRTS. Timil H. Patel -S Digitally signed by Timil H. Patel -S Date: 2025.04.22 17:20:00 -04'00'			
Statistical Reviewer	Somak Chatterjee, PhD	CDER/OTS/OB/DBV	Sections: 1, 8	Select one: ☒ Authored ☐ Approved
	Signature: Somak Chatterjee -S Digitally signed by Somak Chatterjee -S Date: 2025.04.22 18:36:43 -04'00'			
Statistical Team Leader	Xiaoxue Li, PhD	CDER/OTS/OB/DBV	Sections: 1, 8	Select one: ☒ Authored ☒ Approved
	Signature: Xiaoxue Li -S Digitally signed by Xiaoxue Li -S Date: 2025.04.22 14:05:05 -04'00'			
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NDA/BLA Multi-Disciplinary Review and Evaluation

Disclaimer: In this document, the sections labeled as “Data” and “The Applicant’s Position” are completed by the Applicant, which do not necessarily reflect the positions of the FDA.

Application Type	BLA
Application Number(s)	761258
Priority or Standard	Standard
Submit Date(s)	July 16, 2021
Received Date(s)	July 16, 2021
PDUFA Goal Date	October 16, 2022
Division/Office	Division of Oncology 2
Review Completion Date	
Established Name	Penpulimab-kcqx
(Proposed) Trade Name	
Pharmacologic Class	Programmed death receptor-1 (PD-1) blocking antibody
Code name	
Applicant	Akeso Biopharma Co., Ltd.
Formulation(s)	10 mg/mL, 10 mL
Dosing Regimen	Injection for IV infusion
Applicant Proposed Indication(s)/Population(s)	Nasopharyngeal carcinoma
Recommendation on Regulatory Action	Complete Response
Recommended Indication(s)/Population(s) (if applicable)	For the treatment of adult [REDACTED] (b) (4) [REDACTED] with metastatic non-keratinizing nasopharyngeal carcinoma with disease progression on or after platinum-based chemotherapy and at least one other prior line of therapy.

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Abbreviations: ADL, Associate Director for Labeling; DHOT, Division of Hematology, Oncology, and Toxicology; OB, Office of Biostatistics; OCP, Office of Clinical Pharmacology; OOD, Office of Oncologic Diseases .

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NDA/BLA Multi-disciplinary Review and Evaluation- BLA 761258

Penpulimab

Abbreviations: DEPI, Division of Epidemiology; DMEPA, Division of Medication Error Prevention and Analysis; DRISK, Division of Risk Management; OPQ, Office of Pharmaceutical Quality; OPDP, Office of Prescription Drug Promotion; OSE, Office of Surveillance and Epidemiology; OSI, Office of Scientific Investigations.

Glossary

AC	advisory committee
ADA	anti-drug antibody
ADCC	antibody-dependent cell-mediated cytotoxicity
ADCP	antibody dependent cellular phagocytosis
ADCR	antibody dependent cytokine release
ADME	absorption, distribution, metabolism, excretion
AE	adverse event
ALT	alanine aminotransferase
ALP	alkaline phosphatase
ALB	serum albumin
AST	aspartate aminotransferase
BLA	biologics license application
BTB	Breakthrough Therapy Designation
CDC	complement dependent cytotoxicity
CDER	Center for Drug Evaluation and Research
CFR	Code of Federal Regulations
CMC	chemistry, manufacturing, and controls
CNS	central nervous system
COSTART	Coding Symbols for Thesaurus of Adverse Reaction Terms
CRF	case report form
CSR	clinical study report
CTLA-4	Cytotoxic T-lymphocyte associated protein 4
CL	Clearance
CLCr	creatinine clearance
CYP	cytochrome P450
DCR	disease control rate
DoR	duration of response
ECG	electrocardiogram
ECOG	Eastern Cooperative Oncology Group
FDA	Food and Drug Administration
GCP	good clinical practice
GLP	good laboratory practice
ICH	International Conference on Harmonization
IL	Interleukin
IND	Investigational New Drug
irAEs	immune-related adverse events
ISS	integrated summary of safety

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IV	intravenous infusion
LDH	lactic dehydrogenase
MedDRA	Medical Dictionary for Regulatory Activities
NCI-CTCAE	National Cancer Institute-Common Terminology Criteria for Adverse Event
NDA	new drug application
NME	new molecular entity
NOAEL	no observed adverse effect level
NPC	nasopharyngeal carcinoma
OPQ	Office of Pharmaceutical Quality
ORR	overall response rate
OSI	Office of Scientific Investigation
PBMC	peripheral blood mononuclear cell
PFS	progression-free survival
PD	pharmacodynamics
PD-1	programmed death receptor-1
PD-L1	programmed death ligand-1
PI	prescribing information
PK	pharmacokinetics
PPI	patient package insert
PPQ	Process performance qualification
PREA	Pediatric Research Equity Act
PRO	patient reported outcome
Q2W	every 2 weeks
REMS	risk evaluation and mitigation strategy
RTOR	Real-time Oncology Review
SAE	serious adverse event
SAP	statistical analysis plan
SOC	standard of care
TBIL	total bilirubin
TCR	tissue cross-reactivity
TEAE	treatment emergent adverse event
TK	toxicokinetics
TNF	tumor necrosis factor
TTR	time to response

1. Executive Summary

1.1. Product Introduction

Penpulimab is a human IgG1 monoclonal antibody targeting PD-1, thereby blocking the immunosuppressive interaction between PD-1 and PD-L1 and PD-L2. It is not approved for any indication in the U.S.

The recommended dosage regimen for the proposed indication is penpulimab 200 mg intravenously (IV) every two weeks until disease recurrence or unacceptable toxicity.

1.2. Conclusions on the Substantial Evidence of Effectiveness

Data from Study AK105-202, a single arm, open label study of penpulimab in patients with metastatic non-keratinizing NPC who had received prior therapy, conducted entirely in China, was provided as the primary evidence in support of the proposed indication. A total of 130 patients with metastatic non-keratinizing NPC, who had progressed on platinum-based chemotherapy and at least one other line of therapy, were enrolled and received penpulimab 200 mg every 2 weeks (Q2W). The primary efficacy outcome measure was overall response rate (ORR) by Independent Radiologic Review Committee (IRRC) per RECIST v1.1. The key secondary endpoint was duration of response (DOR).

Amongst the 111 patients in the primary efficacy population, the ORR was 30% (95% CI 21, 39) (data cutoff date of February 3, 2021). The median DOR was not reached (range 3.8, 17.1+); a total of 39% of the 33 responding patients had a DOR $\geq$ 9 months.

During FDA's review of this BLA, FDA toripalimab-tpzi, an anti-PD-1 antibody, in combination with cisplatin and gemcitabine was granted traditional approval for the first-line treatment of adult patients with metastatic or recurrent, locally advanced NPC based on a randomized trial which demonstrated a 3.7-month improvement in progression-free survival (PFS) with the addition of toripalimab-tpzi to cisplatin and gemcitabine. This approval changed the standard of care for patients with metastatic or recurrent, locally advanced NPC with the inclusion of anti-PD-1-based therapy in the first-line treatment setting. At the time of this approval, toripalimab-tpzi was also approved as a single agent for patients with unresectable or metastatic NPC with disease progression on or after a platinum-containing chemotherapy based on ORR and DOR results from a single arm study of patients with metastatic NPC (ORR 21% (95% CI 15, 28); median DOR 14.9 months (95% CI 10.3, not estimable).

Given the approvals of toripalimab-tpzi for patients with NPC, the efficacy of penpulimab, based on the results of Study AK105-202, does not demonstrate a clear advantage over currently available therapeutic options for patients with metastatic, non-keratinizing NPC.

According to the U.S. Code of Federal Regulations (CFR), Section 21.314.500, new drug products that have been studied for their safety and effectiveness in treating serious or life-threatening

illnesses and that provide meaningful therapeutic benefit to patients over existing treatments (e.g., ability to treat patients unresponsive to, or intolerant of, available therapy, or improved patient response over available therapy), may be considered for accelerated approval. This regulation is generally considered applicable to original biologic products in addition to new drug products.

In addition, following the pre-license inspection (PLI) of Akeso Biopharma, Co., Ltd., Guangdong, China (FEI 3017057933), deficiencies in CGMP operations were identified in penpulimab drug substance and drug product manufacturing facility listed in this application. FDA has reviewed the responses from the facility and concluded that not all deficiencies have been satisfactorily resolved.

Further, during the review of this application, the Office of Pharmaceutical Quality (OPQ) identified various deficiencies related to the cell bank system used to manufacture penpulimab, process control strategy, validation of analytical procedures and drug product filling operation. After reviewing the Applicant's responses, OPQ concluded that the data submitted in this application are not sufficient to support a conclusion that the manufacture of penpulimab-kcqx is well-controlled and will lead to a product that is pure and potent.

The FDA recommendation is Complete Response.

1.3. Benefit-Risk Assessment (BRA)

Benefit-Risk Summary and Assessment

NPC is a rare, life-threatening disease with distinct geographical distribution and histologies. In 2018, approximately 129,000 new cases of NPC were diagnosed globally (0.7% of all cancers diagnosed in 2018) (Chen Lancet 2019). There are three pathological subtypes of NPC: keratinizing squamous cell carcinoma (type 1), non-keratinizing differentiated carcinoma (type 2), and non-keratinizing undifferentiated carcinoma (type 3). Types 2 and 3 are typically associated with Epstein Barr virus (EBV), and account for 97% of NPC cases diagnosed in China. In North America, Type 1 and Type 3 NPC account for 25% and 63% of cases respectively.

The prognosis for patients with recurrent, unresectable, or metastatic NPC is poor. On October 27, 2023, FDA approved toripalimab-tpzi with cisplatin and gemcitabine for the first-line treatment of adults with metastatic or recurrent, locally advanced NPC. In the randomized, double-blind JUPITER-02 trial, toripalimab-tpzi with cisplatin and gemcitabine demonstrated a median progression-free survival (PFS) of 11.7 months and a median overall survival (OS) not yet reached. Patients who received placebo with cisplatin and gemcitabine had a median PFS of 8.0 months and median OS of 33.7 months (LOQTORZI [toripalimab-tpzi] USPI). On October 27, 2023, FDA also approved toripalimab-tpzi as a single agent for adult patients with recurrent unresectable or metastatic NPC with disease progression on or after a platinum-containing therapy based on results of POLARIS-02, an open-label, multicohort trial, which demonstrated an overall response rate (ORR) as assessed by a Blinded Independent Review Committee (BIRC) of 21% and median duration of response (DOR) of 14.9 months.

Penpulimab is a monoclonal antibody targeting programmed death-1 (PD-1), an immune checkpoint inhibitor with an established pharmacological class of PD-1 blocking antibody. The proposed dosing regimen is 200 mg intravenously (IV) every two weeks (Q2W) until disease progression or unacceptable toxicity.

The primary efficacy data providing evidence in support of the proposed indication is derived from Study AK105-202, a single arm, multicenter, open label study conducted in China that enrolled 130 patients with metastatic NPC who had disease progression on or after platinum-based chemotherapy and at least one other prior line of therapy. All patients received penpulimab 200 mg IV Q2W until disease progression or unacceptable toxicity.

The primary efficacy population from Study AK105-202 is comprised of 111 patients with non-keratinizing undifferentiated NPC (64%); 32% of patients had non-keratinizing differentiated NPC, and 3.6% of patients had non-keratinizing NPC of unknown differentiation. In the primary efficacy population, the ORR by IRRC was 30% (95% CI 21, 39) (data cut off February 3, 2021). Median duration of response (DOR) was not reached (range 3.8, 17.1+); Among the 33 patients with an objective response, 39% had a DOR $\geq$ 9 months.

The evaluation of safety for penpulimab was primarily based upon safety data from 130 patients enrolled in Study AK105-202 supported by a pooled population of 372 patients with advanced solid tumors or classical Hodgkin lymphoma treated with penpulimab 200 mg Q2W. Among the 372 patients in the pooled safety population, the most common adverse reactions ($\geq$ 10%) were hepatitis (27%), hypothyroidism (24%), rash (20%), upper respiratory tract infection (18%), pyrexia (15%), fatigue (13%), musculoskeletal pain (11%), weight increased (11%), weight decreased (11%), colitis (11%), and cough (11%). Among the 130 patients with NPC treated with penpulimab in Study AK105-202, the most common adverse reactions ($\geq$ 10%) were hypothyroidism (32%), hepatitis (28%), musculoskeletal pain (22%), weight decreased (17%), pyrexia (15%), rash (12%), upper respiratory tract infection (12%), and cough (10%). Serious adverse reactions occurred in 19% of the patients in the primary safety population; the most common serious adverse reactions ($\geq$ 1%) were pneumonia, death, hepatitis, respiratory failure, pneumonitis, and rash.

Adverse reactions leading to permanent discontinuation of penpulimab occurred in five patients (3.8%) in the primary safety population including one event (0.8%) each of pleural effusion, herpes zoster disseminated infection, spinal cord compression, hepatitis, and pemphigoid. A total of four patients (3.1%) in the primary safety population had a fatal adverse reaction; these included one event of respiratory failure and three events of death due to unknown cause.

Immune-related adverse events (irAEs) occurred in 22% of patients, including Grade 3 to 4 irAEs in 2% of patients in the primary safety population. The most common irAE ($\geq$ 10%) was hypothyroidism (15%). There were no fatal irAEs observed in the pooled or primary safety population.

The overall safety profile of penpulimab was similar to that observed with other PD-1 blocking antibodies.

A major limitation of the data is that the primary trial supporting the marketing application was conducted exclusively in China. Therefore, the patient population is not reflective of the racial and ethnic diversity of U.S.

patients with NPC. Although a flexible regulatory approach may be warranted for treatment settings with high unmet need, penpulimab no longer addresses an unmet need for patients with NPC given the recent approvals of toripalimab-tpzi for patients with NPC. Based on the approvals of toripalimab-tpzi, the Study AK105-202 results do not demonstrate a clear advantage over currently available therapy. While the accelerated approval program allows for the demonstration of a meaningful advantage over currently available therapy outside of efficacy (e.g., through a more convenient route of administration or improved toxicity profile), the mechanisms of action, routes of administration, and toxicity profiles of penpulimab and toripalimab-tpzi are very similar and do not support an advantage for penpulimab over toripalimab-tpzi.

Additionally, the Office of Pharmaceutical Quality (OPQ), CDER, has completed an assessment of penpulimab-kcqx manufactured by Akeso Biopharma Co., Ltd. The data submitted in this application are not sufficient to support a conclusion that the manufacture of penpulimab-kcqx is well-controlled and will lead to a product that is pure and potent.

Given the efficacy results that do not demonstrate a clear advantage over currently available therapy and the substantial identified manufacturing deficiencies, FDA does not consider the current data supportive of a favorable risk-benefit assessment for penpulimab and recommends a Complete Response action.

Dimension	Evidence and Uncertainties	Conclusions and Reasons
Analysis of Condition	- Nasopharyngeal carcinoma (NPC) originates in the nasopharynx from the base of the skull to the palate. - There were 133,354 cases of NPC worldwide in 2020 with the majority of cases (>75%) in South and East Asia; 1.6% of cases occurred in Northern America. Approximately 80,000 people died from NPC in 2020.	The incidence of NPC is substantially higher in Southeast Asia relative to the U.S. A higher proportion of NPC patients in North America develop the keratinizing squamous subtype compared with China, where the vast majority of patients develop the non-keratinizing undifferentiated subtype. The prognosis of metastatic NPC remains poor.

Dimension	Evidence and Uncertainties	Conclusions and Reasons
	• NPC is rare in the United States, with <1 case per 100,000 people each year. Approximately 220 cases of NPC were diagnosed within the US in 2018 (Chen Lancet 2019). • The incidence of NPC in children and adolescents varies between different regions and races and accounts for approximately 2% of cases of NPC in the US. According to SEER registries, of 129 children and adolescents reported to have NPC from 1988-2006 in the US, the median age was 16 years (range, 7-19 years) (Sultan et al, 2010). • There are three major histologic subtypes of NPC based on WHO classification, with differences in subtype distribution between North America and China: Type 1 keratinizing squamous cell carcinoma (25% vs 2%), Type 2 non-keratinizing differentiated carcinoma (12 vs 3%), and Type 3 non-keratinizing undifferentiated carcinoma (63% vs 95%). • For metastatic NPC, the median overall survival is 21 to 29 months with platinum-based chemotherapy.	
Current Treatment Options	• Toripalimab-tpzi-tpzi in combination with cisplatin and gemcitabine is approved for the first-line treatment of NPC based on a median PFS of 11.7 months versus 8.0 months for placebo with cisplatin and gemcitabine in the JUPITER-02 trial. • Toripalimab-tpzi is also approved for NPC with disease progression on or after a platinum-containing chemotherapy based on an ORR of 21% and median DOR of 14.9 months in the POLARIS-02 trial. • Prior to the approval of toripalimab-tpzi, in the metastatic setting, standard of care treatment for first line therapy was cisplatin plus	Metastatic NPC represents a life-threatening disease. For patients with metastatic or recurrent NPC, FDA recently approved toripalimab-tpzi in combination with cisplatin and gemcitabine in the first line setting and toripalimab-tpzi as a single agent with disease progression on or after a platinum-containing therapy.

Dimension	Evidence and Uncertainties	Conclusions and Reasons
	gemcitabine, with a reported median PFS of 7.0 months and median OS of 29.1 months. Treatment of NPC in adolescents generally follows the same treatment paradigms used in adults.	
Benefit	- The primary trial supporting this BLA is Study AK105-202, a single-arm, single-cohort study conducted solely in China of patients with metastatic non-keratinizing NPC with disease progression on or after platinum-based chemotherapy and at least one other prior line of therapy. - The ORR per IRRC observed in the primary efficacy population (n=111) was 30% (95% CI: 21, 39). Median duration of response (DOR) was not reached (range 3.8, 17.1+); 39% of the 33 responding patients had a DOR $\geq$ 9 months.	Penpulimab demonstrated a durable response in patients treated in Study AK105-202. However, given the recent FDA approvals of toripalimab-tpzi, these results do not demonstrate a meaningful advantage over available therapies. Therefore, the proposed indication for penpulimab does not address an unmet need for patients with NPC. Additionally, a major limitation of the data is that the primary trial supporting this marketing application was conducted exclusively in China and all patients enrolled were Asian. Therefore, the patient population in the trial is not reflective of the racial and ethnic diversity of patients with NPC in the United States. Regulatory flexibility is not warranted as penpulimab does not address an unmet need.
Risk and Risk Management	The primary safety population for this marketing application included 130 patients enrolled in Study AK105-202 who were treated with penpulimab 200 mg every two weeks (Q2W).	The overall safety profile of penpulimab was similar to that observed with other PD-1 blocking antibodies.

Dimension	Evidence and Uncertainties	Conclusions and Reasons
	- Supportive safety data was provided from a pooled population of 372 patients with advanced solid tumors or classical Hodgkin lymphoma who were treated with penpulimab 200 mg Q2W. - Serious adverse reactions occurred in 19% of patients in Study AK105-202; the most common serious adverse reactions ($\geq 1\%$) were pneumonia (3.8%), death (3.1%), hepatitis (2.3%), respiratory failure (1.5%), pneumonitis (1.5%), and rash (1.5%). - There were 4 (3.1%) fatal adverse reactions in the primary safety population, including one event of respiratory failure and three events of death. - Permanent discontinuation of penpulimab due to an adverse reaction occurred in 3.8% of patients in Study AK105-202. Adverse reactions resulting in permanent discontinuation of penpulimab were pleural effusion, herpes zoster disseminated infection, spinal cord compression, hepatitis, and pemphigoid (0.8% each). - Immune-related adverse events (irAEs) occurred in 22% of patients (Grade 3 to 4, 2.3%) in Study AK105-202 and 20% of patients (Grade 3 to 4, 0.8%) in the pooled safety population. - In Study AK105-202, the most common irAEs ($\geq 10\%$) was hypothyroidism (15%).	Safety issues identified as significant and serious during the BLA review were irAEs and IRRs. Penpulimab appears to have an acceptable safety profile when assessed in the context of a life-threatening disease. A major amendment was issued on June 14, 2022, to allow the FDA review team additional time to evaluate the data submitted by Akeso to address OPQ deficiencies related to microbial control. While these microbial control deficiencies were resolved during review cycle, OPQ has determined that the data submitted in this application related to product quality and overall control strategy are not sufficient to support a conclusion that the manufacture of penpulimab-kcqx is well-controlled and will lead to a product that is pure and potent.

Dimension	Evidence and Uncertainties	Conclusions and Reasons
	• Infusion-related reactions (IRRs) occurred in 3.8% of patients in the pooled safety population. No IRRs were reported in the primary safety population. • During the review of this application, the Office of Pharmaceutical Quality (OPQ) identified validation deficiencies related to drug product sterility and endotoxin control, which may potentially impact product safety. Clinically, failure to demonstrate adequate sterility assurance and endotoxin control for penpulimab manufacturing could result in microbial and endotoxin contamination of the product.	

1.4. Patient Experience Data

Patient Experience Data Relevant to this Application (check all that apply)

☐	The patient experience data that was submitted as part of the application, include:		Section where discussed, if applicable
	☐	Clinical outcome assessment (COA) data, such as	[e.g., Section 6.1 Study endpoints]
		☐ Patient reported outcome (PRO)	
		☐ Observer reported outcome (ObsRO)	
		☐ Clinician reported outcome (ClinRO)	
		☐ Performance outcome (PerfO)	
	☐	Qualitative studies (e.g., individual patient/caregiver interviews, focus group interviews, expert interviews, Delphi Panel, etc.)	
	☐	Patient-focused drug development or other stakeholder meeting summary reports	[e.g., Section 2.1 Analysis of Condition]
	☐	Observational survey studies designed to capture patient experience data	
	☐	Natural history studies	
	☐	Patient preference studies (e.g., submitted studies or scientific publications)	
	☐	Other: (Please specify)	
☐	Patient experience data that was not submitted in the application, but was considered in this review.		
	☐	Input informed from participation in meetings with patient stakeholders	
	☐	Patient-focused drug development or other stakeholder meeting summary reports	
	☐	Observational survey studies designed to capture patient experience data	
	☐	Other: (Please specify):	
☐	Patient experience data was not submitted as part of this application.		

X

Cross-Disciplinary Team Leader

2. Therapeutic Context

2.1. Analysis of Condition

Nasopharyngeal carcinoma (NPC) is a kind of malignancy arising in the top or lateral wall of nasopharyngeal cavity. Although NPC, comprised of keratinizing, non-keratinizing differentiated, and nonkeratinizing 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). Based on high-level evidence, radiotherapy or chemoradiotherapy has become the mainstay of treatment for patients with early or locally advanced nasopharyngeal carcinoma, and the 5-year survival rate is approximately 85%. However, tumor metastasis remains the leading cause of treatment failure in these patients. Moreover, approximately 15% of NPC patients develop distant metastases at initial diagnosis, and patients with recurrent/metastatic NPC have a very poor prognosis, with a median overall survival of approximately 20 months.

The FDA's Assessment

There were approximately 133,354 cases of NPC diagnosed worldwide in 2020 with the majority of cases (>75%) in South and East Asia and 1.6% in Northern America, and approximately 80,000 people died from NPC in 2020 (Globocan, 2020). NPC is rare in the United States, with <1 case per 100,000 people each year (Cancer.Net, 2022).

The FDA agrees with the Applicant's position but notes that the Applicant provided little information specific to the demographics or disease characteristics for patients with NPC in the U.S. A review of data from the Surveillance, Epidemiology, and End Results (SEER) registry reported by Sun et al (2017) identified 3919 patients with histologically confirmed NPC between 2004 and 2013. Among the 3919 patients, median age was 54 years (range 44, 63) and 71% of patients were male. Information on race was included for 3672 patients with 49% White, 12% Black, and 39% Asian (including 18% Chinese ethnicity). Information on histology was included for 1087 patients; of these, 83% were non-keratinizing and 17% were keratinizing.

2.2. Analysis of Current Treatment Options

The Applicant's Position

Platinum-containing chemotherapy is generally considered the standard of care for patients with recurrent/metastatic for all types of nasopharyngeal carcinoma. Currently, cisplatin in combination with continuous intravenous infusion of fluorouracil is the global standard

treatment used in patients with recurrent/metastatic nasopharyngeal carcinoma, and available Phase II studies have reported objective response rates between 54% to 78% and the median progression-free survival of 7 to 11 months. However, adverse reactions, common mucosal complications, and requirements for deep venous catheterization remain major limitations to the fluorouracil plus cisplatin regimen. A Phase III randomized controlled study demonstrated that gemcitabine plus cisplatin significantly improved the objective tumor response rate from 42% to 64% and the median progression-free survival from 5.6 months to 7.0 months compared to fluorouracil plus cisplatin.

For patients who have failed platinum-containing first-line chemotherapy, the subsequent second-line therapy depends on patient performance status, toxicity, and the time interval to relapse after a platinum-containing regimen. For patients who have failed platinum-containing first-line chemotherapy but have no disease progression for more than 1 year, the re-treatment of platinum-containing combination chemotherapy may be considered. For patients who have failed first-line platinum-containing chemotherapy and whose disease has relapsed within one year after the chemotherapy regimen, the second-line chemotherapy includes gemcitabine, capecitabine, or paclitaxel, monotherapy. However, after relapse on 2nd line treatment there is no recognized standard third-line systemic therapy. Increasing evidence suggests that further use of chemotherapy after second- or third-line chemotherapy may not prolong survival in most patients.

It has been reported that NPC is closely associated with EB virus infection, and there is high PD-L1 expression in the tumor, suggesting that PD-1 blockade may be an ideal treatment option for NPC.

The FDA's Assessment

The FDA agrees with the Applicant's position regarding the standard of care first and second line therapies for advanced NPC at the time of submission of this BLA (July 2021). However, on October 27, 2023, FDA granted traditional approval to toripalimab-tpzi in combination with cisplatin and gemcitabine for the first-line treatment of adults with metastatic or recurrent, locally advanced NPC based on the results of the JUPITER-02 trial. The median PFS was 11.7 months for patients treated with toripalimab-tpzi with cisplatin and gemcitabine versus 8.0 months for patients treated with placebo with cisplatin and gemcitabine (PFS HR 0.52; 95% CI 0.36, 0.74; p=0.0003). A statistically significant OS improvement was also observed with median OS not reached (95% CI: 38.7 months, not estimable) for the toripalimab-tpzi-containing regimen and 33.7 months (95% CI: 27.0, 44.2) for the placebo-containing regimen (HR 0.63 [95% CI: 0.45, 0.89], p-value=0.0083). On October 27, 2023, FDA also granted traditional approval to toripalimab-tpzi as a single agent for the treatment of adults with recurrent unresectable or metastatic NPC with disease progression on or after a platinum-containing chemotherapy based on results of the POLARIS-02 trial. In 172 patients, the ORR by BICR was 21% (95% CI: 15, 28) and median DOR was 14.9 months (95% CI: 10.3, not estimable).

2.3. U.S. Regulatory Actions and Marketing History

The Applicant's Position

Penpulimab is not currently approved or marketed in the US or any other country. The clinical development program for penpulimab is being conducted under Investigational New Drug (IND) 138576 with Division of Regulatory Operations -Oncologic Diseases for DO2, and the relevant regulatory history is included in Section [3.2](#).

The FDA's Assessment

The FDA agrees with the Applicant's position.

2.4. Summary of Presubmission/Submission Regulatory Activity

The Applicant's Position

Penpulimab is an Anti-PD-1 monoclonal antibody received the Phase I Study May Proceed letter on Apr 11, 2018, under IND 138576, for the treatment of advanced solid tumors.

A summary of the key activities and Agency advice are provided in [Table 1](#).

Table 1 – Applicant: Key Regulatory Activities

Regulatory Event	Date	Description
Study may proceed	Apr 11, 2018	Penpulimab is received the Phase I Study May Proceed letter under IND 138576 for the treatment of advanced solid tumors.
Fast track granted	October 13, 2020	Penpulimab was granted Fast Track Designation for the treatment of patients with metastatic NPC with disease progression on or after two or more prior lines of therapy including platinum-containing chemotherapy.
Type B pre-BLA meeting preliminary comments	January 13, 2021	The FDA provided preliminary comments on accelerated approval, safety narratives, the proposed content and format for the BLA submission, RTOR, Assessment Aid, CMC, nonclinical, clinical study design and data report, initial pediatric study plan, clinical pharmacology, labeling, safety analysis strategy, inspection, and nonproprietary name.
Teleconference type B Pre-BLA meeting	January 19, 2021	The FDA provided feedback on accelerated approval, safety narratives, the content of a complete application and submission format requirement, RTOR, Assessment Aid, CMC only meeting, nonclinical, clinical study design and data report, initial pediatric study plan, clinical pharmacology, labeling, safety analysis strategy, inspection, and nonproprietary name.
Orphan drug granted	February 23, 2021	Penpulimab was granted Orphan Drug Designation for the treatment of nasopharyngeal carcinoma.
BTB granted	March 24, 2021	Penpulimab was granted Breakthrough Therapy Designation for the treatment of metastatic non-keratinizing NPC with disease progression after two or more prior lines of therapy, including platinum-containing chemotherapy.

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Penpulimab

Regulatory Event	Date	Description
Written responses: type F initial pediatric study plan meeting	April 7, 2021	FDA recommended (b) (4)
Type C pre-BLA meeting-CMC preliminary comments	April 16, 2021	The FDA provided preliminary comments on PPQ, product specifications, stability plans, strategy for transportation validation and sterilization, and microbiology.
RTOR acceptance	May 11, 2021	Acceptance of submission of the BLA under the RTOR program was received.
Teleconference type C pre-BLA meeting-CMC	May 18, 2021	The FDA provided comments on PPQ, product specifications, stability plans, strategy for transportation validation and sterilization, and microbiology.

Source:

Abbreviations: BTD, breakthrough therapy designation; CMC, chemistry; manufacturing and controls; IND, investigational new drug; NPC, nasopharyngeal carcinoma; PPQ, process performance qualification; RTOR; real-time oncology review.

The FDA's Assessment

The FDA agrees with the Applicant's position with the following additions. Study AK105-101, a first in human dose escalation study of penpulimab in patients with advanced solid tumors other than NPC, was the IND-enabling trial for IND 138576.

Study AK105-202 was conducted in China and initiated on March 27, 2019; it was not submitted to IND 138576 for FDA review prior to its initiation or during its conduct. The Fast Track Designation Request, submitted on August 14, 2020, was the first interaction FDA had with the Applicant about Study AK105-202, which provided the data in support of Fast Track Designation. The next interaction with the FDA about Study AK105-202 was at the pre-BLA meeting, held on January 19, 2021. During this meeting, FDA stated that justification that patients enrolled on Study AK105-202 adequately represent the US population in terms of disease characteristics, sex, race/ ethnicity, age, and standards of care, would be required as part of a marketing application submission. (b) (4)

The initial RTOR submission for this BLA was received on May 24, 2021, and the final RTOR submission was received on July 16, 2021.

3. Significant Issues From Other Review Disciplines Pertinent to Clinical Conclusions on Efficacy and Safety

3.1. Office of Scientific Investigations (OSI)

Clinical site inspections were initially planned but delayed due to restrictions related to the COVID-19 global pandemic. After the application was determined to have an unfavorable benefit-risk profile due to a change in the treatment landscape (i.e., due to the approvals of toripalimab-tpzi) and manufacturing deficiencies, clinical site inspections were not further pursued. No clinical sites were inspected for this application.

3.2. Product Quality

The Office of Pharmaceutical Quality (OPQ), CDER, has completed an assessment of BLA 761258 for penpulimab-kcqx manufactured by Akeso Biopharma Co., Ltd. The data submitted in this application are not sufficient to support a conclusion that the manufacture of penpulimab-kcqx is well-controlled and will lead to a product that is pure and potent. From a chemistry, manufacture, and control (CMC) standpoint, OPQ recommends that a Complete Response letter be issued to Akeso Biopharma Co., Ltd. to outline the following identified deficiencies, and the information and data that will be required to support approval.

1. Following the pre-license inspection (PLI) of Akeso Biopharma, Co., Ltd., Guangdong, China (FEI 3017057933), the drug substance and drug product manufacturing facility listed in this application, FDA conveyed deficiencies to the representative of the facility. FDA has reviewed the responses from the facility, and not all deficiencies have been satisfactorily resolved. Satisfactory responses to these deficiencies should be provided by the facility to the email address provided on the Form FDA 483 Inspectional Observations, prior to submitting your complete response. Your complete response should include the date of the facility's response to the Post-action Letter. The assessment of application approvability and the resolution of inspection deficiencies would be evaluated upon receipt of the complete response and may require re-inspection of the facility.
2. Reference is made to information and data provided during the PLI at Akeso BioPharma Co., Ltd. (FEI 3017057933; Zhongshan, China), and in response to the Agency's IRs dated February 24, 2022, March 11, 2022, May 12, 2022, and September 28, 2023, concerning the cell bank (b) (4)

(b) (4)



Taken

together, an adequate, well-controlled, and stable production cell bank(s) is currently unavailable for the manufacture of penpulimab-kcqx with continued product quality and sustainable commercial supply.

To resolve these deficiencies, provide data and information to support the qualification of an adequate and well-controlled cell bank(s) to ensure the manufacture of penpulimab-kcqx that is of continued product safety, purity, and potency. These should include, but not be limited to, safety testing results for the new cell bank(s), available cell bank stability test results, comparisons of cell growth data (e.g., growth kinetics, viability, VCD, characteristics of fermentation process, etc.), drug substance release data, and extended analytical characterization data (e.g., glycan analyses, primary, secondary and higher structure, results for product variants using sufficiently sensitive methods, etc.) from materials produced using the new cell bank(s) to historical at-scale manufacturing experience with properly qualified cell bank(s) and clinical experience (where applicable).

3. Reference is made to information provided in the original submission and in response to the Agency's IRs dated March 11, 2022, and August 18, 2022. The totality of information and data provided is inadequate to support the suitability of the following quality control methods for their intended use.

(b) (4)



To resolve these deficiencies, further optimize these methods and validate the optimized methods for their intended use. Provide updated method procedures (if applicable) and method validation/revalidation results to support the suitability of these methods for routine process and product control.

4. Reference is made to the information and data provided in the original submission and in response to the Agency's IR dated September 9, 2021, concerning the penpulimab-kcqx drug product (DP) manufacturing process control strategy. The information provided is insufficient to support the following process control ranges.

(b) (4)



To resolve these deficiencies, provide additional information and data from appropriate process validation and stability studies to support these process control ranges for routine manufacture.

3.3. Clinical Microbiology

Not applicable for this application.

3.4. Devices and Companion Diagnostic Issues

There was no device or companion diagnostic test reviewed as part of this application.

4. Nonclinical Pharmacology/Toxicology

4.1. Executive Summary

Penpulimab is a human IgG1 monoclonal antibody that targets programmed cell death protein 1 (PD-1); its established pharmacologic class is PD-1 blocking antibody. PD-1 is expressed on activated T and B cells, natural killer cells, and myeloid lineage cells. Binding of PD-1 to its ligands, programmed death-ligand 1 (PD-L1) and PD-L2, inhibits T-cell activity, T-cell proliferation, and cytokine production. In the tumor microenvironment, PD-1 signaling contributes to the inhibition of T cell-mediated immune surveillance of tumors. Thus, blockade of PD-1 signaling in the tumor microenvironment is intended to enhance tumor immunosurveillance and anti-tumor immune responses.

In in vitro studies, penpulimab bound to human and cynomolgus monkey PD-1 but did not bind rodent PD-1, supporting the use of cynomolgus monkeys as the single pharmacologically relevant species for toxicity assessment. In cellular assays, penpulimab blocked the binding of human PD-1 to human PD-L1 and PD-L2 and also competitively bound to PD-1 expressed on the surface of human PD-1-transfected 293T cells. Additionally, penpulimab induced the secretion of interleukin-2 (IL-2) and interferon-gamma (IFN- γ) in a mixed culture of peripheral blood mononuclear cells (PBMCs) and dendritic cells (DCs) and in a mixed culture of PBMCs, DCs, and Raji Burkitt lymphoma cells. Penpulimab also enhanced IFN- γ secretion by cytomegalovirus (CMV)-responsive human PBMCs during the recall response to CMV antigen.

Given that penpulimab does not bind mouse PD-1, the Applicant investigated the in vivo anti-tumor activity of penpulimab in a human PD-1 knock-in genetically engineered mouse model (HuGEMM) implanted subcutaneously with MC38 mouse colon adenocarcinoma cells. Intraperitoneal administration of penpulimab at doses of 0.8 and 8 mg/kg twice a week for a total of 5 doses resulted in tumor growth inhibition (TGI) compared to the isotype control. The Applicant also evaluated the antitumor activity of penpulimab in immunodeficient mice implanted subcutaneously with Raji cells expressing PD-L1 or a Raji-PD-L1/PBMC mixture. Intravenous (IV) administration of penpulimab (10 mg/kg) on Days 7, 13, and 21 resulted in greater TGI compared to the isotype control.

The Applicant evaluated the safety of penpulimab in cynomolgus monkeys in GLP-compliant repeat-dose toxicology studies of up to 13 weeks duration. In the 6- and 13-week studies, monkeys received IV infusion of penpulimab at doses up to 60 mg/kg once every 2 weeks. There were no mortalities or penpulimab-related findings of toxicological significance. Target organs of toxicity in the 6-week study were the kidney (increased cortical tubular pigment or pigmented interstitial macrophages), spleen (increased cellularity), adrenal gland (cortical hypertrophy), parotid salivary gland (acinar cell atrophy), thymus (increased weight); and in the 13-week study was lymph nodes (erythrophagocytosis and increased cellularity). The incidence of anti-drug antibody formation was 63.33% in the 6-week study and 93.33% in the 13-week

study, which may explain the limited findings noted in the 13-week study. In clinical trials done to support the approval of penpulimab in the proposed patient population, toxicities associated with penpulimab were primarily immune-mediated adverse reactions that are predicted by its mechanism of action. At the recommended clinical dose of 200 mg, the human AUC₀₋₃₃₆ was 26200 µg*h/mL.

Based on its mechanism of action and data from the literature, there is potential for enhanced immune responses to infection following treatment with penpulimab. *Mycobacterium tuberculosis* (Mtb)-infected PD-1 knockout mice exhibited decreased survival compared to wild-type mice, which correlated with increased bacterial proliferation and inflammatory responses in these animals. It is unclear whether decreased survival resulted from an inability to mount an appropriate antibacterial response or a failure to control the immune response leading to normal tissue destruction and organ failure (Lazar-Molnar, et al. 2010). Furthermore, in mouse models of lymphocytic choriomeningitis virus (LCMV) infection, the absence of PD-1 pathway signaling led to fatal CD8+ T cell-mediated killing of virally infected vascular endothelial cells, systemic vascular leakage, and ultimately cardiovascular collapse (Frebel et al. 2012; Mueller et al. 2010). Similarly, PD-L1 deficient mice died early after chronic systemic LCMV infection (Barber et al. 2006). In addition, blockade of PD-1 with an anti-PD-1 antibody in Mtb infection in monkeys can exacerbate the infection and lead to death and severe pulmonary stress in infected monkeys (Kauffman et al. 2021). A brief description of these data was included in Section 13.2 of the label to convey these potential risks to prescribers.

No reproductive or embryo-fetal developmental toxicology studies were conducted with penpulimab. Rather, the Applicant provided a literature-based assessment of the potential reproductive toxicity of penpulimab, consistent with the alternative approach described in the FDA Guidance for Industry Oncology Pharmaceuticals: Reproductive Toxicity Testing and Labeling Recommendations. Data from the literature demonstrate that the PD-1/PD-L1 pathway plays a critical role in maintaining maternal immunological tolerance to the fetus during pregnancy. Blockade of PD-1/PD-L1 signaling in murine models of pregnancy resulted in an increased incidence of fetal loss but no fetal malformations; however, late onset autoimmunity can occur in PD-1-deficient mice. Based on these findings, the potential risks of administering penpulimab during pregnancy include increased rates of abortion or stillbirth and an increased risk in offspring of developing immune-related disorders or altering the normal immune response. As a result, the pharmacology/toxicology team recommends a warning for embryo-fetal toxicity in the prescribing information. Based on a half-life of penpulimab of 23.9 days, females of reproductive potential are advised to use effective contraception during treatment with penpulimab and for 4 months after the last dose. The Applicant did not evaluate transfer of penpulimab to the fetus or milk, but IgG antibodies can be present in milk. Because of the potential adverse effects of penpulimab on a breastfeeding child, the review team included recommendations in the label not to breastfeed during treatment with penpulimab and for 4 months after the last dose. Neither genetic toxicology or carcinogenicity

studies were conducted or required to support the use of an antibody in the currently proposed indication.

There are no outstanding issues from a pharmacology/toxicology perspective that would prevent the approval of penpulimab for the treatment of adult (b) (4) with metastatic non-keratinizing nasopharyngeal carcinoma with disease progression on or after platinum-based chemotherapy and at least one other prior line of therapy.

4.2. Referenced NDAs, BLAs, DMFs

The Applicant's Position

Not Applicable.

4.3. Pharmacology

4.3.1. Primary Pharmacology

The FDA's Assessment (all data presented by FDA):

Primary pharmacology studies NCS105-0001 through NCS105-00010 were reviewed under the original IND by Dr. Wimolnut Manheng. All other pharmacology studies were reviewed under the current BLA by Dr. Kelie Reece.

