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APPLICATION NUMBER:

761381Orig1s000

761429Orig1s000

MULTI-DISCIPLINE REVIEW

Summary Review

Clinical Review

Non-Clinical Review

Statistical Review

Clinical Pharmacology Review

NDA/BLA Multi-disciplinary Review and Evaluation

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

“FDA review was conducted in conjunction with other regulatory authorities under Project Orbis. FDA collaborated Health Canada (HC), and Israel’s Ministry of Health (IMoH). While the conclusions and recommendations expressed herein reflect FDA’s completed review of the application, the applications may still be under review at the other regulatory agencies.”

Application Type	351(a) Biologics License Application (BLA)
Application Numbers	BLA 761381 and BLA 761429
Priority or Standard	Standard (BLA 761381) / Standard (BLA 761429)
Submit Dates	February 29, 2024 (BLA 761381) March 29, 2024 (BLA 761492)
Received Dates	February 29, 2024 (BLA 761381) March 29, 2024 (BLA 761429)
PDUFA Goal Dates	December 29, 2024 (BLA 761381) January 29, 2025 (BLA 761429)
Division/Office	Division of Oncology 3/Office of Oncologic Diseases
Review Completion Date	See attached electronic signature page
Established Name	nivolumab and hyaluronidase-nvhy
(Proposed) Trade Name	OPDIVO QVANTIG
Pharmacologic Class	combination of nivolumab, a programmed death receptor-1 (PD-1)-blocking antibody, and hyaluronidase, an endoglycosidase
Code name	BMS-986298
Applicant	Bristol-Myers Squibb Company (BMS)
Formulation(s)	Injection: 600 mg nivolumab and 10,000 units hyaluronidase per 5 mL (120 mg/2,000 units per mL) in a single-dose vial
Dosing Regimen	(b) (4) 600 mg nivolumab /10,000 units hyaluronidase every 2 weeks or 1,200 mg nivolumab /20,000 units hyaluronidase every 4 weeks.

	In combination with other anticancer drugs: 900 mg nivolumab/15,000 units hyaluronidase with platinum-doublet chemotherapy on the same day every 3 weeks for 3 cycles 900 mg nivolumab /15,000 units hyaluronidase every 3 weeks with cisplatin and gemcitabine on the same day for up to 6 cycles 600 mg nivolumab/10,000 units hyaluronidase every 2 weeks or 1,200 mg/20,000 units every 4 weeks administered in combination with fluoropyrimidine- and platinum-containing chemotherapy 900 mg nivolumab /15,000 units hyaluronidase every 3 weeks with fluoropyrimidine- and platinum-containing chemotherapy every 3 weeks
Applicant Proposed Indication(s)/Population(s)	Advanced Renal Cell Carcinoma • Nivolumab SC, as a single agent, is indicated for the first-line treatment of adult patients with intermediate or poor risk advanced RCC following treatment with OPDIVO and ipilimumab combination therapy. • Nivolumab SC, in combination with cabozantinib, is indicated for the first-line treatment of adult patients with advanced RCC. • Nivolumab SC, as a single agent, is indicated for the treatment of adult patients with advanced RCC who have received prior anti-angiogenic therapy. Adjuvant Treatment of Melanoma • Nivolumab SC is indicated for the adjuvant treatment of adult patients with completely resected Stage IIB, Stage IIC, Stage III, or Stage IV melanoma. Unresectable or Metastatic Melanoma • Nivolumab SC, as a single agent, is indicated for the treatment of adult patients with unresectable or metastatic melanoma. • Nivolumab SC, as a single agent, is indicated for the treatment of adult patients with unresectable or metastatic melanoma following treatment with OPDIVO

	and ipilimumab combination therapy. Neoadjuvant Treatment of Resectable NSCLC - Nivolumab SC, in combination with platinum-doublet chemotherapy, is indicated as neoadjuvant treatment of adult patients with resectable (tumors ≥ 4 cm or node positive) NSCLC. Neoadjuvant and Adjuvant Treatment of Resectable NSCLC <u>Nivolumab SC, in combination with platinum-doublet chemotherapy, is indicated as neoadjuvant treatment of adult patients with resectable</u> (tumors ≥ 4 cm or node positive) NSCLC, followed by nivolumab SC, as a single agent, as adjuvant treatment after surgery Metastatic NSCLC - Nivolumab SC, is indicated for the treatment of adult patients with metastatic NSCLC with progression on or after platinum-based chemotherapy. Patients with EGFR or ALK genomic tumor aberrations should have disease progression on FDA-approved therapy for these aberrations prior to receiving Nivolumab SC. Squamous Cell Carcinoma of the Head and Neck - Nivolumab SC is indicated for the treatment of adult patients with recurrent or metastatic SCCHN with disease progression on or after platinum-based therapy. Urothelial Carcinoma - Nivolumab SC is indicated for the adjuvant treatment of adult patients with UC who are at high risk of recurrence after undergoing radical resection of UC. - Nivolumab SC, in combination with cisplatin and gemcitabine, is indicated for the first-line treatment of adult patients with unresectable or metastatic UC. - Nivolumab SC is indicated for the treatment of adult patients with locally advanced or metastatic UC who: - have disease progression during or following platinum-containing chemotherapy - have disease progression within 12 months of neoadjuvant or adjuvant treatment with platinum-containing chemotherapy. Microsatellite Instability-High or Mismatch Repair Deficient Metastatic CRC
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	- Nivolumab SC, as a single agent, is indicated for the treatment of adult patients with MSI-H or dMMR metastatic CRC that has progressed following treatment with a fluoropyrimidine, oxaliplatin, and irinotecan. This indication is approved under accelerated approval based on overall response rate and duration of response. Continued approval for this indication may be contingent upon verification and description of clinical benefit in confirmatory trials. Hepatocellular Carcinoma - Nivolumab SC, as a single agent, is indicated for the treatment of adult patients with HCC who have been previously treated with sorafenib and following treatment with OPDIVO and ipilimumab combination therapy. This indication is approved under accelerated approval based on overall response rate and duration of response. Continued approval for this indication may be contingent upon verification and description of clinical benefit in the confirmatory trials. Esophageal Cancer - Nivolumab SC is indicated for the adjuvant treatment of completely resected esophageal or gastroesophageal junction cancer with residual pathologic disease in adult patients who have received neoadjuvant chemoradiotherapy. - Nivolumab SC, in combination with fluoropyrimidine- and platinum-containing chemotherapy, is indicated for the first-line treatment of adult patients with unresectable advanced or metastatic esophageal squamous cell carcinoma. - Nivolumab SC is indicated for the treatment of adult patients with unresectable advanced, recurrent, or metastatic esophageal squamous cell carcinoma after prior fluoropyrimidine- and platinum-based chemotherapy. Gastric Cancer, Gastroesophageal Junction Cancer, and Esophageal Adenocarcinoma - Nivolumab SC, in combination with fluoropyrimidine- and platinum-containing chemotherapy, is indicated for
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	the treatment of adult patients with advanced or metastatic gastric cancer, gastroesophageal junction cancer, and esophageal adenocarcinoma.
Recommendation on Regulatory Action	Traditional Approval for all applications excepting HCC and dMMR/MSI-H CRC. These applications are under Accelerated Approval for Opdivo and would remain on AA for Opdivo Qvantig.
Recommended Indication(s)/Population(s) (if applicable)	Opdivo Qvantig is indicated for the following indications: <u>Renal Cell Carcinoma (RCC)</u> - adult patients with intermediate or poor risk advanced RCC, as a first-line treatment following combination treatment with intravenous nivolumab and ipilimumab. <u>Limitations of Use:</u> OPDIVO QVANTIG is not indicated in combination with ipilimumab for the treatment of renal cell carcinoma. - adult patients with advanced RCC, as a first-line treatment in combination with cabozantinib. - adult patients with advanced RCC who have received prior anti-angiogenic therapy. <u>Melanoma</u> - adult patients with unresectable or metastatic melanoma - adult patients with unresectable or metastatic melanoma following combination treatment with intravenous nivolumab and ipilimumab. <u>Limitations of Use:</u> OPDIVO QVANTIG is not indicated in combination with ipilimumab for the treatment of unresectable or metastatic melanoma. - for the adjuvant treatment of adult patients with completely resected Stage IIB, Stage IIC, Stage III, or Stage IV melanoma. <u>Non-Small Cell Lung Cancer (NSCLC)</u> - adult patients with resectable (tumors ≥ 4 cm or node positive) NSCLC in the neoadjuvant setting, in combination with platinum-doublet chemotherapy. - adult patients with metastatic NSCLC and progression on or after platinum-based

	chemotherapy. Patients with EGFR or ALK genomic tumor aberrations should have disease progression on FDA-approved therapy for these aberrations prior to receiving OPDIVO QVANTIG. <u>Limitations of Use:</u> OPDIVO QVANTIG is not indicated in combination with ipilimumab for the treatment of metastatic NSCLC <u>Squamous Cell Carcinoma of the Head and Neck (SCCHN)</u> - adult patients with recurrent or metastatic SCCHN with disease progression on or after a platinum-based therapy. <u>Urothelial Carcinoma (UC)</u> - adjuvant treatment of adult patients with UC who are at high risk of recurrence after undergoing radical resection of UC. - adult patients with locally advanced or metastatic UC who: - have disease progression during or following platinum-containing chemotherapy. - have disease progression within 12 months of neoadjuvant or adjuvant treatment with platinum-containing chemotherapy. <u>Colorectal Cancer</u> - adult patients with MSI-H or dMMR metastatic CRC that has progressed following treatment with a fluoropyrimidine, oxaliplatin, and irinotecan, as monotherapy or as monotherapy following combination treatment with intravenous nivolumab and ipilimumab. <u>Limitations of Use:</u> OPDIVO QVANTIG is not indicated in combination with ipilimumab for the treatment of MSI-H or dMMR metastatic CRC. <u>Hepatocellular Carcinoma (HCC)</u> - adult patients with HCC previously treated with sorafenib and following combination treatment with intravenous nivolumab and ipilimumab.
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	<u>Limitations of Use:</u> OPDIVO QVANTIG is not indicated in combination with ipilimumab for the treatment of HCC. <u>Esophageal Cancer</u> • adult patients with completely resected esophageal or gastroesophageal junction cancer with residual pathologic disease, who have received neoadjuvant chemoradiotherapy (CRT). • adult patients with unresectable advanced or metastatic esophageal squamous cell carcinoma as first-line treatment in combination with fluoropyrimidine- and platinum-containing chemotherapy. <u>Limitations of Use:</u> OPDIVO QVANTIG is not indicated in combination with ipilimumab for the treatment of patients with unresectable advanced or metastatic ESCC • adult patients with unresectable advanced, recurrent or metastatic esophageal squamous cell carcinoma (ESCC) after prior fluoropyrimidine- and platinum-based chemotherapy. <u>Gastric Cancer, Gastroesophageal Junction Cancer, and Esophageal Adenocarcinoma</u> • adult patients with advanced or metastatic gastric cancer, gastroesophageal junction cancer, and esophageal adenocarcinoma in combination with fluoropyrimidine- and platinum-containing chemotherapy.
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Reviewers of Multi-Disciplinary Review and Evaluation

Additional Reviewers of Application

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OPQ Product Quality Team Leader / Application Team Lead	Phillip Angart, PhD
OPQ Microbiology Reviewer	Richard Ledwidge, PhD (drug substance)/ Abigail Marella (drug product)
OPQ Facilities Reviewer	Richard Ledwidge, PhD (drug substance)/ Abigail Marella (drug product)
OPQ Microbiology/Facilities Team Leader	Madushini Dharmasena, PhD
OPQA III Label Reviewer	Vicky Borders-Hemphill, PharmD
OPDP	Emily Dvorsky, PharmD/Andrew Nguyen, PharmD

