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APPLICATION NUMBER:

761347Orig1s000

MULTI-DISCIPLINE REVIEW

Summary Review

Clinical Review

Non-Clinical Review

Statistical Review

Clinical Pharmacology Review

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	351 (a) Biologics License Application (BLA)
Application Number(s)	BLA 761347
Priority or Standard	Standard
Submit Date(s)	November 15, 2023
Received Date(s)	November 15, 2023
PDUFA Goal Date	September 13, 2024
Division/Office	Division of Oncology 2/Office of Oncologic Diseases
Review Completion Date	See attached electronic signature page
Established Name	Atezolizumab and hyaluronidase-tqjs
(Proposed) Trade Name	TECENTRIQ HYBREZA
Pharmacologic Class	Combination product of atezolizumab, a programmed death-ligand 1 (PD-L1) blocking antibody, and hyaluronidase, an endoglycosidase
Code name	RO5541267
Applicant	Genentech, Inc.
Formulation	Liquid: Each 20 mL single-dose vial contains 1875 mg/15 mL (nominal) of atezolizumab and 2000 U/mL rHuPH20.
Dosing Regimen	1875 mg subcutaneous (SC) every 3 weeks (Q3W)
Applicant Proposed Indication(s)/Population(s)	All adult indications for atezolizumab IV USPI
Recommendation on Regulatory Action	Traditional Approval

Recommended Indication(s)/Population(s) (if applicable)	<u>Non-Small Cell Lung Cancer (NSCLC)</u> as adjuvant treatment following resection and platinum-based chemotherapy for adult patients with Stage II to IIIA NSCLC whose tumors have PD-L1 expression on $\geq 1\%$ of tumor cells, as determined by an FDA-approved test. for the first-line treatment of adult patients with metastatic NSCLC whose tumors have high PD-L1 expression (PD-L1 stained $\geq 50\%$ of tumor cells [TC $\geq 50\%$] or PD-L1 stained tumor-infiltrating immune cells [IC] covering $\geq 10\%$ of the tumor area [IC $\geq 10\%$]), as determined by an FDA-approved test, with no EGFR or ALK genomic tumor aberrations. in combination with bevacizumab, paclitaxel, and carboplatin, for the first line treatment of adult patients with metastatic non-squamous NSCLC with no EGFR or ALK genomic tumor aberrations. in combination with paclitaxel protein-bound and carboplatin for the first-line treatment of adult patients with metastatic non-squamous NSCLC with no EGFR or ALK genomic tumor aberrations for the treatment of adult patients with metastatic NSCLC who have disease progression during or following platinum-containing chemotherapy. Patients with EGFR or ALK genomic tumor aberrations should have disease progression on FDA-approved therapy for NSCLC harboring these aberrations prior to receiving TECENTRIQ HYBREZA. <u>Small Cell Lung Cancer (SCLC)</u> • in combination with carboplatin and etoposide, for the first-line treatment of adult patients with extensive-stage small cell lung cancer (ES-SCLC). <u>Hepatocellular Carcinoma (HCC)</u> • in combination with bevacizumab for the treatment of adult patients with unresectable or metastatic HCC who have not received prior systemic therapy. <u>Melanoma</u> • in combination with cobimetinib and vemurafenib for the treatment of adult patients with BRAF V600 mutation-positive unresectable or metastatic melanoma as determined by an FDA-approved test. <u>Alveolar Soft Part Sarcoma (ASPS)</u> • for the treatment of adult patients with unresectable or metastatic ASPS

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OBP=Office of Biotechnology Products
 OPQ=Office of Pharmaceutical Quality
 OPDP=Office of Prescription Drug Promotion
 OPMA=Office of Pharmaceutical Manufacturing Assessment
 OQS=Office of Quality Surveillance
 OSI=Office of Scientific Investigations
 OSE= Office of Surveillance and Epidemiology
 DEPI= Division of Epidemiology
 DMEPA=Division of Medication Error Prevention and Analysis
 DMPP=Division of Medical Policy Programs
 DRISK=Division of Risk Management

Glossary

AC	advisory committee
ADA	anti-drug antibody
ADME	absorption, distribution, metabolism, excretion
ADR	adverse drug reaction
AE	adverse event
AESI	adverse event of special interest
ALK	anaplastic lymphoma kinase
ALP	alkaline phosphatase
AUC _{0-21 d}	area under the concentration–time curve from 0 to 21 days
BLA	biologics license application
BCPA	Best Pharmaceuticals for Children Act
BRF	Benefit Risk Framework
CBER	Center for Biologics Evaluation and Research
CCOD	clinical cut-off date
CDER	Center for Drug Evaluation and Research
C-DOR	confirmed duration of response
CDRH	Center for Devices and Radiological Health
CDTL	Cross-Discipline Team Leader
CFR	Code of Federal Regulations
CI	confidence interval
CIT	cancer immunotherapy
CL	total clearance of drug
C _{max}	maximum serum concentration observed
CMC	chemistry, manufacturing, and controls
CNS	central nervous system
COSTART	Coding Symbols for Thesaurus of Adverse Reaction Terms
CR	complete response
CRF	case report form
CRO	contract research organization
CRT	clinical review template

CSR	clinical study report
CSS	Controlled Substance Staff
C _{trough}	minimum trough serum concentration observed
C _{trough,SS}	trough serum concentration at steady state
CTSQ	Cancer Therapy Satisfaction Questionnaire
DMC	data monitoring committee
DOR	duration of response
ECG	electrocardiogram
ECOG	Eastern Cooperative Oncology Group
eCRF	electronic Case Report Form
eCTD	electronic common technical document
EGFR	epidermal growth factor receptor
EORTC	European Organization for Research and Treatment of Cancer
ER	exposure-response
ETASU	elements to assure safe use
F1	bioavailability
FAS	Full Analysis Set
FDA	Food and Drug Administration
FDAAA	Food and Drug Administration Amendments Act of 2007
FDASIA	Food and Drug Administration Safety and Innovation Act
FFPE	formalin-fixed paraffin-embedded
GCP	good clinical practice
GHS	global health status
GLP	good laboratory practice
GM	geometric mean
GMR	geometric mean ratio
GRMP	good review management practice
HCC	hepatocellular carcinoma
HR	hazard ratio
IC	immune cell
ICH	International Conference on Harmonization

IMP	Investigational Medicinal Product
IND	Investigational New Drug
IRR	infusion-related reaction
ISE	integrated summary of effectiveness
ISR	injection site reaction
ISS	integrated summary of safety
ITT	intent to treat
IV	intravenous
IxRS	interactive voice/web response system
JMC	Joint Monitoring Committee
KA	absorption rate constant
MedDRA	Medical Dictionary for Regulatory Activities
mITT	modified intent to treat
NCI-CTCAE	National Cancer Institute-Common Terminology Criteria for Adverse Event
NDA	new drug application
NME	new molecular entity
NSCLC	non-small cell lung cancer
OCS	Office of Computational Science
OPQ	Office of Pharmaceutical Quality
ORR	objective response rate
OS	overall survival
OSE	Office of Surveillance and Epidemiology
OSI	Office of Scientific Investigation
PBRER	Periodic Benefit-Risk Evaluation Report
PD	pharmacodynamics
PD-L1	programmed death-ligand 1
PDUFA	prescription drug user fee act
PFS	progression-free survival
PI	prescribing information
PK	pharmacokinetic
PMC	postmarketing commitment

PMR	postmarketing requirement
PopPK	population pharmacokinetics
PP	per protocol
PPI	patient package insert
PR	partial response
PREA	Pediatric Research Equity Act
PRO	patient-reported outcome
PSUR	Periodic Safety Update report
PT	preferred term
QoL	quality of life
RECIST v1.1	Response Evaluation Criteria in Solid Tumors, Version 1.1
REMS	risk evaluation and mitigation strategy
SAE	serious adverse event
SAP	statistical analysis plan
SC	subcutaneous
SCLC	small cell lung cancer
SGE	special government employee
SoC	standard of care
SOC	System Organ Class
SWT	satisfaction with therapy
TC	tumor cell
TEAE	treatment emergent adverse event
TSH	thyroid stimulating hormone
UC	urothelial cancer
USPI	United States Packing Insert
V_c	volume of distribution for the central compartment
V_p	volume of distribution for the peripheral compartment
V_{ss}	volume of distribution under steady state conditions (V_c+V_p)

1. Executive Summary

1.1. Product Introduction

Atezolizumab and hyaluronidase-tqjs injection, for subcutaneous (SC) use (TECENTRIQ HYBREZA, which will be referred to as “atezolizumab SC” or “Atezo SC” throughout this review), is a biological product which contains two active ingredients. Hyaluronidase is an endoglycosidase and was approved on December 2, 2005. Atezolizumab is a humanized monoclonal antibody that binds directly to programmed death-ligand 1 (PD-L1), blocking its interactions with the PD-1 and B7.1 receptors. This binding results in a release of inhibition of the antitumor immune response which is mediated by the PD-L1/PD-1 interaction.

The atezolizumab SC product offers patients a different route of administration than intravenous atezolizumab (which will be referred to as “atezolizumab IV” or “Atezo IV” throughout this review). Other aspects that differ between Atezo SC and Atezo IV include:

- Combination with hyaluronidase-tqjs for the Atezo SC product
- Administration of Atezo SC by a healthcare professional takes approximately 7 minutes (rate of 2 mL/min). Administration of Atezo IV is over 60 minutes for the initial dose and if the first infusion is tolerated, all subsequent infusions may be delivered over 30 minutes.

The recommended dose of Atezo SC is:

- 1875 mg administered subcutaneously in the thigh over approximately 7 minutes, every 3 weeks (Q3W).

No dose adjustments for a patient’s body weight or for concomitant chemotherapy regimens are required. When Atezo SC is administered concomitantly with intravenous chemotherapy on the same day, administer Atezo SC prior to chemotherapy.

Atezolizumab SC is not currently approved in the United States (U.S.) or any other part of the world. The Applicant is requesting approval for atezolizumab SC for all of the approved adult indications for atezolizumab IV (TECENTRIQ) at 1200 mg IV Q3W:

- Non-small cell lung cancer (NSCLC):
 - As adjuvant treatment following resection and platinum-based chemotherapy for adult patients with Stage II to IIIA NSCLC whose tumors have PD-L1 expression on $\geq 1\%$ of tumor cells, as determined by an FDA-approved test.
 - For the first-line treatment of adult patients with metastatic NSCLC whose tumors have high PD-L1 expression (PD-L1 stained $\geq 50\%$ of tumor cells [TC $\geq 50\%$] or PD-L1 stained tumor-infiltrating immune cells [IC] covering $\geq 10\%$ of the tumor area [IC $\geq 10\%$]), as determined by an FDA-approved test, with no EGFR or ALK genomic tumor aberrations.

- 35 ○ In combination with bevacizumab, paclitaxel, and carboplatin, for the first-line treatment
36 of adult patients with metastatic non-squamous NSCLC with no EGFR or ALK genomic
37 tumor aberrations.
- 38
- 39 ○ In combination with paclitaxel protein-bound and carboplatin for the first-line treatment
40 of adult patients with metastatic non-squamous NSCLC with no EGFR or ALK genomic
41 tumor aberrations.
- 42
- 43 ○ For the treatment of adult patients with metastatic NSCLC who have disease progression
44 during or following platinum-containing chemotherapy. Patients with EGFR or ALK
45 genomic tumor aberrations should have disease progression on FDA-approved therapy
46 for NSCLC harboring these aberrations prior to receiving TECENTRIQ.
- 47 • Small cell lung cancer (SCLC):
- 48 ○ In combination with carboplatin and etoposide, for the first-line treatment of adult
49 patients with extensive-stage small cell lung cancer (ES-SCLC).
- 50 • Hepatocellular carcinoma (HCC):
- 51 ○ In combination with bevacizumab for the treatment of adult patients with unresectable or
52 metastatic HCC who have not received prior systemic therapy.
- 53 • Melanoma:
- 54 ○ In combination with cobimetinib and vemurafenib for the treatment of adult patients with
55 BRAF V600 mutation-positive unresectable or metastatic melanoma.
- 56 • Alveolar soft part sarcoma (ASPS):
- 57 ○ For the treatment of adult patients with unresectable or metastatic ASPS
- 58 This is the first application submitted to the FDA for an anti-PD-(L)1 antibody for SC
59 administration.

60 1.2. Conclusions on the 61 Substantial Evidence of 62 Effectiveness

63 The marketing application for atezolizumab SC was submitted by the Applicant on November
64 15, 2023, for all of the approved adult indications for atezolizumab IV.

65 The Applicant submitted the results of Study IMscin001 (BP40657, Part 2), a randomized, open-
66 label, multicenter, multiregional trial of atezolizumab SC compared to atezolizumab IV for
67 patients with advanced or metastatic NSCLC who had not previously received cancer
68 immunotherapy and who had disease progression during or following treatment with platinum-
69 based chemotherapy. A total of 371 patients were randomized (2:1) to receive atezolizumab SC
70 (atezolizumab 1875 mg/30000 units hyaluronidase) administered subcutaneously in the thigh or
71 atezolizumab 1200 mg administered intravenously every 3 weeks (Q3W). The coprimary

72 endpoints were C_{trough} at Cycle 1 and $AUC_{0-21\text{days}}$ at Cycle 1 of atezolizumab SC compared to
73 atezolizumab IV. The lower bound of the 90% CI for the pre-specified geometric mean ratio
74 (GMR) was ≥ 0.8 .

75 Analyses of the secondary efficacy endpoints of overall response rate (ORR) per RECIST v1.1
76 by investigator, progression free survival (PFS) by investigator, and overall survival (OS) were
77 descriptive. Safety was an additional secondary endpoint.

78 The trial coprimary endpoints of PK exposure of atezolizumab SC compared to atezolizumab IV
79 were both met. The GMR for serum C_{trough} at Cycle 1 value was 1.05 (90% CI: 0.88, 1.24) and
80 the lower limit of the 90% CI of 0.88 was above the pre-specified threshold of 0.8. The GMR for
81 $AUC_{0-21\text{days}}$ at Cycle 1 value was 0.87 (90% CI: 0.83, 0.92) and the lower limit of the 90% CI of
82 0.83 was also above the pre-specified threshold of 0.8. For the secondary PK exposure endpoints
83 of C_{trough} at steady-state, the GMR value was 1.15 (90% CI: 1.05, 1.25), the GMR for AUC_{inf} at
84 Cycle 1 value was 0.97 (90% CI: 0.91, 1.05), and the GMR for AUC at steady state value was
85 1.01 (0.94, 1.08). All three secondary endpoint values of the lower limit of the two-sided 90% CI
86 were above the pre-specified threshold of 0.8 thereby demonstrating comparable exposure of
87 atezolizumab SC to atezolizumab IV.

88 The ORR for patients treated with atezolizumab SC was 9% (95% CI: 5, 13) and was 8% (95%
89 CI: 4, 14) for atezolizumab IV. Descriptive analyses revealed no differences in PFS and OS
90 between patients who received atezolizumab SC and atezolizumab IV were observed.

91 The safety profile of atezolizumab SC was compared with the safety profile of atezolizumab IV.
92 Local injection site reaction for atezolizumab SC was the only newly identified safety signal.

93 The development approach of atezolizumab SC is consistent with FDA Guidance on “Providing
94 Clinical Evidence of Effectiveness for Human Drug and Biological Products”, which states the
95 following: “In certain cases, effectiveness of an approved drug product for a new indication, or
96 effectiveness of a new product, may be adequately demonstrated without additional adequate and
97 well-controlled clinical efficacy trials. Ordinarily, this will be because other types of data
98 provide a way to apply the known effectiveness to a new population or a different dose, regimen
99 or dosage form.” When being applied to different doses, regimens, or dosage forms, the above
100 FDA Guidance states that “it may be possible to conclude that a new dose, regimen, or dosage
101 form is effective on the basis of PK data without an additional clinical efficacy trial”. In the
102 current application, PK data, together with descriptive analyses of efficacy endpoints (i.e., ORR,
103 PFS, and OS) from IMscin001 can bridge to establish efficacy results between atezolizumab SC
104 and atezolizumab IV.

105 In addition to the atezolizumab IV 1200 mg Q3W dosage, there are two other IV dosages (i.e.,
106 840 mg Q2W, 1680 mg Q4W) approved based on PK comparability with the IV 1200 mg Q3W
107 dosage via modeling and simulation. Given that PK comparability of atezolizumab SC 1875 mg
108 Q3W to atezolizumab IV 1200 mg Q3W has been demonstrated based on results of IMscin001
109 and that the PK is comparable among approved IV dosages of atezolizumab, the data support
110 approval of atezolizumab SC 1875 mg Q3W for all approved adult indications and dosages of
111 atezolizumab IV administered as a single agent or as part of combination therapy. The well-
112 established efficacy and safety profile of atezolizumab IV also supports approval of
113 atezolizumab SC for the indications not studied in IMscin001.

114 The submitted evidence for atezolizumab SC (atezolizumab 1875 mg and 30,000 units
115 hyaluronidase-tqjs injection) for subcutaneous administration (TECENTRIQ HYBREZA), meets
116 the statutory evidentiary standard for traditional approval based on the pharmacokinetic, efficacy
117 and safety data from the IMscin001 multiregional clinical trial. The results of IMscin001
118 demonstrate substantial evidence of effectiveness for atezolizumab SC. Based on a favorable
119 risk-benefit assessment, the review team recommends traditional approval of atezolizumab SC
120 for the proposed indications in adult patients.

1.3. Benefit-Risk Assessment (BRA)

Benefit-Risk Summary and Assessment

Atezolizumab is a humanized monoclonal antibody that binds directly to programmed death-ligand 1 (PD-L1), blocking its interactions with the programmed cell death receptor-1 (PD-1) and B7.1 receptors. This binding results in a release of inhibition of the antitumor immune response which is mediated by the PD-L1/PD-1 interaction. Intravenous (IV) atezolizumab (which will be referred to as “atezolizumab IV” or “Atezo IV” throughout this review) is FDA-approved for multiple indications for the treatment of adult patients with non-small cell lung cancer (NSCLC), small cell lung cancer (SCLC), melanoma, hepatocellular carcinoma (HCC), and alveolar soft part sarcoma (ASPS).

Hyaluronidase is an endoglycosidase that is FDA-approved as an adjuvant to increase the dispersion and absorption of other injected drugs.

Intravenous administration of atezolizumab may present challenges for patients with difficult venous access or patients with poor renal or cardiac function who cannot tolerate larger infusion volumes. Intravenous infusions also generally require longer administration times compared to subcutaneous (SC) administration of the same drug. Atezolizumab and hyaluronidase-tqjs injection (which will be referred to as “atezolizumab SC” or “Atezo SC” throughout this review), is being developed as a co-formulation to allow for SC administration of atezolizumab and offers patients a different route of administration than atezolizumab IV. This is the first application submitted to the FDA for an anti-PD-(L)1 antibody for SC administration.

This application is based on results of Study IMscin001 (BP40657, Part 2), a randomized (2:1), open-label, multicenter, multiregional trial of atezolizumab SC 1875 mg Q3W (n = 247) compared to atezolizumab IV 1200 mg Q3W (n = 124) for patients with advanced or metastatic NSCLC who had not previously received cancer immunotherapy and who had disease progression during or following treatment with platinum-based chemotherapy. Patients received study therapy until disease progression or unacceptable toxicity. The coprimary endpoints were C_{trough} at Cycle 1 and $AUC_{0-21days}$ at Cycle 1. Analyses of the secondary efficacy endpoints of overall response rate (ORR) and progression-free survival (PFS) per RECIST v1.1 by investigator, and overall survival (OS) were all descriptive. Safety was an additional descriptive secondary endpoint.

Part 2 of the IMscin001 trial met its primary pharmacokinetics (PK) exposure endpoints of atezolizumab SC compared to atezolizumab IV, demonstrating comparable exposure of atezolizumab SC to atezolizumab IV. The geometric mean ratio (GMR) for serum C_{trough} at Cycle 1 was 1.05 (90% CI: 0.88, 1.24) and the lower limit of the 90% CI of 0.88 was above the pre-specified threshold of 0.8. The GMR for $AUC_{0-21 days}$ at Cycle 1 was 0.87 (90% CI: 0.83, 0.92) and the lower limit of the 90% CI of 0.83 was also above the pre-specified threshold of 0.8. For the secondary PK exposure endpoints of C_{trough} at steady-state, the GMR was 1.15 (90% CI: 1.05, 1.25), the GMR for AUC_{inf} at Cycle 1 was 0.97 (90% CI: 0.91, 1.05), and the GMR for AUC at steady state was 1.01 (0.94, 1.08). All three secondary endpoint GMR values of the lower limit of the two-sided 90% CI were also above the pre-specified threshold of 0.8.

The secondary efficacy results in IMscin001 Part 2 were comparable for atezolizumab SC and atezolizumab IV. The ORRs for patients treated with atezolizumab SC were 9% (95% CI: 5, 13) and 8% (95% CI: 4, 14) for atezolizumab IV, based on a data cutoff date of April 26, 2022. At the same data cutoff date, median PFS was 2.8 months (95% CI: 2.1, 3.1) for atezolizumab SC and 2.9 months (95% CI: 1.7, 4.2) for atezolizumab IV. However, only 33% of patients had an OS event in the intention-to-treat (ITT) population and OS data were not considered robust by the FDA review team. The Applicant submitted an updated OS analysis with 10 additional months of follow-up, based on a data cutoff date of January 16, 2023. In the updated OS analysis, 60% of patients in the ITT population had an OS event. The median OS was 10.7 months (95% CI: 8.5, 13.8) for atezolizumab SC and 10.1 months (95% CI: 7.5, 12.1) for atezolizumab IV (HR 0.88; 95% CI 0.67, 1.16).

The evaluation of safety for atezolizumab SC was primarily based on data from the 371 patients who received study therapy in IMscin001 Part 2 (247 patients in the atezolizumab SC arm and 124 patients in the atezolizumab IV arm), supported by the known safety profile of atezolizumab IV as a single agent. Among the 247 patients treated on the atezolizumab SC arm in IMscin001 Part 2, the most common adverse reactions ($\geq 10\%$) were fatigue (19%), musculoskeletal pain (15%), cough (13%), dyspnea (12%), and decreased appetite (11%). Serious adverse reactions occurred in 19% of patients who received atezolizumab SC. Serious adverse reactions ($>1\%$) included pneumonia (2.4%), myocardial infarction (1.6%), and pleural effusion (1.2%).

In IMscin001 Part 2, adverse reactions leading to permanent discontinuation of atezolizumab SC occurred in 3.6% of patients. Fatal adverse reactions occurred in 6% of patients who received atezolizumab SC due to pneumonia (2.4%), myocardial infarction (1.2%), head injury (0.4%), ischemic stroke (0.4%), pleural effusion (0.4%), pulmonary embolism (0.4%), respiratory tract infection (0.4%), sepsis (0.4%), and toxic epidermal necrolysis (0.4%).

The overall safety profile of atezolizumab SC was similar to the known safety profile of atezolizumab IV and similar to other PD-1 blocking antibodies. Safety issues identified as significant and serious during the BLA review were immune-related adverse events, which are adequately addressed by the information in the Warnings and Precautions section included in product labeling. Local injection site reaction was the only newly identified safety signal for atezolizumab SC observed in IMscin001 Part 2. In total, 4.5% of patients treated with atezolizumab SC had local injection site reactions leading to inclusion in the USPI of "local injection site reactions" as a clinically relevant adverse reaction in $< 10\%$ of patients who received atezolizumab SC in IMscin001 Part 2.

The incidence of anti-drug antibodies (ADAs) was 20% (43/221) in the atezolizumab SC arm and was 14% (15/108) in the atezolizumab IV arm. Compared to patients who were ADA-negative, there was a 29% increase in clearance in patients who were ADA-positive in the SC arm compared to a 5% increase in clearance for the IV arm. The incidence of neutralizing antibodies (NABs) in patients who tested ADA positive was 49% (21/43) in the SC arm and 60% (9/15) in the IV arm. The effect of ADA and NAB on efficacy endpoints is inconclusive due to small sample sizes. The presence of ADAs and Nabs did not significantly affect the safety profiles of atezolizumab by SC or IV administration.

A limitation of this study is that while IMscin001 Part 2 was a multiregional, international trial, no U.S. patients were enrolled. When the trial was designed, anti-PD-(L)1 antibodies (including atezolizumab IV) were FDA-approved as part of first-line therapy for patients with advanced or metastatic NSCLC. While atezolizumab IV in combination with chemotherapy was approved in the first-line treatment setting, first-line atezolizumab IV monotherapy for metastatic NSCLC with high PD-L1 expression was not approved until May 2020. To better evaluate the

immunogenicity of atezolizumab SC, the Applicant preferred to study atezolizumab SC as a single agent rather than as part of combination therapy. Therefore, IMscin001 Part 2 evaluated atezolizumab SC monotherapy for advanced or metastatic NSCLC after disease progression on platinum chemotherapy. Given that the primary support for the marketing application was derived from results of the primary PK endpoints of IMscin001 and that these were expected to be similar across racial and ethnic groups, particularly given the extensive data and postmarketing experience with atezolizumab IV, the trial outcome is considered applicable to U.S. patients despite not being conducted in the U.S.

During the review of this application, FDA also evaluated results from the patient reported preference study, IMscin002 (NCT03735121). IMscin002 was a randomized, multi-center, open-label crossover trial in 179 patients with either PD-L1-positive early-stage NSCLC receiving adjuvant treatment or PD-L1 high stage IV NSCLC. Patients were randomized (1:1) to receive 3 cycles of atezolizumab SC followed by 3 cycles of atezolizumab IV or 3 cycles of atezolizumab IV followed by 3 cycles of atezolizumab SC. Patients in both arms could continue to receive treatment after the crossover period for up to 16 cycles (patients with early-stage NSCLC) or until disease progression or unacceptable toxicity (patients with stage IV NSCLC). For the evaluation of the patient-reported experience, the primary endpoint for Study IMscin002 is the proportion of patients who preferred atezolizumab SC over atezolizumab IV as assessed by a Patient Preference Questionnaire (PPQ). Eighty-seven of 123 patients (71%) who completed the PPQ reported preferring atezolizumab SC over atezolizumab IV. The main reason patients preferred atezolizumab SC was convenience, while most who preferred atezolizumab IV had less pain/discomfort. Of the 107 patients who reached the treatment continuation period, 85 (79%) patients (42 from IV/SC and 43 from SC/IV) chose to continue treatment with the SC route of administration. Overall, patients who received both routes of administration in IMscin002 stated preference for the subcutaneous route of administration and maintained this preference during the continuation stage. A summary of the PPQ information will be included in the USPI.

On December 9, 2022, FDA approved atezolizumab IV for adult and pediatric patients 2 years of age and older with unresectable or metastatic ASPS. As such, a postmarketing requirement (PMR) will be issued for the Applicant to conduct a molecularly targeted pediatric cancer investigation using an age-appropriate formulation of atezolizumab and hyaluronidase-tqjs to assess dosing, PK, and preliminary safety and efficacy in pediatric patients 12 years of age and older. This PMR is being issued in alignment with Title V of the FDA Reauthorization Act of 2017 (FDARA) which amended the Pediatric Research Equity Act (PREA) to require that any original marketing application for certain adult oncology drugs contain reports of molecularly targeted pediatric cancer investigations. Given the rarity of the cancer types in pediatric patients less than 12 years of age that could potentially benefit from investigational treatment with atezolizumab SC, a partial waiver of this requirement in pediatric patients less than 12 years of age is justified.

In summary, the FDA review teams consider the PK, efficacy, and safety results of the IMscin001 Part 2 trial, and supportive data from IMscin002 and trials of atezolizumab IV, to meet the evidentiary standard for traditional approval. The results of IMscin001 demonstrate substantial evidence of effectiveness for atezolizumab SC. In addition to the atezolizumab IV 1200 mg Q3W dosage, there are two other IV dosages (i.e., 840 mg Q2W, 1680 mg Q4W) approved based on PK comparability with the IV 1200 mg Q3W dosage via modeling and simulation. Given that PK comparability of atezolizumab SC 1875 mg Q3W to atezolizumab IV 1200 mg Q3W has been demonstrated based on results of IMscin001 and PK is comparable among approved IV dosages of atezolizumab, the data support approval of atezolizumab SC 1875 mg Q3W for all approved adult indications and dosages of atezolizumab IV administered as a single agent or as part of combination therapy. The well-established efficacy and safety profile of atezolizumab IV also supports approval of atezolizumab SC for the indications not studied in IMscin001. Based on a favorable risk-benefit assessment, the review teams recommend traditional approval of atezolizumab and

hyaluronidase-tqjs for subcutaneous use for all of the approved adult indications for atezolizumab IV in patients with NSCLC, SCLC, melanoma, HCC, and ASPS.

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Dimension	Evidence and Uncertainties	Conclusions and Reasons
Analysis of Condition	Anti-PD-(L)1 antibodies have demonstrated efficacy across multiple tumor types, including NSCLC, SCLC, melanoma, HCC, and ASPS. (1) While the malignancies have different risk factors, growth patterns, and treatment regimens, they are all solid tumor malignancies that are serious and life threatening.	NSCLC, SCLC, melanoma, HCC, and ASPS are solid tumor malignancies that are serious and life threatening diseases
Current Treatment Options	Atezolizumab IV is approved either as a single agent or in combination with chemotherapy for indications across the following tumor types: • NSCLC • SCLC • melanoma • HCC • ASPS Atezolizumab is administered intravenously. The first administration is over 60 minutes and if the first infusion is well-tolerated, all subsequent infusions may be delivered over 30 minutes.	Atezolizumab IV is an anti-PD-L1 antibody approved for multiple tumor types. Atezolizumab IV has demonstrated efficacy and safety for the specific FDA approved indications.
Benefit	Atezolizumab SC provides patients with a different route of administration compared to atezolizumab IV. Part 2 of the IMscin001 trial met is coprimary pharmacokinetic (PK) endpoints of Cycle 1 C_{trough} and AUC_{0-21days}. The geometric mean ratio (GMR) for serum C_{trough} at Cycle 1 was 1.05 (90% CI: 0.88, 1.24). The GMR for AUC_{0-21days} at Cycle 1 value was 0.87 (90% CI: 0.83, 0.92). The lower limits of the GMR (90% CI) for both C_{trough} and AUC_{0-21days} were above the pre-specified threshold of 0.8 to demonstrate PK exposure comparability for atezolizumab SC and atezolizumab IV.	The PK exposures of atezolizumab SC and atezolizumab IV are comparable. Based on exploratory analyses, no differences in ORR, PFS, and OS were observed for atezolizumab SC and atezolizumab IV in IMscin001 Part 2.

Dimension	Evidence and Uncertainties	Conclusions and Reasons
	IMscin001 Part 2 included secondary, descriptive analyses of ORR, PFS, and OS. The ORR for patients treated with atezolizumab SC was 9% (95% CI: 5, 13) and was 8% (95% CI: 4, 14) for atezolizumab IV. No differences in PFS and OS were observed between atezolizumab SC and atezolizumab IV. The randomized, open-label, crossover IMscin002 trial (NCT03735121) evaluated patient-reported preferences between atezolizumab SC and atezolizumab IV in patients with NSCLC. Patients who received both routes of administration stated preference for the subcutaneous route of administration and maintained this preference during a continuation stage of the trial. The main reason patients preferred atezolizumab SC was convenience.	Atezolizumab SC offers patients another route of administration to receive the anti-PD-L1 antibody therapy.
Risk and Risk Management	The primary safety population in IMscin001 Part 2 included 247 patients who received atezolizumab SC 1875 mg Q3W and 124 patients who received atezolizumab 1200 mg IV Q3W. For patients on the atezolizumab SC arm, serious adverse reactions (>1%) included pneumonia (2.4%), myocardial infarction (1.6%), and pleural effusion (1.2%). There were 16 (6%) fatal events in the atezolizumab SC arm compared to 6 (4.8%) fatal events in the atezolizumab IV arm. Adverse reactions leading to permanent discontinuation of atezolizumab SC occurred in 9 patients (3.6%) compared to 6 patients (4.8%) in the atezolizumab IV arm. Local injection site reactions consisting of pain, edema, erythema, rash, or bruising occurred in 11 (4.5%) of the patients on the atezolizumab SC arm.	The observed safety profile of atezolizumab SC is similar to the known safety profile of atezolizumab IV. Local injection site reaction was the only newly identified safety signal for atezolizumab SC observed in IMscin001 Part 2. Safety concerns of atezolizumab SC can be adequately addressed through product labeling. There were no significant safety concerns identified during the review of this application warranting consideration for a Risk Evaluation and Mitigation Strategy (REMS) to ensure the safe use of atezolizumab SC.

124 Acronyms: SC: Subcutaneous; NSCLC: non-small-cell lung cancer; SCLC: small-cell lung cancer; HCC: hepatocellular carcinoma.

125 1.4. Patient Experience Data

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

BLA Multi-disciplinary Review and Evaluation BLA 761347
 Atezolizumab and Hyaluronidase-tqjs Solution for Subcutaneous Injection

☒	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)	Sections 8.1.2, 8.2.6, 19.6
	☐ 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)	Section 19.6
	☐ Other: (Please specify)	
☐	Patient experience data that was not submitted in the application, but was considered in this review.	

X

- 128
- 129 Paz Vellanki
- 130 Cross-Disciplinary Team Leader

131 2. Therapeutic Context

132 2.1. Analysis of Condition

133 The Applicant's Position: The marketed formulation of atezolizumab is a concentrated solution
134 for intravenous (IV) infusion administered over a period of 60 minutes, with subsequent
135 infusions delivered in 30 minutes, if well tolerated. For many patients, IV administration infusion
136 time may be a taxing experience and for some patients, such as those with difficult venous access
137 or poor renal or cardiac function, the need for IV infusions may constitute a major challenge.
138 Furthermore, increasing usage of intravenously administered monoclonal antibodies combined
139 with or without chemotherapy places a strain on medical centers with respect to time and
140 resources required to prepare and administer the IV infusions that are currently commercially
141 available. The change to the subcutaneous (SC) route of administration for monoclonal
142 antibodies such as trastuzumab, rituximab, and trastuzumab plus pertuzumab has demonstrated a
143 reduction in treatment burden for patients, with improved time and resource utilization at the
144 treating facility (Pivot et al. 2013; Rummel et al. 2015; De Cock et al. 2016a; De Cock et al.
145 2016b; O'Shaughnessy et al. 2021). Furthermore, available data for subcutaneously administered
146 monoclonal antibodies (daratumumab [Darzalex], trastuzumab [Herceptin], rituximab
147 [MabThera/Rituxan], and pertuzumab plus trastuzumab [Phesgo] pertuzumab plus trastuzumab
148 [Phesgo]) consistently demonstrate that subcutaneous formulations are well tolerated and anti-
149 tumor activity remains the same regardless of administration route (Ismael et al. 2012; Davies et
150 al. 2014; Assouline et al. 2015; Tan et al. 2021).

151 In view of the above aspects, the Applicant has developed a new formulation of atezolizumab for
152 SC injection. Atezolizumab SC is a ready-to-use formulation of atezolizumab co-formulated with
153 rHuPH20, a human recombinant hyaluronidase, developed to improve dispersion of large
154 volumes of drugs (i.e., it functions as a permeation enhancer).

155 The FDA's Assessment: FDA agrees with the Applicant's position that IV administration of
156 atezolizumab may present challenges for patients with difficult venous access or patients with
157 poor renal or cardiac function who cannot tolerate larger infusion volumes. FDA also
158 acknowledges that IV infusions often require longer administration times compared to SC
159 administration of monoclonal antibodies. However, FDA disagrees with the Applicant that the
160 trial(s) used to support approval of the subcutaneous formulations of the other aforementioned
161 monoclonal antibodies (daratumumab, trastuzumab, rituximab, and pertuzumab plus
162 trastuzumab) demonstrated the "same" anti-tumor activity between the SC and IV formulations.
163 Rather, descriptive results from the trials were generally used to evaluate the "comparability" of
164 efficacy between the SC and IV formulations.

165 FDA agrees with the Applicant's description of atezolizumab SC.

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2.2. Analysis of Current Treatment Options

The Applicant’s Position: Atezolizumab IV (TECENTRIQ®), available as a concentrated solution (60 mg/mL) for IV infusion, is approved in the U.S. at dosing regimens of 840 mg every 2 weeks (Q2W), 1200 mg every 3 weeks (Q3W), 1680 mg every 4 weeks (Q4W) as single agent and/or in combination.

Tecentriq is currently approved in the U.S. under accelerated approval for the following indications:

- Patients with locally advanced or metastatic Urothelial Carcinoma (UC) who:
 - Are not eligible for cisplatin-containing chemotherapy, and whose tumors express programmed death-ligand 1 (PD-L1 [PD-L1 stained tumor-infiltrating immune cell (IC) covering $\geq 5\%$ of the tumor area]), as determined by an FDA-approved test, or
 - Are not eligible for any platinum-containing chemotherapy regardless of PD-L1 status

Tecentriq is also currently approved in the U.S. for the following indications:

- Non-Small Cell Lung Cancer (NSCLC):
 - For the 1L treatment of adult patients with metastatic NSCLC whose tumors have high PD-L1 expression (PD-L1 stained $\geq 50\%$ of tumor cell (TC) [TC $\geq 50\%$] or PD-L1 stained tumor-infiltrating IC covering $\geq 10\%$ of the tumor area [IC $\geq 10\%$]), as determined by an FDA-approved test, with no epidermal growth factor receptor (EGFR) or anaplastic lymphoma kinase (ALK) genomic tumor aberrations.
 -
 - In combination with bevacizumab, paclitaxel, and carboplatin, for the 1L treatment of adult patients with metastatic non-squamous NSCLC with no EGFR or ALK genomic tumor aberrations.
 -
 - In combination with paclitaxel protein-bound and carboplatin for the 1L treatment of adult patients with metastatic non-squamous NSCLC with no EGFR or ALK genomic tumor aberrations.
 -
 - For the treatment of adult patients with metastatic NSCLC who have disease progression during or following platinum-containing chemotherapy. Patients with EGFR or ALK genomic tumor aberrations should have disease progression on FDA-approved therapy for these aberrations prior to receiving Tecentriq.
 -
 - As adjuvant treatment following resection and platinum-based chemotherapy for adult patients with stage II to IIIA non-small cell lung cancer (NSCLC) whose tumors have PD-L1 expression on $\geq 1\%$ of tumor cells, as determined by an FDA-approved test

- Small Cell Lung Cancer (SCLC):

- 205 ○ in combination with carboplatin and etoposide, for the 1L treatment of adult patients with
206 extensive-stage SCLC.
- 207 • Hepatocellular Carcinoma (HCC):
- 208 ○ in combination with bevacizumab for the treatment of patients with unresectable or
209 metastatic HCC who have not received prior systemic therapy.
- 210 • Melanoma:
- 211 ○ in combination with cobimetinib and vemurafenib for the treatment of patients with
212 *BRAF* V600 mutation-positive unresectable or metastatic melanoma.
- 213 The FDA’s Assessment: FDA agrees with the Applicant’s position with the following
214 exceptions:
- 215 • On November 14, 2022, the Applicant requested withdrawal of the accelerated approval of
216 atezolizumab IV for the first line treatment of metastatic urothelial carcinoma (mUC).
217 Subsequently, on December 2, 2022, FDA approved the withdrawal of the mUC accelerated
218 approval indication from the atezolizumab IV United States Prescribing Information (USPI).
- 219 • On June 30, 2022, the Applicant submitted an sBLA for a proposed new indication for
220 atezolizumab, as a single agent, for the treatment of adult and pediatric patients 2 years of
221 age and older with unresectable or metastatic alveolar soft part sarcoma (ASPS). On
222 December 9, 2022, the FDA granted approval for this indication.

223 **3. Regulatory Background**

224 **3.1. U.S. Regulatory Actions and** 225 **Marketing History**

226 The Applicant’s Position: Atezolizumab SC is not currently registered or approved in the U.S. or
227 in any other part of the world.

228 The FDA’s Assessment: FDA agrees with the Applicant’s position.

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3.2. Summary of Presubmission/Submission Regulatory Activity

232 The Applicant's Position:

233 **Table 1 Applicant-Key FDA Interactions Relevant to Atezolizumab SC**

Type of Meeting	Date of Meeting	Purpose and Key Request/Agreements (If Relevant)
Type B pre-IND Meeting	13 November 2018	FDA offered guidance on the proposed clinical and nonclinical programs.
Type C pre-IND Meeting	10 December 2019	FDA agreed with the updated IMscin001 Part 2 design, which was modified in accordance with FDA's feedback from 13 November 2018 meeting.
General Correspondence via e-mail	19 August 2020	FDA agreed to the selected doses for IMscin001 Part 2, and recommended that both AUC _{0-tau} and C _{trough} at Cycles 1 be the primary PK measures.
Type B pre-BLA Meeting	26 September 2022	Discussed the clinical results from IMscin001 Part 2 as the basis of a BLA for the approval of atezolizumab SC in the proposed indications. Discussed the content and format of the dossier and planned safety update.

234 Source:
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236

237 Specifically, IMscin001 study was conducted in 2L NSCLC to study atezolizumab SC in the
238 absence of any confounding effects of chemotherapy or other combination compounds, based on
239 feedback received in 2018 Type B pre-IND meeting. As further discussed with the Agency in
240 2019 Type C pre-IND meeting, the Agency expressed concerns on the feasibility to enroll this
241 patient population in the U.S. given the evolving standard of care in 1L NSCLC. The Applicant
242 acknowledged this feedback and communicated the plan to conduct the study in other countries
243 where cancer immunotherapy (CIT) is partially or not reimbursed, which is reflected in the final
244 list of countries for IMscin001.

245 The FDA's Assessment: FDA agrees with the Applicant's timeline of regulatory interactions but
246 notes the following clarifications. FDA provided feedback and recommendations during the
247 meetings listed in Applicant Table 1; however, the "FDA agreed" text for both the Type C pre-
248 IND meeting on December 10, 2019, and the August 19, 2020, response to Sponsor's
249 information request, should be interpreted as "FDA agreed with the Applicant's approach to
250 update IMscin001 Part 2 design", and "FDA agreed with the Applicant's approach to select a
251 dose for atezolizumab for subcutaneous administration for IMscin001 Part 2".

252 For clarity, at the 2019 Type C guidance meeting, FDA expressed concerns regarding the
253 feasibility to enroll U.S. patients with NSCLC who have progressed on platinum based
254 chemotherapy and did not receive prior anti-PD-(L)1 antibody therapy given the U.S. standard of
255 care at that time. By December 2019, the U.S. standard of care for the first-line treatment of
256 patients with NSCLC already included anti-PD-(L)1 antibody-based regimens, either in

257 combination with chemotherapy regardless of tumor PD-L1 status or as monotherapy for patients
258 with PD-L1 positive tumors.

259 FDA also notes that the Applicant originally submitted a 351(a) BLA for atezolizumab and
260 hyaluronidase-tqjs for subcutaneous injection on November 15, 2022. However, the Applicant
261 withdrew the application on August 31, 2023, (b) (4)

262 (b) (4)
263 (b) (4) The Applicant submitted the current BLA on November 15, 2023.

264 On April 20, 2024, the Applicant also provided an appendix to the Assessment Aid and datasets
265 for Study MO43576 (IMscin002). The IMscin002 trials was conducted to evaluate the patient
266 reported preference for the route of administration of atezolizumab (IV vs SC).

267 4. Significant Issues From Other Review 268 Disciplines Pertinent to Clinical 269 Conclusions on Efficacy and Safety

270 4.1. Office of Scientific 271 Investigations (OSI)

272 Please refer to the Clinical Inspection Summary uploaded to DARRTS dated August 7, 2023, for
273 a full discussion of clinical inspections. The clinical inspections were performed during the
274 review period for the initial 351(a) BLA for atezolizumab and hyaluronidase-tqjs for
275 subcutaneous injection submitted on November 15, 2022.

276 Two clinical investigators, Drs. Mehmet Ali Sendur (Site #328478) and Yotsawaj
277 Runglodvatana (Site #328384) were selected for clinical inspection in collaboration with the
278 Office of Scientific Investigations (OSI).

279 Dr. Sendur was inspected as a routine Prescription Drug User Fee Act (PDUFA) inspection and
280 enrolled 29 patients into the IMscin001 clinical trial. Source records were compared with data
281 listing tables submitted to the BLA. The inspection identified two discrepancies concerning
282 disease staging at diagnosis in 2 patients:

- 283 • Subject ID # (b) (6): staging at initial diagnosis was incorrectly reported as IIA, according to
284 source records, while the actual staging at diagnosis was IIIA. This patient was randomized
285 to receive atezolizumab SC.
- 286 • Subject ID # (b) (6): staging at initial diagnosis was incorrectly reported as IIB, according to
287 source records, while the actual staging at diagnosis was IVA. This patient was randomized
288 to receive atezolizumab IV.

289 FDA assessed that the above isolated incidents would not impact the interpretation of the results
290 for IMscin001 because both patients had confirmed stage IV disease at the time of enrollment to
291 this second-line trial, as required by protocol.

292 Dr. Runglodvatana was also inspected as a routine PDUFA inspection and enrolled 13 patients
293 into the trial. Source records were compared with data listing tables submitted to the BLA.
294 The inspection identified seven patients who met the exclusion criteria and did not meet the
295 inclusion criteria. These patients are listed below:

- 296 • Six of the 13 patients (Subject IDs # (b) (6)) had
297 positive HBcAb tests at screening and were randomized into the study before the results of
298 the HBV DNA test became available. The results were reported to be <20 IU/mL for all 6
299 patients. There was no evidence of patient harm related to the described protocol deviation.
300 Two patients (Subject IDs # (b) (6)) were randomized to receive atezolizumab IV
301 and four patients (Subject ID # (b) (6)) were randomized to
302 atezolizumab SC.
- 303 • One patient (ID # (b) (6)) did not meet the inclusion criterion requiring a baseline lymphocyte
304 count $\geq 0.5 \times 10^9/L$ (500 μ/L). Although the baseline lymphocyte count was below 500 μ/L ,
305 there was no evidence of harm to the patient and the patient's lymphocyte count was normal
306 at 1559 μ/L in the subsequent laboratory assessment. This patient was randomized to receive
307 atezolizumab IV.

308 These protocol deviations are unlikely to have significantly impacted the interpretation of data
309 generated from this site. Dr. Runglodvatana provided corrective action plans that were reviewed
310 and found to be adequate.

311 Overall, the data generated by the two inspected clinical investigators and submitted by the
312 Applicant appear acceptable in support of the proposed indications for atezolizumab SC.

313 4.2. Product Quality

314 Atezolizumab and hyaluronidase-tqjs (TECENTRIQ HYBREZA) is a recombinant humanized
315 immunoglobulin G1 (IgG1) monoclonal antibody (mAb) that binds to programmed death-ligand
316 1 (PD-L1) and blocks its interaction with programmed death protein 1 (PD-1) as well as B7.1
317 (CD80). The interference of this reaction enhances the tumor-specific T-cell response and T-cell
318 mediated tumor cell killing. The primary mechanism of action (MOA) is the binding of the
319 fragment antigen binding (Fab) domain to soluble PD-L1. Hyaluronidase is a glycosylated
320 single-chain protein with 447 amino acids that depolymerizes hyaluronan (hyaluronic acid) at the
321 site of injection, resulting in a decreased resistance to fluid flow and a transient increase in
322 permeability of the local subcutaneous tissue. The overall control strategy for Tecentriq Hybreza
323 manufacture incorporates control over raw materials, facilities and equipment, the manufacturing
324 process, and adventitious agents. The manufacturing control strategy coupled with in-process
325 controls, as well as release and stability testing ensure process consistency and the manufacture
326 of drug substance and drug product that have appropriate quality and are free of adventitious
327 agents.

328 The Office of Pharmaceutical Quality (OPQ), CDER, has completed review of BLA 761347 for
329 Tecentriq Hybreza (atezolizumab and hyaluronidase-tqjs) manufactured by Genentech, Inc. The
330 data submitted in this application are adequate to support the conclusion that the manufacture of

331 Tecentriq Hybreza is well-controlled and leads to a product that is pure and potent for the
332 duration of the shelf-life. It is recommended that this product be approved for human use under
333 conditions specified in the package insert. Refer to the OPQ Executive Summary dated August
334 16, 2024, for full details.

335 **4.3. Clinical Microbiology**

336 Not applicable for this application as no clinical microbiology data or information were provided
337 in this application.

338 **4.4. Devices and Companion** 339 **Diagnostic Issues**

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

341 **5. Nonclinical Pharmacology/Toxicology**

342 **5.1. Executive Summary**

343 Atezolizumab is a monoclonal antibody that binds to programmed death-ligand 1 (PD-L1),
344 blocking its interactions with both programmed cell death protein 1 (PD-1) and cluster of
345 differentiation 80 (B7.1) receptors, leading to enhanced antitumor immune responses.
346 Intravenous atezolizumab (Tecentriq) has been US FDA-approved since 2016 and is indicated
347 for the treatment of multiple oncology indications. Hyaluronidase is a spreading or diffusing
348 substance that modifies the permeability of connective tissue through hydrolysis of the
349 mucopolysaccharide hyaluronic acid, resulting in enhanced drug delivery and allowing
350 subcutaneous (SC) administration of larger drug volume. Recombinant human hyaluronidase
351 (rHuPH20) is a purified, neutral pH-active preparation of human hyaluronidase generated by
352 recombinant DNA technology in Chinese Hamster Ovary cells. rHuPH20 (Hylenex) has been US
353 FDA-approved since 2005 and is indicated as an adjuvant to increase the absorption and
354 dispersion of other injected drugs for SC fluid administration and as an adjunct in SC urography
355 for improving the resorption of radiopaque agents. The Applicant has developed a new product
356 containing atezolizumab and rHuPH20 for SC injection (atezolizumab SC) for the same adult
357 indications as Tecentriq. The Applicant cross-references the nonclinical packages previously
358 reviewed by the FDA under BLA 761034 for atezolizumab and BLA 21859 for rHuPH20 to
359 support the current application. No new nonclinical studies (pharmacology/toxicology) were
360 submitted for this application. The nonclinical data cross-referenced from BLAs 761034 and
361 21859 are adequate to support the current application.

362 During the review, the DMEPA reviewer consulted the review team regarding potential
363 medication errors between atezolizumab SC versus atezolizumab IV. The main differences
364 between the two formulations are the presence of methionine and hyaluronidase in the

365 atezolizumab SC formulation. We determined that if the formulation for SC is accidentally given
366 via the intravenous (IV) route, patients will be exposed to ^(b)₍₄₎ mg methionine. As methionine has
367 been administered IV up to 4800 mg, the concentration of methionine received via IV does not
368 raise a safety concern from the pharmacology/toxicology perspective.

369 The nonclinical team also made edits to the Applicant's proposed USPI in Sections 5.4, 8.2, 8.3,
370 13.2, and 17 to reflect current labeling practices, including updated language for the lactation
371 section (see labeling review memo in DARRTs).

372 There are no outstanding issues from a pharmacology/toxicology perspective that would prevent
373 approval of Tecentriq Hybreza for the proposed indications.

374 **5.2. Referenced NDAs, BLAs, DMFs**

375 The Applicant's Position: The nonclinical strategy to support the current application of
376 atezolizumab SC leverages the available comprehensive nonclinical data packages
377 (pharmacology, pharmacokinetic, and toxicology) from the following initial BLAs:

- 378 • Tecentriq (BLA 761034)
- 379 • Hylenex (BLA 021859, Halozyme Therapeutics Inc.)

380 The FDA's Assessment: FDA agrees.

381 **5.3. Pharmacology**

382 The Applicant's Position: The nonclinical characterization of the pharmacodynamics of
383 atezolizumab is described in previously approved dossiers (refer to BLA 761034). No dedicated
384 pharmacology studies with atezolizumab SC have been conducted.

385 The FDA's Assessment: FDA agrees.

386 **5.4. ADME/PK**

387 The Applicant's Position: The nonclinical characterization of the pharmacokinetics of
388 atezolizumab is described in previously approved dossiers (refer to BLA 761034). No dedicated
389 pharmacokinetics studies with atezolizumab SC have been conducted.

390 The FDA's Assessment: FDA agrees.

391

5.5. Toxicology

392

5.5.1. General Toxicology

393 The Applicant's Position: The toxicity of atezolizumab has been thoroughly investigated in
394 nonclinical studies following IV administration (refer to BLA 761034). The toxicity and
395 toxicokinetics of atezolizumab following SC administration were well characterized in a Good
396 Laboratory Practice repeat-dose study in cynomolgus monkey (Study 08-1148), demonstrating
397 that the nonclinical safety profile of atezolizumab is similar between IV and SC administration.

398 The FDA's Assessment: FDA agrees. General toxicology studies, including Study 08-1148 for
399 atezolizumab referenced by the Applicant, were previously reviewed by FDA for Tecentriq and
400 Hylenex.

401

5.5.2. Genetic Toxicology

402 The Applicant's Position: No dedicated genotoxicity studies with atezolizumab SC have been
403 conducted.

404 The FDA's Assessment: FDA agrees. Genetic toxicology studies with atezolizumab are not
405 warranted as it is a monoclonal antibody and is not expected to interact with DNA. Additionally,
406 no genetic toxicology studies with rHuPH20 have been conducted and are not required since it is
407 an endogenous human enzyme.

408

5.5.3. Carcinogenicity

409 The Applicant's Position: No dedicated carcinogenicity studies with atezolizumab SC have been
410 conducted.

411 The FDA's Assessment: FDA agrees. Carcinogenicity studies are not warranted to support this
412 BLA submission.

413

5.5.4. Reproductive and Developmental Toxicology

414 The Applicant's Position: No dedicated reproductive and developmental toxicity studies with
415 atezolizumab SC have been conducted.

416 The FDA's Assessment: FDA agrees. Reproductive and development toxicology studies were
417 previously reviewed by FDA and incorporated into labeling for Tecentriq and Hylenex. Results
418 from these studies from both labels were collated into the Tecentriq Hybreza label, with no major
419 changes except for updating animal-to-human exposure margins for rHuPH20 and language to
420 comply with PLLR.

421 **5.5.5. Other Toxicology Studies**

422 The Applicant's Position: No dedicated other toxicity studies with atezolizumab SC have been
423 conducted.

424 The FDA's Assessment: FDA agrees.

425

426

X

X

427
428 Kelie Reece, PhD
429 Primary Reviewer
430

Claudia P. Miller, PhD
Supervisor

431 **6. Clinical Pharmacology**

432 **6.1. Executive Summary**

433 The FDA's Assessment: Atezolizumab is a PD-L1 blocking antibody approved for intravenous
434 (IV) administration for multiple indications including NSCLC, SCLC, HCC, melanoma and
435 alveolar soft part sarcoma (ASPS). In the current BLA submission, the Applicant is seeking
436 approval of an atezolizumab/hyaluronidase co-formulation for subcutaneous (SC) administration
437 in all the adult indications approved for the atezolizumab IV formulation. Hyaluronidase is an
438 endoglycosidase that facilitates the SC absorption. The proposed dosage for atezolizumab SC
439 administration is 1875 mg Q3W injected in the thigh.