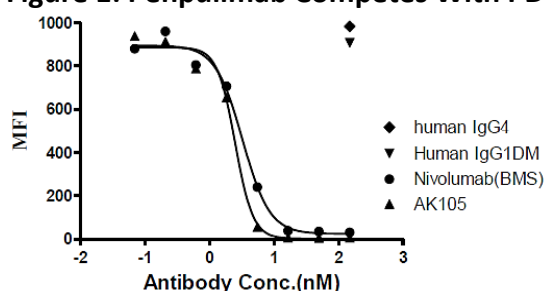
In Vitro Studies

The Applicant determined the binding affinities of penpulimab for human (Study NCS105-0001), cynomolgus monkey (Study NCS105-0005), mouse (Study NCS105-0006), and rat PD-1 (Study NCS105-0007) using the enzyme-linked immunoassay (ELISA). Penpulimab (0.0014–1 µg/mL) bound to human PD-1-mFc fusion protein (human PD-1 extracellular domain fused to murine IgG Fc domain) and monkey PD-1-hFc fusion protein (monkey PD-1 extracellular domain fused to human IgG1 Fc domain) with EC₅₀ values of 0.053 and 0.215 nM, respectively, but did not bind to mouse or rat PD-1, supporting the use of cynomolgus monkeys as a pharmacologically relevant species for toxicity assessment.

The Applicant determined the binding activity of penpulimab to PD-1 expressed on the surface of human PD-1-transfected 293T cells (293T-PD-1 cells) by fluorescence activated cell sorting (FACS) analysis (Study NCS105-0008). Penpulimab (0.1–20 nM) bound to human PD-1 in a dose-dependent manner, with an EC₅₀ of 2.53 nM. As assessed by surface plasmon resonance, penpulimab (1.56–50 nM) exhibited high binding affinity for human PD-1, with a K_D of 0.588 nM (Study NCS105-0002), which was similar to the K_D of the anti-PD-1 comparator antibody nivolumab.

The Applicant used competitive ELISA to evaluate the activity of penpulimab in competing with PD-L1 (Study NCS105-0003) and PD-L2 (Study NCS105-0004) for binding to PD-1. Penpulimab (0.002–3 $\mu\text{g/mL}$) blocked the binding of immobilized human PD-1-hFc to human PD-L1-mFc and human PD-L2-His fusion proteins in a dose-dependent manner, with EC_{50} values of 0.878 and 1.483 nM, respectively. The Applicant used FACS to evaluate the activity of penpulimab in competing with PD-L1 for binding to 293T-PD-1 cells (Study NCS105-0009). Penpulimab (0.07–150 nM) competitively bound to PD-1 on 293T-PD-1 cells in a dose-dependent manner, with an EC_{50} of 2.526 nM (Figure 1). Binding of penpulimab was comparable to the positive control, nivolumab, which competitively bound to PD-1 with an EC_{50} of 3.281 nM.

Figure 1: Penpulimab Competes With PD-L1 for Binding to Cell Surface PD-1

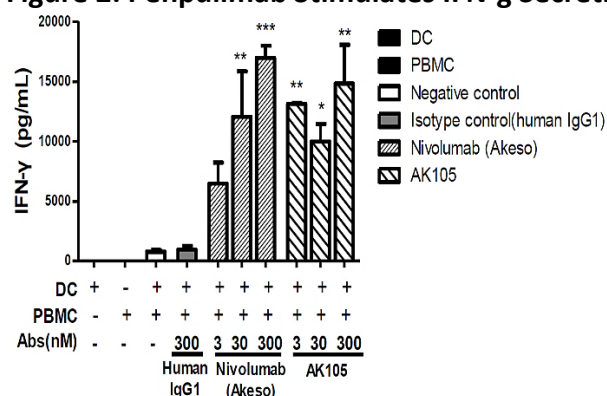


Source: Excerpted from the Applicant's submission: Study NCS105-0009.

Abbreviations: Conc, concentration; Ig, immunoglobulin; MFI, median fluorescence intensity.

To evaluate the effect of penpulimab on the secretion of IFN- γ and IL-2 from lymphocytes, the Applicant conducted an allogeneic mixed lymph reaction (MLR) experiment (Study NCS105-00010). In this MLR, investigators incubated in vitro-differentiated DCs of one donor (stimulator) with allogeneic PBMCs of another donor (responder) at a ratio of 10:1, followed by the addition of penpulimab (3, 30, 300 nM). Nivolumab Akeso (synthesized by the Applicant) was used as a positive control. IFN- γ and IL-2 levels were measured by ELISA. Compared with the isotype and negative controls, penpulimab significantly enhanced the secretion of IFN- γ (Figure 2) and IL-2 (Figure 3) in the mixed culture of PBMCs and DCs in a dose-independent manner.

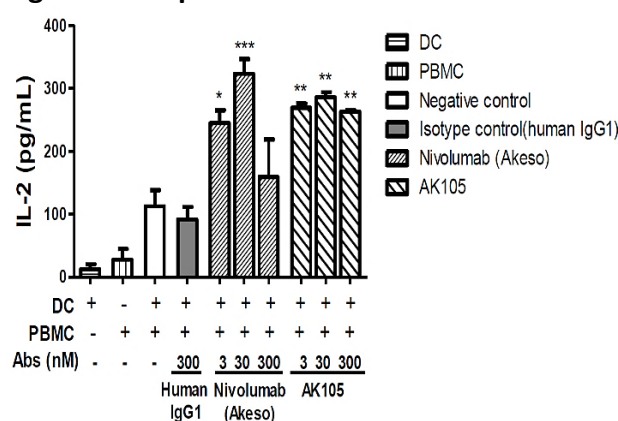
Figure 2: Penpulimab Stimulates IFN- γ Secretion in a Mixed Culture of PBMCs and DCs



Source: Excerpted from the Applicant's submission: Study NCS105-00010.

Abbreviations: Abs, absorbance; DC, dendritic cell; IFN, interferon; Ig, immunoglobulin; PBMC, peripheral blood mononuclear cells.

Figure 3: Penpulimab Stimulates IL-2 Secretion in a Mixed Culture of PBMCs and DCs

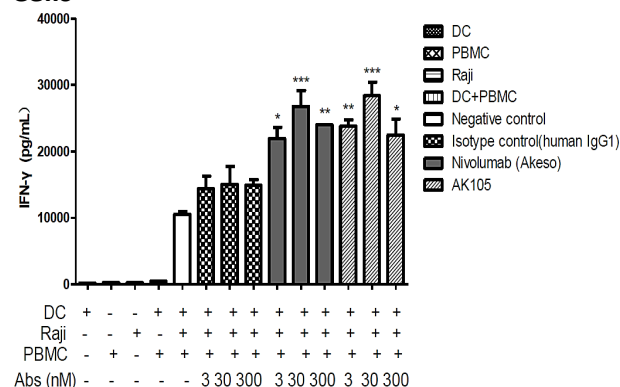


Source: Excerpted from the Applicant's submission: Study NCS105-00010.

Abbreviations: Abs, absorbance; DC, dendritic cell; Ig, immunoglobulin; IL, interleukin; PBMC, peripheral blood mononuclear cells.

The Applicant further studied the effects of penpulimab on IFN- γ and IL-2 secretion in a mixed culture of human PBMCs, DCs, and the Raji B-cell lymphoma line (Study NCS105-0021). In this MLR assay, penpulimab (3, 30, 300 nM) significantly enhanced the secretion of IFN- γ (Figure 4) and IL-2 (Figure 5) in the mixed culture of PBMCs, DCs, and Raji cells in a dose-dependent manner.

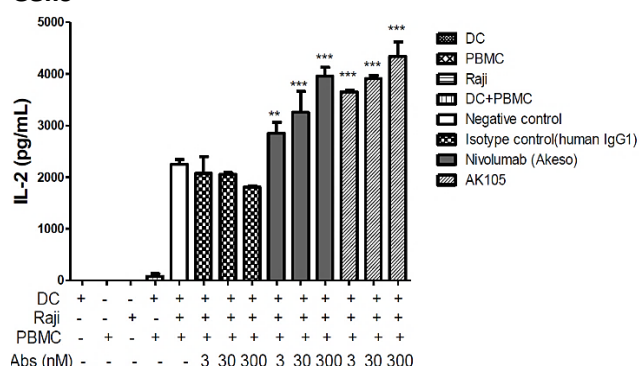
Figure 4: Penpulimab Stimulates IFN- γ Secretion in a Mixed Culture of PBMCs, DCs, and Raji Cells



Source: Excerpted from the Applicant's submission: Study NCS105-00021.

Abbreviations: Abs, absorbance; DC, dendritic cell; IFN, interferon; Ig, immunoglobulin; PBMC, peripheral blood mononuclear cells.

Figure 5: Penpulimab Stimulates IL-2 Secretion in a Mixed Culture of PBMCs, DCs, and Raji Cells

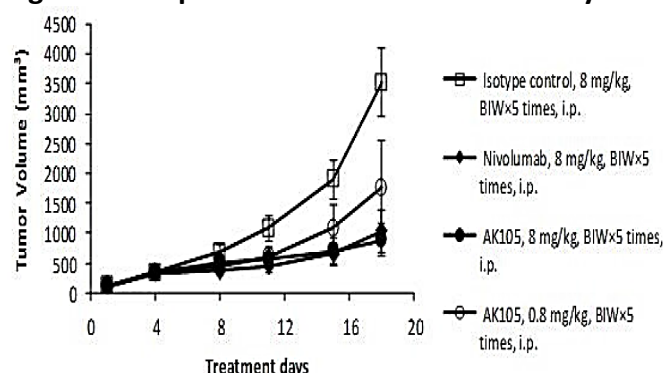


Source: Excerpted from the Applicant's submission: Study NCS105-00021.

Abbreviations: Abs, absorbance; DC, dendritic cell; IL, interleukin; PBMC, peripheral blood mononuclear cells.

The Applicant conducted a cellular assay to evaluate the effect of penpulimab on IFN- γ secretion by CMV-responsive human PBMCs during the recall response to CMV antigen (Study NCS105-0024). PBMCs from two donors were prescreened for a CMV recall response using a serially diluted CMV peptide pool. As assessed by ELISA on Day 4, the CMV peptide pool effectively induced the secretion of IFN- γ in a dose-dependent manner, demonstrating that the PBMCs were previously infected by CMV and could re-respond to CMV antigen. The CMV-responsive PMBCs were stimulated with CMV antigen in the absence or presence of penpulimab (0.1–300 nM). Pembrolizumab and nivolumab were assessed as positive controls, and ipilimumab (anti-cytotoxic T lymphocyte antigen-4 antibody) served as a negative control. After a 4-day incubation, the antigen-induced IFN- γ response was measured by ELISA. Compared with the isotype and negative controls, penpulimab significantly enhanced the secretion of IFN- γ in a dose-dependent manner by CMV-responsive human PBMCs during the recall response to CMV antigen, showing comparable activity with nivolumab and

Figure 7: Penpulimab Has Antitumor Activity in PD-1 HuGEMM MC38-Bearing Mice

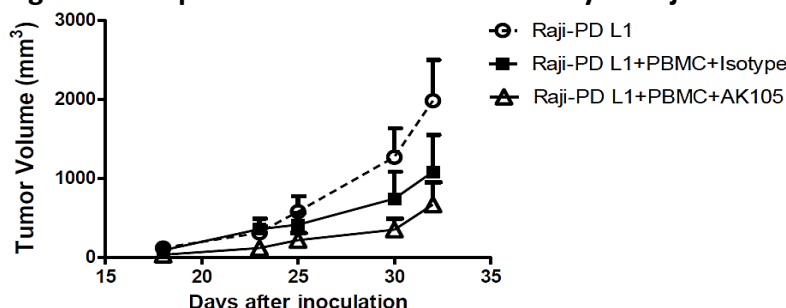


Source: Excerpted from the Applicant's submission: Study E3174-B1701.

Abbreviations: BIW, twice a week; HuGEMM, human genetically engineered mouse model.

The Applicant also evaluated the antitumor activity of penpulimab in female SCID/Beige mice implanted subcutaneously with Raji cells expressing PD-L1 (Raji-PD-L1 cells) or a Raji-PD-L1/PBMC mixture, in order to provide an immune component that is responsive to anti-PD-1 antibody and can generate an anti-tumor immune response (Study NCS105-0014). Intravenous administration of penpulimab (10 mg/kg) on Days 7, 13, and 21 resulted in greater TGI compared to the isotype control ([Figure 8](#)), without inducing significant toxicity based on body weight loss.

Figure 8: Penpulimab Has Antitumor Activity in Raji-PD-L1-Bearing Mice



Source: Excerpted from the Applicant's submission: Study NCS105-00014.

Abbreviations: PBMC, peripheral blood mononuclear cells; Raji-PD L1, Raji cells expressing PD-L1.

4.3.2. Secondary Pharmacology

The Applicant's Position

In the Fc domain of penpulimab, point mutations were introduced to eliminate a series of Fc receptor mediated effects, including antibody-dependent cell-mediated cytotoxicity (ADCC), antibody dependent cellular phagocytosis (ADCP), complement dependent cytotoxicity (CDC) and Fc receptor mediated cytokine release. The affinity of penpulimab to Fc-receptor FcγRIIIa, FcγRI and C1q were evaluated by Fortebio Octet molecular interaction assay and confirmed lack of binding. Cellular assays were further conducted to evaluate the ADCC, ADCP, CDC and

antibody dependent cytokine release (ADCR) activity of penpulimab, and penpulimab shows no ADCC, ADCP, CDC activity or ADCR of IL-6 and IL-8 from human macrophages. In binding selectivity assay, penpulimab binds to human PD-1 but not to human CTLA-4, which is a homologous protein of PD-1. Penpulimab also does not bind to human lymphocyte-activation gene 3 (LAG3) or human T cell immunoglobulin and ITIM domain (TIGIT), which are co-inhibitory receptors like PD-1. The activity of penpulimab to elicit cytokine IL-1 β , IL-6 and TNF- α release from peripheral blood mononuclear cells (PBMCs) was also tested and penpulimab does not elicit cytokine release of these cytokines from PBMC, suggesting the low risk of triggering cytokine release syndrome.

The FDA's Assessment

The FDA agrees with the Applicant's conclusions.

4.3.3. Safety Pharmacology

The Applicant's Position

Safety pharmacology studies were conducted during cynomolgus monkey toxicity studies, and effect of penpulimab on vital functions in cardiovascular system, central nervous system (CNS) and respiratory system were investigated. The evaluation of safety pharmacology endpoints including body temperature, respiratory rate, blood oxygen saturation, electrocardiograms, and blood pressure upon treatment with penpulimab was incorporated into the repeat-dose toxicology study in cynomolgus monkey conducted under GLP condition. There were no treatment-related effects on body temperature, respiratory rate, blood oxygen saturation, electrocardiograms, or blood pressure found in the repeat dose toxicology study. Thus, no specific concerns were observed on vital functions in cardiovascular system, CNS, and respiratory system.

The FDA's Assessment

The FDA agrees with the Applicant's conclusions. In vivo, cardiovascular parameters were assessed pre-treatment; 2 to 5 hours after dosing on Days 1, 15, 29, and 43; and 1 day prior to recovery necropsy (Day 84) in the 13-week repeat-dose monkey study. Findings were reviewed under the General Toxicology below (Section [5.5.1](#)). There were no toxicologically significant changes observed at doses up to 60 mg/kg/day.

4.4. ADME/PK

The Applicant's Position

Single dose pharmacokinetics (PK) and repeat-dose toxicokinetics (TK) evaluation of penpulimab were performed in cynomolgus monkey which is the specie showing cross-

Penpulimab

reactivity to penpulimab. In single dose PK study, systemic exposure of penpulimab (AUC and C_{max}) was approximately dose-proportional in cynomolgus monkeys from 1 mg/kg to 10 mg/kg. No significant differences in systemic exposure were noted. A high incidence of anti-drug antibody (ADA) formation was observed, which was related to the accelerated elimination of penpulimab in ADA-positive animals at the end of the elimination phase. Repeat dose PK (TK) of penpulimab was investigated in the 6-week and 13-week toxicity study. Dose-dependent increase in systemic exposure of penpulimab (AUC and C_{max}) was noted following repeat intravenous dosing. Decreases in systemic exposure levels were noted in a few animals (Day 29 or 71, respectively), which is due to the formation of ADAs. There was no significant systemic accumulation after repeat dosing of penpulimab once every two weeks for 6 weeks or 13 weeks.

The FDA's Assessment

The FDA agrees with the Applicant's summary of the nonclinical ADME/PK data. Traditional distribution, metabolism, and excretion studies were not conducted with penpulimab because it is a monoclonal antibody.

Type of Study	Major Findings								
Absorption	Cynomolgus monkeys received penpulimab at a single IV dose of 1, 3, or 10 mg/kg. - Exposure increased dose proportionally. - There were no significant sex-related differences in exposure. - On Day 8, anti-drug antibodies (ADAs) were detected in 1/3 animals in each dose group. On Days 15, 22, and 29, ADAs were detected in all animals except one female at 3 mg/kg and one female at 10 mg/kg.								
Study P16-048-YD (reviewed by Dr. Manheng): Pharmacokinetic Study of a Monoclonal Antibody AK105 by Intravenous Infusion to Cynomolgus Monkeys									

Mean Toxicokinetic Parameters in Monkeys Following Single IV Administration of Penpulimab									
Dosage	Sex		t _{1/2} h	C _{max} µg/ml	AUC _{0-672h} h*µg/ml	AUC _{INF} h*µg/ml	V _z ml/kg	Cl ml/h/kg	MRT h
1 mg/kg	Male	mean	122.80	26.10	2894.87	3078.22	57.40	0.33	144.75
		SD	28.67	3.28	276.07	277.60	11.04	0.03	30.60
	Female	mean	140.31	23.37	2592.18	3141.56	63.69	0.32	121.24
		SD	39.99	2.53	512.74	472.24	9.90	0.05	40.56
3 mg/kg	Male	mean	121.65	76.71	9080.55	9616.25	54.73	0.32	145.43
		SD	29.05	4.28	1508.91	1537.93	9.19	0.05	34.86
	Female	mean	166.94	67.87	10557.56	11383.25	62.54	0.27	180.40
		SD	54.70	4.09	1699.32	2425.98	9.99	0.05	32.25
10 mg/kg	Male	mean	64.03	340.18	42364.40	42756.89	22.04	0.25	151.15
		SD	60.00	94.71	12599.87	12627.73	19.36	0.08	24.32
	Female	mean	167.16	280.71	50391.10	55254.51	44.01	0.20	201.21
		SD	57.55	12.32	14572.59	17963.73	7.68	0.08	43.33

(Excerpted from the Applicant’s submission: Study P16-048-YD)

4.5. Toxicology

4.5.1. General Toxicology

The Applicant's Position

In 6-week repeat-dose toxicity study, no apparent toxicity was observed in cynomolgus monkeys following intravenous infusion of penpulimab at 4, 15, or 60 mg/kg once every two weeks for 6 weeks. Treatment-related histopathological change of kidneys (increased cortical tubular pigment or pigmented interstitial macrophages) was noted in some animals but no impact on kidney functions. Pigment in the cortical tubular epithelium of the kidneys is not reported as a common background finding in cynomolgus monkeys. In this study, there were no apparent changes in clinical chemistry, urinalysis, or organ weights which would indicate an impact of treatment on kidney function. There were also no other histopathological changes associated with the pigment which were indicative of damage to the kidneys. These changes were therefore considered not to be adverse. The no observed adverse effect level (NOAEL) was considered to be 60 mg/kg.

In 13-week repeat-dose toxicity study, no apparent toxicity and histopathological change of kidney was observed in cynomolgus monkeys following intravenous infusion of penpulimab at 4, 15, or 60 mg/kg once every two weeks for 13 weeks, the NOAEL was considered to be 60 mg/kg.

The FDA's Assessment

In general, the FDA agrees with the Applicant's assessment of the toxicology data. In the 6-week repeat-dose toxicology study, clinical chemistry findings included a dose-dependent decrease in total bilirubin and increase in creatine kinase levels at all dose levels in males, which were present at the end of the recovery period. In addition to the kidney, as noted by the Applicant, other target organs of toxicity in the 6-week study were the spleen (increased cellularity of the red and white pulp), adrenal gland (cortical hypertrophy), parotid salivary gland (acinar cell atrophy), and thymus (increased weight). Changes in the adrenal gland, spleen, and thymus (females) were present at the end of the recovery period. Of the 30 monkey serum samples tested, 19 were ADA-positive with an incidence of 63.33%.

In the 13-week toxicity study, histological findings included erythrophagocytosis and increased cellularity in the lymph nodes (inguinal, mandibular, mesenteric), which were present at the end of the recovery period. Limited findings may be reflective of ADA formation. Of the 30 monkey serum samples tested, 28 were ADA-positive with an incidence of 93.33%.

Study title/number: A 13-Week Intravenous Infusion Toxicity Study of AK105 Injection with a 6-Week Recovery Period in Cynomolgus Monkeys/P18-172-RD

Key Study Findings

- There were no mortalities or penpulimab-related findings of toxicological significance.
- Histological findings included increased cellularity and erythrophagocytosis in the inguinal, mandibular, and mesenteric lymph nodes.
- The NOAEL was 60 mg/kg.

GLP Compliance: Yes

Methods

Dose and frequency of dosing: 0, 4, 15, and 60 mg/kg
Once every 2 weeks for 13 weeks

Route of administration: Intravenous

Formulation/Vehicle: Sodium chloride injection

Species/Strain: Monkey/Cynomolgus

Number/Sex/Group: Main: 3 monkeys/sex/group
Recovery: 2 monkeys/sex/group; 6-week recovery period

Age: 3.5 to 4 years old

Satellite groups/unique design: Toxicokinetic: 5 monkeys per sex per group/lymphocyte subsets, cytokine assay, immunogenicity, immunoglobulin assay, complement assay, body temperature, blood pressure

Deviation from study protocol affecting interpretation of results: No

Observations and Results: changes from control

Parameters	Major findings
Mortality	None
Clinical Signs	No penpulimab-related findings; signs noted were also present in the controls, were infrequent, had no dose-response relationship, and/or were common spontaneous changes in monkeys.
Body Weight	Unremarkable
Feed Consumption	Unremarkable
Body Temperature	Unremarkable

Penpulimab

ECG	No penpulimab-related findings; the changes observed in QTcB and Q-T were considered individual variations due to lack of a dose-relationship and small magnitude.
Blood Pressure	Unremarkable
Ophthalmoscopy	Unremarkable
Hematology	Unremarkable
Coagulation	Unremarkable
Clinical Chemistry	Unremarkable
Urinalysis	Unremarkable
Gross Pathology	No penpulimab-related lesions
Organ Weights	No penpulimab-related findings; although there were statistically significant increases in brain weight at 4 and 60 mg/kg, ovary weight at 15 mg/kg, and thymus weight at 60 mg/kg in females, due to the lack of a clear dose-relationship and corresponding microscopic findings, the Applicant considered the increases to be incidental.
Histopathology (Adequate battery: Yes)	Treatment-related histopathology findings were limited to the lymph nodes (Table 2).
Lymphocyte Subsets	No penpulimab-related changes in CD3 ⁺ , CD4 ⁺ , CD8 ⁺ , CD20 ⁺ , or CD4 ⁺ /CD8 ⁺ ratios
Cytokine Assay	No penpulimab-related changes in TNF- α , IFN- γ , IL-2, IL-4, IL-5, or IL-6
Immunoglobulin Assay	No penpulimab-related changes in IgA, IgG, or IgM
Complement Assay	No penpulimab-related changes in C3 or C4
Immunogenicity	At the end of the 13-week treatment period, ADAs were detected in 10/10, 9/10, and 10/10 monkeys dosed with 4, 15, and 60 mg/kg penpulimab, respectively. Neutralization activities were detected in 28/30 of the ADA-positive serum samples. All recovery animals (4 per group) were ADA-positive at the end of the recovery period. ADAs resulted in lower penpulimab concentrations in several animals (5, 5, and 2 animals in the 4, 15, and 60 mg/kg groups, respectively).
Toxicokinetics	C_{max} and AUC_{last} generally increased dose proportionally on Day 1. In females, C_{max} and AUC_{last} increased in a greater than dose-proportional manner on Day 71; in males, the C_{max} increased dose proportionally and the AUC_{last} increased in a less than dose-proportional manner. - The only sex-related differences were lower exposure in males than females at 15 mg/kg on Day 71 due to ADA. - There was no significant accumulation of penpulimab.

Toxicokinetic Parameters for Penpulimab						
	Males			Females		
mg/kg	4	15	60	4	15	60
Day 1						
C _{max} (ng/mL)	0.08	0.36	1.30	0.09	0.31	1.23
AUC _{last} (h*mg/mL)	9.86	39.94	153.24	10.32	37.30	142.19
Day 71						
C _{max} (ng/mL)	0.10	0.23	1.56	0.09	0.38	1.74
AUC _{last} (h*mg/mL)	13.84	11.40	156.33	8.90	42.94	194.11

h = hours; AUC_{last} = AUC from the time of dosing to the time the last serum drug was detected (up to 336 hours)
On Day 71, TK parameters were not calculated in 3 monkeys (2 in 4 mg/kg group and 1 in 15 mg/kg group) due to severe ADA effects

Table 2 – FDA: Selected Histopathology Findings (13-Week Study; Monkeys)

Table 2. T2R-Selected Histopathology Findings (15-Week Study) Monkeys											
		Dose (mg/kg)		Male				Female			
				0	4	15	60	0	4	15	60
		Number of Monkeys Examined		3/2R	3/2R	3/0R	3/2R	3/2R	3/2R	3/0R	3/2R
Organ/Tissue	Finding	Result Modifier	Severity								
Lymph node	Cellularity, increased	Inguinal; mandibular; mesenteric	Slight		1		2/2R	1			2/2R
	Erythrophagocytosis	Inguinal; mandibular; mesenteric	Min	1	1	2	1/2R	1	3	1	2R
		Inguinal	Slight		1		1				1
			Mar		2/1R	1	1				

Abbreviations: Min, minimal; Mar, marked; R, recovery.

4.5.2. Genetic Toxicology

The Applicant's Position

Genetic toxicology studies were not conducted with penpulimab. As described in ICH Guidance S6, the range and type of genotoxicity studies routinely conducted for pharmaceuticals are not applicable to biotechnology-derived pharmaceuticals.

The FDA's Assessment

The FDA agrees that genetic toxicology studies are not needed to support the use of penpulimab per ICH S6.

4.5.3. Carcinogenicity

The Applicant's Position

Carcinogenicity studies were not conducted with penpulimab, which is consistent with its use in patients with advanced malignancies (see the ICH Guidance S9). If penpulimab is developed for use in other indications, an assessment of its carcinogenic potential may be warranted;

however rodent bioassays are inappropriate, as penpulimab does not appear to be active in rodents.

The FDA's Assessment

The FDA agrees that carcinogenicity studies are not needed to support the use of penpulimab in the currently proposed indication per ICH S9.

4.5.4. Reproductive and Developmental Toxicology

The Applicant's Position

Fertility, embryonic fetal development, or pre- and postnatal developmental toxicity studies were not conducted with penpulimab. As described in ICH Guidance S9, fertility and early embryonic developmental toxicity study is not warranted for marketing of pharmaceuticals for the treatment of patients with advanced cancer. Information available from general toxicology studies on the pharmaceutical's effect on reproductive organs were used as the basis of the assessment of impairment of fertility. In the 6-week and 13-week repeat-dose toxicity studies, there were no notable effects in the male and female reproductive organs.

Embryo-fetal development toxicity studies were not conducted with penpulimab. Literature data shows that a central function of the PD-1/PD-L1 pathway is to preserve pregnancy by maintaining maternal immune tolerance to the fetus. Blockade of PD-L1 signaling has been shown in murine models of pregnancy to disrupt tolerance to the fetus and to increase fetal loss. There are potential reproductive risks when giving penpulimab during pregnancy, including increased rates of miscarriage or stillbirth. Penpulimab is an IgG1 antibody drug with high affinity to human FcRn, thus it is expected to cross the placenta during third-trimester pregnancy in human, though the exposure of penpulimab in fetus under treatment dose level is undetermined. Based on its mechanism of action, fetal exposure to penpulimab may increase the risk of developing immune-mediated disorders or altering the normal immune response and immune-mediated disorders have been reported in PD-1 knockout mice.

Pre- and postnatal toxicity studies were not conducted with penpulimab. As described in ICH Guidance S9, pre- and postnatal toxicity study is not warranted for marketing of pharmaceuticals for the treatment of patients with advanced cancer.

The FDA's Assessment

The FDA agrees that dedicated reproductive and developmental toxicity studies are not needed to support this BLA submission. To address the potential effects of penpulimab on embryo-fetal development, the Applicant submitted an assessment of the potential reproductive toxicity of penpulimab using a weight-of-evidence approach. The FDA agrees that this approach is reasonable.

The PD-1/PD-L1 pathway plays a critical role in maintaining maternal immunological tolerance to the fetus during pregnancy (Guleria et al. 2005). PD-L1 is expressed in the human placenta throughout pregnancy and at the maternal-fetal interface in fetal villous syncytiotrophoblasts and extravillous cytotrophoblasts (Petroff et al. 2003). Blockade of PD-L1 signaling in murine models of pregnancy disrupts tolerance to the fetus, resulting in increased fetal loss (Guleria et al. 2005).

Penpulimab is a humanized IgG1 antibody, and human IgG is known to cross the placenta; thus, penpulimab may be transmitted from the mother to the fetus. Based on its mechanism of action and findings from murine models of pregnancy (Guleria et al. 2005), administration of penpulimab is likely to disrupt the maintenance of normal pregnancy. Potential risks associated with administration of penpulimab during pregnancy include increased rates of abortion and stillbirth. In addition, as PD-1 knockout mice develop late onset autoimmune phenotypes (Okazaki and Honjo 2007), fetal exposure to penpulimab may alter the normal immune response or increase the risk of developing immune-related disorders. As inhibition of the PD-1/PD-L1 pathway can lead to increased risk of immune-mediated rejection of the developing fetus, resulting in fetal death, a warning for embryofetal toxicity is recommended for penpulimab. Based on a half-life of approximately 24 days, females of reproductive potential are advised to use effective contraception during treatment with penpulimab and for 4 months after the last dose of penpulimab.

Fertility studies have not been conducted with penpulimab and are not needed to support a BLA for the proposed indication. In 6- and 13-week repeat-dose toxicity studies in monkeys, there were no notable effects on male and female reproductive organs up to the highest dose tested of 60 mg/kg (approximately ≥ 4.7 times the human exposure based on AUC at the 200 mg clinical dose); however, most animals in these studies were not sexually mature.

4.5.5. Other Toxicology Studies

The Applicant's Position

The investigation of tissue cross-reactivity of penpulimab with normal human and normal cynomolgus monkey frozen tissues revealed that penpulimab reacted with normal human spleen and lymph nodes and normal cynomolgus monkey spleen, mesenteric lymph node, thymus, jejunum, and colon. PD-1 is expressed on the surface of activated T cells, B cells, and macrophages, and as the results of penpulimab tissue cross-reactivity (TCR) studies showed no unexpected binding of penpulimab to human or cynomolgus monkey tissues was found. In hemolysis study, penpulimab at the concentration of 10 mg/mL had no hemolytic or aggregation effect on human red blood cells.

The FDA's Assessment

The FDA agrees with the Applicant's conclusions. Standard positive controls confirmed the sensitivity and validity of these GLP-compliant studies.

Literature-Based Assessment of Potential for Effects of Infection

Reviewed by Drs. Shawna Weis and Stephanie Aungst.

While loss of PD-1 function enhances clearance of some tumors and viral infections, it increases susceptibility to certain other pathogens such as tuberculosis in some animal models.

PD-1-deficient mice (C57BL/6) infected with *M. tuberculosis* exhibited a decrease in survival, which correlated with uncontrolled bacterial proliferation and a larger inflammatory response in the lungs of PD-1-deficient mice compared with wild-type controls. Thus, PD-1 appears to be required to control infection and the inflammatory responses in the lungs of mice infected with *M. tuberculosis* (Lazar-Molnar, et al. 2010); however, the pathogenesis of this observation has not been clearly-defined. In particular, it is unclear whether the decreased survival reflects rampant bacterial growth resulting from an inability to mount appropriate antibacterial responses and/or whether it is a failure to downregulate the immune reaction that leads to massive tissue destruction and organ failure.

In a recent publication, Kauffman et al. (2021) evaluated the role of PD-1 during *Mycobacterium tuberculosis* (Mtb) infection of rhesus macaques. Monkeys (~2 years old; males) were infected with 30-50 colony forming units of fluorescently labeled Mtb into the right lower lung lobe. Tissue from Mtb infected monkeys was harvested 15-16 weeks post infection and assessed for PD-1 expression using flow cytometry. Additional Mtb infected monkeys were intravenously infused with 10 mg/kg of isotype control (DSPR4) or a primatized anti-PD-1 monoclonal antibody (n=6/group) at 2, 4, 6-, 8-, 10-, and 13-weeks post infection to determine the role of PD-1 during an Mtb infection. PET scans and 18FDG (18F-fluoro-2-deoxy-D-glucose) uptake, granuloma size and number, and colony forming units per granuloma were used to evaluate infection. Monkeys in both studies were necropsied at 15-16 weeks post infection. Treatment of Mtb infected monkeys with an anti-PD-1 antibody led to early euthanasia in one monkey due to severe pulmonary stress and another monkey developed cachexia and showed elevated 18FDG uptake in the lungs but survived until study termination. PD-1 expression in Mtb infected monkeys occurred more frequently on antigen specific CD4 and CD8 T cells in lung granulomas compared to other tissues. Mtb infected monkeys treated with an anti-PD-1 showed similar numbers of granulomas compared to controls, but these were characterized as larger granulomas, with increased 18FDG uptake and a higher bacterial load. The increased bacterial loads noted with PD-1 blockade occurred primarily within the site of infection (pulmonary lymph nodes and granulomas), suggesting it did not result in disseminated infection. The mechanism underlying the increased bacterial loads after PD-1 blockade in Mtb infection are not clear, but IFN γ and TNF have been previously implicated. Evaluation of cytokines in granulomas of isotype and anti-PD-1 treated monkeys indicated that IFN γ , TNF, and

IL-18 were the most dysregulated cytokines and positively correlated with bacterial loads after PD-1 blockade. Data from Kauffman et al. (2021) indicate that blockade of PD-1 with an anti-PD-1 antibody can exacerbate Mtb infection in monkeys consistent with previous findings noted in PD-1 knockout mice infected with Mtb (Lazar-Molnar et al. 2010).

X	X
Kelie M. Reece, PhD Primary Reviewer	Claudia P. Miller, PhD Acting Supervisor

5. Clinical Pharmacology

5.1. Executive Summary

The FDA's Assessment

Penpulimab is a programmed death receptor 1 (PD-1) blocking antibody and it is a humanized immunoglobulin G1 (IgG1) immunoglobulin. The Applicant seeks accelerated approval of penpulimab for the treatment of patients with metastatic non-keratinizing nasopharyngeal carcinoma (NPC) in patients with disease progression on or after platinum-based chemotherapy and at least one other prior line of therapy. The proposed recommended dosage of penpulimab is 200 mg every 2 weeks (Q2W) in adult (b) (4)

The Clinical Pharmacology review team evaluated the immunogenicity, population pharmacokinetic (PPK), and exposure-response (E-R) data obtained from Study AK105-202. PPK analyses of the adult data suggest that there was no clinically significant effect of various covariates (e.g., age, sex, body weight, mild and moderate renal or hepatic impairment, and ECOG status) on penpulimab PK. The effect of race and ethnicity on penpulimab PK was not fully characterized, given that the patients in PPK dataset did not represent the overall racial and ethnic diversity of the US patient population. As part of the post-marketing requirement (PMR), the Applicant will collect sparse PK samples in the confirmatory clinical trial that includes sufficient representation of racial and ethnic diversity of the US patient population for supportive PPK analyses. The E-R analysis for efficacy was considered to be inconclusive, given that data were limited with one dose level. The E-R analyses for safety did not identify any apparent correlation between exposures and treatment emergent adverse events (any TEAEs or TEAEs $\geq$ Grade 3).

As Study AK105-202 was conducted in China, FDA assessed whether the proposed penpulimab dosing regimen is appropriate for the US population. Simulation based on the PPK model showed similar exposure of penpulimab in virtual patients from the US as compared to that of patients from China with mean exposure ($C_{max,ss}$, $C_{min,ss}$, and AUC_{ss}) difference less than 20% between these two populations. Therefore, the 200 mg Q2W dosing regimen appears appropriate for US patients based this analysis; the confirmatory trial will provide additional data to evaluate and confirm the acceptability of the recommended dosage in the US patient population.

(b) (4)

(b) (4) Refer to Section [6.2.2](#) for further details on therapeutic individualization.

The incidences of treatment emergent anti-drug antibodies (ADAs) and neutralizing antibodies (NABs) against penpulimab were 27% and 7%, respectively in Study AK105-202. There was no clear evidence of any clinically relevant impact of anti-penpulimab antibody development on penpulimab PK. There is insufficient information to characterize the effects of anti-penpulimab antibodies on the pharmacodynamics, safety, and efficacy of penpulimab.

5.1.1. Recommendations

The Office of Clinical Pharmacology has reviewed the information and data submitted in BLA 761258. This BLA is approvable from a clinical pharmacology perspective with no major review issues as described in [Table 3](#) below.

Table 3 – FDA: Clinical Pharmacology Review Issues and Recommendations

Review Issue	Recommendations and Comments
Pivotal and supportive evidence of effectiveness	The primary evidence of effectiveness is derived from 111 adult patients with metastatic nonkeratinizing NPC who were enrolled in Study AK105-202 and were treated with penpulimab 200 mg Q2W. The ORR (95% CI) was 30% (95% CI 21, 39); 73% of responders had a DoR greater than 6 months and 39% had a DoR greater than 9 months (median DoR not reached). Refer to the FDA's assessment in Section 8.1.2 , for details.
General dosing instructions	The Applicant's proposed dosing regimen for penpulimab is 200 mg Q2W in adult (b) (4). This dosing regimen in adult patients is supported by the clinical benefit as demonstrated by the ORR and DoR with a manageable safety profile observed in Study AK105-202. (b) (4) Refer to Section 6.2.1 and 6.2.2 , General Dosing and Therapeutic Individualization for further details.
Dosing in patient subgroups (intrinsic and extrinsic factors)	No dosage adjustment is recommended for intrinsic and extrinsic patient factors (age, body weight, sex, serum albumin, baseline LDH, mild and moderate renal or hepatic impairment, tumor type, and ECOG status) according to the results of PPK analyses.
Immunogenicity	Of the 119 evaluable patients in Study AK105-202 with NPC who received penpulimab 200 mg Q2W, 27% of patients tested positive for treatment emergent ADAs and 7% of patients for treatment-emergent NABs against penpulimab. Per the PPK analysis, treatment emergent ADA had no significant impact on penpulimab PK. There is insufficient information to characterize the effects of anti-penpulimab antibodies on the pharmacodynamics, safety, and efficacy of penpulimab.
Labeling	Review of the proposed labeling recommendations is pending due to complete response action.

Source: Module 5.3

Abbreviations: ADA, anti-drug antibody; CI, confidence interval; DoR, duration of response; ECOG, Eastern Cooperative Oncology Group; LDH, lactic dehydrogenase; Nab, neutralizing antibodies NPC, nasopharyngeal carcinoma; ORR, overall response rate; PK, pharmacokinetic; PPK, population pharmacokinetic; Q2W, every 2 weeks.

5.2. Summary of Clinical Pharmacology Assessment

Data

Penpulimab is a humanized immunoglobulin G1 (IgG1) monoclonal antibody targeting programmed cell death-1 (PD-1). Penpulimab binds specifically to human PD-1 with high affinity and competitively blocks the binding of PD-1 to its ligand programmed cell death-1 (PD-L1) and programmed cell death ligand-2 (PD-L2), thereby relieving immunosuppression of T lymphocytes, promoting the proliferation of lymphocytes and the secretion of related cytokines, and ultimately recovering cytotoxic activities of T cells to block tumor growth.

The typical antibody structure of penpulimab is composed of two heavy chains of IgG1 and two light chains of kappa subclass, which are covalently linked to each other by disulfide bonds. Penpulimab was engineered to eliminate Fc receptor mediated effector function, consequently, may prevent ADCC and ADCP mediated depletion of PD-1 expressing T lymphocytes. This may help preserve maximal anti-tumor activity of lymphocytes. The Fc mutation also causes reduced induction of proinflammatory cytokines like IL-6 and IL-8, which may help reduce immune related adverse events commonly seen for a typical PD-1 antibody.

Pharmacokinetic (PK) data of penpulimab were derived from 4 clinical studies. A total of 379 patients were included in the population PK analysis and 320 patients (including 31 patients who underwent intensive sampling) were included in the non-compartmental model-based PK analysis. The above patients received penpulimab at 1, 3 or 10 mg/kg or 200 mg Q2W. According to the non-compartmental analysis, the drug exposure, expressed as peak concentration (C_{max}) and area under the concentration-time curve from 0 h to day 14 postdose (AUC_{0-14d}) increased proportionally within the dose range of 1 mg/kg to 10 mg/kg. Following single-dose and multi-dose IV infusion of penpulimab (200 mg Q2W, n=11), the mean peak concentration at steady-state ($C_{max,ss}$) was 136 $\mu\text{g/mL}$, the mean average concentration at steady-state ($C_{avg,ss}$) was 88.5 $\mu\text{g/mL}$, the mean trough concentration at steady-state ($C_{min,ss}$) was 58.7 $\mu\text{g/mL}$, the mean area under the concentration-time curve at dose interval ($AUC_{(0-\tau)}$) was 29900 $\text{h}\cdot\mu\text{g/mL}$. The mean accumulation rate ($\pm\text{SD}$) calculated based on C_{max} and area under the concentration-time curve (AUC) on Cycle3 Day15 (the 6th dose) was 1.84 ± 0.495 and 2.69 ± 0.749 , respectively, a likely tendency of drug accumulation following multi-dose administration of penpulimab.

Penpulimab is administered via IV infusion and the drug directly enters blood circulation. According to population PK simulation, after a single IV infusion of penpulimab at 200 mg, the volume of distribution (V_z) ($\pm\text{SD}$) was 7.18 ± 2.52 L, the volume of distribution at steady-state (V_{ss}) ($\pm\text{SD}$) was 6.59 ± 2.01 L, the clearance (CL) ($\pm\text{SD}$) was 0.223 ± 0.0740 L/d, and the half-life ($t_{1/2}$) ($\pm\text{SD}$) was 23.9 ± 9.98 days.