BLA Multi-disciplinary Review and Evaluation {BLA 761381 and BLA 761429}
OPDIVO (nivolumab and hyaluronidase - nvhy) injection, for subcutaneous use

DMPP	Jeena Sun, PharmD/Susan Redwood, PharmD
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OSE/DEPI	Steven Bird, PharmD
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OPQ=Office of Pharmaceutical Quality

OPDP=Office of Prescription Drug Promotion

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 Planning

Project Orbis - Health Canada (HC; Canada) Review team	
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Clinical Manager (Clinical Evaluation Division – Oncology & Hematology)	
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Risk Management Reviewer	
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BLA Multi-disciplinary Review and Evaluation {BLA 761381 and BLA 761429}
OPDIVO (nivolumab and hyaluronidase - nvhy) injection, for subcutaneous use

Glossary

%CV	Percent coefficient of variation	IgG4	immunoglobulin G4
2L	second line	IMAE	immune-mediated adverse event
ADA	anti-drug antibody	IMDC	International mRCC Database Consortium
ADME	absorption, distribution, metabolism, and excretion	IMM	immune-modulating medications
AE	adverse event	IND	Investigational New Drug
AJCC	American Joint Commission on Cancer	IO	Immuno-oncology
ALK	anaplastic lymphoma kinase	IPD	important protocol deviation
ALT	alanine transaminase	IQR	interquartile range
AST	aspartate aminotransferase	IRB	Institutional Review Board
AUC	area under the concentration vs time curve	IRT	Interactive Response Technologies
AUC(TAU)	area under the concentration time curve within a dosing interval	ITT	intent to treat
BICR	Blinded Independent Central Review Committee	IV	intravenous
BLA	Biologics License Application	K/KA	absorption/absorption rate
BLQ	below limit of quantification	KPS	Karnofsky Performance Status
BMS	Bristol-Myers Squibb	LDH	lactate dehydrogenase
BOR	best overall response	LPLV	last patient last visit
C1D1	cycle 1 day 1	mCRC	metastatic colorectal carcinoma
Cavg1	time averaged concentration after the first dose	MedDRA	Medical Dictionary for Regulatory Activities
Cavgd28	average serum concentration over 28 days	MEL	melanoma
Cavgd84	average serum concentration over 84 days	MHRA	UK Medicines and Healthcare Products Regulatory Agency
Cavgss	time averaged serum concentration at steady state	MIDD	model-informed drug development
ccRCC	clear cell renal cell carcinoma	Min, Max	minimum, maximum
CFR	Code of Federal Regulations	mRCC	Metastatic Renal Cell Carcinoma
CI	confidence interval	MSI-H	microsatellite instability-high
CL	clearance	MTD	maximum tolerated dose
CLss	clearance steady state	mUC	metastatic urothelial carcinoma
Cmax	maximum serum concentration	NA	Not Available
Cmax1	maximum serum concentration after the first dose	NCI CTCAE	National Cancer Institute's Common Terminology Criteria for Adverse Events

BLA Multi-disciplinary Review and Evaluation {BLA 761381 and BLA 761429}
OPDIVO (nivolumab and hyaluronidase - nvhy) injection, for subcutaneous use

Cmaxd84	maximum serum concentration at Day 84	NCT	National Clinical Trial
Cmaxss	peak serum concentration at steady-state	NDA	New Drug Application
CMH	Cochran Mantel-Haenszel	NONMEM	Nonlinear Mixed Effects Model
Cmin	trough serum concentration	NSCLC	non-small cell lung cancer
Cmind28	trough serum concentration on Day 28	OESI	other events of special interest
Cmind84	trough serum concentration on Day 84	ORR	objective response rate
Cminss	trough serum concentration at steady state	OS	overall survival
CNS	central nervous system	OTC	over-the-counter
COA	clinical outcome assessment	pcVPC	prediction-corrected Visual Predictive Check
COVID-19	coronavirus disease 2019	PD	progressive disease pharmacodynamics
CR	complete response	PD-1	programmed death protein 1
CRC	colorectal cancer	PD-L1	programmed death–ligand 1
CRF	case report form	PD-L2	programmed death-ligand 2
CSR	clinical study report	PEPQ	Patient Experience and Preference Questionnaire
Ctau	observed concentration at the end of a dosing interval	PFS	progression-free survival
CTR	clinical trial regulation	PK	Pharmacokinetic
Ctrough	trough serum concentration	PP	persistent positive
DBL	database lock	popPK	population pharmacokinetics
DC	discontinued	PR	partial response
DCR	disease control rate	PREA	Pediatric Research Equity Act
DMC	Data Monitoring Committee	PRO	patient-reported outcome
dMMR	deficient mismatch repair	PS	performance status
DOR	duration of response	PT	Preferred Term
EAC	esophageal adenocarcinoma	Q1, Q3	first quartile, third quartile
ECG	electrocardiogram	Q2W	every 2 weeks
ECL	electrochemiluminescence	Q3W	every 3 weeks
ECOG	Eastern Cooperative Oncology Group	Q4W	every 4 weeks
eCRF	electronic case report form	RCC	renal cell carcinoma
eCTD	Electronic Common Technical Document	RECIST	Response Evaluation Criteria in Solid Tumors

BLA Multi-disciplinary Review and Evaluation {BLA 761381 and BLA 761429}
OPDIVO (nivolumab and hyaluronidase - nvhy) injection, for subcutaneous use

EGFR	epidermal growth factor receptor	REML	restrictive maximum likelihood
ELISA	Enzyme-linked Immunosorbent Assay	rHuPH20	recombinant human hyaluronidase PH20
Emax	maximal drug effect	RPD	relevant protocol deviation
EU-5D-5L	5-level version of the EuroQol Group's EQ-5D questionnaire	RR	response rate
ESCC	esophageal squamous cell carcinoma	SAE	serious adverse event
EU	European	SAP	Statistical Analysis Plan
F	bioavailability	SARS-Cov-2	severe acute respiratory syndrome-coronavirus-2
FACIT	Functional Assessment of Chronic Illness Therapy	SC	subcutaneous
FDARA	FDA Reauthorization Act	SCCHN	squamous cell carcinoma of the head and neck
FDASIA	FDA Safety and Innovation Act	SCE	Summary of Clinical Efficacy
FD&C	Food Drug and Cosmetic Act	SCS	Summary of Clinical Safety
FDA	Food and Drug Administration	SD	standard deviation stable disease
FSKI-19	Functional Assessment of Cancer Therapy Kidney Symptom Index - 19 Item Version	SMQ	Standardized MedDRA query
GBDS	Global Biometric and Data Sciences	SOC	System Organ Class
GC	gastric cancer	T1/2	half life
GCP	Good Clinical Practice	Tmax	time to peak drug concentration
GEJC	gastroesophageal junction cancer	TRAE	treatment related adverse event
GLP	Good Laboratory Practices	TRSAE	treatment-related serious adverse event
GMR	geometric mean ratio	TTR	time to response
HCC	hepatocellular carcinoma	US	United States
HCP	health care practitioner	UC	urothelial carcinoma
HR	hazard ratio	USPI	United States Prescribing Information
HRQoL	health-related quality of life	UTD	unable to determine
ICE	intercurrent event	VAS	visual analog scale
ICH	International Conference on Harmonization	VC	volume of distribution of the central component
IEC	Independent Ethics Committee	VP	volume of distribution of the peripheral component
IFN γ	interferon gamma	Vs	versus

1 Executive Summary

1.1. Product Introduction

Nivolumab and hyaluronidase-nvhy (OPDIVO QVANTIG) is a fixed-combination drug product containing nivolumab, a programmed death receptor (PD-1) blocking antibody, and hyaluronidase, an endoglycosidase used to increase dispersion and absorption of co-administered drugs when administered subcutaneously.

Nivolumab was initially approved as an intravenous (IV) injection on December 22, 2014, for the treatment of patients with unresectable or metastatic melanoma and disease progression following ipilimumab and, if BRAF V600E mutation positive, a BRAF inhibitor. Nivolumab has since been approved for multiple indications across solid and hematological tumors. Human recombinant hyaluronidase was approved on December 2, 2005.

At the time of submission of the current BLA 761381 on February 29, 2024, and BLA 761429 on March 29, 2024, nivolumab and hyaluronidase-nvhy (nivolumab SC or nivo SC) was not approved for any indication in the United States or by any other health regulatory agency. The Applicant has requested approval of nivolumab SC to be administered as monotherapy or monotherapy maintenance or in combination with cabozantinib or platinum-containing chemotherapy for approved solid tumor indications. In this application, BMS did not submit data to support the use of nivolumab SC in combination with ipilimumab.

The Applicant's proposed dosing regimens are as follows:

- 600 mg nivolumab and 10,000 units hyaluronidase every 2 weeks subcutaneously, or
- 1200 mg nivolumab and 20,000 units hyaluronidase every 4 weeks subcutaneously, or
- 900 mg nivolumab and 15,000 units hyaluronidase every 3 weeks subcutaneously.

1.2. Conclusions on the Substantial Evidence of Effectiveness

Substantial evidence of effectiveness of nivolumab SQ is supported by one adequate and well controlled trial, CA20967T, of SQ nivolumab plus confirmatory evidence of multiple clinical trials supporting the IV use of nivolumab (see Opdivo labeling).

CA20967T is a multicenter, randomized, open-label study that evaluated the PK and efficacy (based on ORR) noninferiority of nivolumab SC compared to nivolumab IV in patients with clear cell renal cell carcinoma (ccRCC). The study enrolled 492 patients randomized 1:1 who received either nivolumab SC (1200 mg nivolumab and 20,000 units hyaluronidase every 4 weeks) or nivolumab IV (3 mg/kg every 2 weeks). The study co-primary endpoints were C_{avgd28} (the time-averaged serum nivolumab concentration over the

first 28 days of treatment) and C_{minss} (the trough serum nivolumab concentration at steady state). The key secondary endpoint was objective response rate (ORR) assessed by blinded independent central review per RECIST v1.1. The Applicant conducted a noninferiority comparison of ORR between nivolumab SC and nivolumab IV; however the noninferiority margin was not based on a comparative result from a meta-analysis or placebo controlled trial and therefore the preservation of treatment effect is not well defined for this comparison and the results of the non-inferiority test are difficult to interpret.

The data provided by the Applicant in Study CA20967T and data submitted to support the approval of nivolumab IV for each proposed indication are sufficient to support regular approval of nivolumab SC. This conclusion is based on the results for the PK analysis which demonstrated that the co-primary PK endpoints of C_{avgd28} and C_{minss} between nivolumab SC and nivolumab IV met the prespecified margin with the lower boundary of the 90% confidence intervals (CIs) of the geometric mean ratio not lower than 0.8 and below safety margin established by nivolumab IV. The efficacy analysis showed an ORR of 24.2% (95% CI: 19.0, 30.0) in the nivolumab SC arm and an ORR of 18.2% (95% CI: 13.6, 23.6) in the nivolumab IV arm. Although the noninferiority analysis is considered descriptive, the data suggests that there is no notable difference in the activity of nivolumab SC and nivolumab IV.

The data from Study CA20967T was adequate to characterize the safety of nivolumab SC in patients with ccRCC. The safety profiles including serious adverse events (AEs) and Grade ≥ 3 AEs were comparable between the nivolumab SC and nivolumab IV arms. Since Study CA20967T met its primary endpoints and considering supportive safety data submitted to support the approval of nivolumab IV for each proposed indication, the review team considers the safety profile of nivolumab SC to be acceptable in the context of a serious and life-threatening disease.