440 Study IMscin001 was conducted in patients with advanced or metastatic NSCLC who were
441 cancer immunotherapy naive and who had disease progression during or after treatment with
442 platinum-based chemotherapy. The dosage of SC 1875 mg Q3W was selected and supported by
443 modeling and simulation of data from clinical studies. Pharmacokinetic (PK) comparability
444 between atezolizumab/hyaluronidase 1875 mg Q3W SC and atezolizumab 1200 mg Q3W IV on
445 the coprimary PK endpoints of atezolizumab exposure (Cycle 1 AUC_{0-21 days} and C_{trough}) was
446 demonstrated as the geometric mean ratios (GMRs) and 90% CI for Cycle 1 C_{trough} was 1.05
447 (90% CI: 0.88, 1.24) and was 0.87 (90% CI: 0.83, 0.92) for AUC_{0-21days}; both met the pre-
448 specified comparability criteria with the lower bound of the 90% CI of the GMR at 0.8 or above.

449 Additional descriptive efficacy outcome measures were overall response rate (ORR),
450 progression-free survival (PFS) and overall survival (OS). The confirmed ORR was 9%

451 (95% CI: 5, 13) in the atezolizumab SC arm and 8% (95% CI: 4, 14) in the atezolizumab IV arm.
452 No differences in PFS and OS were observed between the two arms.

453 The incidence of anti-drug antibodies (ADAs) was 20% (43/221) in the atezolizumab SC arm
454 and 14% (15/108) in the atezolizumab IV arm. Compared to patients who were ADA-negative,
455 atezolizumab clearance increased by 29% in the SC arm and by 5% in the IV arm in patients who
456 were ADA-positive. The incidence of neutralizing antibodies (NAbs) in patients who tested
457 ADA positive was 49% (21/43) in the SC arm and 60% (9/15) in the IV arm. The presence of
458 ADAs and Nabs did not significantly affect the safety profiles of atezolizumab by SC or IV
459 administration. The effect of ADAs and NAbs on efficacy endpoints is inconclusive due to small
460 sample sizes.

461 In addition to the atezolizumab IV 1200 mg Q3W dosage, there are two other IV dosages (i.e.,
462 840 mg Q2W, 1680 mg Q4W) approved based on PK comparability with the IV 1200 mg Q3W
463 dosage via modeling and simulation. Given that PK comparability of atezolizumab SC 1875 mg
464 Q3W to atezolizumab IV 1200 mg Q3W has been demonstrated based on results of IMscin001
465 and PK is comparable among approved IV dosages of atezolizumab, the switch from all
466 atezolizumab IV dosages to atezolizumab SC 1875 mg Q3W dosage is considered reasonable.

467 **6.2. Summary of Clinical** 468 **Pharmacology Assessment**

469 **6.2.1. Pharmacology and Clinical Pharmacokinetics**

470 The Applicant's Position: IMScin001 was a two-part PK-bridging study that (1) provided the
471 rationale for the dosing regimen used for atezolizumab SC in Part 2 (dose-finding; Part 1) and
472 (2) demonstrated the non-inferiority of Cycle 1 drug exposure (with respect to atezolizumab
473 trough concentration [C_{trough}] and model-predicted area under the concentration–time curve
474 from 0 to 21 days [$AUC_{0-21 \text{ d}}$]) following treatment with atezolizumab SC at the 1875 mg Q3W
475 dosing regimen compared with atezolizumab IV at the approved 1200 mg Q3W dosing regimen
476 (Phase III, randomized, dose-confirmation; Part 2).

477 In Part 2, the co-primary endpoints (observed C_{trough} and model-predicted $AUC_{0-21 \text{ d}}$ at
478 Cycle 1) were met and atezolizumab exposure remained well above the target concentration of 6
479 $\mu\text{g/mL}$ (Deng et al. 2016). The approximate exposure metrics at steady state (minimum trough
480 serum concentration at steady state [$C_{\text{trough,SS}}$] and AUC_{SS} model-predicted at Cycle 10) were
481 also similar between the atezolizumab SC and IV arms (hereinafter Atezo SC and Atezo IV,
482 respectively). Higher PK variability was observed for the SC arm compared to the IV arm. The
483 incidence of treatment emergent anti-drug antibodies (ADAs) to atezolizumab was comparable
484 between the arms (19.5% [43/221] in Atezo SC and 13.9% [15/108] in Atezo IV) and within the
485 historical range of ADA incidence in prior studies (Wu et al. 2022). There did not appear to be a
486 clinically relevant impact of atezolizumab ADA on pharmacokinetics, efficacy, or safety. The

487 baseline prevalence and post-baseline incidence of antibodies to rHuPH20 was 11.4% and 5.4%,
 488 respectively.

489 The Phase I population pharmacokinetics (popPK) model for atezolizumab IV (Stroh et al.
 490 2017), extended with first-order absorption parameters, well described the concentration–time
 491 course of atezolizumab after IV and SC administrations in IMscin001, suggesting atezolizumab
 492 exposure was in concordance with historical data. Atezolizumab SC absorption was
 493 characterized by a first-order absorption with an oral bioavailability (F1) of 71.8% (ranging from
 494 23.3% to 91.7%) and an absorption rate constant (KA) of 0.304 per day (Table 3). Following
 495 covariate analysis, hemoglobin and albumin were identified as statistically significant covariates
 496 on F1 and KA, respectively, in addition to the known significant covariates on the atezolizumab
 497 pharmacokinetics (i.e., body weight, ADA status, albumin levels, and [REDACTED]).

498 There were no statistically significant exposure-safety or -efficacy relationships identified
 499 following 1875 mg Q3W SC atezolizumab.

500 The FDA’s Assessment: FDA generally concurs with the Applicant’s position. Selection of the
 501 atezolizumab SC dose of 1875 mg Q3W administered in the thigh for the pivotal study was
 502 based on comparable exposure to the atezolizumab IV dose of 1200 mg Q3W observed in the
 503 historical OAK study and supported by modeling and simulation and higher estimated
 504 bioavailability of 83% for thigh injections relative to 71% for abdomen injections.

505 **Comparable PK Exposure Between Atezolizumab SC and Atezolizumab IV Arms:**

506 FDA Table 2 shows that the lower limit of the 90% CI of the GMR for the coprimary endpoints
 507 of observed C_{trough} (1.05 [90% CI: 0.88, 1.24]) and model-based AUC_{0-21days} (0.87 [90% CI: 0.83,
 508 0.92]) are above 0.8 thereby demonstrating PK comparability between atezolizumab SC and
 509 atezolizumab IV. The GMRs for steady state PK exposure also met the pre-specified
 510 comparability criteria demonstrating PK comparability between atezolizumab SC and
 511 atezolizumab IV.

512 **FDA Table 2. PK of Atezolizumab SC Versus Atezolizumab IV (co-Primary and Secondary PK**
 513 **Endpoints) From Study IMscin001**

PK Endpoints	Geometric Mean Ratio (90% CI) (SC:IV) (n=246:n=122)*
Primary PK Endpoints	
Observed serum C _{trough} at Cycle 1	1.05 (0.88, 1.24)
Model based AUC _{0-21days} at Cycle 1	0.87 (0.83, 0.92)
Secondary PK Endpoints	
Model based C _{trough,ss} at steady state	1.15 (1.05, 1.26)
Model based AUC at Cycle 1	0.97 (0.91, 1.05)
Model based AUC at steady state	1.01 (0.94, 1.08)

514 Source: summary-clin-pharm: Mod2.7.2/Table 9, Table 10, Table 16/page 31,32 & 44.

515 * n=205 (SC): n=97 (IV) for observed C_{trough}.

516

517 The covariate analysis conducted with the popPK model identified hemoglobin and albumin as
518 significant covariates on absorption parameters in addition to the previously identified known
519 significant covariates on the PK parameters after IV infusion including ADA status, body
520 weight, albumin and sex.

521 **Descriptive Efficacy and Safety Comparisons Between SC and IV Arms:**

522 At the time of the primary analysis with a data cutoff date of April 26, 2022, the ORR was 9%
523 (95% CI: 5, 13) in the SC arm and 8% (95% CI: 4, 14) in the IV arm. At the same data cutoff
524 date, median PFS was 2.8 months (95% CI: 2.1, 3.1) for atezolizumab SC and 2.9 months (95%
525 CI: 1.7, 4.2) for atezolizumab IV. However, only 33% of patients had an OS event in the
526 intention-to-treat (ITT) population and OS data were not considered robust by the FDA review
527 team. The Applicant submitted an updated OS analysis with 10 additional months of follow-up,
528 based on a data cutoff date of January 16, 2023. In the updated OS analysis, 60% of patients in
529 the ITT population had an OS event. The median OS was 10.7 months (95% CI 8.5, 13.8) for
530 atezolizumab SC and 10.1 months (95% CI: 7.5, 12.1) for atezolizumab IV (HR 0.88; 95% CI
531 0.67, 1.16). The safety profiles, including serious adverse effects (AEs) and Grade ≥ 3 AEs, were
532 also comparable between the atezolizumab SC and atezolizumab IV arms.

533 **Effect of ADA and NAb on PK, Efficacy and Safety:**

534 Compared to ADA-negative patients, the C_{trough} was 34% lower in ADA-positive patients in the
535 atezolizumab SC arm and 10% lower for the atezolizumab IV arm. The ADAs increased
536 atezolizumab clearance (CL) by 29% in the SC arm and by 5% in the IV arm.

537 ADA-positive patients showed a trend of a lower median OS (6.9 months [95% CI:5.0, NE])
538 compared to ADA-negative patients (12.6 months [95% CI:10.6,16.5]) in the atezolizumab SC
539 arm while such an effect was not observed in the atezolizumab IV arm; however, the median OS
540 was 10.7 months for atezolizumab SC and 10.1 months for atezolizumab IV. Of note, the data
541 are limited to adequately characterize the effect of ADA on efficacy and the observed difference
542 in median OS between ADA-positive and ADA-negative patients in the SC arm may also be
543 attributed and confounded by the presence of imbalanced baseline factors associated with disease
544 prognosis including CRP.

545 The incidence of neutralizing antibodies (NAbs) in the atezolizumab SC arm who were ADA-
546 positive was 49% (21/43) and 60% (9/15) in the atezolizumab IV arm. The effect of NAbs on
547 efficacy endpoints is inconclusive due to small sample sizes, although OS trended lower in
548 ADA-positive and NAb positive patients (6.3 months (95% CI: 4.2, NE) compared to the ADA-
549 positive and Nab-negative (8.3 months (95% CI: 5.1, NE) patients in the atezolizumab SC arm.

550 The presence of ADAs and NAbs did not significantly affect the safety profiles of atezolizumab
551 SC or atezolizumab IV.

552 **6.2.2. General Dosing and Therapeutic**
553 **Individualization**

554 **6.2.3. General Dosing**

555 Data: In Part 1, patients were enrolled to three single-arm SC dosing cohorts. Patients received
556 one (Cohort 1) or up to three (Cohorts 2 and 3) administrations of atezolizumab 1200 mg or
557 1800 mg SC co-mix followed by treatment with atezolizumab IV 1200 mg Q3W for subsequent
558 cycles until disease progression, loss of clinical benefit, unacceptable toxicity, or withdrawal of
559 consent.

560 In Part 2, patients were enrolled to a two-arm, randomized, multicenter pivotal clinical study.
561 Patients were randomized in a 2:1 ratio to receive atezolizumab as monotherapy with either
562 1875 mg of atezolizumab SC administered in thigh Q3W or 1200 mg of atezolizumab IV Q3W,
563 respectively.

564 The Applicant's Position: The atezolizumab SC dosing regimen of 1875 mg Q3W is
565 recommended in all approved and future indications where the dosing regimen of 1200 mg IV
566 Q3W is approved.

567 The FDA's Assessment: FDA concurs with the Applicant's position on the proposed SC dosage
568 of 1875 mg atezolizumab/30,000 units hyaluronidase at the same dosing schedule of Q3W, as
569 atezolizumab 1200 mg IV. The PK exposure between 1875 mg SC and 1200 mg IV was
570 comparable in patients receiving second-line therapy for advanced or metastatic NSCLC who
571 were cancer immunotherapy naive and who progressed on prior platinum-based chemotherapy in
572 Study IMscin001.

573 The Applicant proposes the atezolizumab/hyaluronidase SC dosage of 1875 mg Q3W for all of
574 the adult indications that were previously approved for atezolizumab IV at a dosage of 1200 mg
575 Q3W. This proposal is supported by the observation that no statistically significant ($p>0.05$)
576 difference was detected in atezolizumab PK across previous studies conducted with different
577 tumor types after atezolizumab IV treatment (see [Figure 9](#), Section 7.2.1.1). Although
578 atezolizumab/hyaluronidase SC has been formally evaluated only in patients receiving second
579 line therapy for advanced or metastatic NSCLC, it is anticipated that atezolizumab PK exposure
580 will be comparable in different tumor types after SC administration as seen after IV
581 administration.

582

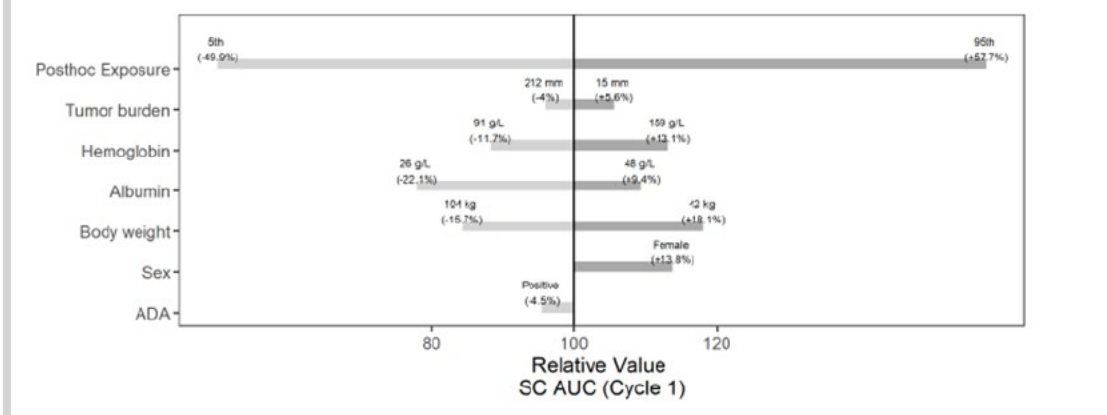
6.2.4. Therapeutic Individualization

583 Data: Covariate effects based on body weight, sex, age, race, ethnicity, geographic region, renal
584 impairment, and hepatic impairment on atezolizumab exposure were numerically compared to
585 evaluate the effects on atezolizumab pharmacokinetics. Patients in the lowest body weight
586 quartile presented 29.9% and 23% higher model-predicted $AUC_{0-21\text{ d}}$ geometric mean (GM)
587 compared to the highest body weight quartile following atezolizumab SC 1875 mg Q3W and
588 atezolizumab IV 1200 mg Q3W, respectively. Similarly, female patients presented higher
589 exposure metrics than male with 26.1% and 20.9% higher geometric means of $AUC_{0-21\text{ d}}$ for
590 atezolizumab SC 1875 mg Q3W and atezolizumab IV 1200 mg Q3W, respectively. This is
591 consistent with the known significant covariates on atezolizumab pharmacokinetics (Stroh et al.
592 2017). A minor trend was observed with ethnicity for atezolizumab SC 1875 mg Q3W, where
593 Hispanics have marginally higher exposure metrics (22% higher GM model-predicted $AUC_{0-21\text{ d}}$)
594 than non-Hispanics, although their confidence intervals still largely overlap. No relevant
595 difference was observed for the other covariates of interest.

596 The Applicant's Position: Given the wide therapeutic window for atezolizumab, patient
597 characteristics including body weight, sex, age, race, ethnicity, renal impairment, or hepatic
598 impairment do not warrant a dose modification for the atezolizumab SC dosing regimen.

599 The FDA's Assessment: FDA agrees with the Applicant's position on that there is no dose
600 individualization of atezolizumab required for adult patients. The exposure of atezolizumab after
601 SC administration at 1875 mg Q3W is comparable to the approved atezolizumab IV after 1200
602 mg Q3W. As atezolizumab is a monoclonal antibody with a relatively wide therapeutic window,
603 the observed exposures and covariates (i.e., body weight, ADA status, albumin levels,
604 hemoglobin and sex) (Figure 1) in Study IMscin001 are within the range of what was previously
605 observed with approved atezolizumab IV and do not warrant a dose modification for the
606 atezolizumab SC dosing regimen. Patients in the lower quartiles presented 23%-30% higher
607 model-based $AUC_{0-21\text{ d}}$ geometric mean (GM) compared to the highest body weight quartile
608 following atezolizumab/ hyaluronidase SC 1875 mg Q3W and atezolizumab IV 1200 mg Q3W
609 (FDA Figure 2). A minor trend was observed with ethnicity for atezolizumab SC 1875 mg Q3W,
610 where Hispanics have marginally higher exposure metrics (22% higher GM model-predicted
611 $AUC_{0-21\text{ d}}$) than non-Hispanics with their confidence intervals largely overlapping (Figure 3). The
612 impact of ethnicity is likely confounded with significant covariates (i.e., body weight, tumor
613 burden, ADA status, albumin levels, hemoglobin and sex) identified in the popPK model,
614 because compared to the cohort of non-Hispanic patients, Hispanic patients had a higher
615 proportion of female patients (54% vs. 21%), higher median baseline tumor burden (89 mm vs.
616 75 mm), slightly lower median body weight (63 kg vs. 68 kg), and slightly higher median
617 hemoglobin level (127 g/L vs. 123 g/L).

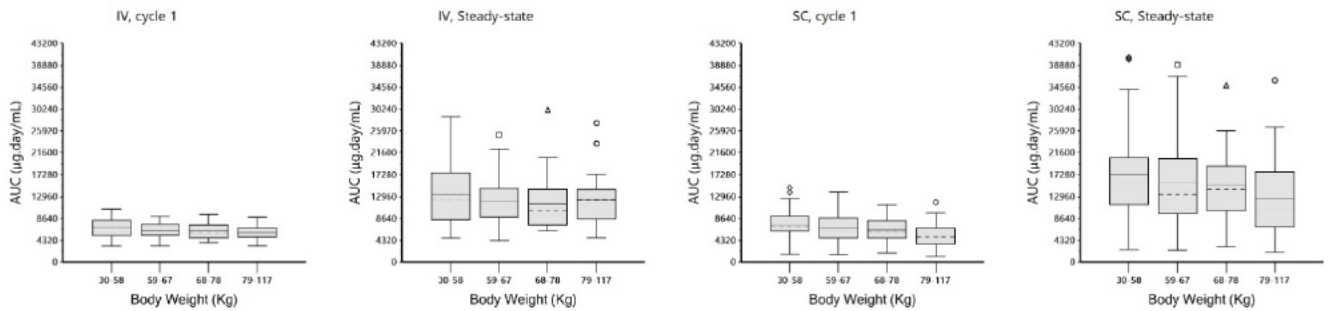
618 **Figure 1. Covariate Effects on AUC_{0-21d} After Atezolizumab SC 1875 mg Q3W Administration**



Source: summary-clin-pharm: Mod2.7.2/Figure 7/page 45.

623 **FDA Figure 2. (a, b): Box Plots of AUC and C_{trough} by Body Weight for Each Treatment Arm**

624 **a. AUC by Baseline Body Weight at Cycle 1 and Steady State for Each Treatment Arm**



625 **b. C_{trough} by Body Weight at Cycle 1 and Steady State for Each Treatment Arm**

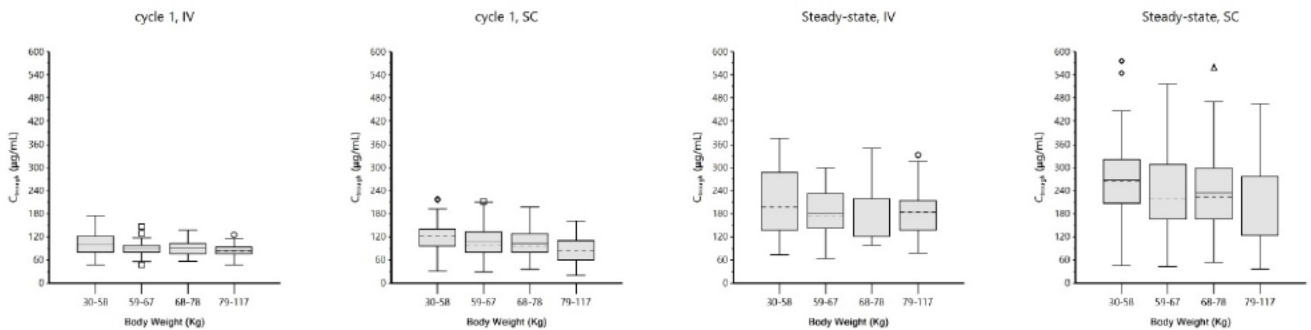
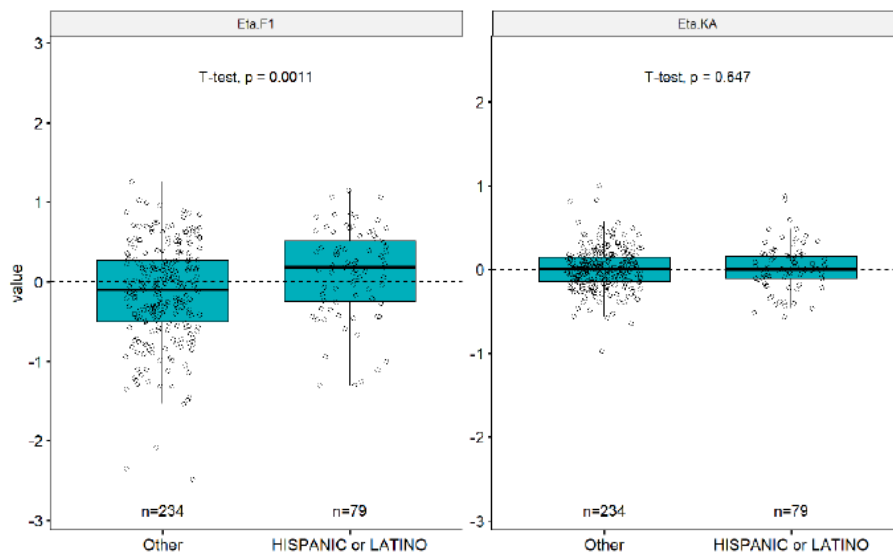


Figure 3. Boxplots of Exploratory Correlation Between Random Effects of Absorption Parameters (Bioavailability, Absorption Constant Rate) and Ethnicity (Hispanic Versus Non-Hispanic/Other) in Patients Receiving SC 1875 mg Q3W Administration



Eta.F1= random effect on bioavailability; Eta.KA= random effect on absorption rate constant;
n=number of patients; p=p-value; PK=pharmacokinetics.

647 Source: popPK report: Appendix 17/page 139.

648 **6.2.4.1. Outstanding Issues**

649 The Applicant's Position: None.

650 The FDA's Assessment: There are no outstanding issues.

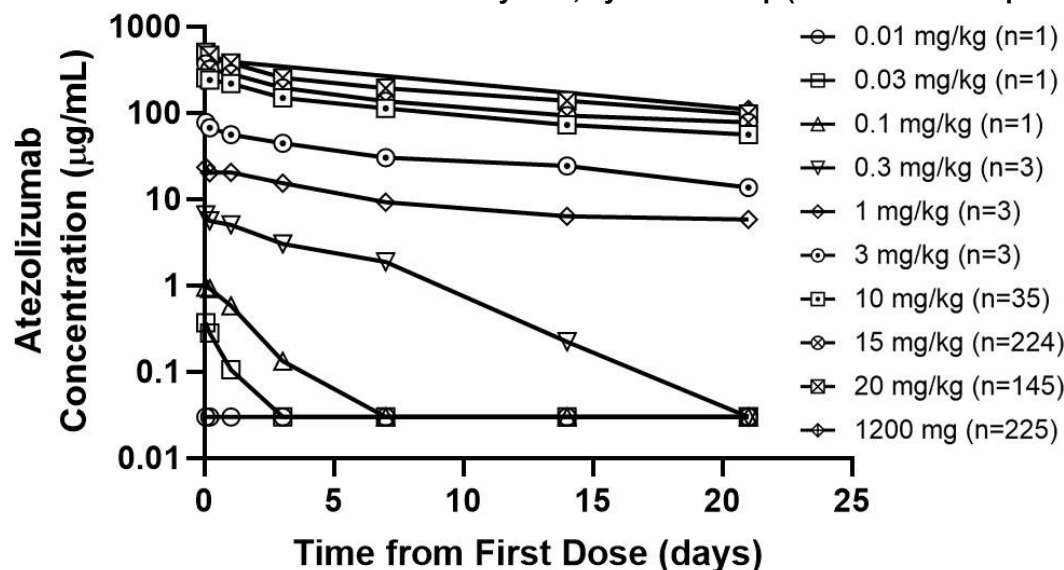
651 **6.3. Comprehensive Clinical** 652 **Pharmacology Review**

653 **6.4. General Pharmacology and** 654 **Pharmacokinetic** 655 **Characteristics**

656 Data: The clinical pharmacology properties of atezolizumab IV and SC were largely
657 characterized in studies where atezolizumab was administered as monotherapy in patients
658 predominantly with 2L NSCLC (Table 3). Atezolizumab IV demonstrated dose
659 proportional- pharmacokinetics at doses ranging from ≥ 1 mg/kg up to 20 mg/kg IV Q3W,

660 including the 1200 mg Q3W IV non-weight-based dosing regimen, in various locally advanced
 661 or metastatic solid tumors or hematologic malignancies in Phase I studies (n = 472) (Figure 1).
 662 Similarly, atezolizumab SC demonstrated dose-dependent exposure increases over a dose range
 663 of 1200 mg to 1800 mg Q3W in the thigh. Based on the observed PK data and popPK modeling,
 664 atezolizumab exposure following IV and SC administrations were comparable across the
 665 approved indications. See Section 6.2.1 for additional information.

666 **Figure 4. Applicant-Phase I Dose-Ranging Study (PCD4989g): Mean Serum Atezolizumab**
 667 **Concentration Versus Time Profile in Cycle 1, by Dose Group (PK Evaluable Population)**



668 Source: Applicant.

669 C_{max} =maximum serum concentration observed; C_{trough} =minimum trough serum concentration observed; PK=pharmacokinetic.
 670 Note: 1200 mg Cycle 1 profile represented by C_{max} and C_{trough} only.

671
 672
 673

674 **Table 3. Applicant-ADME Characteristics Following Atezolizumab IV**

Absorption	Atezolizumab is approved as an IV infusion. For the subcutaneous formulation of atezolizumab, F1 is 71.8% ^a and KA is 0.304 (1/day) ^a
Distribution	V_c is 3.28 L ^a ; V_{ss} is 6.91 L ^a
Metabolism	Antibodies are cleared principally by catabolism (Deng et al. 2012).
Elimination	CL is 0.200 L/day ^a ; terminal elimination $t_{1/2}$ is 27 days ^a ; maximum decrease of CL during treatment (from baseline CL) is 17% (range -6 to -22%) ^b .

675 CL=total clearance of drug; F1=bioavailability; IV=intravenous; KA=rate of absorption; V_c =volume of distribution for the central
 676 compartment; V_p =volume of distribution for the peripheral compartment; V_{ss} =volume of distribution under steady state conditions
 677 (V_c+V_p).

678 ^a Derived from Phase I or SC/IV popPK analysis for the typical patient is a male with anti-drug antibodies (ADA) negative status,
 679 weighing 77 kg, with an albumin level of 40 g/L and a tumor burden of 63 mm, and a hemoglobin level of 123 g/L.

680 ^b Derived from time-varying popPK analysis (Combination Studies [IMpower150, IMpower130, IMpower133, IMpassion130,
 681 IMbrave150]; Monotherapy Studies [OAK, IMvigor211, and PCD4989g]).

682 **The Applicant's Position:** The pharmacokinetics of atezolizumab SC and IV (same active
 683 ingredient) performed similarly with the consideration of the different absorption process
 684 associated with SC delivery. Based on the key results of Part 2, atezolizumab SC administered as
 685 1875 mg Q3W in the thigh confirmed drug exposures were non-inferior to the approved
 686 atezolizumab IV 1200 mg Q3W dosing regimen and the safety, efficacy, and immunogenicity
 687 profiles were consistent with the established profiles of atezolizumab IV in patients with cancer.
 688 The majority of patients (>99%) in the Atezo SC arm had observed serum C_{trough} exceeding
 689 target receptor saturation concentration of 6 $\mu\text{g/mL}$ for efficacy.

690 Higher PK variability was observed for the SC arm compared to the IV arm, but given the
 691 comparable safety and efficacy results in IMscin001 and the exploratory exposure-response
 692 (ER) analyses confirmed atezolizumab exposure following SC was independent to clinical
 693 outcomes (i.e., flat ER), this higher variability was considered not clinically meaningful.

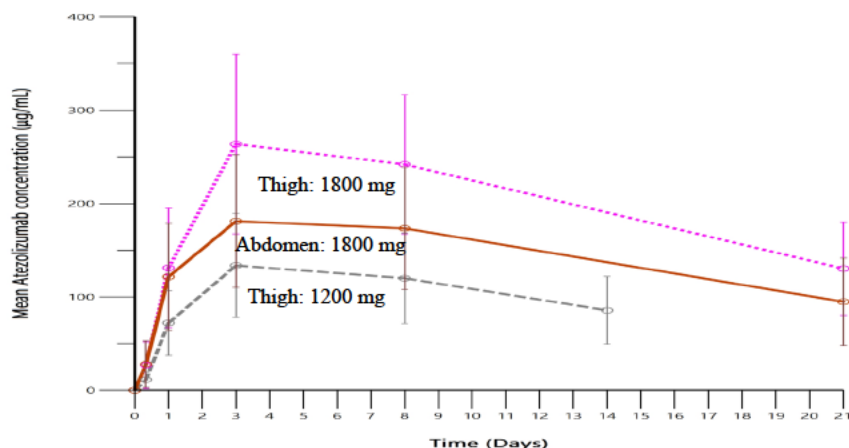
694 Overall, available results from IMscin001 and ER analyses for Part 2 of IMscin001, in
 695 conjugation with clinical experience with atezolizumab IV, suggest that the proposed dosing
 696 regimen of 1875 mg atezolizumab SC provides a similar benefit-risk profile to atezolizumab IV.

697 **The FDA's Assessment:** FDA generally agrees with the Applicant's position on clinical
 698 pharmacology and PK characterization of atezolizumab after IV and SC administration.

699 The objective of this PK bridging was to select the dosage of atezolizumab and human
 700 hyaluronidase (rHuPH20) for SC administration that would provide comparable exposure to the
 701 approved dosage of 1200 mg atezolizumab administered IV. The study was conducted in two
 702 parts, with Part 1 for dose finding and Part 2 for dose confirmation. The PK data from Part 1
 703 showed that a SC dose of 1800 mg Q3W administered in the thigh provided higher exposure than
 704 the same dosage administered in the abdomen (FDA Figure 12, FDA Figure 13).

FDA Figure 5. Mean ($\pm$ SD) Concentration–Time Profiles of Atezolizumab Dose Finding With Atezolizumab SC: Cycle 1

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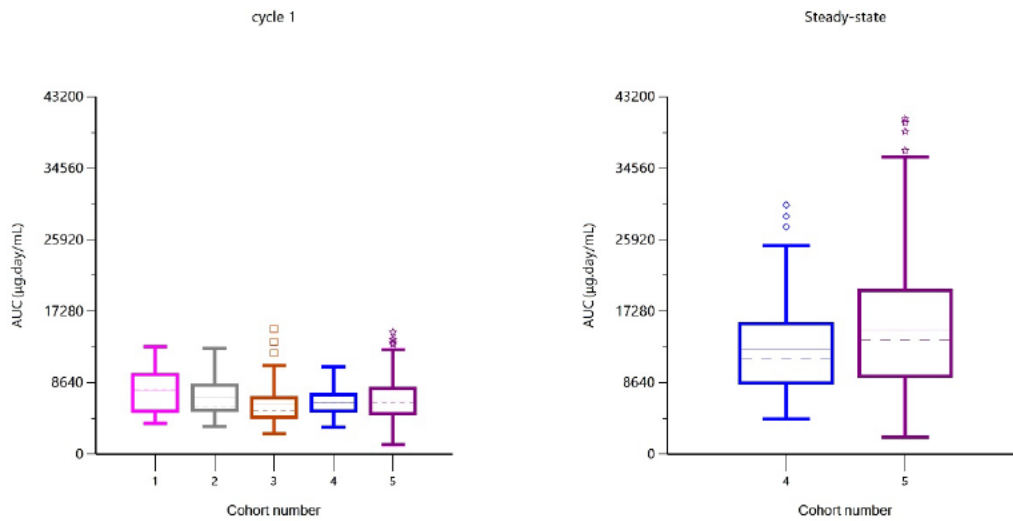
719 Source: Reviewer's analysis

720

721 **FDA Figure 6. (a, b, c): Boxplots of AUC, C_{trough} and C_{max} for all Cohorts Included in Part 1 and**
722 **Part 2 of IMscin001**

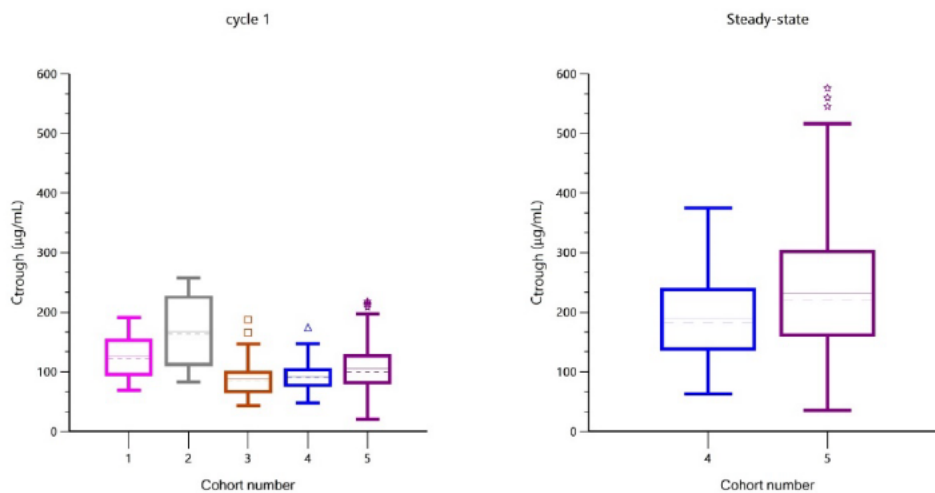
723 Cohort 1: SC (1800 mg, n = 13), Cohort 2: SC (1200 mg, n = 14), Cohort 3: SC
724 (1800 mg, n = 30), Cohort 4: IV (1200 mg, n = 122), Cohort 5: SC (1875 mg, n = 246)

725 **a. AUC at Cycle 1 and at Steady State for Part 1 (Cohort 1,2 &3) and Part 2 (Cohort 4 & 5)**

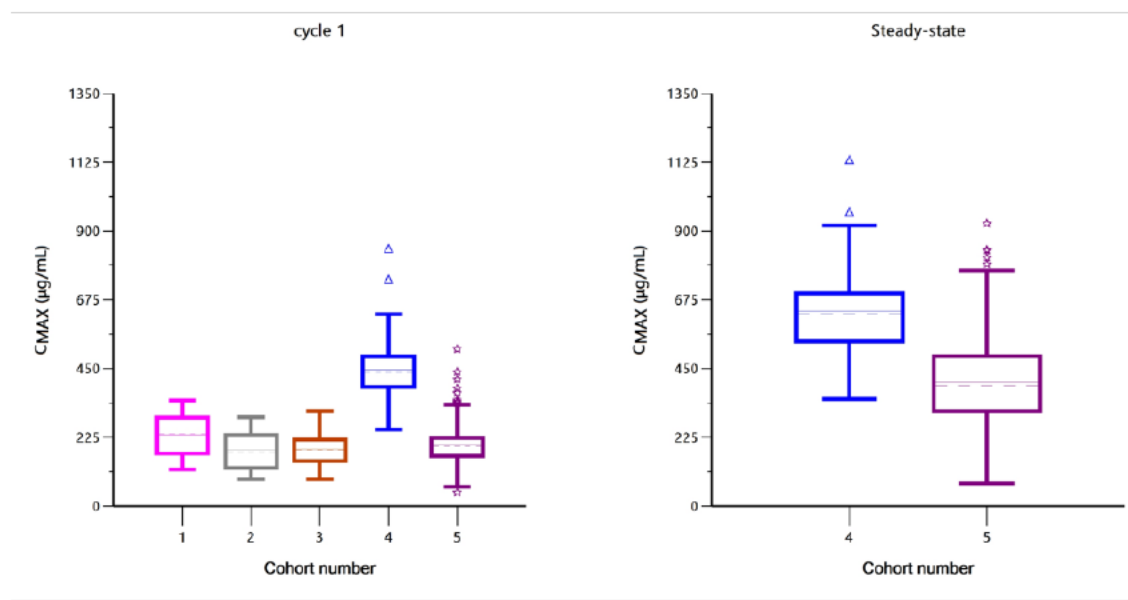


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b. C_{trough} at Cycle 1 and at Steady State for Part 1 (Cohort 1,2 &3) and Part 2 (Cohort 4 & 5)



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732

733 c. C_{max} at Cycle 1 and at Steady State for Part 1 (Cohort 1,2 &3) and Part 2 (Cohort 4 & 5)

Source: Reviewer's analysis.

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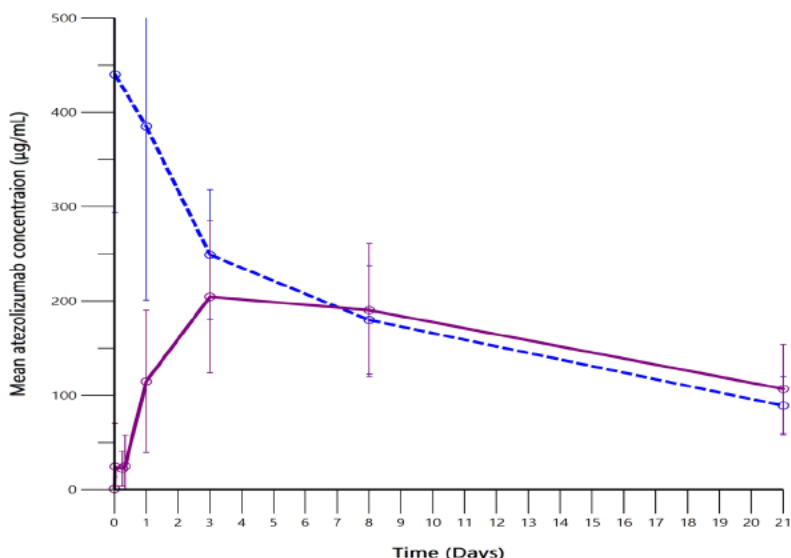
738 An injection volume of 15 mL for atezolizumab SC corresponding to a dose of 1875 mg was
739 considered more appropriate as a dose compared to 1800 mg which corresponds to an injection
740 volume of 14.4 mL (atezolizumab SC strength is 125 mg/mL) which is limited by syringe
741 markings of 1 mL graduations.

742 The popPK model from the previous studies with IV atezolizumab was updated to add the
743 absorption process of atezolizumab SC. The PK of atezolizumab was generally characterized
744 using a two-compartment model with first order absorption estimated from the results of
745 IMscin001 Part 1 and first order elimination. The estimation was based on the results obtained
746 from IMscin001 Part 1 to assess a dose range of 1600 mg to 2000 mg including an 1875 mg dose
747 administered in the thigh and abdomen.

748 The concentration-time profile from the pivotal study (IMscin001 Part 2) showed overlapping
749 elimination phase for atezolizumab SC and atezolizumab IV (FDA Figure 6). The popPK model
750 constructed following Part 1 of the study was used to fit the population from Part 2 of the study.
751 The typical bioavailability (F) of atezolizumab was estimated as 71.8% with an inter-individual
752 variability of 83% along with a median T_{max} of 4.6 days. The geometric mean (GM) of $C_{trough,ss}$
753 following atezolizumab SC at 1875 mg was 13% higher than that of atezolizumab IV 1200 mg
754 (205 µg/mL vs. 179 µg/mL).

755

756 **FDA Figure 7. Mean ($\pm$ SD) Concentration–Time Profiles of Atezolizumab in IMscin001 Part 2. Dose**
757 **Confirmation With Atezolizumab SC Versus Atezolizumab IV: Cycle 1**



758
759 Source: Reviewer's analysis.

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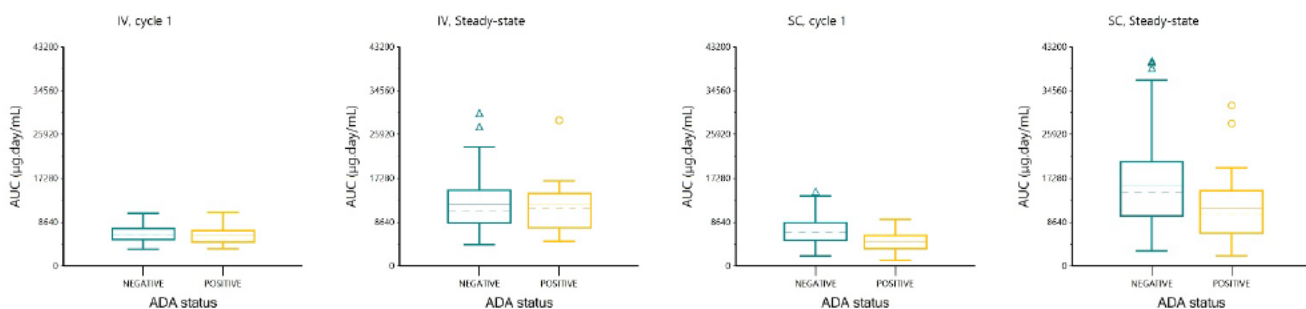
762 **Impact of Immunogenicity on PK**

763 Numerically higher ADA incidence for the SC arm was observed (19.5%, 43/221) when
764 compared to the IV arm (13.9%, 15/108) (FDA Figure 7). The median time to detection of
765 ADA's was 3 weeks after first dosing in both the atezolizumab SC and IV arms.

766 The magnitude of increase (22%) in atezolizumab clearance in patients who tested positive for
767 ADA in the atezolizumab SC arm was similar (19%) to previous clinical study conducted in
768 NSCLC patients with atezolizumab IV administration.

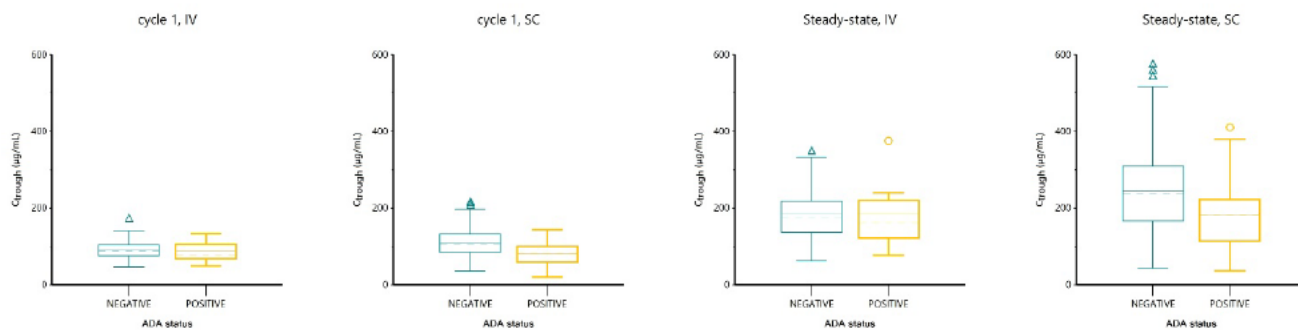
769 **FDA Figure 8. (a, b). Boxplots of AUC and C_{trough} by ADA Status for Each Treatment Arm in**
770 **IMscin001 Part 2**

771 a. AUC by ADA status at Cycle 1 and at steady state for each treatment arm



772

773 **b. C_{trough} by ADA status at Cycle 1 and at steady state for each treatment arm**



774 Source: Reviewer's analysis.
775
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777

778 **6.5. Clinical Pharmacology**
779 **Questions**

780 **6.5.1. Does the Clinical Pharmacology Program**
781 **Provide Supportive Evidence of Effectiveness?**

782 The Applicant's Position: The flat exposure-efficacy and -safety relationship across doses of
783 10–20-mg/kg IV (one patient received 1 mg/kg), including the 1200 mg Q3W IV dosing regimen
784 was previously established in pooled monotherapy studies. This relationship was also confirmed
785 for pivotal trials in the combination setting at the exposure levels of the 840 mg Q2W and
786 1200 mg Q3W IV dosing regimens in the approved indications. Finally, based on Part 2 results,
787 there was no statistically significant exposure-efficacy relationships were identified with
788 objective response rate (ORR), progression-free survival (PFS), or overall survival (OS) in
789 patients treated with SC atezolizumab 1875 mg Q3W.

790 The FDA's Assessment: Efficacy was a secondary endpoint for IMscin001 Part 2 including
791 evaluation of ORR, PFS, OS and duration of response. Overall, there are limited data based on
792 the limited follow-up time and number of patients in the study to characterize the exposure-
793 efficacy relationship in patients treated with atezolizumab SC 1875 mg Q3W. Previous studies
794 conducted with atezolizumab IV have shown a flat exposure-efficacy relationship. Refer to
795 Section 8.1 of the Assessment Aid for additional details regarding the efficacy results for
796 IMscin001 Part 2.

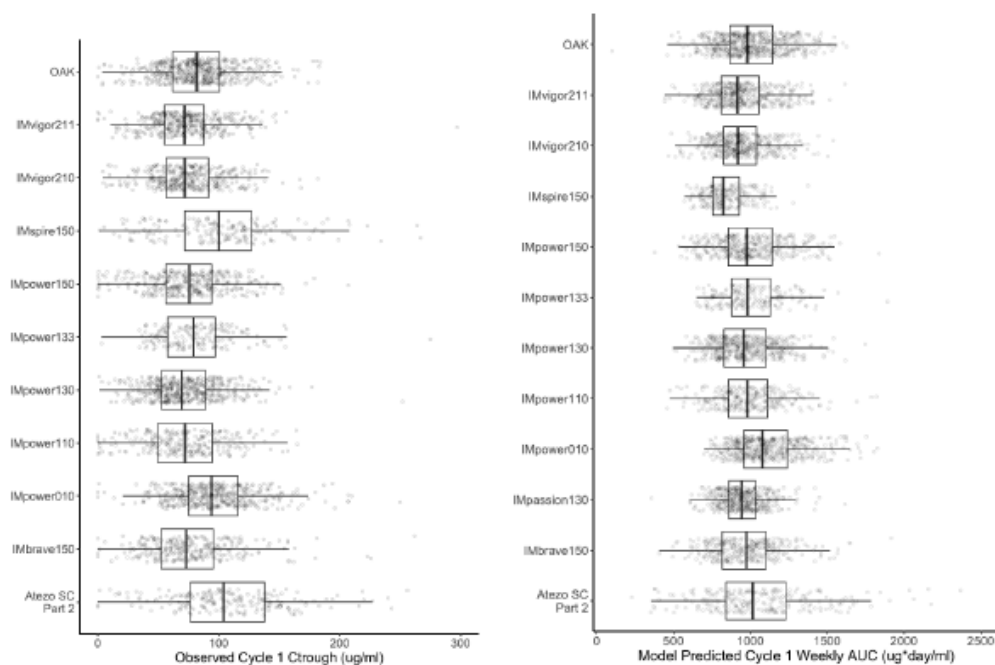
797 **6.5.1.1. Is the Proposed Dosing Regimen Appropriate for the**
798 **General Patient Population for Which the Indication**
799 **is Being Sought?**

800 The Applicant's Position: Given the primary objective of the dose-confirmation study (Part 2)
801 was to demonstrate non-inferiority of the pharmacokinetics of atezolizumab SC compared to the

802 approved 1200 mg Q3W IV dosing regimen, and the clinical pharmacology properties of
803 atezolizumab IV were largely characterized in previous studies where atezolizumab was
804 administered as monotherapy in patients predominantly with 2L NSCLC, the Applicant expects
805 this patient population to be appropriate for the comparison. Additionally, there was no
806 statistically significant exposure-efficacy or -safety relationships identified in patients treated
807 with SC atezolizumab 1875 mg Q3W.

808 The FDA's Assessment: FDA agrees with the Applicant's position that the atezolizumab SC
809 1875 mg Q3W dosing regimen is appropriate for the general population for the proposed
810 indications because the active ingredient, atezolizumab, is the same for the SC formulation and
811 the approved IV formulation intended for the same patient populations. The clinical
812 pharmacology of atezolizumab was primarily characterized via studies conducted for
813 atezolizumab IV administration. The pivotal study, IMscin001 Part 2, supporting the SC
814 formulation demonstrated that the exposure of atezolizumab SC at 1875 mg and IV at 1200 mg
815 Q3W were comparable in patients receiving second line therapy for advanced or metastatic
816 NSCLC. A cross-study comparison, across different tumor types, conducted with atezolizumab
817 IV showed that tumor type was not a significant covariate on atezolizumab PK (e.g., post-hoc
818 clearance estimates [FDA [Figure 9](#)]).

819 **Figure 9. Cross-Study Boxplots Across Different Tumor Types With C_{trough} on Left and**
820 **AUC_{0-21} on Right**



For observed C_{trough} , x-axis is capped at 300, actual data extends to ~600 $\mu\text{g}/\text{mL}$

Pivotal studies of approved Tecentriq indications for mUC: IMvigor210, IMvigor211; NSCLC: IMpower010, IMpower110, IMpower130, IMpower150, OAK; SCLC: IMpower131; TNBC: IMpassion130; melanoma: IMSipre150; HCC: IMbrave150

Observed Cycle 1 C_{trough} ($\mu\text{g}/\text{mL}$) not collected in IMpassion130

821

822 Source: summary-clin-pharm: Mod2.7.2/Figure 8/ page 52.

823

6.5.1.2. Is an Alternative Dosing Regimen or Management Strategy Required for Subpopulations Based on Intrinsic Patient Factors (e.g., Race, Ethnicity, Age, Performance Status, Genetic Subpopulations, etc.)?

824

825

826

827 The Applicant's Position: See Section 6.2.4 for the effects of patient demographics on
828 atezolizumab pharmacokinetics. Additionally, the effects of tumor type on atezolizumab
829 pharmacokinetics was previously evaluated and found insignificant. Drug exposure following
830 atezolizumab SC was consistent to the other approved IV clinical studies across the other
831 approved atezolizumab (IV) indications to atezolizumab SC in the IMscin001 study. Given the
832 wide therapeutic window for atezolizumab and confirmed flat exposure-response relationship
833 following atezolizumab 1875 mg Q3W SC, patient characteristics including body weight, sex,
834 age, race, ethnicity, renal impairment, or hepatic impairment do not warrant a dose modification
835 for the atezolizumab SC dosing regimen.

836 The FDA's Assessment: FDA agrees with the Applicant's position that no dose adjustment is
837 recommended for atezolizumab SC 1875 mg as monotherapy based on intrinsic factors including

838 body weight, sex, age, race, ethnicity, renal impairment, or hepatic impairment. Exposure of
839 atezolizumab/hyaluronidase SC at 1875 mg Q3W has been demonstrated to be comparable to
840 that of the atezolizumab IV 1200 mg Q3W. The geometric means of AUC_{0-21d} were higher in
841 patients in the first quartile weight group (30-59.8 kg) by 8.2% for atezolizumab SC 1875 mg
842 and 23% for atezolizumab IV 1200 mg compared to the fourth quartile weight group (78-117
843 kg). However, weight effects on exposure metrics were not considered clinically important based
844 on a flat exposure response relationship for efficacy of atezolizumab. Additionally, most of the
845 patients (>99%) had a C_{trough} level about 10-fold higher than the target efficacious concentration
846 of 6 µg/mL.

847 **6.5.1.3. Are There Clinically Relevant Food-Drug or Drug-**
848 **Drug Interactions, and What is the Appropriate**
849 **Management Strategy?**

850 The Applicant's Position: No new information is provided in the current submission.

851 The FDA's Assessment: The potential of drug-drug interactions with monoclonal antibodies is
852 low.

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853
854 Ritu Chadda
855 Primary Reviewer

Hong Zhao
Team Leader

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857 Ye Xiong
858 Pharmacometrics reviewer
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Youwei Bi
Pharmacometrics Team Leader

860 **7. Sources of Clinical Data**

861 **Table of Clinical Studies**

862 Data:

863 **Table 4. Applicant-Listing of Clinical Trials Relevant to this BLA**

Trial Identity	NCT no.	Trial Design	Regimen/ Schedule/ Route	Primary Study Endpoints	Treatment Duration/ Follow-Up	No. of Patients Enrolled	Study Population	No. of Centers and Countries
<i>Controlled Studies to Support Efficacy and Safety</i>								
BP40657 (IMSCIN001), Part 2 (Part 1 not in scope for efficacy and safety)	NCT03735121	Phase III, open-label, randomized, two-arm, multicenter study	1875 mg atezo SC q3w vs. 1200 mg atezo IV q3w	Observed serum C _{trough} at Cycle 1 (pre-dose Cycle 2) Model-predicted AUC _{0-21 d} at Cycle 1	Until disease progression, loss of clinical benefit, unacceptable toxicity, or withdrawal of consent	Atezo SC=247 Atezo IV=124	Patients with locally advanced or metastatic NSCLC who were CIT-naive and for whom prior platinum therapy had failed	68 centers in 19 countries

864

865 Additional safety information from 8 previous studies is obtained from a total of 3178 patients treated with atezolizumab IV
 866 monotherapy in multiple indications. This safety population is pooled from different tumor types, mainly including patients in the 2L+
 867 lines of anti-cancer therapies in NSCLC, UC, and 1L+ renal cell carcinoma, providing a large comprehensive safety dataset for
 868 atezolizumab IV monotherapy.

869 The FDA's Assessment: FDA agrees with the Applicant's description of the clinical trials relevant to this application. The primary
870 objective of BP40657 (IMscin001 Part 2) was to demonstrate that atezolizumab SC has comparable exposure to atezolizumab IV
871 based on PK endpoints. IMscin001 was the primary trial submitted by the Applicant to support this BLA.

872 FDA agrees with the Applicant's position that the pooled safety population consists of patients with different tumor types who
873 received atezolizumab IV administered as a single agent across 8 clinical trials.