Receptor occupancy (RO) is an important measure of the in vivo biological activity of penpulimab and also an important parameter underlying the determination of the recommended dose in clinical studies. In the Phase Ia clinical study conducted in Australia

(AK105-101 study), patients with advanced solid tumors received penpulimab therapy (1, 3 and 10 mg/kg Q2W). PD-1 RO reached 80% to 100% starting from two days post-dose for all these cohorts. No apparent correlation between RO value and dose level was noted.

The Applicant's Position

Penpulimab exhibited linear PK in patients who received penpulimab by intravenous administration within the dose range of 1 mg/kg to 10 mg/kg. Population pharmacokinetic analysis indicated that distribution of penpulimab was limited to the central vascular compartment with an elimination half-life of 23.9 days and mild drug accumulation upon repeat dosing.

The FDA's Assessment

The FDA agrees with the Applicant's position that the exposure to penpulimab increased dose proportionally over the dose range of 1 mg/kg to 10 mg/kg after a single dose. It is unknown whether the clearance of penpulimab is time-dependent after multiple doses given the limited availability of PK data.

5.2.1. General Dosing

Data

In the Phase Ia dose-escalation trial, no DLT occurred at the highest dose cohort of 10 mg/kg Q2W and no maximum tolerated dose (MTD) was explored, therefore the maximum administered dose (MAD) for this study was 10 mg/kg Q2W. Phase Ia PK data showed a linear relationship between exposure of penpulimab and dose over the dose range of 1 mg/kg Q2W to 10 mg/kg Q2W; receptor occupancy analysis showed 80% to 100% PD-1 receptor occupancy starting on day 2 after administration. There was no significant difference in receptor occupancy between 1, 3 and 10 mg/kg doses level. The efficacy results showed anti-tumor activities at doses ranging from 1 mg/kg to 10 mg/kg Q2W. Since higher drug concentrations can be obtained with the 3 mg/kg dosing regimen than with the 1 mg/kg dosing regimen, this may ensure to achieve more stable blood concentrations after multiple doses for better sustained receptor occupancy.

Results of study AK105-101 showed that, following administration of penpulimab 1 mg/kg, 3 mg/kg, and 10 mg/kg as a single IV infusion, drug exposure expressed as C_{max} and $AUC_{(0-14d)}$ increased proportionally with dose from 1 mg/kg to 10 mg/kg; the 90% confidence interval (CI) of β values of $AUC_{(0-14d)}$ and C_{max} was 0.676-1.15 and 0.844-1.13, respectively; namely, a linear PK profile was exhibited.

Based on the final PopPK model, serum concentrations were simulated for 379 patients after IV infusion of 200 mg penpulimab, and PK parameters were calculated by non-compartmental modeling. Simulated PK parameters following single-dose IV infusion of penpulimab 200 mg are

as follows: the median T_{max} was 1.00 h, the mean C_{max} was 62.7 ± 14.3 $\mu\text{g/mL}$, the mean $AUC_{(0-\infty)}$ was 23700 ± 7560 $\mu\text{g}\cdot\text{h/mL}$, the mean CL was 0.223 ± 0.0740 L/d, the mean V_z was 7.18 ± 2.52 L, the mean V_{ss} was 6.59 ± 2.01 L, the mean $t_{1/2}$ was 23.9 ± 9.98 d, and the mean residence time (MRT) extrapolated to infinity (MRT_{inf}) was 31.9 ± 12.9 d.

Based on the final population PK model, serum penpulimab concentrations at each time point within 42 weeks following multi-dose (200 mg Q2W) IV infusion in 379 patients were simulated. Following multi-dose administration of penpulimab 200 mg Q2W, the steady state was reached at about Week 16 (after the 8th dose); the mean steady-state trough concentration ($\pm$ SD) at Week 16 was 49.4 ± 17.5 $\mu\text{g/mL}$.

Population PK simulation of steady-state drug concentrations following administration of penpulimab 200 mg Q2W in 379 patients are presented. *In vitro* studies indicated 0.2 $\mu\text{g/mL}$ penpulimab was associated with a receptor occupancy close to 90%. Population PK analysis showed that, with a penpulimab dose of 200 mg Q2W, the steady-state trough concentration in more than 97.5% of patients was >10 $\mu\text{g/mL}$, which is 100-fold higher than those at which 80% of the receptors (0.1 $\mu\text{g/mL}$) could be occupied or 20-fold higher than those at which 90%~100% of the receptors (0.5 $\mu\text{g/mL}$) could be occupied.

Simulated drug concentrations of 379 patients after IV infusion of penpulimab with fixed dose regimen (200 mg Q2W) and body weighted adjustment (3 mg/kg Q2W) using a population PK model showed that the trough concentration, peak concentration, and variation range were basically the same between these two regimen, thus supporting a fixed dose regimen of 200 mg Q2W.

A logistic regression analysis was performed to examine exposure-efficacy and exposure-safety relationship. Results of the univariable analyses evaluating relationships between efficacy (Complete response or partial response: CR/PR) and PK exposure (observed serum concentration at: Cycle 1 Day 1 end of infusion, Cycle 2 Day 1 before infusion, Cycle 5 Day 1 before infusion, or simulated steady state exposure) demonstrated a relatively flat exposure-response relationship without dose dependency.

The relationship between PK exposure (the same as above) and safety response (any TRAE or TRAE ≥ 3) were analyzed by logistics regression. And the result showed no apparent correlation between safety and drug exposure.

The Applicant's Position

The recommended dosage of penpulimab was 200 mg Q2W administered with intravenous infusion (IV). Dose selection is based on the following considerations:

- In all patients treated with penpulimab therapy, penpulimab 200 mg Q2W was safe and tolerable, and there was no apparent correlation between the incidence of TRAEs and drug exposure.

- Penpulimab 200 mg Q2W showed notable clinical benefits in patients with NPC and demonstrated a relatively flat exposure-response curve without apparent correlation between efficacy (CR/PR) and drug exposure.
- In vitro studies showed that 0.5 µg/mL of penpulimab resulted in 90-100% receptor occupancy. According to the population PK analysis of penpulimab, at the dose of 200 mg Q2W, more than 97.5 % of patients achieved steady-state trough concentrations (10 µg/mL), which is at or above 20 times the concentrations corresponding to 90-100% receptor occupancy.
- In all patients who received penpulimab 200 mg Q2W, treatment emergent ADA did not have a significant impact on PK exposure.
- Population PK modeling analysis showed that concentration ranges of penpulimab following administration at a fixed dose (200 mg Q2W) and at a body-weighted dose (3 mg/kg Q2W) were basically consistent, supporting the 200 mg Q2W fixed-dose regimen.

The FDA's Assessment

FDA generally agrees that the proposed recommended dosage of 200 mg Q2W is supported by the observed clinical safety, efficacy, and pharmacodynamic data. FDA disagrees that it can be concluded that the E-R analysis for efficacy is relatively flat; FDA concludes that the E-R analysis for efficacy is inconclusive given that the analysis only included one dose level. FDA also found no correlation between safety and penpulimab exposure given FDA did not identify any apparent correlation between the incidence of TEAEs and drug exposure (refer to Appendix 19.4 for details).

As Study AK105-202 was conducted in China, FDA assessed whether the proposed penpulimab dosing regimen is appropriate for the US population. Simulation based on PPK model showed similar exposure of penpulimab in US virtual patients as compared to that in Chinese patients with mean exposure ($C_{max,ss}$, $C_{min,ss}$, and AUC_{ss}) difference less than 20% between these two populations. Therefore, the 200 mg Q2W dosing regimen appears appropriate for US patients based on PK comparability with Chinese patients.

5.2.2. Therapeutic Individualization

Data

Intrinsic factors that might have an impact on penpulimab PK were subjected to covariate analysis by the population PK approach to identify main contributors to the PK variability.

Covariate analysis was performed with respect to sex, age, race, weight, immunogenicity, hepatic function related factors [including total bilirubin (TBIL), aspartate aminotransferase (AST), alanine aminotransferase (ALT), alkaline phosphatase (ALP)], renal function related factors (creatinine clearance (CLCr) estimated by Cockcroft Gault formula), serum albumin

(ALB), lactic dehydrogenase (LDH), tumor type, and Eastern Cooperative Oncology Group (ECOG) score.

The results of the covariate analyses demonstrated that body weight and sex had statistically significant effects on CL and V_1 , and ALB and ECOG had significant effects on CL. Initial analysis found a trend of AST effect on V_2 , which may result from the influence of an extreme value; the final covariate model removed the effect of AST on V_2 . To further investigate the impacts of covariates on PK of penpulimab, the relationship between the identified covariates and exposure in steady state was assessed. Impacts of covariates retained in the final model on the area under concentration-time curve within the dosing interval in steady state (AUC_{ss}), the steady-state maximum observed concentration ($C_{max,ss}$) and the steady-state minimum observed concentration ($C_{trough,ss}$) are described in [Table 4](#) the table below. Based on these results, FDA concludes that the effects of these covariates were not clinically meaningful (defined as within 30% percentage of change).

Table 4 – Applicant: Population PK Parameter Estimates From the Final Model for Penpulimab

	AUC_{ss}		$C_{max, ss}$		$C_{trough, ss}$	
	GMR	95% CI	GMR	95% CI	GMR	95% CI
ECOG 0 vs. ECOG > 1	0.865	0.850-0.880	0.934	0.924-0.945	0.816	0.797-0.836
10% quantile of ALB vs a typical patient	0.879	0.864-0.894	0.936	0.925-0.947	0.835	0.816-0.856
90% quantile of ALB vs a typical patient	1.093	1.074-1.112	1.052	1.040-1.064	1.123	1.097-1.149
10% quantile of body weight vs typical patients	1.102	1.084-1.122	1.127	1.115-1.140	1.106	1.080-1.132
90% quantile of body weight vs typical patients	0.882	0.867-0.898	0.874	0.864-0.884	0.869	0.849-0.890
Female to male	0.866	0.851-0.881	1.002	0.991-1.013	0.794	0.775-0.813

Source: Module 5.3.3.5 Population Pharmacokinetics Pharmacodynamics Report Table 21.

Note: A typical patient, ie, a male patient with a body weight of 62 kg (median), ALB of 42.5 g/L (median), and ECOG of 1

Abbreviations: ALB, albumin; ECOG, Eastern Cooperative Oncology Group; AUC_{ss} , area under the serum concentration-time curve during the dosing interval at steady state, CI, confidence interval; $C_{max, ss}$, maximum concentration at steady state; $C_{trough,ss}$, trough concentration at steady state; GMR, geometric mean ratio, PK, pharmacokinetic

Age

Among the 379 patients included into the population PK analysis set, the median age was 51 years (range: 18-91 years); patients >65 years of age accounted for 20.1% (n=76). Age within this range did not have a statistically significant impact on population PK parameters of penpulimab.

Sex

Females accounted for 37.2% (n=141), and males accounted for 62.8% (n=238). The CL and apparent volume of distribution of central compartment V_1 of penpulimab were 15.9% and 12.8% lower in females than in males with the same weight and conditions, indicating sex had a statistically significant impact on CL and V_1 . The female/male geometric mean ratio of exposure indicators AUC_{ss} , $C_{max,ss}$ and $C_{trough,ss}$ was 0.866, 1.002 and 0.794, respectively; namely, the

differences were all within 30%. Overall, the impact of sex on PK exposure was not clinically significant.

Race

There were 291 (76.8%) Asians, and 88 (23.2 %) non-Asian patients. Population PK covariate screening results showed that race did not have a statistically significant impact on population PK parameters of penpulimab.

Body Weight

The median weight was 62.0 kg (range: 35.2 - 113.0 kg). Population PK covariate screening results showed that penpulimab Volume of distribution of central compartment (V_1) increased with CL and body weight. In a patient with an extremely low weight (42 kg, 2.5% quantile) comparing to the patient with median weight (62 kg), V_1 and CL was 16.0% and 13.2% lower, respectively; In a patient with an extremely high weight (98.46 kg, 97.5% quantile) comparing to the patient with median weight (62 kg), V_1 and CL was 29.2% and 24.1% higher, respectively. Weight had a statistically significant impact on CL and V_1 . The geometric mean ratios of PK parameters (AUC_{SS} , $C_{max,SS}$, $C_{trough,SS}$) in patients with weights at 10% and 90% quantile levels versus the typical patient (weight at the median level) were between 0.8 and 1.2; namely, the differences were less than 30%. Hence, it is considered that the impact of weight on AUC_{SS} , $C_{max,SS}$ and $C_{trough,SS}$ was not clinically significant.

Renal Impairment

In accordance with the Guidance on Pharmacokinetics in Patients with Impaired Renal Function released by FDA in 2020, renal impairment in the 379 patients included into the population PK analysis set was graded by creatinine clearance (CLCr). The grading criteria and included patients are summarized as follows. Normal renal function, $CLCr \geq 90$ mL/min (n=220); mild renal impairment: $CLCr < 90$ mL/min and $CLCr \geq 60$ mL/min (n=113); moderate renal impairment: $CLCr < 60$ mL/min and $CLCr \geq 30$ mL/min (n=45); 1 patient with severe renal impairment ($CLCr < 30$ mL/min) has been included.

Through population PK covariate screening, it was found that the renal function related factor (CLCr) did not have a statistically significant impact on population PK parameters of penpulimab. The results showed that there was no significant difference in clearance between patients with mild or moderate renal impairment and patients with normal renal function.

Data of penpulimab in patients with severe renal impairment are not adequate.

Hepatic Impairment

Hepatic impairment of the 379 patients included into the population PK analysis set was graded by Total bilirubin (TBIL) and Aspartate Aminotransferase (AST). Grading criteria and included

patients are summarized as follows. Normal hepatic function: $TBIL < \text{upper limit of normal (ULN)}$ and $AST < ULN$ ($n=286$); mild hepatic impairment: $TBIL \leq ULN$ and $AST > ULN$ or $TBIL = 1.0$ to $1.5 \times ULN$, regardless of AST ($n=84$); moderate hepatic impairment: $TBIL = 1.5$ to $3.0 \times ULN$, regardless of AST ($n=9$); no patient with severe hepatic impairment ($TBIL > 3.0 \times ULN$, regardless of AST) has been included.

Through population PK covariate screening, it was found that the hepatic function related factors ($TBIL$, AST , Alanine Aminotransferase [ALT] and Alkaline Phosphatase [ALP]) did not have a statistically significant impact on population PK parameters of penpulimab. The results showed that there was no significant difference in clearance between patients with mild or moderate hepatic impairment and patients with normal hepatic function. Data of penpulimab in patients with severe hepatic impairment are not adequate.

Tumor Type

Among the 379 patients included into the population PK analysis set, there were 130 (34.3%) patients with nasopharyngeal carcinoma and 249 (65.7%) with other tumor types. Population PK covariate screening results showed that tumor type did not have a statistically significant impact on population PK parameters of penpulimab .

Eastern Cooperative Oncology Group (ECOG) Score

Among the 379 patients included into the population PK analysis set, there were 120 (31.7%) patients with an Eastern Cooperative Oncology Group (ECOG) score of 0 and 259 (68.3%) patients with an ECOG score of 1. Population PK covariate screening results showed that ECOG score did not have a statistically significant impact on PK parameters of penpulimab .

Serum Albumin

Among the 379 patients included into the population PK analysis set, the median albumin (ALB) was 42.50 g/L (range: 22.00 - 54.50 g/L). Population PK covariate screening results showed that penpulimab CL decreased with increase of ALB ; Clearance (CL) of the patient with ALB at the 2.5% quantile level was 25.6% higher than CL of the patient with ALB at the median level; CL of the patient with ALB at the 97.5% quantile was 12.30% lower than CL of the patient with ALB at the median level. Therefore, ALB had a statistically significant impact on CL . The geometric mean ratios of PK parameters (AUC_{SS} , $C_{max,SS}$, $C_{trough,SS}$) in patients with ALB at 10% or 90% quantile levels versus the typical patient (ALB at the median level) were between 0.8 and 1.1; namely, the differences were less than 30%. Hence, the impact of ALB on AUC_{SS} , $C_{max,SS}$ and $C_{trough,SS}$ was not clinically significant.

Impacts of Extrinsic Factors on PK

Impacts of extrinsic factors (e.g., food, alcohol, or smoking) on penpulimab PK have not been assessed in this study.

Impacts of Immunogenicity on PK

Impacts of post-baseline positive/negative ADA on PK parameters were analyzed by population PK analysis approach. Population PK covariate screening results showed that immunogenicity did not have a statistically significant impact on population PK parameters of penpulimab .

The Applicant's Position

The population PK profile of penpulimab could be described using a two-compartmental model with first order elimination. Covariate analysis showed that age, race, immunogenicity, hepatic function related factors (TBIL, AST, ALT, ALP), renal function (CLCr), tumor type and LDH score did not have an impact on PK parameters of penpulimab; the impacts of weight, ALB, ECOG and sex on CL and impacts of weight and sex on V_1 were statistically significant, but these factors were not clinically significant.

According to population PK analysis results, compared to patients with normal renal function, mild or moderate renal impairment did not have a significant impact on PK and does not necessitate dose modifications; compared to patients with normal hepatic function, mild or moderate hepatic impairment did not have a significant impact on PK and does not necessitate dose modifications; data in patients with severe hepatic or renal function are inadequate.

The recommended dosage of penpulimab was 200 mg Q2W administered intravenous infusion (IV). This fixed dose (200 mg Q2W) with consideration to the covariate estimated and analyzed by PopPk is appropriate.

No dose adjustment is required based on age, race, body weight or sex. No dose adjustment is required in patients with mild, moderate renal or hepatic impairment, data of penpulimab in patients with severe renal or hepatic impairment are not adequate.

Use of penpulimab in this age group is supported by evidence from adequate and well-controlled studies of penpulimab in adults with additional population pharmacokinetic data demonstrating that age and body weight had no clinically meaningful effect on the steady state exposure of penpulimab (b) (4)

The FDA's Assessment

The FDA agrees with the Applicant's position that no dosage adjustment is required based on intrinsic factors including age (18-91 years), sex, body weight (35-113 kg), serum albumin (22-54.5 g/L), baseline LDH, ECOG score, tumor type, and mild or moderate renal and hepatic impairment according to the results of PPK analyses. However, as 77% of subjects in the population PK dataset were from a single region (China) and the non-Asian population in the population PK analysis does not represent the racial and ethnic diversity of the US population, the effect of race and ethnicity on the PK of penpulimab has not been fully characterized. As a post-marketing requirement, the Applicant will conduct a multiregional randomized clinical trial that includes sufficient representation of racial and ethnic subpopulations reflecting the US population of patients with non-keratinizing nasopharyngeal carcinoma to confirm the clinical benefit of penpulimab in the intended patient population. The Applicant will collect sparse PK samples in the trial for supportive PPK analyses of the effect of race and ethnicity on penpulimab PK.

(b) (4)

5.2.3. Outstanding Issues

Data

Not Applicable.

The Applicant's Position

Not Applicable.

The FDA's Assessment

There are no outstanding issues.

5.3. Comprehensive Clinical Pharmacology Review

5.3.1. General Pharmacology and Pharmacokinetic Characteristics

Data

The clinical pharmacology of penpulimab has been studied in patients with malignant solid tumors such as NPC or non-solid tumors such as cHL who received penpulimab by intravenous infusion administration once every 2 weeks. Levels of serum penpulimab were measured using validated methods and the results were used to evaluate PK parameters.

PK data of penpulimab were derived from 4 clinical studies. A total of 379 patients were included into population PK analysis, and 320 patients (including 31 who underwent intensive sampling) into non-compartmental model-based PK analysis. The above patients received penpulimab at 1, 3 or 10 mg/kg or 200 mg Q2W. The PK profile is outlined as follows:

Absorption

Penpulimab is administered via IV infusion, and the drug directly enters blood circulation.

Distribution

As the sampling interval after the first dose was short (Day 1 to Day 15), the serum concentration of penpulimab had not reached the terminal part of the elimination phase, so V_z calculated in non-compartmental PK analysis was analyzed based on population PK simulated data.

According to population PK simulation, following administration of penpulimab 200 mg as a single IV infusion, the $V_z (\pm SD)$ of penpulimab was 7.18 ± 2.52 L, and the $V_{ss} (\pm SD)$ was 6.59 ± 2.01 L.

Elimination

As the sampling interval after the first dose was short (Day 1 to Day 15), the serum concentration of penpulimab had not reached the terminal part of the elimination phase, so CL and $t_{1/2}$ calculated in non-compartmental PK analysis were analyzed based on population PK simulated data.

According to population PK simulation, following administration of penpulimab 200 mg as a single IV infusion, the CL($\pm$ SD) of penpulimab was 0.223 ± 0.0740 L/d, and the half-life($t_{1/2}$)($\pm$ SD) was 23.9 ± 9.98 d.

Linearity/Non-Linearity

According to the non-compartmental analysis, the drug exposure, expressed as C_{max} and $AUC_{(0-14d)}$, increased proportionally with dose within the dose range of 1 mg/kg to 10 mg/kg following single-dose IV infusion of penpulimab. Following multi-dose IV infusion of penpulimab (200 mg Q2W, n=11), the mean accumulation rate ($\pm$ SD) calculated based on C_{max} and AUC on Cycle3Day15 (the 6th dose) was 1.84 ± 0.495 and 2.69 ± 0.749 , respectively.

Steady-State

According to population PK simulation, the penpulimab concentration was approximate to the steady state at Week 16 following IV infusion of penpulimab 200 mg Q2W. The mean steady-state trough concentration ($\pm$ SD) at Week 16 was 49.4 ± 17.5 μ g/mL.

Other Population PK Analysis Results

The population PK profile of penpulimab could be described using a two-compartmental model with first order elimination. Typical values of penpulimab PK parameters based on the final model were as follows: CL, 0.233 L/day; V_1 , 3.40 L; distribution rate from central compartment to peripheral compartment (Q), 0.706 L/day; volume of distribution of peripheral compartment (V_2) 3.02 L. Covariate analysis showed that age, race, immunogenicity, hepatic function related factors (TBIL, AST, ALT, ALP), renal function (CLCr), tumor type and LDH score did not have an impact on PK parameters of penpulimab; the impacts of weight, ALB, ECOG and sex on CL and impacts of weight and sex on V_1 were statistically significant, but these factors were not clinically significant.

According to population PK analysis results, compared to patients with normal renal function, mild or moderate renal impairment did not have a significant impact on PK and does not necessitate dose modifications; compared to patients with normal hepatic function, mild or moderate hepatic impairment did not have a significant impact on PK and does not necessitate dose modifications; data in patients with severe hepatic or renal function are inadequate.

Immunogenicity Results

In clinical studies in patients treated with penpulimab at a dose of 1 mg/kg every 2 weeks, 3 mg/kg every 2 weeks, 200 mg every 2 weeks, or 10 mg/kg every 2 weeks, 43 (12.3%) of 349 evaluable patients tested positive for treatment-emergent anti-penpulimab antibodies of whom 14 (4.0%) patients had neutralizing antibodies against penpulimab. The treatment emergent ADA did not have a significant impact on the PK exposure or safety.

Penpulimab

For NPC patients receiving penpulimab 200 mg Q2W, the incidence of ADA positive after administration was 5.9% (7/119), with neutralizing antibodies detected in 3.4% (4/119) patients. Treatment emergent ADA did not have a significant impact on PK exposure, safety, or efficacy (CR/PR).

The Applicant's Position

The information from clinical studies contributing to the clinical pharmacology evaluation of penpulimab was included in the submitted reports (*Module 2.7.2 Summary of Clinical Pharmacology, Module 5.3.5.2 AK105-202 CSR*). Penpulimab exhibited linear PK (from dose 1 mg/kg to 10 mg/kg) with an estimated terminal half-life of 23.9 days and indicating a likely tendency of drug accumulation following multi-dose administration of penpulimab.

No dedicated clinical drug-drug interaction studies have been conducted in humans. Penpulimab is a humanized monoclonal antibody, PK interactions with other drugs have not been studied. As monoclonal antibodies are not metabolized by cytochrome P450 (CYP) or other drug metabolizing enzymes, inhibition, or induction of these enzymes by co-administered medicinal products is not anticipated to affect the pharmacokinetics of penpulimab.

Overall, penpulimab administered by intravenous infusion at fixed 200mg Q2W regimen, demonstrated a favorable benefit-risk profile for patients with metastatic NPC patients in patients with metastatic nonkeratinizing NPC with disease progression on or after platinum-based chemotherapy and at least one other prior line of therapy.

The FDA's Assessment

The FDA agrees with the Applicant's summary of the PK characteristics of penpulimab. Regarding the immunogenicity results, two different assays were used to characterize the ADAs and NABs in the Phase 1 study conducted in Australia and the three Phase 2 studies conducted in China, respectively. (b) (4)

In an Information Request, the Applicant was asked to re-analyze the immunogenicity data by considering ADA positivity as the occurrence of treatment-emergent ADAs at one or more post-dose time points relative to the baseline for each individual patient. According to the updated analysis, of the 119 evaluable patients in Study AK105-202 with NPC who received penpulimab 200 mg Q2W, 27% of patients tested positive for treatment emergent ADA and 7% of patients for treatment-emergent NAB. Considering all clinical studies conducted in China using the same bioanalytical assay at the proposed recommended dosage of 200 mg Q2W, 34% of patients tested positive for treatment emergent ADA and 7% of patients for treatment emergent NAB. Per PPK analysis, treatment emergent ADA had no significant impact on penpulimab PK. There is insufficient information to characterize the effects of anti-penpulimab antibodies on the safety and efficacy of penpulimab.

5.3.2. Clinical Pharmacology Questions

5.3.2.1. *Does the Clinical Pharmacology Program Provide Supportive Evidence of Effectiveness?*

Yes, the clinical pharmacology program provides supportive evidence of penpulimab effectiveness in patients with metastatic nonkeratinizing NPC with disease progression on or after platinum-based chemotherapy and at least one other prior line of therapy.

Data

For AK105-202 study, patients with stage IVb NPC who have failed at least 2 lines of prior therapy containing platinum-based chemotherapy were enrolled in the study. Among the 111 patients included in the primary efficacy population, 33 patients had a BOR of confirmed CR or PR based on IRRC assessment, with a confirmed ORR of 29.7% (95% CI: 21.4%, 39.1%).

To support the clinical efficacy observed with penpulimab dosed at fixed 200mg Q2W regimen, exposure-efficacy relationship was evaluated in NPC population (AK105-202 study), see [Module 2.7.2, Section 3.3.1]. Univariate logistic regression analysis was conducted to assess the relationship between penpulimab PK exposures and model-predicted ORR response (CR/PR). Results of the univariate analyses demonstrated a relatively flat exposure-response curve without apparent correlation between efficacy (CR/PR) and PK exposure (observed serum concentration: Cycle 1 Day 1 end of infusion, Cycle 2 Day 1 before infusion, Cycle 5 Day 1 before infusion, or simulated steady state exposure such as $AUC_{\tau,SS}$, $C_{max,SS}$, $C_{trough,SS}$).

The Applicant's Position

Penpulimab 200 mg Q2W showed notable clinical benefits in patients with metastatic NPC and demonstrated a relatively flat exposure-response curve as above without apparent correlation between efficacy (CR/PR) and drug exposure. Penpulimab therapy is recommended treatment until disease progression or intolerable toxicity to allow continued blockade of the PD-1 pathway. The safety profile of penpulimab 200 mg Q2W in 130 patients with NPC from AK105-202 is consistent with the well-characterized safety profile of penpulimab 200 mg/kg Q2W in 372 patients with various solid tumors or blood tumors and in line with the known safety profile of other mAbs with similar mechanism of action.

The FDA's Assessment

FDA generally agrees with the Applicant's position. However, FDA notes that the Applicant's E-R analysis for efficacy is inconclusive due to limited exposure range of penpulimab at one dose level.

5.3.2.2. Is the Proposed Dosing Regimen Appropriate for the General Patient Population for Which the Indication Is Being Sought?

Yes, penpulimab administered by intravenous infusion at 200mg Q2W regimen is appropriate for patients with metastatic nonkeratinizing NPC with disease progression on or after platinum-based chemotherapy and at least one other prior line of therapy. The proposed dosing regimen is supported by the observed efficacy, safety, and PK data.

Data

In the Phase Ia dose-escalation trial, no DLT occurred at the highest dose cohort of 10 mg/kg Q2W and no MTD was explored, therefore the maximum administered dose(MAD) for this study was 10 mg/kg Q2W. Phase Ia PK data showed a linear relationship between exposure of penpulimab and dose over the dose range of 1 mg/kg Q2W to 10 mg/kg Q2W; receptor occupancy analysis showed 80% to 100% PD-1 receptor occupancy starting on day 2 after dosing. There was no significant difference in receptor occupancy between the 1, 3 and 10 mg/kg doses. According to the non-compartmental analysis, the drug exposure, expressed as C_{max} and AUC_(0-14d), increased proportionally with dose within the dose range of 1 mg/kg to 10 mg/kg following single-dose IV infusion of penpulimab.

In vitro studies showed that 0.5 µg/mL of penpulimab resulted in 90-100% receptor occupancy. According to the population PK analysis of penpulimab, at the dose of 200 mg Q2W, more than 97.5 % of patients achieved steady-state trough concentrations (10µg/ml), which is at or above 20 times the concentrations corresponding to 90-100% RO.

Univariate logistic regression analysis was conducted to assess the relationship between penpulimab PK exposures and model-predicted ORR response (CR/PR). Results of the univariate analyses demonstrated a relatively flat exposure-response curve without apparent correlation between efficacy (CR/PR) and PK exposure (observed serum concentration: Cycle 1 Day 1 end of infusion, Cycle 2 Day 1 before infusion, Cycle 5 Day 1 before infusion, or simulated steady state exposure such as AUC_{t,SS}, C_{max,SS}, C_{trough,SS}).

Similarly, univariate logistic regression analyses were performed to evaluate the relationship between safety and PK exposure. The same reference points described above were used for PK exposure, while safety endpoints were any TRAE or TRAE ≥ grade 3 occurred in the integrated penpulimab 200 mg population from 4 clinical monotherapy studies. The analysis showed no apparent correlation between safety parameters of interest and PK exposure.

The population PK result showed that age, race, immunogenicity, hepatic function related factors (TBIL, AST, ALT, ALP), renal function (CLCr), tumor type and LDH score have no impact on PK parameters of penpulimab. While weight, ALB, ECOG and sex on CL and impacts of weight and sex on V₁ were statistically significant, but these factors were not clinically significantly relevant. Renal function and hepatic function did not have a significant impact on PK and does not necessitate dose modifications; data in patients with severe hepatic or renal function are inadequate.

The Applicant's Position

The recommended dose of penpulimab is 200 mg Q2W via intravenous infusion (IV). The dose is selected based on efficacy and safety results, population PK modeling, simulation analyses, and ER analysis, as well as pharmacokinetic and pharmacodynamic analysis. These data and analysis support the selection of 200 mg Q2W as the dosing regimen for proposed indication.

The FDA's Assessment

FDA generally agrees with the Applicant's position. Refer to FDA's assessment in Section [6.2.1](#) on general dosing for more details.

5.3.2.3. Is an Alternative Dosing Regimen or Management Strategy Required for Subpopulations Based on Intrinsic Patient Factors?

No, penpulimab administered by intravenous infusion at 200mg Q2W regimen is appropriate for patients with metastatic nonkeratinizing NPC with disease progression on or after platinum-based chemotherapy and at least one other prior line of therapy.

Data

The population PK profile of penpulimab could be described using a two-compartmental model with first order elimination. Covariate analysis showed that age, race, hepatic function related factors (TBIL, AST, ALT, ALP), renal function (CLCr), tumor type and LDH score did not have an impact on PK parameters of penpulimab; the impacts of weight, ALB, ECOG and sex on CL and impacts of weight and sex on V_1 were statistically significant, but these factors were not clinically significantly relevant. There was no significant difference in clearance between patients with different grades of renal function or hepatic function.

In summary, mild or moderate renal impairment did not have a significant impact on penpulimab PK as compared with patients with normal renal function. Data of penpulimab in patients with severe renal impairment are not adequate. Mild or moderate hepatic impairment did not have a significant impact on penpulimab PK as compared with patients with normal hepatic function. Data of penpulimab in patients with severe hepatic impairment are not adequate.

The Applicant's Position

No dose adjustment is required based on age, race, body weight or sex. No dose adjustment is required in patients with mild, moderate, or severe renal impairment, data of penpulimab in patients with severe renal impairment are not adequate. No dose adjustment is required in patients with mild or moderate hepatic impairment. Data of penpulimab in patients with severe hepatic impairment are not adequate.

Use of penpulimab in this age group is supported by evidence from adequate and well-controlled studies of penpulimab in adults with additional population pharmacokinetic data demonstrating that age and body weight had no clinically meaningful effect on the steady state exposure of penpulimab, (b) (4)

The FDA's Assessment

FDA generally agrees with the Applicant's position. Refer to FDA's assessment in Section [6.2.2](#). on therapeutic individualization for more details.

5.3.2.4. Are There Clinically Relevant Food-Drug or Drug-Drug Interactions, and What Is the Appropriate Management Strategy?

No, penpulimab is intended for intravenous infusion administration; therefore, food-drug interactions are not expected.

The Applicant's Position

Penpulimab is intended for intravenous infusion administration; therefore, food-drug interactions are not expected.

Penpulimab is a humanized monoclonal antibody, and PK interactions with other drugs have not been studied. As monoclonal antibodies are not metabolized by cytochrome P450 (CYP) or other drug metabolizing enzymes, inhibition, or induction of these enzymes by co-administered medicinal products is not anticipated to affect the pharmacokinetics of penpulimab.

Penpulimab belongs to a class of drugs called immune checkpoint inhibitors. Because the mechanism of action of this class of drugs is to block inhibitory signal that prevents activation of T cells, there is a potential that these drugs may cause immune-mediated adverse drug reactions. Withhold or permanently discontinue penpulimab depending on severity. In general, if penpulimab requires interruption or discontinuation, administer systemic corticosteroid therapy (1 mg to 2 mg/kg/day prednisone or equivalent) until improvement to Grade 1 or less. Upon improvement to Grade 1 or less, initiate corticosteroid taper and continue to taper over at least 1 month. Consider administration of other systemic immunosuppressants in patients whose immune-mediated adverse reactions are not controlled by corticosteroid therapy.

The FDA's Assessment

The FDA agrees with the Applicant's position that no food-drug or drug-drug interactions for penpulimab are anticipated.

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X	X
Yajun Liu, Ph.D.	Jeanne Fourie Zirkelbach, Ph.D.
Ye Xiong, Ph.D. Primary Reviewer	Jiang Liu, Ph.D. Team Leader

6. Sources of Clinical Data

6.1. Table of Clinical Studies

Data

The penpulimab is being studied in clinical trials across different tumor types. The entire clinical development program, as of 3 Feb 2021, included 372 patients who have been exposed to one or more doses of penpulimab monotherapy at the 200 mg Q2W dose.

This application is based primarily on the totality of efficacy and safety data from patients in the target population of metastatic nasopharyngeal carcinoma at the 200 mg Q2W dose in Study AK105-202. Further supportive safety data for penpulimab are also included from 3 studies in patients of multiple tumor types.

Table 5 – Applicant: Listing of Clinical Trials Relevant to This BLA

Study Number	Study Design	Patient Population	Penpulimab Dosing Regimen	Number of Patients Enrolled and Treated as of DCO (N=372)
AK105-202	A multicenter, open-label, single-arm clinical study	Metastatic nasopharyngeal carcinoma	Penpulimab 200 mg Q2W	130
AK105-101	A multicenter, open-label, dose escalation and dose expansion study	Advanced solid tumors (in Australia)	Phase Ib dose expansion stage: Penpulimab 200 mg Q2W	83
AK105-201	A multicenter, open-label, single-arm clinical study	Relapsed or refractory cHL	Penpulimab 200 mg Q2W	94
AK105-204	A multicenter, open-label, single-arm, basket-designed clinical study	Advanced solid tumors	Penpulimab 200 mg Q2W	65

The Applicant's Position

All studies listed above are pertinent to the evaluation of safety penpulimab to support the proposed indication.

The FDA's Assessment

The FDA agrees with the Applicant's position that the primary efficacy and safety data supporting the proposed indication are derived from Study AK105-202. Pooled safety data from 372 patients enrolled in Studies AK105-202, AK105-101, AK105-201, and AK105-204 were used

to further define the safety profile of penpulimab 200 mg Q2W. As noted in [Table 5](#), 83 patients enrolled in Study AK105-101 and included in the pooled safety population were from Australia. The remaining 289 patients included in the pooled safety population were from China.

7. Statistical and Clinical Evaluation

7.1. Review of Relevant Individual Trials Used to Support Efficacy

7.1.1. Study AK105-202

7.1.1.1. Trial Design

The Applicant's Description

Study AK105-202 is a single-arm, open-label, multicenter phase II clinical study to evaluate the efficacy and safety of penpulimab in patients with metastatic nonkeratinizing NPC with disease progression on or after platinum-based chemotherapy and at least one other prior line of therapy. Patients were excluded from the study based on history of autoimmune disease, medical conditions requiring systemic immunosuppression, prior organ or allogeneic stem cell transplantation, prior treatment with anti-PD-1, anti-PD-L1 or CTLA-4 antibodies, active central nervous system (CNS) metastases, or ECOG performance score > 2.

Patients received penpulimab 200 mg intravenously every 2 weeks until disease progression as determined by the investigator, or unacceptable toxicity, or a maximum of 24 months, whichever occurred first. Administration of penpulimab was permitted beyond RECIST-defined disease progression if the patients were assessed as clinically beneficial and tolerated to the study drug by the investigator. Tumor measurements were performed every 8 weeks in first year and every 12 weeks thereafter, to determine response by RECIST v1.1 criteria.

The primary objective of the study was to evaluate the objective response rate (ORR) assessed by blinded independent radiology review committee (IRRC) per RECIST v1.1. Secondary objectives included duration of response (DoR), progression-free survival (PFS) and overall survival (OS).

The FDA's Assessment

The FDA agrees with the Applicant's description of the trial design for AK105-202. FDA notes that the study was conducted at 26 sites in China.

7.1.1.2. Study Endpoints

The Applicant's Description

- Primary Efficacy Endpoint: ORR assessed by IRRC per RECIST v1.1.
 - ORR is defined as the proportion of patients whose best overall response (BOR) is confirmed CR or PR. The confirmation of CR or PR by repeated imaging assessments is performed not less than 28 days (4 weeks) after the first observation of a CR or PR, and there is no evidence of PD between the follow-up of the first observed CR or PR and the follow-up for confirmation of CR or PR. BOR is defined as the best response recorded from the start of treatment until progressive disease or the last evaluable tumor assessment without prior to initiation of subsequent anti-cancer therapy.
- Key Secondary Efficacy Endpoints: duration of response (DoR)
- Other Secondary Endpoints:
 1. ORR assessed by investigator, Disease control rate (DCR), time to response (TTR), PFS assessed by IRRC and investigator per RECIST v1.1 and OS.
 2. Pharmacokinetic (PK) and immunogenicity assessment
 3. Safety: incidence and severity of adverse events, abnormal laboratory findings with clinical significance.
 4. Correlation analysis between the expression of EBV-DNA in blood and the anti-tumor activity of penpulimab.

The FDA's Assessment

The FDA agrees with the Applicant's description of the study endpoints. The final efficacy analysis is based upon a data cutoff of February 3, 2021. In a single arm trial such as Study AK105-202, FDA considers time-to-event endpoints such as PFS and OS as not interpretable and descriptive only. The efficacy evaluation of this study was based on ORR and DOR.

7.1.1.3. Statistical Analysis Plan and Amendments

The Applicant's Description

The sample size calculation was based on the primary endpoint of ORR. A total of 110 patients were needed for an ORR of 15% to be excluded using the lower limit of a two-sided 95% CI. If an ORR of 26% is assumed for penpulimab, there is 82% chance of observing at least 25 responses (an ORR of 22.7%), with the lower limit of the 95% CI excluding a historical response rate of 15%. In this study, an interim analysis was originally planned after at least 110 patients were enrolled and completed at least 16 weeks of follow-up (an interval between the data cutoff date and the date of first dose $\geq$ 16 weeks), and the results of the interim analysis was planned to be used for communicating with the regulatory agencies. There were no plans to

stop the trial based on either of these analyses and no formal statistical adjustments were planned.

Per communication with the FDA with respect to marketing application, in order to provide an adequate assessment of durability of response in a marketing application, all responders would have follow-up of at least 6 months past onset of response. Given the refractory population with metastatic NPC, approximately 50% of responders having follow up of at least 6 months past onset of response is acceptable to support filing of the market application. An interim analysis of efficacy was conducted after approximately 110 patients treated with penpulimab had an opportunity to be followed for at least 8 months prior to data cutoff date (to allow at least 6 months follow-up past onset of response assuming the response occurs at the first follow-up scan). The efficacy results from this interim analysis included in the initial submission for marketing application were presented below.

Definition of Key Analysis Sets

Enrollment Analysis Set

The Enrollment Analysis Set (ENR) includes all patients who have signed the ICF and been enrolled into the study.

Primary Efficacy Population

The Primary Efficacy Population includes all patients in the ENR who have received at least one dose of penpulimab and meet the following inclusion criteria:

- Patients diagnosed with disease stage of IVb in accordance with Chinese Nasopharyngeal Carcinoma Staging 2017 (2008 Expert Consensus on Nasopharyngeal Cancer Staging Revision) at enrollment.
- Patients who had disease progression on or after platinum-based chemotherapy and at least one other prior line of therapy. Prior neoadjuvant chemotherapy, concurrent chemoradiotherapy, or adjuvant chemotherapy would be considered as the first line of therapy if recurrence/metastasis occurs within 6 months since the last dose of chemotherapy. Switching treatment regimen due to intolerability were not counted as additional lines of therapy.
- Patients with at least one measurable lesion at baseline per RECIST v1.1 as assessed by IRRC if efficacy summary based on IRRC assessment, or at least one measurable lesion at baseline per RECIST v1.1 as assessed by the investigator if efficacy summary based on investigator assessment.
- Patients who had an opportunity to be followed for at least 8 months prior to data cutoff date (to allow at least 6 months follow-up past onset of response assuming the response occurs at the first follow-up scan).