The review team recommends granting regular approval to nivolumab and hyaluronidase-nvhy SC as a monotherapy or monotherapy maintenance therapy after administration of nivolumab IV in combination with ipilimumab, or in combination with cabozantinib or platinum-containing chemotherapy for the proposed indications. This approach to the review, with approval based on PK and ORR comparison, is consistent with the approach taken for Tecentriq Hybreza

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1.3. Benefit-Risk Assessment (BRA)

Benefit-Risk Summary and Assessment

Immune checkpoint inhibitor (ICPI) therapy has been approved for the treatment of multiple solid and hematologic cancers. Nivolumab IV, an anti-PD-1 checkpoint inhibitor, is administered intravenously as a 30-minute infusion (OPDIVO USPI). For patients receiving ICPI therapies temporary IV access must be obtained at each treatment visit or long-term access, generally achieved with placement of a chemotherapy port, is arranged. Although many oncology drugs are administered intravenously, administration of IV medications may be time-consuming for patients and can be complicated by a patient's underlying condition (e.g. inability to deal with large volume infusions) or adverse reactions associated with drug administration such as chemotherapy infiltration or extravasation. Some patients with cancer may have poor intravenous access and long-term indwelling catheters may increase the risk for infection. A subcutaneous approach may allow for an alternative approach to administration.

Nivolumab and hyaluronidase-nvhy (nivolumab SC) is a fixed-combination product being developed as a subcutaneous formulation and is intended to be an alternative to nivolumab IV for patients receiving monotherapy or monotherapy maintenance regimens after administration of nivolumab IV and ipilimumab, or for patients receiving nivolumab in combination with cabozantinib or platinum-containing chemotherapy regimens.

The Applicant submitted data from Study CA20967T to support the approval of nivolumab SC. Study CA20967T is a multicenter, randomized, open-label study evaluating the PK and efficacy noninferiority of nivolumab SC compared to nivolumab IV in patients with clear cell renal cell carcinoma (ccRCC). The study met its primary objective and demonstrated that the co-primary PK endpoints of C_{avgd28} and C_{minss} between nivolumab SC and nivolumab IV met the prespecified margin with the lower boundary of the 90% confidence intervals (CIs) of the geometric mean ratio not lower than 0.8 and below safety margin established by nivolumab IV. Although the study was not formally designed for a noninferiority comparison between nivolumab SC and nivolumab IV, the efficacy analysis did not show a notable difference in the ORR of the nivolumab SC arm compared to the nivolumab IV arm (24.2% (95% CI: 19.0, 30.0) and 18.2% (95% CI: 13.6, 23.6), respectively).

The data submitted to support the safety review of nivolumab SC is adequate to characterize the toxicity in patients enrolled in the pivotal study. Considering the study met its primary PK objectives and the safety profile of nivolumab IV, as demonstrated in the pivotal trials that support the approval of the nivolumab IV in each proposed indications, serves as supportive data regarding the safety of nivolumab SC.

The review team recommends that nivolumab and hyaluronidase-nvhy be approved for use as monotherapy or monotherapy maintenance after administration of nivolumab IV and ipilimumab, or in combination with cabozantinib or platinum-based chemotherapy for the treatment of patients with solid tumors, including RCC, melanoma, NSCLC, squamous cell carcinoma of the head and neck, urothelial cancer, MSI-H/dMMR mCRC, HCC, esophageal cancer, gastric cancer and gastroesophageal junction (GEJ) cancer.

A postmarketing requirement will be issued to the Applicant to conduct molecularly targeted pediatric cancer investigation using an age-appropriate formulation of nivolumab and hyaluronidase-nvhy in pediatric patient 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 nivolumab SC, a partial waiver of this requirement in pediatric patients less than 12 years of age is justified.

Dimension	Evidence and Uncertainties	Conclusions and Reasons
Analysis of Condition	Nivolumab has been approved for treatment of multiple solid tumors, including RCC, melanoma, NSCLC, squamous cell carcinoma of the head and neck, urothelial cancer, MSI-H/dMMR mCRC, HCC, esophageal cancer, gastric cancer and gastroesophageal junction (GEJ) cancer.	Substantial evidence of safety and effectiveness has been provided for the use of nivolumab IV in the treatment of multiple solid tumors. The solid tumors for which nivolumab IV is approved to treat are serious and life-

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Dimension	Evidence and Uncertainties	Conclusions and Reasons
		threatening conditions.
Current Treatment Options	Nivolumab is administered as an intravenous 30-minute infusion and is approved as either monotherapy or in combination with other anti-cancer agents for multiple tumor types.	Nivolumab IV as a monotherapy or in combination with other anti-cancer therapies has demonstrated efficacy and safety in multiple tumor types for the FDA-approved indications.
Benefit	- Study CA20967T met its primary PK objective and demonstrated that the co-primary PK endpoints of Cavgd28 and Cminss between nivolumab SC and nivolumab IV met the prespecified margin with the lower boundary of the 90% confidence intervals (CIs) of the geometric mean ratio not lower than 0.8 and below safety margin established by nivolumab IV. - No notable difference was observed in the efficacy of nivolumab SC and nivolumab IV with ORRs of 24.2% (95% CI: 19.0, 30.0) and 18.2% (95% CI: 13.6, 23.6), respectively. - FDA notes that the noninferiority margin was not based on a comparative result from a historical trial and therefore the preservation of treatment effect is not well defined for this comparison and the results of the non-inferiority test are difficult to interpret.	The PK analysis of nivolumab SC and nivolumab IV showed that the two formulations are comparable. Although the results of the efficacy analysis are descriptive, no notable differences were observed for the key secondary endpoint of BICR-ORR between study arms. Nivolumab SC offers patient an alternative route of administration to receive ICPI therapy.
Risk and Risk Management	- The overall safety profile of the nivolumab SC arm was similar to the safety profile observed with the nivolumab IV arm in Study CA20967T and in the larger nivolumab IV development program. - The most common adverse reactions ($\geq 10\%$) were	The data from Study CA20967T is adequate to characterize the safety of nivolumab SC. The observed safety profile of nivolumab SC is consistent with the safety profile that has

Dimension	Evidence and Uncertainties	Conclusions and Reasons
	musculoskeletal pain, fatigue, pruritus, rash, hypothyroidism, diarrhea, cough, and abdominal pain. • Immune-mediated adverse events (IMAEs) were reported in 15% of patients in both the nivolumab SC and nivolumab IV arms. The majority of IMAEs reported were Grade 1 or Grade 2. • Serious adverse reactions occurred in 28% of patients who received nivolumab SC. • Permanent discontinuation of nivolumab SC due to an adverse reaction occurred in 10% of patients. The most common adverse reaction which resulted in permanent discontinuation was pneumonitis (2%). • Dosage interruptions due to an adverse reaction occurred in 34% of patients who received nivolumab SC. • Fatal adverse reactions occurred in 1.2% of patients treated with nivolumab SC compared to 0.4% of patients treated with nivolumab IV. • Local injection site reactions were reported in 8% (20 of 247) of patient in the nivolumab SC arm. No local injection site reactions were reported in the nivolumab IV arm.	been observed with nivolumab IV. Injection site reactions were an adverse reaction uniquely associated with

1.4. Patient Experience Data

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

☐	The patient experience data that was submitted as part of the application, include:	Section where discussed, if applicable
☐	Clinical outcome assessment (COA) data, such as	[e.g., Section 6.1 Study endpoints]

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☐	Patient reported outcome (PRO)	
☐	Observer reported outcome (ObsRO)	
☐	Clinician reported outcome (ClinRO)	
☐	Performance outcome (PerfO)	
☐	Qualitative studies (e.g., individual patient/caregiver interviews, focus group interviews, expert interviews, Delphi Panel, etc.)	
☐	Patient-focused drug development or other stakeholder meeting summary reports	[e.g., Section 2.1 Analysis of Condition]
☐	Observational survey studies designed to capture patient experience data	
☐	Natural history studies	
☐	Patient preference studies (e.g., submitted studies or scientific publications)	
☐	Other: (Please specify)	
☐	Patient experience data that was not submitted in the application, but was considered in this review.	

X

Jamie R. Brewer, MD

Cross-Disciplinary Team Leader

2 Therapeutic Context

2.1. Analysis of Condition

The Applicant's Position:

BMS has previously provided analyses of condition and characterization of disease in applications for OPDIVO®, a PD-1-blocking antibody. BMS plans to seek approval for nivolumab co-formulated with hyaluronidase (rHuPH20) for subcutaneous use (hereafter referred to as nivolumab SC) for the following indications already approved for OPDIVO (nivolumab IV):

Advanced Renal Cell Carcinoma

- Nivolumab SC, as a single agent, is indicated for the first-line treatment of adult patients with intermediate or poor risk advanced RCC following treatment with OPDIVO and ipilimumab combination therapy.
- Nivolumab SC, in combination with cabozantinib, is indicated for the first-line treatment of adult patients with advanced RCC.
- Nivolumab SC, as a single agent, is indicated for the treatment of adult patients with advanced RCC who have received prior anti-angiogenic therapy.

Adjuvant Treatment of Melanoma

- Nivolumab SC is indicated for the adjuvant treatment of adult patients with completely resected Stage IIB, Stage IIC, Stage III, or Stage IV melanoma.

Unresectable or Metastatic Melanoma

- Nivolumab SC, as a single agent, is indicated for the treatment of adult patients with unresectable or metastatic melanoma.
- Nivolumab SC, as a single agent, is indicated for the treatment of adult patients with unresectable or metastatic melanoma following treatment with OPDIVO and ipilimumab combination therapy.

Neoadjuvant Treatment of Resectable NSCLC

- Nivolumab SC, in combination with platinum-doublet chemotherapy, is indicated as neoadjuvant treatment of adult patients with resectable (tumors ≥4 cm or node positive) NSCLC.

Metastatic NSCLC

- Nivolumab SC, is indicated for the treatment of adult patients with metastatic NSCLC with progression on or after platinum-based chemotherapy. Patients with EGFR or ALK genomic tumor aberrations should have disease progression on FDA-approved therapy for these aberrations prior to receiving Nivolumab SC.

Squamous Cell Carcinoma of the Head and Neck

- Nivolumab SC is indicated for the treatment of adult patients with recurrent or metastatic SCCHN with disease progression on or after platinum-based therapy.

Urothelial Carcinoma

- Nivolumab SC is indicated for the adjuvant treatment of adult patients with UC who are at high risk of recurrence after undergoing radical resection of UC.
- Nivolumab SC is indicated for the treatment of adult patients with locally advanced or metastatic UC who:
 - have disease progression during or following platinum-containing chemotherapy
 - have disease progression within 12 months of neoadjuvant or adjuvant treatment with platinum-containing chemotherapy.

Microsatellite Instability-High or Mismatch Repair Deficient Metastatic CRC

- Nivolumab SC, as a single agent, is indicated for the treatment of adult patients with MSI-H or dMMR metastatic CRC following combination treatment with OPDIVO and ipilimumab.

This indication is approved under accelerated approval based on overall response rate and duration of response. Continued approval for this indication may be contingent upon verification and description of clinical benefit in confirmatory trials.

- Nivolumab SC, as a single agent, is indicated for the treatment of adult patients with MSI-H or dMMR metastatic CRC that has progressed following treatment with a fluoropyrimidine, oxaliplatin, and irinotecan.

This indication is approved under accelerated approval based on overall response rate and duration of response. Continued approval for this indication may be contingent upon verification and description of clinical benefit in confirmatory trials.

Hepatocellular Carcinoma

- Nivolumab SC, as a single agent, is indicated for the treatment of adult patients with HCC who have been previously treated with sorafenib and following treatment with OPDIVO and ipilimumab combination therapy.

This indication is approved under accelerated approval based on overall response rate and duration of response. Continued approval for this indication may be contingent upon verification and description of clinical benefit in the confirmatory trials.