874 On April 20, 2024, the Applicant submitted the results from Study MO43576 (IMscin002), a patient preference study, during the
875 review of the application. The results from IMscin002 patient preference trial are provided in Section [19.6](#) of the Assessment Aid.

876 **8. Statistical and Clinical Evaluation**

877 **8.1. Review of Relevant Individual** 878 **Trials Used to Support Efficacy**

879 **8.1.1. Study BP40657 (IMscin001)**

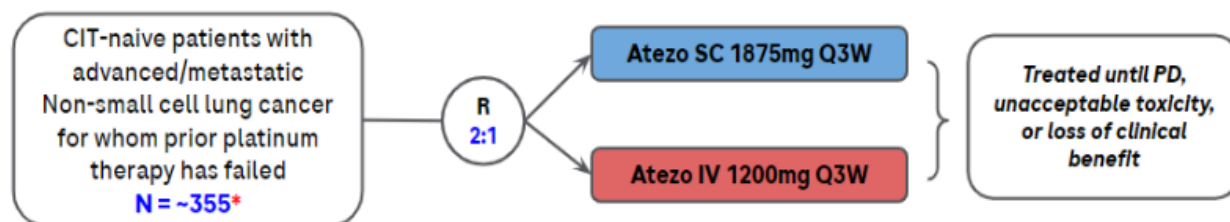
880 **Trial Design**

881 The Applicant's Description:

882 **Basic Study Design:**

883 IMscin001 is a two-part, open-label, multicenter Phase Ib/III study designed to investigate the
884 pharmacokinetics, efficacy, safety, and immunogenicity of atezolizumab SC in comparison with
885 atezolizumab IV in patients with locally advanced or metastatic NSCLC who were CIT-naive
886 and for whom prior platinum therapy had failed. The aim of Part 1 (Phase Ib, dose-finding) was
887 to identify the dose of atezolizumab SC that yields drug exposure that is comparable to that of
888 atezolizumab IV. The aim of Part 2 (Phase III, dose-confirmation) is to demonstrate the non-
889 inferiority of observed drug exposure following treatment with atezolizumab SC at the identified
890 dose compared with drug exposure following treatment with atezolizumab IV (Figure 10). The
891 data in Part 1 of the study was analyzed on an ongoing basis to inform and justify the dose
892 selection and site of administration for SC administration of atezolizumab in Part 2 of the study,
893 and thus is not in scope for this document.

894 **Figure 10. Applicant-Study Part 2 Schema**



895 **The planned sample size (including dropout) provides $\geq 80\%$ power to conclude non-inferiority based on the co-primary endpoints*

896 CIT=cancer immunotherapy; LOCB=loss of clinical benefit; N=planned number of patients; NSCLC=non—small cell lung cancer;
897 Q3W=every three weeks; R=randomization.

898
899

900 **Trial Location:** Part 2 of the study was conducted in 68 different centers across Asia-Pacific,
901 Australia, Central or South America, and Europe and Middle East. For applicability of the results

902 to the U.S. population, please see the Applicant’s position in Section 8.1.2’s Demographic
903 Characteristics section.

904 Choice of Control Group: To demonstrate non-inferiority of atezolizumab SC compared to
905 atezolizumab IV, the control group received the approved 1200 mg Q3W atezolizumab IV
906 dosing regimen.

907 Diagnostic Criteria: Patients with locally advanced or metastatic NSCLC (per the Union
908 Internationale contre le Cancer [UICC]/American Joint Committee on Cancer [AJCC] staging
909 system, 8th edition) were enrolled in IMscin001. Participants were required to have measurable
910 disease as defined by the Response Evaluation Criteria in Solid Tumors, Version 1.1 (RECIST
911 v1.1). Previously irradiated lesions were only considered as measurable disease if disease
912 progression had been unequivocally documented at that site since radiation, and the previously
913 irradiated lesion was not the only site of disease.

914 Key Inclusion/Exclusion Criteria: Patients were included in the study if the following key
915 efficacy-related inclusion/exclusion criteria were met:

916 **General inclusion Criteria:**

- 917 • Measurable disease as defined by RECIST v1.1. Previously irradiated lesions were only
918 considered as measurable disease if disease progression had been unequivocally documented
919 at that site since radiation, and the previously irradiated lesion was not the only site of
920 disease.
- 921 • Histologically or cytologically documented NSCLC that is currently locally advanced or
922 metastatic (i.e., Stage IIIB not eligible for definitive chemoradiotherapy, Stage IV, or
923 recurrent) NSCLC (per the UICC /AJCC staging system, 8th edition)
- 924 • Disease progression during or following treatment with a platinum-containing regimen for
925 locally advanced, unresectable/inoperable or metastatic NSCLC or disease recurrence within
926 6 months of treatment with a platinum-based adjuvant/neoadjuvant regimen or combined
927 modality (e.g., chemoradiation) regimen with curative intent
- 928 • Patients were required to have recovered (i.e., improvement to Grade 1 or better) from all
929 acute toxicities from previous therapy, excluding alopecia. For peripheral neuropathy,
930 improvement to Grade ≤ 2 was considered acceptable.
- 931 • Eastern Cooperative Oncology Group (ECOG) Performance Status of 0 or 1
- 932 • Life expectancy ≥ 12 weeks
- 933 • Adequate hematologic and end-organ function

934 **Inclusion Criteria Specific to Part 2 Patients:**

- 935 • Patients whose tumor may harbor a sensitizing EGFR mutation must have known EGFR test
936 results at the time of randomization. However, patients with sensitizing EGFR mutations
937 were to be excluded once 10% of the total sample size was reached. Of note, the 10% limit
938 was not reached so no such patients were excluded.

- 939 • Availability of a pre-study treatment representative formalin-fixed paraffin-embedded
940 (FFPE) tumor specimen in paraffin block (preferred) or at least six slides containing
941 unstained, freshly cut, serial sections from an FFPE tumor specimen for exploratory
942 biomarker analysis

943 **General Exclusion Criteria:**

- 944 • Symptomatic, untreated, or actively progressing central nervous system (CNS) metastases;
945 asymptomatic CNS lesions were permitted providing all the protocol criteria were met.
- 946 • Spinal cord compression not definitively treated with surgery and/or radiation, or previously
947 diagnosed and treated spinal cord compression without evidence that disease has been
948 clinically stable for ≥ 2 weeks prior to enrollment.
- 949 • History of leptomeningeal disease.
- 950 • Uncontrolled pleural effusion, pericardial effusion, or ascites requiring recurrent drainage
951 procedures (once monthly or more frequently). Patients with indwelling catheters were
952 allowed.
- 953 • Uncontrolled tumor-related pain.
- 954 • Uncontrolled or symptomatic hypercalcaemia (ionized calcium > 1.5 mmol/L,
955 calcium > 12 mg/dL, or corrected serum calcium $>$ upper limit of normal [ULN]).
- 956 • History of malignancy other than NSCLC within 5 years prior to screening, with the
957 exception of those with a negligible risk of metastasis or death and treated with expected
958 curative outcome.
- 959 • Significant cardiovascular disease, such as New York Heart Association cardiac disease
960 (Class II or greater), myocardial infarction within 3 months prior to initiation of study
961 treatment, unstable arrhythmias, or unstable angina.
- 962 • General medical criteria or medications that would preclude the patient's safe participation in
963 and completion of the study.

964 **Exclusion Criteria Specific to Part 2 Patients:**

- 965 • Tested tumor PD-L1 expression status with an intention to treat the patient if positive

966 Dose Selection: The recommended atezolizumab dosing regimen of 1875 mg every three weeks
967 (Q3W), co-formulated with rHuPH20 (2,000 U/mL), was selected based on the results of Part 1
968 (Phase Ib, dose-finding) of the IMscin001 study. Part 1 determined that 1875 mg Q3W of
969 atezolizumab SC in the thigh achieved exposure non-inferior to the approved 1200 mg Q3W
970 atezolizumab IV dosing regimen, based on observed C_{trough} at Cycle 1 results.

971 Study Treatments: In Part 2, patients received monotherapy with either 1875 mg of atezolizumab
972 SC Q3W or 1200 mg of atezolizumab IV Q3W, respectively, starting on Day 1 of each 21-day
973 cycle. Patients continued to receive atezolizumab SC or atezolizumab IV, as indicated, until
974 disease progression, loss of clinical benefit, unacceptable toxicity, or withdrawal of consent.

975 Assignment to Treatment: Patients were randomly assigned to one of two treatment arms: Atezo
976 SC or Atezo IV. Randomization occurred in a 2:1 ratio using a permuted-block randomization
977 method to ensure a balanced assignment to each treatment arm.

978 Blinding: IMscin001 is an open-label study. However, the study management team was
979 unblinded to study treatments. To further protect the integrity of the study, any treatment
980 assignment information, such as randomization files from the interactive voice/web response
981 system (IxRS) and PK data, was withheld from the Sponsor until the primary analysis. Data for
982 safety purposes were mainly reviewed at aggregate level. Individual patient review was not
983 performed routinely, but when deemed necessary for patients of special interest.

984 Dose Modification/Dose Discontinuation: No dose modification was permitted for atezolizumab
985 in this study. In the event of toxicity considered to be related to the study drug, atezolizumab
986 could be temporarily suspended or delayed for up to 12 weeks.

987 Administrative Structure: A Joint Monitoring Committee (JMC) was convened to evaluate
988 pharmacokinetics and safety data during Part 2. The JMC was composed of internal and external
989 members.

990 **Procedures and Schedule:**

991 Pharmacokinetic and Immunogenicity: In Part 2, pharmacokinetic assessments were performed
992 in the SC arm on Days 1 (pre- and post-dose), 2, 4, and 8 of Cycle 1, Day 1 (pre-dose only) of
993 Cycles 2, 3, 4, 8, 12, and 16 as well as at treatment discontinuation visit. The corresponding PK
994 sampling in the IV arm, on Days 1 (pre- and post-dose), 2 (SC only), 4, and 8 of Cycle 1, Day 1
995 (pre-dose and post-dose) of Cycle 2, and Day 1 (pre-dose) of Cycles 3, 4, 8, 12, and 16 as well as
996 at treatment discontinuation visit. Immunogenicity assessments were performed on Day 1 (pre-
997 dose) as well as at treatment discontinuation visit of corresponding cycles where PK samples
998 were collected.

999 Efficacy: The tumor assessments to evaluate efficacy took place every 6 weeks (± 3 business
1000 days) for the first 36 weeks following treatment initiation, and every 9 weeks (± 7 days)
1001 thereafter, regardless of treatment delays. Assessments continued until radiographic disease
1002 progression per RECIST v1.1 or (for patients who continued atezolizumab after radiographic
1003 disease progression) loss of clinical benefit as determined by the investigator. Assessments were
1004 continued per schedule if treatment was discontinued for reasons other than disease progression
1005 or loss of clinical benefit, even if new anti-cancer therapy was initiated. These assessments were
1006 repeated at the investigator's discretion if progressive disease was suspected.

1007 Patient-Reported Experience: The European Organization for Research and Treatment of Cancer
1008 (EORTC) IL57 Questionnaire was completed at the site by patients on Day 1 of Cycles 1–6, and
1009 every even-numbered cycle thereafter (i.e., Cycles 8, 10, etc.) during study treatment, and at the
1010 treatment discontinuation visit. The satisfaction with therapy (SWT) scale was completed at the
1011 site by patients at the Cycle 3 visit, or at the treatment discontinuation visit if the study treatment
1012 was discontinued prior to the Cycle 3 visit.

1013 Safety: The reporting period for safety assessments began after initiation of the study drug and
1014 continued until 30 days after the final dose of study treatment or until initiation of new systemic

1015 anti-cancer therapy (whichever occurred first) for adverse events (AEs), and until 90 days after
1016 the final dose of study treatment or until initiation of new systemic anti-cancer therapy
1017 (whichever occurred first) for serious adverse events (SAEs) and adverse events of special
1018 interest (AESIs). Additionally, SAEs caused by a protocol-mandated intervention after informed
1019 consent was obtained but prior to initiation of study drug (screening) were to be reported; and
1020 after the end of the reporting period, all deaths, regardless of cause, were to be reported. For each
1021 AE, an assessment of seriousness, severity, and causality was performed. SAEs, AESIs, and
1022 pregnancies required immediate reporting to the Sponsor.

1023 Concurrent Medications: The protocol specifies concomitant medications that were allowed, for
1024 which caution had to be exerted, or which were prohibited.

1025 Investigational therapy was prohibited within 28 days prior to initiation of study treatment and
1026 during study treatment. Any concomitant therapy intended for the treatment of cancer (including,
1027 but not limited to, chemotherapy, hormonal therapy, immunotherapy, radiotherapy, and herbal
1028 therapy), whether health authority–approved or experimental, was prohibited for various time
1029 periods prior to starting study treatment (depending on the anti-cancer agent per the exclusion
1030 criteria), and during study treatment, until disease progression was documented and the patient
1031 had discontinued study treatment, with the exception of palliative radiotherapy and local therapy
1032 under certain circumstances. In addition, the following medications were also prohibited during
1033 the study, unless otherwise noted: any live, attenuated vaccine within 4 weeks prior to initiation
1034 of study treatment, during atezolizumab treatment, and for 5 months after the final dose of
1035 atezolizumab; systemic immunostimulatory agents (including, but not limited to, interferons and
1036 IL 2) were prohibited within 4 weeks or 5 half-lives of the drug (whichever is longer) prior to
1037 initiation of study treatment and during study treatment.

1038 Treatment Compliance: Accurate records of all investigational medicinal products (IMPs)
1039 received at, dispensed from, returned to, and disposed of by the study site were recorded on the
1040 Drug Accountability Log.

1041 Subject Completion, Discontinuation, or Withdrawal: At any point in time and without reason,
1042 patients could withdraw their consent to discontinue treatment from the study. Patients had to
1043 permanently discontinue study treatment if they experienced any of the following: intolerable
1044 toxicity related to study treatment, including development of an immune-mediated adverse event
1045 determined by the investigator to be unacceptable given the individual patient's potential
1046 response to therapy and severity of the event; any medical condition that may jeopardize the
1047 patient's safety if they continued study treatment; investigator or Sponsor determination that
1048 treatment discontinuation was in the best interest of the patient; use of another non-protocol anti-
1049 cancer therapy; pregnancy; loss of clinical benefit as determined by the investigator after an
1050 integrated assessment of radiographic and biochemical data, local biopsy results (if available),
1051 and clinical status (e.g., symptomatic deterioration such as pain secondary to disease).

1052 Patients who discontinued study treatment prematurely were not replaced. After treatment
1053 discontinuation, information on survival follow-up and new anti-cancer therapy would be
1054 collected until death (unless the patient withdrew consent or the Sponsor terminated the study).

1055 The FDA's Assessment: FDA agrees with the Applicant's position and clarified that Study
1056 IMscin001 was only powered for PK endpoints and the sample size calculation was not driven
1057 by an efficacy endpoint. All efficacy endpoints were descriptive in nature.

1058 FDA evaluated the patient-reported experience of atezolizumab SC and atezolizumab IV based
1059 on results from Study IMscin002. Please refer to the Appendix to BLA 761347 Multi-
1060 disciplinary Review and Evaluation (Section 19.6) for a full description of Study IMscin002.

1061 **Study Endpoints**

1062 The Applicant's Description: The primary objective of Part 2 of the study was to demonstrate
1063 non-inferiority of exposure to atezolizumab SC compared with atezolizumab IV based on the
1064 corresponding co-primary endpoints (for more details, please see Section 6.2.1):

- 1065 • Observed serum C_{trough} at Cycle 1 (pre-dose Cycle 2)
- 1066 • Model-predicted area under the concentration–time curve (AUC) from 0 to 21 days
1067 (AUC_{0–21 d}) at Cycle 1

1068 The efficacy of atezolizumab SC compared with atezolizumab IV was evaluated as a secondary
1069 objective of the study in Part 2. The four secondary endpoints were:

- 1070 • ORR, defined as the proportion of patients with a complete response (CR) or partial response
1071 (PR), as determined by the investigator according to RECIST v1.1
- 1072 • PFS, defined as the time from study entry to the first occurrence of disease progression or
1073 death from any cause (whichever occurs first), as determined by the investigator according to
1074 RECIST v1.1
- 1075 • OS, defined as the time from study entry to death from any cause
- 1076 • Duration of response (DOR), defined as the time from first occurrence of a documented
1077 objective response to disease progression or death from any cause (whichever occurs first), as
1078 determined by the investigator according to RECIST v1.1

1079 Additionally, the patient experience with atezolizumab SC compared with atezolizumab IV was
1080 evaluated with the two following endpoints:

- 1081 • Functioning and global health status over time, as assessed by the physical functioning, role
1082 functioning, and global health status (GHS)/quality of life (QoL) scales of the EORTC IL57
- 1083 • Overall satisfaction with treatment over time, as assessed by the modified SWT scale of the
1084 Cancer Therapy Satisfaction Questionnaire (CTSQ)

1085 The FDA's Assessment: FDA agrees with the Applicant's description. All efficacy endpoints
1086 were descriptive in nature. There was no pre-specified testing plan for secondary endpoints.
1087 Additionally, the study did not include a testing strategy and was not powered to detect
1088 differences in the patient experience with atezolizumab SC as compared to atezolizumab IV.

1089 Please refer to the Appendix to BLA 761347 Multi-disciplinary Review and Evaluation
1090 (Section 19.6) for a full description of Study IMscin002.

1091 **Statistical Analysis Plan and Amendments**

1092 The Applicant's Description:

1093 **SAP Amendments:** The original statistical analysis plan (SAP) for IMscin001 v1, dated
1094 November 2021, was amended twice:

- 1095 • SAP v2, dated March 2022, incorporated minor changes, including:
- 1096 ○ References to an extended recruitment in China were removed.
 - 1097 ○
 - 1098 ○ Supplementary analysis for observed serum trough plasma concentration (C_{trough}) at
1099 Cycle 1 (pre-dose Cycle 2) was added in Section 5.3.3.
 - 1100 ○
 - 1101 ○ Response-evaluable population was added in Section 4 to clarify the population to be
1102 used for ORR analysis.
 - 1103 ○
 - 1104 ○ An appendix section was added to describe in detail the blinded study sample size
1105 re-estimation process as planned in study protocol when approximately 210–250 patients
1106 had been randomized.
- 1107 • SAP v3, dated June 2022, incorporated the following changes:
- 1108 ○ Confirmed duration of response (C-DOR) evaluable population was added to the analysis
1109 set in Section 4.
 - 1110 ○
 - 1111 ○ The name of Population PK analysis set was changed to PK-evaluable set.
 - 1112 ○
 - 1113 ○ Minor updates were made to the definition of Per-Protocol PK population and
1114 PK-evaluable population to improve clarity.

1115 In addition, one change pertaining to patient-reported outcomes (PROs) was implemented
1116 outside of a SAP amendment: the SWT section from the CTSQ had two questions replaced by
1117 mistake. As a result, the score for the domain SWT could not be computed as described in the
1118 scoring manual. Instead, the score was computed using the five correct questions of the SWT
1119 scale (instead of seven), and descriptive statistics for the score of the SWT scale and for the
1120 individual items including the two items that did not correspond to the scale were reported.

1121 **Statistical Analyses:** The non-inferiority analysis was carried out as a 1-sided hypothesis testing
1122 using the Hochberg procedure based on the logarithmic values of the co-primary endpoints
1123 respectively, by comparing the 90% confidence interval (CI) geometric mean ratio (GMR) of the
1124 primary endpoint between arms against a pre-defined non-inferiority margin. The CI of the GMR
1125 is estimated using an analysis of covariance model.

1126 An overview of the statistical analyses for the secondary efficacy endpoints of ORR, PFS, OS,
1127 and DOR is shown in [Table 5](#).

1128 **Table 5. Applicant-Overview of Efficacy Analyses**

Variable	Statistical Methods	Censoring
ORR	95% CI according to Pearson-Clopper within treatment arm; 95% two-sided CIs (Hauck-Andersen) for difference between arms	Not applicable
PFS	Kaplan-Meier analysis; 95% CI from Greenwood's formula for event-free rates at 6 and 12 months; Cox regression for HR	Patients who have not progressed and have not died at the time of the analysis: last available tumor assessment Patients without post-baseline tumor assessment: date of study entry +1 day
OS	Kaplan-Meier analysis; 95% CI from Greenwood's formula for event-free rates; Cox regression for HR	Patients without death record: last date they were known to be alive Patients with no post-baseline information: day of study entry +1 day
DOR	Kaplan-Meier analysis; 95% CI from Greenwood's formula for event-free rates at 6 and 12 months; Cox regression for HR	Patients who have not progressed and not died at the time of analysis: time of last tumor assessment date Patients with no tumor assessments after the date of the first occurrence of a complete or partial response: date of the first occurrence of a complete or partial response +1 day

1129 CI=confidence interval; DOR=duration of response; HR=hazard ratio; ORR=objective response rate; OS=overall survival;
 1130 PFS=progression-free survival.
 1131
 1132

1133 Patient-reported experience was assessed using descriptive analyses, including summary
 1134 statistics, and presented by treatment arm for each measure (item- and scale-level, as
 1135 appropriate).

1136 Analysis populations: Analysis sets in Part 2 were defined as follows:

- 1137 • Per-Protocol PK-evaluable: All patients randomized to the Atezo SC and Atezo IV treatment
 1138 arms who did not have protocol deviations that could affect Cycle 1 observed C_{trough} results
- 1139 • PK-evaluable: All patients randomized to the Atezo SC and Atezo IV treatment arms with at
 1140 least one post-baseline PK sample
- 1141 • Full Analysis Set (FAS): All patients who were randomized, with patients grouped according
 1142 to their assigned treatment
- 1143 • Response-evaluable: All patients included in the FAS and with measurable disease at
 1144 baseline
- 1145 • DOR–evaluable: All patients with a measurable disease at baseline and with a post-baseline
 1146 objective response
- 1147 • C-DOR–evaluable: All patients with a measurable disease at baseline and with a
 1148 post-baseline confirmed objective response (defined as CR or PR on two consecutive
 1149 occasions ≥28 days apart, as determined by the investigator according to RECIST v1.1)
- 1150 • Safety-evaluable: All randomized patients who received at least one dose of protocol
 1151 treatment

- 1152 • Post-treatment ADA–evaluable: All randomized patients who have received at least one dose
 1153 of protocol treatment and have at least one post-treatment ADA result

1154 **The FDA’s Assessment:** FDA agrees with the Applicant’s description of the statistical analysis
 1155 plan. The sample size calculation was based on PK endpoints and the analyses of efficacy
 1156 endpoints were descriptive in nature. The analyses of ORR and PFS were based on the data cut-
 1157 off date of April 26, 2022. At that time, 33% of patients had an OS event in the ITT population.
 1158 There was a subsequent efficacy update for OS based on a data cut-off date of January 16, 2023,
 1159 with approximately 10 additional months of follow-up, at which point 60% of patients had an OS
 1160 event in the ITT population.

1161 **Protocol Amendments**

1162 **The Applicant’s Description:** The first version of the protocol was issued on 5 August 2018. The
 1163 protocol was globally amended five times (versions 2 to 6). Key changes to the conduct of the
 1164 study since the fourth version of the protocol and their rationale are summarized in [Table 6](#) (no
 1165 changes affected Part 2 conduct in the first two amendments).

1166 **Table 6. Applicant-Summary of Key Protocol Amendments**

Protocol Version	Key Changes and Rationale
Amendment 3, Version 4 (28 August 2020)	A randomized control arm comprising of patients treated with atezolizumab IV as per standard of care was added in Part 2. Investigational treatment in Part 2 was modified to atezolizumab monotherapy and inclusion criteria modified to include patients in whom platinum therapy had failed, to allow for assessment of atezolizumab SC without confounding factors associated with use in combination with chemotherapy.
Amendment 4, Version 5 (10 February 2021)	In response to feedback from health authorities, a new co-primary pharmacokinetic endpoint was introduced (model-predicted AUC _{0-21 d} at Cycle 1). Number of patients enrolled in Part 2 was increased to 327 to accommodate the new co-primary pharmacokinetic endpoint.
Amendment 5, Version 6 (25 February 2022)	Decision made to remove extended recruitment in China.

1167 AUC_{0-21 d}=area under the concentration-time curve from 0 to 21 days; IV=intravenous; Q3W=every 3 weeks; Q4W=every 4 weeks;
 1168 SC=subcutaneous.
 1169
 1170

1171 **The FDA’s Assessment:** FDA agrees with the Applicant’s presentation of the key protocol
 1172 changes listed in the table above. As indicated by the Applicant, protocol amendments 1 and 2
 1173 were not listed in the table as these were for Part 1 of the study. The information for amendments
 1174 1 and 2 are listed below for completeness.

1175 **Amendment 1, version 2 (June 1, 2019) - Cohort 3 in Part 1 of the trial was modified as follows:**

- 1176 • The first dose of study drug site administration was changed from the thigh to the abdomen
 1177 • The SC dosing was changed from 2400 mg every 4 weeks (Q4W) to 1800 mg every 3 weeks
 1178 (Q3W)

- 1179 • The cohort size was increased from 12 to 20-30 patients.
- 1180 Amendment 2, version 3 (March 30, 2020) - the following major revision were made to the
1181 protocol:
- 1182 • The protocol was modified to align with the atezolizumab IV investigator’s brochure, version
1183 15 to modify “immune-related” to “immune-mediated” when describing events associated
1184 with atezolizumab.
- 1185 • The protocol was modified to include management guidelines for systemic immune
1186 activation, hemophagocytic lymphohistiocytosis (HLH) and macrophage activation
1187 syndrome (MAS).
- 1188 • The protocol was modified to include procedures for reporting infusion-related and injection-
1189 related reactions and to include reporting of cytokine release syndrome (CRS).
- 1190 • The protocol was modified to include laboratory and cardiac imaging abnormalities to
1191 monitor for potential events of myocarditis.

1192 **8.1.2. Study Results**

1193 **Compliance with Good Clinical Practices**

1194 The Applicant’s Position: IMscin001 was conducted in accordance with the principles of Good
1195 Clinical Practice, the principles of the Declaration of Helsinki, and local laws and regulations of
1196 the countries in which the studies were conducted. The appropriate Ethics Committees and
1197 Institutional Review Boards reviewed and approved each of the studies. No critical audit findings
1198 were observed in IMscin001.

1199 The FDA’s Assessment: FDA agrees with the Applicant’s description of compliance with Good
1200 Clinical Practices. The Applicant provided attestation that the study was conducted in
1201 accordance with good clinical practice. Clinical trial IMscin001 was not conducted under the
1202 IND for atezolizumab SC (IND 140100) as the multiregional clinical trial was conducted entirely
1203 ex-U.S. IMScin001 is a foreign clinical study that was conducted in accordance with 21 CFR
1204 312.120.

1205 FDA also notes Study IMscin002 was conducted under the IND 140100 in accordance with the
1206 principles of Good Clinical Practice, the principles of the Declaration of Helsinki, and local laws
1207 and regulations of the countries in which the study was conducted.

1208 **Financial Disclosure**

1209 Data: Details of financial disclosure are presented in Section 19.2.

1210 The FDA’s Assessment: FDA agrees.

1211 **Patient Disposition**

1212 Data: In Part 2 of IMscin001, a total of 371 patients were randomized across 68 different centers
1213 in 19 countries (number of sites per country; number of patients per country at the time of
1214 clinical cut-off date [CCOD]): Thailand (8; 69), Russian Federation (8; 44), Turkey (5; 54),
1215 Brazil (5; 22), China (5; 10), Ukraine (4; 28), Peru (4; 18), Guatemala (4; 7), Chile (3; 32), New
1216 Zealand (3; 13), Argentina (3; 7), South Africa (3; 3), Spain (2; 20), Greece (2; 9), Costa Rica (2;
1217 8), Mexico (2; 8), Hungary (2; 7), Poland (2; 6), and Latvia (1; 6). The first patient was
1218 randomized on 2 December 2020 and the last patient on 30 March 2022.

1219 Of the 371 randomized patients, 247 were allocated to the Atezo SC arm and 124 to the Atezo IV
1220 arm. All patients received at least one dose of the study treatment. There were the following
1221 number of patients in the major analysis populations ([Table 7](#)).

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1222 **Table 7. Applicant-Summary of Analysis Populations (Part 2)**

Analysis Populations	Atezo IV (N=124)	Atezo SC (N=247)	All Patients (N=371)
Full Analysis Set (FAS)	124	247	371
Per Protocol PK-Evaluable Set	97	205	302
Total Exclusions	27	42	69
Patients are missing the Ctrough pre-dose Cycle 2 Day 1 PK sample	19	31	50
Patients had a Ctrough sample collected with at least 2 days deviation from the planned on Day 21	8	11	19
Patients had a Duplicate Ctrough sample collected	0	0	0
Patients were given a Cycle 1 dose amount that deviates from the planned dose by >20%	0	0	0
Patients with a subcutaneous injection site other than thigh is used on Cycle 1	0	1	1
PK-Evaluable Set	122	247	369
Total Exclusions	2	0	2
No post-baseline PK sample	2	0	2
Safety-Evaluable Set	124	247	371
Response-Evaluable Set	124	245	369
Total Exclusions	0	2	2
No measurable disease at baseline	0	2	2
DOR-Evaluable Set	12	29	41
Total Exclusions	112	218	330
No PR or CR response	112	216	328
No measurable disease at baseline	0	2	2
Confirmed DOR-Evaluable Set	10	21	31
Total Exclusions	114	226	340
No PR or CR response	112	216	328
No confirmed response	2	8	10
No measurable disease at baseline	0	2	2
Post-Treatment ADA-Evaluable Set	108	221	329
Total Exclusions	16	26	42
No post-baseline ADA result	16	26	42

Source: t_pop_P2_AP_26APR2022_40657.

Per Protocol PK-Evaluable, PK-Evaluable, Safety-Evaluable and ADA-Evaluable sets are actual treatment received, other sets are randomized treatment. For Per Protocol PK-Evaluable Set, a patient can have more than 1 exclusion reason.

1226 At the CCOD for the primary analysis, the median survival follow-up was 4.7 months in the
 1227 overall population and was comparable between the two treatment arms (4.8 months in Atezo SC
 1228 vs. 4.4 months in Atezo IV). In each treatment arm, 43% of patients were still receiving
 1229 treatment. The proportions of patients discontinuing from study treatment was comparable
 1230 between treatment arms (58% in Atezo SC vs. 57% in Atezo IV), with the main reasons for
 1231 treatment discontinuation being progressive disease (40% vs. 37%) and symptomatic
 1232 deterioration (11% vs. 13%). The proportions of patients who had discontinued from the study
 1233 were comparable between the two treatment arms (36% in Atezo SC vs. 33% in Atezo IV), with
 1234 the most common reason being death (35% vs. 30%).

1235 The Applicant’s Position: IMscin001 is a global, multiregional study with a diverse patient
 1236 population. At the time of the CCOD, all randomized patients received at least one dose of study
 1237 treatment. Overall, the proportion of patients discontinuing treatment was comparable between
 1238 the two arms.

1239 The FDA’s Assessment: FDA agrees with the Applicant’s description of patient disposition;
 1240 however, FDA clarifies that there were 6 patients who changed study sites during the study as a
 1241 result of the Russia-Ukraine conflict. Due to limitations in the Applicant’s clinical database
 1242 management system, it was not possible to record the change in study site in the study database.
 1243 The Applicant presented the patients as being treated at the new study sites at the time of
 1244 database lock and did not provide information about the previous sites. The table below
 1245 summarizes the 6 patients who changed study sites as a result of the ongoing conflict in Ukraine.

1246 **FDA Table 8. Patients who Changed Clinical Sites During the Study due to Russia-Ukraine Conflict**

Unique Subject ID	Previous SITEID	Current SITEID	Age (Years)/Race/Sex	Treatment Arm
BP40657 (b) (6)	336965	325867 Poland	68/White/M	Atezolizumab IV
BP40657	336961	325867 Poland	60/White/M	Atezolizumab SC
BP40657	336965	336204 Poland	64/White/M	Atezolizumab SC
BP40657	336965	336961 Ukraine	58/White/F	Atezolizumab SC
BP40657	336965	336961 Ukraine	70/White/M	Atezolizumab IV
BP40657	336965	336966 Ukraine	64/White/M	Atezolizumab SC

Source: BP40657 CSR

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1249 The patients continued to receive the same treatment, either atezolizumab IV or atezolizumab
 1250 SC, that the patient was randomized to prior to the site change. Of these 6 patients, 3 patients
 1251 went to Poland and 3 patients went to a different site in Ukraine. The transition of these 6
 1252 patients to new clinical sites did not appear to have any major impact on the study results.

1253 **Protocol Violations/Deviations**

1254 Data: Major protocol deviations for the FAS are summarized by category in [Table 9](#).

1255 COVID-19 Impact Assessment in IMscin001 (Part 2): The recruitment of Part 2 started about
 1256 eight months into the global pandemic period (declared on 11 March 2020 by the World Health
 1257 Organization), almost a year after the onset of pandemic defined by the Sponsor (1 December
 1258 2019) and ended about 16 months later. However, because the recruitment was not paused or
 1259 stopped, the impact of the pandemic was estimated to be minor. The impact on the study conduct

1260 and/or data collection was determined to be minor and there was minimal impact on the study
1261 results and conclusions. There were 6 major protocol deviations related to COVID-19 (1 in
1262 Atezo SC and 5 in Atezo IV).

1263 Russia-Ukraine Conflict Impact Assessment in IMcin001 (Part 2): Overall, the conflict has had a
1264 minor impact on the study conduct and/or data collection and no impact on the study results and
1265 conclusions.

1266 **Table 9. Applicant-Summary of Major Protocol Deviations (Part 2, FAS)**

Category Description	Atezo IV (N=124)	Atezo SC (N=247)	All Patients (N=371)
Total number of patients with at least one major protocol deviation	64 (51.6%)	103 (41.7%)	167 (45.0%)
Total number of major protocol deviations	111	156	267
EXCLUSION CRITERIA			
Total	6 (4.8%)	10 (4.0%)	16 (4.3%)
Exclusion-related test not done	3 (2.4%)	3 (1.2%)	6 (1.6%)
Symptomatic, untreated or actively progression CNS metastases	1 (0.8%)	3 (1.2%)	4 (1.1%)
Clinically significant cardiovascular disease	0	2 (0.8%)	2 (0.5%)
Major surgical procedure within 4 weeks prior to study treatment or anticipation of need	0	1 (0.4%)	1 (0.3%)
Prior treatment with immunotherapy or immunostimulatory or immunosuppressive agents	0	1 (0.4%)	1 (0.3%)
Tested PD-L1 expression status	1 (0.8%)	0	1 (0.3%)
Uncontrolled or symptomatic hypercalcemia	1 (0.8%)	0	1 (0.3%)
INCLUSION CRITERIA			
Total	12 (9.7%)	19 (7.7%)	31 (8.4%)
Inclusion-related test not done	9 (7.3%)	10 (4.0%)	19 (5.1%)
Lung cancer criteria not met	2 (1.6%)	5 (2.0%)	7 (1.9%)
Inadequate hematologic & organ function at baseline	0	2 (0.8%)	2 (0.5%)
No signed informed consent	1 (0.8%)	1 (0.4%)	2 (0.5%)
Non-measurable disease only	0	2 (0.8%)	2 (0.5%)
Unknown EGFR status at the time of randomization	1 (0.8%)	0	1 (0.3%)
MEDICATION			
Total	8 (6.5%)	8 (3.2%)	16 (4.3%)
Dose (atezo SC co-mix/atezo SC/atezo IV) missed or significantly out of window	8 (6.5%)	7 (2.8%)	15 (4.0%)
Other significant medication deviation affecting	0	1 (0.4%)	1 (0.3%)

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Category	Atezo IV (N=124)	Atezo SC (N=247)	All Patients (N=371)
patient's safety, PK or immunogenicity			
PROCEDURAL			
Total	56 (45.2%)	87 (35.2%)	143 (38.5%)
Key PK or ADA sample not done or outside of window	37 (29.8%)	55 (22.3%)	92 (24.8%)
Key assessment not done or done outside of window	17 (13.7%)	24 (9.7%)	41 (11.1%)
Tumor assessment not done or repetitively done out of window	7 (5.6%)	5 (2.0%)	12 (3.2%)
Other significant procedural deviation affecting safety/PK/immunogenicity	3 (2.4%)	8 (3.2%)	11 (3.0%)
Failure to report SAE/AESIs per protocol	3 (2.4%)	7 (2.8%)	10 (2.7%)
New ICF version not signed at next patient's visit	3 (2.4%)	4 (1.6%)	7 (1.9%)
Patient Questionnaires not completed at BL	2 (1.6%)	1 (0.4%)	3 (0.8%)
Complete blood panel (haem/biochem/coagulation) not done or done out of window	1 (0.8%)	1 (0.4%)	2 (0.5%)
Incorrect place of SC administration	0	1 (0.4%)	1 (0.3%)

Source: t_dv_P2_FAS_26APR2022_40657.

For frequency counts by deviation, multiple occurrences of the same deviation in an individual are counted only once.

For the total number of deviations, multiple occurrences of the same deviation in an individual are counted separately.

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1272 **The Applicant's Position:** In the FAS, the frequency of major protocol deviations was lower in
 1273 Atezo SC (42%) compared with Atezo IV (52%). The difference was mostly driven by PK or
 1274 ADA samples not taken or taken outside the pre-specified window (22% Atezo SC vs. 30%
 1275 Atezo IV). None of the major protocol deviations posed an increased safety risk to any patient
 1276 continuing on study treatment or were considered to have affected the integrity of the study
 1277 findings. In addition, the COVID-19 pandemic disruption and Russia-Ukraine conflict had a
 1278 minor impact on the frequency or nature of major protocol deviations and on the overall data
 1279 quality and outcome of the study.

1280 **The FDA's Assessment:** FDA agrees that the difference in rates of major protocol deviations
 1281 between treatment arms (atezolizumab IV compared to atezolizumab SC) does not appear to
 1282 impact the overall data quality, safety, or efficacy of the trial results. The protocol deviations did
 1283 not impact PK analyses.

1284 **Table of Demographic Characteristics**

1285 **Data:** The FAS comprised predominately White (67%) or Asian (22%) men (69%) with a median
 1286 age of 64 years and the majority had an ECOG score of 1 (74%) (Table 10). Most patients came
 1287 from Europe and Middle East regions (48%), Central or South America (28%), and Asia-Pacific
 1288 (21%). Numerical differences between the Atezo SC and IV arms were seen for race
 1289 (White: 70% SC vs. 60% IV) and regions of Europe and the Middle East (51% vs. 40%). The
 1290 demographics in the PK-evaluable set and per-protocol PK-evaluable set were generally
 1291 comparable with those in the FAS, except for sex (74% male in Atezo SC vs. 62% in Atezo IV)

1292 in the per-protocol PK-evaluable set. These differences were not considered to have a significant
 1293 impact on efficacy or pharmacokinetics.

1294 **Table 10. Applicant-Summary of Baseline Demographic Characteristics (Part 2, FAS)**

	Atezo IV (N=124)	Atezo SC (N=247)	All Patients (N=371)
Age (years)			
n	124	247	371
Mean (SD)	64.4 (9.8)	62.2 (9.8)	63.0 (9.9)
Median	66.0	63.0	64.0
Min - Max	42 - 85	27 - 85	27 - 85
Age Group (years)			
n	124	247	371
< 65	58 (46.8%)	137 (55.5%)	195 (52.6%)
>= 65	66 (53.2%)	110 (44.5%)	176 (47.4%)
Age Group (years)			
n	124	247	371
< 65	58 (46.8%)	137 (55.5%)	195 (52.6%)
65 to 74	50 (40.3%)	86 (34.8%)	136 (36.7%)
75 to 84	15 (12.1%)	23 (9.3%)	38 (10.2%)
>= 85	1 (0.8%)	1 (0.4%)	2 (0.5%)
Sex			
n	124	247	371
Male	82 (66.1%)	175 (70.9%)	257 (69.3%)
Female	42 (33.9%)	72 (29.1%)	114 (30.7%)

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	Atezo IV (N=124)	Atezo SC (N=247)	All Patients (N=371)
Race			
n	124	247	371
American Indian or Alaska Native	9 (7.3%)	15 (6.1%)	24 (6.5%)
Asian	33 (26.6%)	47 (19.0%)	80 (21.6%)
Black or African American	1 (0.8%)	2 (0.8%)	3 (0.8%)
Native Hawaiian or other Pacific Islander	2 (1.6%)	1 (0.4%)	3 (0.8%)
White	74 (59.7%)	174 (70.4%)	248 (66.8%)
Multiple	5 (4.0%)	6 (2.4%)	11 (3.0%)
Unknown	0	2 (0.8%)	2 (0.5%)
Ethnicity			
n	124	247	371
Hispanic or Latino	36 (29.0%)	61 (24.7%)	97 (26.1%)
Not Hispanic or Latino	88 (71.0%)	185 (74.9%)	273 (73.6%)
Unknown	0	1 (0.4%)	1 (0.3%)
Region			
n	124	247	371
Asia-Pacific	32 (25.8%)	47 (19.0%)	79 (21.3%)
Australia	5 (4.0%)	8 (3.2%)	13 (3.5%)
Central or South America	37 (29.8%)	65 (26.3%)	102 (27.5%)
Europe and Middle East	50 (40.3%)	127 (51.4%)	177 (47.7%)

Source: Applicant data.

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1298 **Table 11. Applicant-Summary of Baseline Demographic Characteristics (Part 2, FAS) (Cont.)**

	Atezo IV (N=124)	Atezo SC (N=247)	All Patients (N=371)
Weight (kg) at baseline			
n	124	244	368
Mean (SD)	69.37 (15.13)	69.85 (16.06)	69.69 (15.74)
Median	69.10	67.80	68.00
Min - Max	34.6 - 114.0	30.0 - 117.0	30.0 - 117.0

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	Atezo IV (N=124)	Atezo SC (N=247)	All Patients (N=371)
Body Mass Index (kg/m ²) at baseline			
n	123	243	366
Mean (SD)	25.29 (4.42)	24.96 (4.81)	25.07 (4.68)
Median	24.81	24.60	24.67
Min - Max	15.3 - 35.7	12.9 - 41.4	12.9 - 41.4
ECOG Score			
n	124	247	371
0	28 (22.6%)	67 (27.1%)	95 (25.6%)
1	96 (77.4%)	180 (72.9%)	276 (74.4%)
Tobacco Use History			
n	124	247	371
Never	40 (32.3%)	71 (28.7%)	111 (29.9%)
Current	20 (16.1%)	40 (16.2%)	60 (16.2%)
Previous	64 (51.6%)	136 (55.1%)	200 (53.9%)

Source: t_dm_P2_FAS_26APR2022_40657.

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 1300
 1301

1302 The Applicant's Position: Demographic characteristics in the FAS were generally comparable
 1303 between the two treatment arms.

1304 In addition, the Applicant considers Imscin001 data are applicable to the U.S. for PK-bridging.
 1305 Imscin001 is a global, multiregional study with a diverse patient population. The Applicant
 1306 enrolled patients across 5 continents, including countries where CIT is partially or not
 1307 reimbursed. More specifically, in Part 2 of the study, 371 patients were enrolled across 68
 1308 different sites in 19 countries. The number of patients enrolled by region were: Europe and
 1309 Middle East (including South Africa): 177 patients; Central or South America: 102 patients;
 1310 Asia-Pacific: 79 patients; Australia 13 patients. The study population was comprised of 67%
 1311 White patients. In addition, 22% of the population was Asian, 6.5% American Indian or Alaskan
 1312 Native, and 0.8% Black, allowing investigation of minority populations. Approximately half of
 1313 the study population was older than 65 years, and 31% of patients were women, reflecting the
 1314 heterogeneity of the enrolled population.

1315 In addition, region and race were investigated using a population PK analysis and were not found
 1316 to have statistically significant effects on the systemic PK parameters of atezolizumab (Tecentriq
 1317 IV USPI, Section 12.3, Stroh et al. 2017). Furthermore, geographical region, race, and ethnicity
 1318 are not statistically significant covariates on the absorption parameters of atezolizumab when
 1319 administered subcutaneously (Section 6.2.2). Therefore, the PK results from Imscin001 are
 1320 expected to be representative of the exposure of atezolizumab across regions, including the U.S.

1321 In summary, based on the diverse nature of the study and no impact of region and race on
 1322 atezolizumab exposure, the Applicant believes that data from Imscin001 are relevant to the U.S.

1323 population and the objective to consider atezolizumab SC an equivalent option to atezolizumab
1324 IV in all approved and future indications.

1325 **The FDA's Assessment:** FDA agrees with the Applicant's statement that Imscin001 is a
1326 multiregional trial and that the demographic characteristics appear to be well balanced between
1327 the treatment arms. FDA notes slightly higher tumor PD-L1 expression for patients on the
1328 atezolizumab SC arm (39%) vs the atezolizumab IV arm (30%), which is shown in [FDA Table](#)
1329 [12](#) below. While PD-L1 expression may impact the efficacy of atezolizumab, this does not
1330 change our overall interpretation of the descriptive efficacy results for IMscin001.

1331 FDA notes the trial enrolled only three (0.8%) Black or African American patients (two in the
1332 atezolizumab SC arm and one in the atezolizumab IV arm). Although Black or African American
1333 patients are underrepresented in the clinical trial, FDA has previously evaluated atezolizumab IV
1334 across racial subgroups and no clinically significant effect on systemic exposure of atezolizumab
1335 IV has been observed (Tecentriq IV USPI). Approximately 26% of patients in the overall
1336 population for IMScin001 reported their ethnicity as Hispanic or Latino.

1337 **FDA Table 12. Tumor PD-L1 Expression in IMScin001**

Characteristics, n(%) ¹	Atezolizumab SC N=247	Atezolizumab IV N=124
PD-L1 Status		
Negative	121 (49)	78 (63)
Positive	97 (39)	37 (30)
Unknown	29 (12)	9 (7)

1338 Source: Sponsor-provided analysis dataset adsl.xpt.

1339 FDA clarifies that data from IMscin001 are being used to demonstrate comparable exposure
1340 between atezolizumab SC and atezolizumab IV, rather than that they are "equivalent" options as
1341 indicated by the Applicant.

1342 **Other Baseline Characteristics (e.g., Disease Characteristics, Important Concomitant**
1343 **Drugs)**

1344 **Data:** Most patients had metastatic (94%) non-squamous NSCLC (65%) and had received 1 prior
1345 anti-cancer therapy (80%) ([Table 13](#)). PD-L1 positive expression (tumor cells or immune cells
1346 $\geq 1\%$) was reported in 40% of patients. Overall, 5% and 2% of patients were positive for EGFR
1347 mutation and EML4-ALK mutation, respectively. More patients in Atezo SC than in Atezo IV
1348 had liver metastases at baseline (31% vs 21%) and PD-L1 positive tumors (45% vs 32%). These
1349 differences were not considered to have a significant impact on efficacy.

1350

1351 **Table 13. Applicant-Baseline Disease Characteristics and NSCLC History (Part 2, FAS)**

	Atezo IV (N=124)	Atezo SC (N=247)	All Patients (N=371)
Staging at Initial Diagnosis			
n	124	247	371
STAGE IA	2 (1.6%)	4 (1.6%)	6 (1.6%)
STAGE IB	3 (2.4%)	3 (1.2%)	6 (1.6%)
STAGE IIA	2 (1.6%)	3 (1.2%)	5 (1.3%)
STAGE IIB	6 (4.8%)	9 (3.6%)	15 (4.0%)
STAGE IIIA	10 (8.1%)	32 (13.0%)	42 (11.3%)
STAGE IIIB	14 (11.3%)	25 (10.1%)	39 (10.5%)
STAGE IIIC	5 (4.0%)	9 (3.6%)	14 (3.8%)
STAGE IVA	52 (41.9%)	92 (37.2%)	144 (38.8%)
STAGE IVB	30 (24.2%)	70 (28.3%)	100 (27.0%)
Current Disease Status			
n	124	247	371
Locally Recurrent Disease	0	4 (1.6%)	4 (1.1%)
Locally Advanced Unresectable Disease	10 (8.1%)	8 (3.2%)	18 (4.9%)
Metastatic Disease	114 (91.9%)	235 (95.1%)	349 (94.1%)
Histology at Initial Diagnosis			
n	124	247	371
Squamous	48 (38.7%)	82 (33.2%)	130 (35.0%)
Non-Squamous	76 (61.3%)	165 (66.8%)	241 (65.0%)
Histology if Non-Squamous			
n	76	165	241
Adenocarcinoma	72 (94.7%)	153 (92.7%)	225 (93.4%)
Large Cell	0	2 (1.2%)	2 (0.8%)
Large Cell with Neuroendocrine Diff.	0	0	0
Poorly Differentiated	1 (1.3%)	5 (3.0%)	6 (2.5%)
Mixed (Not Including Small Cell)	0	0	0
NSCLC/NOS	1 (1.3%)	2 (1.2%)	3 (1.2%)
Other	2 (2.6%)	3 (1.8%)	5 (2.1%)

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	Atezo IV (N=124)	Atezo SC (N=247)	All Patients (N=371)
Number of Anatomical Locations of Metastatic Disease at Enrollment			
n	124	247	371
Mean (SD)	2.87 (1.36)	3.15 (1.44)	3.06 (1.42)
Median	3.00	3.00	3.00
Min - Max	1.0 - 7.0	1.0 - 8.0	1.0 - 8.0
Time from 1st Diagnosis of Locally Recurrent Disease to Initial Dose Admin. (Months)			
n	0	4	4
Mean (SD)	NE (NE)	8.54 (7.92)	8.54 (7.92)
Median	NE	6.95	6.95
Min - Max	NE - NE	0.8 - 19.5	0.8 - 19.5

1352
 1353
 1354

1355 **Table 14. Applicant-Baseline Disease Characteristics and NSCLC History (Part 2, FAS) (cont.)**

	Atezo IV (N=124)	Atezo SC (N=247)	All Patients (N=371)
Time from 1st Diagnosis of Locally Advanced Unresectable Disease to Initial Dose Admin. (Months)			
n	10	8	18
Mean (SD)	8.27 (6.53)	8.25 (7.32)	8.26 (6.68)
Median	7.67	7.43	7.43
Min - Max	1.4 - 18.8	1.1 - 24.6	1.1 - 24.6
Time from 1st Diagnosis of Metastatic Disease to Initial Dose Admin. (Months)			
n	114	234	348
Mean (SD)	13.51 (14.40)	12.67 (13.31)	12.95 (13.66)
Median	9.40	9.02	9.22
Min - Max	0.5 - 95.8	0.2 - 88.6	0.2 - 95.8

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	Atezo IV (N=124)	Atezo SC (N=247)	All Patients (N=371)
EGFR Mutation Status			
n	124	247	371
Positive	8 (6.5%)	11 (4.5%)	19 (5.1%)
Negative	95 (76.6%)	198 (80.2%)	293 (79.0%)
Not-Evaluable	2 (1.6%)	2 (0.8%)	4 (1.1%)
Not Done	16 (12.9%)	33 (13.4%)	49 (13.2%)
Unknown	3 (2.4%)	3 (1.2%)	6 (1.6%)
EML4-ALK Mutation Status			
n	124	247	371
Positive	2 (1.6%)	4 (1.6%)	6 (1.6%)
Negative	100 (80.6%)	196 (79.4%)	296 (79.8%)
Not-Evaluable	3 (2.4%)	3 (1.2%)	6 (1.6%)
Not Done	19 (15.3%)	44 (17.8%)	63 (17.0%)
Other Mutations (KRAS, RET, ROS1, MET, B-RAF)			
n	124	247	371
Positive	9 (7.3%)	14 (5.7%)	23 (6.2%)
Negative	20 (16.1%)	57 (23.1%)	77 (20.8%)
Not-Evaluable	7 (5.6%)	8 (3.2%)	15 (4.0%)
Not Done	74 (59.7%)	143 (57.9%)	217 (58.5%)
Unknown	14 (11.3%)	25 (10.1%)	39 (10.5%)
Baseline Target Tumor Sum Longest Diameter (mm)			
n	124	245	369
Mean (SD)	80.74 (49.63)	91.18 (58.36)	87.67 (55.73)
Median	68.45	79.00	74.00
Min - Max	14.0 - 245.0	10.0 - 319.0	10.0 - 319.0
Liver Metastases at Baseline			
n	124	247	371
Yes	26 (21.0%)	77 (31.2%)	103 (27.8%)
No	98 (79.0%)	170 (68.8%)	268 (72.2%)
Brain Metastases at Baseline			
n	124	247	371
Yes	19 (15.3%)	42 (17.0%)	61 (16.4%)
No	105 (84.7%)	205 (83.0%)	310 (83.6%)

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	Atezo IV (N=124)	Atezo SC (N=247)	All Patients (N=371)
Bone Metastases at Baseline			
n	124	247	371
Yes	35 (28.2%)	84 (34.0%)	119 (32.1%)
No	89 (71.8%)	163 (66.0%)	252 (67.9%)
Albumin at Baseline			
n	123	247	370
Mean (SD)	40.26 (5.73)	39.38 (7.03)	39.67 (6.63)
Median	41.00	40.00	40.85
Min - Max	4.0 - 53.6	3.9 - 51.0	3.9 - 53.6
Prior (Neo) Adjuvant Treatment			
n	124	247	371
Yes	26 (21.0%)	42 (17.0%)	68 (18.3%)
No	98 (79.0%)	205 (83.0%)	303 (81.7%)

1356

1357 **Table 15. Applicant-Baseline Disease Characteristics and NSCLC History (Part 2, FAS) (cont.)**

	Atezo IV (N=124)	Atezo SC (N=247)	All Patients (N=371)
PD-L1 Status			
n	115	218	333
Positive	37 (32.2%)	97 (44.5%)	134 (40.2%)
Negative	78 (67.8%)	121 (55.5%)	199 (59.8%)
TC / IC categories			
TC0 and IC0	78 (62.9%)	121 (49.0%)	199 (53.6%)
TC1/2/3 or IC1/2/3	37 (29.8%)	97 (39.3%)	134 (36.1%)
TC2/3 or IC2/3	14 (11.3%)	38 (15.4%)	52 (14.0%)
TC3 or IC3	3 (2.4%)	13 (5.3%)	16 (4.3%)
Number of prior therapies			
n	124	247	371
1	97 (78.2%)	200 (81.0%)	297 (80.1%)
2	21 (16.9%)	41 (16.6%)	62 (16.7%)
3	5 (4.0%)	6 (2.4%)	11 (3.0%)
4	1 (0.8%)	0	1 (0.3%)

1358 Source: t_dm_dx_P2_FAS_26APR2022_40657
 1359 For EGFR, EML4-ALK central values are used, if central value is not available for a patient, local value is used instead. For Other
 1360 Mutations (KRAS, RET, ROS1, MET, B-RAF) local values are used. For PDL1 and TC/IC scores central values are used. EGFR
 1361 mutation = Sensitizing EGFR mutations include all EGFR activating mutations in exons 18-21.
 1362 EML4-ALK positive = ALK translocation. NOS: Not Otherwise Specified. Number of prior therapies is calculated as the number of
 1363 unique start dates of agents administered entered in the Prior Cancer Therapy eCRF page, with a start date available, and placebo
 1364 is excluded.