Safety Analysis Set

The Safety Analysis Set includes all enrolled patients who have received at least one dose of penpulimab.

Pharmacokinetics Set

The pharmacokinetics set (PKS) includes all enrolled patients in the safety analysis set who have at least one quantifiable concentration data at the scheduled time point and no major and critical protocol violations affecting the concentration data.

Immunogenicity Set

The immunogenicity set (IMMS) includes all enrolled patients for safety analysis who have received at least one immunogenicity assessment at baseline and postbaseline, respectively.

The FDA's Assessment

The FDA agrees with the Applicant's description of the statistical analysis plan.

7.1.1.4. Protocol Amendments

The Applicant's Description

[Table 6](#) lists major modifications to Study AK105-202 protocol with each amendment.

Table 6 – Applicant: Protocol Amendments

Amendment Date	Major Changes Introduced Into the Protocol
4 March, 2019 Version 2.0	- Expanded the enrollment age ≥ 18 years and ≤ 75 years. - Clarified patients with stage IVb metastatic NPC at enrollment. - Removed the requirement of "No more than 3 prior regimens of systemic therapy for recurrent/metastatic nasopharyngeal carcinoma" and clarified the definition of first-line treatment for patients with neoadjuvant chemotherapy, concurrent chemoradiotherapy, or adjuvant chemotherapy. - Modified exclusion criteria "Patients with other active malignancies within 5 years prior to enrollment" to "Patients with other active malignancies within 2 years prior to enrollment." - Deleted ORR assessed by IRRC as the primary endpoint, but ORR assessed by IRRC and investigator will be submitted to the agency for the marketing application. - Add the content of planned interim analysis.

Amendment Date	Major Changes Introduced Into the Protocol
6 July, 2020 Version 3.0	- Deleted the PD-L1 positive analysis set from the study objectives and endpoints, and deleted ORR in the PD-L1 positive population used as a co-primary endpoint for this study. - Clarified that the primary endpoint is ORR assessed by IRRC per RECIST v1.1. - Clarified PD-L1 cut-off value and added definition of PD-L1 positive/negative subgroups. - Redefined treatment discontinuation criteria. - Modified the planned enrollment sample size and adjusted the corresponding statistical analysis plan, including the planned interim analysis. - Clarified whether disease progression required for reporting as SAEs and clarified the reporting requirements for AESIs. - Updated SAE reporting process instructions in accordance with the requirements of Good Clinical Practice (Version 2020).

The FDA's Assessment

The FDA agrees with the Applicant's description of major protocol amendments with one exception: The first protocol amendment to Study AK105-202 was submitted to FDA on March 15, 2018, not March 4, 2019, as stated in [Table 6](#).

7.1.2. Study Results

The analysis data cut-off date was 3 Feb 2021.

7.1.2.1. Compliance With Good Clinical Practices

Data

The study protocols and informed consent documents were reviewed by local IRB/IEC as required by regulations prior to implementation at practicing institutions.

The Applicant's Position

The study was conducted and monitored in compliance with the protocol, the ethical principles that have their origin in the Declaration of Helsinki and the ICH consolidated Guideline E6 for GCP and applicable regulatory requirement(s).

The FDA's Assessment

The FDA agrees with the Applicant's position.

7.1.2.2. Financial Disclosure

Data

Not Applicable.

The Applicant's Position

Appropriate financial disclosure was collected during the course of Study AK105-202, and no financial arrangements with the Investigator impacted the validity of the study. Additional information regarding financial disclosures can be found in Section [20.2](#).

The FDA's Assessment

The FDA agrees with the Applicant's position.

7.1.2.3. Patient Disposition

Data

A total of 171 patients were screened and 130 patients were enrolled. The reason for all screen failure was not meeting eligibility criteria. The first patient was enrolled on March 27, 2019, and the last patient was enrolled on September 14, 2020.

As of the data cutoff, 114 patients with metastatic NPC had an opportunity to be followed for at least 8 months (i.e., initiated penpulimab therapy at least 8 months prior to the data cut-off date). Of those 114 patients, 1 patient had only one line of prior therapy, 1 patient did not have measurable lesion at baseline as assessed by both the investigator and IRRC, and 1 patient did not have measurable lesion at baseline as assessed by IRRC.

At the data cutoff for the interim analysis, 111 patients comprised primary efficacy population that was used for efficacy data based on IRRC assessment, and 112 patients comprised primary efficacy population that was used for efficacy data based on investigator assessment. The median duration of follow-up was 14.7 months (range: 0.9 to 22.3) for the primary efficacy population. In the primary efficacy population, 28 patients (25.2%) were continuing on penpulimab, and 83 patients (74.8%) had patients discontinued penpulimab. [Table 12](#) summarizes the reasons for discontinuation. The most common reason for discontinuation was radiographic disease progression (53.2%).

Table 7 – Applicant: Patient Disposition - Primary Efficacy Population

Patient Disposition Category	Total (N=111)
Number of enrolled patients, n	111
Number of patients still on treatment, n (%)	28 (25.2)
End of treatment, n (%)	83 (74.8)
Adverse event	5 (4.5)
Radiographic disease progression	59 (53.2)
Symptomatic deterioration without radiographic evidence	2 (1.8)
Patient withdrawal consent	3 (2.7)
Lost to follow-up	1 (0.9)
Death	4 (3.6)
Other ^a	9 (8.1)
Number of patients still under follow-up, n (%)	59 (53.2)

Data source: ADSL.xpt Module 5.3.5.2, Study AK105-202 CSR Table 14.1.1.2

^a 7 patients voluntarily requested to discontinue the study treatment by themselves or their dependents, 1 patient discontinued study treatment due to more than 8 weeks of drug interruption interval, and 1 patient discontinued the study treatment due to disease progression evaluated by the investigator.

Abbreviations: CSR, clinical study report; N, total number of subjects; n, number of subjects in category.

The Applicant's Position

As of data cutoff date, the median duration of follow-up was 14.7 months (range: 0.9 to 22.3) for the primary efficacy population. The data can be used to assess durability of response based on percentage of patients with DoR for at least 6 months, but the data was not mature for assessing the durability of response based on percentage of patients with DoR for at least 12 months and 12-months PFS rate.

The FDA's Assessment

The FDA agrees with the Applicant's position. At least 6 months of post-response follow up is generally considered adequate to evaluate the durability of responses.

7.1.2.4. Protocol Violations/Deviations

Data

In the primary efficacy population, there were 6 major violations in 6 patients (5.4%). [Table 9](#) summarizes the major protocol deviations identified in Study AK105-202 for primary efficacy population. The critical protocol deviation is defined as a protocol deviation that may affect the interpretation of results or conclusion of the efficacy and/or safety data. No critical protocol deviation was identified. Patients were excluded from the primary efficacy population due to major protocol violations: one patient had only one line of prior therapy, and 1 patient did not have measurable lesion at baseline as assessed by the investigator.

Table 8 – Applicant: Major Protocol Deviations - Primary Efficacy Population

Patient ID	Protocol Deviation
Eligibility criteria	
25001	Patient received anticancer treatment (cinobufacini injection) within 4 weeks prior to first dosing of study drug.
Study procedures	
05006	Patient was illiterate and signed the informed consent while there was no impartial witness involved in the informed consent process.
05019	Patient was illiterate and signed the informed consent while there was no impartial witness involved in the informed consent process.
05017	Patient did not sign the most recent version of the supplemental informed consent form for treatment beyond disease progression.
08001	Investigator failed to report a SAE “leukocytosis” to sponsor, local EC, and relevant parties.
09001	Investigator failed to report a SAE “abnormal liver function” to sponsor, local EC, and relevant parties.

Source: ADDV.xpt Module 5.3.5.2, Study AK105-202 CSR Listing 16.2.2

Abbreviations: EC, ethics committee; CSR, clinical study report; SAE, serious adverse event

The Applicant’s Position

No deviations were identified that would substantially impact the integrity of the study or affect the interpretation of results or conclusion of the efficacy and/or safety data.

The FDA’s Assessment

FDA acknowledges the protocol deviations noted by the Applicant and agrees that these deviations do not impact the integrity of Study AK105-202 or interpretation of the study results.

7.1.2.5. Table of Demographic Characteristics

Data

[Table 9](#) shows baseline patient demographics.

Table 9 – Applicant: Demographic Information – Primary Efficacy Population

Characteristic	Total (N = 111)
Age (years)	
≤65 years	109 (98.2)
>65 years	2 (1.8)
Median	49.59
Min, max	20.8, 65.7
Sex (n (%))	
Male	84 (75.7)
Female	27 (24.3)

Characteristic	Total (N = 111)
ECOG, n (%)	
0	34 (30.6)
1	77 (69.4)

Source: ADSL.xpt Module 5.3.5.2, Study AK105-202 CSR Table 14.1.2

Abbreviations: CSR, clinical study report; ECOG, Eastern Cooperative Oncology Group; max, maximum; Min, minimum; N, total number of subjects; n, number of subjects in category.

The Applicant's Position

The majority of patients were male (76%), the median age was 50 years (range: 21 to 66 years), and the ECOG performance score was 0 (31%) or 1 (69%).

The FDA's Assessment

The FDA agrees with the results for the patient characteristics in the Primary Efficacy Population of Study AK105-202. FDA notes that the male predominance of the study population is consistent with the US patient population with NPC. The median age of patients enrolled in Study AK105-202 (50 years) is slightly younger than the median age of US patients with NPC (53-54 years). Furthermore, given that all patients in the efficacy population were of Chinese ethnicity, the efficacy populations do not reflect the racial and ethnic diversity of the US patient population with NPC.

7.1.2.6. Other Baseline Characteristics (E.G., Disease Characteristics, Important Concomitant Drugs)

Data

[Table 10](#) shows other baseline characteristics.

Table 10 – Applicant: Clinical and Disease Characteristics at Baseline – Primary Efficacy Population

Characteristic	Total (N = 111)
PD-L1 (Shuwen SAB-028)	
Positive (TPS≥50%)	43 (38.7)
Negative (TPS<50%)	66 (59.5)
NA	2 (1.8)
Clinical stage at diagnosis, n (%)	
Stage II	3 (2.7)
Stage III	29 (26.1)
Stage IV	0
Stage IVA	28 (25.2)
Stage IVB	40 (36.0)

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Characteristic	Total (N = 111)
Unknown	10 (9.0)
Neoplasm histological type, n (%)	
Non keratinizing differentiated NPC	36 (32.4)
Non keratinizing undifferentiated NPC	71 (64.0)
Non keratinizing with unknown differentiation NPC	4 (3.6)
Time from initial diagnosis to first dose (months) ^a	
Median	31.28
Min, max	7.2, 109.5
Cancer stage at study entry	
Primary metastasis	40 (36.0)
Recurrent metastasis	71 (64.0)
Prior radiotherapy of primary lesion, n (%)	
Yes	95 (85.6)
No	16 (14.4)
Location of metastasis ^b	
Breast	1 (0.9)
Head and neck	1 (0.9)
Liver	56 (50.5)
Lymph node	41 (36.9)
Lung	66 (59.5)
Peritoneum	1 (0.9)
Pleura	4 (3.6)
Spleen	1 (0.9)
Bone	54 (48.6)
Other	6 (5.4)
Number of location of metastasis	
< 3	73 (65.8)
≥ 3	38 (34.2)
Prior line of therapy, n (%)	
0-1	0
2	69 (62.2)
≥3	42 (37.8)
Median	2.0
Min, max	2, 6
Peripheral blood EBV level at baseline (IU/mL), n (%)	
<500 ^c	18 (16.2)
≥500 ^c	93 (83.8)

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Characteristic	Total (N = 111)
LDH at baseline, n (%)	
< ULN	52 (46.8)
≥ ULN	59 (53.2)

Source: ADSL.xpt Module 5.3.5.2, Study AK105-202 CSR Table 14.1.2

^aTime from initial diagnosis to first dose of study drug (months) = (date of first dose of study drug - date of initial diagnosis + 1)/30.4375.

^bMetastatic sites were derived from the baseline tumor diagnosis form including at the discretion of the investigator, lesions present at baseline and lesions that present previously unequivocally but not indicated at baseline.

^cThe lower limit of detection for EBV DNA level in this study is 500 IU/mL.

Abbreviations: CSR, clinical study report; EBV, Epstein-Barr virus; LDH, lactate dehydrogenase; max, maximum; Min, minimum; N, total number of subjects; n, number of subjects in category; NA, no assessment; NPC, nasopharyngeal carcinoma; PD-L1, programmed cell death - Ligand 1; TPS, tumor proportion score; ULN, upper limit of normal.

The Applicant's Position

Thirty-two percent of patients had non-keratinizing differentiated NPC, 64% were non-keratinizing undifferentiated NPC, and 4% had non-keratinizing NPC with unknown differentiation. Sixty-two percent of patients had received 2 prior lines of chemotherapy and 38% patients had received 3 or more prior lines of chemotherapy including prior platinum-based chemotherapy. Fifty-one percent of patients had liver metastasis.

The FDA's Assessment

The FDA agrees with the Applicant's representation of patient characteristics in Study AK105-202.

The FDA notes that the male predominance of the study population is consistent with the US patient population with NPC.

The following table provides FDA's summary of additional patient demographics and disease characteristics.

Table 11 – FDA: AK105-202 Baseline Demographic and Disease Characteristics

Demographic/Baseline Characteristic, n (%)	Penpulimab 200 mg Q2W N=111
Age, median (range)	50 (21, 66)
Sex, n (%)	
Female	27 (24)
Male	84 (76)
Tumor histology, n (%)	
Non keratinizing differentiated NPC	36 (32)
Non keratinizing undifferentiated NPC	71 (64)
Non keratinizing with unknown differentiation NPC	4 (3.6)
PD-L1 expression ^a , n (%)	
TPS <50%	66 (60)
TPS ≥50%	43 (39)

Demographic/Baseline Characteristic, n (%)	Penpulimab 200 mg Q2W N=111
Prior lines of therapy, n (%)	
2	69 (62)
≥3	42 (38)
ECOG, n (%)	
0	34 (31)
1	77 (69)
Cancer stage at study entry	
Primary metastasis	40 (36)
Recurrent metastasis	71 (64)
Peripheral blood EBV level at baseline, n (%)	
<500	18 (16)
≥500	93 (84)

Source: FDA reviewer's analyses.

^a As determined by Shuwn SAB-28 assay

Abbreviations: EBV; Epstein-Barr virus; ECOG, Eastern Cooperative Oncology Group; N, total number of subjects; n, number of subjects in category; NPC, nasopharyngeal carcinoma; PD-L1, programmed cell death protein L1; TPS, tumor proportion score; Q2W, every 2 weeks.

7.1.2.7. Treatment Compliance, Concomitant Medications, and Rescue Medication Use

Data

Treatment compliance was not analyzed because penpulimab was administered as an intravenous infusion at the study center. No patient was discontinued from study treatment due to protocol non-compliance. The most common concomitant medications were anti-inflammatory and anti-rheumatic drugs, followed by analgesics.

The Applicant's Position

Noncompliance, concomitant, and rescue medication use are variables unlikely to affect the study results or the overall assessment of efficacy of penpulimab for patients with metastatic NPC.

The FDA's Assessment

The FDA agrees with the Applicant's position.

7.1.2.8. Efficacy Results – Primary Endpoint (Including Sensitivity Analyses)

Data

Among the 111 patients included in the primary efficacy population, 33 patients had a BOR of CR or PR based on IRRC assessment, with a confirmed **ORR of 29.7% (95% CI: 21.4%, 39.1%)**. [Table 12](#) provides further details of the responses for the primary efficacy population.

Table 12 – Applicant: Summary of Best Overall Response Per RECIST 1.1 - Primary Efficacy Population

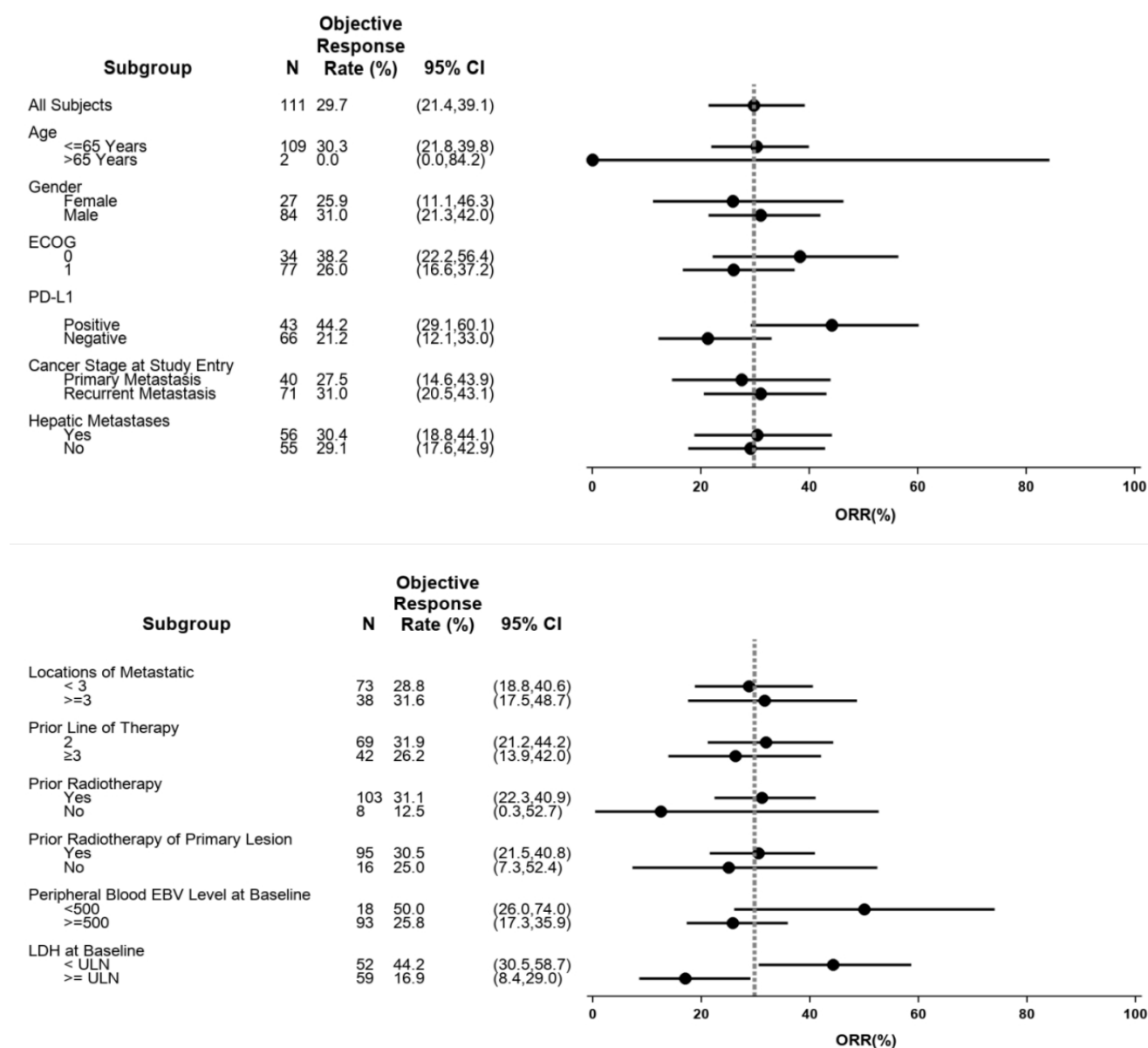
Endpoint	IRRC (N = 111)
Response evaluation	
Confirmed objective response rate, n (%)	33 (29.7%)
[95% CI]	[21.4,39.1]
Complete response	1 (0.9%)
Partial response	32 (28.8%)
Disease control rate, n (%)	55 (49.5%)
[95% CI]	[39.9%, 59.2%]
Stable disease	22 (19.8%)
Disease progression	45 (40.5%)
No assessment	11 (9.9%)

Source: ADRS.xpt Module 5.3.5.2 AK105-202 CSR Table 14.2.1.1

Response rates were compared across several subgroups of interest to examine consistency of effect. These subgroups were defined by age, ECOG performance status score, PD-L1 expression, tumor stage at study entry, liver metastasis, number of metastatic sites, prior line of therapy, prior radiotherapy, prior radiotherapy to primary lesions, EBV DNA level in peripheral blood at baseline, and LDH at baseline. The comparison of response rates across these subgroups are presented in [Figure 9](#).

Subgroup analyses based on IRRC assessment showed that tumor response was observed across all subgroups (with exception for age > 65 years [n=2]). While numerical differences in point estimates across some subgroups were noted, sample sizes were small and 95% CIs overlapped for most subgroup comparisons. In the subgroups, the patients with positive PD-L1 expression (defined as TPS ≥ 50% using Shuwen SAB-028), baseline LDH < ULN or EBV-DNA level in peripheral blood < 500 IU/mL at baseline seems to have a higher response rate. It was also noticed that the ORRs in key subgroups were comparable, such as prior line of therapy, patients with liver metastasis, disease status (primary or recurrent metastasis).

Figure 9 – Applicant: Forest Plot of Objective Response Rate (ORR) Based on RECIST 1.1 per IIRC by Subgroup Factors – Primary Efficacy Population



Data source: ADRS.xpt Module 5.3.5.2 AK105-202 CSR Figure 14.2.1.1

Abbreviations: CI, confidence interval; EBV, Epstein-Barr virus; ECOG, Eastern Cooperative Oncology Group; IIRC, Independent Radiology Review Committee; LDH, lactate dehydrogenase; N, total number of subjects; ORR, objective response rate; ULN, upper limit of normal.

The Applicant's Position

Results based on an interim analysis of ORR demonstrate substantial evidence of effectiveness of penpulimab monotherapy in patients with metastatic nonkeratinizing NPC with disease progression on or after at least two prior lines of therapy, a serious disease where there is a

clear unmet medical need. The primary analysis showed promising ORR by IRRC in the Primary Efficacy Population. The confirmed ORR of 29.7% (95% CI: 21.4%, 39.1%) compares favorably with the overall response rate of < 10% of historical commonly used chemotherapy agents.

The FDA's Assessment

FDA generally agrees with the Applicant's summary and position of the efficacy results of the primary endpoint of ORR as assessed by IRRC. Note that FDA considers DCR to be an exploratory endpoint only. The subgroup results of ORR by PD-L1 expression (TPS <50 vs. TPS ≥50% by the Shuwen SAB-028 assay) were summarized in [Figure 9](#). [Table 13](#) provides the results of an exploratory subgroup analysis of ORR by PD-L1 TPS <1%, TPS 1-49%, and TPS ≥50%. The response rates across PD-L1 expression levels are somewhat discrepant, with a lower ORR observed for patients with PD-L1 < 50%, although the 95% confidence intervals overlap with those observed at patients with PD-L1 TPS ≥ 50%. Given that this post-hoc analysis is exploratory in nature and that the impact of PD-L1 status and cutoff on NPC outcomes is not well defined, the significance of these results is unknown and should be interpreted with caution. In addition, the ORR of 21% (95% CI: 12, 33) for patients with TPS <50% likely represents an improvement over available therapies for this refractory population.

Table 13 – FDA: ORR and DoR Results by PD-L1 Status

Efficacy Parameter	PD-L1 Status (N=111) ^c		
	TPS <1% (N=11)	TPS 1-49% (N=55)	TPS ≥50% (N=43)
ORR by IRRC, % (95% CI)	0 (0, 29)	25 (15, 39)	44 (29, 60)
DoR	N=0	N=14	N=19
Median ^a , months (Range)		NR (3.8, 16.8+)	NR (3.8+, 22.3+)
% with DoR ≥6 months ^b		86%	84%

Source: FDA reviewer's analyses.

^a Based on Kaplan-Meier Method.

^b Based on observed DoR data.

^c Two patients did not have a reported PD-L1 TPS score

Abbreviations: CI, confidence interval; DoR, duration of response; IRRC, Independent Radiology Review Committee; N, total number of subjects; NR, not reached; ORR, overall response rate; PD-L1, programmed cell death – Ligand 1; TPS, tumor proportion score.

7.1.2.9. Data Quality and Integrity

Data

None.

The Applicant’s Position

The submission contained all the required components of the electronic Common Technical Document (eCTD) and was of adequate quality and integrity to allow for review of the clinical trial data supporting the proposed indication.

The quality assurance procedures were implemented during the conduct of the study including but not limited to regular site monitoring, conducting investigator meetings and training sessions for clinical research associates, and site initiation visits to review the clinical protocol, CRF, and study procedures. Additionally, independent Quality Assurance audits were conducted for selected sites, and no concerns on data integrity were reported following site inspections by the independent Quality Assurance audits.

The FDA’s Assessment

Overall, there were no significant data quality or integrity issues identified during the review of this BLA.

7.1.2.10. Efficacy Results – Secondary and Other Relevant Endpoints

Data

DoR and TTR

The median TTR in the primary efficacy population was 1.84 months (range: 1.64 to 7.39 months). As of the data cutoff date, the longest durable response was 17.05+ months (ongoing), 75.8% of responders remained ongoing, and the median DoR has not reached. The DoR ≥ 6 months was 72.7% (24/33) at the data cutoff. The Kaplan-Meier estimate for the percent of patients with a 6-month duration of response is 93.4% (95% CI: 75.9%, 98.3%), and the estimate for the percent of patients with a 9-month duration of response is 77.6% (95% CI: 52.6%, 90.4%).

A summary of DoR and TTR in the primary efficacy population is presented below in [Table 14](#). [Figure 10](#) provides a graphic representation of time to response and duration of response of the responders in the primary efficacy population.

Table 14 – Applicant: DoR and TTR Assessment Per RECIST v1.1 – Primary Efficacy Population

	IRRC (N = 111)
Number of patients with response, n	33
Time to response (months), median (min – max)	1.84 (1.64 – 7.39)
Number (%) of patients with ongoing response, n(%)	25 (75.8%)

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IRRC (N = 111)	
Duration of response (DoR) (months) ^a	
Median (min – max)	NR (3.78+ - 17.05+)
95% CI	[9.23, NE]
6 months DoR rate (%) [95% CI] ^a	93.4 [75.9, 98.3]
9 months DoR rate (%) [95% CI] ^a	77.6 [52.6, 90.4]
Patients with duration of response ≥ 6 months, n (%) ^b	24 (72.7%)
Patients with duration of response ≥ 9 months, n (%) ^b	13 (39.4%)

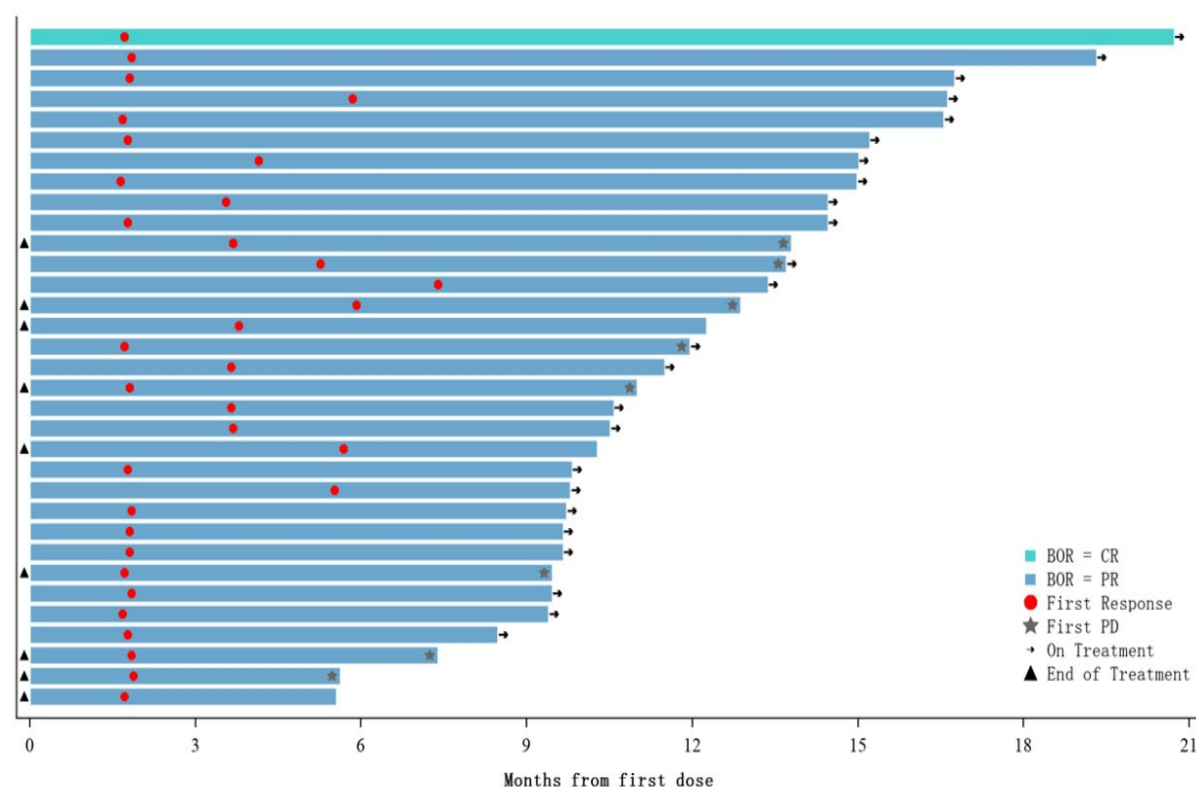
Source: ADTTE.xpt Module 5.3.5.2 AK105-202 CSR Table 14.2.2

^aThe Kaplan-Meier method was used. + indicated censored value.

^bFrequency was calculated based on descriptive statistics. The percentage was calculated based on the number of responders regarding of whether the follow-up time past onset of response is more than 6 or 9 months. Due to lack of sufficient follow-up past onset of response, patients with DoR ≥ 9 months would be under-estimated.

Abbreviations: CI, confidence interval; CSR, clinical study report; DoR, duration of response; IRRC, Independent Radiology Review Committee; max, maximum; min, minimum; N, total number of subjects; n, number of subjects in category; NE, not estimable; NR, not reached; RECIST, response evaluation criteria in solid tumors; TTR, time to response.

Figure 10 – Applicant: Swimmer Plot for Time to Response and the Duration Response Based on RECIST v1.1 per IRRC, Responders in the Primary Efficacy Population



Source: ADTTE.xpt Module 5.3.5.2 AK105-202 CSR Figure 14.2.2.1

Abbreviations: BOR, best of all response; CR, complete response; IRRC, Independent Radiology Review Committee; PD, progressive disease; PR, partial response.

Progression-Free Survival

The median PFS based on IRRC assessment in the primary efficacy population was 3.65 months. The 3-month PFS rate was 52.3% (95% CI: 42.3%, 61.4%), the 6-month PFS rate was 41.3% (95% CI: 31.7%, 50.6%), and the 9-month PFS rate was 37.1% (95% CI: 27.8%, 46.4%).

A summary of PFS in the primary efficacy population is shown in [Table 15](#).

Table 15 – Applicant: PFS Assessed Per RECIST v1.1 – Primary Efficacy Population

	IRRC (N = 111)
Number of PFS events, n (%)	77 (69.4)
Median PFS (months) ^a , 95% CI	3.65 [1.87, 6.60]
PFS rate ^[a]	
3 months PFS Rate (%) [95% CI]	52.3 [42.3, 61.4]
6 months PFS Rate (%) [95% CI]	41.3 [31.7, 50.6]
9 months PFS Rate (%) [95% CI]	37.1 [27.8, 46.4]

Source: ADTTE.xpt Module 5.3.5.2 AK105-202 CSR Table 14.2.3

^a From product-limit (Kaplan-Meier) method.

Abbreviations: PFS, progression-free survival;

Overall survival (OS)

The median OS in the primary efficacy population was 18.63 months (95% CI: 13.77, NE). The 6-month OS rate was 80.3% (95% CI: 71.4%, 86.7%), and the 9-month OS rate was 73.6% (95% CI: 64.1%, 80.9%).

A summary of OS in the primary efficacy population is shown in [Table 16](#).

Table 16 – Applicant: Overall Survival – Primary Efficacy Population

	Total (N = 111)
Number of death events, n (%)	44 (39.6)
Median OS (months) ^a , 95% CI	18.63 [13.77, NE]
OS rate, n (%) ^a	
3 months OS Rate (%) [95% CI]	90.8 [83.5, 94.9]
6 months OS Rate (%) [95% CI]	80.3 [71.4, 86.7]
9 months OS Rate (%) [95% CI]	73.6 [64.1, 80.9]

Source: ADTTE.xpt Module 5.3.5.2 AK105-202 CSR Table 14.2.4.1

^a From product-limit (Kaplan-Meier) method.

The Applicant's Position

Results based on an interim analysis of additional secondary efficacy variables including DoR, PFS and OS demonstrate substantial evidence of effectiveness of penpulimab monotherapy in patients with metastatic nonkeratinizing NPC with disease progression on or after at least two prior lines of therapy, a serious disease where there is a clear unmet medical need.

The responses were durable. After a median follow-up time of 14.7 months, median DoR has not yet been reached at the time of DCO, the DoR ≥ 6 months was 72.7% (24/33), and 25 (75.8%) of 33 responders had an ongoing response. The OS results were encouraging in this heavily pretreated NPC population. The median OS was 18.63 months, and the 9-month OS rate was 73.6% (95% CI: 64.1%, 80.9%). The percentage of DoR ≥ 6 months, median OS, and the 9-month OS rate compare favorably with those seen with historical commonly used chemotherapy agents.

The FDA's Assessment

FDA generally agrees with the Applicant's summary of the efficacy results of DoR. Per FDA's request, the Applicant also submitted the updated DoR data with a DCO of May 12, 2021, for the 33 patients who had a response as assessed by IRRC. The data was reviewed and included in the product labeling. At the updated DCO, the range of the DoR was (3.8+, 22.3+) and the median DoR was still not reached; the percentage of responding patients with DoR ≥ 6 months was 85% and the percentage of responding patients with DoR ≥ 9 months was 73%. The updated DoR data showed a longer durability of response compared to the data from the DCO of February 3, 2021.

Table 17 – FDA: DoR Assessment Per RECIST v1.1 by IRRC (DCO: May 12, 2021)

Endpoint	N=33
Median (95% CI), months ^a	NR (10.2, NE)
Range, months	(3.8+ - 22.3+)
Median follow-up (95% CI), months ^b	11.9 (9.3, 15.0)
Patients with DoR ≥ 6 months, n (%) ^c	28 (85%)
Patients with DoR ≥ 9 months, n (%) ^c	24 (73%)

Source: FDA reviewer's analysis.

^a The Kaplan-Meier method was used.

^b Based on Reversed Kaplan-Meier Method.

^c Frequency was calculated based on observed DoR.

Note: + indicated censored value.

Abbreviations: CI, confidence interval; DoR, duration of response; IRRC, Independent Radiology Review Committee; N, total number of subjects; n, number of subjects in category; NE, not estimable; NR, not reached; RECIST, response evaluation criteria in solid tumors

The Applicant submitted updated DoR data, in which all responders were followed for at least 24 months from the date of initial response or onset of disease progression. At the DCO of September 28, 2022, the median DoR among the 33 responders by IRRC was 17.5 months (95% CI: 9.2, 28.6); the percentage of responding patients with DoR ≥ 12 months was 48% and the percentage of responding patients with DoR ≥ 24 months was 30%.

Table 18 – FDA: DoR Assessment Per RECIST v1.1 by IRRC (DCO: Sep 28, 2022)

Endpoint	N=33
Median (95% CI), months ^a	17.5 (9.2, 28.6)
Range, months	(3.8+ - 36.8+)
Median follow-up (95% CI), months ^b	30.9 (25.8, 33.5)
Patients with DoR ≥ 6 months, n (%) ^c	29 (88%)
Patients with DoR ≥ 12 months, n (%) ^c	16 (48%)
Patients with DoR ≥ 24 months, n (%) ^c	10 (30%)

Source: FDA reviewer's analysis.

^a The Kaplan-Meier method was used.

^b Based on Reversed Kaplan-Meier Method.

^c Frequency was calculated based on observed DoR.

Note: + indicated censored value.

Abbreviations: CI, confidence interval; DCO, data cutoff; DoR, duration of response; IRRC, Independent Radiology Review Committee; N, total number of subjects; n, number of subjects in category; RECIST, response evaluation criteria in solid tumors

FDA reviewed the summary of the PFS and OS data above. However, FDA considers these results to be uninterpretable in the absence of a comparator arm.

The median follow-up time of 14.7 months described above was for the primary efficacy population per IRRC assessment and was defined starting from the date of first dose to the last known survival time or cutoff date. This represents follow-up time for the study, rather than follow-up time for DoR. The median follow-up time for DoR was 9.0 months at the DCO of February 3, 2021, 11.9 months at the DCO of May 12, 2021, and 30.9 months at the DCO of September 28, 2022 (based on the reversed Kaplan-Meier method).

FDA considers TTR to be an exploratory endpoint only.

7.1.2.11. Dose/Dose Response

Data

Not Applicable.

The Applicant's Position

All patients with NPC in the primary efficacy population received penpulimab 200 mg every two weeks. Therefore, dose response relationships for efficacy could not be evaluated. Univariate logistic regression analyses showed a flat relationship between penpulimab PK exposures and model-predicted ORR (CR/PR).

The FDA's Assessment

The FDA agrees that a dose response relationship is not evaluable given the Q2W dosing regimen of penpulimab.

7.1.2.12. Durability of Response

Data

A summary of DoR and TTR in the primary efficacy population is presented in [Table 14](#) provides a graphic representation of time to response and duration of response of the confirmed responders in the primary efficacy population.

The Applicant's Position

As of the data cutoff date, after a median follow-up time of 14.7 months, 75.8% of responders remained ongoing, the median DoR has not reached, and the DoR $\geq$ 6 months was 72.7%. The Kaplan-Meier estimate for patients with a 6-month duration of response is 93.4% (95% CI: 75.9%, 98.3%), and the estimate for patients with a 9-month duration of response is 77.6% (95% CI: 52.6%, 90.4%).

Given refractory population with metastatic NPC with disease progression on or after at least two prior lines of therapy, the responses were durable, which compare favorably with those seen with historical commonly used chemotherapy agents.

The FDA's Assessment

The FDA agrees with the Applicant's position regarding the durability of response.

7.1.2.13. Persistence of Effect

Data

Not Applicable.

The Applicant's Position

As of data cut off, the median duration of follow-up was 14.7 months. The data can be used to assess durability of response based on percentage of patients with DoR for at least 6 months, but the data was not mature enough for assessing the durability of response for a longer period. Additional follow-up past onset of response was warranted to better estimate the DoR and assess persistence effect of penpulimab monotherapy in patients with metastatic NPC.

The FDA's Assessment

The FDA agrees with the Applicant's position.

7.1.2.14. Efficacy Results – Secondary or Exploratory COA (PRO) Endpoints

Data

Not Applicable.

The Applicant's Position

Not Applicable.

The FDA's Assessment

Not Applicable.

7.1.2.15. Additional Analyses Conducted on the Individual Trial

Data

IRRC assessments and investigator assessments were comparable in terms of the efficacy endpoints ORR, DoR, DCR, and PFS (Table 19). The concordance between the IRRC- and investigator-assessed ORR in the primary efficacy population was high (80.2%).

Table 19 – Applicant: Comparison Between IRRC and Investigator Assessments of Efficacy Endpoints Per RECIST V1.1 – Primary Efficacy Population

	ORR (%) (95% CI)	Median DoR (months) (95% CI) ^a	Patients with DoR ≥ 6 months (%) ^b	DCR (%) (95% CI)	Median PFS (months) (95% CI) ^a
Per investigator	25.9% (18.1,35.0)	13.34 (7.89, NE]	72.4%	54.5% (44.8, 63.9)	3.71 (1.94, 7.23)
Per IRRC	29.7% (21.4,39.1)	NR (9.23, NE)	72.7%	49.5% (39.9,59.2)	3.65 (1.87, 6.60)

Source: ADTTE.xpt Module 5.3.5.2 AK105-202 CSR Table 14.2.1.1, 14.2.2, 14.2.3 ,Listing 16.2.6.3.1,16.2.6.3.2

^a From product-limit (Kaplan-Meier) method.

^b Frequency was calculated based on descriptive statistics.

o, The Applicant's Position

IRRC assessments and investigator assessments were comparable in terms of the efficacy endpoints ORR, DoR, DCR, and PFS per RECIST v1.1.

The FDA's Assessment

FDA reviewed the Applicant's summary of the additional analyses above. The FDA agrees that the results by IRRC assessment and investigator assessments were generally consistent.

7.1.3. Assessment of Efficacy Across Trials

This section is not applicable because the application is supported by one pivotal trial (AK105-202).

8. Integrated Assessment of Effectiveness

Data

The key efficacy results for the primary efficacy population were summarized below:

- ORR: Confirmed ORR assessed by IRRC was 29.7% (95% CI: 21.4%, 39.1%).
- DCR: The DCR assessed by IRRC was 49.5% (95% CI: 39.9%, 59.2%).
- DoR: At of the data cutoff, 75.8% of responders had ongoing response, the median DoR has not reached, and the DoR $\geq$ 6 months was 72.7%. The Kaplan-Meier estimate for patients with a 6-month DoR is 93.4% (95% CI: 75.9%, 98.3%), and the estimate for patients with a 9-month DoR is 77.6% (95% CI: 52.6%, 90.4%).
- PFS: Median PFS assessed by IRRC was 3.65 months (95% CI: 1.87, 6.60) and the 9-month PFS rate assessed by IRRC was 37.1% (95% CI: 27.8%, 46.4%).
- OS: The median OS was 18.63 months (95% CI: 13.77, not estimable), and the 9-month OS rate was 73.6% (95% CI: 64.1%, 80.9%).