Esophageal Cancer

- Nivolumab SC is indicated for the adjuvant treatment of completely resected esophageal or gastroesophageal junction cancer with residual pathologic disease in adult patients who have received neoadjuvant chemoradiotherapy.
- Nivolumab SC, in combination with fluoropyrimidine- and platinum-containing chemotherapy, is indicated for the first-line treatment of adult patients with unresectable advanced or metastatic esophageal squamous cell carcinoma.
- Nivolumab SC is indicated for the treatment of adult patients with unresectable advanced, recurrent, or metastatic esophageal squamous cell carcinoma after prior fluoropyrimidine- and platinum-based chemotherapy.

Gastric Cancer, Gastroesophageal Junction Cancer, and Esophageal Adenocarcinoma

- Nivolumab SC, in combination with fluoropyrimidine- and platinum-containing chemotherapy, is indicated for the treatment of adult patients with advanced or metastatic gastric cancer, gastroesophageal junction cancer, and esophageal adenocarcinoma.

The FDA's Assessment:

The Applicant is proposing that nivolumab plus hyaluronidase be indicated for all currently approved adult solid tumor indications for nivolumab IV monotherapy and monotherapy maintenance following completion of nivolumab IV and ipilimumab combination therapy. The Applicant is also proposing the approval of nivolumab SC in combination with cabozantinib or platinum-containing chemotherapy. The Applicant is not proposing nivolumab SC be administered in combination with ipilimumab or that the approval of nivolumab SC be granted for the treatment of classical Hodgkin lymphoma.

Final labeling for MSI-H/dMMR CRC will reflect use in current Opdivo labeling (following treatment with a fluoropyrimidine, oxaliplatin, and irinotecan).

The Applicant has submitted a Partial Waiver for the requirement to complete molecularly targeted pediatric investigations in patients less than 12 years of age as the necessary molecularly targeted studies in this population are impossible or highly impracticable based on the incidence of pediatric cancers. The Applicant has requested a deferral for the submission of a molecularly targeted pediatric cancer investigation in children ages 12 to less than 17 years, as its product will be ready for approval for use in adults before pediatric studies are complete.

2.2. Analysis of Current Treatment Options

The Applicant's Position:

BMS has previously provided analyses of current treatment options in applications for OPDIVO®.

SC administration represents an important treatment option for patients with advanced or metastatic cancers, as well as potentially in locally advanced or perioperative treatment settings, and offers potential advantages over current nivolumab IV formulation to both HCPs and patients. Potential advantages to HCPs of SC dosing with a flat dose of a biologic drug product include decreasing the time needed for dose preparation, reducing the potential for dosing errors,¹ and alleviating IV infusion center occupancy. Potential advantages to patients include reducing administration time from 30 to 60 minutes with IV infusion to average times of < 5 minutes with SC and alleviating the need for IV ports. Thus, nivolumab SC injection compared with IV infusion may allow for improved patient experience as well as efficiencies in medical resource utilization.² Additionally, the COVID-19 pandemic caused significant disruptions to delivery of cancer care, with dose delays and

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discontinuation, and a negative impact on patient quality of life. This disruption heightened the criticality of providing alternative routes of cancer treatment, such as SC delivery, as an option for patients and providers.

The FDA's Assessment:

FDA generally agrees with the Applicant's assessment.

3 Regulatory Background

3.1. U.S. Regulatory Actions and Marketing History

The Applicant's Position:

Nivolumab SC is not currently approved or marketed in the US or any other country globally. The clinical development program for nivolumab SC is being conducted under IND 150904 with Division of Oncology 3. Relevant regulatory history is described in Section 3.2.

The FDA's Assessment:

FDA agrees with the Applicant's position.

In addition to the submission of BLA 761381 on February 29, 2024, the Applicant also submitted a Type 9 application for BLA 761429 on March 29, 2024, for the approval of nivolumab and hyaluronidase-nvhy for the following indications:

NSCLC

- adult patients with resectable (tumors ≥ 4 cm or node positive) non-small cell lung cancer in the neoadjuvant setting, in combination with platinum-doublet chemotherapy, followed by single-agent nivolumab and hyaluronidase-nvhy in the adjuvant setting after surgery.

Urothelial Carcinoma

- adult patients with unresectable or metastatic urothelial carcinoma, as first-line treatment in combination with cisplatin and gemcitabine.

BLA 761429 will be administratively closed after approval of nivolumab and hyaluronidase.

3.2. Summary of Presubmission/Submission Regulatory Activity

The Applicant's Position:

Table 1: Applicant - Key Regulatory Milestones

Date	Regulatory Milestone
13-Dec-2019	FDA MIDD Paired Meeting discussing MIDD approach for nivolumab SC.
02-Mar-2020	FDA Type B End of Phase 1 Meeting to discuss trial design.
05-Oct-2020	FDA Type C Meeting to discuss clinical endpoints.
20-Dec-2022 09-Jun-2023	FDA MIDD 1st and 2nd Paired Meeting to further discuss MIDD approach for nivolumab SC.

Table 1: Applicant - Key Regulatory Milestones

Date	Regulatory Milestone
18-Dec-2023	Type B pre-BLA - FDA agreed that the clinical data package (CA20967T/CA2098KX) is sufficient to support review of the nivolumab SC BLA. - FDA agreed that BMS can participate in the Assessment Aid pilot project. - FDA agreed with BMS' request for Project Orbis for the nivolumab SC BLA.

The FDA's Assessment:

FDA generally agrees with the Applicant's overview of the regulatory interactions during development. Additional details of some of these interactions include:

- On March 2, 2020, in an end of Phase 1 (EOP1) meeting FDA stated that a separate randomized trial that demonstrates PK comparability and is also powered to demonstrate comparable efficacy and safety would be a more appropriate approach compared to the proposal to (b) (4)
- On October 5, 2020, in a Type C Meeting FDA agreed that the proposed 600 mg every 2 weeks subcutaneous regimen would be acceptable. FDA also provided agreement regarding the study co-primary PK endpoints of average serum concentration over 28 days (Cavgd28) and the trough serum concentration at steady state (Cminss).
- On December 19, 2023, at a Type B Pre-BLA meeting FDA agreed that the clinical data package (CA20967T/CA2098KX) was sufficient to support review. FDA advised the Applicant to submit a supplemental BLA(s) for additional nivolumab SC indications that would be based on pending nivolumab IV indications that are not approved at the time of the original BLA. BMS proposed submission of a Type 9 BLA for nivolumab SC to obtain approval of indications that are under review but not yet approved for nivolumab IV at the time of the original nivolumab SC BLA submission. FDA did not object.
- On February 29, 2024, the Applicant submitted BLA 761381.
- On March 29, 2024, the Applicant submitted the Type 9 application for two additional indications including:
 - Neoadjuvant treatment with nivolumab SC in combination with platinum-doublet chemotherapy followed by nivolumab SC monotherapy as adjuvant treatment in adult patients with NSCLC
 - First line treatment with nivolumab SC in combination with cisplatin and gemcitabine in adult patients with unresectable or metastatic urothelial carcinoma

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

4.1. Office of Scientific Investigations (OSI)

The Division of Oncology 3 consulted OSI to discuss an audit of overall trial conduct for Study CA20967T. It was decided that one foreign clinical investigator (CI), Dr. Maria Teresa Bourlon de los Rios, and the imaging contract research organization (CRO), (b) (4) would be inspected. The inspection for Dr. Bourlon deLos Rios did not find significant concerns regarding the study conduct and management of the clinical trial, GCP, or regulatory compliance. Inspection of the imaging CRO, (b) (4) revealed no significant discrepancies or regulatory violations or Good Clinical Practice (GCP) noncompliance.

The inspection of the CRO verified the key secondary efficacy endpoint, ORR, for 132 efficacy responders by comparison of tumor dimensional measurements and tumor response / progression source records with data line listings at baseline and key secondary endpoint time points, inclusive of the 4-week objective response confirmation. There were no discrepancies identified.

4.2. Product Quality

Opdivo Qvantig (nivolumab and hyaluronidase-nvhy) is a fixed combination drug product provided as a sterile, preservative-free, clear to opalescent, colorless to yellow solution, that may contain a few translucent-to-white particles. Each single-dose vial contains 600 mg nivolumab and 10,000 units hyaluronidase per 5 mL formulated with 7.75 mg histidine, 10.5 mg histidine hydrochloride monohydrate, 3.73 mg methionine, 0.0985 mg pentetic acid, 2.50 mg polysorbate 80, and 428 mg sucrose per 5 mL, to a target pH of (b) (4). Nivolumab and hyaluronidase-nvhy is provided in a (b) (4) glass vial, stoppered with an elastomeric stopper, and sealed with an aluminum cap.

The Office of Pharmaceutical Quality, CDER, recommends approval of BLAs 761381 and 761429 for Opdivo Qvantig manufactured by Bristol Myers Squibb. The data submitted in this application are adequate to support the conclusion that the manufacture of Opdivo Qvantig is well-controlled and leads to a product that is pure and potent. It is recommended that this product be approved for human use under conditions specified in the package insert. Refer to the OPQ Executive Summary dated November 15, 2024, and addendum dated December 16, 2024, for full details.

The CMC post-marketing commitment (PMC) listed below should be included in the action letter.

1. Establish and validate/qualify an appropriate method (existing or new), for determining the number and size of product-related visible particles in nivolumab subcutaneous injection drug product and implement the method for evaluation of visible particles in nivolumab subcutaneous injection drug product stability testing.

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4.3. Clinical Microbiology

The OPQ review found that microbial control and sterility assurance strategy is sufficient to support consistent manufacture of a sterile product. The DP sterilized using a validated filtration process (b) (4)

(b) (4)

4.4. Devices and Companion Diagnostic Issues

Not applicable. Labeling will be c/w Opdivo.

5 Nonclinical Pharmacology/Toxicology

5.1. Executive Summary

Opdivo Qvantig (nivolumab and hyaluronidase-nvhy) is a combination of nivolumab, a programmed death receptor-1 (PD-1)-blocking antibody, and hyaluronidase, an endoglycosidase.

5.2. Referenced NDAs, BLAs, DMFs

The Applicant's Position:

Cross reference the OPDIVO BLA 125554 for nonclinical pharmacology, PK, and toxicology information. Cross reference the Hylenex BLA 021859 for nonclinical toxicology information.

5.3. Pharmacology

Primary pharmacology

Nonclinical primary pharmacology has been well characterized and the data is referred to in OPDIVO BLA 125554 and Hylenex BLA 021859.

The FDA's Assessment:

The FDA generally agrees with the Applicant's position.

Secondary Pharmacology

Secondary pharmacology studies were not conducted for nivolumab SC, nivolumab IV, or rHuPH20.

The FDA's Assessment:

The FDA agrees with the Applicant's position.

Safety Pharmacology

The nonclinical safety pharmacology of nivolumab and rHuPH20 has been well

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characterized; refer to OPDIVO BLA 125554 and Hylenex BLA 021859. No additional studies were conducted for nivolumab SC.

The FDA's Assessment:

The FDA generally agrees with the Applicant's position.

Pharmacodynamic Interactions

Pharmacodynamic interactions have been well characterized; refer to OPDIVO BLA 125554. No additional studies were conducted for nivolumab SC. No studies were performed to assess the effects of other agents on the Pharmacodynamic Interactions of rHuPH20.

The FDA's Assessment:

The FDA generally agrees with the Applicant's position.

5.4. ADME/PK

The Applicant's Position:

Nonclinical ADME and PK data has been well characterized; refer to OPDIVO BLA 125554 and Hylenex BLA 021859. No additional studies were conducted for nivolumab SC.

The FDA's Assessment:

The FDA generally agrees with the Applicant's position.