1365 **The Applicant’s Position:** Baseline disease characteristics in the FAS were generally comparable
 1366 between the two treatment arms.

1367 **The FDA’s Assessment:** FDA agrees with the Applicant’s statement. For PD-L1 status, the
 1368 proportion of patients with PD-L1 positive or negative should be based on the ITT population,
 1369 including missing data in the denominator.

1370 During the clinical site inspection for Dr. Sendur, FDA noted two discrepancies concerning
 1371 disease staging at initial diagnosis. Please see Section 4.1 of the Assessment Aid for further
 1372 information. FDA corrected this information and produced the table below for the staging at
 1373 initial diagnosis.

1374 **FDA Table 16. Disease Staging at Initial Diagnosis for Patients in IMscin001**

Characteristics, n (%)	Atezolizumab SC N=247	Atezolizumab IV N=124
Staging at Initial Diagnosis		
IA	4 (1.6)	2 (1.6)
IB	3 (1.2)	3 (2.4)
IIA	2 (0.8)	2 (1.6)
IIB	9 (3.6)	5 (4.0)
IIIA	33 (13)	10 (8)
IIIB	25 (10)	14 (11)
IIIC	9 (3.6)	5 (4.0)
IVA	92 (37)	53 (43)
IVB	70 (28)	30 (24)

1375 Source: Sponsor-provided analysis dataset adsl.xpt.

1376 **Treatment Compliance, Concomitant Medications, and Rescue Medication Use**

1377 Data: The median dose intensity as a measure of treatment compliance was 100% in both
 1378 treatment arms (range: 100–100% Atezo SC vs. 80–100% Atezo IV) ([Table 17](#)).

1379 **Table 17. Applicant-Treatment Compliance (Part 2, Safety-Evaluable Population)**

	Atezo IV (N=124)	Atezo SC (N=247)
Dose Intensity (%)		
n	124	247
Mean (SD)	99.8 (1.8)	100.0 (0.0)
Median	100.0	100.0
Min - Max	80 - 100	100 - 100

1380 Source: t_ex_P2_SE_26APR2022_40657.

1381 Dose Intensity is the number of doses actually received divided by the expected number of doses.

1384 Overall, 89% of patients received at least one concomitant medication unrelated to cancer during
 1385 Part 2 of the study with the most common being paracetamol (22%), omeprazole (13%),
 1386 tramadol (12%), and acetylsalicylic acid (11%). The type and frequency of concomitant
 1387 medication unrelated to cancer was generally comparable between the arms.

1388 The Applicant’s Position: The two treatment arms were balanced with respect to treatment
 1389 compliance and concomitant medications.

1390 The FDA’s Assessment: Based on a data cutoff date of September 2, 2022, the median dose
 1391 intensity was 100% in both the Atezo SC and Atezo IV treatment arms.

1392 FDA disagrees that you can necessarily determine if a concomitant medication is “related” or
 1393 “unrelated” to a patient’s diagnosis of cancer. The FDA table below provides the most common
 1394 (≥10%) concomitant medications administered during the trial based on a data cutoff date of
 1395 September 2, 2022, provided by the Applicant with the 120 day safety update. The concomitant

1396 administration of paracetamol (24%), omeprazole (15%), tramadol (14%) and acetylsalicylic
1397 acid (14%) were comparable between Atezo SC and Atezo IV treatment arms.

1398 **FDA Table 18. Most Common (≥10%) Concomitant Medications Administered During the IMscin001**
1399 **Clinical Trial**

Medication	Atezo SC N=247 n(%)	Atezo IV N=124 n(%)	Total N=371 n(%)
Paracetamol	57 (23)	32 (26)	89 (24)
Tramadol	34 (14)	16 (13)	50 (14)
Omeprazole	30 (12)	24 (19)	54 (15)
Acetylsalicylic Acid	29 (12)	12 (10)	41 (11)

1400 Source: Applicant-provided analysis dataset adcm.xpt.
1401

1402 **Efficacy Results – Primary Endpoint (Including Sensitivity Analyses)**

1403 The Applicant’s Position: The efficacy of atezolizumab SC compared with atezolizumab IV was
1404 evaluated as a secondary objective of the study in the FAS, which included all randomized
1405 patients. The efficacy results at the primary analysis are summarized below in [Table 19](#).

1406 The FDA’s Assessment: FDA clarifies that there were no primary efficacy endpoints for the
1407 IMscin001 Part 2 study. Primary endpoints for this study were the GMR of SC versus IV for the
1408 PK parameters including AUC and C_{trough}. Refer to Section [6](#) Clinical Pharmacology for a
1409 discussion of the PK endpoints for the IMscin001 clinical trial. All efficacy endpoints and their
1410 corresponding analyses were considered descriptive.

1411 **Data Quality and Integrity**

1412 The Applicant’s Position: Information requested by the Office of Scientific Investigations (OSI)
1413 for IMscin001 Part 2 is provided as part of the submission to the initial BLA application.

1414 The FDA’s Assessment: FDA agrees. Refer to Section [4.1](#) of the Assessment Aid.

1415 **Efficacy Results – Secondary and Other Relevant Endpoints**

1416 Data: A summary of efficacy results for Part 2 primary analysis is provided in [Table 19](#).

1417 **Table 19. Applicant-Summary of Key Secondary Efficacy Endpoints**

Key Secondary Efficacy Endpoints	Atezo IV (1200 mg) N=124	Atezo SC (1875 mg) N=247
ORR (Unconfirmed)	N=124	N=245
Responders, N (%)	12 (9.7%)	29 (11.8%)
(95% CI)	(5.10, 16.29)	(8.07, 16.56)
ORR (Confirmed)	N=124	N=245
Responders, N (%)	10 (8.1%)	21 (8.6%)
(95% CI)	(3.94, 14.33)	(5.38, 12.80)
PFS	N=124	N=247
Patients with event (%)	84 (67.7%)	168 (68.0%)
Median time to event, months (95% CI)	2.9 (1.7, 4.2)	2.8 (2.1, 3.1)
DOR (Unconfirmed)	N=12	N=29
Patients with event (%)	5 (41.7%)	10 (34.5%)
Median time to event, months (95% CI)	11.2 (2.9, NE)	5.6 (3.2, NE)
DOR (Confirmed)	N=10	N=21
Patients with event (%)	3 (30.0%)	6 (28.6%)
Median time to event, months (95% CI)	11.2 (4.2, NE)	NE (5.2, NE)
OS (FAS)	N=124	N=247
No. of deaths (%)	37 (29.8%)	86 (34.8%)
Median time to event, months (95% CI)	NE (7.9, NE)	8.9 (7.2, NE)

1418 Source: t_ef_all_P2_FAS_26APR2022_40657.

1419 CI=confidence interval; DOR=duration of response; NE=not estimable; ORR=objective response rate; OS=overall survival;
1420 PFS=progression-free survival; SC=subcutaneous.

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1422

1423 **Subgroup Analyses**

1424 The consistency of ORR and PFS results across subgroups was investigated in an exploratory
1425 manner by estimating the treatment effect in pre-defined subgroups based on key demographics
1426 (age, sex, race) and baseline disease characteristics (e.g., histology, number of prior line of
1427 therapy, ECOG performance status, smoking history, location of metastases, PD-L1 status, etc.).

1428 There were no meaningful differences in ORR between arms in any subgroup. The same was
1429 true for PFS, except for the subgroup of current tobacco users, which showed a trend in favor of
1430 atezolizumab IV. This finding is believed to be due to the small size of this subgroup (40 and 20
1431 current tobacco users in Atezo SC and IV, respectively), and there is no reason to believe that
1432 atezolizumab SC behaves differently in this subpopulation.

1433 The Applicant's Position: The per-protocol ORR (defined as the proportion of patients with a CR
1434 or PR, as determined by the investigator according to RECIST v1.1) was comparable between
1435 Atezo SC and Atezo IV. The confirmed ORR (defined as the proportion of patients with a CR or
1436 PR on two consecutive occasions ≥ 28 days apart, as determined by the investigator according to
1437 RECIST v1.1), conducted as part of a sensitivity analysis to verify robustness of the ORR result,
1438 was comparable between Atezo SC and Atezo IV. PFS was comparable between Atezo SC and
1439 Atezo IV. The OS and DOR data were not mature due to short follow-up time at the CCOD. No
1440 meaningful differences were observed between arms across the subgroups for ORR and PFS.

1441 The FDA’s Assessment: All efficacy endpoints for Part 2 of the IMscin001 study were secondary
 1442 endpoints with no pre-specified testing plan. Hence, analyses of the secondary endpoints are
 1443 considered descriptive in nature. [FDA Table 20](#) provides the results of the analyses of secondary
 1444 efficacy endpoints for this study. The analyses of ORR and PFS were based on the data cut-off
 1445 date of April 26, 2022. At that time, median OS was 8.9 months (95%: CI 7.2, not evaluable
 1446 [NE]) for the atezolizumab SC arm and not reached (NR) (95% CI: 7.9, NE) for the
 1447 atezolizumab IV arm (HR 1.18; 95% CI 0.81, 1.74). However, only 33% of patients had an OS
 1448 event in the ITT population and data were not considered robust by the FDA review team. The
 1449 FDA review team requested an updated OS analysis with an additional 10 months of follow up.
 1450 The Applicant submitted the updated OS analysis and the corresponding dataset based on a data
 1451 cutoff date of January 16, 2023. In the updated OS analysis, 60% of patients in the ITT
 1452 population had an OS event. The updated OS analysis based on the data cut-off date of January
 1453 16, 2023, are shown in the table below. No major differences in the efficacy results between the
 1454 two treatment arms were identified.

1455 **FDA Table 20. Analysis of Secondary Efficacy Endpoints in Part 2 of IMscin001**

Endpoint	Atezolizumab SC N=245	Atezolizumab IV N=124
Confirmed ORR*, n (%)	21 (9)	10 (8)
95% CI	(5, 13)	(3.9, 14)
Median DOR in months	NR	11.2
95% CI	(5.2, NE)	(4.2, NE)
DOR ≥ 6 months, n (%) [†]	6 (29)	3 (30)
	Atezolizumab SC N=247	Atezolizumab IV N=124
Deaths, n (%)	144 (58)	79 (64)
Median OS in months	10.7	10.1
95% CI	(8.5, 13.8)	(7.5, 12.1)
OS HR (95% CI)		0.88 (0.67, 1.16)
Events, n (%)	168 (68)	84 (68)
Median PFS in months	2.8	2.9
95% CI	(2.1, 3.1)	(1.7, 4.2)
PFS HR (95% CI)	1.07 (0.82, 1.39)	

1456 Source: Sponsor-provided analysis datasets adrs.xpt and adtte.xpt.

1457 * In the SC arm, 2 patients were not evaluable for response and were excluded from the ORR analysis population.

1458 [†] Based on observed DOR.

1459 NR = Not reached; NE = Not evaluable.

1460 There were no major differences between the two treatment arms, with overlapping confidence
 1461 intervals, in terms of ORR, PFS and OS. The following table provides the exploratory subgroup
 1462 analysis based on confirmed ORR. Overall, there is no major difference in ORR among the
 1463 subgroups considered below; however, these are exploratory analyses and results should be
 1464 interpreted with caution.

1465 **FDA Table 21. Exploratory Subgroup Analysis for Confirmed ORR in IMscin001.**

Characteristic	Atezolizumab SC N=245		Atezolizumab IV N=124	
	Responders/n	ORR (95% CI)	Responders/n	ORR (95% CI)
Female	6/72	8 (3, 17)	3/42	7 (1, 19)
Male	15/173	9 (5, 14)	7/82	9 (4, 17)
Age (years)				
<65	9/138	7 (3, 12)	3/58	5 (1, 14)
≥65	12/107	11 (6, 19)	7/66	11 (4, 21)
Race				
White	14/173	8 (4, 13)	8/74	11 (5, 20)
Black/African American	0/2	-	0/1	-
Asian	7/46	15 (6, 29)	1/33	3 (0, 16)
Native Hawaiian/Pacific Islanders	0/1	-	0/2	-
American Indian/Alaskan Native	0/15	-	1/9	11 (0, 48)
Other/Unknown	0/8	-	0/5	-
Ethnicity				
Hispanic or Latino	3/61	5 (1, 14)	2/36	6 (1, 19)
Not Hispanic or Latino	18/183	10 (6, 15)	8/88	9 (4, 17)
Unknown	0/1	-	0/0	-
Histology				
Squamous	7/80	9 (4, 17)	6/48	12 (5, 25)
Non-squamous	14/165	8 (5, 14)	4/76	5 (1, 13)
PD-L1 Status				
Negative	9/121	7 (3, 14)	7/78	9 (4, 18)
Positive	11/96	11 (6, 20)	3/37	8 (2, 22)
Unknown	1/28	4 (0, 18)	0/9	-

Source: Sponsor-provided analysis dataset adrs.xpt.

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1467

1468 **Dose/Dose Response**

1469 **The Applicant's Position:** Exposure-efficacy and -safety analyses were performed in patients
1470 with CIT-naive 2L NSCLC in Part 2 of IMScin001. No statistically significant exposure-efficacy
1471 relationships were identified with ORR, PFS, or OS in patients treated with SC atezolizumab
1472 1875 mg Q3W. No statistically significant exposure-safety relationships were identified with
1473 SAE, AESI, Grade 3–5 AEs, or injection site reactions (ISRs) in patients treated with SC
1474 atezolizumab 1875 mg Q3W.

1475 **The FDA's Assessment:** FDA agrees with the Applicant's position with the exception that the
1476 clinical trial was powered for PK endpoints. The efficacy analyses were descriptive in nature.
1477 Refer to Section 6 Clinical Pharmacology regarding exposure.

1478 **Durability of Response**

1479 **The Applicant's Position:** The IMscin001 primary analysis demonstrated that the efficacy of
1480 atezolizumab SC was comparable to atezolizumab IV (see text above on Efficacy Results –
1481 Secondary and other relevant endpoints). These efficacy findings will be further supported by
1482 more mature data available at later analyses. (b) (4)
1483

1484 **The FDA's Assessment:** There were no major differences between the two treatment arms with
1485 respect to duration of response. For additional information, refer to [FDA Table 20](#).

1486 FDA clarifies that based on the descriptive analysis for durability of response, one cannot
1487 conclude that there is no tolerance or treatment resistance to atezolizumab.

1488 **Persistence of Effect**

1489 **The Applicant's Position:** As per protocol, patients receive atezolizumab SC or atezolizumab IV,
1490 as indicated, until disease progression, loss of clinical benefit, or unacceptable toxicity. Tumor
1491 assessments continue according to schedule in patients who discontinue treatment for reasons
1492 other than disease progression or loss of clinical benefit. At the time of the primary analysis, the
1493 main reason for treatment discontinuation was progressive disease and symptomatic
1494 deterioration. Due to that and to the short median survival follow-up of 4.7 months, the
1495 persistence of efficacy data are not mature at this time. Additional efficacy data will be available
1496 at later analyses.

1497 **The FDA's Assessment:** The FDA agrees that the data pertinent to the evaluation of persistence
1498 of effect was not mature at the time of this review. The evaluation of persistence of effect were
1499 not conducted by the FDA.

1500 **Efficacy Results – Secondary or Exploratory COA (PRO) Endpoints**

1501 **Data:** The rate of EORTC IL57 questionnaire completion for the two arms was generally
1502 comparable (96.4% and 90.3% of patients completed all of the questions in the questionnaire in
1503 Atezo SC and Atezo IV at baseline, respectively). Mean EORTC IL57 physical functioning, role
1504 functioning, and GHS/QoL scores were similar over time between the Atezo SC and Atezo IV
1505 arms, with largely overlapping 95% CIs at each visit. Additionally, the mean score changes from

1506 baseline were similar over time between the two arms, with largely overlapping 95% CIs at each
1507 visit, except for the mean GHS/QoL score, with a smaller change from baseline observed for the
1508 Atezo SC arm compared with the Atezo IV arm after Cycle 4 Day 1.

1509 The rate of CTSQ completion at Cycle 3 for the two arms was generally comparable between
1510 both treatment groups: 85.5% in Atezo SC and 91.1% in Atezo IV. At Cycle 3, patients in the
1511 two treatment arms reported comparable levels of SWT (75.9 in Atezo SC and 77.3 in Atezo IV).

1512 The Applicant's Position: No clinically meaningful deterioration in the average health-related
1513 quality of life, role functioning, or physical functioning scores as measured by the EORTC IL 57
1514 was observed in Atezo SC or Atezo IV, suggesting health-related quality of life and
1515 patient-reported functioning was maintained for patients remaining on treatment.

1516 The FDA's Assessment: Study IMscin001 was designed to evaluate the PK exposure endpoints;
1517 and the patient-reported outcome (PRO) endpoints were considered exploratory in nature. FDA
1518 agrees that results were similar between arms, however these results should be interpreted with
1519 caution as they were not prespecified, alpha-controlled endpoints, and the trial was not designed
1520 to demonstrate maintenance of patient-reported functioning and quality of life.

1521 Please refer to Section [19.6](#) of the Assessment Aid for a full description of Study IMscin002

1522 **Additional Analyses Conducted on the Individual Trial**

1523 The Applicant's Position: No additional analyses were conducted.

1524 The FDA's Assessment: FDA agrees with the Applicant's statement.

1525 **8.1.3. Integrated Review of Effectiveness**

1526 The FDA's Assessment: The IMscin001 clinical trial was not designed to formally compare the
1527 efficacy of atezo SC to atezo IV. All efficacy endpoints for the IMscin001 trial were descriptive
1528 in nature. With a data cut-off date of September 2, 2022, Study IMscin001 met the trial's
1529 coprimary endpoints of PK exposure of Atezo SC to Atezo IV. See Section [6](#), Clinical
1530 Pharmacology of the Assessment Aid for a discussion of the PK primary endpoints and results.

1531 At the data cut-off date of April 26, 2022, the secondary efficacy analysis of ORR for patients
1532 treated with Atezo SC was 9% (95% CI: 5, 13) and was 8% (95% CI: 4, 14) for Atezo IV. The
1533 median DOR was not reached (95% CI: 5.2, NE) for the Atezo SC treatment arm and 11.2
1534 months (95% CI: 4.2, NE) for the Atezo IV. The median PFS was 2.8 mo (95% CI: 2.1, 3.1) for
1535 Atezo SC and 2.9 mo (95% CI: 1.7, 4.2) for Atezo IV. As noted in [Table 19](#), the median OS was
1536 8.9 months (95% CI: 7.9, NE) for the Atezo SC treatment arm and not estimable (NE) (95% CI:
1537 7.9, NE) for the Atezo IV treatment arm (HR 1.18, 95% CI: 0.81, 1.74). FDA noted only 33% of
1538 the patients had an OS event in the ITT population and data were not considered robust. FDA
1539 requested an updated OS analysis with an additional 10 months of follow-up. In the updated OS
1540 analysis, 60% of the patients in the ITT population had an OS event. With a data cut-off date of
1541 January 16, 2023, the median OS was 10.7 mo (95% CI: 8.5, 13.8) for Atezo SC and 10.1 mo
1542 (95% CI: 7.5, 12.1) for Atezo IV (HR 0.88, 95% CI: 0.67, 1.16). Based on descriptive analyses

1543 and the additional 10 months of follow-up, no differences in PFS and OS between patients who
1544 received Atezo SC and Atezo IV were observed.

1545 **8.1.4. Assessment of Efficacy Across Trials**

1546 The Applicant's Position: Not applicable to this review, since this application is based on
1547 efficacy from a single study.

1548 The FDA's Assessment: All efficacy endpoints for the IMscin001 study were descriptive in
1549 nature and the trial was not designed to formally compare the efficacy of atezolizumab SC to
1550 atezolizumab IV.

1551 **8.1.5. Integrated Assessment of Effectiveness**

1552 The Applicant's Position: See text in Section [8.1.2](#).

1553 The FDA's Assessment: The clinical trial, IMscin001 was a multiregional, randomized, open-
1554 label study to compare the pharmacokinetics, efficacy and safety of atezolizumab SC to
1555 atezolizumab IV in patients with advanced or metastatic NSCLC who have not received anti-PD-
1556 L1 antibody therapy and who had disease progression on platinum-based chemotherapy. The
1557 trial demonstrated comparability of C_{trough} at Cycle 1 and model-based AUC 0-21 days at Cycle 1
1558 of atezolizumab SC compared to atezolizumab IV. The geometric mean ratio for the observed
1559 serum C_{trough} at Cycle 1 was 1.05 (90% CI: 0.88, 1.24) and model-based AUC 0-21 days at Cycle
1560 1 was 0.87 (90% CI: 0.83, 0.92) for atezolizumab exposure with 90% CIs within 80 to 125%.
1561 Refer to Section [7](#) Clinical Pharmacology of the Assessment Aid.

1562 Substantial evidence of effectiveness for all of the proposed adult indications for atezolizumab
1563 SC was established based on demonstration of comparability of atezolizumab C_{trough} and AUC
1564 GMRs of atezolizumab SC 1875 mg/hyaluronidase 30,000 Units compared to atezolizumab 1200
1565 mg administered intravenously; and descriptive efficacy results from IMscin001 which
1566 demonstrated comparable efficacy of ORR, PFS, and OS between atezolizumab SC and
1567 atezolizumab IV.

1568 The efficacy of atezolizumab SC across adult indications is extrapolated from the atezolizumab
1569 IV indications, based on the following:

- 1570 • Demonstration of comparability of atezolizumab C_{trough} levels of atezolizumab SC to
1571 atezolizumab IV in patients with NSCLC who have not received anti-PD-L1 antibody
1572 therapy and had disease progression on platinum-based chemotherapy.
- 1573 • Treatment of atezolizumab IV in patients have shown a flat exposure-efficacy relationship.
1574 Refer to Section [7](#) Clinical Pharmacology of the Assessment Aid.
- 1575 • The mechanism of action of atezolizumab in the adult indications are the same and
1576 atezolizumab IV showed that the tumor type was not a significant covariate on atezolizumab
1577 PK. Refer to Section [7](#) Clinical Pharmacology of the Assessment Aid.

1578

8.2. Review of Safety

1579 The Applicant's Position: The overall safety evaluation of atezolizumab SC is based on data
1580 from IMscin001. For atezolizumab IV, in addition to IMscin001, pooled safety data from
1581 3178 patients treated with single-agent atezolizumab regardless of tumor type from previous
1582 atezolizumab IV studies (OAK, BIRCH, POPLAR, FIR, PCD4989g, IMvigor210, IMvigor211,
1583 and IMmotion150) are presented in [Table 23](#), [Table 34](#), and [Table 40](#) as reference for additional
1584 context.

1585 The pooled data (hereinafter Atezo Mono pooled population) is not intended for a head-to-head
1586 comparison to IMscin001 data due to the variation in sample sizes, line of therapies, treatment
1587 duration, and different indications. However, the pooled population allows for a comprehensive
1588 overview of the safety profile of atezolizumab IV when given as monotherapy.

1589 The FDA's Assessment: FDA agrees with the Applicant's description of the primary and pooled
1590 safety populations evaluated during the review of this application. The primary safety data are
1591 derived from IMscin001 Part 2 in which patients with locally advanced or metastatic NSCLC
1592 who had not had prior anti-PD-(L)1 antibody therapy but had disease progression on prior
1593 platinum-based therapy were randomized 2:1 to receive atezolizumab SC (n = 247) or
1594 atezolizumab IV (n = 124).

1595 FDA notes that the Applicant originally submitted a 351(a) BLA for atezolizumab and
1596 hyaluronidase-tqjs for subcutaneous injection on November 15, 2022, with safety data based on a
1597 data cutoff date of April 26, 2022. During that review cycle, the Applicant submitted a 120-day
1598 safety update based on a data cutoff date of September 2, 2022. The Applicant withdrew the
1599 application on August 31, 2023, (b) (4)

1600 (b) (4)

1601 The Applicant submitted the current 351(a) BLA on November 15, 2023. FDA's current safety
1602 review includes evaluation of safety data from both the April 26, 2022, and September 2, 2022,
1603 data cutoff dates. In this Assessment Aid, the Applicant primarily presents data based on the
1604 April 26, 2022, data cutoff date; FDA also has provided results and analyses based on the
1605 September 2, 2022, data cutoff date. Throughout the review of safety data, FDA sent multiple
1606 requests for additional clinical information including about fatal adverse events, and
1607 hypersensitivity and injection site reactions, which are further detailed in the relevant sections of
1608 the Assessment Aid.

1609 **8.2.1. Safety Review Approach**

1610 The Applicant’s Position: Safety of atezolizumab SC compared to atezolizumab IV was assessed based on descriptive analyses of
 1611 incidence and severity of AEs, SAEs, AESIs, selected AEs; laboratory test abnormalities, according to NCI-CTCAE v5.0, vital signs,
 1612 and overall patient-reported adverse event burden over time, as assessed by the treatment-related symptom burden item from the
 1613 EORTC IL57. AESIs and selected AEs (i.e., local ISRs) were analyzed based on prior experience with atezolizumab.

1614 The FDA’s Assessment: FDA agrees with the Applicant’s position.

1615 **8.2.2. Review of the Safety Database**

1616 **Overall Exposure**

1617 **Data:**

1618 **Table 22. Applicant-Safety Population, Size, and Denominators**

Safety Database for the Study Drug¹
Individuals Exposed to the Study Drug in This Development Program for the Indication Under Review
N=247*

Clinical Trial Groups	IMscin001 Part 2		Pooled Population
	Atezo IV (n=124)	Atezo SC (n=247)	Atezo Mono (n=3178)
Controlled trials conducted for this indication ²	1 study (n=124)	1 study (n=247)	0
All other than controlled trials conducted for this indication ³	0	0	0
Controlled trials conducted for other indications ⁴	0	0	3178

1619 ¹ *study drug* means the drug being considered for approval.
 1620 ² to be used in product’s labeling.
 1621 ³ if placebo arm patients switch to study drug in open-label extension, the n should include their number; do not count twice patients who go into extension from randomized study drug
 1622 arm.
 1623 ⁴ include n in this column only if patients exposed to the study drug for indication(s) other than that in the marketing application have been included in the safety database under
 1624 review. Consider n=0 in this column if no patients treated for other indication(s) were included in this safety database.
 1625 * Sum of patients receiving atezolizumab SC in IMscin001 Part 2.

1626 **Table 23. Applicant-Exposure to Atezolizumab (Atezo Mono Treated Patients)**

	IMSCIN001		Pooled Population
	Atezo IV (N=124)	Atezo SC (N=247)	Atezo Mono (N=3178)
Number of doses			
n	124	247	3178
Mean (SD)	5.8 (4.6)	5.7 (4.2)	9.9 (9.8)
Median	4.0	4.0	6.0
Min - Max	1 - 24	1 - 23	1 - 64
Treatment duration in Months			
n	124	247	3178
Mean (SD)	3.5 (3.3)	3.4 (3.0)	6.6 (7.5)
Median	2.2	2.2	3.5
Min - Max	0 - 16	0 - 15	0 - 53
Treatment duration in Months			
n	124	247	3178
<= 3	75 (60.5%)	146 (59.1%)	1469 (46.2%)
>3-6	23 (18.5%)	52 (21.1%)	545 (17.1%)
>6-12	24 (19.4%)	48 (19.4%)	513 (16.1%)
>12-18	2 (1.6%)	1 (0.4%)	341 (10.7%)
>18-24	0	0	222 (7.0%)
>24	0	0	88 (2.8%)

Source: t_ex_SE_atezo_26APR2022_40657P.

Treatment duration is the date of the last dose of study medication minus the date of the first dose plus one day.

1627 **The Applicant's Position:** The overall exposure was comparable between the SC and IV arms of
 1630 IMscin001 Part 2 (median duration of treatment of 2.2 months in both arms). The median
 1631 duration of treatment was shorter in IMscin001 (2.2 months) compared to the Atezo Mono
 1632 pooled population (3.5 months). This is likely due to the relatively short median safety follow-up
 1633 of IMscin001 compared to the Atezo Mono pooled population. The median number of
 1634 atezolizumab doses administered was 4 in IMscin001 and 6 in the pooled population.

1635 **The FDA's Assessment:** FDA agrees with the Applicant's position. Among the 247 patients in
 1636 the atezolizumab SC arm in IMscin001 Part 2, 19% of the patients were exposed to atezolizumab
 1637 SC for 6 months or longer and 0.4% of the patients were exposed for more than one year.

1638 **Relevant Characteristics of the Safety Population:**

1639 **Data/The Applicant's Position:** The demographic and baseline characteristic profile of the safety
 1640 population in IMscin001 was the same as that of the FAS (see Section 8.1.2).

1641 The FDA's Assessment: FDA agrees with the Applicant's position. The majority of patients
1642 were male, and White or Asian. On the atezolizumab SC arm, 25% of patients were Hispanic or
1643 Latino while 29% of patients were Hispanic or Latino on the atezolizumab IV arm. The median
1644 age of patients was 63 years old on the atezolizumab SC arm versus 66 years old on the
1645 atezolizumab IV arm.

1646 At baseline, 39% of patients had PD-L1 expressing tumors in the atezolizumab SC arm
1647 compared to 30% in the atezolizumab IV arm. Most patients had non-squamous histology; 67%
1648 of patients on the atezolizumab SC arm had non-squamous histology compared to 61% on the
1649 atezolizumab IV arm.

1650 The treatment arms were well-balanced except for a higher percentage of patients on the
1651 atezolizumab SC arm with PD-L1 positive tumors at baseline compared to the atezolizumab IV
1652 arm.

1653 Adequacy of the Safety Database:

1654 The Applicant's Position: The safety profile of atezolizumab is well established and safety data
1655 from the Atezo Mono pooled population provides a comprehensive overview of the safety profile
1656 of atezolizumab IV when given as monotherapy in mixed tumor types. The safety data from this
1657 pooled population forms the basis for the comprehensive and well-characterized safety profile
1658 for atezolizumab monotherapy. The size of the atezolizumab SC safety population in IMscin001
1659 was considered to provide sufficient data to adequately establish the safety profile of
1660 atezolizumab SC. The safety profile of atezolizumab SC in IMscin001 was consistent with the
1661 known safety profile of atezolizumab IV.

1662 The FDA's Assessment: FDA agrees with the Applicant's position that the safety profile of
1663 atezolizumab IV is well established, and that the safety profile of atezolizumab SC in IMscin001
1664 was consistent with the known safety profile of atezolizumab IV. FDA also agrees with the
1665 Applicant that the safety data from IMscin001 are adequate to support a benefit-risk assessment
1666 of atezolizumab and hyaluronidase-tqjs for SC administration. FDA issued several information
1667 requests (IRs) to the Applicant during the review cycle to obtain the correct datasets for the 120-
1668 day safety update and to obtain clarification and additional information regarding safety data
1669 included in the BLA; all requests were addressed appropriately.

1670 **8.2.3. Adequacy of Applicant's Clinical Safety** 1671 **Assessments**

1672 Issues Regarding Data Integrity and Submission Quality

1673 The Applicant's Position: No important issues impacting data integrity and quality were
1674 identified.

1675 The FDA's Assessment: FDA agrees with the Applicant's position.

1676 **Categorization of Adverse Event**

1677 **The Applicant's Position:** The severity of all AEs was graded according to the National Cancer
1678 Institute Common Terminology Criteria for AEs, Version 5.0 (NCI-CTCAE v5.0) for IMscin001
1679 and the pooled Atezo Mono population and reported in detail in the electronic Case Report Form
1680 (eCRF). Multiple occurrences of the same event in the same patient were counted once at the
1681 maximum severity (worst grade) in summary tables. The protocol provided guidance to
1682 investigators to determine whether an AE was considered to be related to any study treatment.
1683 Verbatim descriptions of AEs were mapped to the Medical Dictionary for Regulatory Activities
1684 (MedDRA) thesaurus terms. MedDRA Version 25.0 was used for both IMscin001 and the
1685 pooled Atezo Mono population.

1686 For the purpose of the analysis, a set of comprehensive definitions comprising Standard
1687 MedDRA Queries, MedDRA High Level Terms (HLTs), and Sponsor-defined AE Grouped
1688 Terms were used to identify AESIs from the AE clinical database by medical concept. The
1689 medical concepts correspond to the identified risks and potential risks for atezolizumab.

1690 **The FDA's Assessment:** FDA agrees with the Applicant's description of the categorization of
1691 adverse events (AEs) for the IMscin001 trial and the pooled atezolizumab monotherapy IV
1692 population. MedDRA v 25.0 was used for categorizing AEs and CTCAE v 5.0 was used for
1693 grading AEs.

1694 **Routine Clinical Tests**

1695 **The Applicant's Position:** The reporting period for safety assessments began after initiation of
1696 the study drug and continued until 30 days after the final dose of study treatment or until
1697 initiation of new systemic anti-cancer therapy (whichever occurred first) for AEs, and until
1698 90 days after the final dose of study treatment or until initiation of new systemic anticancer
1699 therapy (whichever occurred first) for SAEs and AESIs. Additionally, SAEs caused by a
1700 protocol-mandated intervention after informed consent was obtained but prior to initiation of
1701 study drug (screening) were to be reported; and after the end of the reporting period, all deaths,
1702 regardless of cause, were to be reported.

1703 Patients underwent a complete physical examination at screening and a limited physical
1704 examination at all treatment cycles and at the discontinuation visit. A coagulation panel (aPTT,
1705 INR) was run at screening and sampling for C-reactive protein was done at screening and at all
1706 treatment cycles. An assessment of routine laboratory tests (hematology, serum chemistry,
1707 urinalysis, thyroid stimulating hormone [TSH]), vital signs, weight, and ECOG performance
1708 status was performed at screening, at the beginning of all treatment cycles, and at the
1709 discontinuation visit. Pregnancy testing was performed at screening, at all treatment cycles, at the
1710 discontinuation visit, and when clinically indicated during the follow-up. Serum and plasma
1711 samples for PK and ADA assessments were performed at protocol-defined treatment cycles and
1712 discontinuation visit. Electrocardiograms (ECGs) were conducted at screening and when
1713 clinically indicated at treatment cycles and discontinuation visit. Echocardiograms were
1714 conducted at screening and treatment cycles when clinically indicated. Patient-reported
1715 experience questionnaires were provided at all treatment cycles and discontinuation visit.

1716 **The FDA's Assessment:** FDA agrees with the Applicant's position.

1717 **8.2.4. Safety Results**

1718 **Deaths**

1719 **Data:** The proportion of patients who had died at the time of CCOD was 35% of patients in
 1720 Atezo SC and 30% in Atezo IV, with the leading cause being progressive disease (84% vs. 87%
 1721 of all deaths in IMscin001 Part 2, respectively; [Table 24](#)). There was one death in the Atezo IV
 1722 arm classified as ‘other’; this event was due to multi-organ failure and it occurred outside the AE
 1723 reporting window. The frequency of deaths was lower in the Atezo SC arm of IMscin001 (35%)
 1724 compared to the Atezo Mono pooled population (60%), with the leading cause of death being
 1725 disease progression in all populations.

1726 Grade 5 AEs were reported at a numerically higher rate in Atezo SC (14/247 [6%] patients)
 1727 compared to Atezo IV (4/124 [3%] patients) ([Table 25](#)). Grade 5 AEs were reported across
 1728 multiple System Organ Classes (SOCs) and the majority were single occurrences except for
 1729 myocardial infarction (3 occurrences), COVID-19 pneumonia and aspiration pneumonia (2
 1730 occurrences each). The Grade 5 AEs of myocardial infarction were attributed to the risk factors
 1731 in the patient such as atherosclerosis disease, coronary artery disease, hypertension, and
 1732 smoking. The Grade 5 AEs of COVID-19 pneumonia and aspiration pneumonia were
 1733 confounded by underlying infection. Of the 14 Grade 5 AEs in Atezo SC, 2 were considered by
 1734 the investigator as treatment-related (pneumonia aspiration and toxic epidermal necrolysis)
 1735 versus none in Atezo IV.

1736 The frequency of Grade 5 AEs was higher in the Atezo SC arm of IMscin001 compared to the
 1737 Atezo Mono pooled population (6% vs. 4%). Grade 5 AEs were reported in a variety of SOCs,
 1738 and the most common AEs by preferred term (PT) reported in the Atezo Mono pooled
 1739 population were pneumonia and death (not otherwise specified).

1740 **Table 24. Applicant-Summary of Deaths by Cause (Part 2, Safety-Evaluable Population)**

	Atezo IV (N=124)	Atezo SC (N=247)
Total number of deaths	37 (29.8%)	86 (34.8%)
Primary cause of death		
n	37	86
Adverse event	4 (10.8%)	14 (16.3%)
Progressive disease	32 (86.5%)	72 (83.7%)
Other	1 (2.7%)	0
MULTI-ORGAN FAILURE	1 (2.7%)	0
Days from last study drug administration		
n	37	86
<=30 days	12 (32.4%)	32 (37.2%)
>30 days	25 (67.6%)	54 (62.8%)

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	Atezo IV (N=124)	Atezo SC (N=247)
Primary cause by days from last study drug administration		
<=30 days		
n	12	32
Adverse event	3 (25.0%)	10 (31.3%)
Progressive disease	9 (75.0%)	22 (68.8%)
>30 days		
n	25	54
Adverse event	1 (4.0%)	4 (7.4%)
Progressive disease	23 (92.0%)	50 (92.6%)
Other	1 (4.0%)	0

Source: t_dd_P2_SE_26APR2022_40657.

Percentages for Total Number of Deaths are relative to total N. All other percentages are relative to n within each module.

1741
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1743
1744

1745 **Table 25. Applicant- Grade 5 Adverse Events (Part 2, Safety-Evaluable Population)**

MedDRA System Organ Class MedDRA Preferred Term	Atezo IV (N=124)	Atezo SC (N=247)
Total number of patients with at least one adverse event	4 (3.2%)	14 (5.7%)
Overall total number of events	4	14
Infections and infestations		
Total number of patients with at least one adverse event	2 (1.6%)	7 (2.8%)
Total number of events	2	7
COVID-19 pneumonia	0	2 (0.8%)
Pneumonia aspiration	0	2 (0.8%)
COVID-19	1 (0.8%)	0
Pneumonia	0	1 (0.4%)
Respiratory tract infection	0	1 (0.4%)
Sepsis	0	1 (0.4%)
Upper respiratory tract infection	1 (0.8%)	0
Cardiac disorders		
Total number of patients with at least one adverse event	0	3 (1.2%)
Total number of events	0	3
Myocardial infarction	0	3 (1.2%)

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MedDRA System Organ Class	Atezo IV (N=124)	Atezo SC (N=247)
MedDRA Preferred Term		
Respiratory, thoracic and mediastinal disorders		
Total number of patients with at least one adverse event	1 (0.8%)	1 (0.4%)
Total number of events	1	1
Pulmonary embolism	1 (0.8%)	1 (0.4%)
Injury, poisoning and procedural complications		
Total number of patients with at least one adverse event	0	1 (0.4%)
Total number of events	0	1
Head injury	0	1 (0.4%)
Metabolism and nutrition disorders		
Total number of patients with at least one adverse event	1 (0.8%)	0
Total number of events	1	0
Hypercalcaemia	1 (0.8%)	0
Nervous system disorders		
Total number of patients with at least one adverse event	0	1 (0.4%)
Total number of events	0	1
Ischaemic stroke	0	1 (0.4%)
Skin and subcutaneous tissue disorders		
Total number of patients with at least one adverse event	0	1 (0.4%)
Total number of events	0	1
Toxic epidermal necrolysis	0	1 (0.4%)

1746 Source: t_ae_FATAL_P2_SE_26APR2022_40657.
 1747 Investigator text for AEs encoded using MedDRA version 25.0. For frequency counts by preferred term, multiple occurrences of the
 1748 same AE in an individual are counted only once.
 1749 For frequency counts of "Total number of events" rows, multiple occurrences of the same AE in an individual are counted
 1750 separately. Includes AEs with onset from first dose of study drug through the clinical cut-off.

1751
1752

Table 26. Applicant-Listing of Grade 5 Adverse Events within 30 days of Last Dose of Atezolizumab (Part 2, Safety-Evaluable Population)

Action	Center/Patient ID - Age/Sex/Race	Date of First Study Drug Admin.	Study Day of Onset	AE dur. in days	Serious	Most			
						Extreme NCI CTCAE Grade	Caused by Study Drug	Outcome (1)	Taken with Atezo (2)
Treatment: Atezolizumab IV 1200 mg Q3W (N=12)									
	332205/ (b) (6) - 58/F/American Indian or Alaska Native	(b) (6)	38	10	Yes	5	No	1	2
	Upper respiratory tract infection	(b) (6)							
	336962/ (b) (6) - 74/M/White	(b) (6)	11	1	Yes	5	No	1	
	Pulmonary embolism	(b) (6)							
	337226/ (b) (6) - 64/M/Black or African American	(b) (6)	1	12	Yes	5	No	1	2
	Hypercalcaemia	(b) (6)							
Treatment: Atezolizumab SC 1875 mg Q3W (N=32)									
	317797/ (b) (6) - 38/F/White	(b) (6)	16	6	Yes	5	No	1	2
	COVID-19 pneumonia	(b) (6)							
	326729/ (b) (6) - 61/M/White	(b) (6)	11	2	Yes	5	No	1	
	Sepsis	(b) (6)							
	328475/ (b) (6) - 68/M/White	(b) (6)	11	5	Yes	5	No	1	4
	Pneumonia	(b) (6)							
	328476/ (b) (6) - 44/M/White	(b) (6)	4	1	Yes	5	No	1	
	Myocardial infarction	(b) (6)							
	328476/ (b) (6) - 57/M/White	(b) (6)	12	8	Yes	5	No	1	
	Pneumonia aspiration	(b) (6)							

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Action	Center/Patient ID - Age/Sex/Race Adverse Event MedDRA	Study Date of First Study	Day of	AE dur. in	Most				
					Extreme NCI CTCAE	Caused by Study	Outcome	Taken with Atezo	(1)
Preferred Term	Drug Admin.	Onset	days	Serious	Grade	Drug	(1)	(2)	
329203/ (b) (6) - 76/F/White Head injury	(b) (6)	114	1	Yes	5	No	1		
336931/ (b) (6) - 74/M/White Ischaemic stroke	(b) (6)	54	4	Yes	5	No	1	2	
336931/ (b) (6) - 80/M/White Myocardial infarction	(b) (6)	21	9	Yes	5	No	1	4	
338242/ (b) (6) - 56/F/American Indian or Alaska Native Toxic epidermal necrolysis	(b) (6)	37	1	Yes	5	Yes	1		
338245/ (b) (6) - 67/F/American Indian or Alaska Native Pulmonary embolism	(b) (6)	104	1	Yes	5	No	1		

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Source: I_ae_LD30_FATAL_P2_SE_26APR2022_40657.out.
 Investigator text for AEs encoded using MedDRA version 25.0.
 (1) Outcome: 1 = fatal; 2 = not recovered/not resolved; 3 = recovered/resolved; 4 = recovered/resolved with sequelae; 5 = recovering/resolving; 6 = unknown.
 (2) Action taken with study drug: 1 = dose increased; 2 = dose not changed; 3 = dose reduced; 4 = drug interrupted; 5 = drug withdrawn; 6 = not applicable; 7 = unknown.
 * Study day derived from imputed onset date.
 ** Duration derived from imputed onset date and/or end date.

1763 **The Applicant's Position:** No new safety signal was identified following review of the Grade 5
 1764 events in IMscin001. There was no pattern or trend in the types of Grade 5 events reported.

1765 **The FDA's Assessment:** FDA reviewed all fatal adverse events that occurred in patients from the
 1766 primary safety population in Trial IMscin001 Part 2. Based on the 120-safety update dataset,
 1767 with a data cutoff date of September 2, 2022, a total of 6% of patients (n = 16) had an event of
 1768 death due to AEs that were not clearly related to disease progression in the atezolizumab SC arm
 1769 compared to 4.8% of patients (n = 6) in the atezolizumab IV arm. The 16 fatal AEs in the
 1770 atezolizumab SC arm were due to pneumonia (2.4%); myocardial infarction (1.2%); and head
 1771 injury, ischemic stroke, pleural effusion, pulmonary embolism, respiratory tract infection, sepsis,
 1772 and toxic epidermal necrolysis (0.4% each). Brief summaries of the fatal AEs are provided in the
 1773 table below.

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FDA Table 27. Assessment of Causality for Fatal Adverse Events Not Clearly Attributable to Disease Progression in the Primary Safety Population of IMscin001

Patient ID	Brief Narrative	FDA Assessment of Causality	Included in USPI
(b) (6)	37 year-old-female presented on day 14 with progressive respiratory distress. PCR was positive for COVID-19 and patient was diagnosed with Grade 3 COVID-19 pneumonia. She was hospitalized on day 16 and died on day 21. No autopsy was performed.	COVID-19 pneumonia The narrative supports the diagnosis of COVID-19 pneumonia. Although COVID-19 pneumonia was unlikely related to treatment with atezolizumab SC, this cannot be completely ruled out.	Yes
(b) (6)	41 year-old-male was hospitalized on day 82 due to Grade 2 pneumothorax seen on chest X-ray. Atezolizumab SC was discontinued on day 84. On day 85 the patient was discharged. On day 87 he was re-hospitalized with COVID-19 pneumonia (Grade 2), which was confirmed by PCR testing. The patient died on Day 100 due to COVID-19 pneumonia and disease progression.	COVID-19 pneumonia The narrative supports the diagnosis of COVID-19 pneumonia. Although COVID-19 pneumonia was unlikely related to treatment with atezolizumab SC, this cannot be completely ruled out.	Yes
(b) (6)	65 year-old-male who last received study therapy on day 85 (Cycle 5). On day 105, the patient presented with Grade 1 fever and possible respiratory tract infection. On day 111, he developed dyspnea and was started on antibiotics (amoxicillin/clavulanate). On day 127, the patient died of cardiorespiratory failure per the death certificate and an autopsy was not performed.	Respiratory Tract Infection FDA requested additional information including diagnostic imaging studies, vital signs, and cultures; however, none were available. The Applicant assessed this to be a fatal AE of respiratory tract infection and FDA agrees based on the provided information.	Yes
(b) (6)	61 year-old white male was hospitalized on day 11 with sepsis of presumed respiratory origin, fever, and acute neurological deterioration. Bacterial meningitis was ruled out. C-reactive protein was elevated at 170 mg/L and fibrinogen was elevated at 740 mg/dl. The patient was treated with ceftriaxone, vancomycin,	Sepsis FDA requested additional information including vital signs, blood cultures and imaging studies; however, none were available. Based on the narrative, FDA concurs with the Applicant's assessment of sepsis as the cause of death.	Yes

Patient ID	Brief Narrative	FDA Assessment of Causality	Included in USPI
	ampicillin, and acyclovir. The patient died on day 12. No autopsy was performed.		
(b) (6)	62 year-old-female was determined to have disease progression based on imaging assessment on day 42; however, the study treatment was continued. On day 77, the patient was hospitalized with Grade 3 pleural effusion and atezolizumab SC was interrupted. On Day 125, the patient died due to a pleural effusion. No autopsy was performed. The Applicant assessed this as a grade 5 event of pleural effusion.	Pleural Effusion An IR was sent requesting additional information on this patient's death, but no additional information was available. Based on the information provided and the Applicant's assessment, FDA agrees with the diagnosis of pleural effusion and that atezolizumab SC's contribution to the patient's death cannot be ruled out. However, FDA notes that the pleural effusion was more likely due to disease progression.	Yes
(b) (6)	68 year-old-male presented to the ER with dyspnea on day 11 and was diagnosed with Grade 3 pneumonia (diagnostic details were not reported). On day 13 the patient developed Grade 4 sepsis (diagnostic details not reported). The patient experienced cardiac arrest and was resuscitated and intubated. The patient was treated with antibiotics and steroids. On day 15 the patient died due to pneumonia and septic shock. No autopsy was performed.	Pneumonia FDA requested additional information including vital signs, blood cultures and imaging studies; however, none were available. Based on the information provided, FDA agrees with the diagnosis of pneumonia and that atezolizumab SC's contribution to the patient's death cannot be ruled out.	Yes
(b) (6)	80-year-old-male experienced Grade 2 chest pain on day 22. Atezolizumab SC was reportedly discontinued due to myocardial infarction. Troponin testing or cardiology consultation was not reported. On day 28 chest pain worsened. On day 29, the patient experienced a cardiac arrest and resuscitation was attempted but unsuccessful and the patient was declared dead after 30 minutes. Autopsy results	Myocardial infarction FDA requested additional information on this patient's death. However, no additional information was available. Based on the information provided, FDA agrees with the diagnosis of myocardial infarction and that	Yes

Patient ID	Brief Narrative	FDA Assessment of Causality	Included in USPI
	revealed coronary atherosclerotic disease and acute left ventricular failure.	atezolizumab SC's contribution to the patient's death cannot be ruled out.	
(b) (6)	44-year-old-male was called on cycle 1 day 4 to schedule a clinic visit and investigators were notified of the patient's death due to a myocardial infarction. The patient had no prior history of cardiovascular disease, and no autopsy was performed.	Myocardial infarction Based on the information provided, FDA agrees with the Applicant's diagnosis of myocardial infarction and that atezolizumab SC's contribution to the patient's death cannot be ruled out.	Yes
(b) (6)	66-year-old-female with history of coronary artery disease and hypertension, died of a myocardial infarction (on day 116). On day 116 the study site was informed by the patient's family that the patient died of a myocardial infarction. No autopsy was performed. The patient was first noted to have disease progression on day 40 but treatment was continued. On day 82, imaging again showed disease progression and treatment was discontinued on day 92.	Myocardial Infarction FDA considers this event unlikely due to atezolizumab SC given imaging assessments demonstrating disease progression. However, death occurred within the 90-day follow up period from the last study dose of atezolizumab SC and the Applicant reported this as a fatal event due to myocardial infarction. Based on the information provided, FDA agrees with the Applicant's diagnosis of myocardial infarction and that atezolizumab SC's contribution to the patient's death cannot be ruled out.	Yes
(b) (6)	76 year-old-female who experienced disease progression on day 84 based on imaging assessment. Patient continued to receive study treatment even after disease progression. The most recent dose of atezolizumab SC was administered on day 85 (Cycle 5). On day 114, the patient died in an accident due to a head injury (frontal hematoma/fall with occipital blow).	Head injury FDA considers this head injury as unlikely related to atezolizumab SC, particularly in the setting of disease progression. However, given the Applicant's assessment of head injury as a fatal AE, FDA has assessed that the contribution of atezolizumab SC to the patient's death cannot be ruled out.	Yes

Patient ID	Brief Narrative	FDA Assessment of Causality	Included in USPI
(b) (6)	59 year-old-male who on day 8 developed grade 3 brain edema and was treated with dexamethasone. On day 38, the patient was hospitalized due to a suspected pulmonary infection which was assessed as Grade 3 aspiration pneumonia. There was concern for dysphagia in the setting of increased intracranial pressure. On day 39, CT imaging revealed disease progression. On day 41, food was found in the patient’s trachea, consistent with a diagnosis of aspiration pneumonia. The patient developed respiratory failure and sepsis. COVID-19 PCR was negative.	Aspiration Pneumonia The narrative supports the diagnosis of aspiration pneumonia and atezolizumab SC cannot be ruled out as possibly contributing to death. Confounding factors include evidence of disease progression on CT imaging.	Yes
(b) (6)	57-year-old-male, presented with left sided weakness on day 2. Diffusion MRI showed acute cerebral infarctions. Patient was hospitalized with Grade 4 ischemic stroke. On day 5, the patient had an elevated temperature (specific temperature not provided). His sputum culture revealed upper respiratory tract flora. On day 12 the patient was diagnosed with Grade 4 splenic infarction and grade 4 aspiration pneumonia. Blood culture was positive for Staphylococcus lugdunensis. On day 19 the patient developed septic shock and died, due to Grade 5 aspiration pneumonia.	Aspiration Pneumonia The narrative supports the diagnosis of aspiration pneumonia and atezolizumab SC cannot be ruled out as possibly contributing to death.	Yes
(b) (6)	56 year-old-female developed Grade 3 pruritic rash 24 hours after receiving Cycle 2 of atezolizumab SC. On day 25, the patient was seen by dermatology and started on treatment with steroids. On day 32, the rash was noted to be worse. The patient was diagnosed with toxic epidermal necrolysis (TEN) and died on day 37 due to TEN.	Toxic epidermal necrolysis FDA agrees with the investigator’s assessment of the cause of death of TEN likely due to atezolizumab SC.	Yes

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Patient ID	Brief Narrative	FDA Assessment of Causality	Included in USPI
(b) (6)	74 year-old-male with an imaging assessment on, day 43 which showed disease progression. Atezolizumab SC was discontinued. On day 54 the patient presented with signs and symptoms of grade 4 ischemic stroke with the diagnosis confirmed by CT imaging. On day 55, repeat CT brain was consistent with an ischemic stroke in the right frontal, parietal, and occipital lobes. On day 57 the patient died due to ischemic stroke and disease progression.	Ischemic stroke FDA agrees with the investigator's assessment of the cause of death as due to ischemic stroke. Atezolizumab SC cannot be ruled out as possibly contributing to death	Yes
(b) (6)	67 year-old-female presented with sudden dyspnea on day 104 and was diagnosed with pulmonary embolism (diagnostic details not reported), leading to hospitalization; she died two hours later. Her last dose of atezolizumab SC was on day 85 (Cycle 5).	Pulmonary embolism FDA requested additional information on this patient's death. However, no additional information was available. Based on the information provided, FDA agrees with the Applicant's diagnosis of pulmonary embolism and atezolizumab SC cannot be ruled out as possibly contributing to the patient's death.	Yes
(b) (6)	81 year-old-male was hospitalized due to shortness of breath on day 152 and diagnosed with Grade 3 pneumonia. Study treatment was discontinued due to pneumonia. On day 154, the patient's symptoms worsened and the patient died. No additional details were available regarding the diagnosis and treatment of pneumonia. An autopsy was not performed.	Pneumonia Based on the available information, FDA agrees with the investigator's assessment of the cause of death as pneumonia. Atezolizumab SC cannot be ruled out as possibly contributing to the patient's death.	Yes

1776

Source: Module 5.3.5.3 (patient narratives) 2023-05-05, data cutoff date: September 02, 2022.

1777 **Serious Adverse Events**

1778 Data: The most frequently reported SAEs by PT in IMscin001 Part 2 were pneumonia and
 1779 COVID-19 ([Table 28](#)). There were no SAEs that were at least 2% higher in incidence in Atezo
 1780 SC compared to Atezo IV. The proportions of patients with treatment-related SAEs were
 1781 comparable between the two treatment arms (2% vs. 2%).