The Applicant's Position

Results based on an interim analysis of ORR and DoR demonstrate substantial evidence of effectiveness of penpulimab monotherapy in patients with metastatic nonkeratinizing NPC with disease progression on or after at least two prior lines of therapy, a serious disease where there is a clear unmet medical need. The primary analysis showed promising ORR and DoR by IRRC in the Primary Efficacy Population. The confirmed ORR of 29.7% (95% CI: 21.4%, 39.1%) compares favorably with the overall response rate of < 10% of historical commonly used chemotherapy agents. The responses were durable. After a median follow-up time of 14.7 months, median DoR has not yet been reached at the time of DCO, the DoR $\geq$ 6 months was 72.7% (24/33), and 25 (75.8%) of 33 responders had an ongoing response.

The OS results were encouraging in this heavily pretreated NPC population. The median OS was 18.63 months (95% CI: 13.77, not estimable), and the 9-month OS rate was 73.6% (95% CI: 64.1%, 80.9%).

Collectively, these data provide compelling evidence of the clinically meaningful benefit of penpulimab 200mg Q2W in patients with metastatic nonkeratinizing NPC with disease progression on or after platinum-based chemotherapy and at least one other prior line of therapy.

The FDA's Assessment

The assessment of efficacy of penpulimab in patients with metastatic NPC with disease progression on platinum-based chemotherapy and at least one other therapy was based on results from the primary efficacy population enrolled on Study AK105-202, a single arm trial conducted entirely in China. The ORR observed in the primary efficacy population was 30% (95% CI 21, 39). The median DOR was not reached (range 3.8, 17.1+); 39% of responders had a DOR $\geq$ 9 months.

The overall response rate and duration of response do not provide a meaningful advantage over available therapy given the recent approvals of toripalimab-tpzi for the treatment of patients with metastatic or recurrent, locally advanced NPC, with overlapping 95% confidence intervals around the ORR observed in a similar population of patients who received toripalimab-tpzi.

Another major limitation of the data is that the primary trial supporting this marketing application was conducted exclusively in China and all patients enrolled were Asian. For discussion of this issue, see Section [1](#) and Section [9.2](#) of this review. Regulatory flexibility is not warranted in this instance as penpulimab does not address an unmet need.

8.1. Review of Safety

Data

The integrated safety analysis of penpulimab include 372 patient's data from the following four studies:

1. AK105-101 (phase Ib)
1. AK105-201
2. AK105-202
1. AK105-204

The primary evidence for the safety of penpulimab in patients with metastatic NPC comes from the pivotal study AK105-202.

The study AK105-101 phase Ib, AK105-201, AK105-202, and AK105-204, which comprise all patients treated with 200 mg Q2W penpulimab monotherapy for various tumor types, will provide safety data in support of the penpulimab safety profile.

The Applicant's Position

Data from the pivotal study AK105-202 allowed for a comprehensive and adequate assessment of the overall benefit-risk in adult patients with metastatic NPC at a dose of 200 mg Q2W. Together with other penpulimab monotherapy studies, the 372 patients included in the safety

population are considered adequate for the detection of common AE signals and characterization of the safety profile of penpulimab.

The following 2 safety populations were included in the overall safety evaluation, and the comparisons between those two safety populations were discussed in this document.

Integrated Penpulimab 200 mg Safety Population

This population included all the patients who received at least 1 dose of penpulimab 200 mg Q2W in Study AK105-101 (phase Ib), AK105-201, AK105-202, and AK105-204.

NPC Safety Population (Targeted Population)

This population included all the patients with NPC in Study AK 105-202.

The FDA's Assessment

The FDA agrees with the Applicant's description of the safety populations included in this application. FDA's review of the safety profile of penpulimab 200 mg Q2W was based on data from 130 patients with NPC who received at least one dose of penpulimab on Study AK105-202 supported by pooled data from multiple trials of penpulimab 200 mg Q2W as a single agent for patients with advanced solid tumors and classic Hodgkin's lymphoma (cHL).

8.1.1. Safety Review Approach

Data

Not Applicable.

The Applicant's Position

The safety evaluation performed as part of the penpulimab clinical development program was consistent with ICH guidelines.

The safety analyses supporting this application were comprehensive and included all SAEs, all AEs, especially Grade ≥ 3 all-causality and treatment-emergent AEs, AEs leading to discontinuations, AEs leading to interruption, laboratory abnormalities.

A consistent approach for the categorization of an AE as immune-related AE (irAE) was also applied following a prespecified case definition consisting of both programmatic checks and medical review (see Module 2.7.4 Appendix 9.1, irAE charter)

The FDA's Assessment

The FDA agrees with the Applicant's position that the safety data permit adequate assessment of penpulimab's safety profile. The FDA utilized the safety datasets generated for Study AK105-202 and pooled safety population to review the safety profile of penpulimab. Throughout the review of safety data, the FDA sent multiple information requests (IRs) requesting additional clinical information on various data elements, including medical causes of death when the patient narratives were unclear or vague.

8.1.2. Review of the Safety Database

8.1.2.1. Overall Exposure

Data

The summary of clinical safety includes safety data from 372 patients, including 130 patients with NPC (target population) and 242 patients with various other solid tumors or classic Hodgkin's lymphoma (cHL) (Study AK105-101 phase Ib, AK105-201, and AK105-204).

NPC Safety Population (Targeted Population)

In the NPC safety population, 130 patients were treated with penpulimab at a dose of 200 mg Q2W. The median total duration of exposure was 139.5 days (range: 14-644 days), median number of penpulimab doses was 9.5 (range: 1-43), median relative dose intensity was 97.67% (range: 50.0% - 103.7%). Approximately 68.5% of patients were treated for more than 3 months, 43.1% for more than 6 months, 18.5% of patients received treatment for at least 12 months.

Integrated Penpulimab 200 mg Safety Population

A total of 372 patients have been treated with penpulimab at a dose of 200 mg Q2W. The median duration of exposure was 168 days (range, 13 to 778 days). The median number of doses received was 11.5 (range: 1-54), median relative dose intensity was 98.3% (range: 50.0% - 103.7%). Approximately 66.1% of patients were treated for more than 3 months, 48.7% for more than 6 months, 28.0% of patients received treatment for at least 12 months.

The Applicant's Position

The eligibility criteria in the pivotal study were clinically relevant for the target population who would receive penpulimab following regulatory approval in the proposed indication.

The exposure to study drug was considered adequate to support characterization of the safety profile of penpulimab and allow for a comprehensive assessment of safety in all patients treated with penpulimab.

The FDA's Assessment

The FDA agrees with the Applicant's position regarding the overall exposure of penpulimab being adequate to support characterization of its safety profile. Patients in the primary safety population had a median total duration of exposure of 4.6 months (range 0.5 to 21.2 months) whereas patients in the pooled safety population had a median duration of exposure of 5.5 months (range 0.4 to 25.6 months).

8.1.2.2. Relevant Characteristics of the Safety Population

Data

NPC Safety Population (Targeted Population)

The median age was 49.5 years (range: 20 to 66 years), 76.2% of whom were male, 23.8% were female. All patients had an ECOG score of 0 (30.8%) or 1 (69.2%). The median BMI was 21.48 kg/m² (range:13.2-21.4).

Integrated Penpulimab 200 mg Safety Population

The median age was 51 years (range: 18 to 91 years), 64.0% of whom were male, 36.0% were female. All patients had an ECOG score of 0 (41.9%) or 1 (58.1%). The median BMI was 22.81 kg/m² (range:13.2-42.7).

The Applicant's Position

The demographic characteristics were generally comparable across NPC safety population and all other studies where penpulimab was used as a monotherapy.

The FDA's Assessment

[Table 20](#) presents the baseline demographic and disease characteristics of the primary safety population from Study AK105-202 as well as from the pooled safety population.

Table 20 – FDA: Patient Characteristics in AK105-202 (NPC) and in the Pooled Safety Population

	NPC (AK105-202) N = 130 N (%)	All Tumor N = 372 N (%)
Sex		
Male	99 (76)	238 (64)
Female	31 (24)	134 (36)

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	NPC (AK105-202) N = 130 N (%)	All Tumor N = 372 N (%)
Age		
Mean (SD)	48 (10)	50 (16)
Median (min – max)	49 (20 – 66)	51 (18 – 91)
Age group		
<65	128 (98)	303 (81)
>=65	2 (1.5)	69 (19)
ECOG		
1	90 (69)	216 (58)
0	40 (31)	156 (42)
Race		
Asian	130 (100)	300 (81)
White	0 (0)	67 (18)
Other	0 (0)	3 (0.8)
Multiple	0 (0)	2 (0.5)
Ethnicity		
CHN – HAN	125 (96)	280 (75)
CHN – Other	5 (3.8)	9 (2.4)
AUS – Caucasian	0 (0)	67 (18)
AUS – Asian	0 (0)	11 (3.0)
AUS – Other	0 (0)	5 (1.3)
Country		
CHN	130 (100)	289 (78)
AUS	0 (0)	83 (22)

Source: ADSL (Subject Level Analysis) – 2021-06-01. Variables used: USUBJID, TRT01A, SAFFL, SEX, AAGE, AGEGR1, ECOGBL, RACE, NATIONTY, COUNTRY

Abbreviations: AUS, Australia; CHN, China; ECOG, Eastern Cooperative Oncology Group; max, maximum; min, minimum; N, total number of subjects; n, number of subjects in category; NPC, nasopharyngeal carcinoma; SD, standard deviation

The FDA agrees that the male predominance of the safety population is consistent with the U.S. patient population with NPC (Cancer.Net, 2022). However, the median age of patients in AK105-202 (49 years) is slightly younger than the median age for US patients with NPC (53-54 years). Furthermore, given that all patients in the primary safety population were of Chinese ethnicity, the safety populations do not reflect the racial and ethnic diversity of the US patient population with NPC.

Despite the differences noted above, the FDA agrees that the safety data from AK105-202 and the pooled population provide sufficient data for evaluations of the safety profile of penpulimab in adults with metastatic non-keratinizing nasopharyngeal carcinoma (NPC) with disease progression on or after platinum-based chemotherapy and at least one other prior line of therapy.

8.1.2.3. Adequacy of the Safety Database

Data

Integrated penpulimab 200 mg safety population included 372 patients who received at least 1 dose of penpulimab 200 mg Q2W from four clinical studies. Of those patients, 130 patients in proposed patient population were included for overall safety evaluation.

The Applicant's Position

The safety database was considered adequate to support the characterization of the safety profile of penpulimab in the proposed patient population.

The FDA's Assessment

The FDA agrees with the Applicant's position. The data submitted was organized and adequate to perform a complete review of the safety of penpulimab. FDA issued several information requests during the review cycle to obtain clarification and additional information regarding safety data included in the NDA and all requests were addressed appropriately.

8.1.3. Adequacy of Applicant's Clinical Safety Assessments

8.1.3.1. Issues Regarding Data Integrity and Submission Quality

Data

All safety evaluations conducted during NPC safety population (Study AK105-202), including monitoring for AEs, reporting SAEs, physical examinations, vital sign measurements, clinical laboratory tests, and ECGs are considered standard (i.e., widely used and generally recognized as reliable, accurate, and relevant).

Study AK105-202 was conducted according to procedures that incorporate the general principles of GCP.

The Applicant's Position

No issues were identified in the quality and integrity of the submitted datasets and individual case narratives.

The FDA's Assessment

The FDA agrees with the Applicant's position. However, throughout the review of safety data, FDA sent multiple IRs requesting additional clinical information about medical causes of death

when the patient narratives were unclear or did not provide sufficient information. The FDA also sent an IR requesting submission of a revised dataset of laboratory results.

8.1.3.2. Categorization of Adverse Event

Data

The data collection of AEs from the 4 clinical studies is provided in [Table 21](#).

Table 21 – Applicant: Summary of Key Differences in Reporting of AEs Across the Studies

Study No.	AE Data Collected During Treatment
AK105-101	The AEs (including SAEs) that occurred during treatment (from the first dosing date through 90 days after the last dose of penpulimab).
AK105-201	
AK105-202	
AK105-204	The AEs (including SAEs) that occurred during treatment (from the first dosing date through 30 days after the last dose of penpulimab or until initiation of subsequent anticancer therapy) and irAEs that occurred within 90 days after the last dose, regardless of whether the patient had started a new anti-tumor therapy or not. Before first dosing, only SAE should be reported.

The Applicant's Position

The safety of penpulimab was evaluated on the basis of the:

- Frequency, type, severity, and causal relationship of AEs to study treatment.
- Frequency of deaths, SAEs, and other clinically significant AEs (including AEs leading to discontinuation and AEs requiring dose interruption).
- Frequency and type of AEs in key demographic subgroups.
- Changes in laboratory variables.

The approach to the analysis of AEs was appropriate in evaluating the safety data.

The FDA's Assessment

The FDA agrees with the Applicant's description of the categorization of adverse events (AEs) for Studies AK105-101, AK105-201, AK105-202, AK105-204. MedDRA v 22.0 was used for mapping of AEs and CTCAE v 4.03 was used for grading of AEs.

8.1.3.3. Routine Clinical Tests

Data

Clinical laboratory data were collected routinely throughout the study. Clinical laboratory values were graded according to NCI CTCAE version 4.03, when applicable. Results outside predefined normal ranges and NCI CTCAE grade were flagged in the data listings for further investigations.

Clinical laboratory tests items included hematology, blood chemistry, coagulation function tests, thyroid function tests, urinalysis, virological tests, and pregnancy tests. The schedule of main laboratory tests for each study is presented in Module 2.7.4, Table 4.

The Applicant's Position

The laboratory evaluation (laboratory tests and timepoints) as described in the protocols was reasonable and adequate to monitor the safety of the penpulimab.

The FDA's Assessment

The FDA agrees with the Applicant's position.

8.1.4. Safety Results

8.1.4.1. Deaths

Data

NPC Safety Population (Targeted Population)

A total of 47 (36.2%) deaths occurred in NPC safety population. A total of 2 (1.5%) deaths occurred within 30 days after the last dose.

Eighteen (13.8%) patients had AEs that resulted in death, regardless of causality. Excluding disease progression, AEs with an outcome of death were reported in 7 (5.4%) patients:

unexplained death in 3 patients (SID (b) (6)), respiratory failure in 2 patients, septic shock in 1 patient, and sudden death (SID (b) (6)) in 1 patient. Drug-related AE leading to death occurred in 2 patients (SID (b) (6) "death" as PT, causality unable to be assessed; SID (b) (6) "death" as PT, causality unable to be assessed).

SID (b) (6): On Day 3 after the 4 doses, the family found the patient fell in the bathroom at home without vital signs. The investigator judged the death was highly likely caused by trauma. SID (b) (6): The patient received the two doses after enrollment in the study and died 34 days after the last dose. No autopsy was performed, and the family members were unable to provide medical records and subsequently refused to answer the telephone, so a clear cause of death could not be obtained. SID (b) (6): On (b) (6), the patient slipped on the floor at home and did not hurt the head. At about 3:00 pm on (b) (6), the patient was accompanied by his family member for urinate at home, and the patient was unable to stand up and showed no response to voice. The family moved the patient to bed and did not send him to the hospital. SID (b) (6): On (b) (6), the patient experienced a car accident, and radiography showed multiple fractures of ribs and ruptured spleen. The patient was hospitalized in another hospital, and on (b) (6),

the patient was discharged from the hospital. On (b) (6), the patient was unconscious, and sent to the hospital by ambulance. The patient died from failure to rescue on the same day and was judged as sudden death by the local hospital.

Of those 7 patients, 3 patients were reported with primary cause of death as AE (SID (b) (6), "death" as PT; SID (b) (6), "septic shock" as PT; SID (b) (6), "sudden death " as PT).

Integrated Penpulimab 200 mg Safety Population

A total of 113 (30.4%) deaths occurred in the studies on dosing regimen of penpulimab 200 mg Q2W. A total of 12 (3.2%) deaths occurred within 30 days after the last dose of penpulimab.

Thirty-four (9.1%) patients had AEs that resulted in death, regardless of causality. Excluding disease progression, AEs with an outcome of death were reported in 12 (3.4%) patients. Of the 12 patients, 3 patients had AEs of unexplained death (SID (b) (6), SID (b) (6), SID (b) (6)), 3 patients had AEs of respiratory failure, and sudden death (SID (b) (6), pneumonia, septic shock, gastrointestinal hemorrhage, hemophagocytic lymphohistiocytosis, or cerebral infarction in 1 patient each. Drug-related AE leading to death occurred in 3 patients (SID (b) (6), "death" as PT, causality unable to be assessed; SID (b) (6), "death" as PT, causality unable to be assessed; SID (b) (6), "gastrointestinal hemorrhage" as PT, causality unable to be assessed).

Of those 12 patients, 7 patients were reported with primary cause of death as AE (SID (b) (6), "death" as PT; SID (b) (6), "septic shock" as PT; SID (b) (6), "sudden death " as PT; SID (b) (6), "pneumonia " as PT; SID (b) (6), "Respiratory failure" as PT; SID (b) (6), "gastrointestinal hemorrhage " as PT;). (SID (b) (6), "Hemophagocytic lymphohistiocytosis " as PT).

Deaths are summarized in [Table 22](#).

Full narratives for all fatal AEs in studies following penpulimab 200 mg Q2W are provided in Module 2.7.4 Appendix 9.3 Narratives of Deaths, Other Serious and Significant Adverse Events.

Table 22 – Applicant: Summary of Deaths

	7NPC 200mg Q2W (N=130)	200mg Q2W (N=372)
Death	47 (36.2%)	113 (30.4%)
Reason for death		
Adverse event	3 (2.3%)	7 (1.9%)
Disease progression	41 (31.5%)	94 (25.3%)
Unknown	1 (0.8%)	9 (2.4%)
Other	2 (1.5%)	3 (0.8%) ^[a]

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	7NPC 200mg Q2W (N=130)	200mg Q2W (N=372)
Death within 30 days after the last dose	2 (1.5%)	12 (3.2%)
Adverse event	0	2 (0.5%)
Disease progression	1 (0.8%)	8 (2.2%)
Other	1 (0.8%)	2 (0.5%)
Death within 90 days after the last dose	21 (16.2%)	62 (16.7%)
Adverse event	3 (2.3%)	7 (1.9%)
Disease progression	16 (12.3%)	51 (13.7%)
Unknown	0	1 (0.3%)
Other	2 (1.5%)	3 (0.8%)

Source: ADSL.xpt Module 5.3.5.3, Appendix 9.3, Table 10.

the investigator entered "other" as the primary cause of death in 3 patients: SID (b) (6) (Clinical progression), SID (b) (6) (Unexplained deaths), SID (b) (6) (The family refused to provide information).

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AEs leading to death are summarized in [Table 23](#).

Table 23 – Applicant: Grade 5 Adverse Events

System Organ Class Preferred Term†	NPC 200 mg Q2W N=130 n (%)	200 mg Q2W N=372 n (%)
Deaths due to adverse event	18 (13.8%)	34 (9.1%)
Deaths due to adverse event (excluding disease progression)	7 (5.4%)	12 (3.2%)
General disorders and administration site conditions		
Disease progression	11 (8.5%)	22 (5.9%)
Death	3 (2.3%)	3 (0.8%)
Sudden death ^a	1 (0.8%)	1 (0.3%)
Respiratory, thoracic, and mediastinal disorders		
Respiratory failure	2 (1.5%)	3 (0.8%)
Infections and infestations		
Pneumonia	0	1 (0.3%)
Septic shock	1 (0.8%)	1 (0.3%)
Gastrointestinal disorders		
Gastrointestinal hemorrhage	0	1 (0.3%)
Immune system disorders		
Hemophagocytic lymphohistiocytosis	0	1 (0.3%)
Nervous system disorders		
Cerebral infarction	0	1 (0.3%)

Source: ADAE.xpt Module 5.3.5.3, Appendix 9.3, Listing13.1, Listing17.

^a See Module 2.7.4 Appendix 9.2 Narratives of Deaths, Other Serious and Significant Adverse Events for details.

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Table 24 – Applicant: Grade 5 Adverse Events Within 30 Days of Last Dose of Penpulimab

Study	Patient ID	Age/	Study Day of Death	PT	Cause of Death	Related to Study Drug
AK105-202	(b) (6)	61/male	(b) (6)	Death	Other: trauma	Unlikely related
AK105-202		54/male		Disease progression	Disease progression	Not related
AK105-204		72/male		Gastrointestinal hemorrhage	Gastrointestinal hemorrhage	Not evaluable
AK105-204		63/female		Hemophagocytic lymphohistiocytosis syndrome	Infection related secondary hemophagocytic syndrome	Not related
AK105-204		61/female		Disease progression	Disease progression	Not related
AK105-204		64/female		Disease progression	Disease progression	Not related
AK105-101		63/male		Cerebral infarction	Disease progression	Not related
AK105-101		73/female		Malignant neoplasm progression	Other :clinical progression	Not related
AK105-201		63/female		Hemophagocytic lymphohistiocytosis	Hemophagocytic syndrome	Unlikely related

Source: ADSL.xpt, ADAE.xpt Module 5.3.5.3, Appendix 9.4, Table 1.1

The Applicant's Position

Most death cases in the clinical studies were related to disease progression. This is consistent with patients' underlying medical conditions, and possibly concomitant medications.

The FDA's Assessment

The FDA reviewed all fatal adverse events that occurred in patients from the primary safety population in Study AK105-202. A total of 5% of patients (n=7) had an event of death due to AEs that were not clearly related to disease progression. Of the 7 patients with a fatal AE, FDA only considers four events (3.1%) to be adverse reactions, including one event of respiratory failure (Patient (b) (6)) and three events of death (Patients (b) (6)) to be fatal adverse reactions. Patient (b) (6) (sudden death) died after a car accident. Patient (b) (6) (respiratory failure) likely died of disease progression. Patient (b) (6) (septic shock) died of fungal pneumonia. [Table 25](#) below describes the fatal AEs and FDA's determination of death causality in greater detail.

Table 25 – FDA: Assessment of Causality for Fatal Adverse Events Not Clearly Attributable to Disease Progression in Primary Safety Population

Patient ID	Brief Narrative	FDA's Assessment of Causality	(b) (4)
(b) (6)	65-year-old -female was hospitalized for Grade 3 bullous herpes simplex (pemphigoid), penpulimab was interrupted for 8-weeks during which the patient fell ^a at home without injuring her head. A few days later she was unable to stand and died at home. No autopsy was performed.	Death Given the history of Grade 3 bullous herpes simplex (pemphigoid), a CT scan performed a few weeks prior to death showed stable disease, and symptoms of being unable to stand developing several days after the fall, penpulimab's contribution to the patient's death cannot be ruled out.	Yes
(b) (6)	61-year-old-male who was found by family fallen ^a in the bathroom with no vital signs three days after the patient's last dose of penpulimab.	Sudden death Given the lack of information describing the circumstances of this patient's death, penpulimab's contribution to the event cannot be ruled out.	Yes
(b) (6)	63-year-old-male was hospitalized for Grade 2 pneumonia. ^a Chest X-ray showed pulmonary inflammation, treated with antibiotics and antipyretics. The patient was subsequently lost to follow up with unknown outcome of pneumonia. Patient died 34 days after the last dose of penpulimab; family was unreachable.	Death Given the lack of information describing the circumstances of this patient's death, penpulimab's contribution to the event cannot be ruled out.	Yes
(b) (6)	32-year-old male who received a total of 3 doses of study drug; CT scans post 3 rd dose showed disease progression with new hydrothorax in thoracic cavity and bilateral lower lungs, multiple new bone metastases. Patient was taken off the study and died of respiratory failure ^a 2 weeks later.	Disease progression Given the patient's known widespread metastatic disease, FDA determined that this patient's death was most likely due to disease progression.	No

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Patient ID	Brief Narrative	FDA's Assessment of Causality	(b) (4)
(b) (6)	31-year-old male was hospitalized for pneumonitis (Pneumonia). A fungal smear showed yeast-like fungus and candida albicans; treated with antifungal, antibiotics, and glucocorticoids. CT scan showed new left lobe inflammation and increased pleural effusion on the right side. Patient experienced recurrent pleural effusions. Repeat CT showed new infectious lesions, tracheal and bronchial narrowing, and increased pericardial effusion. Patient was discharged with a diagnosis of septic shock and superior vena cava syndrome ^a Two days later the patient died at home.	Fungal pneumonia FDA considers this death to be most likely due to progressive fungal pneumonia.	No
(b) (6)	60-year-old-female developed respiratory failure. ^a The patient had abnormal hepatic function at baseline defined by gamma-glutamyl transpeptidase 223 U/L, alkaline phosphatases 272 U/L, lactate dehydrogenase 3625 U/L, aspartate transaminases 77 U/L, adenosine deaminase 33 U/L, and aspartate aminotransferase 17.6 U/L. She was hospitalized with Grade 2 hepatic dysfunction after the first dose of penpulimab. However, after discharge she did not follow up and did not receive any subsequent therapy. She died 46 days later.	Death Given the lack of details around patient's death, penpulimab's contribution to death cannot be ruled out.	Yes
(b) (6)	51-year-old-male had a car accident with splenic rupture, and rib fracture. He was eventually discharged home with recovering rib fractures and unrecovered splenic rupture. Four days from hospital discharge he was found unconscious at home and brought to the ER but suffered sudden death ^a on the same day. No autopsy was done.	Sudden death FDA considers this event unlikely to be due to penpulimab given the recent car accident and unrecovered splenic rupture	No

Source: Module 5.3.5.3 (patient narratives)

^a AE is the condition to which the investigator attributed the patient's death

Abbreviations: CT, computed tomography; USPI; United States Prescribing Information

[Table 26](#) provides FDA’s summary of deaths in the primary safety population and pooled safety population.

Table 26 – FDA: Summary of Deaths in the Primary Safety Population and Pooled Safety Population

Summary of Deaths	NPC	All Tumor
	N = 130 N (%)	N = 372 N (%)
Total deaths	47 (36)	113 (30)
Disease progression	41 (32)	94 (25)
Adverse event	3 (2.3)	7 (1.9)
Other	2 (1.5)	3 (0.8)
Unknown	1 (0.8)	9 (2.4)
Within 30 days after last dose	0 (0)	2 (0.5)
Disease progression	0 (0)	1 (0.3)
Other	0 (0)	1 (0.3)
Beyond 30 days after last dose	45 (35)	101 (27)
Disease progression	40 (31)	86 (23)
Adverse event	3 (2.3)	5 (1.3)
Other	1 (0.8)	1 (0.3)
Unknown	1 (0.8)	9 (2.4)

Source: ADL (Subject Level Analysis) - 2021-06-01. Variables used: USUBJID, TRT01A, SAEFL, DTHREAS, DTB30TFL, DTA30TFL, DTHDT, DTHFL, TRTEDT

Abbreviations: N, total number of subjects; NPC, nasopharyngeal carcinoma

In the pooled safety population, death occurred in 12 (3.2%) patients due to AEs that were not clearly related to disease progression, including events of gastrointestinal hemorrhage, hemophagocytic lymphohistiocytosis, cerebral infarction, pneumonia, and respiratory failure.

8.1.4.2. Serious Adverse Events

Data

NPC Safety Population (Targeted Population)

Twenty-nine patients (22.3%) experienced at least one SAE. Excluding disease progression, 18 patients (13.8%) experienced at least one SAE. The most commonly (the incidence of PT ≥ 1%) reported SAEs (excluded disease progression) included, pneumonia, respiratory failure, pneumonitis, hepatic function abnormal and rash.

(b) (6)

Nine patients (6.9%) had SAEs that were considered by the investigator to be treatment-related, included death (SID (b) (6), SID (b) (6)) and pneumonitis occurred in 2 patients each. Other PTs were reported in 1 patient each, included pneumonia,

abdominal infection, herpes zoster disseminated, transaminases increased, pleural effusion, hepatic function abnormal, pemphigoid, and rash.

Integrated Penpulimab 200 mg Safety Population

Ninety-six (25.8%) patients had at least one SAE. Excluding disease progression, 74 patients (19.9%) experienced at least one SAE. The most commonly (the incidence of PT $\geq$ 1%) reported SAEs (excluded disease progression) included, pneumonia, gastrointestinal obstruction, abdominal pain, diarrhea, and musculoskeletal pain.

Twenty-five (6.7%) patients had SAEs that were considered by the investigator to be treatment-related. PTs reported in > 1 patient each included pneumonia, alanine aminotransferase increased, aspartate aminotransferase increased, pneumonitis, immune-mediated pneumonitis, death (SID (b) (6), SID (b) (6)), and hepatic function abnormal (2 patients each).

For the detailed description of each SAE, see Module 2.7.4 Appendix 9.3, Narratives of Deaths, Other Serious and Significant Adverse Events for details.

SAEs occurred are summarized by SOC and PT in [Table 27](#).

Table 27 – Applicant: Serious Adverse Events by SOC and PT (PT $\geq$ 1%)

System Organ Class Preferred Term†	NPC 200 mg Q2W N=130 n (%)	200 mg Q2W N=372 n (%)
Patients with at least one SAE	29 (22.3%)	96 (25.8%)
General disorders and administration site conditions		
Disease progression	11 (8.5%)	22 (5.9%)
Death ^a	3 (2.3%)	3 (0.8%)
Infections and infestations		
Pneumonia	5 (3.8%)	13 (3.5%)
Gastrointestinal disorders		
Gastrointestinal obstruction	0	6 (1.6%)
Abdominal pain	0	4 (1.1%)
Diarrhea	0	4 (1.1%)
Respiratory, thoracic, and mediastinal disorders		
Respiratory failure	2 (1.5%)	3 (0.8%)
Pneumonitis	2 (1.5%)	2 (0.5%)
Hepatobiliary disorders		
Hepatic function abnormal	2 (1.5%)	3 (0.8%)
Musculoskeletal and connective tissue disorders		
Musculoskeletal pain	1 (0.8%)	4 (1.1%)

	NPC 200 mg Q2W N=130 n (%)	200 mg Q2W N=372 n (%)
System Organ Class		
Preferred Term†		
Skin and subcutaneous tissue disorders		
Rash	2 (1.5%)	2 (0.5%)

Source: ADAE.xpt Module 5.3.5.3, Appendix 9.4, Table 1.2

† See Module 2.7.4 Appendix 9.2 Narratives of Deaths, Other Serious and Significant Adverse Events for details .

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The Applicant's Position

The most commonly reported SAE was pneumonia. The frequency and nature of SAEs were generally similar between the NPC safety population and studies on dosing regimen of penpulimab 200 mg Q2W and there were no clinically meaningful differences between these two populations for any SAEs.

The FDA's Assessment

The FDA agrees with the Applicant's position that the type and frequency of SAEs were generally similar between the two safety populations. The most common SAE across populations was pneumonia. The four SAEs of death among the patients in the primary safety population are described in further detail in Section 8.2.4.1 above. Overall, serious adverse events excluding events of disease progression occurred in 19% of patients in the primary safety population. Serious adverse events excluding events of disease progression occurred in 23% of patients in the pooled safety population.

Table 28 – FDA: Serious Adverse Events Occurring in ≥1% of Patients in the NPC and All Tumor Safety Populations

	NPC N = 130 N (%)	All Tumor N = 372 N (%)
Preferred Term		
Pneumonia ^a	5 (3.8)	13 (3.5)
Death ^b	4 (3.1)	4 (1.1)
Hepatitis ^c	3 (2.3)	7 (1.9)
Pneumonitis ^d	2 (1.5)	4 (1.1)
Respiratory failure	2 (1.5)	3 (0.8)
Rash ^e	2 (1.5)	2 (0.5)
Diarrhea ^f	0	4 (1.1)
Musculoskeletal pain ^g	1 (0.8)	4 (1.1)
Hemorrhage ^h	0	4 (1.1)

	NPC	All Tumor
	N = 130	N = 372
Preferred Term	N (%)	N (%)
Abdominal pain ⁱ	0	4 (1.1)

Source: ADSL (Subject Level Analysis) - 2021-06-01, ADAE (Adverse Events Analysis) - 2021-06-01. Variables used: USUBJID, TRT01A, SAFFL, TRTEMFL, AEDECOD, AETOXGRN, AEACN, AEBODSYS, AESER

^a Pneumonia includes lung infection, pneumonia, lower respiratory tract infection, pneumocystis jirovecii pneumonia.

^b Death includes death and sudden death

^c Hepatitis includes alanine aminotransferase increased, aspartate aminotransferase increased, blood bilirubin increased, hepatic function abnormal, and transaminases increased

^d Pneumonitis includes pneumonitis, immune-mediated pneumonitis.

^e Rash includes pemphigoid, rash, rash generalized

^f Diarrhea includes diarrhea, colitis.

^g Musculoskeletal pain includes back pain, musculoskeletal pain, pain in extremity, non-cardiac chest pain.

^h Hemorrhage includes gastrointestinal hemorrhage, hemoptysis.

ⁱ Abdominal pain includes abdominal pain, abdominal pain lower

Abbreviations: N, total number of subjects; NPC, nasopharyngeal carcinoma.

8.1.4.3. Dropouts and/or Discontinuations Due to Adverse Effects

Data

NPC Safety Population (Targeted Population)

Disease progression was the primary cause of treatment discontinuation (66/130, 50.8%). AE leading to discontinuation was reported in 5 (3.8%), the AEs were transaminase abnormal, spinal cord compression, disseminated herpes zoster, pemphigoid, and pleural effusion (1 patient each).

Integrated Penpulimab 200 mg Safety Population

Disease progression was the primary cause of treatment discontinuation (176/372, 47.3%). AE leading to discontinuation was reported in 22 (5.9%) patients. AEs resulting in permanent discontinuation of penpulimab reported in > 1 patient each were immune-mediated pneumonitis (in 3 patients), pleural effusion (in 2 patients), and gastrointestinal hemorrhage (in 2 patients).

Table 29 – Applicant: Summary of Treatment Discontinuation

	NPC 200 mg Q2W	200 mg Q2W
	N=130	N=372
	n (%)	n (%)
Treatment discontinuation due to adverse event	6 (4.6%) ^a	21 (5.6%)
Treatment discontinuation due to disease progression	66 (50.8%)	176 (47.3%)
Treatment discontinuation due to other	24 (18.5%)	56 (15.1%)

Source: ADAE.xpt Module 5.3.5.3, Appendix 9.4, Table 1.3.

^a SID (b) (6): Reason for ending treatment was indicated as “Sudden Death” (AE), but the investigator chose “not applicable” as the action taken with the investigational product for this AE.

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Table 30 – Applicant: Adverse Events Leading to Treatment Discontinuation

System Organ Class Preferred Term†	NPC 200 mg Q2W N=130 n (%)	200 mg Q2W N=372 n (%)
AEs leading to treatment discontinuation	5 (3.8%)	22 (5.9%) ^a
Respiratory, thoracic, and mediastinal disorders		
Immune-mediated pneumonitis	0	3 (0.8%)
Pleural effusion	1 (0.8%)	2 (0.5%)
Gastrointestinal disorders		
Gastrointestinal hemorrhage	0	2 (0.5%)
Ascites	0	1 (0.3%)
Colitis	0	1 (0.3%)
Infections and infestations		
Herpes zoster disseminated	1 (0.8%)	1 (0.3%)
Pelvic infection	0	1 (0.3%)
Septic shock	0	1 (0.3%)
Nervous system disorders		
Cerebral infarction	0	1 (0.3%)
Epilepsy	0	1 (0.3%)
Spinal cord compression	1 (0.8%)	1 (0.3%)
Immune system disorders		
Hemophagocytic lymphohistiocytosis	0	1 (0.3%)
Hypersensitivity	0	1 (0.3%)
Renal and urinary disorders		
Mesangioproliferative glomerulonephritis	0	1 (0.3%)
Renal injury	0	1 (0.3%)
Hepatobiliary disorders		
Cholangitis	0	1 (0.3%)
Investigations		
Transaminases increased	1 (0.8%)	1 (0.3%)
Skin and subcutaneous tissue disorders		
Pemphigoid	1 (0.8%)	1 (0.3%)

Source: ADAE.xpt Module 5.3.5.3, Appendix 9.4, Table 1.4.

^a SID (b) (6): Reason for ending treatment was indicated as “disease progression”, but this patient has “colitis” as AE leading to permanently discontinued. SID (b) (6): Reason for ending treatment was indicated as “the patient has not returned to the hospital for a long time to follow up and take drugs”, but this patient has “Immune-mediated pneumonitis” as AE leading to permanently discontinued.

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The Applicant's Position

The incidence of AEs resulting in permanent discontinuation of penpulimab was low and similar between AK105-202 and studies on dosing regimen of penpulimab 200 mg Q2W. There were no appreciable differences between the two populations for any of the SOC or PTs. AEs resulting in discontinuation of penpulimab were distributed across a broad range of PTs, with no specific SOC or PT accounting for most of the events (occurred in ≤1% of patients).

The FDA's Assessment

In Study AK105-202, permanent discontinuation of penpulimab due to an adverse event occurred in 5 (3.8%) patients. These were pleural effusion, herpes zoster disseminated infection, pemphigoid, spinal cord compression, and hepatitis (0.8% each).

In the pooled safety population, permanent discontinuation of penpulimab due to an adverse event occurred in 22 (6%) patients. These were immune mediated pneumonitis (0.8%), pleural effusion (0.5%), gastrointestinal hemorrhage (0.5%), hepatitis (0.3%), pemphigoid (0.3%), herpes zoster disseminated infection (0.3%), ascites (0.3%), cerebral infarction (0.3%), cholangitis (0.3%), colitis (0.3%), epilepsy (0.3%), hemophagocytic lymphohistiocytosis (0.3%), hypersensitivity (0.3%), nephritis (0.3%), pelvic infection (0.3%) septic shock (0.3%) and spinal cord compression (0.3%).

Table 31 – FDA: Adverse Events Leading to Permanent Discontinuation of Treatment in the NPC and All Tumor Safety Populations

Adverse Events	NPC N = 130 N (%)	All Tumor N = 372 N (%)
Herpes zoster disseminated	1 (0.8)	1 (0.3)
Pemphigoid	1 (0.8)	1 (0.3)
Pleural effusion	1 (0.8)	2 (0.5)
Hepatitis ^a	1 (0.8)	1 (0.3)
Spinal cord compression	1 (0.8)	1 (0.3)
Pneumonitis ^b	0	3 (0.8)
Ascites	0	1 (0.3)
Cerebral infarction	0	1 (0.3)
Cholangitis	0	1 (0.3)
Colitis	0	1 (0.3)
Epilepsy	0	1 (0.3)
Gastrointestinal hemorrhage	0	2 (0.5)
Hemophagocytic lymphohistiocytosis	0	1 (0.3)
Hypersensitivity	0	1 (0.3)
Nephritis ^c	0	2 (0.5)
Pelvic infection	0	1 (0.3)
Septic shock	0	1 (0.3)

Source: ADSL (Subject Level Analysis) - 2021-06-01. Variables used: USUBJID, TRT01A, SAFFL, DCTREAS

^a Hepatitis includes transaminases increased and abnormal hepatic function

^b Pneumonitis includes immune-mediated pneumonitis

^c Nephritis includes mesangioproliferative glomerulonephritis and renal injury

Abbreviations: N, total number of subjects; NPC, nasopharyngeal carcinoma

8.1.4.4. Dose Interruption/Reduction Due to Adverse Effects

Data

NPC Safety Population (Targeted Population)

Thirty-three (25.4%) patients experienced at least one AE leading to drug interruption. AEs resulting in drug interruption in > 1% of patients were alanine aminotransferase increased, pneumonia, hypothyroidism, hepatic function abnormal, anemia, and rash.

Integrated Penpulimab 200 mg Safety Population

Eighty-eight (23.7%) patients experienced at least one AE leading to drug interruption. AEs resulting in drug interruption in > 1% of patients were alanine aminotransferase increased, aspartate aminotransferase increased, pneumonia, diarrhea, hypothyroidism, hepatic function abnormal, anemia, musculoskeletal pain, and rash.

AEs leading to drug interruption are summarized by SOC and PT in [Table 32](#).

Table 32 – Applicant: Summary of Drug Interruption

System Organ Class Preferred Term†	NPC 200 mg Q2W N=130 n (%)	200 mg Q2W N=372 n (%)
Adverse events leading to drug interruption	33 (25.4%)	88 (23.7%)
Investigations		
Alanine aminotransferase increased	2 (1.5%)	8 (2.2%)
Aspartate aminotransferase increased	1 (0.8%)	7 (1.9%)
Infections and infestations		
Pneumonia	4 (3.1%)	8 (2.2%)
Gastrointestinal disorders		
Diarrhea	0	6 (1.6%)
Endocrine disorders		
Hypothyroidism	4 (3.1%)	7 (1.9%)
Hepatobiliary disorders		
Hepatic function abnormal	3 (2.3%)	5 (1.3%)
Blood and lymphatic system disorders		
Anemia	4 (3.1%)	5 (1.3%)
Musculoskeletal and connective tissue disorders		
Musculoskeletal pain	1 (0.8%)	5 (1.3%)
Skin and subcutaneous tissue disorders		
Rash	2 (1.5%)	6 (1.6%)

Source: ADAE.xpt Module 5.3.5.3, Appendix 9.4, Table 1.5.

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The Applicant's Position

The overall incidence of AEs resulting in drug interruption in AK105-202 was generally similar to that of the studies on dosing regimen of penpulimab 200 mg Q2W. There were no marked differences between the two populations for any of the SOC's or PTs.

The FDA's Assessment

In the primary safety population, interruption of penpulimab due to an adverse event occurred in 25% of patients (n=33). Adverse events which required dosage interruption in ≥ 1 of patients were hepatitis, hypothyroidism, pneumonia, anemia, pneumonitis, and rash.

In the pooled safety population, dosage interruption of penpulimab due to an adverse event occurred in 24% of patients (n=88). Adverse events which required interruption in $\geq 1\%$ of patients were hepatitis, hypothyroidism, anemia, pneumonia, musculoskeletal pain, rash, and diarrhea.