5.5. Toxicology

5.5.1. General Toxicology

The Applicant's Position:

Table 2: Applicant - General Toxicology: 24/25 Day Subcutaneous Combination Repeat-dose Toxicity Study in Monkeys

Study Title	A single-dose intravenous and repeat-dose (Q3WX2) SC PK, pharmacodynamic, and local tolerance study in monkeys
Study Number	DN18044
Study Type	Repeat-dose
eCTD Location	4.2.3.6
GLP Compliance	Yes
Key Drug-related Adverse Findings	No drug-related adverse findings observed
Methods	
Dose and frequency of dosing	Nivolumab (BMS-986298) administered subcutaneously at 0 or 50 mg/kg Q3W for 2 doses; with or without 1000 U rHuPH20 co-administration [Nivolumab IV (BMS-936558) 50 mg/kg single dose described in Other Toxicology Studies]
Route of Administration	Nivolumab (BMS-986298) administered subcutaneously +/- rHuPH20
Formulation/Vehicle	For Control and SC groups: (b) (4) histidine, (b) (4) sucrose, (b) (4) polysorbate 80, (b) (4) pentetic acid, pH (b) (4)
Species/Strain	Monkey/cynomolgus
Number/Sex/Group	3/sex/group
Age	Approximately 2 to 6 years of age

Satellite groups	Not applicable
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The FDA's Assessment:

The FDA generally agrees with the Applicant's position. Findings were unremarkable.

5.5.2. Genetic Toxicology

The Applicant's Position:

No study was conducted with nivolumab or with rHuPH20.

The FDA's Assessment:

The FDA agrees with the Applicant's position.

5.5.3. Carcinogenicity

The Applicant's Position:

No study was conducted with nivolumab or with rHuPH20.

The FDA's Assessment:

The FDA agrees with the Applicant's position.

5.5.4. Reproductive and Developmental Toxicology

The Applicant's Position:

Reproductive and developmental toxicology of nivolumab and rHuPH20 has been well characterized; refer to OPDIVO BLA 125554 and Hylenex BLA 021859. No additional studies were conducted with nivolumab SC.

The FDA's Assessment:

The FDA generally agrees with the Applicant's position.

5.5.5. Other Toxicology Studies

The Applicant's Position:

Table 3: Applicant – Other: Single-dose Intravenous Bridging/Comparability Toxicity Study in Monkeys

Study Title	A single-dose intravenous and repeat-dose (Q3WX2) SC PK, pharmacodynamic, and local tolerance study in monkeys
Study Number	DN18044
Study Type	Bridging/Comparability
eCTD Location	4.2.3.6
GLP Compliance	Yes
Key Drug-related Adverse Findings:	No drug-related adverse findings observed
Methods	
Dose and frequency of dosing	Nivolumab IV (BMS-936558) 50 mg/kg single dose nivolumab (b) (4) [Nivolumab (BMS-986298) administered subcutaneously at 0 or 50 mg/kg Q3W for 2 doses; with or without 1000 U rHuPH20 co-administration described in General Toxicology]

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Route of Administration Formulation/Vehicle	Nivolumab (BMS-936558) administered intravenously 20 mM sodium citrate, 50 mM sodium chloride, 3.0% (w/v) mannitol, (b) (4) pentetic acid; or 20 mM sodium citrate, 50 mM sodium chloride, 3.0% (w/v) mannitol, (b) (4) pentetic acid, 0.02% Tween 80, pH (b) (4)
Species/Strain	Monkey/cynomolgus
Number/Sex/Group	3/sex/group
Age	Approximately 2 to 6 years of age
Satellite groups	Not applicable
Results	Nivolumab, (b) (4) (administered IV as a single dose), at 50 mg/kg, was well tolerated. The process change for nivolumab (b) (4) (b) (4), when administered IV, did not lead to any exposure or pharmacodynamic differences.

The FDA's Assessment:

The FDA generally agrees with the Applicant's position.

X

X

Primary Reviewer

Supervisor

6 Clinical Pharmacology

6.1. Executive Summary

In BLA 761381 and BLA 761429, the Applicant is seeking approval of a nivolumab/hyaluronidase co-formulation for subcutaneous (SC) administration in all the approved adult solid tumor indications in which nivolumab IV is administered as a single agent or in combination with cabozantinib or chemotherapy. The proposed dosages for nivolumab SC administration are 600 mg nivolumab/10000 units hyaluronidase every 2 weeks (Q2W), 900 mg nivolumab/(b) (4) units hyaluronidase Q3W, and 1200 mg nivolumab/20000 units hyaluronidase Q4W injected in the abdomen or thigh over (b) (4)-5 minutes, corresponding to the approved recommended dosages of 240 mg Q2W, 360 mg Q3W, or 480 mg Q4W for IV administration.

The proposed SC dosage of 1200 mg nivolumab Q4W was identified in a dose finding study, and alternative SC dosages of 600 mg nivolumab Q2W and 900 mg nivolumab Q3W were supported by modeling and simulation. The pivotal clinical trial (CA20967T) was conducted in patients with ccRCC which demonstrated the primary exposure endpoints of C_{avgd28} and C_{minss} between nivolumab 1200 mg SC Q4W and nivolumab 3 mg/kg IV Q2W met

the prespecified margin with the lower boundary of the 90% confidence intervals (CIs) of the geometric mean ratio not lower than 0.8 and below safety margin established by nivolumab IV.

The key secondary efficacy endpoint, overall response rate (ORR), of 24.2% (95% CI: 19.0, 30.0) in the nivolumab SC arm demonstrated non-inferiority to the nivolumab IV arm (ORR: 18.2%, 95% CI: 13.6, 23.6). However, the non-inferiority margin was not based on a comparative result from a historical meta-analysis or placebo controlled trial, and therefore the preservation of treatment effect is not well defined for this comparison and the results of the non-inferiority test are difficult to interpret. The safety profiles including serious adverse events (AEs) and Grade ≥ 3 AEs were comparable between the SC and IV arms.

The incidence of anti-drug antibodies (ADA) against nivolumab was 23% (46/202) in the nivolumab SC arm and 7% (15/215) in the nivolumab IV arm. Compared to ADA negative patients, ADA positive patients had 24-32% lower trough concentrations at Week 4, 8 and 16 in the SC arm and 38-55% lower trough concentrations at Week 4 and 8 in the ADA positive patients in the IV arm. The incidence of neutralizing antibodies (NAb) in patients who tested ADA positive was 4% (2/46) in the SC arm and 0% (0/15) in the IV arm. The presence of ADA and NAb did not significantly affect safety profiles of nivolumab in both SC and IV arms. ADA positive patients were reported by the Applicant to have a trend of a lower ORR (15% [95% CI: 6, 29]) compared to ADA negative patients (28% [95% CI: 21, 36]) in the SC arm while ADA positive patients also showed a trend of lower ORR (0% [95% CI: 0, 22]) compared to ADA negative patients (21% [95% CI: 15, 27]) in the IV arm. The data are limited to adequately characterize the effect of ADA or NAb on efficacy.

A Postmarketing Requirement (PMC) will be issued to the Applicant to conduct a molecularly targeted pediatric cancer investigation using an age-appropriate formulation of nivolumab and hyaluronidase-nvhy in pediatric patients 12 years of age and older. (b) (4)
has communicated with the Applicant (b) (4)
(b) (4)

6.2. Summary of Clinical Pharmacology Assessment

This application discusses results from two separate popPK analyses; one analysis included concentration-time data from across the nivolumab IV clinical development program pooled with data from the Phase 1/2 multi-tumor study, CA2098KX, of nivolumab SC monotherapy, where four doses of nivolumab SC (720 mg with and without rHuPH20, 960 mg with and without rHuPH20, and 1,200 mg with rHuPH20 Q4W and an alternative SC dosing regimen of 600 mg with rHuPH20 Q2W) were administered to subjects with NSCLC, RCC, gastric SCCHN, melanoma, HCC, CRC, or mUC.^{3,4} The PK parameters from this analysis served as prior information in the second popPK analysis that only included concentration-time data

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from nivolumab SC and nivolumab IV administered to 2L RCC subjects in the Phase 3 Study CA20967T. The exposure measures (ie, Cavgd28 and Cminss) from the CA20967T popPK analysis were the endpoints in the primary PK noninferiority analysis for the study. Immunogenicity data from studies CA2098KX and CA20967T are also summarized.

In addition, results are provided from simulation-based analyses to support bridging to two alternative nivolumab SC dosing regimens (ie, 600 mg SC Q2W and 900 mg SC Q3W) coformulated with rHuPH20, and to currently approved solid tumor indications in adults for OPDIVO (nivolumab IV) when administered as monotherapy/monotherapy maintenance or in combination with chemotherapy/cabozantinib.⁵

The main results are shown in the following sections, and additional information is provided in the Attached Appendix.

6.2.1. Pharmacology and Clinical Pharmacokinetics

Data:

Table 4: Applicant - Primary Statistical Analyses of Nivolumab SC and Nivolumab IV Pharmacokinetic Co-primary Endpoints - Stratification Factors from CRF - PK Evaluable Subjects in CA20967T

PK parameter = Cavgd28 (µg/mL)								
TREATMENT AND COMPARISON	N	On Natural Logarithmic Scale				On Original Scale		
		ADJUSTED MEAN	ADJUSTED MEAN DIF	STANDARD ERROR	90% CI	ADJUSTED GEO MEAN	ADJUSTED GMR	90% CI
SC	242	4.349		0.0225	(4.312, 4.386)	77.373		(74.555, 80.297)
IV	245	3.608		0.0220	(3.571, 3.644)	36.875		(35.565, 38.235)
SC vs. IV			0.741	0.0288	(0.694, 0.789)		2.098	(2.001, 2.200)
PK parameter = Cminss (µg/mL)								
TREATMENT AND COMPARISON	N	On Natural Logarithmic Scale				On Original Scale		
		ADJUSTED MEAN	ADJUSTED MEAN DIF	STANDARD ERROR	90% CI	ADJUSTED GEO MEAN	ADJUSTED GMR	90% CI
SC	242	4.806		0.0394	(4.741, 4.871)	122.227		(114.552, 130.416)
IV	245	4.233		0.0384	(4.169, 4.296)	68.901		(64.676, 73.402)
SC vs. IV			0.573	0.0504	(0.490, 0.656)		1.774	(1.633, 1.927)
MODEL INFORMATION								
Estimation Method		- REML						
Residual Variance Method		- Profile						
Fixed Effects SE Method		- Model-Based						
Degrees of Freedom Method		- Residual						
Fixed Effects		- Weight categorization (CRF), IMDC risk group (CRF) and treatment						

Note: Nivolumab exposure measures were determined from the popPK analysis.

Datasets: ADSL, ADPP

Table 5: Applicant - Summary Statistics - All PK Endpoints - PK Evaluable Subjects in CA20967T

PARAMETER STATISTIC	Nivolumab SC	Nivolumab IV
CMAX1 (ug/mL) GEO.MEAN [N] CV (%)	108 [242] (33)	91.7 [245] (35)
CMIND28 (ug/mL) GEO.MEAN [N] CV (%)	50.8 [242] (44)	31.9 [245] (30)
CAVGD28 (ug/mL) GEO.MEAN [N] CV (%)	78.8 [242] (36)	37.7 [245] (25)
CMAXSS (ug/mL) GEO.MEAN [N] CV (%)	230 [242] (39)	160 [245] (28)
CMINSS (ug/mL) GEO.MEAN [N] CV (%)	126 [242] (51)	71.5 [245] (40)
CAVGSS (ug/mL) GEO.MEAN [N] CV (%)	182 [242] (44)	92.5 [245] (34)
CTROUGH AT WEEK 17 (ug/mL) GEO.MEAN [N] CV (%)	123 [154] (46)	66.3 [148] (33)

Note: All nivolumab exposure measures with the exception of Ctrough at Week 17 (observed) were determined from the popPK analysis. Values below LLOQ (0.200 µg/mL) were set to 1/2×LLOQ (0.100 µg/mL) for computation of Ctrough at Week 17 summary statistics.