1782 The proportions of patients with SAEs was lower in the Atezo SC arm of IMscin001 (15%)
 1783 compared to the Atezo Mono pooled population (41%). The incidence of SAEs by PT were
 1784 comparable or lower in the Atezo SC arm of IMscin001 compared to the Atezo Mono pooled
 1785 population, with the exception of COVID-19 (note that the data cut-off dates of the atezolizumab
 1786 monotherapy studies precede the COVID-19 pandemic). There were no SAEs that were at least
 1787 2% higher in incidence in the Atezo SC arm of IMscin001 compared to the Atezo Mono pooled
 1788 population. The proportion of patients with treatment-related SAEs was lower in the Atezo SC
 1789 arm of IMscin001 (2%) compared to the Atezo Mono pooled population (11%).

1790 **Table 28. Applicant-Serious Adverse Events With an Incidence Rate of at Least 1% in Any**
 1791 **Treatment Arm by System Organ Class and Preferred Term (Safety-Evaluable Population)**

MedDRA System Organ Class	Atezo IV	Atezo SC
MedDRA Preferred Term	(N=124)	(N=247)
Infections and infestations		
Pneumonia	4 (3.2%)	5 (2.0%)
COVID-19	3 (2.4%)	1 (0.4%)
COVID-19 pneumonia	0	4 (1.6%)
Urinary tract infection	2 (1.6%)	0
Respiratory, thoracic and mediastinal disorders		
Pleural effusion	2 (1.6%)	2 (0.8%)
Cardiac disorders		
Myocardial infarction	0	4 (1.6%)
General disorders and administration site conditions		
Pyrexia	2 (1.6%)	1 (0.4%)

1792 Source: t_ae_inc_1per_SER_P2_SE_26APR2022_40657.
 1793 Investigator text for AEs encoded using MedDRA version 25.0. For frequency counts by preferred term, multiple occurrences of the
 1794 same AE in an individual are counted only once.
 1795 Includes AEs with onset from first dose of study drug through the clinical cut-off.
 1796
 1797

1798 The Applicant’s Position: The nature of SAEs observed in IMscin001 Part 2 was generally
 1799 comparable with the known safety profile of atezolizumab in the monotherapy setting.

1800 The FDA’s Assessment: The FDA agrees with the Applicant’s position regarding the data
 1801 provided with the original submission (data cutoff date April 26, 2022). FDA also reviewed data
 1802 from the 120-day safety update (data cutoff date September 2, 2022).

1803 Data from the 120-day safety update revealed that the type and frequency of SAEs were
 1804 generally similar between the SC and IV arms of the safety populations in IMscin001 and
 1805 generally comparable with the known safety profile of atezolizumab IV, except for injection site
 1806 reactions in the atezolizumab SC arm. Based on the 120-day safety update for IMscin001 Part 2,
 1807 SAEs occurred in 19% of patients who received atezolizumab SC. The incidence of serious
 1808 adverse reactions occurring in >1% of patients in IMscin001 Part 2 is shown in the FDA table
 1809 below:

1810 **FDA Table 29. Serious Adverse Events Occurring in >1% of Patients in IMscin001 Part 2**

Serious Adverse Event	ATEZO SC	ATEZO IV
	N=247 N (%)	N=124 N (%)
All	19%	24%
Pneumonia ¹	7 (2.8)	4 (3.2)
Myocardial Infarction	4 (1.6)	0
Pleural Effusion	1 (1.2)	4 (3.2)

1811 Source: ADAE (Analysis Dataset) 2023-05-05, data cutoff date: September 02, 2022.
 1812 Variables used: USUBJID, TRT01A, AEDECOD, SAFFL, AETOXGR, AEOUT, AESER, AETERM, AEOUT
 1813 ¹Composite term includes aspiration pneumonia, COVID-19 pneumonia, pneumonia.

1814 **Dropouts and/or Discontinuations Due to Adverse Effects**

1815 Data: The proportion of patients with AEs leading to atezolizumab withdrawal was comparable
 1816 between the two treatment arms (2% Atezo SC vs. 3% Atezo IV) (Table 30). No AEs by PT that
 1817 led to withdrawal occurred in ≥1% of patients across both arms.

1818 The proportion of patients with AEs leading to atezolizumab withdrawal was lower in the Atezo
 1819 SC arm of IMscin001 (2%) than the Atezo Mono pooled population (7%). Across all
 1820 populations, there were no AEs leading to withdrawal that were reported in ≥1% of patients.

1821 **Table 30. Applicant-Adverse Events Leading to Treatment Discontinuation**

MedDRA System Organ Class	Atezo IV	Atezo SC
MedDRA Preferred Term	(N=124)	(N=247)
Total number of patients with at least one adverse event	4 (3.2%)	4 (1.6%)
Overall total number of events	4	6
Infections and infestations		
Total number of patients with at least one adverse event	1 (0.8%)	2 (0.8%)
Total number of events	1	2
COVID-19	1 (0.8%)	0
COVID-19 pneumonia	0	1 (0.4%)
Pneumonia aspiration	0	1 (0.4%)
MedDRA System Organ Class	Atezo IV	Atezo SC
MedDRA Preferred Term	(N=124)	(N=247)
General disorders and administration site conditions		

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Total number of patients with at least one adverse event	1 (0.8%)	0
Total number of events	1	0
Fatigue	1 (0.8%)	0
Injury, poisoning and procedural complications		
Total number of patients with at least one adverse event	1 (0.8%)	0
Total number of events	1	0
Infusion related reaction	1 (0.8%)	0
Investigations		
Total number of patients with at least one adverse event	0	1 (0.4%)
Total number of events	0	3
Alanine aminotransferase increased	0	1 (0.4%)
Aspartate aminotransferase increased	0	1 (0.4%)
Gamma-glutamyltransferase increased	0	1 (0.4%)
Nervous system disorders		
Total number of patients with at least one adverse event	0	1 (0.4%)
Total number of events	0	1
Ischaemic stroke	0	1 (0.4%)
Respiratory, thoracic and mediastinal disorders		
Total number of patients with at least one adverse event	1 (0.8%)	0
Total number of events	1	0
Pneumonitis	1 (0.8%)	0

1822 Source: t_ae_DSCALL_P2_SE_26APR2022_40657.
 1823 Investigator text for AEs encoded using MedDRA version 25.0. For frequency counts by preferred term, multiple occurrences of the
 1824 same AE in an individual are counted only once.
 1825 For frequency counts of "Total number of events" rows, multiple occurrences of the same AE in an individual are counted
 1826 separately. Includes Aes with onset from first dose of study drug through the clinical cut-off.
 1827
 1828

1829 **The Applicant's Position:** The proportion of patients with AEs leading to atezolizumab
 1830 withdrawal was comparable between the two treatment arms in Imscin001.

1831 **The FDA's Assessment:** The FDA agrees with the Applicant's position regarding the data
 1832 provided with the original submission (data cutoff date April 26, 2022). The FDA also reviewed
 1833 the safety datasets for Imscin001 Part 2 provided by the Applicant in the 120-day safety update,
 1834 with a data cutoff date of September 2, 2022. A similar proportion of patients in the
 1835 atezolizumab SC arm (3.6%) experienced AEs leading to permanent discontinuation of
 1836 atezolizumab compared to the atezolizumab IV arm (4.8%). The table below shows the adverse
 1837 events leading to permanent discontinuation of atezolizumab SC or atezolizumab IV in
 1838 Imscin001 Part 2, at the time of the 120-day safety update.

1839 **FDA Table 31. Adverse Events Leading to Permanent Discontinuation of Study Therapy in Imscin001 Part 2**

Adverse Event Leading to Discontinuation	ATEZO SC N=247 N (%)			ATEZO IV N=124 N (%)		
	All Grades	Grade 3-4	Grade 5	All Grades	Grade 3-4	Grade 5
Pneumonia ¹	5 (2.0)	0	5 (2.0)	0	0	0
Increased gamma-glutamyltransferase	1 (0.4)	1 (0.4)	0	0	0	0
Increased aspartate aminotransferase	1 (0.4)	0	0	0	0	0
Ischemic stroke	1 (0.4)	1 (0.4)	0	0	0	0
Increased alanine aminotransferase	1 (0.4)	1 (0.4)	0	0	0	0
Infusion related reaction	0	0	0	1 (0.8)	1 (0.8)	0
Intestinal perforation	0	0	0	1 (0.8)	0	1 (0.8)
Pneumonitis	0	0	0	1 (0.8)	1 (0.8)	0
Asthma	0	0	0	1 (0.8)	1 (0.8)	0
Hypercalcemia	0	0	0	1 (0.8)	0	1 (0.8)
COVID-19	0	0	0	1 (0.8)	1 (0.8)	0

1840 Source: ADAE (Analysis Dataset) 2023-05-05, data cutoff date: September 02, 2022.
 1841 Variables used: USUBJID, TRT01A, AEDECOD, SAFFL, AETOXGR, AEACN3, AEACN4.
 1842 ¹Composite term includes aspiration pneumonia, COVID-19 pneumonia, pneumonia.

1843 **Dose Interruption/Reduction Due to Adverse Effects**

1844 Data: The proportion of patients with AEs leading to atezolizumab dose interruption was comparable between the two treatment arms
 1845 (25% Atezo SC vs. 27% Atezo IV). The most frequent AEs by PT that led to dose interruption were COVID-19 (4% vs. 6%) and
 1846 pneumonia (2% vs. 2%) ([Table 32](#)).

1847 Dose increases/reductions for atezolizumab were not allowed per protocol. One dose interruption led to a one-time dose reduction in
 1848 Atezo IV for AE management; no dose modifications were reported in Atezo SC.

1849 The proportions of patients with AEs leading to atezolizumab dose interruption were comparable between the Atezo SC arm of
 1850 Imscin001 (25%) and the Atezo Mono pooled population (28%). The events that led to atezolizumab interruption were distributed
 1851 across multiple PTs, with no noteworthy differences between the populations.

1852 **Table 32. Applicant-Summary of Adverse Events Leading Dose Interruptions in ≥1% of Patients in**
 1853 **Either Arm (Part 2, Safety-Evaluable Population)**

MedDRA System Organ Class	Atezo IV	Atezo SC
MedDRA Preferred Term	(N=124)	(N=247)
Infections and infestations		
COVID-19	7 (5.6%)	10 (4.0%)
Pneumonia	3 (2.4%)	5 (2.0%)
Respiratory tract infection viral	1 (0.8%)	3 (1.2%)
Bronchitis	2 (1.6%)	0
General disorders and administration site conditions		
Pyrexia	2 (1.6%)	2 (0.8%)
Investigations		
Alanine aminotransferase increased	0	4 (1.6%)
Aspartate aminotransferase increased	0	4 (1.6%)
Metabolism and nutrition disorders		
Hypercreatininaemia	2 (1.6%)	0

1854 Source : t_ae_DSMALL_P2_SE_26APR2022_40657.
 1855 Investigator text for AEs encoded using MedDRA version 25.0. For frequency counts by preferred term, multiple occurrences of the
 1856 same AE in an individual are counted only once.
 1857 For frequency counts of "Total number of events" rows, multiple occurrences of the same AE in an individual are counted
 1858 separately. Includes AEs with onset from first dose of study drug through the clinical cut-off.
 1859
 1860

1861 **The Applicant’s Position:** The proportion of patients with AEs leading to atezolizumab dose
 1862 interruption was comparable between the Atezo SC and IV arms in IMscin001.

1863 **The FDA’s Assessment:** FDA agrees with the Applicant’s position regarding the data provided
 1864 with the original submission (data cutoff date April 26, 2022).

1865 FDA also reviewed the safety datasets for IMscin001 Part 2 provided by the Applicant in the
 1866 120-day safety update with a data cutoff date of September 2, 2022. Based on the 120-day safety
 1867 update, dosage interruptions due to an AE occurred in 32% of patients in the atezolizumab SC
 1868 arm compared to 30% in the atezolizumab IV arm. Adverse events which required dosage
 1869 interruption in ≥1% of patients in the atezolizumab SC arm are shown in the table below.

1870 **FDA Table 33. Adverse Events Leading to Treatment Interruption in ≥1% of Patients in IMscin001**
 1871 **Part 2**

Adverse Event Leading to Dose Interruption in ≥1%	ATEZO SC N=247 N (%)		ATEZO IV N=124 N (%)	
	All Grades	Grade 3-4	All Grades	Grade 3-4
COVID-19	12 (4.9)	4 (1.2)	10 (8)	0
Increased aspartate aminotransferase	7 (2.8)	4 (1.2)	1 (0.8)	0
Increased alanine aminotransferase	6 (2.4)	2 (0.8)	1 (0.8)	0
Pneumonia	6 (2.4)	1 (0.4)	4 (3.2)	4 (3.2)
Anemia	4 (1.6)	2 (0.8)	0	0
Dyspnea	4 (1.6)	3 (1.2)	1 (0.8)	0
Viral respiratory tract infection viral	3 (1.2)	0	1 (0.8)	0
Fatigue	3 (1.2)	0	0	0

1872 Source: ADAE (Analysis Dataset) 2023-05-05, data cutoff date: September 2, 2022.
 1873 Variables used: USUBJID, TRT01A, AEDECOD, SAFFL, AETOXGR, AEACN3, AEACN4.
 1874
 1875

1876 **Significant Adverse Events**

1877 Data: The proportion of patients with at least one Grade 3–4 AE was lower in Atezo SC (18%)
 1878 compared with Atezo IV (26%). The most frequent (≥2%) Grade 3–4 AEs by PT were
 1879 pneumonia (1% Atezo SC vs. 3% Atezo IV), hyponatraemia (2% vs. 3%), hypokalaemia (0.4%
 1880 vs. 2%), and anaemia (4% vs. 2%).

1881 A lower proportion of patients experienced Grade 3–4 AEs in the Atezo SC arm of IMscin001
 1882 (18%) compared to the Atezo Mono pooled population (47%). No Grade 3–4 AEs with a ≥2%
 1883 difference in incidence between the Atezo SC arm of IMscin001 and the Atezo Mono pooled
 1884 population had a higher incidence in the Atezo SC arm. The most frequent Grade 3–4 AE across
 1885 all populations was anaemia (4% IMscin001 Atezo SC vs. 5% Atezo Mono pooled).

1886 The Applicant’s Position: The proportion of patients with at least one Grade 3–4 AE was lower
 1887 in Atezo SC compared with Atezo IV.

1888 The FDA’s Assessment: FDA agrees with the Applicants position regarding the data provided
 1889 with the original submission (data cutoff date April 26, 2022). The FDA also reviewed the safety
 1890 datasets for IMscin001 Part 2 provided by the Applicant in the 120-day safety update, with a data
 1891 cutoff date of September 2, 2022, that showed that the proportion of patients with at least one
 1892 Grade 3 – 4 AE was lower in the atezolizumab SC arm (22%) compared to the atezolizumab IV
 1893 arm (35%). See [FDA Table 36](#) below which shows the incidence of Grade 3 – 4 AEs for adverse
 1894 events occurring in ≥10% of patients.

1895 **Treatment Emergent Adverse Events and Adverse Reactions**

1896 Data: An overview of the key safety results of IMscin001 alongside the pooled safety results for
 1897 the Atezo Mono Pooled population is presented in [Table 34](#). Due to the differences in the line of
 1898 therapies, disease areas, patient populations, duration of follow-up, and collection methodologies
 1899 between IMscin001 and the Atezo Mono pooled population, caution should be exercised in the
 1900 interpretation of these data.

1901 **Table 34. Applicant-Overview of Treatment Emergent Adverse Events (Atezo Mono Treated**
 1902 **Patients)**

	IMSCIN001		Pooled Population
	Atezo IV	Atezo SC	Atezo Mono
	(N=124)	(N=247)	(N=3178)
Total number of patients with at least one AE	104 (83.9%)	212 (85.8%)	3051 (96.0%)
Total number of events	451	874	33377
Total number of patients with at least one			
Atezo-related AE	47 (37.9%)	93 (37.7%)	2167 (68.2%)
Grade 3-4 AE	32 (25.8%)	44 (17.8%)	1482 (46.6%)
Atezo-related Grade 3-4 AE	4 (3.2%)	9 (3.6%)	496 (15.6%)
Grade 5 AE	4 (3.2%)	14 (5.7%)	119 (3.7%)
Atezo-related Grade 5 AE	0	2 (0.8%)	11 (0.3%)
Serious AE	22 (17.7%)	38 (15.4%)	1309 (41.2%)
Atezo-related serious AE	3 (2.4%)	4 (1.6%)	353 (11.1%)
AE leading to Atezo withdrawal	4 (3.2%)	4 (1.6%)	226 (7.1%)
AE leading to Atezo interruption	33 (26.6%)	61 (24.7%)	881 (27.7%)

Source: t_ae_sum_SE_26APR2022_40657P.

Only events reported in the Adverse Events Form are included.

Investigator text for AEs encoded using MedDRA v25.0. Percentages are based on N in the column headings.

Multiple occurrences of the same AE in one individual are counted only once except for "Total number of events" row in which multiple occurrences of the same AE are counted separately. All treatment emergent AEs are included. For the counts in the rows by grade, the patients are counted once at the highest grade.

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1911 Overall, the safety profile in Atezo SC was comparable to the safety profile in Atezo IV. No new
 1912 safety concerns were identified for atezolizumab in this study. The proportions of patients who
 1913 experienced AEs, SAEs, and AEs leading to treatment discontinuation/interruption were
 1914 comparable between the two study arms. The proportions of patients who experienced Grade 3–4
 1915 AEs was lower in Atezo SC (18%) compared to Atezo IV (26%). Grade 5 AEs were reported in
 1916 14 patients (6%) in Atezo SC and 4 patients (3%) in Atezo IV.

1917 The safety profile of atezolizumab in the Atezo SC Arm of IMscin001 was generally comparable
 1918 with the safety profile of atezolizumab in the Atezo Mono pooled population. The incidence of
 1919 AEs across all categories in the Atezo SC Arm of IMscin001 was lower or comparable to the
 1920 Atezo Mono pooled population, with the exception of Grade 5 AEs.

(b) (4)

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1925 **Table 35. Applicant-Adverse Reactions Occurring in ≥5% of Patients Receiving Atezolizumab SC**
1926 **in Part 2 of IMscin001**

Adverse Reaction*	Atezolizumab SC N=247		Atezolizumab IV N=124	
	All Grades (%)	Grades 3–4 (%)	All Grades (%)	Grades 3–4 (%)
Metabolism and Nutrition Disorders				
Decreased appetite	9.7	0	8.1	0
Hyponatremia	6.1	2.0	9.7	3.2
General Disorder and Administration Site Conditions				
Fatigue	10	0.4	14	0.8
Asthenia	6.5	0.4	4.8	0
Infections and infestations				
Pneumonia	6.1	0.8	4.0	3.2
COVID-19	5.3	0.8	8.9	1.6
Respiratory, Thoracic and Mediastinal				
Dyspnea	9.3	0.4	13	0.8
Cough	9.3	0	5.6	0
Blood and lymphatic				
Anemia	15	3.6	15	1.6
Musculoskeletal and Connective Tissue disorders				
Back pain	6.9	0.4	5.6	1.6
Arthralgia	6.1	0	4.0	0
Gastrointestinal Disorders				
Nausea	6.1	0	1.6	0
Constipation	5.7	0	4.0	0
Endocrine Disorders				
Hypothyroidism	5.3	0	3.2	0

Sources: t_ae_inc_5per_P2_SE_26APR2022_40657; t_ae_SE_26APR2022_40657; t_ae_ctc_P2_SE_26APR2022_40657.

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1930 The methodology that was used to identify any new adverse drug reaction (ADR) in IMscin001
1931 Part 2 was the following: if the incidence in Atezo SC was higher than in Atezo IV by ≥5% (all
1932 grades) and ≥2% (Grade 3–4), the AE was identified as an ADR. Otherwise, a medical review
1933 was conducted. Based on medical judgment, a decision could be made to include terms that had
1934 not met any of the pre-defined criteria, or not to include terms that had met one or more
1935 numerical criteria. Medical judgment includes knowledge of biological plausibility, experience
1936 with similar-in-class agents, exclusion of alternate causes, and general medical knowledge of
1937 human pathophysiology.

1938 One new ADR of ISR was identified for atezolizumab SC based on an incidence of 4.5%
1939 (11/247) for ISRs (terms included in HLT injection site reactions) that was observed in Atezo SC
1940 versus 0% in Atezo IV. In IMscin001, local ISRs were defined as selected adverse events (more
1941 information in Section 8.2.5). Therefore, given the new SC route of administration for
1942 atezolizumab has a potential for local ISRs and the difference between the SC arm and IV arm
1943 (4.5% vs. 0%), an AE analysis was conducted to further investigate the possible causal
1944 association between ISRs and atezolizumab SC. Based on the review of ISRs from IMscin001, as
1945 well as the potential for other monoclonal antibodies or SC anti-cancer drugs to evoke similar

1946 reactions, the current evidence is sufficient to establish a causal relationship between ISRs and
 1947 atezolizumab SC.

1948 **The Applicant’s Position:** Overall, the types and incidence of adverse reactions observed in
 1949 IMscin001 Part 2 were comparable with the known safety profile of atezolizumab and/or the
 1950 underlying disease. The most common adverse reactions of any grade (occurring in $\geq 10\%$ of
 1951 patients) to atezolizumab SC (TRADE NAME) were anemia (15%) and fatigue (10%). ISR has
 1952 been added as an ADR for atezolizumab SC in the labeling information.

1953 **The FDA’s Assessment:** FDA generally agrees with the Applicant’s position that the type of
 1954 adverse reactions observed in IMscin001 Part 2 were comparable to the known safety profile of
 1955 atezolizumab IV.

1956 Adverse events occurring in $\geq 10\%$ of patients in the primary safety population for IMscin001
 1957 Part 2, based on the data provided by the Applicant in the 120-day safety update, with a data
 1958 cutoff date of September 2, 2022, are summarized in [FDA Table 36](#) below.

1959 **FDA Table 36. Adverse Events Occurring in $\geq 10\%$ of Patients with NSCLC in IMscin001**

Adverse Reaction*	Atezolizumab SC N=247		Atezolizumab IV n=124	
	All Grades (%)	Grades 3 – 4 (%)	All Grades (%)	Grades 3 – 4 (%)
General Disorder and Administration Site Conditions				
Fatigue ¹	19	0.8	18	0
Musculoskeletal and Connective Tissue disorders				
Musculoskeletal Pain ²	15	0.4	13	3.2
Respiratory, Thoracic and Mediastinal				
Cough ³	13	0	7	0
Dyspnea ⁴	12	1.2	15	1.6
Metabolism and Nutrition Disorders				
Decreased appetite	11	0	11	0

1960 Source: ADAE (Analysis Dataset) 2023-05-05, data cutoff date: September 02, 2022.

1961 Graded per NCI CTCAE v5.0.

1962 ¹Composite term includes fatigue, asthenia.

1963 ²Composite term includes back pain, myalgia, bone pain, arthralgia, musculoskeletal chest pain, pain in extremity, neck pain, spinal
 1964 pain, non-cardiac chest pain and arthritis.

1965 ³Composite term includes cough, productive cough.

1966 ⁴Composite term includes dyspnea, dyspnea at rest, dyspnea exertional.

1967 Adverse event types were generally comparable between the atezolizumab SC arm and
 1968 atezolizumab IV arms of IMscin001.

1969 **Laboratory Findings**

1970 **Data:** Laboratory data are presented in the dossier for IMscin001 only (i.e., the data were not
 1971 pooled). Selected laboratory data are classified according to NCI-CTCAE v5.0 and summarized
 1972 as clinically relevant shifts from baseline per treatment arm (shift from Grade 0, 1, or 2 at
 1973 baseline to Grade 3 or 4 post-baseline).

1974 There was no notable difference between the arms with respect to the incidence of clinically
 1975 relevant shifts from baseline in laboratory safety parameters. The most frequent clinically
 1976 relevant shifts were low lymphocyte counts, low hemoglobin, sodium, and potassium levels.

1977 Among patients for whom pre- and post-baseline TSH levels were available, the majority
 1978 maintained normal levels during the course of the study. Treatment-emergent TSH laboratory
 1979 abnormalities (defined as normal at baseline and abnormal at post-baseline) were reported in a
 1980 higher proportion of patients in Atezo SC (TSH high 16% SC vs. 9% IV, TSH low 18% SC vs. 4% IV).

1981 Six patients in Atezo SC (2%) versus none in Atezo IV fulfilled the laboratory criteria suggestive
 1982 for Hy's law (post-baseline ALT and AST > 3 × ULN in combination with an elevated total
 1983 bilirubin [$> 2 \times \text{ULN}$]). All 6 patients had plausible explanations for the laboratory abnormalities;
 1984 4 patients had medical histories of liver metastases, liver lesions, or Gilbert's disease, which are
 1985 known to impact liver function, and 2 patients had concurrent events (immune-mediated
 1986 hepatitis, alkaline phosphatase [ALP] increase, and pneumonia aspiration) that contributed to
 1987 the liver function abnormalities.

(b) (4)

1990 **Table 37. Applicant-Laboratory Abnormalities Worsening from Baseline Occurring in $\geq 20\%$ of**
 1991 **Patients Receiving Atezolizumab SC in IMscin001**

Laboratory Abnormality ¹	Atezolizumab SC N=247		Atezolizumab IV N=124	
	All Grades (%)	Grades 3–4 (%)	All Grades (%)	Grades 3–4 (%)
Hematology				
Decreased Hemoglobin	61	4.7	59	3.4
Decreased lymphocytes	33	9.0	41	12
Chemistry				
Decreased Sodium	41	3.4	44	4.3
Decreased Albumin	30	1.7	23	0
Increased Alkaline Phosphatase	29	1.3	23	0
Increased AST	24	2.1	23	1.7
Increased ALT	24	2.6	17	0.9
Increased INR	21	2.1	21	0

Source: t_lb_shift_uspi_inc20_P2_SE_26APR2022_40657.

Each test incidence is based on the number of patients who had both baseline and at least one on-study laboratory measurement available: TRADENAME (48–233) and intravenous atezolizumab (19–117).

¹ Graded per NCI-CTCAE v5.0.

1998 The Applicant's Position: The clinical laboratory results showed no unexpected safety findings
 1999 in Part 2 of IMscin001.

2000 **The FDA’s Assessment:** FDA agrees with the data and position presented by the Applicant. FDA
 2001 also reviewed laboratory abnormalities based on the 120-day safety update with a data cutoff
 2002 date of September 2, 2022, summarized in [FDA Table 38](#) below. Several IRs were sent to clarify
 2003 the variables used to define laboratory abnormalities. Patients with missing baseline laboratory
 2004 assessments are excluded the below.

2005 **FDA Table 38. Laboratory Abnormalities Worsening from Baseline Occurring in ≥20% of Patients**
 2006 **with NSCLC Receiving Atezolizumab SC in IMscin001**

Laboratory Abnormality ¹	Atezolizumab SC (n=247)		Atezolizumab IV (n=124)	
	All Grades (%)	Grades 3–4 (%)	All Grades (%)	Grades 3–4 (%)
Hematology				
Decreased Hemoglobin	67	6	63	5
Decreased lymphocytes	37	9	45	15
Chemistry				
Decreased Sodium	46	3.9	47	5
Decreased Albumin	34	2.1	27	0
Increased Alkaline Phosphatase	33	1.3	27	0
Increased AST	27	2.6	32	2.6
Increased ALT	27	2.6	23	1.7
Decreased calcium	22	2.6	23	1.7
Increased calcium	20	2.6	24	1.7
Increased potassium	21	1.7	22	1.7
Increased INR	54	1.7	62	0

2007 Source: ADLB dataset 2023-05-05, data cutoff date: September 02, 2022

2008 Each test incidence is based on the number of patients who had both baseline and at least one on-study laboratory measurement
 2009 available: subcutaneous atezolizumab (48-233) and intravenous atezolizumab (19-117)¹ Graded per NCI CTCAE v5.0

2010
2011
2012 **Vital Signs**

2013 **The Applicant’s Position:** There were no clinically relevant differences between the two
 2014 treatment arms in IMscin001 with respect to vital sign parameters.

2015 **The FDA’s Assessment:** FDA agrees with the Applicant’s position.

2016 **Electrocardiograms (ECGs)**

2017 **Data:** At baseline, 3 patients in Atezo SC and 1 patient in Atezo IV had a clinically significant
 2018 ECG abnormality. Post-baseline, 1 patient in Atezo SC and 2 patients in Atezo IV had clinically
 2019 significant ECG abnormalities. The patient in Atezo SC experienced Grade 2 cardiac failure
 2020 (reported as worsening of cardiac failure) at the time of the ECG abnormality. The event was
 2021 assessed by the investigator as unrelated to treatment. The ECG abnormalities in Atezo IV were
 2022 not associated with any cardiac disorders.

2023 **The Applicant’s Position:** The proportion of patients with abnormal ECG shift was similar
 2024 between the arms in Part 2 of IMscin001.

2025 **The FDA’s Assessment:** FDA agrees with Applicant’s position.

2026 **QT**

2027 **The Applicant’s Position:** No QT Studies were performed with atezolizumab SC.

2028 **The FDA’s Assessment:** FDA agrees with the Applicant’s position.

2029 **Immunogenicity**

2030 **Data:** The evaluation for the effect of ADAs on safety is based on the IMscin001 study. In Atezo
 2031 SC, the overall safety profile was generally comparable between ADA-positive patients and
 2032 ADA-negative patients. The interpretation of the ADA-positive subgroup data in Atezo IV is
 2033 limited by the small number of ADA-positive patients (n = 15) (Table 39).

2034 In Atezo SC, SAEs were observed at the same frequency (14%) in the ADA-positive compared
 2035 with the ADA-negative subgroup and the reported SAEs were not driven by specific PTs.

2036 In Atezo IV, SAEs were observed in 4 patients (27%) in the ADA-positive subgroup compared
 2037 with 15 patients (16%) in the ADA-negative subgroup. These SAEs were observed in low
 2038 numbers of patients and were not driven by any one PT. In the four ADA-positive patients in
 2039 Atezo IV who experienced SAEs, the reported events were upper respiratory tract infection
 2040 (Grade 5) and asthma (Grade 4) in one patient, pneumonia (Grade 3) in one patient, pyrexia
 2041 (Grade 1) in one patient, and infusion-related reaction (IRR) (Grade 3) in one patient. All of
 2042 these events except the IRR event were considered as unrelated to the study treatment by the
 2043 investigators.

2044 **Table 39. Applicant-Overview of AEs by ADA Status**

	Atezo IV (N=108)		Atezo SC (N=221)	
	ADA- (N=93)	ADA+ (N=15)	ADA- (N=178)	ADA+ (N=43)
Total number of patients with at least one AE	82 (88.2%)	12 (80.0%)	154 (86.5%)	40 (93.0%)
Total number of AEs	383	52	640	179
Total number of patients with Confirmed/ Suspected COVID-19 AE	10 (10.8%)	1 (6.7%)	12 (6.7%)	4 (9.3%)

	Atezo IV (N=108)		Atezo SC (N=221)	
	ADA- (N=93)	ADA+ (N=15)	ADA- (N=178)	ADA+ (N=43)
Total number of patients with at least one				
AE with fatal outcome	1 (1.1%)	1 (6.7%)	5 (2.8%)	2 (4.7%)
Related AE with fatal outcome	0	0	1 (0.6%)	0
Serious AE	15 (16.1%)	4 (26.7%)	25 (14.0%)	6 (14.0%)
Related Serious AE	2 (2.2%)	1 (6.7%)	3 (1.7%)	0
Grade 3-4 AE	27 (29.0%)	3 (20.0%)	31 (17.4%)	9 (20.9%)
Related Grade 3-4 AE	2 (2.2%)	2 (13.3%)	8 (4.5%)	1 (2.3%)
Related AE	35 (37.6%)	9 (60.0%)	73 (41.0%)	18 (41.9%)
AE leading to Atezolizumab discontinuation	3 (3.2%)	1 (6.7%)	2 (1.1%)	0
AE leading to dose interruption of Atezolizumab	27 (29.0%)	3 (20.0%)	45 (25.3%)	11 (25.6%)

Source: t_saf_sum_P2_ADA_26APR2022_40657

Multiple occurrences of the same AE in one individual are counted only once except for 'Total number of AEs' row in which multiple occurrences of the same AE are counted separately. Includes AEs with onset from first dose of study drug through the clinical cut-off. Grade 3-4 categories include only patients with grade 3-4 AEs at the highest grade.

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2051 The Applicant's Position: The atezolizumab treatment-emergent ADA incidence was comparable
 2052 between arms. There did not appear to be a clinically relevant impact of anti-atezolizumab ADAs
 2053 on pharmacokinetics, efficacy, or safety in both treatment arms. The anti-rHuPH20 antibody
 2054 incidence was low in the SC arm and is not expected to have an effect on atezolizumab
 2055 pharmacokinetics, efficacy, or safety.

2056 The FDA's Assessment: During the first year of treatment in IMscin001, the incidence of anti-
 2057 atezolizumab antibodies was 20% (43/221) in the atezolizumab SC arm and 14% (15/108) in the
 2058 atezolizumab IV arm. The data are limited to adequately characterize the effect of ADA on
 2059 atezolizumab efficacy. ADA appears to have no clinically significant effect on atezolizumab
 2060 safety. Refer to Section 6 of the Assessment Aid for a full discussion on immunogenicity of
 2061 atezolizumab SC.

2062 8.2.5. Analysis of Submission-Specific Safety Issues

2063 8.2.5.1. Adverse Events of Special Interest

2064 Data: The proportions of patients with AESIs were comparable between the two treatment arms
 2065 (26% Atezo SC vs. 22% Atezo IV) (Table 40). The most frequently (≥5%) reported identified
 2066 risks (by medical concept) were hepatitis, rash, and hypothyroidism, and the incidences were
 2067 comparable between the Atezo SC and Atezo IV treatment arms. No potential risks for
 2068 atezolizumab were observed in IMscin001. The majority of AESIs were of Grade 1–2 severity

2069 and generally manageable. One Grade 5 AESI (PT: toxic epidermal necrolysis) was reported in
 2070 Atezo SC (0.4%) and was considered by the investigator as treatment-related. The proportions of
 2071 patients with serious AESIs were comparable between the two treatment arms and occurred at a
 2072 low rate (1% Atezo SC vs. 2% Atezo IV). Overall, treatment with atezolizumab SC was
 2073 generally well tolerated as shown by the low proportion of patients who discontinued treatment
 2074 (0.4% vs. 2%) or needed a dose interruption (4% vs. 2%) due to AESIs. The proportions of
 2075 patients with AESIs requiring systemic corticosteroids also were low in both treatment arms (5%
 2076 vs. 2%).

2077 A lower proportion of patients in the Atezo SC arm of IMscin001 (26%) experienced AESIs
 2078 compared to the Atezo Mono pooled population (35%). In comparison to the Atezo Mono pooled
 2079 population, lower rates of Grade 3–4 AEs (4% IMscin001 Atezo SC arm vs. 8% Atezo Mono
 2080 pooled), serious AESIs (1% vs. 5%) and AESIs leading to atezolizumab withdrawal (0.4% vs.
 2081 2%) were reported for Atezo SC. A higher proportion of patients reported hyperthyroidism in the
 2082 Atezo SC arm of IMscin001 (2.4%) compared to the Atezo Mono pooled population (0.9%). The
 2083 hyperthyroidism events in the Atezo SC arm were of Grade 1–2 severity, and were generally
 2084 manageable and resolved. No new safety signal was identified following review of the
 2085 hyperthyroidism events.

2086 In IMscin001 Part 2, a low number of patients (2 [1%] patients) in Atezo SC received an
 2087 immunosuppressive agent other than corticosteroids (mycophenolate) to treat events of hepatitis.
 2088 All events had resolved by the CCOD.

2089 **Table 40. Applicant-Summary of AESIs for Atezolizumab (Safety-Evaluable Population)**

	IMSCIN001		Pooled Population
	Atezo IV (N=124)	Atezo SC (N=247)	Atezo Mono (N=3178)
Total number of patients with at least one AESI	27 (21.8%)	65 (26.3%)	1104 (34.7%)
Total number of events	48	112	2203
Total number of patients with at least one			
Atezo-related AESI	19 (15.3%)	46 (18.6%)	797 (25.1%)
Grade 3-4 AESI	3 (2.4%)	9 (3.6%)	246 (7.7%)
Atezo-related Grade 3-4 AESI	2 (1.6%)	6 (2.4%)	173 (5.4%)
Grade 5 AESI	0	1 (0.4%)	5 (0.2%)
Atezo-related Grade 5 AESI	0	1 (0.4%)	2 (<0.1%)
Serious AESI	2 (1.6%)	3 (1.2%)	152 (4.8%)
Atezo-related Serious AESI	2 (1.6%)	3 (1.2%)	128 (4.0%)
AESI leading to Atezo withdrawal	2 (1.6%)	1 (0.4%)	59 (1.9%)
AESI leading to Atezo interruption	2 (1.6%)	11 (4.5%)	211 (6.6%)
AESI Requiring the Use of Systemic Corticosteroids	3 (2.4%)	13 (5.3%)	247 (7.8%)

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	IMSCIN001		Pooled Population
	Atezo IV (N=124)	Atezo SC (N=247)	Atezo Mono (N=3178)
Medical concepts: patients with at least one			
Immune-Mediated Rash	11 (8.9%)	15 (6.1%)	613 (19.3%)
Immune-Mediated Hepatitis (Diagnosis and Lab Abnormalities)	10 (8.1%)	25 (10.1%)	343 (10.8%)
Immune-Mediated Hepatitis (Lab Abnormalities)	10 (8.1%)	23 (9.3%)	315 (9.9%)
Immune-Mediated Hypothyroidism	5 (4.0%)	17 (6.9%)	164 (5.2%)
Immune-Mediated Pneumonitis	1 (0.8%)	1 (0.4%)	91 (2.9%)
Immune-Mediated Hepatitis (Diagnosis)	0	2 (0.8%)	62 (2.0%)
Immune-Mediated Hyperthyroidism	1 (0.8%)	6 (2.4%)	30 (0.9%)
Infusion-Related Reactions	4 (3.2%)	0	32 (1.0%)
Immune-Mediated Colitis	0	0	34 (1.1%)
Immune-Mediated Severe Cutaneous Reactions	0	1 (0.4%)	22 (0.7%)
Immune-Mediated Pancreatitis	0	0	18 (0.6%)
Immune-Mediated Ocular Inflammatory Toxicity	0	0	16 (0.5%)
Immune-Mediated Adrenal Insufficiency	0	0	12 (0.4%)
Immune-Mediated Myositis (Myositis+Rhabdomyolysis)	0	0	13 (0.4%)
Immune-Mediated Meningoencephalitis	0	0	14 (0.4%)
Immune-Mediated Diabetes Mellitus	0	0	10 (0.3%)
Immune-Mediated Meningitis	0	0	12 (0.4%)
Immune-Mediated Myositis	0	0	8 (0.3%)
Immune-Mediated Vasculitis	0	0	7 (0.2%)
Immune-Mediated Nephritis	0	0	3 (<0.1%)
Immune-Mediated Guillain-Barre Syndrome	0	0	5 (0.2%)
Rhabdomyolysis	0	0	5 (0.2%)
Autoimmune Hemolytic Anaemia	0	0	4 (0.1%)
Immune-Mediated Hypophysitis	0	0	2 (<0.1%)
Immune-Mediated Encephalitis	0	0	2 (<0.1%)
Haemophagocytic Lymphohistiocytosis	0	0	1 (<0.1%)
Immune-Mediated Myasthenia Gravis	0	0	1 (<0.1%)

2090 Source: t_ae_si_sum_SE_AAG6x10_26APR2022_40657P
 2091 Only events reported in the Adverse Events Form are included. Investigator text for AEs encoded using MedDRA v25.0.
 2092 Percentages are based on N in the column headings. Multiple occurrences of the same AE in one individual are counted only once
 2093 except for "Total number of events" row in which multiple occurrences of the same AE are counted separately. All treatment
 2094 emergent AEs are included. For the counts in the rows by grade, the patients are counted once at the highest grade.

2095

2096 The Applicant's Position: The overall AESI profile of atezolizumab SC in IMscin001 Part 2 was
2097 generally consistent with its known safety profile in the IV monotherapy setting. The most
2098 commonly reported AESIs in IMscin001 Part 2 were hepatitis, rash, and hypothyroidism. The
2099 majority of AESIs were Grade 1 or 2 in severity. AESIs were generally manageable.

2100 The higher incidence of hyperthyroidism in the Atezo SC arm of IMscin001 compared to the
2101 Atezo Mono pooled population did not lead to identification of any new signal following review
2102 of the hyperthyroidism events. The hyperthyroidism events in the Atezo SC arm were of
2103 Grade 1–2 severity, and were generally manageable and resolved.

2104 The FDA's Assessment: The FDA generally agrees that the overall AESI profile of atezolizumab
2105 SC in IMscin001 Part 2 was generally consistent with the known safety profile of atezolizumab
2106 IV.

2107 The Applicant defined an immune related AE as a suspected event which based on medical
2108 review is consistent with an immune mediated mechanism of action, with no alternative
2109 etiologies. Additionally, the Applicant indicated in response to an information request submitted
2110 on July 12, 2023 that receipt of immune modulating medications such as systemic corticosteroids
2111 was required for an event to be considered an immune-mediated adverse event. Additionally, the
2112 Applicant indicated in response to an information request submitted on July 12, 2023 that receipt
2113 of immune modulating medications such as systemic corticosteroids was required for an event to
2114 be considered an immune-mediated adverse event.

2115 Per the Applicant, AESIs included, but were not limited to, cases of potential drug-induced liver
2116 injury, suspected transmission of an infectious agent by the study treatment, pneumonitis, colitis,
2117 diabetes mellitus, pancreatitis, adrenal insufficiency, hyperthyroidism, hypophysitis, hepatitis,
2118 systemic lupus erythematosus, Guillain-Barré syndrome, myasthenic syndrome or myasthenia
2119 gravis, meningoencephalitis, events suggestive of hypersensitivity, infusion-related reactions,
2120 cytokine-release syndrome, hemophagocytic lymphohistiocytosis, macrophage activation
2121 syndrome, nephritis, ocular toxicities (e.g., uveitis, retinitis, optic neuritis), and myositis.

2122 AESIs reported in IMscin001 are shown in the table below. The majority of AESIs were
2123 Grade 1–2 in severity. There was one Grade 5 AESI (PT: toxic epidermal necrolysis) reported in
2124 the Atezo SC arm (0.4%) which was considered by the Investigator as treatment-related. See
2125 [FDA Table 27](#) for the narrative describing the fatal adverse event of toxic epidermal necrolysis.

2126 [FDA Table 41](#) summarizes the AESI observed in atezolizumab SC arm in comparison to
2127 atezolizumab IV in IMscin001.

2128 **FDA Table 41. Adverse Events of Special Interest in IMscin001**

Adverse Event of Special Interest (AESI)	ATEZO SC N = 247 N (%)		ATEZO IV N = 124 N (%)	
	All Grades	Grade 3-4	All Grades	Grade 3-4
Immune-Mediated Rash	20 (8)	3 (1.2)	13 (11)	0
Immune-Mediated Hepatitis	28 (11)	8 (3.2)	15 (12)	0
Immune-Mediated Hypothyroidism	25 (10)	0	8 (7)	0
Immune-Mediated Pneumonitis	5 (2)	0	1 (0.8)	0
Immune-Mediated Adrenal Insufficiency	2 (0.8)	0	0	0
Immune-Mediated Hyperthyroidism	6 (2.4)	0	1 (0.8)	0
Immune-Mediated Hypophysitis	1 (0.4)	0	0	0
Immune-Mediated Severe Cutaneous Reactions	1 (0.4)	1 (0.4)	0	0
Toxic Epidermal Necrolysis	1 (0.4)	0	0	0

2129 Source: ADAE (Analysis Dataset) 05-05-2023, data cutoff date: September 02, 2022.

2130 Variables used: USUBJID, TRT01A, AEDECOD, FASFL, AETOXGR, CQ01NAM, CQ04NAM, CQ06NAM, CQ10NAM, CQ16NAM, SMQ02NAM, SMQ03NAM, SMQ05NAM,
 2131 SMQ25NAM, SMQ28NAM.
 2132
 2133

2134 **8.2.5.2. Selected Adverse Events**

2135 Data: Overall, 4.5% of patients in the Atezo SC arm reported at least one ISR. The most frequent ISRs by PT (>1 patient) were
 2136 injection site pain (2%) and injection site reaction (2%). All ISRs were mild or moderate in nature and were well managed (8 patients
 2137 with Grade 1 events and 3 patients with Grade 2 events). None of these events were reported as serious, or led to treatment
 2138 interruptions, discontinuations, or required the use of corticosteroids.

2139 The Applicant’s Position: Overall, 4.5% of patients in Atezo SC reported at least one ISR versus 0% in Atezo IV. Given the new SC
 2140 route of administration for atezolizumab has a potential for local ISR and the difference between the SC arm and IV arm, ISR is
 2141 considered an ADR for atezolizumab SC. ISR has been added as an ADR for atezolizumab SC in the labeling information.

2142 The FDA’s Assessment: FDA agrees with the Applicant’s position. Given the different route of administration of atezolizumab SC
 2143 and infusion-related reactions included in the Warnings and Precautions section of the USPI for atezolizumab IV, FDA also evaluated
 2144 events of injection site reactions, hypersensitivity reactions, and incidence of anaphylaxis.

2145 **FDA Review of Potential Events of Hypersensitivity**

2146 For FDA’s review of potential events of hypersensitivity, FDA sent an information request on June 12, 2023, to the Applicant to
 2147 obtain narratives for the following adverse events: body temperature increased, bronchospasm, chills, drug hypersensitivity, erythema,
 2148 feeling hot, hot flush, hypersensitivity, hyperthermia, hypotension, hypoxia, orthostatic hypotension, injected related reaction,
 2149 presyncope, pyrexia, syncope, sinus tachycardia, tachycardia. There were no events of anaphylaxis reported. Based on review of the
 2150 narratives, there were three adverse events of Grade 1 pyrexia that occurred within 24 hours of receiving atezolizumab SC. Given the
 2151 temporality of the adverse events in relationship to receiving atezolizumab SC and additional details in the narratives, the three events
 2152 were considered as potentially related to atezolizumab SC.

2153 Brief narratives of these adverse events are provided in [FDA Table 42](#) below.

2154 **FDA Table 42. Potential Adverse Events of Hypersensitivity for Patients Who Received Atezolizumab SC in IMScin001 Part 2**

Patient ID	Narrative	Adverse Event	FDA Assessment
(b) (6)	61 Year old male had a blood pressure of 90/60 (decreased from 110/70 at baseline) one hour after receiving Cycle 1 Day 1 of atezolizumab SC. The patient remained under observation in clinic and 5 hours after receiving atezolizumab SC, the patient experienced a Grade 1 event of facial hot flush (preferred term listed as “feeling hot”. Approximately 10 hours after receiving atezolizumab SC, the patient experienced Grade 1 pyrexia with fever to 38 °C. Fever resolved without intervention on the same day and the patients was discharged home from clinic. On Cycle 2 Day 1 of atezolizumab SC administration, the patient’s blood pressure dropped to 80/60 approximately 4 hours after the injection. The patient also experienced Grade 1 pyrexia with fever to 38.5 °C. The patient received ibuprofen and a single dose of amoxicillin/ clavulanic acid. Hypotension and fever fully resolved by cycle 2 day 3.	Pyrexia	Given the temporal relationship between hypotension and fever with receipt of atezolizumab SC, FDA determined these events are likely related to atezolizumab SC and may be consistent with an adverse event of hypersensitivity.

Patient ID	Narrative	Adverse Event	FDA Assessment
(b) (6)	63-year-old-female developed Grade 1 pyrexia with fever to 38.9 °C in the evening after the first dose of atezolizumab SC. She was treated with ketorolac fever resolved on day 2.	Pyrexia	Given the temporal relationship between the onset of fever and receipt of atezolizumab SC, FDA determined this was likely related to atezolizumab SC and may be consistent with an adverse event of hypersensitivity.
(b) (6)	60-year-old-male developed Grade 1 pyrexia on Cycle 2 Day 1 of atezolizumab SC. The patient’s temperature was not reported. No treatment was given and pyrexia was resolved on the same day.	Pyrexia	Based on the information provided and given the temporal relationship between the onset of fever and receipt of atezolizumab SC, FDA determined this was likely related to atezolizumab SC and may be consistent with an adverse event of hypersensitivity.

2155 Source: Patient Narratives

2156 These three cases of pyrexia, including one event with associated hypotension, are likely to be related with receiving atezolizumab SC
 2157 and appear consistent with events of hypersensitivity. However, all events were Grade 1 that resolved with minimal or no intervention.
 2158 Thus, FDA did not determine that “hypersensitivity” should be included in the Warnings and Precautions section of the USPI for
 2159 TECENTRIQ HYBREZA.

2160 **FDA Review of Injection Related Reactions**

2161 To evaluate injection related reactions, FDA requested narratives from the Applicant on June 12, 2023. In total, 11 patients (4.5%)
 2162 treated with atezolizumab SC in IMScin001 Part 2 experienced the following events that FDA determined were consistent with local
 2163 injection site reactions: of injection site pain, injection site rash, injection site reaction, injection site erythema, injection related
 2164 reaction, drug hypersensitivity, and hypersensitivity. The narratives described events of pain, edema, erythema, rash, or bruising. Most
 2165 events were Grade 1, with only three Grade 2 adverse events. There were no Grade 3 to Grade 5 adverse events of local injection site
 2166 reactions. “Local injection site reactions” has been included in the USPI for TECENTRIQ HYBREZA (atezolizumab SC) as a
 2167 clinically relevant adverse reaction in < 10% of patients.

2168 **8.2.6. Clinical Outcome Assessment (COA) Analyses**
2169 **Informing Safety/Tolerability**

2170 Data: At most visits, a similar proportion of patients in both arms reported being not at all, a
2171 little, quite a bit, or very much bothered by treatment symptoms (for Cycles 1–4, the proportion
2172 of patients who were not at all bothered by treatment symptoms was 46%–57% in Atezo SC vs.
2173 43%–50% in Atezo IV).

2174 The Applicant’s Position: Patients in both treatment arms of Part 2 of IMscin001 reported being
2175 comparably affected or bothered by treatment symptoms.

2176 The FDA’s Assessment: FDA relied on the results of IMscin002 to inform the patient experience
2177 regarding administration route. See Section 19.6 below for further details.

2178 **8.2.7. Safety Analyses by Demographic Subgroups**

2179 Data: The incidence of AEs was analyzed by intrinsic factors (age, [REDACTED], and race) and
2180 extrinsic factors (region, tobacco use history, ECOG) in IMscin001.

2181 Since the majority of patients were under 75 years old, subgroup analyses by age were only
2182 meaningful for the <65 and 65–74 years old subgroups. Between arms, there was no noteworthy
2183 difference in the safety profile for these two subgroups. Within each arm, there was no
2184 noteworthy difference in the safety profile between the subgroups. Within and between arms,
2185 there was no clinically relevant difference in the safety profile of atezolizumab by [REDACTED]. Due to
2186 low numbers of patients in subgroups other than White, subgroup analyses by race are not
2187 considered meaningful. There was no noteworthy difference in the safety profile for the White
2188 subgroup.

2189 Since the majority of patients were recruited in Asia-Pacific, Central/South America, and
2190 Europe/Middle East, subgroup analyses by region were only meaningful for these three
2191 subgroups. Between arms, there was no noteworthy difference in the safety profile for these three
2192 subgroups. Within each arm, there was no noteworthy difference in the safety profile between
2193 the subgroups. Since the majority of patients were previous smokers, subgroup analyses by
2194 tobacco use history within each arm are not considered meaningful. Between arms, the safety
2195 profile was generally balanced for previous smokers, except for a higher ($\geq 10\%$) incidence of
2196 Grade 3–4 AEs in Atezo IV compared to Atezo SC. Due to low numbers of ECOG 0 patients,
2197 subgroup analyses by ECOG performance status within each arm are not considered meaningful.
2198 Between arms, the safety profile was generally balanced for ECOG 1 patients, except for a
2199 higher ($\geq 10\%$) incidence of Grade 3–4 AEs in Atezo IV compared to Atezo SC.

2200 The Applicant’s Position: In IMscin001 Part 2, there was no evidence of any clinically relevant
2201 differences in the atezolizumab safety profile across subgroups with sufficient sample size based
2202 on age, [REDACTED], race, geographic region, history of tobacco use, baseline ECOG status.

2203 The FDA’s Assessment: FDA agrees with the Applicant’s assessment that no overall differences
2204 in safety of atezolizumab SC were observed between patients aged 65 years or older and younger
2205 adult patients. FDA did not independently review AEs by race or performance status.

2206 **8.2.8. Specific Safety Studies/Clinical Trials**

2207 The Applicant's Position: No studies were conducted to evaluate a specific safety concern with
2208 atezolizumab SC.

2209 The FDA's Assessment: FDA agrees with Applicant's position.

2210 **8.2.9. Additional Safety Explorations**

2211 **Human Carcinogenicity or Tumor Development**

2212 The Applicant's Position: No new information is provided in the current submission.

2213 The FDA's Assessment: FDA agrees with the Applicant's position.

2214 **Human Reproduction and Pregnancy**

2215 The Applicant's Position: There were no pregnancies in IMscin001.

2216 The FDA's Assessment: FDA agrees with the Applicant's position.

2217 **Pediatrics and Assessment of Effects on Growth**

2218 The Applicant's Position: No studies of atezolizumab SC have been performed in children and
2219 adolescents below 18 years of age (i.e., there is no data available). The Applicant received the
2220 Agreed Initial Pediatric Study Plan Agreement for this study from the Agency on March 9, 2022.

2221 The FDA's Assessment: FDA agrees with the Applicant's position. Refer to Section 10
2222 Pediatrics in the Assessment Aid for additional discussion.

2223 **Overdose, Drug Abuse Potential, Withdrawal, and Rebound**

2224 The Applicant's Position: No new information is provided in the current submission.

2225 The FDA's Assessment: The FDA agrees with Applicant's position.

2226 **8.2.10. Safety in the Postmarket Setting**

2227 **Safety Concerns Identified through Postmarket Experience**

2228 The Applicant's Position: Not applicable because the atezolizumab SC formulation is not
2229 currently registered or approved in the US or in any other part of the world.