Table 33 – FDA: Adverse Events Leading to Treatment Interruption in $\geq 1\%$ of Patients in the NPC or All Tumor Safety Populations

Adverse Events	NPC N = 130 N (%)	All Tumor N = 372 N (%)
Hepatitis ^a	7 (5)	18 (4.8)
Anemia	4 (3.1)	5 (1.3)
Hypothyroidism ^b	4 (3.1)	7 (1.9)
Pneumonia ^c	4 (3.1)	8 (2.2)
Pneumonitis ^d	2 (1.5)	2 (0.5)
Rash ^e	2 (1.5)	4 (1.1)
Musculoskeletal pain ^f	1 (0.8)	5 (1.3)
Diarrhea ^g	0	7 (1.9)

Source: ADSL (Subject Level Analysis) - 2021-06-01, ADAE (Adverse Events Analysis) - 2021-06-01. Variables used: USUBJID, TRT01A, SAFFL, TRTEMFL, AEDECOD, AETOXGRN, AEACN, AEBODSYS, AESER

^a Hepatitis includes alanine aminotransferase increased, aspartate aminotransferase increased, blood bilirubin increased, gamma-glutamyltransferase increased, hepatic function abnormal, liver function test abnormal, liver injury

^b Hypothyroidism includes hypothyroidism, blood thyroid stimulating hormone increased, autoimmune hypothyroidism,

^c Pneumonia includes lung infection, pneumonia

^d Pneumonitis includes immune mediated pneumonitis, pneumonitis, interstitial lung disease.

^e Rash includes rash, dermatitis acneiform, eczema, rash maculo-papular, dermatitis, rash macular, pemphigoid, rash pruritic, lichen planus

^f Musculoskeletal Pain includes back pain, arthralgia, pain in extremity, non-cardiac chest pain, body pain, musculoskeletal pain, musculoskeletal chest pain, neck pain, myalgia, arthritis, musculoskeletal stiffness,

^g Diarrhea includes diarrhea, colitis autoimmune colitis

Abbreviations: N, total number of subjects; NPC, nasopharyngeal carcinoma

8.1.4.5. Significant Adverse Events

Data

Not Applicable.

The Applicant's Position

Select adverse events of special interest are discussed in Section [8.2.5](#).

AEs leading to drug interruption, including withdrawal of treatment are discussed in Section [8.2.4.3](#) and [8.2.4.4](#) above.

The FDA's Assessment

The FDA agrees with the Applicant's position.

8.1.4.6. Treatment Emergent Adverse Events and Adverse Reactions

Data

Study AK105-202

NPC Safety Population (Targeted Population)

One hundred and twenty-two out of 130 (93.8%) patients had at least one AE. Most patients had Grade 1 or 2 events; 41(31.5%) patients had at least one $\geq$ Grade 3 AEs. The incidence of drug-related AEs was 69.2% (90/130), and the incidence of $\geq$ Grade 3 drug-related AEs was 8.5% (11/130).

The most commonly (the incidence of PT $\geq$ 20%) reported AEs, included: anemia, hypothyroidism, and musculoskeletal pain. Common Grade 3-4 AEs (with an incidence of $\geq$ 2%) were rash, hyponatremia, and anemia.

Integrated Penpulimab 200 mg Safety Population

Three hundred and fifty-seven out of 372 patients had at least one AE. Most patients had Grade 1 or 2 events; 136 (36.6%) patients had at least one $\geq$ Grade 3 AEs was. The incidence of TRAEs was 70.4% (262/372), and the incidence of $\geq$ Grade 3 TRAEs was 9.1% (34/372)

The most commonly (the incidence of PT $\geq$ 20%) reported AEs, included: anemia, hypothyroidism, rash, and musculoskeletal pain. Common Grade 3-4 AEs (with an incidence of $\geq$ 2%) were rash.

The summary of all AEs is presented in [Table 34](#). AEs reported by patients are summarized by SOC and PT in [Table 35](#). The PT terms represent a group of relevant medical events were grouped together as one grouped term for the presentation.

Adverse drug reactions (ADRs) with penpulimab have been determined include the known risks associated with the anti-PD-1/PD -L1 drug class and most frequently AEs (≥10% of patients).

The ADR for proposed patient population presented in the prescribing label excluded lab abnormality AE. The lab abnormality by the CTCAE grade derived based on actual value was presented under a separate table included in the prescribing label.

Table 34 – Applicant: Summary of Adverse Events (Excluding Disease Progression)

	NPC 200 mg Q2W N=130 n (%)	200 mg Q2W N=372 n (%)
All-grade AEs	122 (93.8%)	355 (95.4%)
Grade 3-5 AEs	36 (27.7%)	122 (32.8%)
Grade 3-4 AEs	34 (26.2%)	118 (31.7%)
Grade 3	29 (22.3%)	105 (28.2%)
Grade 4	5 (3.8%)	13 (3.5%)
Grade 5 (deaths due to AEs)	7 (5.4%)	12 (3.2%)
SAEs	25 (19.2%)	86 (23.1%)
Treatment discontinuation due to AEs	5 (3.8%)	22 (5.9%)
Dose interruption due to AEs	33 (25.4%)	88 (23.7%)

Source: ADAE.xpt Module 5.3.5.3, Appendix 9.4, Table 1.6.1.

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Table 35 – Applicant: Adverse Events ≥10%

System Organ Class Preferred Term†	NPC 200 mg Q2W (N=130)			200 mg Q2W (N=372)		
	All Grades n (%)	Grade 3 n (%)	Grade 4 n (%)	All Grades n (%)	Grade 3 n (%)	Grade 4 n (%)
Patients with at least one TEAE	122 (93.8%)	21 (16.2%)	2 (1.5%)	357 (96.0%)	92 (24.7%)	9 (2.4%)
Investigations						
Alanine aminotransferase increased	17 (13.1%)	1 (0.8%)				0
Aspartate aminotransferase increased	21 (16.2%)	2 (1.5%)	0	57 (15.3%)	4 (1.1%)	0
White blood cell count decreased ^a	21 (16.2%)	1 (0.8%)	0	56 (15.1%)	6 (1.6%)	0
Weight decreased	22 (16.9%)	1 (0.8%)	0	56 (15.1%)	2 (0.5%)	0
Weight increased	12 (9.2%)	0	0	42 (11.3%)	1 (0.3%)	0
Blood thyroid stimulating hormone increased	15 (11.5%)	0	0	41 (11.0%)	3 (0.8%)	0
Gastrointestinal disorders						
Diarrhea	4 (3.1%)	0	0	42 (11.3%)	4 (1.1%)	0
General disorders and administration site conditions						
Pyrexia	19 (14.6%)	0	0	54 (14.5%)	2 (0.5%)	0
Fatigue ^b	8 (6.2%)	0	0	48 (12.9%)	3 (0.8%)	0
Infections and infestations						
Upper respiratory tract infection ^c	16 (12.3%)	1 (0.8%)	0	66 (17.7%)	1 (0.3%)	0

System Organ Class Preferred Term [†]	NPC 200 mg Q2W (N=130)			200 mg Q2W (N=372)		
	All Grades n (%)	Grade 3 n (%)	Grade 4 n (%)	All Grades n (%)	Grade 3 n (%)	Grade 4 n (%)
Metabolism and nutrition disorders						
Hyperuricemia ^d	10 (7.7%)	0	2 (1.5%)	38 (10.2%)	1 (0.3%)	3 (0.8%)
Hypoalbuminemia ^e	14 (10.8%)	0	0	21 (5.6%)	0	0
Hyponatremia	13 (10.0%)	3 (2.3%)	0	17 (4.6%)	4 (1.1%)	0
Blood and lymphatic system disorders						
Anemia	48 (36.9%)	4 (3.1%)	0	92 (24.7%)	9 (2.4%)	0
Musculoskeletal and connective tissue disorders						
Musculoskeletal pain ^f	29 (22.3%)	1 (0.8%)	0	89 (23.9%)	6 (1.6%)	0
Endocrine disorders						
Hypothyroidism	41 (31.5%)	0	0	83 (22.3%)	0	0
Skin and subcutaneous tissue disorders						
Rash ^g	15 (11.5%)	3 (2.3%)	0	85 (22.8%)	7 (1.9%)	0
Respiratory, thoracic, and mediastinal disorders						
Cough ^h	13 (10.0%)	0	0	41 (11.0%)	0	0

Source: ADAE.xpt Module 5.3.5.3, Appendix 9.4, Table 1.7.

The following terms represent a group of relevant medical events, not just a single event.

^a White blood cell count decreased includes leukopenia and white blood cell count decreased.

^b Fatigue includes asthenia, fatigue, and malaise.

^c Upper respiratory tract infection includes chronic sinusitis, nasopharyngitis, pharyngitis, rhinitis, sinusitis, tonsillitis, upper respiratory tract infection and viral upper respiratory tract infection.

^d Hyperuricemia includes blood uric acid increased and hyperuricemia.

^e Hypoalbuminemia includes blood albumin decreased and hypoalbuminemia.

^f Musculoskeletal pain includes arthralgia, back pain, bone pain, flank pain, limb discomfort, musculoskeletal chest pain, musculoskeletal pain, myalgia, neck pain, non-cardiac chest pain and pain in extremity.

^g Rash includes dermatitis, dermatitis acneiform, dermatitis allergic, dermatitis contact, eczema, lichen planus, miliaria, pemphigoid, pruritus, psoriasis, rash, rash generalized, rash macular, rash maculo-papular, rash pruritic and urticaria.

^h Cough includes cough and productive cough.

The Applicant's Position

The most common AEs (regardless of severity and causality) observed in AK105-202 were comparable to those of the studies on dosing regimen of penpulimab 200 mg Q2W.

Most of the AEs were Grade 1 or 2, indicating a tolerable safety profile of penpulimab.

The FDA's Assessment

Adverse events occurring in $\geq 10\%$ of patients in the primary and pooled safety populations are summarized in [Table 36](#) the table below.

Table 36 – FDA: Adverse Events Occurring in ≥10% of Patients in the NPC and All Tumor Safety Populations

	NPC (N = 130)		All Tumor (N = 372)	
	All Grades n (%)	Gr 3-4 n (%)	All Grades n (%)	Gr 3-4 n (%)
Adverse events (any)	122 (94)	23 (18)	357 (96)	101 (27)
Investigations				
Weight decreased	22 (17)	1 (0.8)	42 (11)	1 (0.3)
Weight increased	12 (9)	0	41 (11)	3 (0.8)
General disorders and administration site conditions				
Pyrexia	19 (15)	0	54 (15)	2 (0.5)
Fatigue ^a	8 (6)	0	48 (13)	3 (0.8)
Endocrine disorders				
Hypothyroidism ^b	41 (32)	0	88 (24)	0
Infections and infestations				
Upper respiratory tract infection ^c	16 (12)	1 (0.8)	66 (18)	1 (0.3)
Gastrointestinal disorders				
Colitis ^d	4 (3.1)	0	42 (11)	5 (1.3)
Musculoskeletal and connective tissue disorders				
Musculoskeletal pain ^e	29 (22)	1 (0.8)	41 (11)	1 (0.3)
Respiratory, thoracic, and mediastinal disorders				
Cough ^f	13 (10)	0	41 (11)	0
Skin and subcutaneous tissue disorders				
Rash ^g	15 (12)	2 (1.5)	73 (20)	5 (1.3)
Hepatobiliary disorders				
Hepatitis ^h	36 (28)	4 (3.1)	102 (27)	14 (3.7)

Source: ADSL (Subject Level Analysis) - 2021-06-01, ADAE (Adverse Events Analysis) - 2021-06-01. Variables used: USUBJID, TRT01A, SAFFL, TRTEMFL, AEDECOD, AETOXGRN, AEACN, AEBODSYS, AESER

a Fatigue includes asthenia, fatigue, and malaise

b Hypothyroidism includes hypothyroidism, primary hypothyroidism, blood thyroid stimulating hormone decreased, autoimmune hypothyroidism, thyroxine decreased, thyroid hormone decreased, thyroxine free decreased, triiodothyronine decreased, tri-iodothyronine free decreased

c Upper respiratory tract infection includes chronic sinusitis, nasopharyngitis, pharyngitis, rhinitis, sinusitis, tonsillitis, upper respiratory tract infection and viral upper respiratory tract infection

d Colitis includes diarrhea, colitis, autoimmune colitis

e Musculoskeletal pain includes musculoskeletal pain, musculoskeletal chest pain, back pain, neck pain, pain in extremity, limb discomfort, non-cardiac chest pain, arthralgia, bone pain, myalgia

f Cough includes cough and productive cough

g Rash includes dermatitis, dermatitis acneiform, dermatitis allergic, dermatitis contact, eczema, lichen planus, miliaria, pemphigoid, rash, rash macular, rash maculo-papular, rash pruritic, rash generalized and urticaria

h Hepatitis includes bilirubin conjugated increased, blood bilirubin increased, alanine aminotransferase increased, aspartate aminotransferase increased, liver injury, drug-induced liver injury, jaundice, hepatic failure, hepatic function abnormal, gamma-glutamyltransferase increased, liver function test abnormal, transaminases increased

Abbreviations: Gr, grade; N, total number of subjects; n, number of subjects in category; NPC, nasopharyngeal carcinoma

Adverse event types were generally similar between the primary safety population (NPC) and the pooled safety population (all tumor types), with the exception of a higher incidence of hypothyroidism in the NPC group compared to the all-tumor group (32% vs. 28%), which may be due to tumor location and history of radiation in the NPC patient population. There were higher incidences of rash and colitis in the all-tumor group compared to the NPC group (17% vs. 9% and 11% vs. 3.1%), although the significance of this finding is not clear.

8.1.4.7. Laboratory Findings

Data

NPC Safety Population (Targeted Population)

Most patients had Grade 1 or 2 laboratory abnormalities, common Grade 3-4 laboratory abnormalities (with an incidence of $\geq 5\%$) included gamma glutamyl transferase increased, phosphate decreased, sodium decreased, alkaline phosphatase increased, and lymphocytes decreased.

Integrated Penpulimab 200 mg Safety Population

Most patients had Grade 1 or 2 laboratory abnormalities, common Grade 3-4 laboratory abnormalities (with an incidence of $\geq 5\%$) included gamma glutamyl transferase increased, phosphate decreased, sodium decreased, and lymphocytes decreased.

The summary of all laboratory abnormalities is presented in [Table 37](#).

Table 37 – Applicant: Laboratory Abnormalities $\geq 10\%$

Category	NPC 200 mg Q2W (N=130)				200 mg Q2W (N=372)			
	All Grades	Grade 3	Grade 4		All Grades	Grade 3	Grade 4	
Laboratory Abnormalities	N	(%)	(%)	(%)	N	(%)	(%)	(%)
Chemistry								
Albumin decreased	129	45.0%	0.0%	0.0%	364	33.0%	0.8%	0.0%
Calcium increased	129	12.4%	0.8%	0.0%	361	19.7%	0.6%	0.3%
Cholesterol increased	128	18.8%	0.0%	0.0%	362	23.8%	0.0%	0.0%
Creatinine increased	129	10.1%	0.0%	0.0%	364	14.8%	0.0%	0.0%
Glucose increased	128	32.8%	0.0%	0.0%	362	34.8%	2.5%	0.3%
Magnesium decreased	129	27.1%	0.8%	0.0%	361	21.6%	0.8%	0.3%
Magnesium increased	129	12.4%	3.1%	0.0%	361	9.4%	2.2%	0.3%
Phosphate decreased	129	45.0%	7.8%	0.0%	363	30.6%	5.8%	0.0%
Potassium decreased	129	16.3%	3.9%	0.0%	364	13.7%	1.4%	0.5%
Sodium decreased	129	44.2%	5.4%	0.0%	364	34.3%	4.4%	0.0%
Triglycerides increased	128	35.9%	3.1%	0.0%	362	40.1%	2.2%	0.6%
Hematology								
Hemoglobin decreased	129	34.1%	3.9%	0.0%	364	32.4%	3.3%	0.0%
Leukocytes decreased	129	15.5%	0.8%	0.8%	364	19.8%	0.5%	0.3%
Lymphocytes decreased	129	43.4%	14.0%	1.6%	364	37.4%	9.6%	0.8%
Neutrophils decreased	129	12.4%	0.8%	0.8%	364	15.7%	0.8%	0.3%
Platelets decreased	129	13.2%	3.1%	1.6%	364	12.9%	1.6%	0.8%

Category	NPC 200 mg Q2W (N=130)				200 mg Q2W (N=372)			
	All Grades	Grade 3	Grade 4		All Grades	Grade 3	Grade 4	
Laboratory Abnormalities	N	(%)	(%)	(%)	N	(%)	(%)	(%)
Liver function								
Alanine aminotransferase increased	129	19.4%	3.9%	0.0%	364	25.5%	2.5%	0.0%
Alkaline phosphatase increased	129	33.3%	5.4%	0.0%	364	27.2%	4.1%	0.0%
Gamma glutamyl transferase increased	129	34.1%	6.2%	1.6%	364	28.6%	7.4%	1.9%
Aspartate aminotransferase increased	129	31.0%	3.9%	0.0%	364	33.0%	4.4%	0.0%
Bilirubin increased	129	13.2%	3.1%	0.0%	364	17.0%	2.7%	0.0%

Source: ADAE.xpt Module 5.3.5.3, Appendix 9.4, Table 2.

Note: If a patient had more than one toxicity grade for a laboratory test, only the worst grade is counted. Only the patients whose post-baseline toxicity grade was worsening than that at baseline are counted in the numerators.

Note: Grades are based on NCI CTCAE V4.03.

Note: Grade 1 of creatinine increases in CTCAE4.03 lacks clinical significance, so the safety CTCAE 5.0 to assess creatinine increase.

Abbreviations: NPC, nasopharyngeal carcinoma; Q2W, every two weeks

The Applicant's Position

Changes in laboratory parameters were predominantly Grade 1 or 2 in severity, and the incidence of any grade worsening to Grade 3 or 4 was generally low, suggesting a well-tolerated safety profile.

The FDA's Assessment

The FDA performed an independent analysis of safety data from the primary and pooled safety populations, summarized in [Table 38](#).

Table 38 – FDA: Select Laboratory Abnormalities (≥20%) Worsening From Baseline in the Primary and Pooled Safety Populations

Laboratory Abnormality	NPC N=130		All Tumor N=372	
	All Grades ^a (%)	Grade 3-4 ^a (%)	All Grades ^a (%)	Grade 3-4 ^a (%)
Chemistry				
Decreased phosphate	45	8	31	6
Decreased sodium	44	5	34	4
Increased triglycerides	36	3.1	40	3
Increased gamma-glutamyl transferase	34	8	29	9
Hematology				
Decreased lymphocytes	43	16	37	10
Decreased hemoglobin	34	3.9	32	3

Source:

^a Each test incidence is based on the number of patients who had both baseline and at least one on-study laboratory measurement available: penpulimab (range of the patient number: 128 to 130).

Abbreviations: N, total number of subjects; NPC, nasopharyngeal carcinoma

8.1.4.8. Vital Signs

Data

Changes from baseline to minimum, maximum value, and the end of treatment visit were summarized in Module 5.3.5.3 ISS, Appendix 9.2, Table 8.1.

The Applicant's Position

Changes from baseline to minimum or maximum and from baseline to end of treatment visit were generally small and not considered to be clinically meaningful for any of the vital parameters.

The FDA's Assessment

The FDA agrees with Applicant's position.

8.1.4.9. Electrocardiograms (ECGs)

Data

Shift table for ECGs of clinical significance from baseline to worst post-baseline were summarized in Module 5.3.5.3 ISS, Appendix 9.3, Table 7.1. For the integrated penpulimab 200 mg Q2W population, the change from normal at baseline to clinical significance at post-baseline for overall ECG finding was 3.6% (13/372).

The Applicant's Position

Electrocardiogram (ECG) assessments are part of routine safety monitoring. There was no evidence of clinically meaningful cardiac effects associated with penpulimab exposure.

The FDA's Assessment

The FDA agrees with Applicant's position.

8.1.4.10. QT Interval

Data

NPC Safety Population (Targeted Population)

No patients had a QTcF value > 500 msec or an increase from baseline > 90 msec. No patients had a QTcF value > 480 msec, 3 patients (2.3%) had an increase from baseline > 60 msec.

Integrated Penpulimab 200 mg Safety Population

Two patients (0.5%) had a QTcF value > 500 msec and 4 patients (1.1%) had an increase from baseline > 90 msec. Seven patients had a QTcF value > 480 msec and 14 patients (3.8%) had an increase from baseline > 60 msec.

The Applicant's Position

Individuals with clinically meaningful QTcF values and changes from baseline were found to have had either cardiac medical history or were receiving potentially cardioactive concomitant medications at the time of the abnormality or had single occurrences above the defined threshold.

The FDA's Assessment

The FDA agrees with Applicant's position.

8.1.4.11. Immunogenicity

Data

NPC Safety Population (Targeted Population)

The incidence of ADA positive after administration was 5.9% (7/119), with neutralizing antibodies detected in 4.2% (5/119). Three patients with ADA positive had at least one AE, no patient occurred drug related AE. Most frequently AEs for patients with ADA positive ($\geq 1\%$ of patients) included weight decreased (2.3%), pyrexia (1.5%), and anemia (1.5%).

Integrated Penpulimab 200 mg Safety Population

The incidence of ADA positive after administration was 12.5% (42/335), with neutralizing antibodies detected in 4.2% (14/335). Twenty-four patients had at least one AE, three patients occurred drug related AE. Most frequently AEs for patients with ADA positive ($\geq 1\%$ of patients) included alanine aminotransferase increased (2.2%), upper respiratory tract infection (2.4%), pyrexia (2.4%), and anemia (2.2%).

The Applicant's Position

In ADA-positive patients, the incidence and occurrence type of AE were generally similar to those of all patients, with no specific type of AE and no increased incidence of infusion-related reactions/hypersensitivities. Treatment emergent ADA had no significant impact on safety.

The FDA's Assessment

The FDA agrees with Applicant's position.

8.1.5. Analysis of Submission-Specific Safety Issues

8.1.5.1. Study AK105-202

Data

The summary of irAEs is presented in [Table 39](#).

Table 39 – Applicant: irAEs by irAE Group, irAE Subgroup and PT

irAE Category	NPC 200 mg Q2W (N=130)			200 mg Q2W (N=372)		
irAE Subcategory Preferred Term†	All Grades n (%)	Grade 3 n (%)	Grade 4 n (%)	All Grades n (%)	Grade 3 n (%)	Grade 4 n (%)
Patients with at least one irAE	29 (22.3%)	3 (2.3%)	0	76 (20.4%)	8 (2.2%)	0
Endocrine toxicity	20 (15.4%)	0	0	45 (12.1%)	0	0
Hypothyroidism	18 (13.8%)	0	0	35 (9.4%)	0	0
Hypothyroidism	17 (13.1%)	0	0	34 (9.1%)	0	0
Thyroxine free decreased	1 (0.8%)	0	0	1 (0.3%)	0	0
Tri-iodothyronine free decreased	1 (0.8%)	0	0	1 (0.3%)	0	0
Hyperthyroidism	8 (6.2%)	0	0	23 (6.2%)	0	0
Hyperthyroidism	6 (4.6%)	0	0	19 (5.1%)	0	0
Blood thyroid stimulating hormone decreased	3 (2.3%)	0	0	5 (1.3%)	0	0
Thyroxine free increased	2 (1.5%)	0	0	3 (0.8%)	0	0
Tri-iodothyronine free increased	0	0	0	2 (0.5%)	0	0
Tri-iodothyronine increased	0	0	0	1 (0.3%)	0	0
Other thyroid diseases	2 (1.5%)	0	0	4 (1.1%)	0	0
Autoimmune thyroid disorder	1 (0.8%)	0	0	1 (0.3%)	0	0
Autoimmune thyroiditis	0	0	0	1 (0.3%)	0	0
Thyroid mass	0	0	0	1 (0.3%)	0	0
Thyroiditis	1 (0.8%)	0	0	1 (0.3%)	0	0
Dermatologic toxicity	11 (8.5%)	3 (2.3%)	0	28 (7.5%)	3 (0.8%)	0
Rash	7 (5.4%)	2 (1.5%)	0	17 (4.6%)	2 (0.5%)	0
Eczema	1 (0.8%)	0	0	2 (0.5%)	0	0
Pruritus	0	0	0	2 (0.5%)	0	0
Rash generalized	0	0	0	2 (0.5%)	0	0
Rash maculo-papular	0	0	0	2 (0.5%)	0	0

irAE Category	NPC 200 mg Q2W (N=130)			200 mg Q2W (N=372)		
irAE Subcategory Preferred Term†	All Grades n (%)	Grade 3 n (%)	Grade 4 n (%)	All Grades n (%)	Grade 3 n (%)	Grade 4 n (%)
Dermatitis	0	0	0	1 (0.3%)	0	0
Dermatitis acneiform	1 (0.8%)	0	0	1 (0.3%)	0	0
Dermatitis allergic	1 (0.8%)	0	0	1 (0.3%)	0	0
Lichen planus	0	0	0	1 (0.3%)	0	0
Pemphigoid	1 (0.8%)	1 (0.8%)	0	1 (0.3%)	1 (0.3%)	0
Lung toxicity (pneumonia)	1 (0.8%)	0	0	4 (1.1%)	2 (0.5%)	0
Immune-mediated pneumonitis	1 (0.8%)	0	0	4 (1.1%)	2 (0.5%)	0
Gastrointestinal toxicity (diarrhea/colitis)	0	0	0	3 (0.8%)	0	0
Diarrhea	0	0	0	2 (0.5%)	0	0
Autoimmune colitis	0	0	0	1 (0.3%)	0	0
Hepatotoxicity (hepatitis)	0	0	0	2 (0.5%)	2 (0.5%)	0
Alanine aminotransferase increased	0	0	0	2 (0.5%)	2 (0.5%)	0
Aspartate aminotransferase increased	0	0	0	2 (0.5%)	2 (0.5%)	0
Renal toxicity (nephritis/ renal insufficiency)	0	0	0	2 (0.5%)	1 (0.3%)	0
Nephritis	0	0	0	1 (0.3%)	0	0
Mesangioproliferative glomerulonephritis	0	0	0	1 (0.3%)	0	0
Renal insufficiency	0	0	0	1 (0.3%)	1 (0.3%)	0
Renal injury	0	0	0	1 (0.3%)	1 (0.3%)	0
Neurotoxicity	0	0	0	1 (0.3%)	1 (0.3%)	0
Nerve injury	0	0	0	1 (0.3%)	1 (0.3%)	0
Rheumatoid / skeletal muscle toxicity	0	0	0	1 (0.3%)	1 (0.3%)	0
Arthralgia	0	0	0	1 (0.3%)	1 (0.3%)	0

Source: ADAE.xpt Module 5.3.5.3, Appendix 9.4, Table 1.10.
,, ; PT, preferred term;

Immune-Mediated Pneumonitis

Immune-mediated pneumonitis occurred in 1.1% (4/372) of patients receiving penpulimab, including two Grade 3 (0.5%), and two Grade 2 (0.5%) adverse reactions. Pneumonitis led to permanent discontinuation of penpulimab in three of those four patients. High-dose of systemic corticosteroids were administered to all four patients with pneumonitis. Pneumonitis resolved with sequelae in 1 patient.

Immune-Mediated Colitis

Immune-mediated colitis occurred in 0.8% (3/372) of patients receiving penpulimab. All were Grade 2 (0.8%) adverse reactions.

Systemic corticosteroids were administered to all 3 patients with colitis. Colitis led to withholding of penpulimab in all 3 patients. Of those 3 patients from whom penpulimab was withheld for colitis, 2 patients reinitiated penpulimab after symptom improvement; 1 of those 2 patients experienced recurrence of colitis. Colitis resolved in 2 of those 3 patients.

Immune-Mediated Hepatitis

Immune-mediated hepatitis occurred in 0.5% (2/372) of patients receiving penpulimab. Both were Grade 3 (0.5%) adverse reactions. Hepatitis led to withholding of penpulimab in both patients.

Systemic corticosteroids were administered to those 2 patients with hepatitis. Hepatitis resolved in one of those 2 patients. Of the 2 patients from whom penpulimab was withheld for immune-mediated hepatitis, one reinitiated penpulimab after symptom improvement and this patient experienced recurrence of hepatitis.

Immune-Mediated Endocrinopathies

Hypothyroidism

Immune-mediated hypothyroidism occurred in 9% (35/372) of patients receiving penpulimab, including twenty-two Grade 2 (6%) and thirteen Grade 1 (3.5%) adverse reactions. No patient permanently discontinued penpulimab due to hypothyroidism. Hypothyroidism led to withholding of penpulimab in 1.9% (7/372) of patients.

All patients (35/35) received endocrine therapy. 1 patient received additional immunosuppressant therapy. Of the 7 patients from whom penpulimab was withheld for hypothyroidism, all reinitiated penpulimab after symptom improvement: 5 experienced recurrences of hypothyroidism. Hypothyroidism resolved in 37% (13/35) of patients.

Hyperthyroidism

Immune-mediated hyperthyroidism occurred in 6% (23/372) of patients receiving penpulimab, including four Grade 2 (1.1%) and nineteen Grade 1 (5.1%) adverse reactions. No patient permanently discontinued of penpulimab due to hyperthyroidism. Hyperthyroidism led to withholding of penpulimab in 0.5% (2/372) of patients. Events resolved in 87% (20) of the 23 patients. Endocrine therapy was administered in 13% (3/23) of patients.

Thyroiditis

Thyroiditis occurred in 0.5% (2/372) of patients receiving penpulimab. Thyroiditis led to withholding of penpulimab in 0.3% (1/372) of patients. One of them (1/2) received endocrine therapy. Events resolved in these two patients.

Immune-Mediated Nephritis With Renal Dysfunction

Immune-mediated nephritis occurred in 0.5% (2/372) of patients receiving penpulimab, including one Grade 3 (0.3%) and one Grade 2 (0.3%) adverse reactions. All patients were permanently discontinued penpulimab due to nephritis. Systemic corticosteroids were administered to those 2 patients. Events resolved in one of these 2 patients.

Immune-Mediated Dermatologic Adverse Reactions

Immune-mediated rash or dermatitis occurred in 7.5% (28 /372) of patients receiving penpulimab, including three Grade 3 (0.8%), eight Grade 2 (2.2%) and seventeen Grade 1 (4.6%) adverse reactions. Systemic corticosteroids were administered in 17.9% (5/28) patients with immune-mediated rash or dermatitis. Immune-mediated dermatologic adverse reactions led to permanent discontinuation of penpulimab in 0.3% (1/372) of patients and withholding of penpulimab in 1.1% (4/372) of patients. Of the 4 patients from whom penpulimab were withheld for dermatologic adverse reactions, all reinitiated penpulimab after symptom improvement; three experienced recurrences of hypothyroidism. Events resolved in 64.3% (18/28) of patients.

Other Immune-Mediated Adverse Reactions

The following clinically significant, immune-mediated adverse reactions occurred at an incidence of <1% in patients who received penpulimab 200 mg Q2W: nerve injury, and arthralgia.

Infusion-Related Reactions

The infusion-related reactions occurred in 15 patients (4%) following dosing regimen of penpulimab 200 mg Q2W, including Grade 1 in 3 patients, Grade 2 in 12 patients. No patients occurred Grade 3-4 infusion-related reactions. One patient (0.8%) experienced Grade 1 hypersensitivity in proposed patient population (Study AK105-202).

The Applicant's Position

The common irAEs ($\geq 5\%$) were hyperthyroidism, hypothyroidism, and rash. The majority of irAEs in studies on dosing regimen of penpulimab 200 mg Q2W were Grade 1 or 2 in severity. $\geq$

Grade 3 irAEs generally occurred at a low rate (< 1%) and were spread among the different categories.

The FDA's Assessment

The Applicant defined an immune related AE as a suspected event which based on medical review is consistent with an immune mediated mechanism of action, and there were no alternative etiologies. When applicable, serologic, immunologic, and histologic (biopsy) data were used to support the characterization of an irAE. Potential irAEs, included but were limited to immune-mediated colitis, dermatitis, pneumonia, hepatitis, encephalitis, nephritis, hypothyroidism, and hyperthyroidism.

In the primary safety population (N=130), the most common irAEs ($\geq 0.5\%$) were hypothyroidism, hyperthyroidism, dermatitis, and pneumonitis. In the pooled safety population (N=372), the most common irAEs ($\geq 0.5\%$) were hypothyroidism, hyperthyroidism, dermatitis, hepatitis, pneumonitis, colitis, and nephritis. There were no fatal irAEs observed in the pooled safety population or the primary safety population. No IRRs were reported in the primary safety population, and infusion related reactions occurred in 4% of patients in the pooled safety population.

Table 40 – FDA: Assessment of irAEs in Primary and Pooled Safety Populations

Composite ^a /Preferred Term, n (%)	NPC 200mg N=130		All Tumor N=372	
	All Grades	Grade 3/4	All Grades	Grade 3/4
Number of patients with any treatment-emergent Applicant-identified irAE, n (%)	29 (22%)	3 (2.3%)	76 (20%)	8 (2.2%)
Hypothyroidism ^a	19 (15%)	0	35 (9%)	0
Hyperthyroidism ^b	8 (6%)	0	23 (6%)	0
Dermatitis ^c	11 (9%)	3 (2.3%)	28 (8%)	3 (0.8%)
Pneumonitis ^d	1 (0.8%)	0	4 (1.1%)	2 (0.5%)
Colitis ^e	0	0	3 (0.8%)	0
Hepatotoxicity/hepatitis ^f	0	0	2 (0.5%)	2 (0.5%)
Nephritis/renal insufficiency ^g	0	0	2 (0.5%)	1 (0.3%)

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Composite ^a /Preferred Term, n (%)	NPC 200mg N=130		All Tumor N=372	
	All Grades	Grade 3/4	All Grades	Grade 3/4
Neurotoxicity ^h	0	0	1 (0.3%)	0
Myositis	0	0	1 (0.3%)	0

Source: ADAE.xpt. Module 5.3.5.3

Note: Each irAE group term includes multiple MedDRA preferred terms. A patient is counted only once for multiple occurrences within an irAE group/preferred term.

^a Hypothyroidism includes blood thyroid stimulating hormone decreased, clinical hypothyroidism, hypothyroidism, free thyroxine decreased by 1 level, free thyroxine decreased, FT3 decreased, FT4 decreased, subclinical hypothyroidism, thyrotropin decreased, triiodothyronine decreased, tri-iodothyronine free decreased, worsening of hypothyroidism.

^b Hyperthyroidism includes hyperthyroidism, elevated thyroid stimulating hormone, thyroiditis, TSH increased, TSH level rose, FT4 increased, thyroglobulin antibody positive, thyrotropin increased, thyroxine free increased

^c Dermatitis includes allergic rash, bullous pemphigoid, dermatitis, eczema, facial rash, facial skin rash, generalized rash, hand, eczema, immune rash, lichen planus limbs rash, low back rash, maculopapular rash (chest and back), rash acneiform, rash maculo-papular bilateral lower legs, rash (inner and outer thighs), rash (unknown location), skin rash, skin rash of extremities, skin rash on face, the feet skin rash, the rash (chest back and limbs), the rash (the legs and belly), the small of the back skin rash, the whole body rash.

^d Pneumonitis includes immune-associated pneumonia, immune-mediated pneumonia, immune-mediated pneumonitis, immunoassociated pneumonitis.

^e Colitis includes autoimmune colitis, colitis, diarrhea.

^f Hepatotoxicity/hepatitis includes alanine aminotransferase increased, ALT increase, aspartate aminotransferase increased, AST increase, bilirubin conjugated increased, blood bilirubin increased, hepatic pain, hepatic function abnormal

^g Nephritis/ renal Insufficiency includes kidney injury, mesangial proliferative glomerulonephritis, nephritis.

^h Neurotoxicity includes immune-related nerve damage.

Abbreviations: ALT, alanine aminotransferase; AST, aspartate aminotransferase; FT3, free triiodothyronine; FT4, free thyroxine; irAE; immune-related adverse event; MedRA, Medical Dictionary for Regulatory Activities; N, total number of subjects; n, number of subjects in category; NPC, nasopharyngeal carcinoma; TSH, thyroid stimulating hormone

Additional results of FDA analyses and review used to inform Section 5 (Warnings and Precautions) of the proposed labeling are presented below.

Pneumonitis

Primary safety population (N=130): Immune-mediated pneumonitis occurred in 0.8% (1/130) of patients receiving penpulimab (Grade 2), which required corticosteroids. There were no Grade 3 or 4 adverse events.

Pooled safety population (N=372): Immune-mediated pneumonitis occurred in 1.1% (4/372) of patients, including two Grade 2 (0.5%) and two Grade 3 (0.5%) adverse reactions. Systemic corticosteroids were required in all four patients. Penpulimab was permanently discontinued due to pneumonitis in three patients and was interrupted and reintroduced following resolution in one patient.

Colitis

Primary safety population (N=130): No patients developed immune-mediate colitis.

Pooled safety population (N=372): Immune-mediated colitis occurred in 0.8%, (3/372) of patients; all were Grade 2 in severity and required systemic corticosteroids. Penpulimab was interrupted and reintroduced following resolution in two patients and permanently discontinued in one patient.

Hepatotoxicity and Immune-Mediated Hepatitis

Primary safety population (N=130): No patients developed immune-mediated hepatitis or hepatotoxicity.

Pooled safety population (N=372): Immune-mediated hepatitis occurred in 0.5% (2/372), both of which were Grade 3. Systemic corticosteroids were required in both patients. Penpulimab was interrupted and reintroduced following resolution in one patient and permanently discontinued in one patient.

Endocrinopathies

Hypothyroidism

Primary safety population (N=130): Immune-mediated hypothyroidism occurred in 14% (19/130) of patients, including six Grade 2 (6%) and thirteen Grade 1 (8%) adverse reaction. Penpulimab was withheld in 3.1% of patients and not permanently discontinued in any of the patients due to hypothyroidism.

Pooled safety population (N=372): Immune-mediated hypothyroidism occurred in 9% (35/372) of patients, including 22 Grade 2 (6%) and thirteen Grade 1 (3.5%) adverse reactions. Penpulimab was withheld in 1.9% (7/372) of patients, all of whom reinitiated penpulimab after symptom improvement. All patients required endocrine therapy.

Hyperthyroidism

Primary safety population (N=130): Immune-mediated hyperthyroidism occurred in 6% (8/130) of patients, including two Grade 2 (1.5%) and six Grade 1 (4.6%) irAEs. No patient permanently discontinued of penpulimab due to hyperthyroidism. Hyperthyroidism led to withholding of penpulimab in 0.8% (1/130) of patients. Antithyroid drug therapy was administered in 13% (1/8) of patients.

Pooled safety population (N=372): Immune-mediated hyperthyroidism occurred in 6% (23/372) of patients, including four Grade 2 (1.1%) and 19 Grade 1 (5%) adverse reaction. Penpulimab was withheld in one patient.

Thyroiditis

Primary safety population (N=130): Thyroid disease occurred in 1.5% (2/130) of patients, including one Grade 1 event of thyroiditis, one Grade 2 event of thyroid disorder. Penpulimab was withheld in one patient and not permanently discontinued in any of the patients due to immune mediated thyroiditis.

Pooled safety population (N=372): Thyroiditis occurred in 0.5% (2/372) of patients, including one Grade 2 and one Grade 1 adverse reaction. Penpulimab was withheld in one patient and not permanently discontinued in any patient due to thyroiditis.

Immune-Mediated Nephritis With Renal Dysfunction

Primary safety population (N=130): No patients developed immune-mediated nephritis.

Pooled safety population (N=372): Immune-mediated nephritis occurred in 0.5% (2/372) of patients, including one Grade 2 and one Grade 3 adverse reaction. Systemic corticosteroids were required and penpulimab was permanently discontinued due to nephritis in both patients. Nephritis resolved in one patient.

Immune-Mediated Rash or Dermatitis

Primary safety population (N=130): Immune-mediated rash or dermatitis occurred in 9% (11 patients), including two Grade 3 rash, one Grade 3 pemphigoid, five Grade 1 /2 rash, one Grade 1 eczema, one Grade 2 allergic dermatitis, one Grade 2 dermatitis acneiform. Systemic corticosteroids were required in 18% (2/11) of the patients with immune-mediated rash or dermatitis. Penpulimab was withheld in 1.5% (2/130) and permanently discontinued in 0.8% (1/130) of patients.

Pooled safety population (N=372): Immune-mediated rash or dermatitis occurred in 8% (28/372) of patients, including three Grade 3 (0.8%). Systemic corticosteroids were required in 18% (5/28) of patients with immune-mediated rash or dermatitis. Penpulimab was withheld in 1.1% (4/372) of patients and permanently discontinued in 0.3% (1/372) of patients. Dermatologic adverse reactions resolved in 64% (18/28) of patients.

8.1.5.2. Clinical Outcome Assessment (COA) Analyses Informing Safety/Tolerability

Data

Not Applicable.

The Applicant's Position

None of the studies supporting this application collected clinical outcome assessment (COA) data.

The FDA's Assessment

The FDA agrees with the Applicant's position.

8.1.6. Safety Analyses by Demographic Subgroups

Data

This section summarizes the relationship between various intrinsic factors and the safety profile of penpulimab. These data are relevant to patient management based on demographic or other 'intrinsic' factors. Only notable differences (≥ 10 -percentage points) are discussed.

The safety profile of penpulimab was assessed in relation to the following intrinsic factors:

- Sex (male, female)
- Age (> 65 , ≤ 65 years)
- ECOG performance status (0, 1)

Sex

In proposed patient population, the AE profile of penpulimab was generally similar in both females and males. AEs leading to drug discontinuation occurred at a higher rate in females than males (6.5% vs 3.0%, respectively), this observation should be interpreted in the context of the small sample size of the female subgroup.

For the integrated penpulimab 200 mg population, there was no appreciable difference between females and males for any of the AE categories.

Age

For the integrated penpulimab 200 mg population, there was no appreciable difference between age subgroups for any of the AE categories. The differences between age subgroups in the proposed patient population cannot be assessed due to only 2 patients with age > 65 years enrolled.

ECOG Performance Status

In proposed patient population, the incidence of events was similar in patients with a baseline ECOG performance status of 0 and 1 for most AE categories. However, notable differences were observed for Grade 3 or higher AEs (17.5% vs 37.8%) and SAEs (12.5% vs 26.7%), all of which occurred at a higher rate in patients with an ECOG performance status of 1 compared with ECOG performance status of 0.