Datasets: ADSL, ADPP

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Table 6: Applicant - Summary Statistics for PK Parameters - Evaluable PK Subjects in CA2098KX

Parameter Statistic	Treatment					
	PART A - GRP 1	PART B - GRP 2	PART B - GRP 3	PART B - GRP 4	PART D	PART E
C _{MAX} (ug/mL) GEO.MEAN [N] (GEO.%CV)	54.8 [22] (51)	56.6 [18] (34)	81.4 [10] (41)	63.9 [17] (30)	106 [34] (46)	57.8 [36] (31)
T _{MAX} (h) MEDIAN [N] (MIN-MAX)	167 [22] (47.0 - 357)	167 [18] (50.1 - 339)	141 [10] (47.2 - 333)	168 [17] (139 - 355)	130 [34] (44.5 - 317)	130 [36] (45.2 - 337)
AUC (TAU) (h*ug/mL) GEO.MEAN [N] (GEO.%CV)	24908 [20] (53)	27909 [16] (36)	40264 [10] (45)	32702 [13] (31)	53561 [33] (40)	15857 [35] (30)
CTAU (ug/mL) GEO.MEAN [N] (GEO.%CV)	22.2 [20] (86)	26.9 [16] (65)	39.2 [10] (67)	34.8 [13] (41)	54.4 [33] (49)	43.6 [35] (36)

The PK values for only Nivolumab (SC) - Cycle 1 are presented
 PART A - GRP 1: nivolumab SC 720 mg + rHuPH20 2000 Units/mL
 PART B - GRP 2: nivolumab SC 720 mg
 PART B - GRP 3: nivolumab SC 960 mg + rHuPH20 2000 Units/mL
 PART B - GRP 4: nivolumab SC 960 mg
 PART D: nivolumab SC + rHuPH20 2000 Units/mL Q4W
 PART E: nivolumab SC coformulated with rHuPH20 2000 Units/mL Q2W
 PK parameters were determined for Cycle 1 by noncompartmental analysis.
 Datasets: ADSL, ADPP

The Applicant's Position:

CA20967T

A linear fixed effect model with treatment and randomization stratification factors as fixed effects was fitted to the log-transformed Cavgd28 and Cminss for use in estimation of effects and construction of CIs. To assess noninferiority of nivolumab SC to nivolumab IV, point estimates and the 2-sided 90% CIs for treatment differences on the log scale were exponentiated to obtain estimates for the ratio of geometric means and respective 90% CIs for Cavgd28 and Cminss on the original scale. Noninferiority of nivolumab SC to nivolumab IV was concluded if the lower limit of the 2 sided 90% CIs for the ratio of geometric means for both nivolumab Cavgd28 and Cminss was above 0.8.

The primary analysis was performed with stratification as recorded in the CRF (ie, weight category [< 80 kg or ≥ 80 kg] and IMDC risk group [favorable, intermediate, or poor]) and treatment (nivolumab SC or nivolumab IV) as fixed effects (Table 4). In this analysis, noninferiority of nivolumab SC to nivolumab IV was concluded with Cavgd28 GMR (90% CI) of 2.098 (2.001, 2.200) and Cminss GMR (90% CI) of 1.774 (1.633, 1.927) as the lower bounds of the 2-sided 90% CIs for both endpoints were above 0.8.

Additional supplementary analyses of Cavgd28 and Cminss were performed using stratification factors as recorded in the IRT (ie, weight category [< 80 kg or ≥ 80 kg] and IMDC risk group [favorable, intermediate, or poor] and treatment (nivolumab SC or nivolumab IV) as fixed effects and without stratification factors. In addition, a supplementary analysis for Cavgd28 and Cminss that removed data derived after treatment discontinuation or death was also conducted. Results from these supportive analyses were consistent with the primary analysis.

As expected, all nivolumab exposure measures determined in the study were higher for nivolumab SC relative to nivolumab IV (Table 5). This is consistent with model-predicted exposures for nivolumab SC and nivolumab IV that were used to support the selection of 1,200 mg Q4W dosing regimen for CA20967T. Of mention, the geometric mean C_{trough} at Week 17 (observed) was 123 µg/mL for nivolumab SC and 66.3 µg/mL for nivolumab IV, and the geometric mean C_{minss} (popPK analysis) was 126 µg/mL for nivolumab SC and 71.5 µg/mL for nivolumab IV. The similarity between C_{trough} at Week 17 and C_{minss} for nivolumab SC and nivolumab IV supports consistency between the model-predicted and observed nivolumab concentrations at steady-state determined for both routes of administration.

CA2098KX

Noncompartmental PK analysis using actual sample collection times was used to determine the PK endpoints in the study. Geometric mean nivolumab exposures increased with increasing nivolumab SC doses in Parts A through D (Table 6). The PK of the 600 mg Q2W (Part E) regimen was relatively similar to that of the 1,200 mg Q4W (Part D) regimen when considering differences in dose and schedule as well as expected accumulation with Q2W SC dosing. Median T_{max} was similar between the 600 mg Q2W and 1,200 mg Q4W SC dosing regimens.

Nivolumab serum concentration-time data for nivolumab SC administered with rHuPH20 in CA2098KX were pooled with existing IV serum concentration-time data from 19 historical nivolumab IV monotherapy clinical studies to develop a combined SC and IV popPK model for nivolumab. As a combined IV/SC popPK model was developed previously, the current model development focused on model refinement, especially covariate selection to define a pre-specified model for the planned popPK analysis to support registrational, Phase 3, study, CA20967T. An extravascular absorption compartment was added to the existing established IV popPK model and the absorption PK parameters (KA and F) were estimated. A two-compartment model, with zero-order infusion into the central compartment (IV route) and first order absorption from the extravascular compartment (SC route), and time-varying CL with random effects on CL, VC, VP, EMAX, KA, and F, and proportional residual error adequately described the data.

Covariate-parameter relationships were assessed with the final popPK model. The effects of baseline body weight, eGFR, PS and sex on nivolumab CL were statistically significant (95% CI did not include the null value); however, the magnitude of these effects was <20% and therefore, not considered clinically relevant. These findings are consistent with those of the previous analysis. Females had ~10% lower F than males; however, the magnitude of the effect was <20% and not expected to be clinically meaningful.

The final model was used to predict individual PK parameters and exposure measures for nivolumab SC and make descriptive comparisons by subject-level ADA status (ADA positive and ADA negative), tumor type (bladder, CRC, HCC, MEL, NSCLC, SCCHN, and RCC), and SC dosing regimen (600 mg Q2W and 1,200 mg Q4W). When evaluating ADA status, the differences in the geometric means for F, KA, Cavgd28, and Cminss between ADA positive and ADA negative subjects were <20% and not expected to be clinically meaningful. Similarly, when evaluating F, KA, Cavgd28, and Cminss by tumor type, the differences in the geometric means across tumor types were <20% and not expected to be clinically meaningful. Lastly, for SC dosing regimen, the differences in the geometric means were <6% for KA and F and <10% for steady-state exposures (Cminss and Cavgss). Cavgd28, Cmaxss, and all Cycle 1 exposures (Cmax1, Cmin1, and Cavg1) were lower for 600 mg Q2W than for 1,200 mg Q4W given the difference in dose and frequency of dosing.

The FDA's Assessment:

FDA generally concurs with the Applicant's position. Selection of nivolumab SC dosage of 1200 mg Q4W administered in the abdomen or thigh for the pivotal study was based on its exposure not less than the exposure of nivolumab IV dosage of 3 mg/kg Q2W observed in historical Study CheckMate-025.

Comparative exposures between SC and IV arms:

FDA performed a PK analysis with data from all PK evaluable patients without stratification factors. The results are comparable to the Applicant's analysis with stratification factors incorporated.

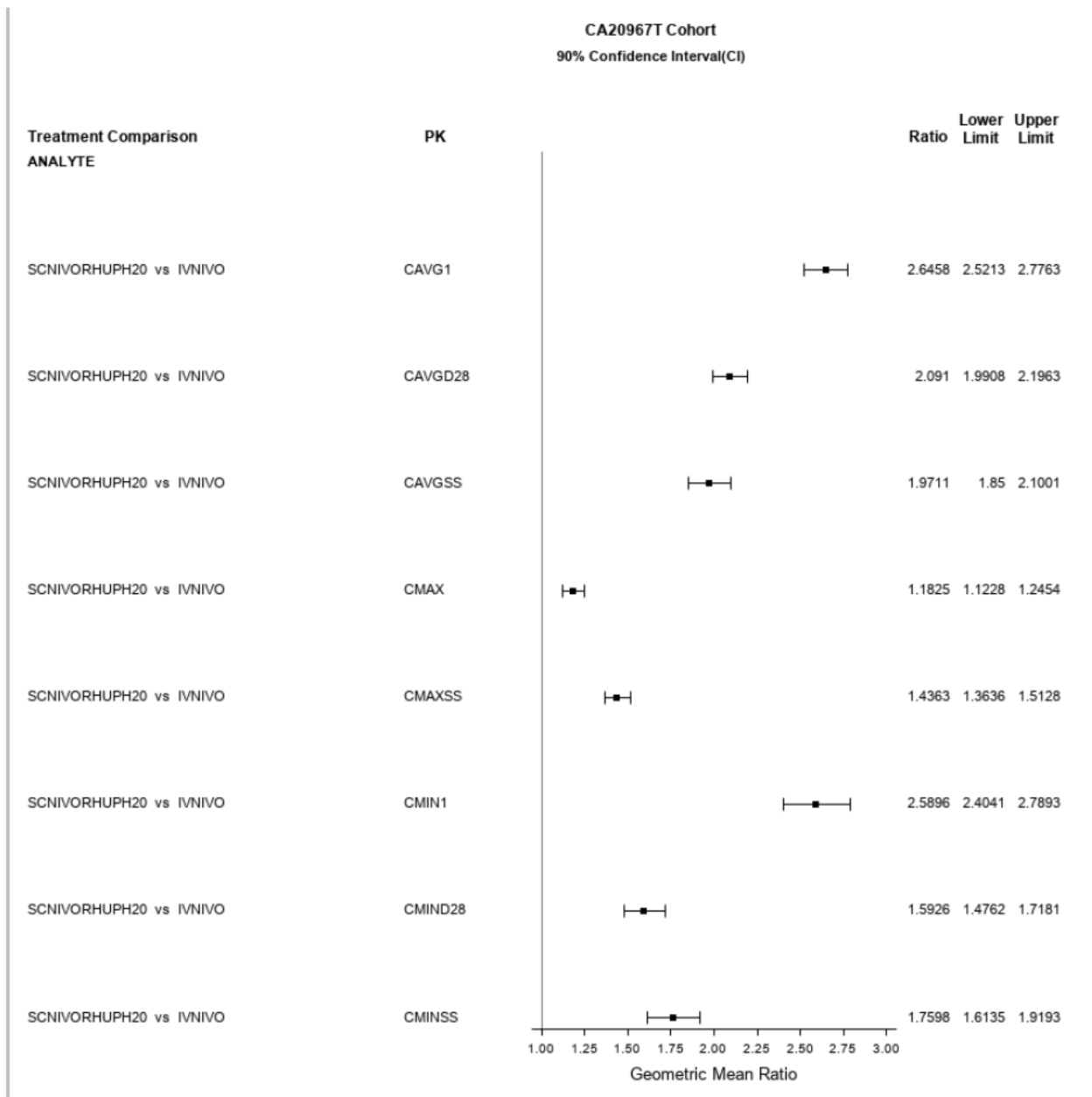
Table 7 and Figure 1 below show that the lower boundary of the 90% CI of the GMR for the co-primary endpoints of C_{avgd28} and C_{minss} met the prespecified margin of not less than 0.8. The secondary exposure endpoints are also not less than the 0.8 margin.