2230 The FDA's Assessment: FDA agrees with the Applicant's position.

2231 **Expectations on Safety in the Postmarket Setting**

2232 The Applicant's Position: Not applicable.

2233 The FDA's Assessment: The FDA agrees.

2234

8.2.11. Integrated Assessment of Safety

2235 The Applicant's Position: Results from IMscin001 demonstrated that atezolizumab SC was well
2236 tolerated. The safety profile in Atezo SC was comparable with the safety profile in Atezo IV and
2237 consistent with the well-established safety profile in the monotherapy setting across multiple
2238 indications. No new safety concerns were identified for atezolizumab in this study. Injection site
2239 reactions associated with atezolizumab SC was low (4.5%), mostly Grade 1 events in severity
2240 and were well managed. Given the new SC route of administration for atezolizumab has a
2241 potential for local ISR and the difference between the SC arm and IV arm, ISR is considered an
2242 ADR for atezolizumab SC. The main safety risks associated with atezolizumab are immune-
2243 mediated events, a checkpoint inhibitor class-effect. The proportion of patients who experienced
2244 immune-mediated events was comparable between Atezo SC and IV. Overall, these events were
2245 mostly low grade, well managed, and resolved. The current labeling information provides
2246 adequate guidance to physicians on the management of immune-mediated AEs, which are
2247 monitored through routine pharmacovigilance activities.

2248 Immunogenicity analyses showed that the post-baseline treatment-emergent ADA to
2249 atezolizumab incidence in Atezo SC was comparable to Atezo IV and there did not appear to be
2250 a clinically relevant impact of anti-atezolizumab antibodies on pharmacokinetics, efficacy, or
2251 safety in either treatment arm.

2252 The FDA's Assessment: FDA agrees that the observed safety profile of atezolizumab SC is
2253 acceptable when considered in the context of a life-threatening disease and comparable to the
2254 safety profile for the atezolizumab IV formulation. FDA reviewed safety data from IMscin001
2255 Part 2 based on an April 26, 2022, data cutoff date as well as data with a data cutoff date of
2256 September 2, 2022, which provided approximately 4 additional months of follow up.

2257 Based on the September 2, 2022, data cutoff date, the most common ($\geq 10\%$) adverse reactions
2258 of any grade for patients treated with atezolizumab SC were fatigue (19%), musculoskeletal pain
2259 (15%), cough (13%), dyspnea (12%), and decreased appetite (11%). Dosage interruptions due to
2260 an adverse reaction occurred in 32% of patients on the atezolizumab SC arm. Adverse reactions
2261 which required dosage interruption in $\geq 1\%$ of patients included COVID-19 (4.9%), increased
2262 aspartate aminotransferase (2.8%), increased alanine aminotransferase (2.4%), pneumonia
2263 (2.0%), anemia (1.6%), dyspnea (1.6%), and viral respiratory tract infection (1.2%). Serious
2264 adverse reactions occurred in 19% of patients who received atezolizumab SC. Serious adverse
2265 reactions ($>1\%$) included pneumonia (2.4%), myocardial infarction (1.6%), and pleural effusion
2266 (1.2%). Fatal adverse reactions occurred in 6% of patients who received atezolizumab SC due to
2267 pneumonia (2.4%), myocardial infarction (1.2%), head injury (0.4%), ischemic stroke (0.4%),
2268 pleural effusion (0.4%), pulmonary embolism (0.4%), respiratory tract infection (0.4%), sepsis
2269 (0.4%), and toxic epidermal necrolysis (0.4%).

2270 No additional safety signals for atezolizumab SC were identified, compared with the known
2271 safety profile of atezolizumab IV, other than local injection site reactions. In total, 11 patients
2272 (4.5%) treated with atezolizumab SC in IMscin001 Part 2 experienced local injection site
2273 reactions of pain, edema, erythema, rash, or bruising. All events were Grade 1 or Grade 2
2274 adverse events. "Local injection site reactions" has been included in the USPI for TECENTRIQ
2275 HYBREZA (atezolizumab SC) as a clinically relevant adverse reaction in $< 10\%$ of patients.

2276 In conclusion, the safety profile of atezolizumab SC is comparable to the safety profile of
2277 atezolizumab IV and offers a new route of administration for patients. The safety profile is
2278 acceptable in the intended patient populations.

2279 SUMMARY AND CONCLUSIONS

2280 8.3. Statistical Issues

2281 The FDA's Assessment: There were no major statistical issues identified during review of this
2282 application. The IMscin001 Part 2 trial was designed to demonstrate the comparability of PK
2283 endpoints, comparing the atezolizumab SC to the atezolizumab IV. This trial was not designed to
2284 evaluate efficacy of atezolizumab SC as compared to atezolizumab IV. Efficacy endpoints
2285 including ORR, PFS and OS were included as secondary endpoints and were considered
2286 descriptive due to lack to pre-specified testing plan.

2287 The analyses of ORR and PFS were based on the data cut-off date of April 26, 2022. At that
2288 time, only 33% of patients had an OS event in the ITT population and data were not considered
2289 robust by the review team. As a result, an information request was sent to the Applicant on April
2290 25, 2023, requesting an updated analysis of OS with an additional 10 months of follow up. In
2291 response to FDA's information request, the Applicant submitted an updated OS analysis and the
2292 corresponding dataset with the data cut off date of January 16, 2023. In the updated OS analysis,
2293 60% of patients in the ITT population had an OS event. No major differences in the efficacy
2294 results between the two treatment arms were identified during the review.

2295 No major dataset or statistical issues were identified for the IMscin002 trial during the review.

2296 8.4. Conclusions and 2297 Recommendations

2298 The FDA's Assessment: IMscin001 (BP40657, Part 2) was a randomized (2:1), open-label,
2299 multiregional clinical trial comparing the pharmacokinetics, efficacy and safety of atezolizumab
2300 SC to atezolizumab IV in patients with advanced or metastatic NSCLC who have not received
2301 prior anti-PD-(L)1 antibody therapy and who had prior disease progression on platinum-based
2302 chemotherapy. The trial results demonstrated comparability of C_{trough} at Cycle 1 and $AUC_{0-21days}$
2303 at Cycle 1 of atezolizumab SC compared to atezolizumab IV. The geometric mean ratio (GMR)
2304 for the observed serum C_{trough} at Cycle 1 was 1.05 (90% CI: 0.88, 1.24) and $AUC_{0-21days}$ at Cycle
2305 1 was 0.87 (90% CI: 0.83, 0.92) for atezolizumab exposure with 90% CIs within 80 to 125%.
2306 The lower limit of the 90% CI of the GMR for the co-primary endpoints of C_{trough} and AUC_{0-}
2307 $21days$ are above 0.8 thereby demonstrating comparable PK exposure of atezolizumab SC and
2308 atezolizumab IV. See Section 6 Clinical Pharmacology of the Assessment Aid for additional
2309 information.

2310 Analyses of the secondary efficacy endpoints of overall response rate (ORR) per RECIST v1.1
2311 by investigator, progression free survival (PFS) by investigator, and overall survival (OS) were
2312 all descriptive. At the time of this BLA submission with a data cutoff date of April 26, 2022, the

2313 ORR for patients treated with atezolizumab SC was 9% (95% CI: 5, 13) and was 8% (95% CI: 4,
2314 14) for atezolizumab IV. At the same data cutoff date, median PFS was 2.8 months (95% CI: 2.1,
2315 3.1) for atezolizumab SC and 2.9 months (95% CI: 1.7, 42) for atezolizumab IV. However, only
2316 33% of patients had an OS event in the intention-to-treat (ITT) population and OS data were not
2317 considered robust by the FDA review team. The Applicant submitted an updated OS analysis
2318 with 10 additional months of follow-up, based on a data cutoff date of January 16, 2023. In the
2319 updated OS analysis, 60% of patients in the ITT population had an OS event. The median OS
2320 was 10.7 months (95%: CI 8.5, 13.8) for atezolizumab SC and 10.1 months (95% CI: 7.5, 12.1)
2321 for atezolizumab IV (HR 0.88; 95% CI 0.67, 1.16). Based on descriptive analyses, no differences
2322 in ORR, PFS, or OS were observed between patients who received atezolizumab SC and
2323 atezolizumab IV. Safety was an additional secondary endpoint. Local injection site reactions for
2324 atezolizumab SC was the only newly identified safety signal compared to the known safety
2325 profile of atezolizumab IV.

2326 The development approach of atezolizumab SC is consistent with the FDA Guidance on
2327 “Providing Clinical Evidence of Effectiveness for Human Drug and Biological Products”, which
2328 states the following: “In certain cases, effectiveness of an approved drug product for a new
2329 indication, or effectiveness of a new product, may be adequately demonstrated without additional
2330 adequate and well-controlled clinical efficacy trials. Ordinarily, this will be because other types
2331 of data provide a way to apply the known effectiveness to a new population or a different dose,
2332 regimen or dosage form.” When being applied to different doses, regimens, or dosage forms, the
2333 above FDA Guidance states that “it may be possible to conclude that a new dose, regimen, or
2334 dosage form is effective on the basis of PK data without an additional clinical efficacy trial”.

2335 In the current application, PK data, together with descriptive analyses of efficacy endpoints (i.e.,
2336 ORR, PFS, and OS) from IMscin001 Part 2 can bridge to establish efficacy results between
2337 atezolizumab SC and atezolizumab IV for all approved adult indications for atezolizumab IV.
2338 The well-established efficacy and safety profile of atezolizumab IV also supports approval of
2339 atezolizumab SC for the indications not studied in IMscin001 Part 2. The results of IMscin001
2340 Part 2 demonstrate substantial evidence of effectiveness for atezolizumab SC. Based on a
2341 favorable risk-benefit assessment, the review team recommends traditional approval of
2342 atezolizumab SC for the following adult indications:

- 2343 • Non-Small Cell Lung Cancer (NSCLC):
- 2344 ○ as adjuvant treatment following resection and platinum-based chemotherapy for adult
2345 patients with Stage II to IIIA NSCLC whose tumors have PD-L1 expression on $\geq 1\%$ of
2346 tumor cells, as determined by an FDA-approved test.
 - 2347 ○
 - 2348 ○ for the first-line treatment of adult patients with metastatic NSCLC whose tumors have
2349 high PD-L1 expression (PD-L1 stained $\geq 50\%$ of tumor cells [TC $\geq 50\%$] or PD-L1
2350 stained tumor-infiltrating immune cells [IC] covering $\geq 10\%$ of the tumor area [IC $\geq$
2351 10%]), as determined by an FDA-approved test, with no EGFR or ALK genomic tumor
2352 aberrations.
 - 2353 ○

- 2354 ○ in combination with bevacizumab, paclitaxel, and carboplatin, for the first line treatment
2355 of adult patients with metastatic non-squamous NSCLC with no EGFR or ALK genomic
2356 tumor aberrations.
2357 ○
2358 ○ in combination with paclitaxel protein-bound and carboplatin for the first-line treatment
2359 of adult patients with metastatic non-squamous NSCLC with no EGFR or ALK genomic
2360 tumor aberrations
2361 ○
2362 ○ for the treatment of adult patients with metastatic NSCLC who have disease progression
2363 during or following platinum-containing chemotherapy. Patients with EGFR or ALK
2364 genomic tumor aberrations should have disease progression on FDA-approved therapy
2365 for NSCLC harboring these aberrations prior to receiving TECENTRIQ HYBREZA.
- 2366 • Small Cell Lung Cancer (SCLC):
- 2367 ○ in combination with carboplatin and etoposide, for the first-line treatment of adult
2368 patients with extensive-stage small cell lung cancer (ES-SCLC).
- 2369 • Hepatocellular Carcinoma (HCC):
- 2370 ○ in combination with bevacizumab for the treatment of adult patients with unresectable or
2371 metastatic HCC who have not received prior systemic therapy.
- 2372 • Melanoma
- 2373 ○ in combination with cobimetinib and vemurafenib for the treatment of adult patients with
2374 BRAF V600 mutation-positive unresectable or metastatic melanoma as determined by an
2375 FDA-approved test.
- 2376 • Alveolar Soft Part Sarcoma (ASPS)
- 2377 ○ for the treatment of adult patients with unresectable or metastatic ASPS

2378 **8.4.1. Approach to Substantial Evidence of** 2379 **Effectiveness**

2380 Select from the options below to indicate how substantial evidence of effectiveness (SEE) was
2381 established (if applicable). If there are multiple indications, repeat items 1–3 for each indication.

- 2382 1. Verbatim indication (*enter approved indication if the application was approved and the*
2383 *Applicant's proposed indication if the application received a complete response*):

2384 [Click here to enter the verbatim indication.](#)

- 2385 2. SEE was established with (*check **one** of the options for traditional or accelerated*
2386 *approval pathways and complete response not due to lack of demonstrating SEE*)

2387 a. Adequate and well-controlled clinical investigation(s):

- 2388 i. Two or more adequate and well-controlled clinical investigations, **OR**

2390 ii. One adequate and well-controlled clinical investigation with highly persuasive
2391 results that is considered to be the scientific equivalent of two clinical
2392 investigations

2393 **OR**

2394 b. One adequate and well-controlled clinical investigation and confirmatory
2395 evidence^{1,2,3}

2396 **OR**

2397 c. Evidence that supported SEE from a prior approval (*e.g.*, 505(b)(2) application
2398 relying only on a previous determination of effectiveness; extrapolation; over-the-
2399 counter switch)²

2400

2401 3. Complete response, if applicable

2402 a. SEE was established

2403 b. SEE was not established (*if checked, omit item 2*)

2404

2405 ¹ FDA draft guidance for industry *Demonstrating Substantial Evidence of Effectiveness for Human Drug and*
2406 *Biological Products* (2019)

2407 ² FDA guidance for industry *Providing Clinical Evidence of Effectiveness for Human Drugs and Biological Products*
2408 (1998)

2409 ³ *Demonstrating Substantial Evidence of Effectiveness Based on One Adequate and Well-Controlled Clinical*
2410 *Investigation and Confirmatory Evidence* (2023)]

2411

2412

2413

2414

X

X

2415

2416 Somak Chatterjee

Xiaoxue Li

2417 Primary Statistical Reviewer

Statistical Team Leader

X

X

2418

2419 Katie Chon

Paz Vellanki

2420 Mona Choudhary

Cross-Disciplinary Team Leader

2421 Primary Clinical Reviewers

Supervisory Associate Director (Acting)

2422

2423 **9. Advisory Committee Meeting and Other**
2424 **External Consultations**

2425 The FDA's Assessment: FDA did not refer this application to an advisory committee as no
2426 significant efficacy or safety issues were identified during the review that required external input
2427 from the proposed indications.

2428 **10. Pediatrics**

2429 The Applicant's Position: Not applicable as the Applicant has not proposed any pediatric
2430 sections in the proposed labeling.

2431 The FDA's Assessment: Title V of the FDA Reauthorization Act of 2017 (FDARA) amended the
2432 Pediatric Research Equity Act (PREA) to create section 505B(a)(1)(B), which requires that any
2433 original marketing application for certain adult oncology drugs (i.e., those intended for treatment
2434 of an adult cancer and with molecular targets that FDA has determined to be substantially
2435 relevant to the growth or progression of a pediatric cancer) that are submitted on or after August
2436 18, 2020, contain reports of molecularly targeted pediatric cancer investigations. These
2437 molecularly targeted pediatric cancer investigations must be "designed to yield clinically
2438 meaningful pediatric study data, gathered using appropriate formulations for each age group for
2439 which the study is required, regarding dosing, safety, and preliminary efficacy to inform
2440 potential pediatric labeling" (section 505B(a)(3)). Applications for drugs or biological products
2441 for which orphan designation has been granted and which are subject to the requirements of
2442 section 505B(a)(1)(B), are not exempt from PREA (see section 505B(k)(2)) and are required to
2443 include plans to conduct the molecularly targeted pediatric investigations as required, unless
2444 such investigations are waived or deferred.

2445 (b) (4)
2446 (b) (4) An agreed iPSP was reached on

2447 March 9, 2022, but this agreed iPSP was not subsequently amended following the approval of
2448 the alveolar soft part sarcoma (ASPS) indication in adults and pediatric patients 2 years of age
2449 and older with unresectable or metastatic alveolar soft part sarcoma (ASPS). During the course
2450 of review of this BLA, the review team, in consultation with the Oncology Subcommittee of the
2451 Pediatric Review Committee (OCE PeRC) and the Office of Regulatory Policy, determined that
2452 it was appropriate to issue a postmarketing requirement under FDARA given the potential
2453 clinical benefits of a subcutaneous formulation of atezolizumab in adolescent patients. See
2454 Section 13 of the Assessment Aid regarding Postmarketing Requirements and Commitment.

2455 On July 25, 2024, the Division met with the Applicant to discuss the reasoning for issuing a
2456 PREA PMR. (b) (4)
2457 (b) (4)
2458 (b) (4)
2459 (b) (4)
2460 (b) (4)
2461 (b) (4)

2462 11. Labeling Recommendations

2463 The Applicant's Position: The USPI submitted to the Agency is the initial USPI for atezolizumab
2464 SC.

2465 The FDA's Assessment: The proposed labeling submitted by the Applicant required extensive
2466 revision by FDA. (b) (4)

2467 (b) (4)
2468 (b) (4)
2469 (b) (4). FDA included supportive safety and efficacy data from the approved intravenous
2470 atezolizumab labeling to support approval for the indications not studied in IMscin001.

2471 The format, language, and content of the proposed labeling was evaluated and revised for
2472 consistency with 21 Code of Federal Regulations (CFR), labeling guidances and current labeling
2473 practices of the Office of Oncologic Diseases. The table below summarizes key changes.

2474 **FDA Table 43. FDA Labeling Revisions**

Label Section	FDA Revision / Agreed Upon Labeling
HIGHLIGHTS	FDA included additional details dosage and administration details. FDA included ADVERSE REACTIONS for each indication.
1 INDICATIONS AND USAGE	FDA revised (b) (4) to monotherapy because TECENTRIQ HYBREZA is a combination product containing atezolizumab and hyaluronidase-tqjs.
2.2 Important Dosage and Administration Information	FDA added text: to reduce the risk of medication errors describe switching between products clarify that this product is not indicated for pediatric patients provide proper administration instructions
2.3 Recommended Dosage and	Table 1 was revised to follow the order and precise text of the indications in Section 1.

Label Section	FDA Revision / Agreed Upon Labeling
Administration Instructions	
2.5 Preparation Instructions	Revised and re-ordered for clarity.
2.6 Storage Instructions	Revised for clarity.
5 WARNINGS AND PRECAUTIONS	This section of labeling follows the anti-PD-(L)1 harmonized format. For this label, FDA incorporated the most severe adverse reactions (AR) in the intravenous atezolizumab label at the beginning of each AR text and then described the ARs observed with the use of TECENTRIQ HYBREZA, and then included text to describe the ARs observed when intravenous atezolizumab was used in combination with other drugs to support these indications (<i>Intravenous Atezolizumab in Combination with Cobimetinib and Vemurafenib</i>). The purpose of this format is to present a complete safety profile, while avoiding copying the entire WARNINGS AND PRECAUTIONS section from the intravenous atezolizumab labeling.
6.1 Clinical Trials Experience	Adverse Reactions of TECENTRIQ HYBREZA in Adult Patients with NSCLC: text revised and edited for consistency with oncology labeling. This text described the safety observed in the IMscin001 study that enrolled patients with locally advanced or metastatic NSCLC. FDA included linkage statements and subheadings to support each of the indications in Section 1 (e.g., Adverse Reactions in Adult Patients with NSCLC Treated with Intravenous Atezolizumab) and included the complete safety data from each pivotal trial supporting each indication.
8.5 Geriatric Use	FDA added complete Geriatric Use data from the intravenous atezolizumab safety datasets 2,616 adult patients with metastatic NSCLC and other tumor types treated with monotherapy intravenous atezolizumab 2,421 adult patients with NSCLC and EC-SCLC treated with intravenous atezolizumab in combination with other antineoplastic drugs in clinical studies
12.3 Pharmacokinetics	The section describing the major outcome measure for the IMscin001 study as the comparison of the pharmacokinetics of TECENTRIQ HYBREZA to intravenous atezolizumab was revised for clarity.
12.6 Immunogenicity	Section revised for clarity and to include full immunogenicity information from intravenous atezolizumab.
14 CLINICAL STUDIES	14.1 IMscin001 trial description revised for clarity and brevity. 14.2 -14.5 Linkage statements were included to introduce the efficacy data from intravenous atezolizumab to support all of the indications. Complete efficacy data from intravenous atezolizumab were added. The Applicant proposed section 14.6 Patient Experience to present the results from the IMscin002 study that compared subjective preference information about route of administration (intravenous vs. subcutaneous). Patients were randomized to receive 3 cycles of subcutaneous TECENTRIQ HYBREZA followed by 3 cycles of intravenous atezolizumab (Arm A) or to receive 3 cycles of intravenous atezolizumab followed by 3 cycles of subcutaneous TECENTRIQ HYBREZA (Arm B).
Medication Guide	Revised for consistency with the Prescribing Information.

2475

2476 **12. Risk Evaluation and Mitigation Strategies** 2477 **(REMS)**

2478 The FDA's Assessment: The clinical review team determined that a risk evaluation and
2479 mitigation strategy (REMS) was not required to ensure safe and effective use of atezolizumab
2480 and hyaluronidase-tqjs for the indicated populations. Recommendations for the safe and effective
2481 use of atezolizumab SC are made in labeling and FDA-approved patient labeling (Medication
2482 Guide). There are no additional risk management strategies required beyond the recommended
2483 labeling. Although atezolizumab SC can cause severe/serious toxicity, it will be prescribed by
2484 oncologists who, by training and experience, understand how to monitor and manage such
2485 toxicities.

2486 **13. Postmarketing Requirements and** 2487 **Commitment**

2488 The FDA's Assessment: Please see Section [10](#) of the Assessment Aid for additional information.
2489 The following clinical postmarketing requirement will be issued for this application:

2490 PMR-PREA

2492 *Conduct a molecularly targeted pediatric cancer investigation using an age-appropriate*
2493 *formulation of atezolizumab and hyaluronidase-tqjs in pediatric patients 12 years of age*
2494 *and older.*

2495
2496 *Final Report Submission: MM/YYYY*

2497 2498 PMR Rationale

2499 On December 9, 2022, FDA approved atezolizumab (BLA 761034/S-047) for adult and
2500 pediatric patients 2 years of age and older with unresectable or metastatic alveolar soft
2501 part sarcoma (ASPS). Atezolizumab (Tecentriq) was granted orphan designation for the
2502 treatment of soft tissue sarcoma.

2503 Atezolizumab (Tecentriq) is also approved for the following indications in adult patients:

- 2504 • Tecentriq, as a single agent, is indicated for the first-line treatment of adult
2505 patients with metastatic non-small cell lung cancer (NSCLC) whose tumors
2506 have high PD-L1 expression (PD-L1 stained $\geq 50\%$ of tumor cells [TC $\geq$
2507 50%] or PD-L1 stained tumor-infiltrating immune cells [IC] covering $\geq 10\%$
2508 of the tumor area [IC $\geq 10\%$]), as determined by an FDA-approved test, with
2509 no EGFR or ALK genomic tumor aberrations.
- 2510 • Tecentriq, in combination with bevacizumab, paclitaxel, and carboplatin, is
2511 indicated for the first-line treatment of adult patients with metastatic
2512 nonsquamous NSCLC with no EGFR or ALK genomic tumor aberrations.

- 2513 • Tecentriq, in combination with paclitaxel protein-bound and carboplatin, is
2514 indicated for the first-line treatment of adult patients with metastatic
2515 nonsquamous NSCLC with no EGFR or ALK genomic tumor aberrations.
- 2516 • Tecentriq, as a single agent, is indicated for the treatment of adult patients
2517 with metastatic NSCLC who have disease progression during or following
2518 platinum-containing chemotherapy. Patients with EGFR or ALK genomic
2519 tumor aberrations should have disease progression on FDA-approved therapy
2520 for NSCLC harboring these aberrations prior to receiving TECENTRIQ.
- 2521 • Tecentriq, as a single agent, is indicated as adjuvant treatment following
2522 resection and platinum-based chemotherapy for adult patients with stage II to
2523 IIIA non-small cell lung cancer (NSCLC) whose tumors have PD-L1
2524 expression on $\geq 1\%$ of tumor cells, as determined by an FDA-approved test.
- 2525 • Tecentriq, in combination with carboplatin and etoposide, is indicated for the
2526 first-line treatment of adult patients with extensive-stage small cell lung
2527 cancer (ES-SCLC).
- 2528 • Tecentriq, in combination with bevacizumab, is indicated for the treatment of
2529 patients with unresectable or metastatic hepatocellular carcinoma (HCC) who
2530 have not received prior systemic therapy.
- 2531 • Tecentriq, in combination with cobimetinib and vemurafenib, is indicated for
2532 the treatment of patients with BRAF V600 mutation-positive unresectable or
2533 metastatic melanoma.

2534 Title V of the FDA Reauthorization Act of 2017 (FDARA) amended the Pediatric
2535 Research Equity Act (PREA) to create section 505B(a)(1)(B), which requires that any
2536 original marketing application for certain adult oncology drugs (i.e., those intended for
2537 treatment of an adult cancer and with molecular targets that FDA has determined to be
2538 substantially relevant to the growth or progression of a pediatric cancer) that are
2539 submitted on or after August 18, 2020, contain reports of molecularly targeted pediatric
2540 cancer investigations. These molecularly targeted pediatric cancer investigations must be
2541 “designed to yield clinically meaningful pediatric study data, gathered using appropriate
2542 formulations for each age group for which the study is required, regarding dosing, safety,
2543 and preliminary efficacy to inform potential pediatric labeling” (section 505B(a)(3)).
2544 Applications for drugs or biological products for which orphan designation has been
2545 granted and which are subject to the requirements of section 505B(a)(1)(B), are not
2546 exempt from PREA (see section 505B(k)(2)) and are required to include plans to conduct
2547 the molecularly targeted pediatric investigations as required, unless such investigations
2548 are waived or deferred.

2549 (b) (4)
2550 (b) (4)
2551 (b) (4) An agreed iPSP was reached on March 9, 2022, but this
2552 agreed iPSP was not subsequently amended following approval of atezolizumab by
2553 intravenous administration for the ASPS indication in adults and pediatric patients 2
2554 years of age and older. Additionally, atezolizumab and hyaluronidase-tqjs is considered
2555 to be a new active ingredient.

2556 Therefore, the Applicant’s obligations under section 505B(a)(1)(B) of the FD&C Act are
 2557 to submit reports from a molecularly targeted pediatric cancer investigation of
 2558 atezolizumab and hyaluronidase-tqjs gathered using appropriate formulations for each
 2559 age group for which the study is required to assess the pharmacokinetics, dosing, and
 2560 preliminary safety and efficacy of atezolizumab co-formulated with hyaluronidase. Given
 2561 the rarity of the cancer types in pediatric patients less than 12 years of age that could
 2562 potentially benefit from investigational treatment with atezolizumab and hyaluronidase-
 2563 tqjs, a partial waiver of this requirement in pediatric patients less than 12 year of age is
 2564 justified.



2572 A CMC postmarketing commitment (PMC) will also be issued. Please refer to the OPQ
 2573 Executive Summary dated August 16, 2024, for full details.

2574 FDA PMC/PMR Checklist for Trial Diversity and U.S. Population Representativeness

The following were evaluated and considered as part of FDA’s review:		Is a PMC/PMR needed?
☐	The patients enrolled in the clinical trial are representative of the racial, ethnic, and age diversity of the U.S. population for the proposed indication.	☐ Yes ☒ No. However, there is extensive experience with atezolizumab IV in U.S. patients and in diverse patient populations. No clinically significant differences in the pharmacokinetics of atezolizumab have been observed based on race or age. Therefore, FDA is not requesting a Diversity PMC. See Section 8.1.2 of the Assessment Aid.
☐	Does the FDA review indicate uncertainties in the safety and/or efficacy findings by demographic factors (e.g., race, ethnicity, sex, age, etc.) to warrant further investigation as part of a PMR/PMC?	☐ Yes ☒ No
☐	Other considerations (e.g.: PK/PD), if applicable:	☒ Yes ☐ No

2575 **14. Division Director (DHOT) (NME ONLY)**

X

2576

2577 **15. Division Director (OCP)**

X

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2579 **16. Division Director (OB)**

X

2580

2581 **17. Division Director (Clinical)**

X

2582

2583

2584 **18. Office Director (or designated signatory**
2585 **authority)**

2586 *This application was reviewed by the Oncology Center of Excellence (OCE) per the OCE*
2587 *Intercenter Agreement. My signature below represents an approval recommendation for the*
2588 *clinical portion of this application under the OCE.*

X

2589
2590 Paz Vellanki
2591 Supervisory Associate Director (Acting)
2592

2593 **19. Appendices**

2594 **19.1. References**

2595 The Applicant's References:

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2601 [monograph/prescribing-information/DARZALEX+Faspro-pi.pdf](https://www.janssenlabels.com/package-insert/product-monograph/prescribing-information/DARZALEX+Faspro-pi.pdf)
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2651
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 2655 [clinical-trials](https://www.fda.gov/regulatory-information/search-fda-guidance-documents/non-inferiority-clinical-trials).
 2656

2657 **19.2. Financial Disclosure**

2658 The Applicant’s Position: A total of 433 out of 433 (100%) principal investigators and
 2659 sub-investigators responded for Part 2 of Study IMscin001. All centers that either screened or
 2660 enrolled patients during Part 2 of the Study (up until the 26 April 2022 CCOD) are included in
 2661 the calculation.

2662 Disclosable financial interests were recorded in 1 out of 433 (<0.25%) investigators who
 2663 participated in Part 2 of Study IMscin001. The investigator’s husband is a Sponsor employee.
 2664 The financial interest was terminated in February 2022.

2665 The FDA’s Assessment: FDA agrees.
 2666

2667 Covered Clinical Study (Name and/or Number): IMscin001 (BP40657)

Was a list of clinical investigators provided:	Yes ☒	No ☐ (Request list from Applicant)
Total number of investigators identified: <u>433</u>		
Number of investigators who are Sponsor employees (including both full-time and part-time employees): <u>1</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>NA</u> Significant payments of other sorts: <u>NA</u> Proprietary interest in the product tested held by investigator: <u>NA</u> Significant equity interest held by investigator in study: <u>NA</u> Sponsor of covered study: <u>NA</u>		
Is an attachment provided with details of the disclosable financial interests/arrangements:	Yes ☒	No ☐ (Request details from Applicant)
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) <u>0</u>		

Is an attachment provided with the reason:	Yes ☐	No ☒ (Since all investigators have provided a financial disclosure form, no Note to Files have been generated for Unable to Obtain Investigators.)

2668 *The table above should be filled by the Applicant, and confirmed/edited by the FDA.

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19.3. Nonclinical Pharmacology/Toxicology

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2672 Data: None.

2673 The FDA's Assessment: FDA agrees.

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19.4. OCP Appendices (Technical Documents Supporting OCP Recommendations)

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19.4.1. Population PK Analysis

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19.4.2. Executive Summary

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(2) The FDA's Assessment: Population PK analysis was conducted by the Applicant and evaluated by the Reviewer. The PK of atezolizumab was characterized by a two-compartment model with first-order absorption and clearance.

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(3) The population PK model described the observed data reasonably well. It was adequate to predict individual PK estimates for non-inferiority analysis of exposures and subsequent E-R analysis. Additional analyses were conducted by the Reviewer to evaluate the effect of ADA on CL with time-varying or time-static model. For atezolizumab, ADA as a static covariate appears more appropriate for evaluating its impact on CL from modeling perspective. Collectively, static subject-level treatment emergent ADA shows ~17-19% increase in CL, which is not considered clinically meaningful.

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19.4.3. PPK Assessment Summary

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The Applicant's Position:

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- Atezolizumab SC absorption was characterized by a first-order absorption with a bioavailability of 71.8% and an absorption rate constant of 0.304 per day.

2693

- 2694 • Hemoglobin and albumin were identified as significant covariates on the absorption
2695 parameters (F1 and KA, respectively), however these covariate effects were deemed not
2696 clinically meaningful, inducing less than 29% change from typical value.
- 2697 • The extended popPK model was adequate to predict atezolizumab pharmacokinetics after IV
2698 and SC administrations in IMscin001 and to predict individual exposure parameters.
- 2699 • Non-inferiority between 1875 mg SC Q3W and 1200 mg IV Q3W administration was
2700 demonstrated for AUC_{ss} and AUC_{inf} (Cycle 1 area under the serum concentration–time curve
2701 from time 0 extrapolated to infinity).

2702 **Table 44. Applicant Table of General Information**

General Information		
Objectives of PPK Analysis	Assess the pharmacokinetic of atezolizumab after SC administration in patients with NSCLC in IMscin001 through PPK analysis Identify the effect of covariates on atezolizumab SC absorption Derive exposure metrics of atezolizumab in IMscin001 patients	
Study Included	BP40657 (IMscin001)	
Dose(s) Included	1200 mg IV Q3W, 1200 mg Q2W SC in thigh, 1800 mg Q3W SC in thigh and abdomen, and 1875 mg Q3W SC in thigh.	
Population Included	Patients in IMscin001 with NSCLC, who had received at least one dose of atezolizumab (atezolizumab SC or atezolizumab IV) and had at least one evaluable post-dose PK sample in Part 1 (Cohorts 1 to 3) or Part 2 (IV Cohort 4, and SC Cohort 5) of IMscin001.	
Population Characteristics (FDA Table 45)	General	Median age of 64 years (ranged 27 to 85 years). 47.1% patients were ≥ 65 yr, 9.4% patients were >75 yr. Median weight of 68.1 kg (ranged 30.0 to 117 kg). 295 (67.8%) were male, 140 (32.2%) were female. White: 300 (69.0%), American Indian or Alaska Native: 24 (5.5%), Asian: 85 (19.5%), Black or African American: 3 (0.7%), Native Hawaiian or other Pacific Islander: 3 (0.7%), Multiple: 11 (2.5%), Unknown: 9 (2.1%). Hispanic or Latino: 114 (26.2%), Not Hispanic or Latino: 312 (71.7%), Not reported: 8 (1.8%), Unknown: 1 (0.2%).
	Organ Impairment	Hepatic (based on NCI-ODWG criteria): 382 (87.8%) normal, 49 (11.3%) mild, 4 (0.920%) moderate. Renal (based on eGFR): 174 (40.0%) normal, 196 (45.1%) mild, 65 (14.9%) moderate.
	Pediatrics (if any)	There were no patients under 18 years of age in the study.

Atezolizumab and Hyaluronidase-tqjs Solution for Subcutaneous Injection

No. of Patients, PK Samples, and BLQ (Table 1 of PPK report)	435 out of 436 patients (99.8%) were included in the analysis (in Cohort 5, one patient who received a single SC injection, in the upper arm, was excluded). Out of 3575 PK concentrations available, 374 (10.5%) were pre-dose BLQ and 82 (2.29%) were post-dose BLQ. An additional 5 (0.140%) and 14 (0.392%) detectable pre- and post-dose concentrations, respectively, were excluded from the analysis due to date/time recording issues. 3100 PK concentrations were included in the analysis.	
Sampling Schedule	Rich Sampling	There was no rich sampling sub-cohort in the study.
	In ITT Population	For Part 1, atezolizumab PK samples were collected at pre-dose, 8 hours, 2 days, 4 days, and 8 days post-dose in Cycle 1 (Cohorts 1 and 2) and in Cycles 1 and 2 (Cohort 3). Samples for maximum serum concentration post-IV administration were collected 30 minutes after IV infusion in Cycles 2, 3, 4, 8, 12, and 16 (Cohort 1) and Cycles 4 and 5 (Cohorts 2 and 3). Pre-dose samples were collected for Cycles 2, 3, 4, 8, 12, and 16 in all cohorts. An additional pre-dose Cycle 5 sample was collected in Cohorts 2 and 3. A sample was also collected at treatment discontinuation in all cohorts. For Part 2, serum samples for atezolizumab PK assessments were collected in the SC arm pre-dose on Day 1 of Cycles 1, 2, 3, 4, 8, 12, and 16 and post-dose on Days 1, 2 (further details on sample collection in study protocol version 5 or later), 4, and 8 of Cycle 1. Serum samples for atezolizumab PK assessments were collected in the IV arm pre-dose on Day 1 of Cycles 1, 2, 3, 4, 8, 12, and 16 and post-dose on Days 1, 4, and 8 of Cycle 1.
Covariates Evaluated	Static	Serum albumin, hemoglobin, serum creatinine, SC formulation, body weight, tumor burden, sex, age, creatinine clearance, ALP, ALT, AST, ECOG, PD-L1, race, ethnicity, hepatic impairment, renal impairment, geographical region, subject level treatment-emergent ADA.
	Time-varying	Site of administration.
Final Model	Summary	Acceptability [FDA's comments]
Software and Version	NONMEM (v7.3), PsN (v4.8.1), R (v4.0.1) with CRAN and Certara packages.	Yes

Model Structure	The atezolizumab pharmacokinetics after IV administration was previously described using a two-compartment disposition model with first-order elimination. The previous model was extended with the addition of an apparent first-order absorption rate constant (KA), and bioavailability (F1).	Yes
Model Parameter Estimates (FDA Table 46)	All parameters and variability terms, except KA and F1 and the residual errors, were fixed to the values in the IV model. Typical values of CL=0.200 L/d, Vc=3.28 L, Vp=3.63 L, Q=0.546 L/d, KA=0.304 per day, F1=71.8%.	Yes. The estimates for CL and V2 when unfixed, showed little bias (<10%) from the published model.
Uncertainty and Variability (RSE, IIV, Shrinkage, Bootstrap) (FDA Table 46)	For the absorption parameters (KA and F1): IIV was 34.6% for KA and 83.0% for F1. RSE is <5% for typical values, <38% for covariate effects, <25% for IIV, and <16% for residual errors. Shrinkage values were <40%. Proportional residual error estimated with the current data were substantially higher than the previously estimated in the IV popPK model (19.0% vs. 4.33%, respectively). Bootstrap was not performed for the analysis.	Yes. The RSE of absorption parameters is in acceptable range. A high shrinkage of IIV for Vc (39%) is acceptable due to established covariate effect on Vc.
BLQ for Parameter Accuracy	<3% of post-dose PK concentrations were BLQ and were excluded from the model estimation.	Yes
GOF, VPC	FDA Figure 11 and FDA Figure 12 Goodness-of-fit plots at the population and individual level suggested that the model adequately described the data . The VPC and pcVPC plots suggested that the median, 95th and 5th percentiles of observed C _{trough} were generally well within the prediction intervals of simulations from the popPK model.	Yes

Significant Covariates and Clinical Relevance	FDA Figure 13 <u>KA</u>: Positive factors: albumin <u>F2</u>: Positive factors: HGB	Yes. No covariates on absorption parameters are likely to have clinically meaningful impact on exposure, and no evident age/race effect is observed after adjustment of weight.
Analysis Based on Simulation (optional)	FDA Figure 14 Comparison of model-predicted exposure metrics distributions between Cohort 4 (IV) and Cohort 5 (SC).	
Labeling Language	Description	Acceptability [FDA's comments]
12.3 Pharmacokinetics See Description	Absorption characteristics were based on PPK parameter estimates. Comparable Cycle 1 and steady-state C_{trough} and AUC_{tau} of atezolizumab between SC and IV administration were established via PPK assessment. Specific population information was based on the impact of covariates for PK and no dose adjustment is suggested.	Yes

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FDA Table 45. Summary of Baseline Characteristics and Laboratory Values in the Dataset, Overall and Stratified by Cohort.

Characteristic	Cohort 1 1800 mg Q3W SC Thigh (N=13)	Cohort 2 1200 mg Q2W SC Thigh (N=15)	Cohort 3 1800 mg Q3W SC Abdomen (N=39)	Cohort 4 1200 mg IV Q3W (N=122)	Cohort 5 1875 mg SC Q3W (N=246)
Body weight (kg)					
Median [Min, Max]	65.4 [49.0, 89.0]	70.0 [52.0, 113]	73.2 [43.6, 94.0]	69.1 [34.6, 114]	67.8 [30.0, 117]
Missing	1 (7.7%)	0 (0%)	1 (2.6%)	0 (0%)	3 (1.2%)
Tumor burden (mm)					
Median [Min, Max]	56.0 [12.0, 120]	70.0 [27.0, 199]	87.0 [27.0, 187]	68.5 [14.0, 245]	79.5 [10.0, 319]
Missing	0 (0%)	0 (0%)	0 (0%)	0 (0%)	2 (0.8%)
ALB (g/L)					
Median [Min, Max]	40.0 [27.0, 45.6]	40.0 [25.0, 47.5]	39.0 [3.58, 46.0]	41.2 [4.01, 53.6]	40.0 [3.86, 51.0]
Missing	0 (0%)	0 (0%)	0 (0%)	1 (0.8%)	0 (0%)
Sex					
Male	5 (38.5%)	9 (60.0%)	27 (69.2%)	80 (65.6%)	174 (70.7%)
Female	8 (61.5%)	6 (40.0%)	12 (30.8%)	42 (34.4%)	72 (29.3%)
ADA status					
Negative	10 (76.9%)	6 (40.0%)	23 (59.0%)	93 (76.2%)	177 (72.0%)
Positive	3 (23.1%)	9 (60.0%)	13 (33.3%)	15 (12.3%)	43 (17.5%)
Missing	0 (0%)	0 (0%)	3 (7.7%)	14 (11.5%)	26 (10.6%)
Age (years)					
Median [Min, Max]	60.0 [49.0, 81.0]	65.0 [39.0, 82.0]	66.0 [31.0, 83.0]	66.0 [42.0, 85.0]	63.0 [27.0, 85.0]
Serum creatinine (mg/dL)					
Median [Min, Max]	0.916 [0.560, 1.23]	1.01 [0.543, 1.47]	0.790 [0.475, 1.44]	0.881 [0.0273, 2.01]	0.840 [0.320, 1.98]
Hemoglobin (g/L)					
Median [Min, Max]	124 [102, 145]	124 [100, 142]	119 [80.0, 165]	122 [87.0, 1440]	123 [79.0, 1160]
Creatinine clearance (mL/min)					
Median [Min, Max]	75.1 [49.3, 139]	74.5 [33.3, 181]	82.7 [45.5, 190]	74.8 [32.3, 2050]	82.9 [29.8, 244]
Missing	1 (7.7%)	0 (0%)	1 (2.6%)	0 (0%)	3 (1.2%)
ALP (U/L)					
Median [Min, Max]	98.0 [68.0, 370]	92.0 [64.0, 172]	96.0 [57.0, 619]	97.0 [23.0, 484]	100 [0.100, 1460]
Missing	0 (0%)	0 (0%)	0 (0%)	1 (0.8%)	1 (0.4%)
ALT (U/L)					
Median [Min, Max]	19.0 [6.00, 65.0]	17.0 [7.00, 52.0]	18.0 [5.00, 82.0]	16.0 [2.50, 108]	16.0 [2.50, 174]
AST (U/L)					
Median [Min, Max]	19.0 [14.0, 87.0]	29.0 [8.60, 43.0]	23.0 [9.00, 70.0]	20.0 [7.00, 65.3]	21.0 [7.00, 146]

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.

Characteristic	Cohort 1 1800 mg Q3W SC Thigh (N=13)	Cohort 2 1200 mg Q2W SC Thigh (N=15)	Cohort 3 1800 mg Q3W SC Abdomen (N=39)	Cohort 4 1200 mg IV Q3W (N=122)	Cohort 5 1875 mg SC Q3W (N=246)
ECOG status					
0 (Fully active)	3 (23.1%)	7 (46.7%)	13 (33.3%)	27 (22.1%)	66 (26.8%)
1 (Strenuous physical activity restricted)	10 (76.9%)	8 (53.3%)	26 (66.7%)	95 (77.9%)	180 (73.2%)
PD-L1 status					
Negative	0 (0%)	0 (0%)	0 (0%)	76 (62.3%)	120 (48.8%)
Positive	0 (0%)	0 (0%)	0 (0%)	37 (30.3%)	97 (39.4%)
Missing	13 (100%)	15 (100%)	39 (100%)	9 (7.4%)	29 (11.8%)
Race					
American Indian or Alaska Native	0 (0%)	0 (0%)	0 (0%)	9 (7.4%)	15 (6.1%)
Asian	2 (15.4%)	2 (13.3%)	1 (2.6%)	33 (27.0%)	47 (19.1%)
Black or African American	0 (0%)	0 (0%)	0 (0%)	1 (0.8%)	2 (0.8%)
Native Hawaiian or other Pacific Islander	0 (0%)	0 (0%)	0 (0%)	2 (1.6%)	1 (0.4%)
White	8 (61.5%)	11 (73.3%)	36 (92.3%)	72 (59.0%)	173 (70.3%)
Multiple	0 (0%)	0 (0%)	0 (0%)	5 (4.1%)	6 (2.4%)
Unknown	3 (23.1%)	2 (13.3%)	2 (5.1%)	0 (0%)	2 (0.8%)
Ethnicity					
Hispanic or Latino	1 (7.7%)	5 (33.3%)	12 (30.8%)	35 (28.7%)	61 (24.8%)
Not Hispanic or Latino	9 (69.2%)	7 (46.7%)	25 (64.1%)	87 (71.3%)	184 (74.8%)
Not reported	3 (23.1%)	3 (20.0%)	2 (5.1%)	0 (0%)	0 (0%)
Unknown	0 (0%)	0 (0%)	0 (0%)	0 (0%)	1 (0.4%)
Hepatic impairment					
Normal	12 (92.3%)	12 (80.0%)	35 (89.7%)	105 (86.1%)	218 (88.6%)
Mild	1 (7.7%)	2 (13.3%)	4 (10.3%)	15 (12.3%)	27 (11.0%)
Moderate	0 (0%)	1 (6.7%)	0 (0%)	2 (1.6%)	1 (0.4%)
Renal impairment					
Normal	5 (38.5%)	2 (13.3%)	22 (56.4%)	42 (34.4%)	103 (41.9%)
Mild	5 (38.5%)	10 (66.7%)	12 (30.8%)	58 (47.5%)	111 (45.1%)
Moderate	3 (23.1%)	3 (20.0%)	5 (12.8%)	22 (18.0%)	32 (13.0%)
Region					
Asia-Pacific	2 (15.4%)	2 (13.3%)	1 (2.6%)	32 (26.2%)	47 (19.1%)

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 Atezolizumab and Hyaluronidase-tqjs Solution for Subcutaneous Injection

Characteristic	Cohort 1 1800 mg Q3W SC Thigh (N=13)	Cohort 2 1200 mg Q2W SC Thigh (N=15)	Cohort 3 1800 mg Q3W SC Abdomen (N=39)	Cohort 4 1200 mg IV Q3W (N=122)	Cohort 5 1875 mg SC Q3W (N=246)
Australia	1 (7.7%)	0 (0%)	3 (7.7%)	5 (4.1%)	8 (3.3%)
Central or South Latin America	1 (7.7%)	5 (33.3%)	12 (30.8%)	36 (29.5%)	65 (26.4%)
Europe and Middle East	9 (69.2%)	8 (53.3%)	23 (59.0%)	49 (40.2%)	126 (51.2%)
Age groups					
<65 years old	8 (61.5%)	7 (46.7%)	19 (48.7%)	58 (47.5%)	138 (56.1%)
65-75 years old	3 (23.1%)	7 (46.7%)	14 (35.9%)	51 (41.8%)	89 (36.2%)
>75 years old	2 (15.4%)	1 (6.7%)	6 (15.4%)	13 (10.7%)	19 (7.7%)

Source: Tables 2 and 3, Appendix 4 of PPK report.

2705

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2706 **FDA Table 46. Parameter Estimates and RSE (%) from Final Population PK Model.**

Parameter (Unit)	Estimate	RSE (%)	Shrinkage
CL (L/d)	0.200	FIX	
Vc (L)	3.28	FIX	
Vp (L)	3.63	FIX	
Q (L/d)	0.546	FIX	
Albumin on CL (ALB/40 in g/L)	-1.12	FIX	
ADA status on CL (additive effect for positive ADA)	0.159	FIX	
Tumor burden on CL (Tumor burden/63 mm)	0.125	FIX	
Bodyweight on CL (BWT/77 in kg)	0.808	FIX	
Albumin on Vc (ALB/40 in g/L)	-0.350	FIX	
Bodyweight on Vc (BWT/77 in kg)	0.559	FIX	
Sex on Vc (additive effect for female)	-0.129	FIX	
Sex on Vp (additive effect for female)	-0.272	FIX	
KA (1/d)	0.304	3.0	
F1	0.718	1.8	
Albumin on KA (ALB/40 in g/L)	0.795	33.1	
Hemoglobin on F1 On logit scale (HGB/123 in g/L)	1.76	37.8	
Omega (standard deviation scale) – Between subject variability			
POPIV CL	29.4%	FIX	8.23
POPIV Vc	18.1%	FIX	39.0
POPIV Vp	33.8%	FIX	15.6
POPIV KA	34.6%	23.7	38.1
POPIV F1	83.0%	18.7	37.4
Sigma (residual error)			
Proportional error (%)	19.0	9.6	13.2
Additive error (µg/mL)	15.4	15.1	13.2

2707 Source: Table 4 of PPK report.

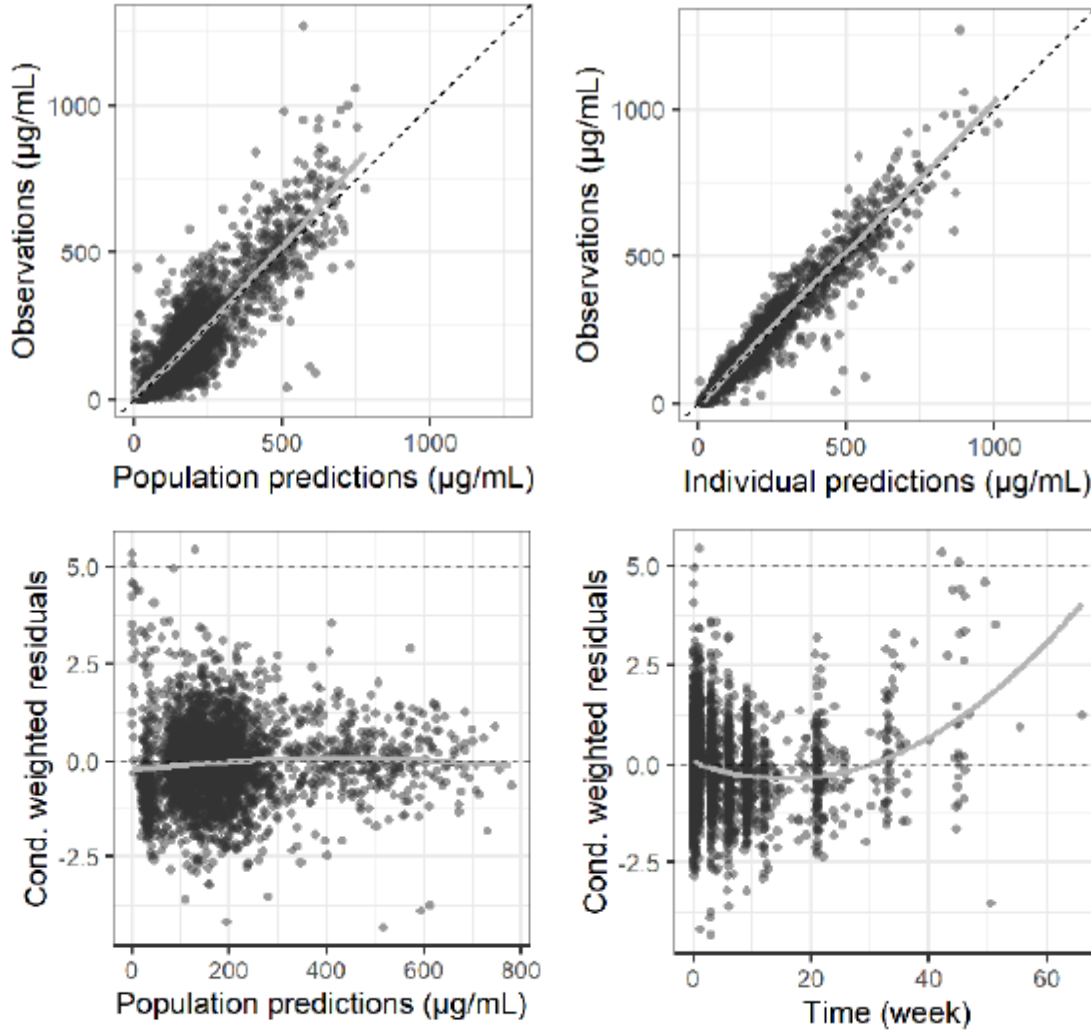
2708 Parameters except those for absorption (Ka, F1, and respective covariates) were fixed to values from a published model¹. Covariate
 2709 effect was parameterized using power function for continuous covariate BWT, ALB, tumor burden, and hemoglobin normalized to
 2710 median value (i.e., (COVi/COVref)^{theta}), or proportional shift for categorical covariate sex, and ADA (i.e., 1+theta).

2711

2712

¹ Stroh M et al. Clinical Pharmacokinetics and Pharmacodynamics of Atezolizumab in Metastatic Urothelial Carcinoma. Clin Pharmacol Ther. 2017 Aug;102(2):305-312. doi: 10.1002/cpt.587.

2713 **FDA Figure 11. Goodness-of-Fit Plots for the Final Population PK Model (OBS-PRED/IPRED,**
2714 **CWRES- PRED/TIME).**

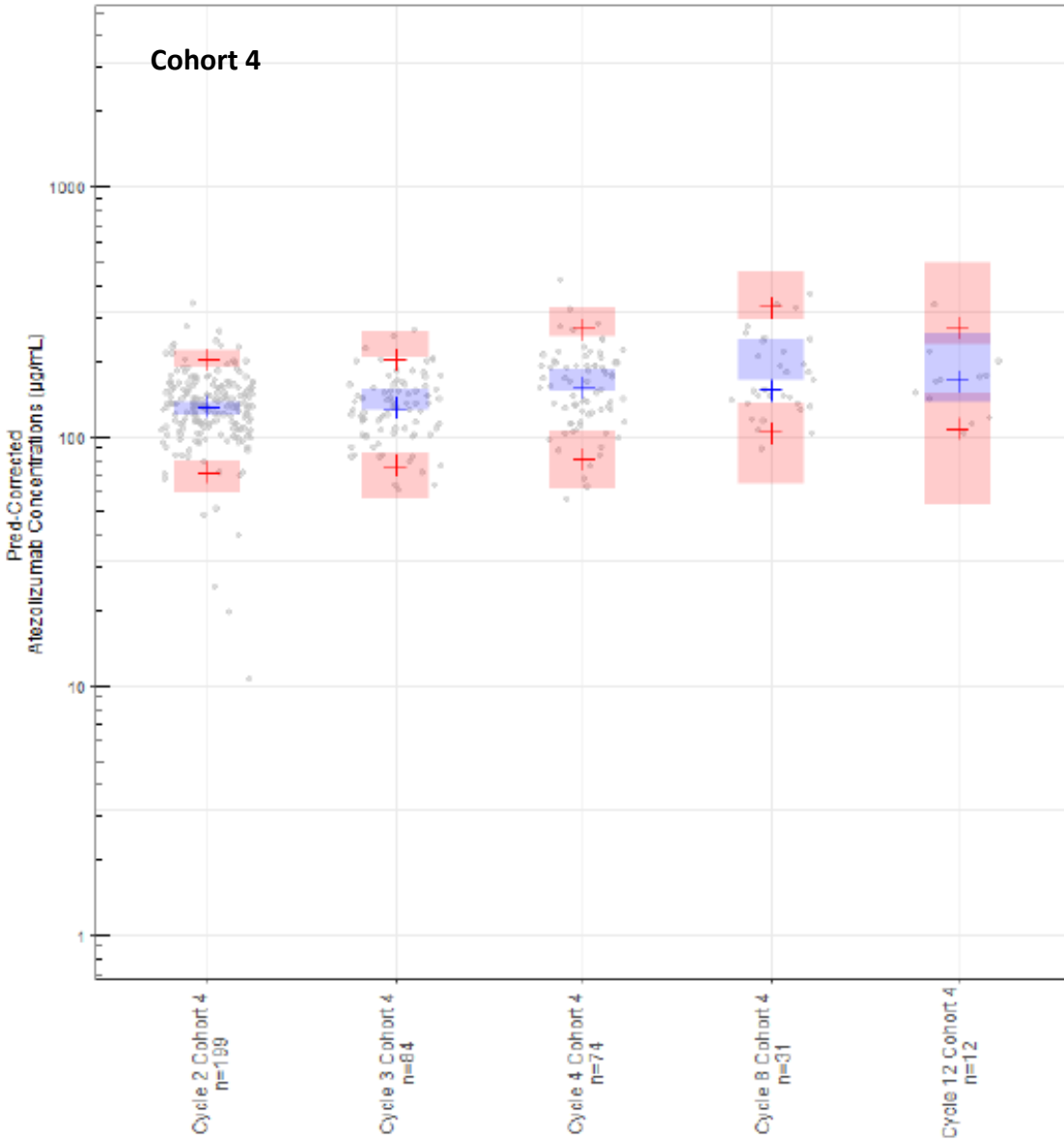


2715
2716 Source: Figures 7 and 8 of PPK report.