For the integrated penpulimab 200 mg population, the AE profile of penpulimab was generally similar in patients with a baseline ECOG performance status of 0 and 1, except for Grade 3 or higher AEs (31.4% vs 40.3%) and SAEs (20.5% vs 29.6%), both of which occurred at a lower rate in patients with an ECOG performance status of 0.

The Applicant's Position

The AE profile for integrated penpulimab 200 mg population was generally similar across subgroups based on age and sex.

The incidence of AEs of any grade was generally similar between ECOG subgroup, and lower incidence rate of grade 3 or higher AEs and SAEs in patients with ECOG performance status of 0 were observed.

The FDA's Assessment

FDA reviewed the incidence of AEs by age and sex in the primary and pooled safety populations. A review of safety by race and ethnicity was not possible for the primary safety population given that all patients enrolled in Study AK105-202 were Asian.

In Study AK105-202, 128 (98%) and 2 (1.5%) patients treated with penpulimab were < 65 and ≥ 65 years, respectively. Given that only 2 patients in the primary safety population were older than 65 years of age, no conclusions can be drawn about the differences in AEs between older and younger patients. In the pooled safety population, 303 (81%) and 69 (19%) of patients were age <65 and ≥65 years, respectively. In Study AK105-202, 32 (25%) patients < 65 years had at least one Grade 3-4 AE while 2 (100%) of patients ≥ 65 years of age had a Grade 3-4 AE. In the pooled safety population, Grade 3-4 AEs occurred in 90 (30%) and 28 (41%) patients age <65 and ≥65 years, respectively.

Among the 130 patients who received penpulimab in Study AK105-202, 99 (76%) were male and 31 (24%) were female. In the pooled safety population, 238 (64%) patients were male and 134 (36%) were female. In Study AK105-202, the incidence of Grade 3-4 AEs in male patients vs female patients were 27 (28%) vs 4 (13%), respectively. In the pooled safety population, the incidence of Grade 3 and 4 AEs among male patients vs female patients were 85 (38%) and 32 (24%), respectively.

In the primary safety population, 90 (69%) patients had an ECOG performance status (PS) of 1 and 40 (31%) patients had an ECOG PS of 0. The incidence of all grade AEs was similar among ECOG PS of 1 or 0; however, Grade 3 or higher AEs occurred in 38% of patients with ECOG PS 1 compared to 18% of patients with ECOG PS of 0. In the pooled safety population, 216 (58%) patients had an ECOG PS of 1 and 156 (42%) patients had an ECOG PS of 0. The incidence of Grade 3 or higher AE occurred in 150 (40%) patients with ECOG PS of 1 and 117 (31%) with an ECOG PS 0. The higher incidence of Grade 3 or higher AEs in patients with ECOG PS of 1 compared to those with an ECOG PS of 0 is likely due to the relatively poorer baseline condition of these patients.

The FDA agrees with the Applicant's position that age and sex did not appear to have a major impact on the safety profile of penpulimab.

Table 41 – FDA: AEs That Lead to Discontinuation Based on Age and Sex in Primary Safety Population

AE Resulting in Discontinuation	NPC N=130		
	N (%)	Sex	Age
Bullous pemphigoid	1 (0.8%)	F	>65
Transaminases increased	1 (0.8%)	M	≤65
Pleural effusion	1 (0.8%)	M	≤65
Spinal cord compression	1 (0.8%)	M	≤65
Herpes zoster disseminated	1 (0.8%)	F	≤65

Source: ADAE (Adverse Events Analysis) - 2021-06-01.

Abbreviations: AE, adverse event; F, female; M, male; N , total number of patients; NPC, nasopharyngeal carcinoma

8.1.7. Specific Safety Studies/Clinical Trials

Data

Not Applicable.

The Applicant's Position

Not Applicable.

The FDA's Assessment

Not Applicable.

8.1.8. Additional Safety Explorations

8.1.8.1. Human Carcinogenicity or Tumor Development

Data

Not Applicable.

The Applicant's Position

No assessment of human carcinogenicity or tumor development was performed.

The FDA's Assessment

Not Applicable.

8.1.8.2. Human Reproduction and Pregnancy

Data

Not Applicable.

The Applicant's Position

Penpulimab has not been studied in pregnant or breastfeeding women. As of the DCO dates for studies on dosing regimen of penpulimab 200 mg Q2W, there were no reports of pregnancies or pregnancy-related events in either study. Based on its mechanism of action, penpulimab has the potential to impact maintenance of pregnancy and may cause fetal harm when administered to a pregnant woman. Human IgG1 is known to cross the placental barrier; therefore, penpulimab has the potential to be transmitted from the mother to the developing fetus. penpulimab is not recommended during pregnancy and in women of childbearing potential not using effective contraception during treatment and for at least 3 months after the last dose.

There is no information regarding the presence of penpulimab in human milk, the absorption and effects on the breastfed infant, or the effects on milk production. Human IgG is excreted in human milk. Because of the potential for adverse reactions in breastfed infants from penpulimab, advise a lactating woman not to breastfeed during treatment and for at least 5 months after the last dose.

The FDA's Assessment

The FDA agrees with the Applicant's position.

8.1.8.3. Pediatrics and Assessment of Effects on Growth

Data

There are no available human data on penpulimab use in pediatrics.

The Applicant's Position

 (b) (4)
The safety and effectiveness of penpulimab have not been established in pediatric patients <12 years old.

The FDA's Assessment

The FDA agrees with Applicant's position that the safety and effectiveness of penpulimab has not been established in pediatric patients under 12 years of age.

8.1.8.4. Overdose, Drug Abuse Potential, Withdrawal, and Rebound

Data

There are no available safety data for penpulimab overdose.

The Applicant's Position

There is no specific treatment in the event of penpulimab overdose and possible symptoms have not been established.

As a result of its use, mode of action, physiological and pharmacological activity, and lack of stimulant properties, penpulimab monotherapy is unlikely to be abused. Because penpulimab has no known potential for dependence and is not continuously dosed, withdrawal or rebound events are not relevant to penpulimab dosing.

The FDA's Assessment

The FDA agrees with the Applicant's position.

8.1.9. Safety in the Postmarket Setting

8.1.9.1. Safety Concerns Identified Through Postmarket Experience

Data

Not Applicable.

The Applicant's Position

Penpulimab is not currently approved or marketed in any country.

The FDA's Assessment

The FDA agrees with the Applicant's position.

8.1.9.2. Expectations on Safety in the Postmarket Setting

Data

Not Applicable.

The Applicant's Position

In post market setting, a confirmatory phase 3 study in the first-line treatment of recurrent or metastatic NPC will be completed. Patients were randomized to receive penpulimab 200 mg Q3W/placebo in combination with chemotherapy.

The FDA's Assessment

The FDA agrees that there is an ongoing randomized trial of penpulimab in combination with platinum-based chemotherapy; however, given the planned Complete Response action, this section is not applicable.

8.1.10. Integrated Assessment of Safety

Data

Not Applicable.

The Applicant's Position

The safety profile of proposed patient population is consistent with the well-characterized safety profile of the integrated penpulimab 200 mg population. The overall safety profile of penpulimab was tolerable, manageable, and consistent with other marketed PD-1 inhibitors.

The demographic and disease characteristics of patients in the NPC safety analysis set were representative of the intended population to be treated in clinical practice.

In proposed patient population, the most commonly (the incidence of PT $\geq$ 20%) reported AEs, included: anemia, hypothyroidism, and musculoskeletal pain. Common Grade 3-4 AEs (with an incidence of $\geq$ 2%) were rash, hyponatremia, and anemia.

The incidence of high-grade AEs and AEs resulting in discontinuation of penpulimab was low and consistent between the two populations. In proposed patient population:

- Common Grade 3-4 AEs (with an incidence of $\geq$ 2% of patients) included hyponatremia, anemia, and rash. These were generally manageable and reversible.
- Excluding disease progression, 18 patients (13.8%) experienced at least one SAE. The most commonly (the incidence of PT $\geq$ 1%) reported SAEs (excluded disease progression) included, pneumonia, respiratory failure,.
- 5 (3.8%) AEs led to treatment discontinuation, included transaminase abnormal, spinal cord compression, disseminated herpes zoster, pemphigoid, and pleural effusion (1 patient each).

Overall, the incidence of irAE were similar across proposed patient population and integrated penpulimab 200 mg safety population. In proposed patient population:

- Twenty-nine (22.3%) patients experienced at least one irAE; a majority of the confirmed irAEs were Grade 1 or 2 severity. The most common irAEs ($\geq 1\%$ of patients) including hypothyroidism (17, 13.1%), rash (7, 5.4%), hyperthyroidism (6, 4.6%), blood thyroid stimulating hormone decreased (3, 2.3%), and thyroxine free increased (2, 1.5%).
- 3 patients (2.3%) experienced Grade 3 irAEs, including rash (Grade 3) in 2 patients (1.5%) and pemphigoid (Grade 3) in 1 patient (0.8%). There were no CTCAE Grade 4 or 5 irAEs. One patient (0.8%) experienced hypersensitivity and no infusion-related reactions occurred.

Changes in laboratory parameters were predominantly Grade 1 or 2 in severity, and the incidence of any grade worsening to Grade 3 or 4 was generally low. Laboratory abnormalities reported as AEs infrequently resulted in discontinuation of penpulimab, suggesting a tolerable safety profile.

The safety profile was generally not affected by age, [REDACTED], and other factor (e.g., ECOG performance status).

The FDA's Assessment

FDA conducted the safety review of penpulimab in 130 patients with metastatic NPC who had disease progression on or after platinum-based chemotherapy and at least one other prior line of therapy who received penpulimab 200 mg Q3W on Study AK105-202 (primary safety population) and in 372 patients with other solid tumors who received penpulimab 200 mg Q3W across the development program (pooled safety population).

FDA's review of deaths due to AEs, SAEs, irAEs, or AEs leading to treatment discontinuation in patients enrolled in Study AK105-202 and in patients in the pooled safety population did not raise concern for an unexpected safety signal relative to other agents in this class.

Serious adverse events occurred in 19% of patients in the primary safety population and in 23% of patients in the pooled safety population. Among patients in the primary safety population, the most common SAEs ($\geq 2\%$) were pneumonia, death, and hepatitis.

Discontinuation of penpulimab due to an adverse event occurred in a total of 6% of patients in the pooled safety population and in 3.8% of patients in the primary safety population. In the primary safety population, the most common events leading to treatment discontinuation were pleural effusion, herpes zoster disseminated, spinal cord compression, hepatitis, and pemphigoid, occurring in 1 patient (0.8%) each.

Adverse events leading to drug interruptions occurred in 25% of patients in the primary safety population and in 24% of patients in the pooled safety population. Among patients in the primary safety population, the most common events ($\geq 1\%$) leading to drug interruption were hepatitis, pneumonia, hypothyroidism, anemia, pneumonitis, and rash.

Immune-related adverse events (irAEs) occurred in 22% of patients in the primary safety population (Grade 3-4, 2.3%) and in 20% of patients in the pooled safety population (Grade 3-4, 2.2%). In the primary safety population, the most common irAEs ($\geq 10\%$) was hypothyroidism. There were no fatal irAEs observed in the primary safety population and the rates of irAEs overall and Grade 3-4 irAEs are similar to that reported for other agents in this class, with the exception of hypothyroidism. The relatively higher incidence of hypothyroidism observed in the primary safety population (15%) is likely related to the high proportion of patients who received prior radiation as treatment for NPC.

No infusion-related reactions (IRRs) were reported in the primary safety population; 4% of patients in the pooled safety population had an IRR. All events were Grade 1-2 in severity.

In Study AK105-202, the most frequent AEs ($\geq 10\%$) were hypothyroidism, hepatitis, weight decreased, pyrexia, musculoskeletal pain, upper respiratory tract infection, and cough. The most frequent laboratory abnormalities ($\geq 20\%$) worsened from baseline were decreased phosphate, decreased sodium, decreased lymphocytes, increased triglycerides, increased gamma-glutamyl transferase, and decreased hemoglobin.

The safety profile of penpulimab is similar to other PD-(L)1 blocking antibodies when administered as single agents. The most significant adverse reactions include immune-related adverse events. Penpulimab, appears to have an acceptable safety profile when assessed in the context of a life-threatening disease.

9. Summary and Conclusions

9.1. Statistical Issues

The FDA's Assessment

There were no major statistical issues identified during review of this application. In the primary efficacy population (n=111) enrolled in Study AK105-202, the confirmed ORR per IRRC assessment was 30% (95% CI: 21%, 39%) at the DCO of February 3, 2021, and the tumor responses appeared durable with a median follow-up time of 11.9 months at the DCO of May 12, 2021. The treatment benefit appeared to be similar across all relevant subgroups, with the exception of patients with PD-L1 TPS < 50%, in which the point estimate of the ORR was 21%.

Follow-up was not sufficient to estimate the median duration of response and the upper limit of its 95% confidence interval. In addition, there are limitations to interpretation of certain study results from a non-randomized study; the analyses of time-to-event endpoints such as PFS and OS are not interpretable in the absence of a comparator arm.

Study AK105-202 was conducted in a single country resulting in homogeneity of patient race and region. FDA analyses of marketing application data generally include subgroup analyses by

key demographic characteristics such as age, sex, race, and region, to assess the consistency of findings across these populations and whether the study results are applicable to the U.S. population. Given the population of Asian patients enrolled on this trial, FDA was not able to conduct subgroup analyses by race or region, resulting in the inability to examine the consistency of the trial results by these factors.

9.2. Conclusions and Recommendations

The FDA's Assessment

Study AK105-202 is a single-arm, open-label study conducted solely in China that enrolled 130 patients with metastatic NPC with disease progression on platinum-based chemotherapy and at least one other line of therapy and received penpulimab 200 mg Q2W. The primary outcome measure was ORR assessed by independent radiology review committee (IRRC) using Response Evaluation Criteria in Solid Tumors (RECIST) v1.1. The key secondary outcome measure was DOR. Among the 111 patients with measurable disease at baseline who had the opportunity for at least 8 months of follow-up who comprised the primary efficacy population, the ORR was 30% (95% CI: 21, 39) (data cut off February 3, 2021). The median DOR was not reached (range 3.8, 17.1+); 39% of the 33 responding patients had a DOR $\geq$ 9 months. Given the approvals of toripalimab-tpzi during the review period for this application, the magnitude of effect of penpulimab on the ORR and DOR does not demonstrate a meaningful therapeutic benefit over currently available therapies for the treatment of patients with metastatic non-keratinizing NPC.

The safety profile of penpulimab is similar to that observed with other PD-1 blocking antibodies. Safety issues identified as significant and serious during the BLA review were immune-related adverse events and infusion-related reactions.

Study AK105-202 was conducted exclusively in China. Section 21 CFR 314.106(b) outlines three requirements to establish the acceptability of foreign data as the sole basis for marketing approval:

1. The foreign data are applicable to the U.S. population and U.S. medical practice.
2. The studies have been performed by clinical investigators of recognized competence.
3. FDA is able to validate the data through an onsite inspection or other appropriate means.

FDA will apply this policy in a flexible manner according to the nature of the drug and data being evaluated.

At the time of submission of this BLA, a flexible regulatory approach was warranted given that there were no FDA-approved treatment options for the proposed population. The incidence of NPC is much higher in China relative to the United States, where NPC is a relatively rare disease, making enrollment to clinical trials more feasible in China. However, during the review of this BLA for penpulimab, FDA granted traditional approval to toripalimab-tpzi, another anti-PD-1 antibody, in combination with cisplatin and gemcitabine for the first-line treatment of adult

patients with metastatic or recurrent, locally advanced NPC. This approval was based on a randomized (1:1) trial in 289 patients which demonstrated a 3.7-month improvement in progression-free survival (PFS) with the addition of toripalimab-tpzi to cisplatin and gemcitabine. This approval changed the standard of care for patients with metastatic or recurrent, locally advanced NPC, with the inclusion of anti-PD-1-based therapy in the first-line treatment setting. Toripalimab-tpzi also received traditional approval as a single agent for patients with unresectable or metastatic NPC with disease progression on or after a platinum-containing chemotherapy.

The Office of Pharmaceutical Quality (OPQ) also determined that the data submitted are not sufficient to support a conclusion that the manufacture of penpulimab-kcqx is well-controlled and will lead to a product that is pure and potent. See Section 3.2 for additional details.

The results from Study AK105-202 do not demonstrate a meaningful advantage over available therapy, given the recent approvals of toripalimab-tpzi for patients with NPC and therefore do not meet the requirements for accelerated approval as described in 21 CFR 314 subpart H.

Therefore, the FDA recommendation is Complete Response.

X	X
X	
Primary Statistical Reviewer	Statistical Team Leader
X	X
Primary Clinical Reviewer	Clinical Team Leader

APPEARS THIS WAY ON ORIGINAL

10. Advisory Committee Meeting and Other External Consultations

The FDA's Assessment

FDA did not refer this application to an advisory committee as no significant efficacy or safety issues were identified during the review that required external input for the proposed indication.

11. Pediatrics

The Applicant's Position

The Applicant will submit the iPSP (initial Pediatric Study Plan) on Jun 10, 2021.

In the iPSP, the Applicant requests a waiver of studies in pediatric NPC patients (b) (4).
(b) (4) The request is based on the extremely low incidence in this age group (b) (4) and necessary studies are impossible or highly impracticable in the pediatric population.



The FDA's Assessment

The FDA agrees with the Applicant's position.

On May 10, 2021, FDA agreed with the Applicant's plan to request a waiver for the conduct of studies of penpulimab in pediatric patients (b) (4) given the extremely low incidence of NPC in these age groups.

12. Labeling Recommendations

Data

This is an original application. Please see annotated label in Module 1.14.1.2 for proposed labeling.

The Applicant's Position

Not Applicable.

The FDA's Assessment: Due to the Complete Response action, final agreement on labeling was not reached during this review cycle.

Table 42 – FDA: Key Labeling Revisions

(b) (4)



13. Risk Evaluation and Mitigation Strategies (REMS)

The Applicant's Position

The risks of penpulimab could be managed by routine pharmacovigilance activities and labeling. REMS is not necessary to ensure that the benefits outweigh the risk for penpulimab for the following reasons:

- The benefit of penpulimab in the treatment of NPC was demonstrated in the pivotal study of AK105-202.
- The risks observed with penpulimab will be communicated through labeling. The risks associated with penpulimab are in part due to its inhibitory effects of PD-1. If approved, penpulimab will belong to a class with many other drugs (nivolumab, pembrolizumab, atezolizumab, durvalumab and avelumab, etc.) in which irAEs are labeled in Warnings and Precautions. The prescribers are likely aware of the risks of irAEs and the management with other drugs in this class.
- Sponsor has robust pharmacovigilance system, which includes data intake, case management, regulatory reporting, literature monitoring, signal management and aggregate reporting.
- In the postmarket setting, Akeso will conduct routine surveillance of the safety profile of penpulimab including all reports of adverse drug experiences and product compliant reports, and will revise RMP, RSI, and USPI if an evaluation of the safety data yields significant new information.

The FDA's Assessment

A risk evaluation and mitigation strategy (REMS) is not required given the Complete Response action.

14. Postmarketing Requirements and Commitment

The FDA's Assessment: No PMC or PMR agreements were reached since the action on the application will be a Complete Response.

1. Division Director (DHOT) (NME ONLY)

X

15. Division Director (OCP)

X

16. Division Director (OB)

X

17. Division Director (Clinical)

X

18. Office Director (or Designated Signatory Authority)

This application was reviewed by the Oncology Center of Excellence (OCE) per the OCE Intercenter Agreement. My signature below represents an approval recommendation for the clinical portion of this application under the OCE.

X

19. Appendices

19.1. References

The Applicant's References

Not Applicable.

The FDA's References

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line chemotherapy in recurrent or metastatic nasopharyngeal carcinoma: a systematic review and meta-analysis. *Annals of translational medicine*, 6(11), 201.

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12. Sultan I, Casanova M, Ferrari A, et al. Differential features of nasopharyngeal carcinoma in children and adults: a SEER study. *Pediatr Blood Cancer*. 2010; 55: 279-284.

19.2. Financial Disclosure

The Applicant's Position

All financial disclosures are described in Section [20.2](#).

The FDA's Assessment

Covered Clinical Study (Name and/or Number): AK105-202

Was a list of clinical investigators provided:	Yes ☒	No ☐ (Request list from Applicant)
Total number of investigators identified: <u>176</u>		
Number of investigators who are Sponsor employees (including both full-time and part-time employees): <u>0</u>		
Number of investigators with disclosable financial interests/arrangements (Form FDA 3455): <u>0</u>		
If there are investigators with disclosable financial interests/arrangements, identify the number of investigators with interests/arrangements in each category (as defined in 21 CFR 54.2(a), (b), (c) and (f)): Compensation to the investigator for conducting the study where the value could be influenced by the outcome of the study: <u>N/A</u> Significant payments of other sorts: <u>N/A</u> Proprietary interest in the product tested held by investigator: <u>N/A</u> Significant equity interest held by investigator in study: <u>N/A</u> Sponsor of covered study: <u>N/A</u>		
Is an attachment provided with details of the disclosable financial	Yes ☐	No ☐ (Request details from Applicant)

interests/arrangements:		
Is a description of the steps taken to minimize potential bias provided:	Yes ☐	No ☐ (Request information from Applicant)
Number of investigators with certification of due diligence (Form FDA 3454, box 3) 0		
Is an attachment provided with the reason: N/A	Yes ☐	No ☐ (Request explanation from Applicant)

19.3. Nonclinical Pharmacology/Toxicology

Data

Not Applicable.

The Applicant's Position

Not Applicable.

The FDA's Assessment

Not Applicable.

19.4. OCP Appendices (Technical Documents Supporting OCP Recommendations)

19.4.1. Bioanalytical Review

The FDA has determined that the bioanalytical methods used in the current submission are acceptable to support the clinical pharmacology program.

The concentration of penpulimab in human serum was quantitatively determined by enzyme-linked immunosorbent assay (ELISA). Bioanalysis for Study AK105-101 was conducted by (b) (4) (b) (4) whereas samples from all other trials was analyzed by (b) (4) (b) (4). The method was identical and cross-validation was conducted by (b) (4) All methods were fully validated and adequate. All samples were analyzed within the demonstrated stability window.

19.4.2. Population PK Analysis

19.4.2.1. Executive Summary

The FDA's Assessment

- PPK modeling supported the PK simulation of ITT (adults (b) (4))
- The proposed dosage (200 mg Q2W) is applicable in US adults (b) (4) based on PK simulations.

19.4.2.2. PPK Review Summary

Table 43 – FDA: Summary of PPK Review

General Information		
Goal of PPK Analysis:		
• Characterize penpulimab's PK profile • Explore the source of PK variability for the potential need of individualized dosing • Predict concentration profile in US patients to examine PK comparability with Chinese patients • Predict individual exposure for E-R assessment		
Study included	AK105-202 (ITT), AK105-101, AK105-201, AK105-204	
Dose(s) included	Weight-based: 1 (n=3), 3 (n=6), 10 mg/kg Q2W (n=7) Flat: 200 mg Q2W (proposed recommended dosage, n=363)	
Population included	Metastatic nasopharyngeal carcinoma (ITT), Hodgkin's lymphoma, advanced/metastatic solid malignancies	
Population characteristics (median/range, n/%) (Table)	General	Age: 51 yr (18-91 yr), 76 (20%) ≥65 yr, 24 (6%) ≥75 yr Weight: 62 kg (35-113 kg) : 238 (63%) male Race: 291 (77%) Asian, 81 (21%) White, 7 (2%) Other
	Organ impairment	Hepatic (NCI): 84 (22%) mild, 9 (2%) moderate Renal (CLCr): 113 (30%) mild, 45 (12%) moderate, 1 (0.3%) severe
	No. of patients, PK samples, BLQ	379 subjects, 3653 PK samples, 390 BLQ (368 prior to first dose) excluded for PPK analysis.
Sampling schedule	Rich sampling	Cycle 1/3: predose, end of infusion, 3h, day 1, day 2, day 7 Other cycle: Predose, end of infusion
	In ITT	Cycle 1: predose, end of infusion, 3h, day 1, day 2, day 7
	Population	Other cycle: predose, end of infusion
Covariates evaluated	Baseline demographics, body weight, cancer type (NPC, other), CLCr, albumin, ALT, AST, bilirubin, ECOG, ADA, LDH.	
Final Model	Summary	Acceptability/Comment
Software (version)	NONMEM software (Ver 7.2)	Yes
Estimation algorithm	first-order conditional estimation with INTERACTION	Yes
Model structure	2-compartment model with first order elimination	Yes
Model Parameter Estimates	Table	Not Applicable.

NDA/BLA Multi-disciplinary Review and Evaluation- BLA 761258
Penpulimab

General Information		
Uncertainty and Variability (RSE, IIV, Shrinkage, Bootstrap)	All parameters were estimated with good precision ($ \%RSE < 30\%$) except additive residual error (%RSE of 59.7%). The magnitude of the IIV was moderate for CL (28 %CV) and V1 (19.6 %CV), but high for V2 (52.8%). IIV for Q was fixed to 0% due to large shrinkage. Residual variability was small (3.18 SD for additive error, 17.2% CV for proportional error). Eta and epsilon shrinkages were reasonable (<30%) for diagnostics and EBE estimation of most parameters except V2 (52.8%).	Yes. Though V2 shrinkage is too high to accurately predict trough concentrations, an impact on the E-R analysis was not anticipated given the Applicant used observed concentrations as exposure metrics in these analyses.
BLQ for Parameter Accuracy	BLQ excluded in PPK analysis.	Yes. Post infusion BLQ is <1%.
Goodness of Fit (GOF) and Visual Predicted Check (VPC)	Figure 11 & Figure 12 GOF plots showed good agreement between observed and model-predicted concentrations, though time-dependent effect was observed. VPC showed no apparent bias in the overall model fit till 140 day (10 doses). From 140 days, observations were above or close to the upper bound of the corresponding percentile of the predicted concentrations, suggesting an underprediction.	- The PPK model underpredicted concentrations around steady state. Thus, FDA conducted the E-R analysis only using exposures prior to steady-state. - The PPK model can be used to compare PK between Chinese and US patients.
Significant covariates and clinical relevance	Figure 13 & Figure 14 <u>CL:</u> Positive factors: weight, ECOG Negative factors: female, albumin <u>V1:</u> Positive factors: body weight Negative factors: female	Yes. These factors do not have a clinically meaningful effect on PK, and age and race had no effect on PK after adjusting for weight.
PK comparison between US and Chinese subjects based on simulation	Figure 15 Based on PPK to factor in median differences in weight, albumin, and sex ratio, US patients were anticipated to have comparable PK as Chinese patients (<20% decrease in mean $C_{max,ss}$, $C_{min,ss}$ and $AUC_{0-14d,ss}$)	Yes. Race and region are not anticipated to have a clinically meaningful effect on PK.

(b) (4)

NDA/BLA Multi-disciplinary Review and Evaluation- BLA 761258
Penpulimab

General Information		
Labeling language	Description	Acceptability/Action
12.3 Pharmacokinetics	PK characteristics were based on PPK parameter estimates; specific population information was based on the impact of covariates for PK. No dosage adjustment is recommended based on PPK assessment.	Yes

Source: FDA's summary table.

Abbreviations: ADA, anti-drug antibody; ALT, alanine aminotransferase; AST, aspartate aminotransferase; AUC_{0-14d, ss}, area under the concentration-time curve from day 0 to 14 at steady-state; AUC_{ss}, area under the concentration-time curve at steady-state; BLQ, below limit of quantitation; CL, apparent clearance; CLCr, creatine clearance; C_{max, ss}, maximum plasma concentration at steady-state; C_{min, ss}, minimum plasma concentration at steady-state; CV, coefficient of variation; EBE, empirical Bayes estimate; ECOG, Eastern Cooperative Oncology Group; E-R, exposure response; GOF, goodness-of-fit; IIV, interindividual variability; ITT, intention to treat; LDH, lactate dehydrogenase; n, number of subjects in analysis; NCI, National Cancer Institute; No., number; NPC, nasopharyngeal carcinoma; PK, pharmacokinetic; PPK, population pharmacokinetics; Q, intercompartmental clearance; Q2W, once every two weeks; RSE, relative standard error; SD, standard deviation; US, United States of America; V1, volume of distribution of central compartment; V2, volume of distribution of peripheral compartment; Ver, version; VPC, visual predictive check.

Table 44 – FDA: Summary of Baseline Characteristics and Laboratory Values in the Dataset.

Characteristics	Level	AK105-101	AK105-201	AK105-202	AK105-204	Total
N		99	90	130	60	379
Dosing regimen, n (%)	1 mg/kg	3 (3.0%)	0 (0%)	0 (0%)	0 (0%)	3 (0.8%)
	3 mg/kg	6 (6.1%)	0 (0%)	0 (0%)	0 (0%)	6 (1.6%)
	10 mg/kg	7 (7.1%)	0 (0%)	0 (0%)	0 (0%)	7 (1.8%)
	200 mg	83 (83.8%)	90 (100%)	130 (100%)	60 (100%)	363 (100%)
Cancer type, n (%)	NPC	0 (0%)	0 (0%)	130 (100%)	0 (0%)	130 (34.3%)
	Others	99 (100%)	90 (100%)	0 (0%)	60 (100%)	249 (65.7%)
Country, n (%)	China	0 (0%)	90 (100%)	130 (100%)	60 (100%)	280 (73.9%)
	Australia	99 (100%)	0 (0%)	0 (0%)	0 (0%)	99 (26.1%)
Race, n (%)	Asian	11 (11.1%)	90 (100%)	130 (100%)	60 (100%)	291 (76.8%)
	White	81 (81.8%)	0 (0%)	0 (0%)	0 (0%)	81 (21.4%)
	Other	7 (7.1%)	0 (0%)	0 (0%)	0 (0%)	7 (1.8%)
Sex, n (%)	Male	58 (58.6%)	54 (60%)	99 (76.2%)	27 (45%)	238 (62.8%)
	Female	41 (41.44%)	36 (40%)	31 (23.8%)	33 (55%)	141 (37.2%)
ECOG status, n (%)	0	47 (47.5%)	66 (73.3%)	0 (0%)	7 (11.7%)	120 (31.7%)
	1	52 (52.5%)	24 (26.7%)	130 (100%)	53 (88.3%)	259 (68.3%)
ADA status, n (%)	Negative/missing	93 (93.9%)	56 (62.2%)	98 (75.4%)	37 (61.7%)	284 (74.9%)
	Positive	6 (6.1%)	34 (37.8%)	32 (24.6%)	23 (38.3%)	95 (25.1%)
NCI-ODWG	Normal	67 (67.7%)	86 (95.6%)	100 (76.9%)	48 (80.0%)	301 (79.4%)
hepatic impairment category ^a , n (%)	Mild B1	23 (23.2%)	2 (2.2%)	25 (19.2%)	10 (16.7%)	60 (15.8%)
	Mild B2	6 (6.1%)	2 (2.2%)	3 (2.3%)	2 (3.3%)	13 (3.4%)
	Moderate	3 (3.0%)	0 (0%)	2 (1.5%)	0 (0%)	5 (1.3%)
Renal impairment	Normal	41 (41.4%)	85 (94.4%)	74 (56.9%)	20 (33.3%)	220 (58.0%)
classification by CLCr ^b , n (%)	Mild	36 (36.4%)	5 (5.6%)	43 (33.1%)	29 (48.3%)	113 (29.8%)
	Moderate	21 (21.2%)	0 (0%)	13 (10.0%)	11 (18.3%)	45 (11.9%)
	Severe	1 (1.0%)	0 (0%)	0 (0%)	0 (0%)	1 (0.3%)
Age (yr), mean (SD)		66.0 (11.9)	33.9 (12.0)	47.7 (9.90)	56.1 (10.6)	50.5 (16.1)
Weight (kg), mean (SD)		71.4 (14.6)	67.6 (14.3)	58.1 (10.8)	59.6 (9.18)	64.1 (13.7)

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Penpulimab

Characteristics	Level	AK105-101	AK105-201	AK105-202	AK105-204	Total
Albumin (g/L), mean (SD)		35.4 (5.19)	43.4 (5.18)	42.4 (4.66)	44.4 (4.07)	41.1 (5.94)
ALP (U/L), mean (SD)		170 (154)	115 (75.6)	111 (94.0)	114 (89.6)	128 (111)
ALT (U/L), mean (SD)		27.9 (19.4)	19.9 (12.7)	23.8 (18.8)	24.2 (17.3)	24.0 (17.6)
AST (U/L), mean (SD)		38.4 (32.1)	20.2 (9.76)	31.4 (20.9)	30.6 (15.1)	30.5 (22.7)
Bilirubin (μM), mean (SD)		10.1 (7.34)	9.97 (4.46)	9.95 (5.07)	10.6 (5.06)	10.1 (5.61)
CLCr (mL/min), mean (SD)		85.8 (30.7)	142 (40.8)	91.8 (24.3)	80.7 (22.5)	100 (38.3)

Source: Reviewer's summary.

^a NCI-ODWG category defined by baseline labs of bilirubin and AST summarized using adlb.xpt located under integrated safety assessment: bilirubin ≤ ULN and AST ≤ ULN – normal, bilirubin ≤ ULN and AST > ULN – mild B1, ULN < bilirubin ≤ 1.5X ULN – mild B2, 1.5X ULN < bilirubin ≤ 3X ULN – moderate, bilirubin > 3X ULN – severe.

^b CLCr (estimated by Cockcroft-Gault equation): ≥90 mL/min – normal, ≥60 - <90 mL/min – mild, ≥30 - <60 mL/min – moderate, <30 mL/min – severe.

Abbreviations: ADA, anti-drug antibody; ALP, alkaline phosphatase; ALT, alanine aminotransferase; AST, aspartate aminotransferase; CLCr, creatinine clearance; ECOG, Eastern Cooperative Oncology Group; N, total number of subjects; n, number of subjects in category; NCI, National Cancer Institute; NPC, nasopharyngeal carcinoma; ODWG, organ dysfunction working group; SD, standard deviation; ULN, upper limit of normal

Table 45 – Applicant: Parameter Estimates and SE From Final Population PK Model

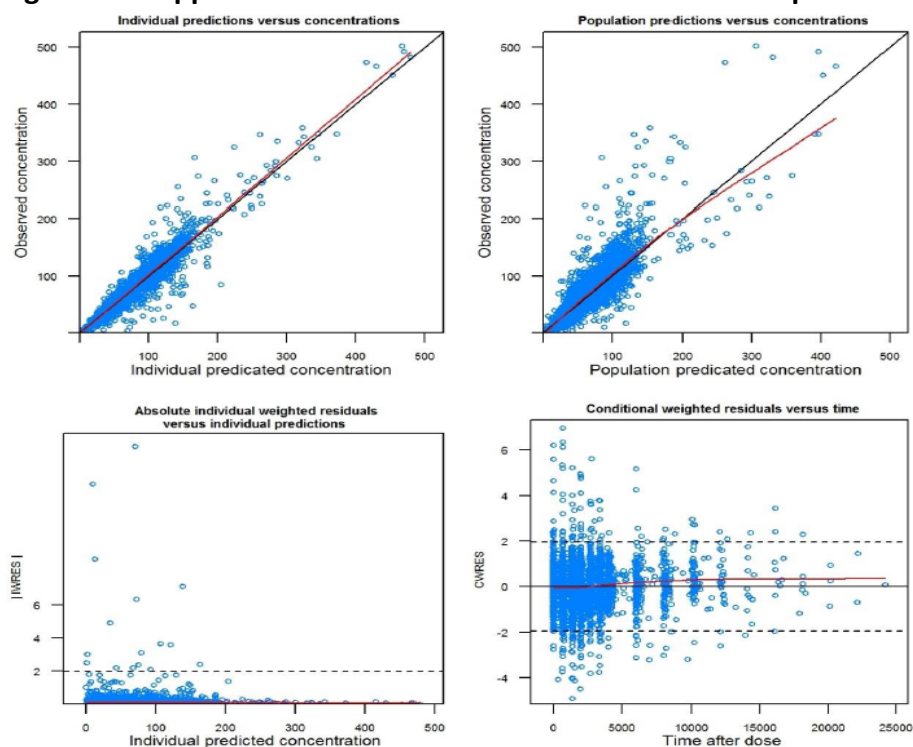
Parameter	Population Mean	Final Parameter Estimate		1000 Bootstrap (81.3% Success Rate)	
		RSE	Shrinkage	Mean	95% CI
CL (L/day)	0.233	2.7%	--	0.232	0.223 – 0.243
V1 (L)	3.4	1.7%	--	3.4	3.31 – 3.49
Q (L/day)	0.706	17.4%	--	0.704	0.567 – 0.846
V2 (L)	3.02	4.2%	--	3.04	2.76 – 3.28
Albumin on CL	-0.0163	21.8%	--	-0.0161	-0.0220 – -0.0105
ECOG=0 on CL	-0.154	17.8%	--	-0.154	-0.199 – -0.109
Female on CL	-0.159	18.5%	--	-0.158	-0.209 – -0.109
Weight on CL	0.00657	21.3%	--	0.00668	0.00422 – 0.00892
Female on V1	-0.128	18.4%	--	-0.18	-0.164 – -0.00921
Weight on V1	0.00804	12.3%	--	0.00805	0.00639 – 0.00928
IIV (CL)	28%	14.4%	11%	27.8%	25.2% – 30.5%
IIV (V1)	19.6%	13.9%	15%	19.5%	17.2% – 21.8%
IIV (V2)	52.8%	29.5%	34%	52.2%	38.8% – 63.9%
Additive residual error SD (μg/mL)	3.18	59.7%	10%	3.37	0.0889 – 6.26
Proportional residual error CV (%)	17.2%	8.9%	10%	17.1%	15.9% – 18.3%

Source: EDR 5.3.3.5 Population PK and PD report Table 23.

Note: Weight refers to body weight (kg). Albumin measured as (g/L). Covariate effect was linearly parameterized: (1+θ) for categorical variable, and (1+ θ*(COV-COVmedian)) for continuous variable.

Abbreviations: CI, confidence interval; CL, clearance; CV, coefficient of variation; ECOG, Eastern Cooperative Oncology Group; IIV, interindividual variability; PD, pharmacodynamic; PK, pharmacokinetic; Q, intercompartmental distribution rate between the central and peripheral compartments; RSE, relative standard error; SD, standard deviation; SE, standard error; V1, central volume of distribution; V2, first peripheral compartment volume of distribution.

Figure 11 – Applicant: Goodness-of-Fit Plots for the Final Population PK Model

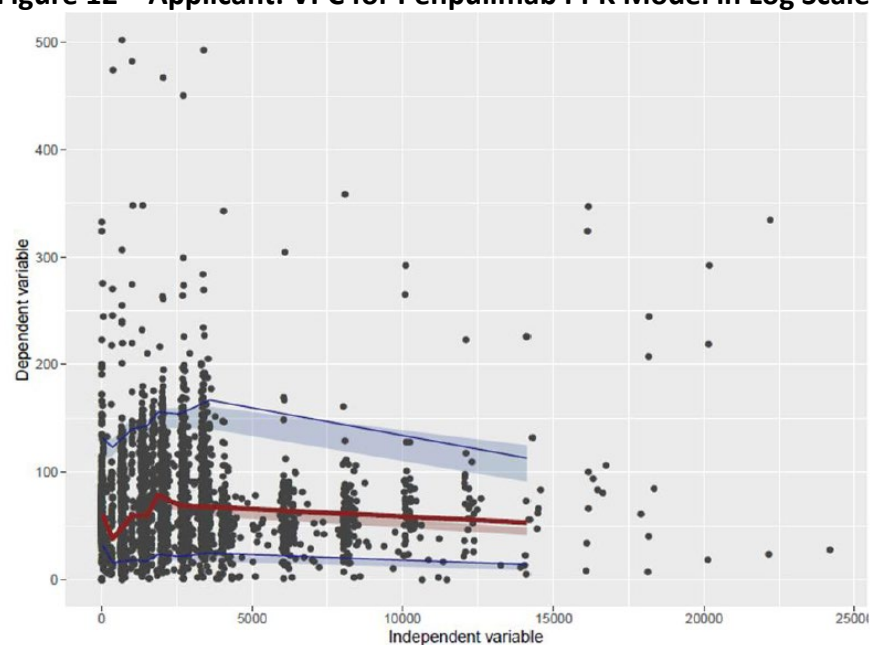


Source: EDR 5.3.3.5 Population PK and PD report (Figure 22).

Note: Open blue scatter is the concentration corresponding to each sampling. Solid black line is the reference line with slope = 1 and intercept = 0, and solid red line is the LOWESS smooth line of the scatter.

Abbreviations: CWRES, conditional weighted residual; IWRES, individual weighted residual; LOWESS, locally weighted scatterplot smoothing; PD, pharmacodynamics; PK, pharmacokinetics.

Figure 12 – Applicant: VPC for Penpulimab PPK Model in Log Scale



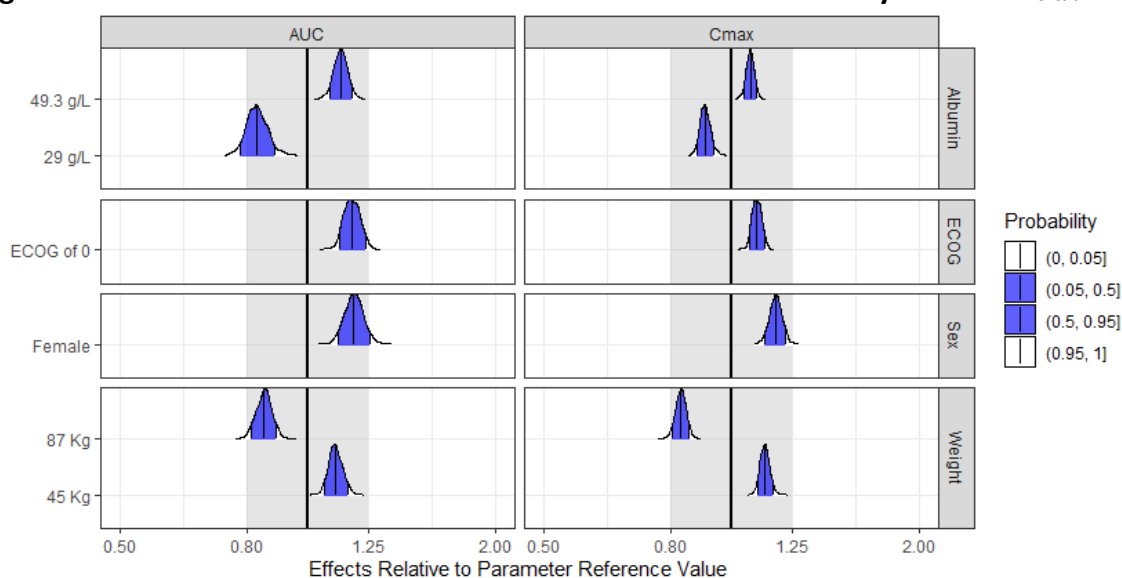
Source: EDR 5.3.3.5 Population PK and PD report (Figure 31).