Table 7: Comparative Exposures of Nivolumab SC vs Nivolumab IV (Co-Primary Endpoints and Secondary Endpoints) from the Pivotal Study CA20967T – All PK Evaluable Patients (Without Stratification Factors)

PK Endpoints (µg/mL)	Geometric mean ratio (90% CI) (SC:IV) n=242 (SC) : n=245 (IV)
Primary PK Endpoints	
Model-based C_{avgd28} at Cycle 1	2.09 (1.99, 2.20)
Model based C_{minss} at steady state	1.76 (1.61, 1.92)
Secondary PK Endpoints	
Model based C_{avgss} at steady state	1.97 (1.85, 2.10)
Model based C_{mind28} at Cycle 1	1.59 (1.48, 1.72)
Model based C_{max1} at Cycle 1	1.18 (1.12, 1.25)
Model based C_{maxss} at steady state	1.44 (1.36, 1.51)

Source: FDA's PK analysis.

Figure 1: Forest Plot of PK Parameters of the Pivotal Study CA20967T



Source: FDA's Forest plot.

Site of SC injection:

The sites of injection (abdomen or thigh) provided comparable bioavailability and exposures. To evaluate the potential impact of the injection site on bioavailability and exposures, individual empirical Bayes estimates of the PK parameters were obtained and used to determine the individual exposures. In Study CA20967T, a total of 16 patients

received majority of their nivolumab SC doses in the thigh, while the remaining 226 PK-evaluable patients received majority of their nivolumab SC injections in the abdomen. The difference between the abdomen versus thigh injection sites was < 1% in the geometric means of bioavailability (Figure 2) and < 2% in the geometric means of exposure at steady state (Figure 3). The small magnitude of these differences is not considered clinically relevant.

In Study CA20967T, drug-related injection site reactions were reported in 8% (20/247) of patients in the nivolumab SC arm, all of which were Grade 1-2 and mostly resolved without any treatment. No injection site reactions were reported among patients with nivolumab SC injected at thigh.

Figure 2: Comparison of Nivolumab SC Bioavailability by Site of Injection

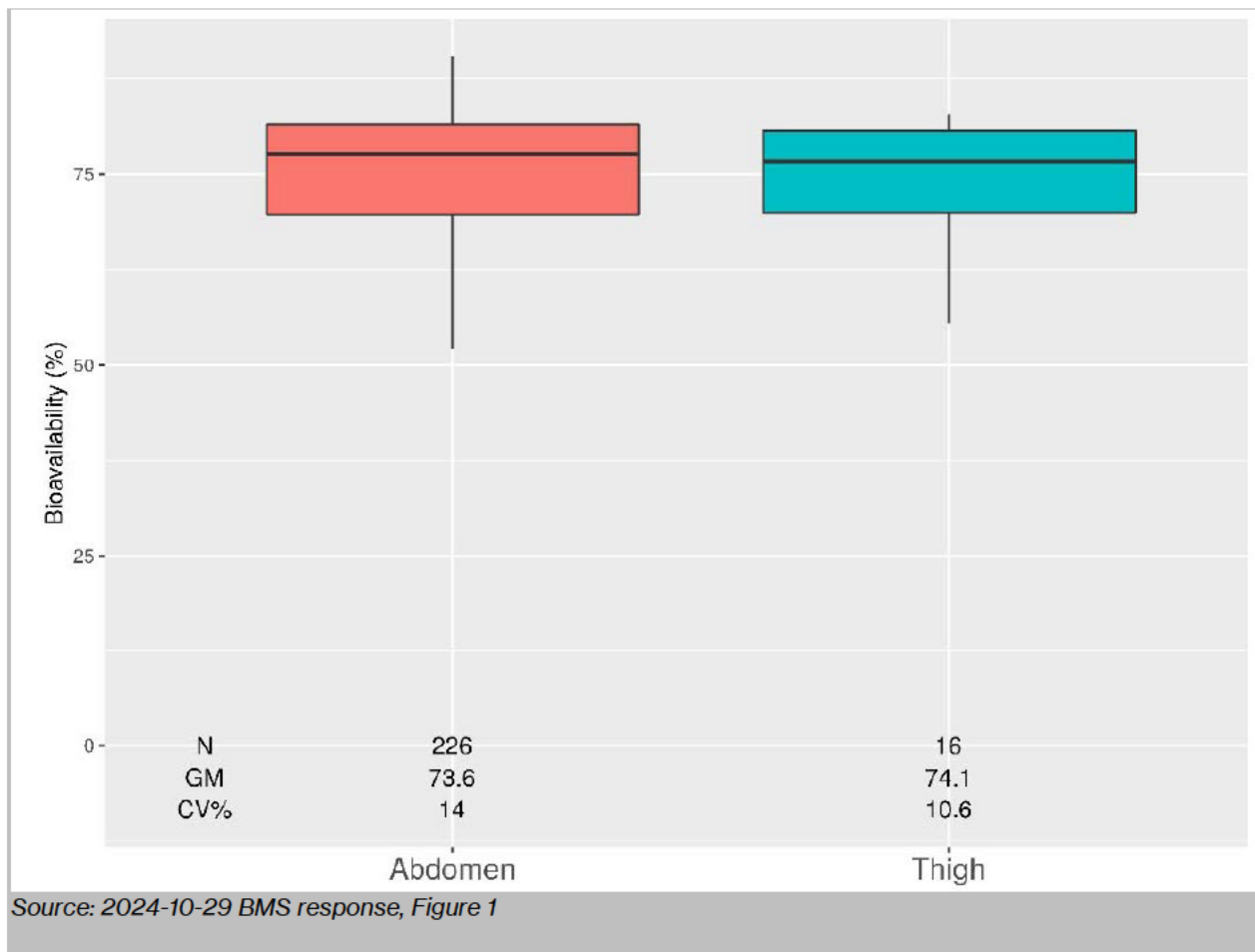
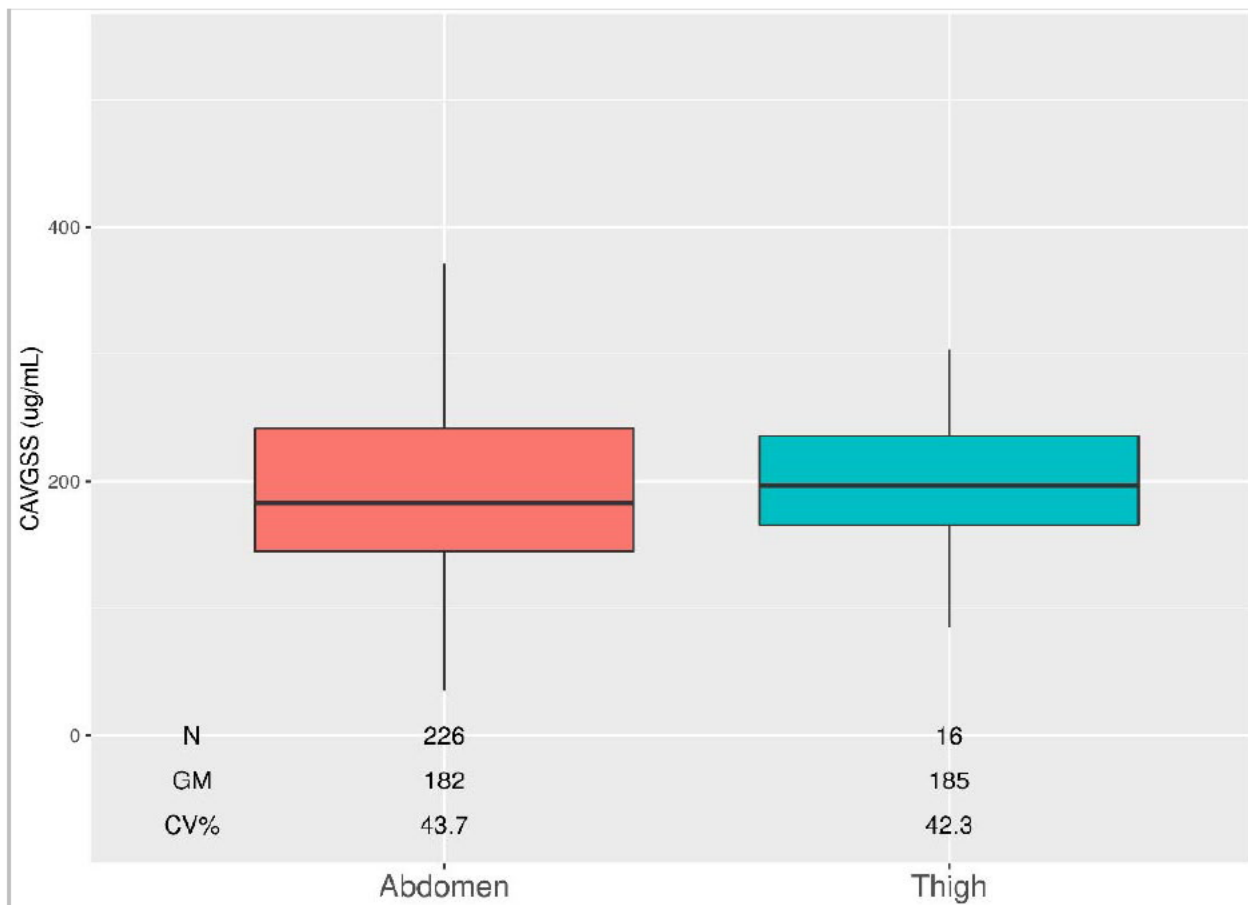
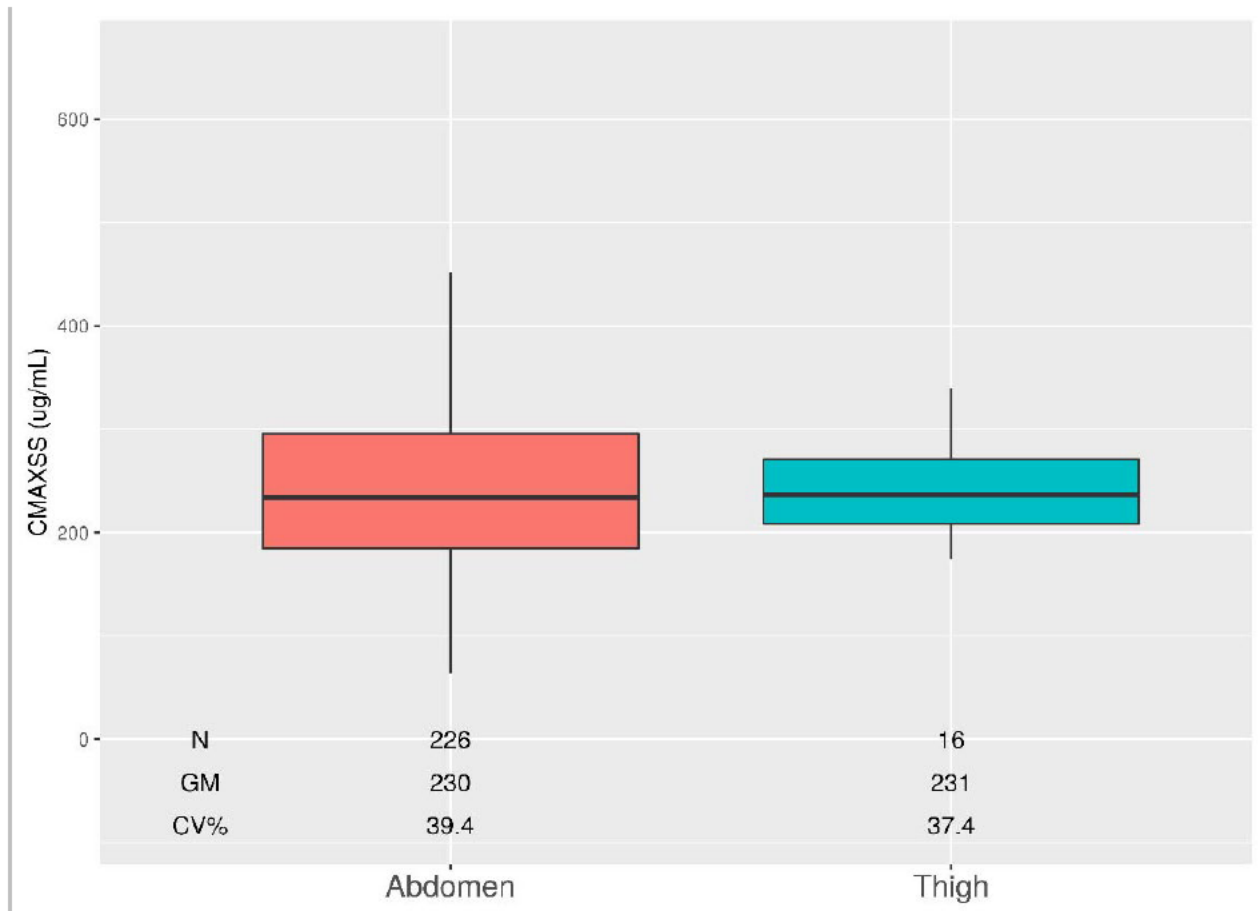
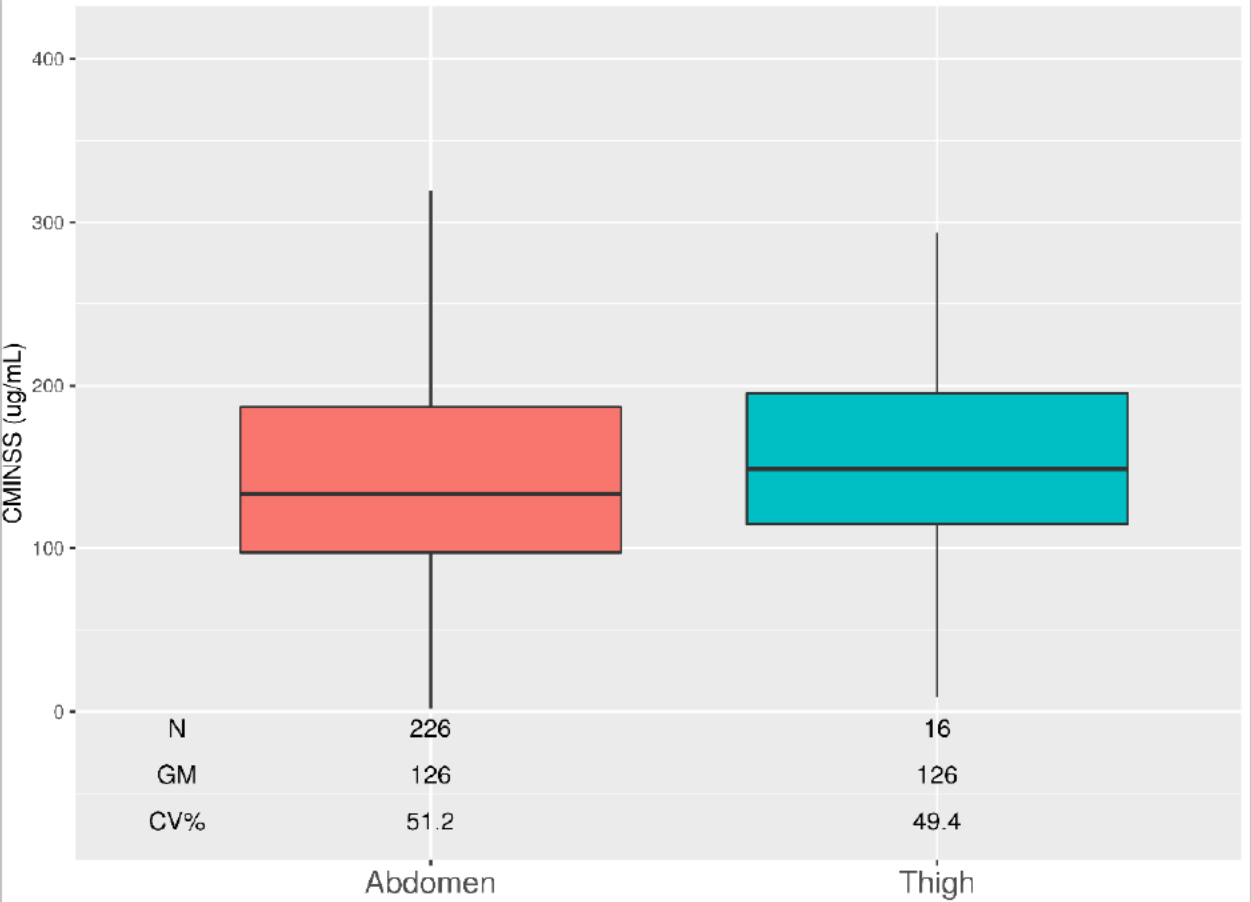