2717

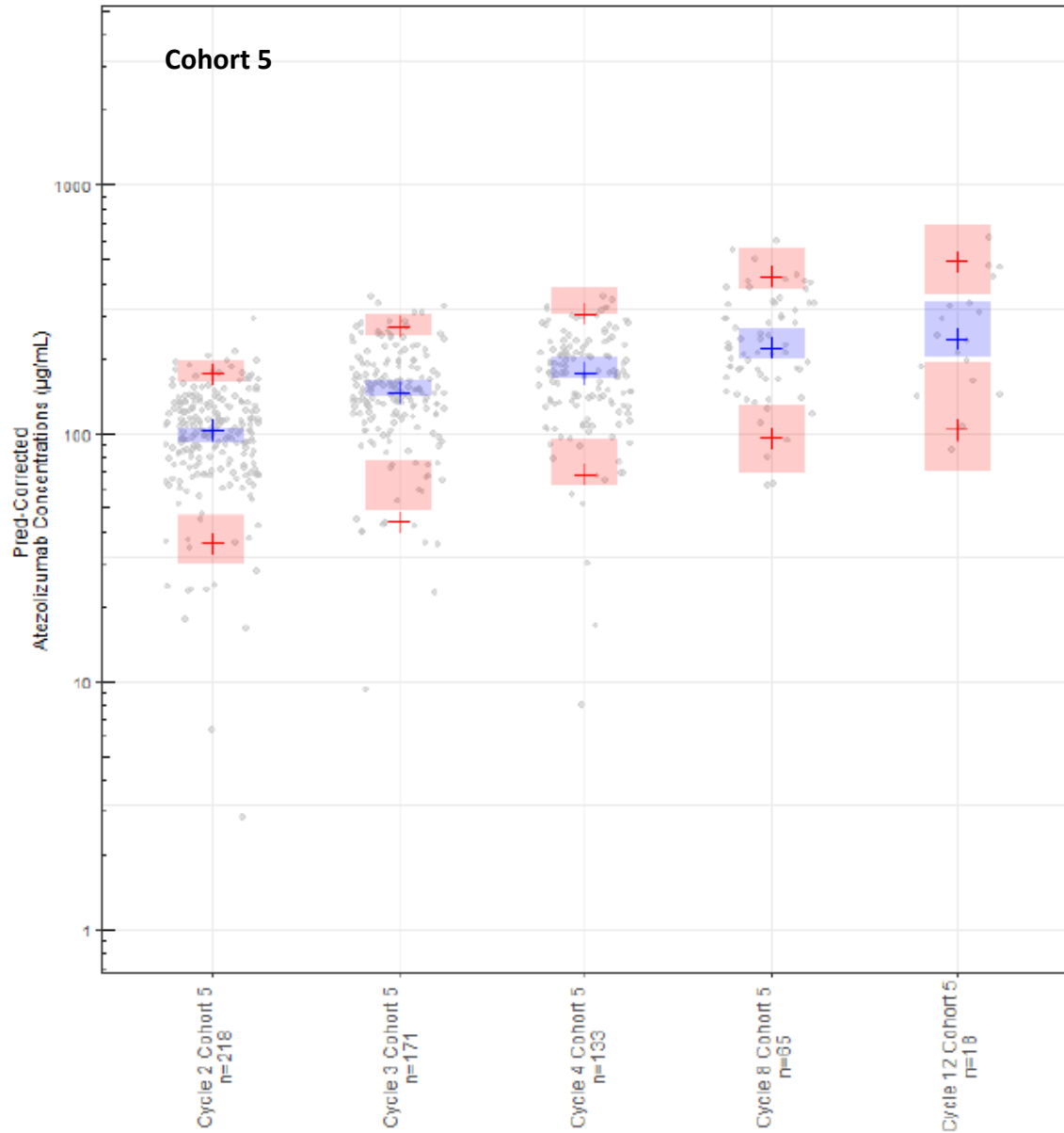
2718

2719 **FDA Figure 12. VPC and pcVPC of Final Population PK Model, Stratified by Cohort.**



2720

2721



2722
2723

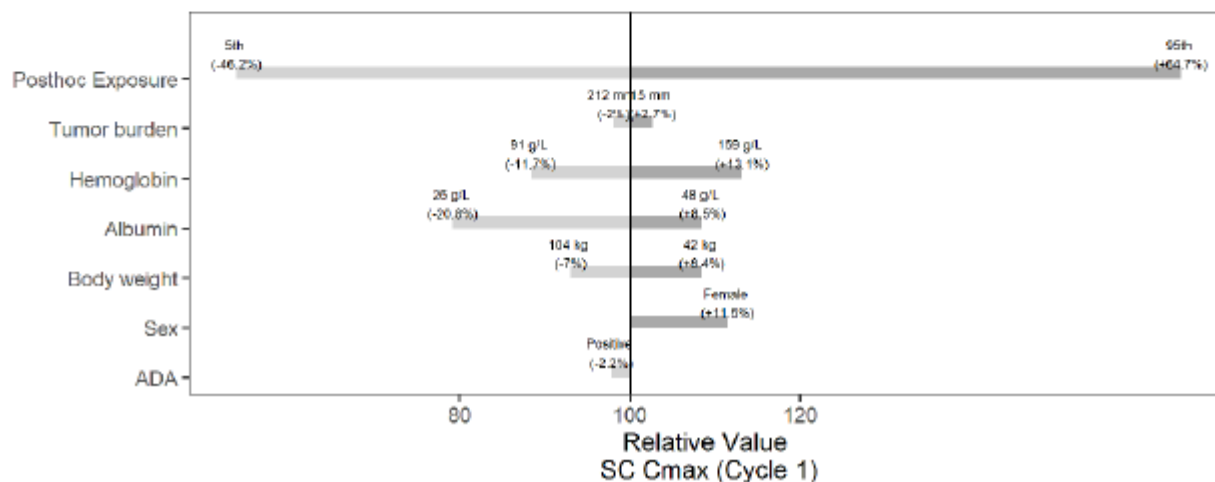
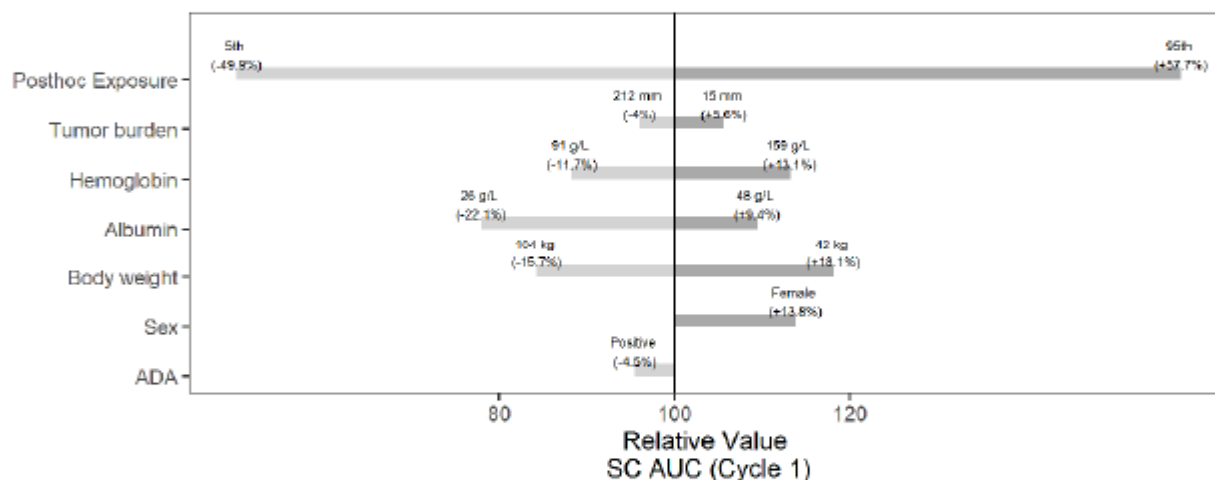
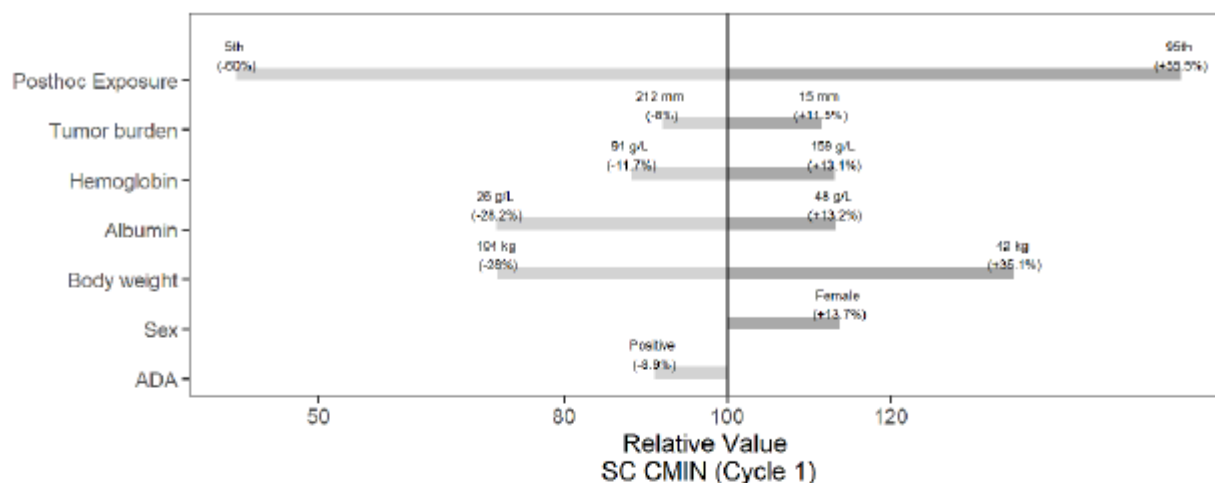
Source: Figures 9 and 10, Appendices 20 and 21 of PPK report.

2724

2725

2726

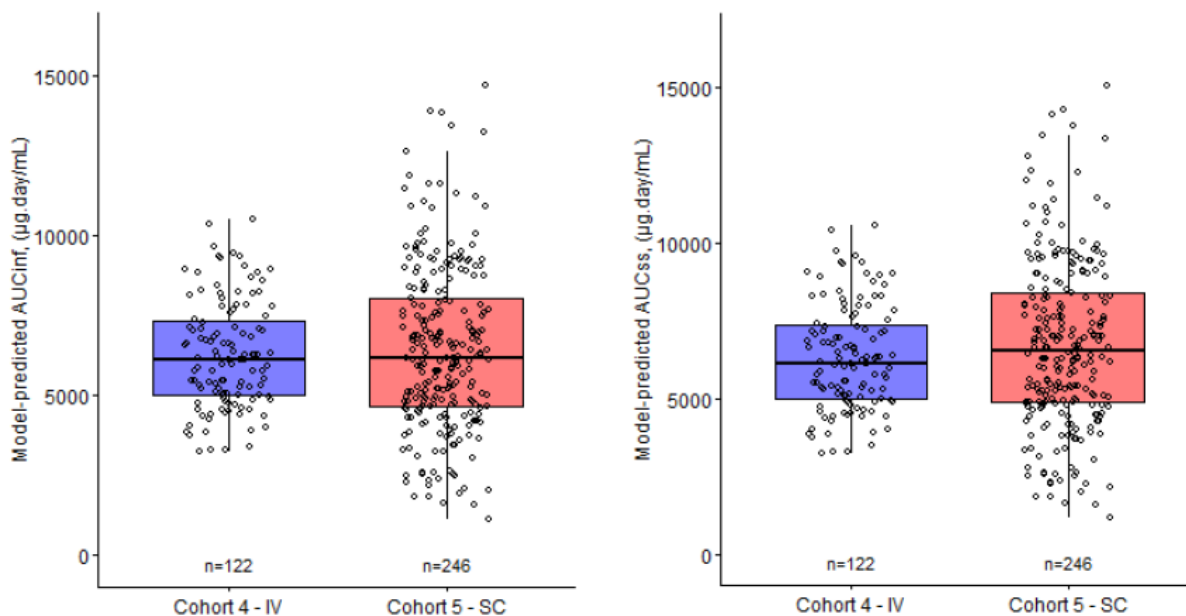
2727 **FDA Figure 13. Impact of Significant Covariates on Exposure.**



2728
 2729 Source: Appendix 16 of PPK report.

2730

2731 **FDA Figure 14. Model-Predicted Atezolizumab Exposure Metrics at Cycle 1 and Steady State by**
2732 **Cohort.**



2733
2734 Source: Figures 11 and 12, Appendix 24 of PPK report.

2735

2736

2737 The FDA's Assessment: FDA agrees with the Applicant's position.

2738 **19.4.4. PPK Review Issues**

2739 **Time Dependent PK**

2740 A trend of increase in trough concentrations as illustrated in [FDA Figure 11](#) was observed,
2741 suggesting the CL is reduced in a time-dependent manner. This change is expected for both SC
2742 and IV administrations. Considering treatment duration and sampling frequency were similar in
2743 the two cohorts (cohort4-IV, cohort5-SC) and the bias occurred after 30 weeks of treatment
2744 when steady-state was established, the time dependent PK is highly unlikely to affect the
2745 analysis for non-inferiority or E-R.

2746 **19.4.5. Reviewer's Independent Analysis**

2747 **ADA Effect on PK**

2748 Applicant included subject-level treatment emergent ADA in the dataset, the effect of which was
2749 fixed based on the published model (16% increase in CL). In order to assess the ADA effect with
2750 PK data that include SC administration, Reviewer re-estimated all parameters with their initial
2751 values unfixed given the PK data are considered adequate for parameter estimation. This model
2752 was further used for evaluating the effect of time-varying ADA (ADA[#]). In addition, models

2753 with time-dependent CL and ALB as a time-varying covariate on CL were assessed; nested
2754 within these models, the effect of ADA on CL as a subject-level (static) or time-varying
2755 covariate was evaluated. The OFV and parameter estimates are shown in FDA [Table 47](#) for
2756 comparison.

2757 When ADA was evaluated as a time-varying covariate, the estimated ADA effect on CL was
2758 consistently smaller with worsened precision than as a static covariate, regardless whether time
2759 dependent CL was imposed or not, and whether ALB was modeled as a time-varying or baseline
2760 covariate. Whilst modeling ADA as a time-varying covariate did not improve goodness of fit, a
2761 measure of which is provided by objective function value (OFV). Therefore, ADA as a static
2762 covariate appears more appropriate for evaluating its impact on atezolizumab CL from modeling
2763 perspective.

2764 Assessing ADA effect with time-varying status or titer reflects the dynamic influence on CL over
2765 time and is often a more sensitive measure. However, for atezolizumab, modeling analysis
2766 suggests static ADA to be a better covariate. One unverified hypothesis is the relatively low
2767 ADA assay sensitivity where positive control of ADA at 500 ng/mL is detected at varying drug
2768 tolerance levels (DT) ranging from approximately 100 to 800 ug/mL across indications. This
2769 detection threshold for ADA is considered high compared to the current recommended assay
2770 sensitivity to detect ADA as low as 100 ng/mL at DT per immunogenicity assay guidance. Due
2771 to increasing drug concentrations after 1st dose, ADA of 100-<500 ng/mL that may be detected
2772 as positive at the lowest trough concentration could turn negative at steady-state, resulting in
2773 false negative ADA samples. Under such circumstances if one evaluates ADA effect using time-
2774 varying ADA status, the difference in CL between ADA+ and ADA- will likely be
2775 underestimated with increasing uncertainty.

2776 This hypothesis aligns with the change in ADA+ rate observed in trials. In IMscin001 Part2,
2777 ADA quickly emerged after atezolizumab administration, with the highest ADA+ rate observed
2778 at trough of 1st dose (16%, IV and SC combined) which declined at steady state to ~10%. The
2779 declining ADA+ rate is not only present in IMscin001 but also in multiple trials of various
2780 indications treated with atezolizumab. However, a declining ADA+ rate (or “transient” ADA)
2781 has not been observed for other PD-1 or PD-L1 inhibitors.

2782 Collectively, for atezolizumab, static subject-level treatment emergent ADA that shows ~17-19%
2783 increase in CL is believed to be a more accurate estimate of the ADA effect. This magnitude of
2784 change on CL is however not likely clinically meaningful.

2785

FDA Table 47. Comparison of Model Parameter Estimates

Model	1	2	3	4	5	6	7	8
Model Characteristics	Time-Static CL				Time-Dependent CL			
	ALB		ALB [#]		ALB		ALB [#]	
	ADA	ADA [#]	ADA	ADA [#]	ADA	ADA [#]	ADA	ADA [#]
OFV	26757	26767	26725	26733	26753	26764	26717	26726
Estimated value (RSE)								
CL	0.194 (3.3%)	0.200 (3%)	0.189 (3.3%)	0.194 (3.2%)	0.2 (3.6%)	0.205 (3.3%)	0.198 (3.6%)	0.203 (3%)
V _c	3.08 (2.1%)	3.07 (2%)	3.06 (2%)	3.06 (2.1%)	3.07 (2%)	3.07 (2%)	3.05 (2%)	3.05 (2%)
V _p	2.81 (6.5%)	2.77 (3.3%)	2.95 (6.6%)	2.93 (6.7%)	2.66 (7.7%)	2.64 (7.7%)	2.71 (7.6%)	2.65 (6.8%)
Q	0.34 (3.9%)	0.341 (3.9%)	0.345 (4.1%)	0.348 (4.1%)	0.344 (3.9%)	0.346 (3.9%)	0.357 (4.5%)	0.359 (4.5%)
CL-ALB	-0.948 (18.9%)	-1.01 (16.9%)	-0.938 (10.9%)	-0.973 (10.5%)	-0.936 (18.7%)	-0.984 (17.6%)	-0.956 (10.2%)	-0.984 (9.8%)
CL-ADA	0.19 (33.6%)	0.0865 (43.1%)	0.174 (36.2%)	0.0898 (44.8%)	0.185 (34.2%)	0.078 (46.5%)	0.163 (37.3%)	0.0724 (54%)
CL-BSLD	0.109 (26.4%)	0.11 (26.7%)	0.103 (26.8%)	0.104 (27.1%)	0.107 (26.7%)	0.109 (26.5%)	0.0975 (27.9%)	0.0971 (28.6%)
CL-BW	0.51 (19.5%)	0.529 (18.8%)	0.531 (18.4%)	0.539 (18%)	0.506 (19.2%)	0.521 (17.4%)	0.537 (17.6%)	0.535 (17.8%)
V _c -ALB	-0.126 (102.4%)	-0.137 (89.8%)	-0.116 (97.4%)	-0.116 (98.3%)	-0.128 (100%)	-0.134 (8.3%)	-0.122 (91%)	-0.117 (2%)
V _c -BW	0.358 (23.8%)	0.369 (23%)	0.335 (24.9%)	0.33 (25.7%)	0.361 (23.6%)	0.356 (1.7%)	0.336 (25%)	0.323 (25.3%)
V _c -SEX	-0.147 (19.7%)	-0.146 (19.5%)	-0.153 (18.4%)	-0.154 (18.4%)	-0.144 (20.1%)	-0.145 (17.9%)	-0.149 (19.3%)	-0.15 (19.1%)
V _p -SEX	-0.334 (19.9%)	-0.328 (20%)	-0.33 (19.9%)	-0.325 (20.5%)	-0.336 (20.4%)	-0.329 (21.3%)	-0.335 (20.4%)	-0.329 (21.2%)
KA	0.287 (3.4%)	0.288 (3.4%)	0.284 (3.4%)	0.285 (3.5%)	0.287 (3.4%)	0.289 (3.2%)	0.285 (3.4%)	0.287 (3.5%)

154

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Model	1	2	3	4	5	6	7	8
Model Characteristics	Time-Static CL				Time-Dependent CL			
	ALB		ALB [#]		ALB		ALB [#]	
	ADA	ADA [#]	ADA	ADA [#]	ADA	ADA [#]	ADA	ADA [#]
OFV	26757	26767	26725	26733	26753	26764	26717	26726
Estimated value (RSE)								
F1	0.664 (2.7%)	0.661 (2.7%)	0.663 (2.7%)	0.661 (2.8%)	0.665 (2.7%)	0.663 (2.7%)	0.664 (2.4%)	0.66 (2.8%)
KA-ALB	0.936 (28.7%)	0.933 (24.7%)	0.405 (49.4%)	0.404 (50%)	0.933 (28.8%)	0.914 (25.2%)	0.4 (49.8%)	0.414 (35%)
F1-HGB	2.1 (23.9%)	2.14 (23.7%)	2.31 (20.9%)	2.37 (20.8%)	2.08 (23.9%)	2.16 (23.4%)	2.27 (7.2%)	2.32 (21.4%)
Kt	--	--	--	--	0.00029 (53.1%)	0.00028 (53.6%)	0.00045 (31.8%)	0.00046 (1.4%)
IIV-CL	0.139 (10.2%)	0.142 (9.6%)	0.132 (10.2%)	0.13 (10.1%)	0.131 (10.8%)	0.131 (10.5%)	0.119 (10.8%)	0.12 (10.2%)
IIV-Vc	0.0228 (20%)	0.0221 (20.1%)	0.0226 (20%)	0.0225 (20.2%)	0.0223 (20.4%)	0.0224 (19.6%)	0.0219 (20.5%)	0.0219 (19.7%)
IIV-Vp	0.458 (13.2%)	0.466 (13.3%)	0.424 (13.3%)	0.427 (13.5%)	0.47 (13.3%)	0.476 (13.4%)	0.443 (13.3%)	0.445 (13.2%)
IIV-KA	0.15* (10.5%)	0.146* (10.5%)	0.153* (10.4%)	0.15* (10.5%)	0.151* (10.5%)	0.146* (10.5%)	0.153* (10.5%)	0.149* (10.6%)
IIV-F1	0.561 (13.4%)	0.571 (13.2%)	0.548 (13.5%)	0.56 (13.5%)	0.559 (13.4%)	0.571 (13.3%)	0.544 (13.4%)	0.55 (13.6%)
ERR-PROP	0.0323 (3.4%)	0.0322 (3.4%)	0.0322 (3.5%)	0.0322 (3.4%)	0.0323 (3.4%)	0.0323 (3.4%)	0.0321 (3.5%)	0.0321 (3.5%)
ERR-ADD	203 (5.6%)	203 (5.7%)	201 (5.6%)	200 (5.7%)	204 (5.6%)	204 (5.7%)	202 (5.6%)	202 (5.6%)

Source: Reviewer's analysis. #Indicate time-varying. Time-dependent CL=CL*exp(-Kt*time) where time unit is day. ALB: albumin, ADA: anti-drug antibody, BW: body weight, HGB: hemoglobin.

2786
2787

2788 **19.4.6. Exposure-Response Analysis**

2789 **19.4.7. ER F(Efficacy) Executive Summary**

2790 (4) The FDA’s Assessment: The E-R analysis for efficacy is considered exploratory. Flat ER relationships were generally
 2791 observed for efficacy endpoints in CIT naïve NSCLC patients based on exposure level achieved with SC 1875 mg Q3W.

2792 **19.4.8. ER (Efficacy) Assessment Summary**

2793 The Applicant’s Position: No statistically significant exposure-efficacy relationships were identified with ORR, PFS, or OS in patients
 2794 treated with SC atezolizumab 1875 mg Q3W.

2795 **Table 48. ER Analysis Information**

General Information	
Goal of ER analysis	The objective of this analysis was to evaluate the potential relationships between atezolizumab SC exposure and efficacy through ER in CIT-naïve patients with locally advanced or metastatic NSCLC receiving atezolizumab SC 1875 mg Q3W in Part 2 of IMscin001.
Study Included	BP40657 (IMscin001) Part/Phase 2/III Atezo SC arm (Cohort 5)
Endpoint	ORR, PFS, OS
No. of Patients (total, and with individual PK)	Out of 247 patients allocated to the Atezo SC arm (Cohort 5), 246 with model-predicted exposure data from PPK analysis were included in the ER analysis (one patient who received a single SC injection, in the upper arm, was excluded from the PPK analysis).

General Information			
Population Characteristics (FDA Table 45)	General	Median age of 63 years (ranged 27 to 85 years). 43.9% patients were ≥ 65 yr, 7.7% patients were > 75 yr. Median weight of 67.8 kg (ranged 30.0 to 117 kg). 174 (70.7%) were male, 72 (29.3%) were female. White: 173 (70.3%), American Indian or Alaska Native: 15 (6.1%), Asian: 47 (19.1%), Black or African American: 2 (0.8%), Native Hawaiian or other Pacific Islander: 1 (0.4%), Multiple: 6 (2.4%), Unknown: 2 (0.8%). Hispanic or Latino: 61 (24.8%), Not Hispanic or Latino: 184 (74.8%), Not reported: 0 (0%), Unknown: 1 (0.4%).	
	Pediatrics (if any)	There were no patients under 18 years of age in the study.	
Dose(s) Included		1875 mg Q3W SC in thigh.	
Exposure Metrics Explored (range)		Cycle 1 AUC_{0-24} : 666 to 6572 $\mu\text{g}\cdot\text{day}/\text{mL}$ Cycle 1 C_{trough} : 20.0 to 218 $\mu\text{g}/\text{mL}$	
Covariates Evaluated		Age, sex, body weight, race, ethnicity, Eastern Cooperative Oncology Group (ECOG) score, albumin, lactate dehydrogenase (LDH), C-reactive protein (CRP), liver metastasis, neutrophil-to-lymphocyte ratio (NLR), smoking history, PD-L1 expressed on tumor-infiltrating immune cells (IC) and tumor cells (TC), as scored by immuno-histochemistry (i.e., present or absent [Yes/No], medium or high [Yes/No], high [Yes/No]), number of metastatic sites and histology of the disease, hepatic impairment, renal impairment.	
Final Model Parameters		Summary	Acceptability [FDA's comments]
Model Structure		Binary endpoint (ORR) was modeled using logistic regression versus exposure as a continuous variable. Time-to-event endpoints (PFS and OS) were first explored using Kaplan-Meier estimation stratified by quartiles of exposure metrics, then by using Cox regression with exposure metrics as continuous variables.	Yes. Multivariate analysis was conducted.
Model Parameter Estimates		FDA Table 49	Yes
Model Evaluation		Not conducted.	

General Information		
Covariates and Clinical Relevance	ORR: None of the covariates was statistically significant ($p > 0.05$). PFS: Positive factor: Age, body weight, albumin Negative factor: Metastasis in the liver, neutrophil-to-lymphocyte ratio, hepatic impairment (mild) OS: Positive factor: albumin Negative factor: LDH, CRP, NLR, hepatic impairment (mild) The number of patients with moderate hepatic impairment is too small to conclude the effect of this category on OS.	Yes. Several common risk factors (e.g., low albumin, high neutrophil-to-lymphocyte ratio, and hepatic impairment) were identified for disease progression/death.
Simulation for Specific Population	None performed.	
Visualization of E-R relationships	FDA Figure 15, FDA Figure 16, FDA Figure 17 ORR: Logistic regression with exposure metrics stratified by quartiles. PFS/OS: Kaplan-Meier plots with exposure metrics stratified by quartiles.	Yes
Overall Clinical Relevance for ER	Atezolizumab exposure metrics were not statistically significant ($p > 0.05$).	Yes
Labeling Language	Description	Acceptability [FDA's comments]
12.2 Pharmacodynamics	None.	

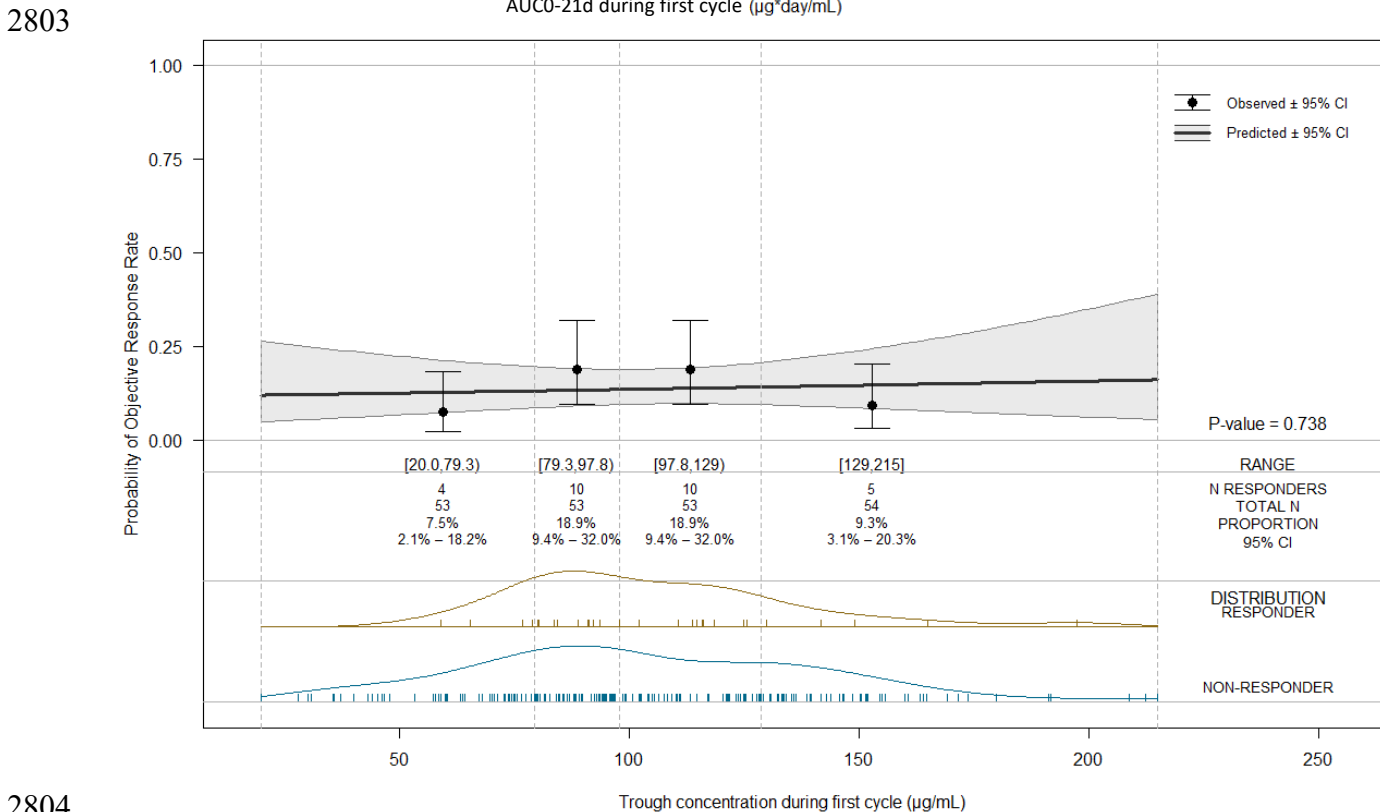
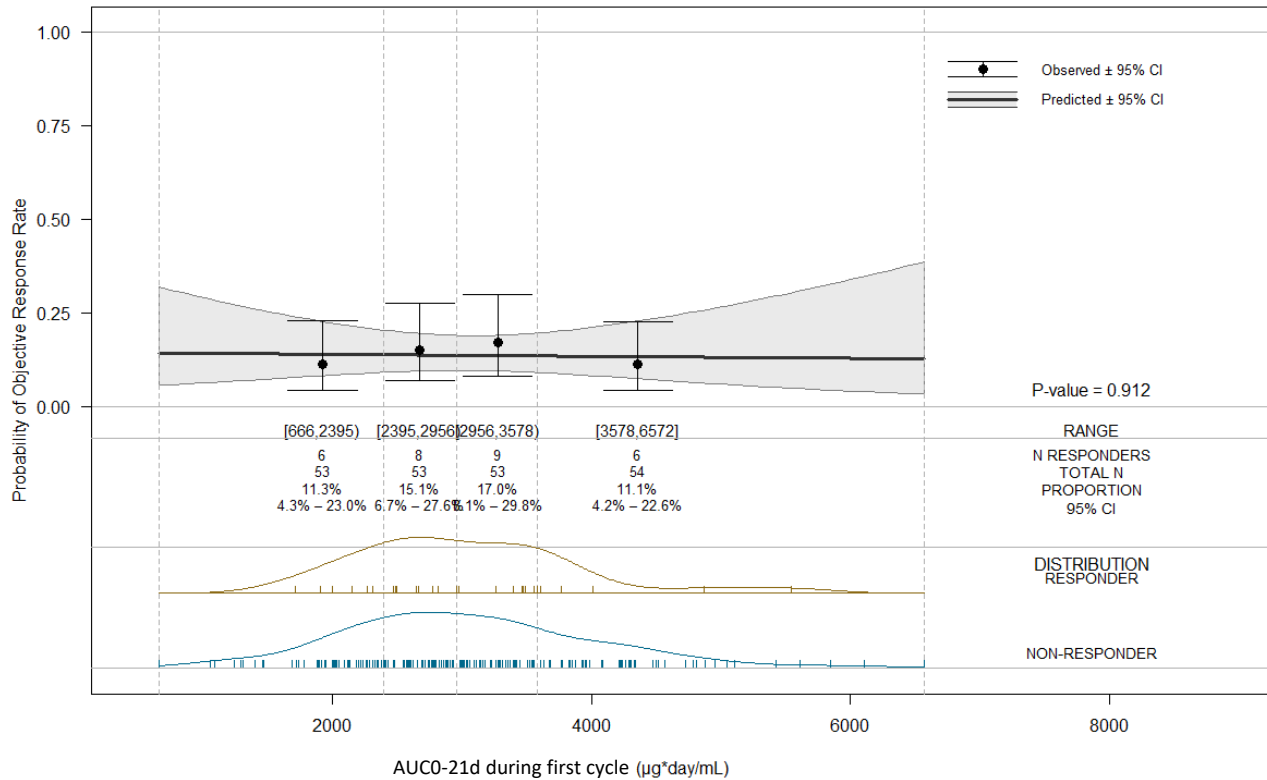
2796 **FDA Table 49. Parameter Estimates From Final ER Model of ORR, PFS, and OS, Respectively.**

Response	Model	Exposure [#]	Covariate [#]	OR/HR (95% CI) [§]	p-Value
ORR	Logistic regression	AUC _{0-21d} /1000	--	-0.0225 (-0.436, 0.368)	0.912
		C _{trough} /50	--	0.0886 (-0.442, 0.604)	0.739
PFS	Cox PH	C _{trough} /10		0.998 (0.949, 1.048)	0.927
			Age	0.975 (0.958, 0.992)	0.00449**
			Body weight /10	0.892 (0.800, 0.994)	0.0385*
			Albumin	0.940 (0.908, 0.974)	<0.001***
			Metastasis in the liver	1.70 (1.21, 2.40)	0.00238**
			NLR	1.05 (1.03, 1.07)	<0.001***
			HI-mild	1.96 (1.22, 3.14)	0.0056**
			HI-moderate	1.05 (0.144, 7.67)	0.961
OS	Cox PH	AUC _{0-21d} /1000		1.14 (0.896, 1.46)	0.281
			Albumin	0.921 (0.874, 0.971)	0.00218**
			LDH /100	1.13 (1.04, 1.23)	0.00398**
			CRP /10	1.08 (1.03, 1.14)	0.00175**
			NLR	1.04 (1.02, 1.07)	0.00111**
			HI-mild	2.55 (1.41, 4.60)	0.00202**
			HI-moderate	1.51 (0.202, 11.3)	0.687

2797 Source: Tables 5, 7, and 9 of ER report and Reviewer's analysis.

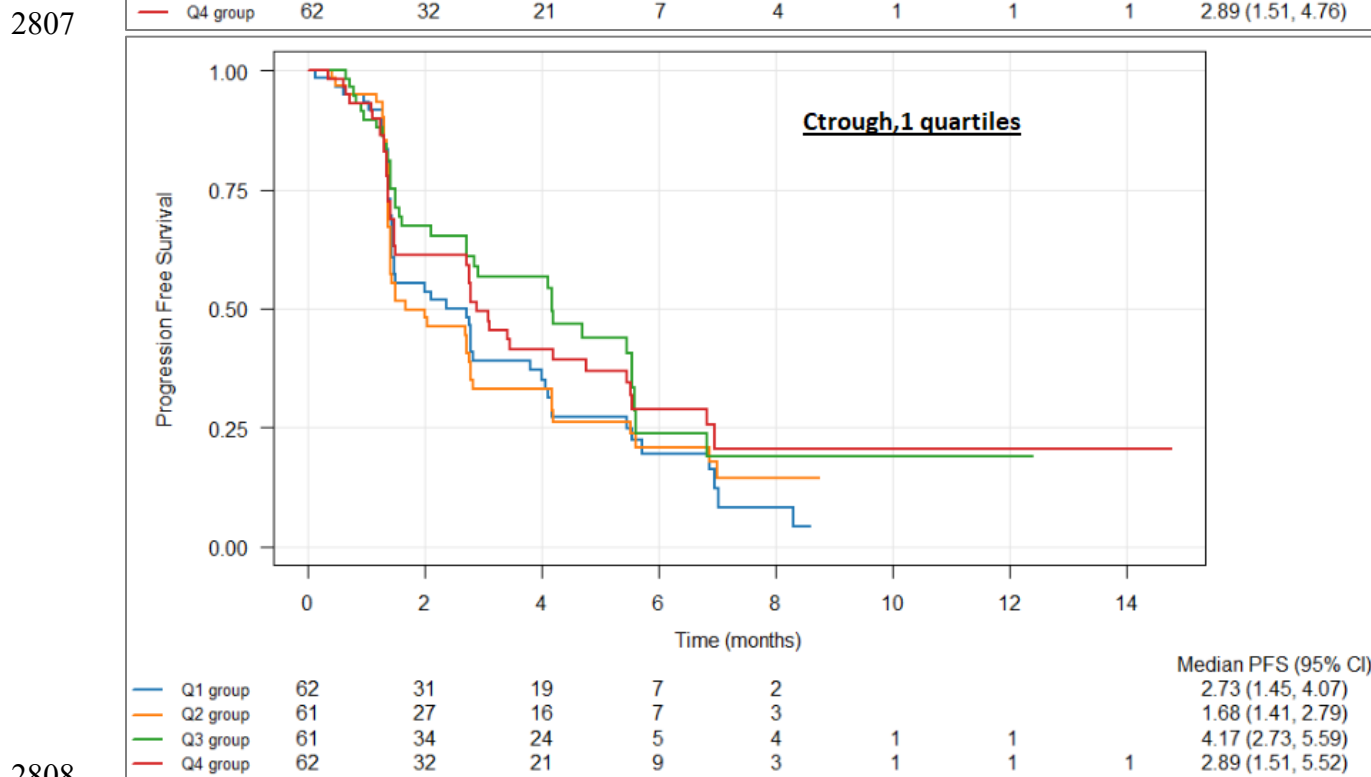
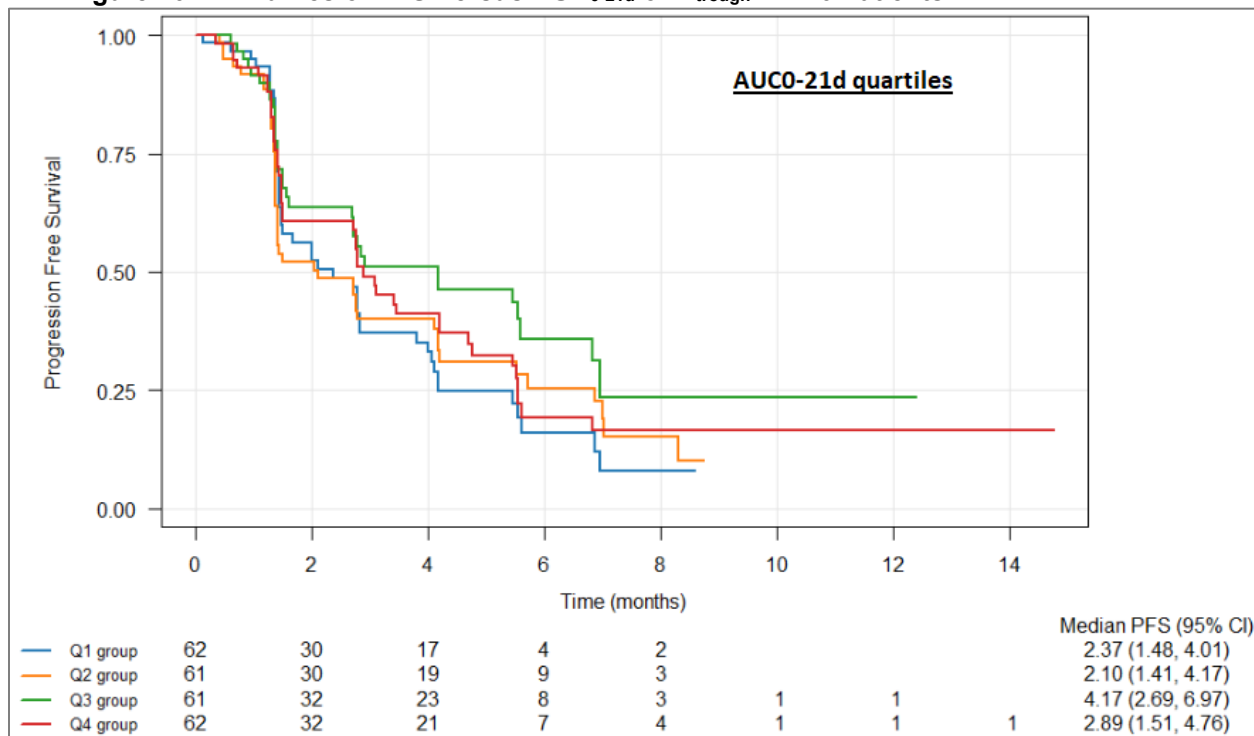
2798 [#]Exposure and some of the covariates were rescaled with the respective scaling factors indicated. [§]OR (odds ratio) for logistic regression and HR (hazard ratio) for Cox PH model
2799 calculated for 1 unit increase of scaled continuous variable or ratio compared to reference level of categorical variable. NLR: neutrophil-to-lymphocyte ratio, LDH: lactate
2800 dehydrogenase, CRP: C-reactive protein, HI: hepatic impairment (NCI-ODWG criteria). Unit: C_{trough} in µg/mL, AUC_{0-21d} in µg*day/mL, age in years, body weight in Kg, albumin in g/L,
2801 LDH in U/mL, CRP in mg/L.

2802 **FDA Figure 15. ER Curves of ORR Versus AUC_{0-21d} or C_{trough} in 246 Patients.**



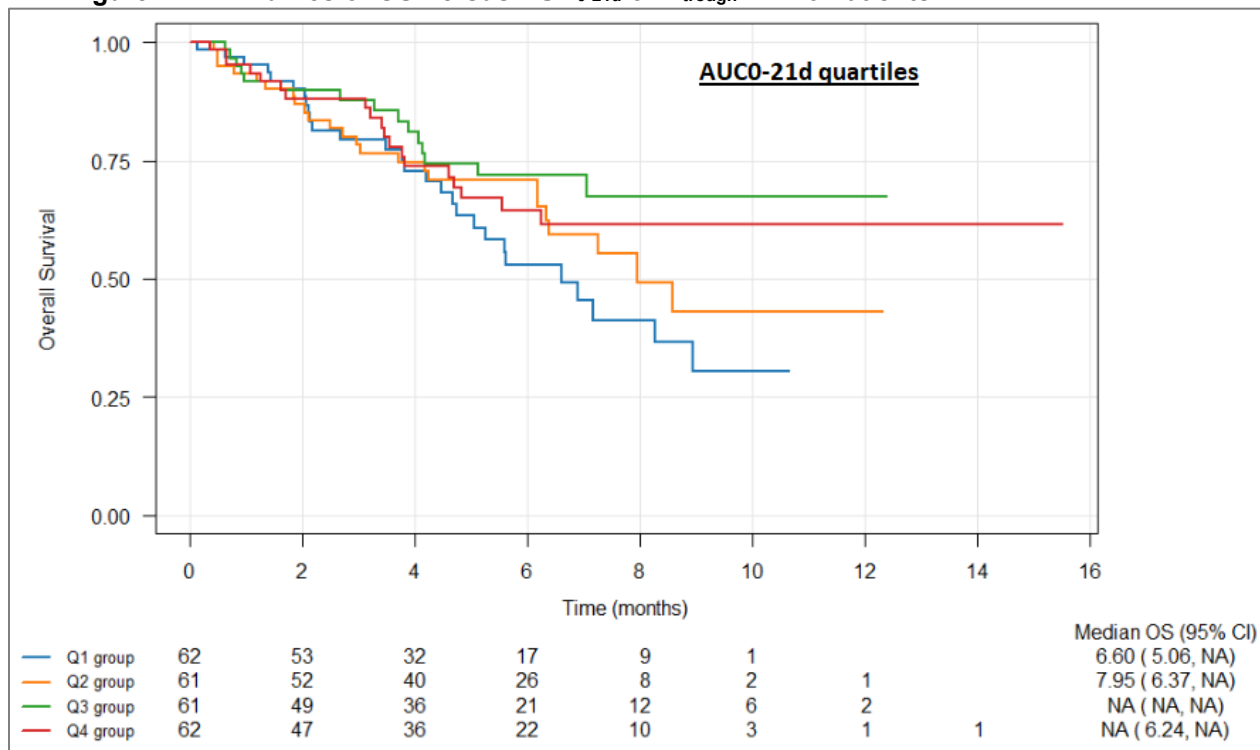
2804
 2805 Source: Figures 1-2 of ER report

2806 **FDA Figure 16. ER Curves of PFS Versus AUC_{0-21d} or C_{trough} in 246 Patients.**

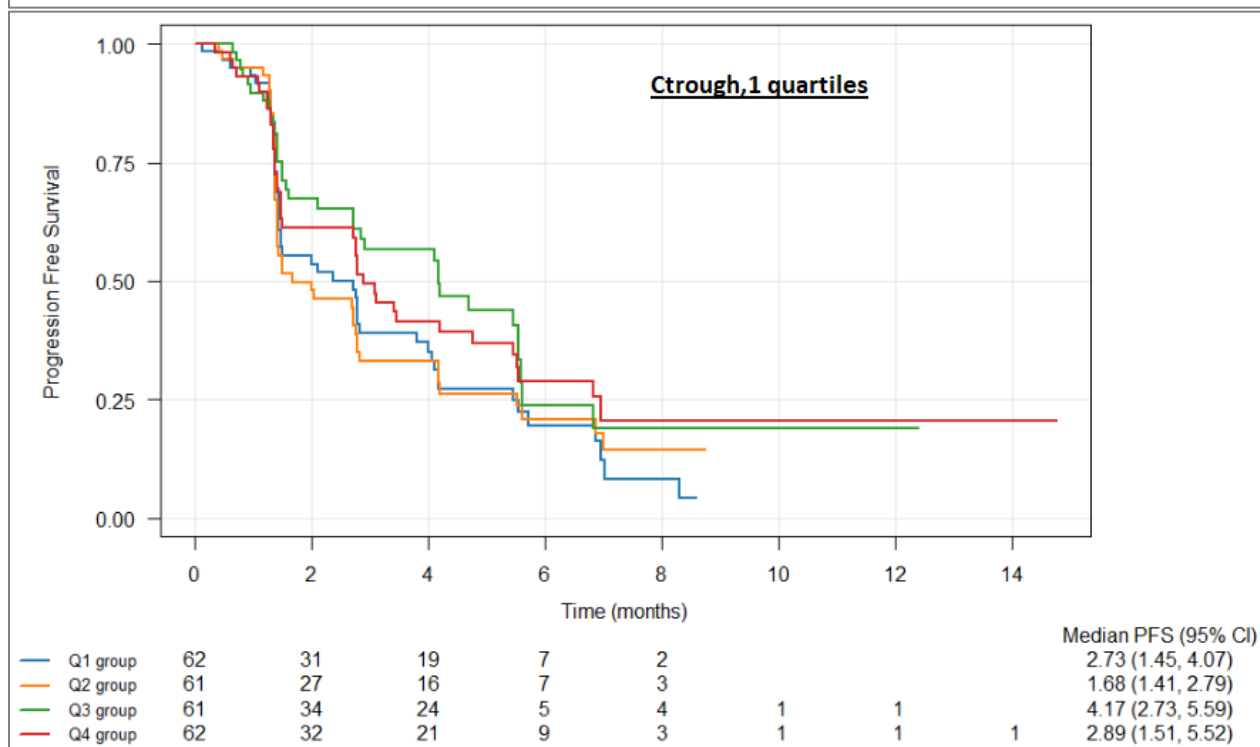


Source: Figures 3-4 of ER report.

2811 **FDA Figure 17. ER Curves of OS Versus AUC_{0-21d} or C_{trough} in 246 Patients.**



2812



2813
2814

Source: Figures 5-6 of ER report.

2815 **19.4.9. ER (Safety) Executive Summary**

2816 The FDA's Assessment: The E-R analysis for safety is considered exploratory. Flat E-R relationships were generally observed for
2817 safety endpoints in CIT naïve NSCLC patients based on exposure level achieved with SC 1875 mg Q3W.

2818 **19.4.10. ER (Safety) Assessment Summary**

2819 The Applicant's Position: No statistically significant exposure-safety relationships were identified with SAE, AESI, adverse events of
2820 Grade 3 to 5 (AEG35), or ISR in patients treated with SC atezolizumab 1875 mg Q3W.

2821 **Table 50. ER Assessment General Information**

General Information	
Goal of ER analysis	The objective of this analysis was to evaluate the potential relationships between atezolizumab SC exposure and safety through ER in CIT-naïve patients with locally advanced or metastatic NSCLC receiving atezolizumab SC 1875 mg Q3W in Part 2 of IMscin001.
Study Included	BP40657 (IMscin001) Part/Phase 2/III Atezo SC arm (Cohort 5)
Population Included	Patients in IMscin001 with NSCLC, who had received at least one dose of atezolizumab SC and had at least one evaluable post-dose PK sample in Part 2 (Cohort 5) of IMscin001.
Endpoint	SAE, AESI, AEG35, IRR, and ISR
No. of Patients (total, and with individual PK)	Out of 247 patients allocated to the Atezo SC arm (Cohort 5), 246 with model-predicted exposure data from PPK analysis were included in the ER analysis (one patient who received a single SC injection, in the upper arm, was excluded from the PPK analysis).

Atezolizumab and Hyaluronidase-tqjs Solution for Subcutaneous Injection

Population Characteristics (FDA Table 45)	General	Median age of 63 years (ranged 27 to 85 years). Median weight of 67.8 kg (ranged 30.0 to 117 kg). 174 (70.7%) were male, 72 (29.3%) were female. White: 173 (70.3%), American Indian or Alaska Native: 15 (6.1%), Asian: 47 (19.1%), Black or African American: 2 (0.8%), Native Hawaiian or other Pacific Islander: 1 (0.4%), Multiple: 6 (2.4%), Unknown: 2 (0.8%). Hispanic or Latino: 61 (24.8%), Not Hispanic or Latino: 184 (74.8%), Not reported: 0 (0%), Unknown: 1 (0.4%).	
	Organ impairment	Hepatic (based on NCI-ODWG criteria): 218 (88.6%) normal, 27 (11.0%) mild, 1 (0.4%) moderate. Renal (based on eGFR): 103 (41.9%) normal, 111 (45.1%) mild, 32 (13.0%) moderate.	
	Pediatrics (if any)	There were no patients under 18 years of age in the study.	
	Geriatrics (if any)	43.9% patients were ≥65 yr, 7.7% patients were >75 yr.	
Dose(s) Included	1875 mg Q3W SC in thigh		
Exposure Metrics Explored (range)	Cycle 1 AUC _{0-21 d} : 666 to 6572 µg*day/mL Cycle 1 C _{max} : 44.8, 514 µg/mL		
Covariates Evaluated	Age, sex, body weight, race, ethnicity, Eastern Cooperative Oncology Group (ECOG) score, albumin, lactate dehydrogenase (LDH), C-reactive protein (CRP), liver metastasis, neutrophil-to-lymphocyte ratio (NLR), smoking history, PD-L1 expressed on tumor-infiltrating immune cells (IC) and tumor cells (TC), as scored by immuno-histochemistry (i.e., present or absent [Yes/No], medium or high [Yes/No], high [Yes/No]), number of metastatic sites and histology of the disease, hepatic impairment, renal impairment.		
Final Model Parameters	Summary	Acceptability [FDA's comments]	
Model Structure	Safety (binary) endpoints were modeled using logistic regression versus exposure as a continuous variable.	Yes	
Model Parameter Estimates	FDA Table 51	Yes	
Model Evaluation	Not conducted.		