Note: Solid dots = individual observed, solid blue lines = 5th and 95th percentiles, solid red line = observed median, shaded area = 90% prediction interval.

Note: Independent variable: time (h) after first dose. Dependent variable: penpulimab concentrations ($\mu\text{g/mL}$).

Abbreviations: PPK, population pharmacokinetics; VPC, visual predictive check.

Figure 13 – FDA: Influence of Covariates in the Final Model on Steady-State AUC_{0-tau} and C_{max}



Source: FDA's analysis.

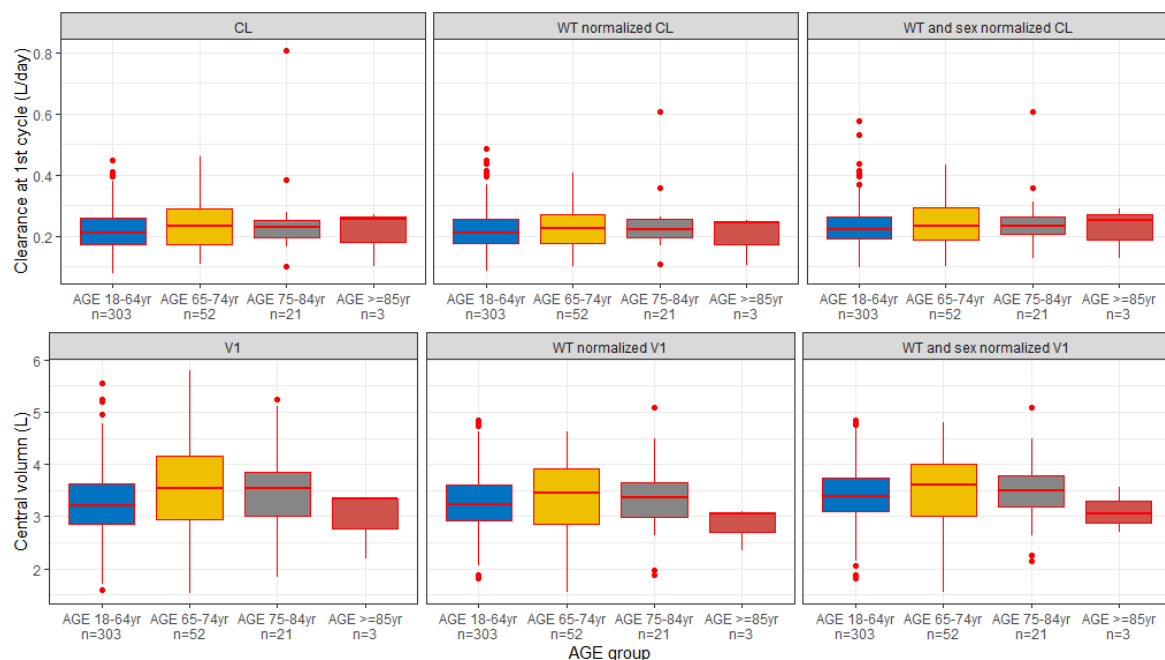
Note: Density plot for each covariate reflects the uncertainty of Applicant's PPK model parameter estimates.

Note: The vertical line represents the predicted steady-state AUC_{0-tau} and C_{max} in the typical subject receiving 200 mg Q2W penpulimab (cancer patient, adult male with weight 62 kg, albumin 42.5 g/L, ECOG of 1). The points show the median ratio in the modeled AUC_{0-tau} or C_{max} as covariates are changed one at a time to indicated values. For continuous variables, the selected values are the 5th and 95th percentiles of the population.

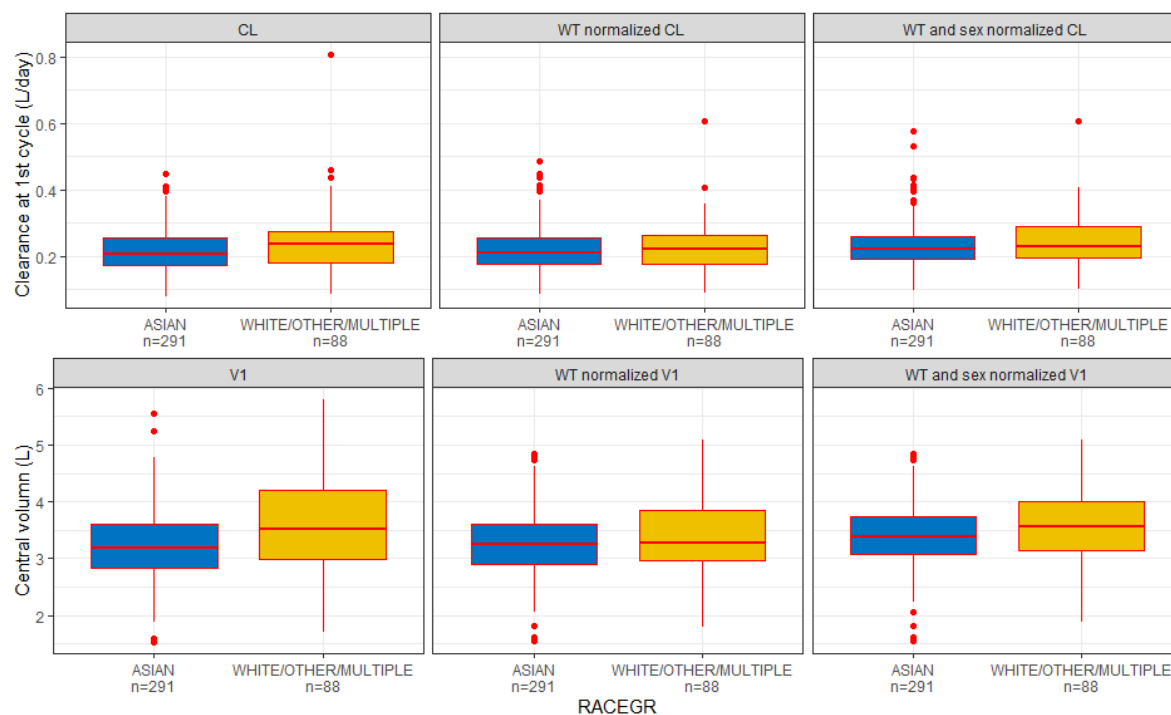
Abbreviations: AUC_{0-tau}, area under the concentration-time curve limited to the end of the dosing interval; C_{max}, maximum plasma concentration; ECOG, Eastern Cooperative Oncology Group; PPK, population pharmacokinetic.

Figure 14 – FDA: Influence of Age or Race on CL or V1

A



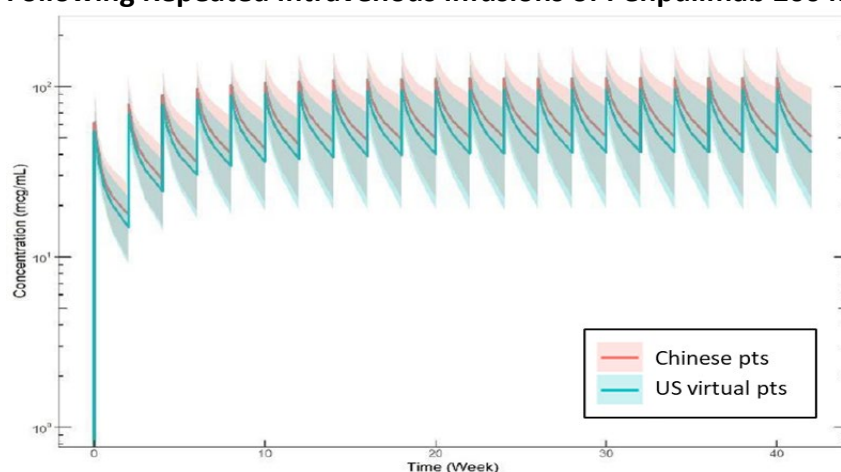
B



Source: FDA's assessment.

Note: Individual CL/V1 (un-normalized, normalized by weight effect, normalized by weight and sex effect) by age group (A), or race (B). Abbreviations: CL, clearance; CL/V1, apparent clearance of central volume of distribution; n, number of subjects in analysis; RACEGR, race group; V1, central volume of distribution; WT, weight.

Figure 15 – Applicant: Comparison of Simulated PK Profiles in the US and Chinese Patients Following Repeated Intravenous Infusions of Penpulimab 200 mg Q2W



Source: EDR 1.11.3 Additional Clinical Pharmacology Comments Response (Figure 1).

Note: Solid line = observed median, shaded area = 5-95th simulated concentrations.

Abbreviations: PK, pharmacokinetics; pts, patients; Q2W, once every two weeks; US, United States of America.

19.4.2.3. Review Issues and Reviewer's Independent Analysis

(b) (4)

19.4.2.3.2. Adequacy of ADA Evaluation

Two ADA assays were used to identify ADA positivity and titer. These data were not discriminated in PPK analysis. Pre-existing ADA was identified in >5% of subjects in Study AK105-202 with titers of >800 in some patients. Since ADA records were imputed as the prior ADA observation, most of the ADA records till 2nd infusion were the same as the baseline except for the pre-2nd dose record. Due to the false positivity ADA rate and the high titer of 800 (compared to the lowest titer of 50), these ADA records may impact PPK assessment. In addition, titer may have incremental impact on PK. As described in the decision tree ([Figure 21](#)), FDA conducted sensitivity analysis to evaluate the impact of ADA with assays of adequate sensitivity and specificity, evaluate treatment emergent ADA (treatment-induced and treatment-boosted), and titer levels in PPK analysis. Overall, ADA was not found to produce a statistically significant effect on PK.

19.4.3. Exposure-Response Analysis

19.4.3.1. Executive Summary

The FDA's Assessment

- No apparent E-R relationship for efficacy endpoint was identified.
- No clinically meaningful E-R relationship for TEAE was identified.
- The proposed recommended dosage is supported by flat E-R relationships for safety and totality of evidence.

19.4.3.2. Exposure-Response Review Summary

Table 47 – FDA: Summary of Exposure Response Review

E-R for Efficacy, General Information		
Study included	AK105-202 (ITT)	
Exposure variable	C1D1 End of Infusion, C2D1 pre-dose (2 doses), C5D1 pre-dose (8 doses)	
Efficacy endpoint	Primary: ORR	
No. of patients in treatment arm	130	
Population age, weight, sex, race (median/range, n/%) (Table 44)	• Age: 48 yr (20-65 yr, 1.5% >=65 yr) • Weight: 57 kg (35-95 kg) • Sex: 98 (75%) male • Race: 130 (100%) Asian	
Dose(s) included	200 mg Q2W (proposed recommended dosage, n=130)	
Exposure explored (max/min ratio)	C1D1 End of Infusion (13), C2D1 pre-dose(16), C5D1 pre-dose(10)	
Model structure	Univariate logistic regression	
Covariates evaluated	None	
Model	Summary	Acceptability/Comments
Significant E-R relationship	No obvious trend observed	Yes
Visualization of E-R	Figure17	Yes. Verified.
E-R for Safety, General Information		
Study included	CIBI308C302 (ITT), CIBI308A101, CIBI308B201, CIBI308A102	
Exposure variable	C_{max} , C_{trough} , AUC	
Safety endpoint	The following AE was evaluated in E-R analysis: • Any Grade and $\geq$ Grade 3 TEAEs • Any Grade and $\geq$ Grade 3 penpulimab-related TEAEs • Any TEAEs with incidence rate $\geq$10%	
No. of patients	379 subjects	

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Penpulimab

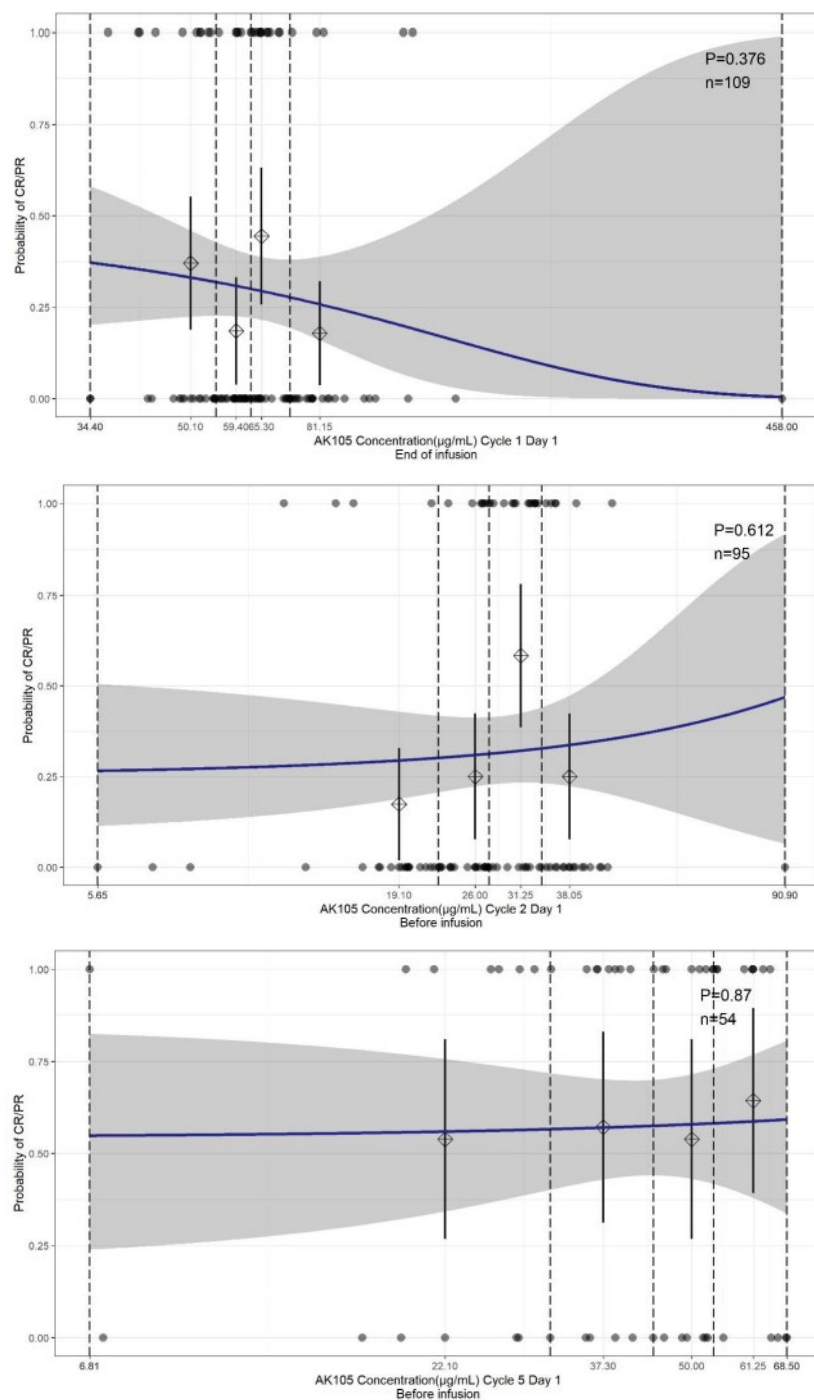
Population age, weight, sex, race (median/range, n/%) (Table 44)	• Age: 51 yr (18-91 yr), 76 (20%) >=65 yr, 24 (6%) >=75 yr • Weight: 62 kg (35-113 kg) • 238 (63%) male • Race: 291 (77%) Asian, 81 (21%) White, 7 (2%) Other	
Dose(s) included	Weight-based: 1 (n=3), 3 (n=6), 10 mg/kg Q2W (n=7) Flat: 200 mg Q2W (proposed recommended dosage, n=363)	
Exposure explored (max/min ratio)	C1D1 End of Infusion (75), C2D1 pre-dose(115), C5D1 pre-dose (44)	
Model structure	Univariate logistic regression	
Covariates evaluated	None	
Model	Summary	Acceptability/Comment
Significant E-R relationship	Within 200 mg Q2W dose, TEAEs generally do not appear to be exposure dependent.	Yes. These TEAEs did not lead to dosage interruption or discontinuation.
	Amongst TEAEs (any Grade >10%), a positive trend was observed for decreased neutrophil count, decreased WBC count, and increased cholesterol.	
Visualization of significant E-R	Figure 18	Added plots (discrepancies in subject number and p-value).
Description	Acceptability/Action	
A required section according to 21 CFR 201.57(c)(13)(i)(B).	A statement was added that the relationships is unknown given E-R for efficacy analysis was inconclusive.	

Source: FDA's summary table.

Note: Goal of E-R analysis: evaluate/explore the E-R relationship for efficacy and safety for potential dose optimization.

Abbreviations: AE, adverse event; AUC, area under the curve; C_{max}, maximum plasma concentration; C_{trough}, trough concentration; C1D1, day 1 of chemotherapy treatment cycle 1; C2D1, day 1 of chemotherapy treatment cycle 2; C5D1, day 1 of chemotherapy treatment cycle 5; E-R, exposure response; ITT, intention to treat; max, maximum; min, minimum; n, number of subjects in category; No., number; ORR, overall response rate; Q2W, every 2 weeks; TEAE, treatment-emergent adverse event; WBC, white blood cell

Figure 17 – Applicant: Probability of ORR Versus Exposures



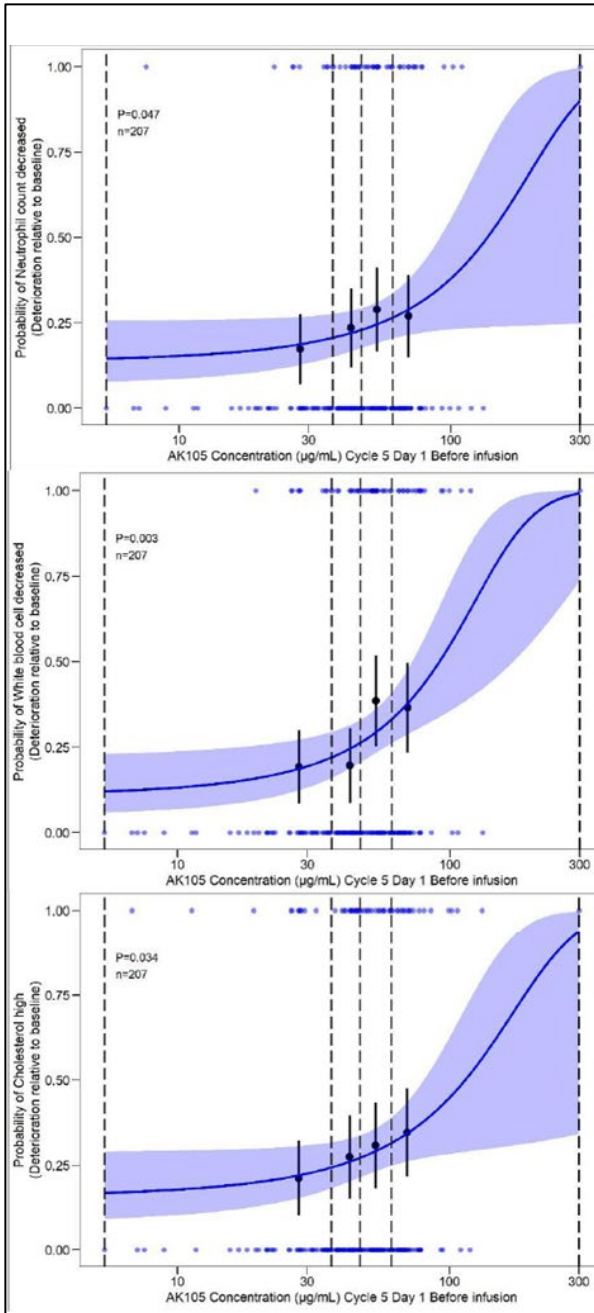
Source: EDR 5.3.3.5 Population PK and PD report Figure 40-42.

Note: The blue line and shaded region are the mean and 95% CI of the simulated probability of CR/PR with logistic regression models. Points are the responses corresponding to individual's AUC. Diamonds and error bars show the median and 95% CI of observed probability of exposure quantiles.

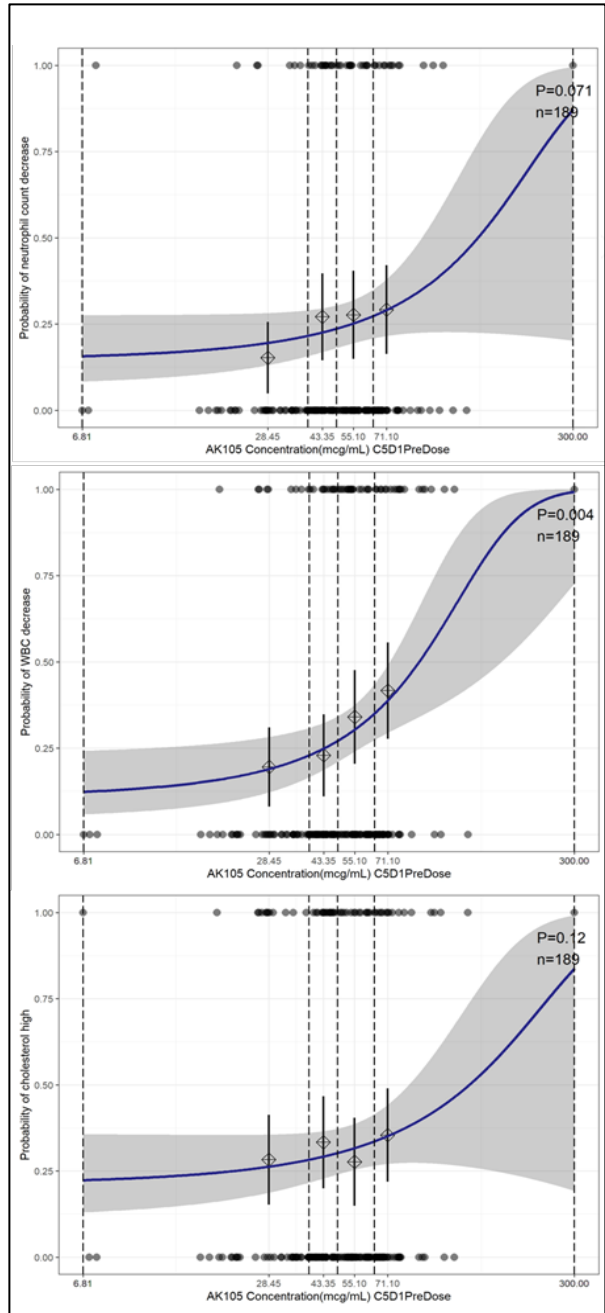
Abbreviations: AUC, area under the concentration-time curve; CI, confidence interval; CR, complete response; n, number of subjects in analysis; ORR, objective response rate; P, probability; PD, pharmacodynamics; PK, pharmacokinetics; PR, partial response.

Figure 18 – Applicant/FDA: Probability of TEAEs Versus Observed C5D1 Predose Concentration

A: Applicant



B: FDA



Source: EDR 1.11.3 Additional Clinical Pharmacology Comments Response (Figure 138, 150, 192) and Reviewer's analysis.

(A) Applicant's analysis.

(B) Reviewer's analysis.

Note: The smooth line and shaded region are the mean and 95% CI of the simulated probability of TEAE event rate with logistic regression models. Points are the responses corresponding to individual's C5D1 pre-dose concentration. Closed circles/diamonds and error bars show the median and 95% CI of observed probability of exposure quantiles.

Abbreviations: C5D1, Cycle 5 Day 1; CI, confidence interval; n, number of subjects in analysis; P, probability; TEAE, treatment emergent adverse event.

19.4.3.3. Review Issues and Reviewer's Independent Analysis

19.4.3.3.1. Steady-State Exposures Are Not Applicable in the Applicant's ER Analysis

Two errors were identified in the Applicant's analysis: 1) The Applicant applied 200 mg Q2W when simulating steady-state concentrations for all subjects, including those who did not receive this dosage; 2) The Applicant's PPK model is not adequate to describe steady-state PK due to underprediction. Therefore, FDA only verified the E-R analysis with C1D1 EOI, C2D1 and C5D1 pre-dose concentrations as the exposure metrics.

19.4.3.3.2. Discrepancies in the Subject Number (C2D1, C5D1) and p-value in ER for Safety Assessment Identified

The Applicant identified a positive relationship between C5D1 pre-dose concentration and 2 safety events of hematology (decreased neutrophil count and decreased WBC), and 1 safety event of clinical biochemistry (increased cholesterol). These TEAEs led to no dosage interruption or discontinuation.

FDA verified the E-R analysis and found discrepancies in the subject number and p-value from the Applicant's analysis. The discrepancies are due to exclusion of C2D1 pre-dose records and C10D1 (9 doses) of Study AK105-204; however, sample size reported in the Applicant's analysis enumerated exposure records including NAs. Of note, the cycle number of Study AK105-204 is different in that each dose is counted as a cycle compared to 2 doses counted as a cycle in other studies. The numbers of observed C2D1 pre-dose and C5D1 (and C10D1 of Study AK105-204 for similar number of doses) pre-dose concentrations were 330 and 187, respectively reported in FDA's analysis compared to 283 and 176, respectively used in the Applicant's analysis.

FDA was only able to confirm the positive relationship ($p < 0.05$) for decreased WBC ([Figure 18](#)). For this particular AE, multivariate logistic regression was performed which included age, sex, race, weight, albumin, baseline ECOG, LDH, ALP, AST as covariates. Stepwise covariate selection using AIC criteria reduced the model to C5D1 pre-dose as the only covariate. With inclusion of the imbalanced baseline covariates across quartiles of C5D1 pre-dose concentrations, namely age, sex, weight, and baseline ECOG, C5D1 pre-dose concentration was still identified as a significant covariate. Overall, given no dosage interruption or discontinuation, the positive relationship between C5D1 pre-dose and decreased WBC is not considered clinically meaningful.

19.4.4. Immunogenicity on Population PK and Efficacy/Safety

19.4.4.1. Immunogenicity Executive Summary

The FDA's Assessment

ADA was not found to have clinically meaningful impact on PK/efficacy/safety.

19.4.4.2. Immunogenicity Review Summary

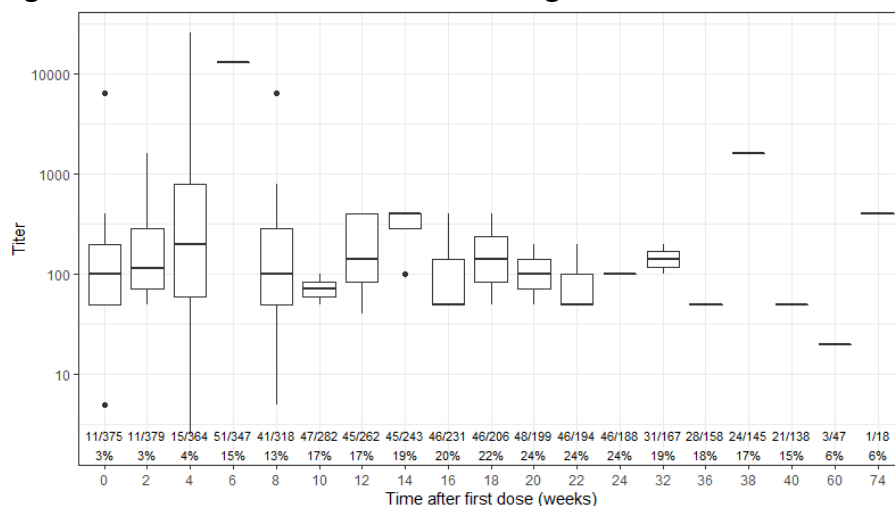
Table 48 – FDA: Summary of Immunogenicity Review

Goal of ADA analysis	- Summarize and/or verify treatment-emergent ADA rate and onset time by study - Evaluate the impact of ADA (status and titer) on PK - Explore the impact of ADA on efficacy/safety	
ADA evaluation scheme	Section Figure 21 .	
ADA assay by study	(b) (4) : AK105-101 (b) (4) : AK105-201, AK105-202, AK105-204	
ADA+ % and titer over time	Figure 19	
ADA Sampling schedule	Pre-dose collected at each cycle (every 2 doses)	
PK profile by ADA status	ADA status or titer does not impact PK via population PK modeling (Section 15320.4.2.2) or visual inspection (Figure 20).	
ER for efficacy by ADA status	ADA status is not found to impact efficacy (Table 49).	
ER for safety by ADA status	TEAE event rate is numerically lower in ADA+ patients (Table 50).	
Labeling language	Description	Acceptability/Action
12.6 Immunogenicity	Description of treatment emergent ADA rate, effect on PK, efficacy, and safety.	Acceptable

Source: FDA's summary table.

Abbreviations: ADA, anti-drug antibody; ER, exposure response; PK, pharmacokinetic; TEAE, treatment emergent adverse event.

Figure 19 – FDA: ADA Titer Kinetics During Treatment

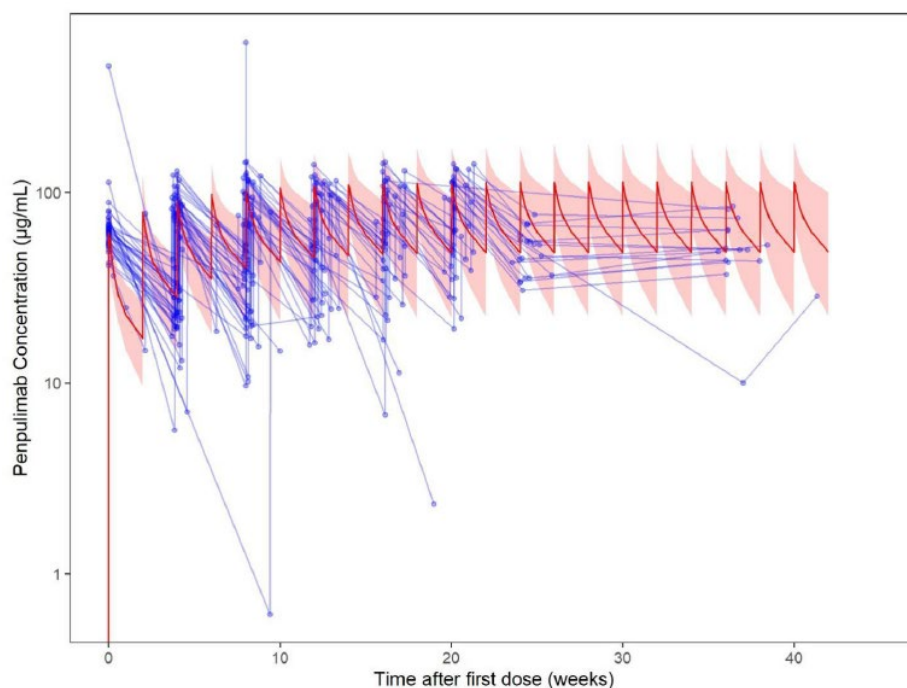


Source: FDA's analysis.

Note: Plot was generated based on population PK data. ADA+ could be without a titer.

Abbreviations: ADA, anti-drug antibodies; PK, pharmacokinetic.

Figure 20 – Applicant: Comparison of ADA Positive Individuals' Concentration Versus Simulated Concentration Range in Study AK105-202



Source: EDR 5.3.3.5 Population PK and PD report Figure 36.

Note: Solid blue dots & line = individual observed (ADA positive subject), solid line = simulated median, shaded area = 95% prediction interval.

Abbreviations: ADA, anti-drug antibody; PD, pharmacodynamic; PK, pharmacokinetic.

Table 49 – FDA: Efficacy by ADA Status (Any Time Post-Baseline)

ADA Status	Positive (n=34)	Negative (n=77)
ORR (%)	38.2%	26.0%
Duration of response (month)	7.4 [3.8, 12]	7.7 [3.8, 17.1]
PFS (month)	3.3 [1.7, 15.4]	1.9 [0.0, 19.8]
OS (month)	9.7 [2.9, 19.4]	11.1 [0.9, 22.3]

Source: FDA's analysis.

Note: Data were presented in % or median [range]. Data from Study AK105-202 (n=111 with ORR reported) were used in the analysis.

Abbreviations: ADA, anti-drug antibody; n, number of subjects in category; ORR, overall response rate; OS, overall survival, PFS, progression-free survival

Table 50 – FDA: All Grade and Grade ≥3 TEAE by ADA Status (Any Time Post-Baseline)

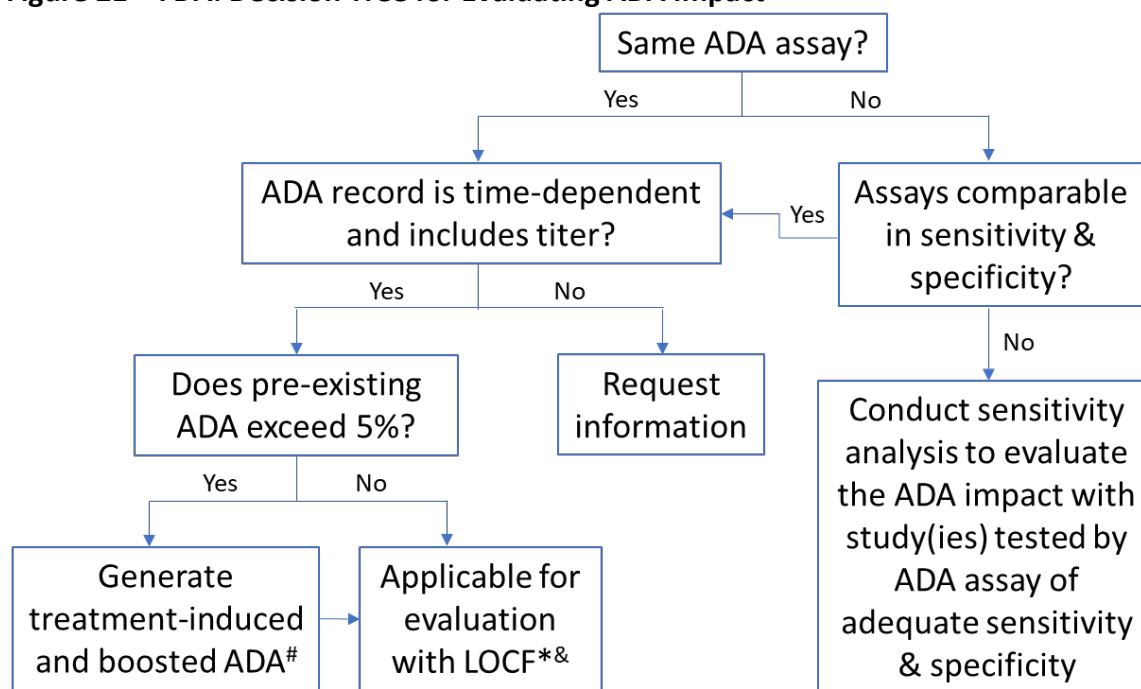
ADA Status	Positive (n=37)	Negative (n=93)
All grade TEAE (%)	89.2%	95.7%
Grade ≥3 TEAE	18.9%	36.6%

Source: FDA's analysis.

Note: Data were presented in %. Data from Study AK105-202 (n=130) were used in the analysis.

Abbreviations: ADA, anti-drug antibody; n, number of subjects in category; TEAE, treatment-emergent adverse event.

Figure 21 – FDA: Decision Tree for Evaluating ADA Impact



Source: FDA's analysis.

#Treatment-boosted ADA is determined according to White Paper by Shankar et al (doi: 10.1208/s12248-014-9599-2).

*When pre-existing ADA>=5%, evaluation of ADA titer on PK/PD is not meaningful.

&Treatment-emergent ADA preceding efficacy/safety event is considered relevant in the analysis. LOCF: location carry forward for ADA imputation.

Abbreviations: ADA, anti-drug antibody; LOCF, last observation carried forward; PD, pharmacodynamic; PK, pharmacokinetic.

19.5. Additional Safety Analyses Conducted by the FDA

The FDA's Assessment

Not applicable. All safety analyses conducted by FDA are captured in the body of the review.

Signatures

DISCIPLINE	REVIEWER	OFFICE/DIVISION	SECTIONS AUTHORED/ APPROVED	AUTHORED/ APPROVED
Nonclinical Reviewer	Kelie Reece, PhD	CDER/OND/OOD/DHOT	Sections: 5	Select one: ☒ Authored ☒ Approved
	Signature: Kelie M. Reece -S Digitally signed by Kelie M. Reece -S Date: 2024.01.18 11:05:27 -05'00'			
Nonclinical Team Leader	Claudia Miller, PhD	CDER/OND/OOD/DHOT	Sections: 5	Select one: ☒ Authored ☒ Approved
	Signature: Claudia Miller -S Digitally signed by Claudia Miller -S Date: 2024.01.18 13:13:01 -05'00'			
Clinical Pharmacology Reviewer	Yajun Liu, PhD	CDER/OTS/OCP/DCPII	Sections: 6	Select one: ☒ Authored ☐ Approved
	Signature: Jeanne Fourie Zirkelbach -S Digitally signed by Jeanne Fourie Zirkelbach -S Date: 2024.01.18 13:17:00 -05'00'			
Clinical Pharmacology Team Leader	Jeanne Fourie Zirkelbach, PhD	CDER/OTS/OCP/DCPII	Sections: 6	Select one: ☒ Authored ☒ Approved
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Nonclinical Division Director	John Leighton, PhD	CDER/OND/OOD/DHOT	Sections: 5	Select one: ☐ Authored ☒ Approved
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Clinical Pharmacology / Pharmacometrics Reviewer	Ye Xiong, PhD	CDER/OTS/OCP/DPM	Sections: 6	Select one: ☒ Authored ☐ Approved
	Signature: Ye Xiong -S Digitally signed by Ye Xiong -S Date: 2024.01.18 14:43:59 -05'00'			
Clinical Pharmacology / Pharmacometrics Team Leader	Jiang Liu, PhD	CDER/OTS/OCP/DPM	Sections: 6	Select one: ☒ Authored ☒ Approved
	Signature: Jiang Liu -S Digitally signed by Jiang Liu -S Date: 2024.01.18 10:56:41 -05'00'			
Clinical Reviewer	Erica Nakajima, MD	CDER/OND/OOD/DOII	Sections: 1.2, 1.3, 8.1, 9.2, 12, 14	Select one: ☒ Authored ☐ Approved
	Signature: Nicole L. Drezner -S Digitally signed by Nicole L. Drezner -S Date: 2024.01.18 13:23:20 -05'00'			

DISCIPLINE	REVIEWER	OFFICE/DIVISION	SECTIONS AUTHORED/ APPROVED	AUTHORED/ APPROVED
Clinical Pharmacology Division Director	Nam Atiqur Rahman, PhD	CDER/OTS/OCP/DCPII	Sections: 6	Select one: ☒ X Approved
	Signature: Nam A. Rahman -S Digitally signed by Nam A. Rahman -S Date: 2024.01.18 14:24:45 -05'00'			
Clinical Reviewer	Satinder Choudhary, PharmD, BCOP	CDER/OND/OOD/DOII	Sections: 1.2, 1.3, 8.1, 9.2, 12, 14	Select one: ☒ X Authored ☐ Approved
	Signature: Satinder K. Choudhary -S Digitally signed by Satinder K. Choudhary -S Date: 2024.01.18 11:21:30 -05'00'			
Clinical Team Leader	Paz Vellanki, MD, PhD	CDER/OND/OOD/DOII	Sections: All	Select one: ☒ X Authored ☒ X Approved
	Signature: Paz J. Vellanki -S Digitally signed by Paz J. Vellanki -S Date: 2024.01.18 14:19:00 -05'00'			
Statistical Reviewer	Mengdie Yuan, PhD	CDER/OTS/OB/DBV	Sections: 7, 8	Select one: ☒ X Authored ☐ Approved
	Signature: Mengdie Yuan -S Digitally signed by Mengdie Yuan -S Date: 2024.01.18 12:05:08 -05'00'			
Statistical Team Leader	Joyce Cheng, PhD	CDER/OTS/OB/DBV	Sections: 7, 8	Select one: ☒ X Authored ☒ X Approved
	Signature: Joyce Cheng -S Digitally signed by Joyce Cheng -S Date: 2024.01.18 13:48:26 -05'00'			
Division Director (OB)	Shenghui Tang, PhD	CDER/OTS/OB/DBV	Sections: 7, 8	Select one: ☒ X Approved
	Signature: Shenghui Tang -S Digitally signed by Shenghui Tang -S Date: 2024.01.18 14:35:23 -05'00'			

DISCIPLINE	REVIEWER	OFFICE/DIVISION	SECTIONS AUTHORED/ APPROVED	AUTHORED/ APPROVED
Associate Director for Labeling (ADL)	Barbara Scepura, MSN	CDER/OND/OOD/DOII	Sections: All	Select one: <u> X </u> Authored <u> </u> Approved
	Signature: Barbara A. Scepura -S  Digitally signed by Barbara A. Scepura -S Date: 2024.01.18 10:54:08 -05'00'			
Cross-Disciplinary Team Leader (CDTL)	Nicole Drezner, MD	CDER/OND/OOD/DOII	Sections: All	Select one: <u> X </u> Authored <u> X </u> Approved
	Signature: See signature in DARRTS.			
Deputy Division Director (Clinical)	Nicole Drezner, MD	CDER/OND/OOD/DOII	Sections: All	Select one: <u> X </u> Approved
	Signature: See signature in DARRTS.			

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/s/

NICOLE L DREZNER
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PAUL G KLUETZ
01/19/2024 03:46:43 PM