Covariates and Clinical Relevance	SAE and AEG35: Positive factor: CRP AESI: None of the covariates was statistically significant (p >0.05). ISR: Positive factor: Ethnicity (small sample size)	Yes. CRP was identified as a common risk factor for SAE and ISR.
Simulation for Specific Population	None performed.	
Visualization of E-R relationships	FDA Figure 18 , FDA Figure 19 , FDA Figure 20 , FDA Figure 21 Logistic regression with exposure metrics stratified by quartiles	Yes
Overall Clinical Relevance for ER	No statistically significant relationship between the probability of SAE/AESI/AEG35/ISR and atezolizumab exposure metrics tested (p >0.05) in the Atezo SC arm.	Yes
Labeling Language	Description	Acceptability [FDA's comments]
12.2 Pharmacodynamics	None.	

2822

2823 **FDA Table 51. Parameter Estimates from Final ER Model of SAE, AESI, AEG35, and ISR, Respectively.**

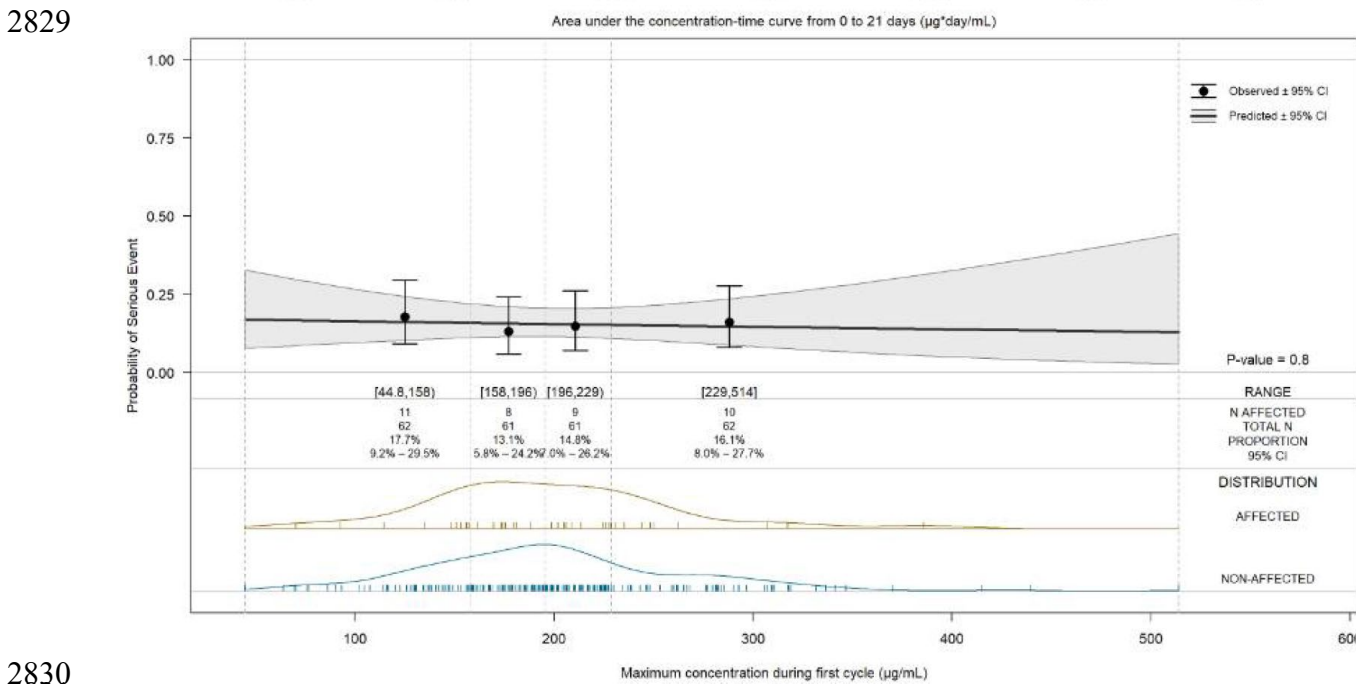
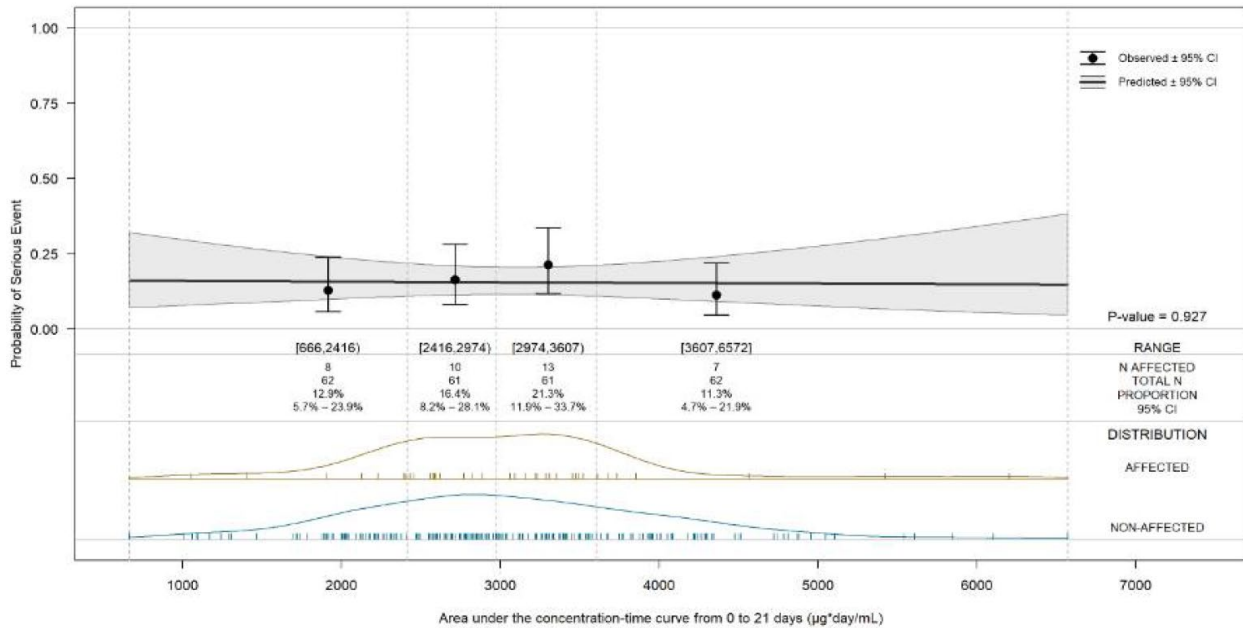
Response	Model	Exposure [#]	Covariate [#]	OR (95% CI) [§]	p-Value
SAE	Logistic regression	C _{max} /100		0.210 (-0.436, 0.368)	0.441
			CRP /10	0.130 (-0.442, 0.604)	<0.001***
AESI	Logistic regression	AUC _{0-21d} /1000	--	0.971 (0.723, 1.29)	0.840
		C _{max} /100	--	0.994 (0.642, 1.51)	0.978
AEG35	Logistic regression	AUC _{0-21d} /1000		1.143 (0.896, 1.459)	0.281
			CRP /10	0.921 (0.874, 0.971)	0.00218**
ISR	Logistic regression	AUC _{0-21d} /1000		1.79 (0.933, 3.40)	0.0793
			Ethnicity: Hispanic or Latino	0.0782 (0.000586, 0.689)	0.0161*
			Ethnic: Unknown	10.9 (0.0684, 258)	0.2559

2824 Source: Tables 13, 14, 16, and 18 of ER report.

2825 [#]Exposure and some of the covariates were scaled with the respective scaling factors indicated.2826 [§]OR (odds ratio) for logistic regression calculated for 1 unit increase of scaled continuous variable or ratio compared to reference level of categorical variable. CRP: C-reactive protein.2827 Unit: C_{max} in µg/mL, AUC_{0-21d} in µg*day/mL, CRP in mg/L.

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.

2828 **FDA Figure 18. ER Curves of SAE Versus AUC_{0-21 d} or C_{max} or in 246 Patients.**

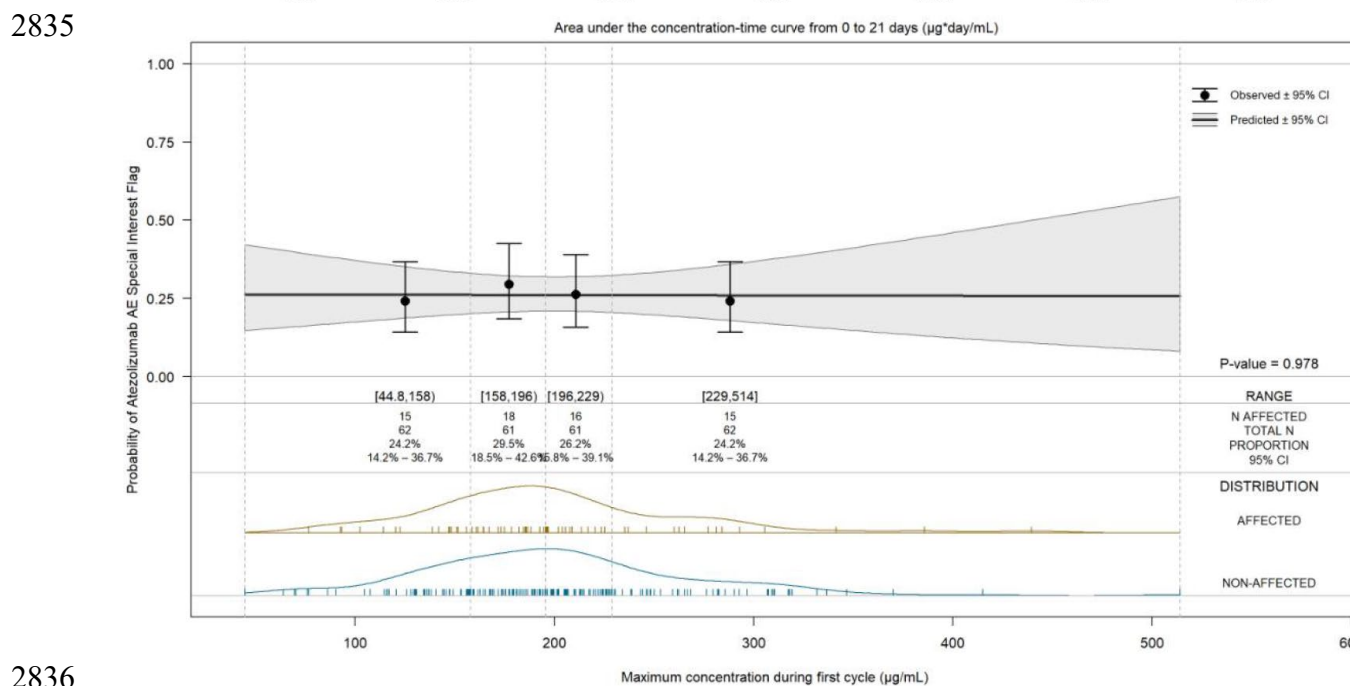
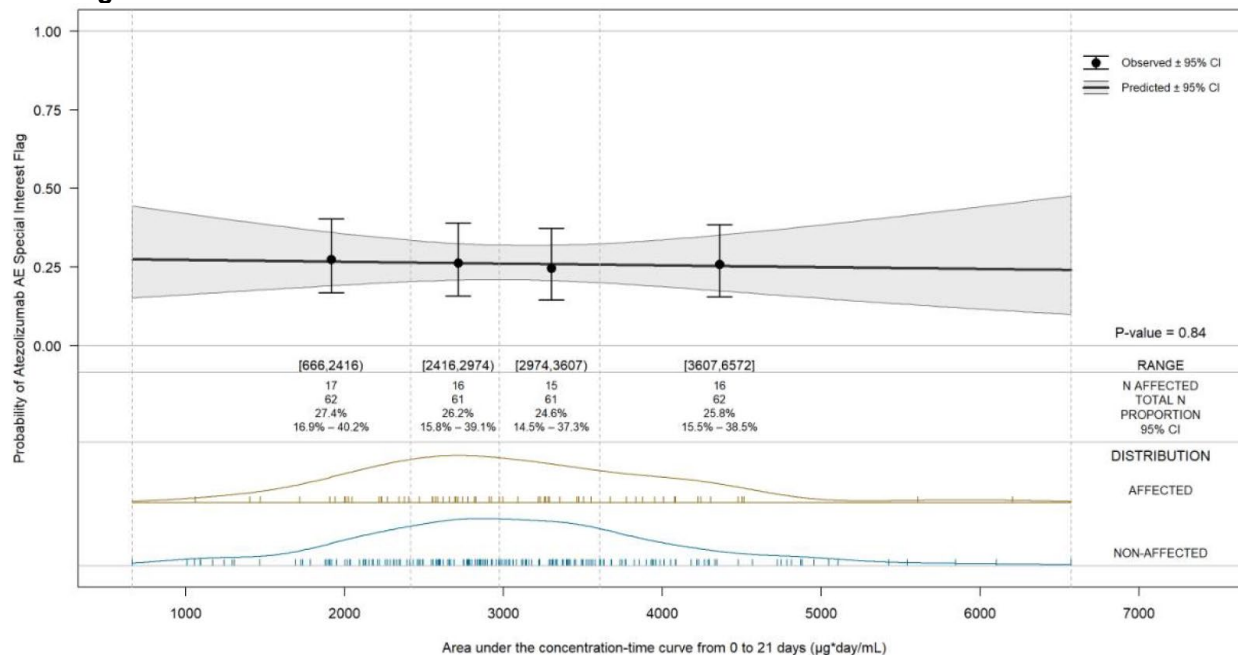


2830
 2831 Source: Figures 7 to 8 of ER report.

2832

2833

2834 **FDA Figure 19. ER Curves of AESI Versus AUC_{0-21 d} or C_{max} or in 246 Patients.**

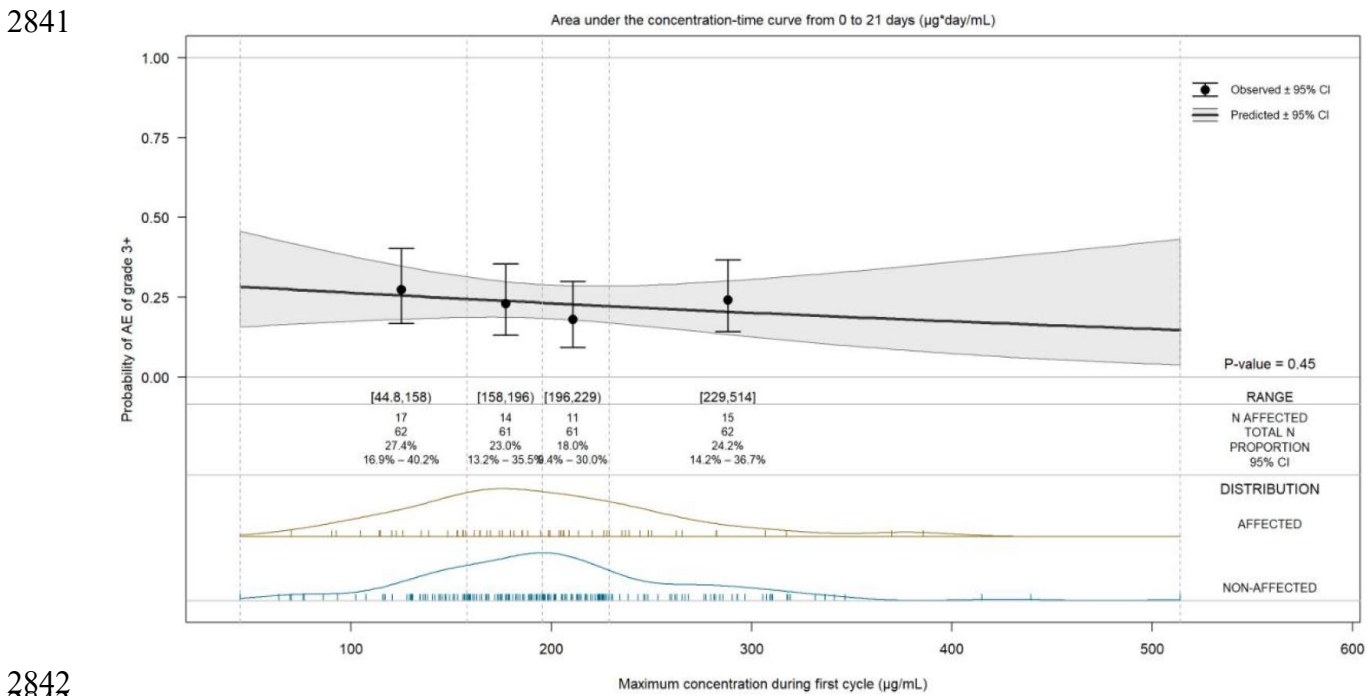
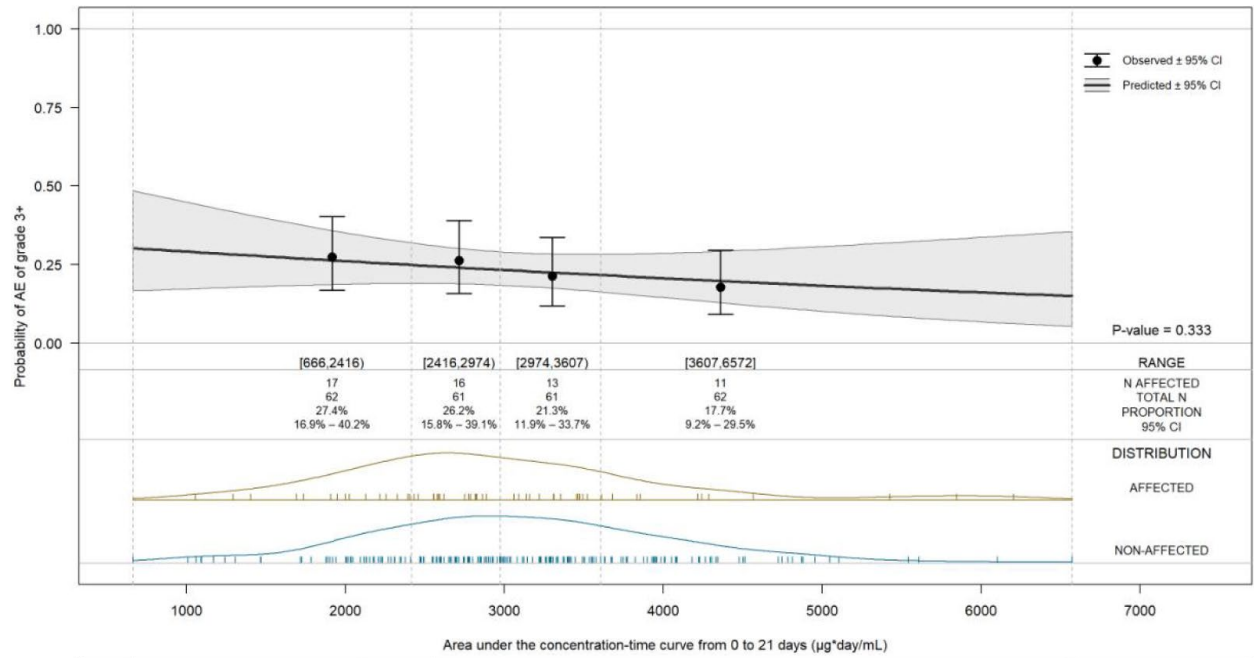


2836
 2837 Source: Figures 9 to 10 of ER report.

2838

2839

2840 **FDA Figure 20. ER Curves of AEG35 Versus AUC_{0-21 d} or C_{max} or in 246 Patients.**

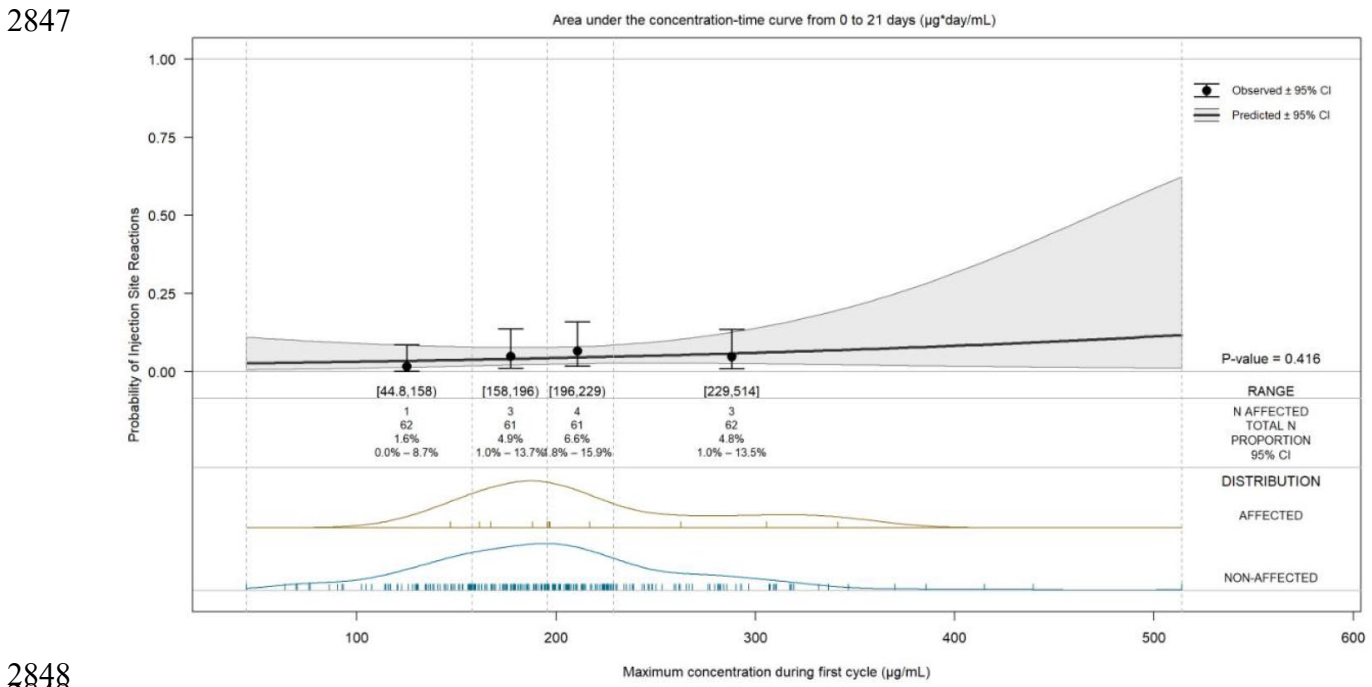
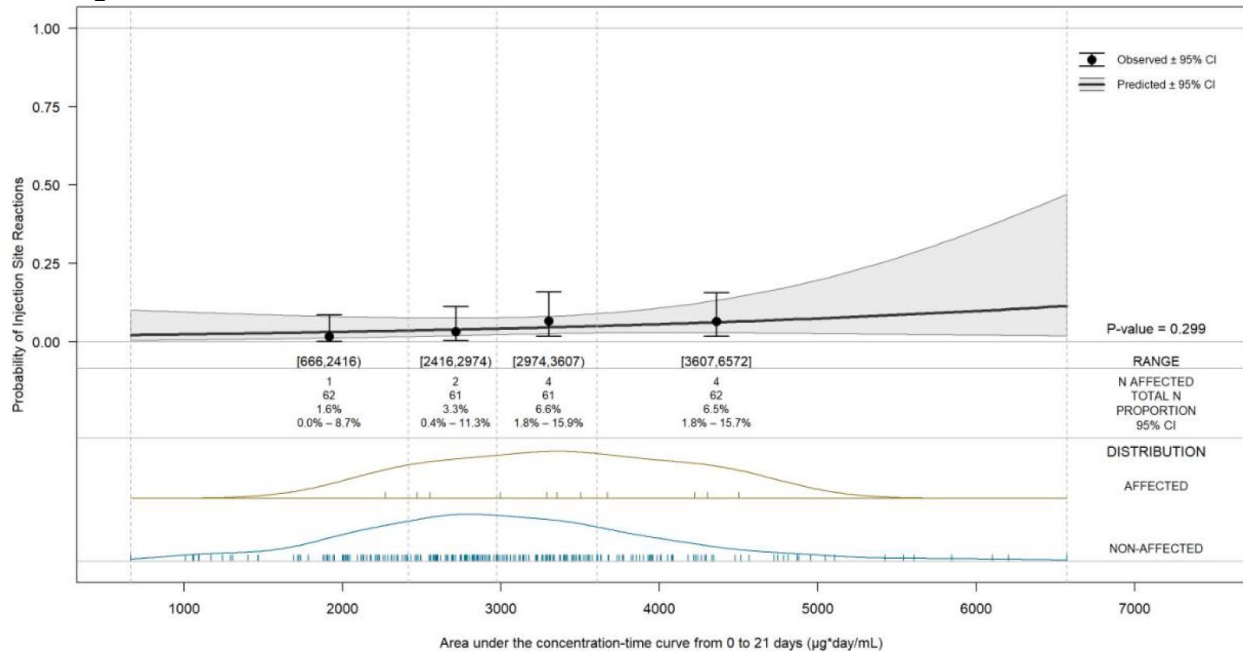


2842
 2843 Source: Figures 11 to 12 of ER report.

2844

2845

2846 **FDA Figure 21. ER Curves of ISR Versus AUC_{0-21 d} or C_{max} or in 246 Patients.**



2848
 2849 Source: Figures 13 to 14 of ER report.

2850
 2851 The FDA's Assessment: FDA agrees with the Applicant's position.

2852 **19.4.11. ER Review Issues**

2853 None.

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.

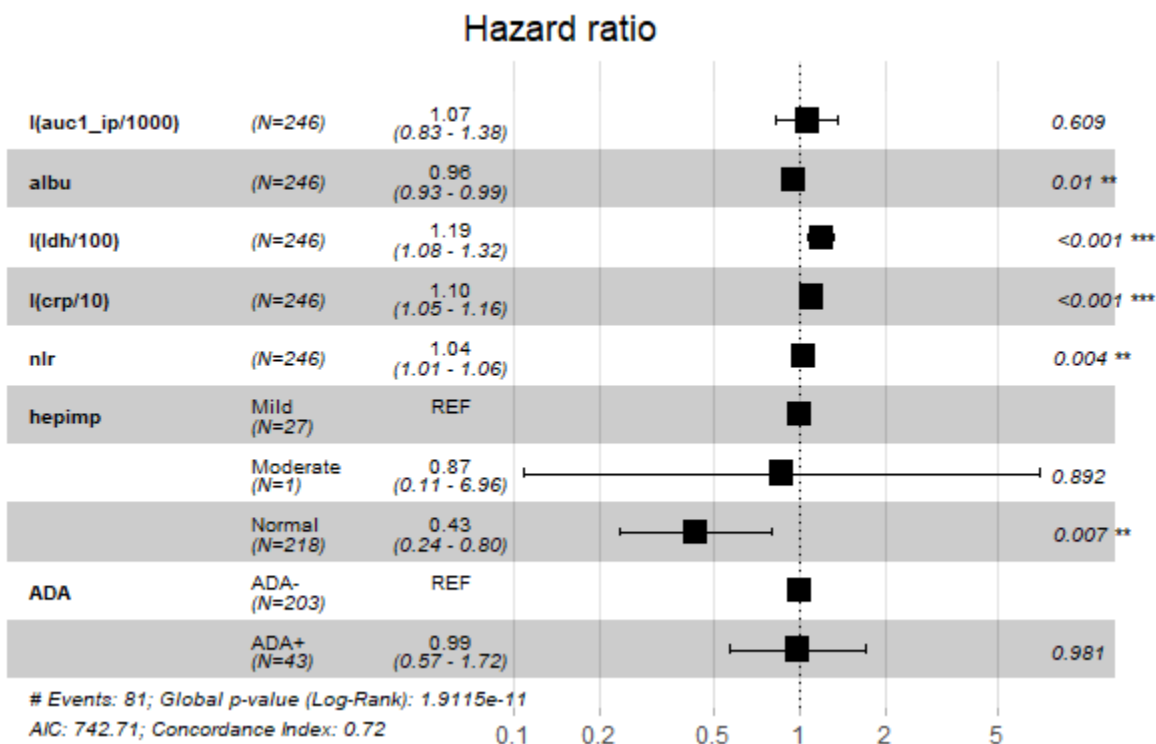
2854 **19.4.12. Reviewer’s Independent Analysis**

2855 **Overall Survival (OS) by ADA Status**

2856 Given the rapid onset of ADA, subject level ADA was further assessed as a covariate using the
 2857 final CoxPH model (refer to [FDA Table 49](#). ADA was not found to be a significant covariate
 2858 ([FDA Figure 22](#)). This analysis was also verified with the updated OS data with 60% events
 2859 (data cutoff: 1/16/2023, results not provided) that showed consistent result.

2860

2861 **FDA Figure 22. Forest plot of the Model Including ADA as a Covariate.**



2862
 2863 Source: Reviewer’s analysis.

2864

2865 **19.4.13. Overall Benefit-Risk Evaluation Based on E-R**
 2866 **Analyses**

2867 The Applicant’s Position: The flat E-R relationships between atezolizumab exposure and
 2868 efficacy/safety support an overall favorable benefit-risk profile for atezolizumab SC 1875 mg
 2869 Q3W.

2870 The FDA’s Assessment: FDA agrees with the Applicant’s position.

2871

19.5. Additional Safety Analyses Conducted by FDA

2872 The FDA’s Assessment: Not applicable.

2873 19.6. Appendix - Study MO43576 (IMscin002)

2874 Table 52. Applicant-Listing of Clinical Trials Relevant to this to this BLA From Appendix

Trial Identity	NCT no.	Trial Design	Regimen/ schedule/ route	Primary Study Endpoints	Treatment Duration/ Follow-Up	No. of patients enrolled	Study Population	No. of Centers and Countries
MO43576 (IMSCIN002),	NCT05171777	Phase II, randomized, multi-center, multinational, open-label, cross-over study	1875 mg atezo SC q3w vs. 1200 mg atezo IV q3w Cross-over regimen: Patients were randomized to 3 cycles of IV followed by 3 cycles of SC, or to SC followed by IV	Proportion of participants who preferred atezolizumab SC to atezolizumab IV, with treatment preference assessed using Question 1 of the Patient Preference Questionnaire (PPQ)	Until Cycle 16 for patients with early- stage NSCLC, or loss of clinical benefit for patients with advanced NSCLC	Atezo IV/SC=89, and Atezo SC/IV=90	Patients with PD-L1 positive NSCLC: • Patients with resected Stage II, IIIA, and selected IIIB NSCLC who have completed adjuvant platinum-based chemotherapy without evidence of disease relapse/recurrence • Chemotherapy-naïve patients with Stage IV NSCLC (PD-L1 high)	37 centers in 12 countries

2875

19.6.1.1. Efficacy Results – PRO Endpoint: Patient Experience Information

Data: Study MO43576 (IMscin002) is being conducted to evaluate patient reported preference for the route of administration within the context of use of Atezo SC. The primary analysis results from this study were submitted to the Agency (per agreement in the Type D written responses dated 12 April 2024) on 30 April 2024, after the initial BLA submission. Key PRO results from the CSR (Report 1128129) are summarized below.

IMscin002 is a Phase II, randomized, multi-center, multinational, open-label, cross-over study in adult patients with resected Stage II, IIIA, and selected IIIB (T3N2) NSCLC who have completed adjuvant platinum-based chemotherapy without evidence of disease relapse/recurrence, and chemotherapy-naïve patients with Stage IV NSCLC. This study is still ongoing and the primary analysis (CCOD: 09 November 2023) took place when all patients had completed their last study treatment administration in the Treatment Cross-over Period. The final study analysis will be conducted after all patients have received 16 cycles of Atezo or discontinued study treatment.

Study Population

The population of patients enrolled in the IMscin002 study was representative of patients with locally advanced or metastatic NSCLC that has not been previously treated. As of the CCOD of this primary analysis a total of 179 patients were included in the study across the treatment arms: 89 patients were randomized to the Atezo IV/SC arm and 90 patients were randomized to the Atezo SC/IV arm.

The treatment arms were well-balanced with respect to baseline demographics and patient history of lung cancer. The majority of patients were White, male, former tobacco users, had not previously received systemic cancer therapy, had non-squamous NSCLC, and had Stage IV at enrollment, with a median age of 67 years old.

The FDA's Assessment: Patient experience was evaluated based on the results from IMscin002 study. Study IMscin002 is a randomized, multi-center, open-label cross-over trial conducted in patients with NSCLC. The study population consisted of patients with PD-L1 positive NSCLC (TC $\geq$ 1% or TPS $\geq$ 1%) with either resected Stage II, IIIA, or early-stage Stage IIIB disease who had completed adjuvant platinum-based chemotherapy without disease relapse, and patients with PD-L1 high (TC $\geq$ 50% or TPS $\geq$ 50%), chemotherapy-naïve Stage IV NSCLC. Randomization was stratified by disease stage (II vs. III vs. IV) and type of surgery (pneumonectomy vs. no surgery vs. any other surgery). Eligible patients were randomly assigned in a 1:1 ratio to two treatment arms:

- Atezolizumab SC 1875 mg Q3W for 3 cycles followed by atezolizumab IV 1200 mg Q3W for an additional 3 cycles
- Atezolizumab IV 1200 mg Q3W for 3 cycles followed by atezolizumab SC 1875 mg Q3W for an additional 3 cycles.

For the evaluation of the patient-reported experience, the primary endpoint for Study IMscin002 is the proportion of patients who preferred atezolizumab SC vs IV as assessed by a Patient Preference Questionnaire (PPQ). The PPQ responses were collected either on Cycle 6 Day 1 (C6D1) or after at least two consecutive administrations of each treatment method in case of treatment discontinuation prior to C6D1. Patients were excluded from the PPQ analysis set in case of study/treatment discontinuation or death prior to responding to the PPQ. Patients who were randomized to a treatment arm but never received any study treatment were also excluded from the PPQ analysis set. Secondary endpoints include patient-reported satisfaction, patients' choice of treatment, and safety.

Sample size was based on the assumption that 70% of patients prefer atezolizumab SC over atezolizumab IV, which meant a total of 126 patients were needed to obtain a 95% CI, where the distance is approximately $\pm 8\%$ from the estimated proportion to the lower or upper limits of the 95% CI. The proposed sample size was 175 to account for a non-evaluable PPQ assessment for 28% of randomized patients. The proposed descriptive analysis included the point estimate and the corresponding 95% CI for the proportion of patients who preferred atezolizumab SC over atezolizumab IV.

IMscin002 Results – PRO endpoints

Data: Of the patients eligible to answer the PPQ, a total of 123/126 patients (97.6%) completed Question 1 of the PPQ. Fifty-six of 179 patients randomized did not answer the PPQ: 4 patients were not treated, 14 patients died prior to answering the PPQ, 35 patients discontinued treatment prior to eligibility for PPQ, and 3 did not respond for other reasons.

The majority of patients preferred Atezo SC administration (70.7%; 95% CI: 61.9%, 78.6%) over Atezo IV administration (21.1%), and 8.1% of patients had no preference in route of administration. The preference for Atezo SC administration was similar regardless of the switching sequence (71.7% for the Atezo IV/SC arm and 69.8% for the Atezo SC/IV arm). Overall, the majority of patients who preferred Atezo SC (86.2%) had a very strong or fairly strong preference for the Atezo SC administration over Atezo IV administration. The most common reasons given for preference of the Atezo SC administration were: “requires less time in the clinic” and “feels more comfortable during administration”. Among the patients who preferred the Atezo IV administration, 72.0% indicated a “very strong” or “fairly strong” preference. The most common reasons given for preference of the Atezo IV administration were: “feels more comfortable during administration” and “lower level of injection site pain”.

Patient preference was supported by patient satisfaction. A majority of patients (85.8%) were “very satisfied” or “satisfied” with Atezo SC administration, compared to 75.2% with Atezo IV. The choice of SC administration during the Treatment Continuation Period was consistent with patient preference, with 79.4% of the 107 patients who entered this period choosing Atezo SC administration. All patients who entered the Continuation Period maintained their chosen administration method as of the CCOD. When asked specific questions about their experience with both Atezo IV and Atezo SC, patients more often cited Atezo SC administration as being the less restrictive route of administration and allowed more time for other activities.

The Applicant's Position: The IMscin002 primary analysis demonstrated that a majority of patients preferred atezolizumab SC (70.7%) over atezolizumab IV (21.1%). The most commonly reported reasons for this preference were “requires less time in the clinic” and “feels more comfortable during administration.” Patient preference was supported by patient satisfaction with a majority of patients (85.8%) being ‘very satisfied’ or ‘satisfied’ with the Atezo SC administration and was further supported by patient choice with 79.4% of patients choosing to continue their treatment with Atezo SC administration during the Treatment Continuation Period.

The FDA's Assessment: FDA conducted an analysis of PPQ data from IMscin002. The IMscin002 study had randomized 179 patients. Of these 179 patients, 53 (30%) were not included in the primary PPQ analysis population. Of these 53 patients, 39 (74%) discontinued treatment in the originally assigned treatment period and 14 (26%) patients discontinued during the crossover treatment period, and thus were not included in the primary PPQ analysis population. A total of 126 (70%) patients were included in the PPQ analysis population.

Of these 126 patients, 123 (98%) completed the PPQ. The results based on these 123 patients are provided in the table below, based on a data cut-off date of November 9, 2023.

FDA Table 53. PPQ Response Analysis (IMscin002 Study)

	Treatment Order		Total N = 126
	Atezo IV/SC N = 61	Atezo SC/IV N = 65	
Number of responders, n (%)	60 (98)	63 (97)	123 (98)
	N = 60	N = 63	N = 123
Preferred mode of administration, n (%)			
SC	43 (72)	44 (70)	87 (71)
IV	12 (20)	14 (22)	26 (21)
No preference	5 (8)	5 (8)	10 (8)
Preference as SC			
Preference rate, n (%)	43 (72)	44 (70)	87 (71)
95% CI	(59, 83)	(57, 81)	(62, 79)
	N = 43	N = 44	N = 87
Level of preference for SC, n (%)			
Very strong	16 (37)	15 (34)	31 (36)
Fairly strong	22 (51)	22 (50)	44 (51)
Not very strong	5 (12)	7 (16)	12 (14)
Primary reasons for preferring SC ¹ , n (%)			
Less distress	15 (35)	11 (25)	26 (30)
Avoid clinic	25 (58)	31 (70)	56 (64)
Less pain	6 (14)	9 (20)	15 (17)
Comfort	18 (42)	22 (50)	40 (46)
Other	1 (2.3)	3 (7)	4 (4.6)

	Treatment Order		Total N = 126
	Atezo IV/SC N = 61	Atezo SC/IV N = 65	
	N = 12	N = 13 ²	N = 25
Level of preference for IV, n (%)			
Very strong	3 (25)	4 (31)	7 (28)
Fairly strong	5 (42)	6 (46)	11 (44)
Not very strong	4 (33)	3 (23)	7 (28)
Primary reasons for preferring IV¹, n (%)			
Less distress	1 (8)	2 (15)	3 (12)
Avoid clinic	0 (0)	0 (0)	0
Less pain	6 (50)	9 (69)	15 (60)
Comfort	9 (75)	11 (85)	20 (80)
Other	2 (17)	0 (0)	2 (8)

Source: adsl.xpt and adqs.xpt datasets provided by the Applicant

¹ Patients are counted in multiple categories.

² One patient (Subject ID: MO43576 (b) (6)) in Atezo SC/IV set preferred IV administration but had no subsequent responses for the "Level of preference" and "Primary reasons for preferring IV" questions. Proportions exclude this particular patient.

Data cut-off: November 9, 2023

Of the 126 patients who were eligible for the PPQ, a total of 107 patients completed the crossover treatment, 10 patients discontinued treatment during the crossover treatment period and 9 patients are still receiving treatment in the crossover treatment period. Of the 107 patients who completed the crossover treatment, 85 (79%) chose to receive SC administration in the treatment continuation period. These 85 patients included 42 patients from the Atezo IV/SC set and 43 patients from the Atezo SC/IV set.

Of the 10 patients who were PPQ-eligible but discontinued treatment during the crossover treatment period (FDA Table 54), two did not respond to the PPQ, five had their response to the PPQ recorded during the "Cycle 6 Day 1" visit, while three patients had their response to the PPQ recorded at their "End of Treatment" visit. The relevant patient-level details for these 10 patients are provided in the table below.

FDA Table 54. Patient-level Information for PPQ-eligible Patients who Discontinued Treatment at the Crossover Stage

Patient ID	Time of PPQ Response	Date of PPQ Response	Reason for Treatment Discontinuation	Date of Treatment Discontinuation	Date of Study Discontinuation
MO43576	(b) (6)	C6D1	Progressive Disease	(b) (6)	
MO43576		C6D1	Death		(b) (6)
MO43576		EOT	Adverse Event		
MO43576	a		Withdrawal By Subject		(b) (6)
MO43576		EOT	Progressive Disease		
MO43576		C6D1	Other		(b) (6)
MO43576	a		Progressive Disease		
MO43576	b	C6D1	Progressive Disease		
MO43576		C6D1	Progressive Disease		(b) (6)
MO43576		EOT	Disease Relapse		

Source: adsl.xpt, adex.xpt and adqs.xpt datasets provided by the Applicant

^a Patients did not respond to the PPQ

^b Patient discontinued treatment on (b) (6), with last date of exposure to study treatment on C6D1, dated (b) (6), but PPQ response was recorded on (b) (6)

C6D1 = Cycle 6 Day 1, EOT = End of treatment

Data cut-off date: November 9, 2023

The table below provides the patient distribution by treatment administration preference per the PPQ and actual administration method in the treatment continuation stage of the trial. A total of 99 patients, out of 107, had a clear preference in mode of treatment administration, while the remaining 8 patients had no preference for method of treatment administration. The rate of disagreement was 1.0% in patients who had a preference per PPQ (one out of 99 patients with a clear preference did not receive the preferred choice as method of administration). Of the 8 patients with no preference, 5 received SC administration and 3 received IV administration.

1 **FDA Table 55. Distribution by Preference and Actual Method of Administration for Patients who**
 2 **Completed Crossover Treatment**

		Treatment in Continuation Stage		Total
		SC	IV	
Preference per PPQ	SC	79	0	79
	IV	1 ^a	19	20
	No preference	5	3	8
Total		85	22	107

3 Source: adsl.xpt and adqs.xpt datasets provided by the Applicant.
 4 ^a One patient (Subject ID: MO43576 (b) (6)) preferred IV administration per PPQ but received SC administration in the treatment
 5 continuation stage.
 6 Data cut-off date: November 9, 2023.

7 Overall, patients who received both routes of administration in the IMscin002 study stated
 8 preference for the subcutaneous route of administration and maintained this preference during
 9 the continuation stage. The main reason patients preferred SC was convenience, while most who
 10 preferred IV had less pain/discomfort. A summary of the PPQ information will be included in the
 11 USPI.

12 **19.6.1.2. MO43576 (IMscin002) Primary Analysis: Safety**
 13 **Results**

14 Overall, the safety profile for all patients during the combined treatment periods of Atezo IV and
 15 Atezo SC of the study is consistent with the established atezolizumab safety profiles of IV and
 16 SC. No new, unexpected safety findings were observed, and results are consistent with Atezo IV.
 17 The safety and tolerability of switching between Atezo IV and Atezo SC were evaluated.
 18 Analysis the safety and tolerability of switching between Atezo IV and Atezo SC route of
 19 administration (and vice versa) did not reveal any new or clinically relevant safety concerns.
 20 Switching between Atezo SC and IV (and vice versa) was generally well-tolerated and well-
 21 managed.

- 22 • Overall, 76.6% of patients experienced at least one AE. During the Crossover Period, a
 23 higher proportion of patients reported AEs during Atezo IV administration (58.8%)
 24 compared with Atezo SC administration (47.7%).
- 25 • Of the overall reported AEs, the majority of patients (89/175 patients [50.9%]) reported a
 26 Grade 1–2 AE at highest intensity.
- 27 • Overall 22.3% of patients experienced a highest Grade 3–4 AE, and 3.4% of patients
 28 experienced a Grade 5 AE.
- 29 • Overall, Grade 5 AEs were reported in 6/175 patients [3.4%]. In the Crossover Period,
 30 Grade 5 AEs were reported at a numerically higher rate during Atezo SC administration
 31 compared with the Atezo IV administration (2.6% vs. 0.6%, respectively). The events were
 32 single occurrences across different system organ classes with no trends identified.
- 33 • Overall, 10.3% of patients discontinued treatment due to an AE.

- 34 • Overall, 52% of patients experienced at least one treatment-related AE. The most common
35 (> 10%) treatment-related AEs by PT were injection site reaction and pruritus (10.3% of
36 patients each).
- 37 • During the Crossover Period, a similar proportion of patients reported treatment-related AEs
38 during Atezo IV administration (31.3% of patients) and Atezo SC administration (33.5% of
39 patients).
- 40 • Overall, 10.3% of patients reported an injection site reaction. A higher proportion of injection
41 site reactions occurred during Atezo SC administration in the Crossover Period (9.7%)
42 compared with the Continuation Period (3.5%). The frequency of site reactions was to be
43 expected due to the mode of administration via SC injection.
- 44 • In the Atezo IV/SC arm, the incidence of AEs during Cycles 1–3 (IV treatment) was 62.9%
45 compared with 39.1% in Cycles 4–6 (SC treatment).
- 46 • In the Atezo SC/IV arm, the incidence of AEs during Cycles 1–3 (SC treatment) was 54.7%
47 compared with 53.5% Cycles 4–6 (IV treatment).

48 The FDA's Assessment: FDA agrees with Applicant's description of the data. FDA notes that
49 safety was a secondary endpoint for IMscin002. FDA did not independently verify the safety
50 results of IMscin002.

51

Signatures

DISCIPLINE	REVIEWER	OFFICE/DIVISION	SECTIONS AUTHORED/ APPROVED	AUTHORED/ APPROVED
Nonclinical Reviewer	Kelie Reece, PhD	CDER/OND/OOD/DH OT	Sections: 5	Select one: ☒ Authored ☒ Approved
	Signature: Kelie M. Reece -S Digitally signed by Kelie M. Reece -S Date: 2024.09.06 16:29:39 -04'00'			
Nonclinical Team Leader	Claudia Miller, PhD	CDER/OND/OOD/DH OT	Sections: 5	Select one: ☒ Authored ☒ Approved
	Signature: Claudia Miller -S Digitally signed by Claudia Miller -S Date: 2024.09.09 09:21:19 -04'00'			
Clinical Pharmacology Reviewer	Ritu Chadda, PhD	CDER/OTS/OCP/DCPII	Sections: 6	Select one: ☒ Authored ☐ Approved
	Signature: Ritu Chadda -S Digitally signed by Ritu Chadda -S Date: 2024.09.09 10:25:44 -04'00'			
Pharmacometrics Reviewer	Ye Xiong, PhD	CDER/OTS/OCP/DPM	Sections: 6; 19.4	Select one: ☒ Authored ☐ Approved
	Signature: Ye Xiong -S Digitally signed by Ye Xiong -S Date: 2024.09.06 16:20:44 -04'00'			
Pharmacometrics Team Lead	Youwei Bi, PhD	CDER/OTS/OCP/DPM	Sections: 6, 19.4	Select one: ☒ Authored ☒ Approved
	Signature: Youwei Bi -S Digitally signed by Youwei Bi -S Date: 2024.09.09 09:17:33 -04'00'			

Master Pharmacokineticist	Hong Zhao, PhD	CDER/OTS/OCP/DCPII	Sections: 6, 19.4	Select one: ☒ Authored ☒ Approved
	Signature: Hong Zhao -S Digitally signed by Hong Zhao -S Date: 2024.09.06 16:02:59 -04'00'			
Clinical Pharmacology Division Director	Nam Atiqur Rahman, PhD	CDER/OTS/OCP/DCPII	Sections: 6, 19.4	Select one: ☒ Approved
	Signature: Nam A. Rahman -S Digitally signed by Nam A. Rahman -S Date: 2024.09.11 11:43:36 -04'00'			
Clinical Reviewer	Katie Chon, PharmD	CDER/OND/OOD/DOII	Sections: 1, 2, 3, 4, 7, 8, 9, 10, 12, 13, 19.2, 19.6	Select one: ☒ Authored ☐ Approved
	Signature: WONME K. CHON -S Digitally signed by WONME K. CHON -S Date: 2024.09.11 08:49:12 -04'00'			
Clinical Reviewer	Satinder Choudhary, PharmD	CDER/OND/OOD/DOII	Sections: 1, 8, 19.6	Select one: ☒ Authored ☐ Approved
	Signature: Satinder K. Choudhary -S Digitally signed by Satinder K. Choudhary -S Date: 2024.09.09 10:00:43 -04'00'			
Statistical Reviewer	Somak Chatterjee, PhD	CDER/OTS/OB/DBV	Sections: 8, 19.6	Select one: ☒ Authored ☐ Approved
	Signature: Somak Chatterjee -S Digitally signed by Somak Chatterjee -S Date: 2024.09.09 10:06:49 -04'00'			
Statistical Team Leader	Xiaoxue Li, PhD	CDER/OTS/OB/DBV	Sections: 8, 19.6	Select one: ☒ Authored ☒ Approved
	Signature: Xiaoxue Li -S Digitally signed by Xiaoxue Li -S Date: 2024.09.06 16:26:58 -04'00'			

Division Director (OB)	Shenghui Tang, PhD	CDER/OTS/OB/DBV	Sections: 8, 19.6	Select one: ☒ Approved
	Signature: Shenghui Tang -S Digitally signed by Shenghui Tang Date: 2024.09.09 14:41:45 -04'00'			
Associate Director for Labeling (ADL)	Barbara Scepura, MSN	CDER/OND/OOD/DOII	Sections:11	Select one: ☒ Authored ☐ Approved
	Signature: Barbara A. Scepura -S Digitally signed by Barbara A. Scepura -S Date: 2024.09.06 16:09:38 -04'00'			
Associate Director for Patient Outcomes	Vishal Bhatnagar, MD	OCE	Sections: All	Select one: ☐ Authored ☒ Approved
	Signature: Vishal Bhatnagar -S Digitally signed by Vishal Bhatnagar -S Date: 2024.09.09 09:24:17 -04'00'			
Cross-Disciplinary Team Leader (CDTL)/Supervisory Associate Director (Acting)	Paz Vellanki, MD, PhD	CDER/OND/OOD/DOII	Sections: All	Select one: ☒ Authored ☒ Approved
	Signature: Paz J. Vellanki -S Digitally signed by Paz J. Vellanki -S Date: 2024.09.11 12:03:15 -04'00'			

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/s/

JEFFREY T INGALLS
09/12/2024 04:52:34 PM

PAZ J VELLANKI
09/12/2024 05:05:24 PM

MEMORANDUM

Date: August 14, 2024
From: Kelie M. Reece, PhD
 Pharmacology/Toxicology Reviewer
 Division of Hematology Oncology Toxicology for Division of Oncology 2
Through: Claudia P. Miller, PhD
 Supervisory Pharmacologist
 Division of Hematology Oncology Toxicology for Division of Oncology 2
To: File for BLA 761347
Re: Supporting Document (SD) 30, Resubmission/BLA

On November 15, 2023, Genentech, Inc. resubmitted BLA 761347 for atezolizumab and recombinant human hyaluronidase (rHuPH20) for subcutaneous (SC) injection. Atezolizumab is a monoclonal antibody that binds to programmed death-ligand 1 (PD-L1), blocking its interactions with both programmed cell death protein 1 (PD-1) and cluster of differentiation 80 (B7.1) receptors, leading to enhanced antitumor immune responses. Intravenous atezolizumab (Tecentriq) has been US FDA-approved since 2016 and is indicated for the treatment of multiple oncology indications. Hyaluronidase is a spreading or diffusing substance that modifies the permeability of connective tissue through hydrolysis of the mucopolysaccharide hyaluronic acid, resulting in enhanced drug delivery and allowing SC administration of larger drug volume. rHuPH20 is a purified, neutral pH-active preparation of human hyaluronidase generated by recombinant DNA technology in Chinese Hamster Ovary cells. rHuPH20 (Hylenex) has been US FDA-approved since 2005 and is indicated as an adjuvant to increase the absorption and dispersion of other injected drugs; for SC fluid administration; and as an adjunct in SC urography for improving the resorption of radiopaque agents.

The Applicant has developed a new product containing atezolizumab and rHuPH20 for SC injection (atezolizumab SC) for the same indications as Tecentriq. A summary of the significant labeling changes made by the nonclinical team are shown in the table below.

Summary of Significant Labeling Changes		
Section	Labeling Edits (red font)	Explanation of FDA’s Edits
8 USE IN SPECIFIC POPULATIONS 8.2 Lactation	There is no information regarding the presence of atezolizumab or hyaluronidase in human milk or its effects on the breastfed child, or on milk production. Maternal IgG is known to be present in human milk. The effects of local gastrointestinal exposure and limited systemic exposure in the breastfed child to TECENTRIQ HYBREZA are unknown. Because of the potential for	Revised this section to include hyaluronidase and to delete terminology the division is no longer using (i.e., (b) (4)). In addition, included text on the unknown effects of local GI exposure and limited systemic exposure in the breastfed child, which is being added to all anti-PD-(L)1 labels.

	serious adverse reactions in breastfed children from TECENTRIQ HYBREZA, advise women not to breastfeed during treatment with TECENTRIQ HYBREZA and for 5 months after the last dose.	
13 NONCLINICAL TOXICOLOGY 13.1 Carcinogenesis, Mutagenesis, Impairment of Fertility	This effect occurred at an estimated AUC approximately 6 times the AUC in patients receiving the recommended intravenous atezolizumab dose and was reversible.	The route of administration was added.
13 NONCLINICAL TOXICOLOGY 13.1 Carcinogenesis, Mutagenesis, Impairment of Fertility	In addition, when up to 220,000 units/kg of subcutaneous hyaluronidase (recombinant human) was administered to cynomolgus monkeys for 39 weeks, which is >223 times higher than the human recommended dose for hyaluronidase, no evidence of toxicity to the male or female reproductive system was found through periodic monitoring of in-life parameters (e.g., semen analyses, hormone levels, menstrual cycles, and also from gross pathology, histopathology and organ weight data).	Included the details in red font for clarity.
13 NONCLINICAL TOXICOLOGY 13.2 Animal Toxicology and/or Pharmacology	In animal models, inhibition of PD-L1/PD-1 signaling increased the severity of some infections and enhanced inflammatory responses. <i>Mycobacterium tuberculosis</i>-infected PD 1 knockout mice exhibit markedly decreased survival compared with wild-type controls, which correlated with increased bacterial proliferation and inflammatory responses in these animals. (b) (4)	(b) (6)

	(b) (4) PD-L1 and PD-1 knockout mice and mice receiving PD-L1 blocking antibody have also shown decreased survival following infection with lymphocytic choriomeningitis virus.	(b) (6) (b) (6) we agreed to omit this sentence, as doing so did not compromise the overall message being conveyed: severity of TB infection may increase with PD/L-1 products. Overall, the nonclinical team agreed that the label remains harmonized with other PD/L-1 labels because the message is consistent regarding severity.

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/s/

KELIE M REECE
08/14/2024 05:46:47 PM

CLAUDIA P MILLER
08/15/2024 08:58:11 AM