Figure 3: Comparison of Nivolumab SC Exposures (C_{avgss} , C_{maxss} and C_{minss}) by Site of Injection



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Source: 2024-10-29 BMS response, Figure 2
Abbreviations: GM, geometric mean; CV%, percent coefficient of variation

Descriptive efficacy and safety comparisons between SC and IV arms:

Overall response rate (ORR) was 24% (95% CI: 19, 30) in the SC arm and 18% (95% CI: 14, 24) in the IV arm. Time to event endpoints were underpowered to assess for differences. Safety profiles including serious adverse effect (AEs) and Grade ≥ 3 AEs were also comparable between the SC and IV arms.

Effect of ADA and NAb on PK, efficacy and safety:
The incidence of positive ADA to nivolumab was 23% (46/202) in the SC arm and was 7% (15/215) in the IV arm. Compared to the patients with negative ADA, trough drug concentration was 24-32% lower in the ADA positive patients at Week 4, 8 and 16 in SC arm, and was 38-55% lower in the ADA positive patients at Week 4 and 8 in the IV arm. Nivolumab clearance (CL) overall was increased by 26%. A higher ADA incidence with a 32% decrease in C_{trough} in ADA+ positive patients receiving nivolumab SC is considered not clinically meaningful given nivolumab exposure was at least 75% higher with SC than with IV.

ADA positive patients were reported by the Applicant to have a trend of a lower ORR (15% [95% CI: 6, 29]) compared to ADA negative patients (28% [95% CI: 21, 36]) in the SC arm. ADA positive patients in the IV arm also showed a trend of lower ORR (0% [95% CI: 0, 22]) compared to ADA negative patients (21% [95% CI: 15, 27]) in the IV arm. Based on an assessment of the presence of nivolumab ADAs and neutralizing antibodies in relation to PFS and BOR per BICR, some ADA positive patients in the SC arm and the IV arm continued to demonstrate clinical benefit, and there was no apparent evidence of an effect of ADAs or neutralizing antibodies on the efficacy of the tested regimens. The data are limited to adequately characterize the effect of ADA on efficacy.

The incidence of neutralizing antibodies (NAb) to nivolumab was 4.3% (2/46) in the SC arm and it was 0% (0/15) in the IV arm. The effect of NAb on efficacy endpoints is inconclusive due to small sample sizes, although the OS trended lower in patients with NAb (6.3 months (95% CI: 4.2, NE) compared to the patients without NAb (8.3 months (95% CI: 5.1, NE) in the nivolumab SC arm.

The incidences of ADA and NAb to hyaluronidase in the SC arm were 9% (19/215) and 26% (5/19), respectively. The effects of these antibodies on the PK, efficacy and safety is unknown due to low incidence.

The presence of ADA and NAb did not significantly affect safety profiles of nivolumab after both SC and IV treatments.

6.2.2. General Dosing and Therapeutic Individualization

6.2.2.1. General Dosing

Data:

Table 8: Applicant - Indications and Dosing Regimens Pursued for Nivolumab SC

Tumor Type	Setting
MEL	Adjuvant (600 mg Q2W and/or 1,200 mg Q4W) 1L/ (b) (4) (600 mg Q2W and/or 1,200 mg Q4W) 1L/ (b) (4) (maintenance) (600 mg Q2W and/or 1,200 mg Q4W)
NSCLC	Neoadjuvant (900 mg Q3W with chemotherapy) (b) (4)
RCC	1L (600 mg Q2W and/or 1,200 mg Q4W with cabozantinib) 1L (maintenance) (600 mg Q2W and/or 1,200 mg Q4W) (b) (4)
SCCHN	(b) (4) (600 mg Q2W and/or 1,200 mg Q4W)
UC	Adjuvant (600 mg Q2W and/or 1,200 mg Q4W) (b) (4) (600 mg Q2W and/or 1,200 mg Q4W)
mCRC	(b) (4) (600 mg Q2W and/or 1,200 mg Q4W) (b) (4) (600 mg Q2W and/or 1,200 mg Q4W)
ESCC	Adjuvant (600 mg Q2W and/or 1,200 mg Q4W) ^a (b) (4) (600 mg Q2W and/or 1,200 mg Q4W) 1L (600 mg Q2W and/or 1,200 mg Q4W with chemotherapy)
GC, GEJC, or EAC	1L (600 mg Q2W with chemotherapy) 1L (900 mg Q3W with chemotherapy)
HCC	(b) (4) maintenance) (600 mg Q2W and/or 1,200 mg Q4W)

^a Including esophageal adenocarcinoma

The Applicant's Position:

Rationale for Dose Selection for Nivolumab SC

Nivolumab SC 1,200 mg coformulated with rHuPH20 (2,000 units/mL) Q4W was selected for evaluation of PK noninferiority relative to nivolumab IV 3 mg/kg Q2W in CA20967T.

Data from participants in Phase 1/2 CA2098KX where nivolumab SC was evaluated at 720 mg or 960 mg with or without rHuPH20, and at 1,200 mg with rHuPH20, and historical nivolumab IV data from across the clinical development program (approximately 3,000 patients) were used to develop a combined IV/SC popPK model and characterize the absorption profile (KA and F) of nivolumab SC. The typical values (90 % CI) for F and the KA were 70% (66% to 74%) and 0.250 day⁻¹ (0.225 to 0.274 day⁻¹), respectively. Other PK parameters (CL and Vd terms) were estimated and found to be consistent with those for nivolumab IV.

The model was used to predict nivolumab exposure measures (C_{avgd28}, C_{mind28}, C_{max1}, C_{avgss}, C_{minss} and C_{maxss}) for 720 mg SC Q4W, 960 mg SC Q4W and 1,200 mg SC Q4W (all coformulated with rHuPH20 [2,000 units/mL]) relative to 3 mg/kg IV Q2W, and exposure measures for 10 mg/kg IV Q2W, a dosing regimen found to be safe and tolerable in early clinical studies. The 10 mg/kg regimen is commonly used as a reference regimen to define nivolumab's safety margin.⁶ The aim was to identify a nivolumab SC dosing regimen that could achieve exposures that were similar to or greater than those for nivolumab IV 3

mg/kg Q2W across a range of body weights and for a scenario of low F (ie, 60%) given the uncertainty in that PK parameter estimate. Based on these assessments, nivolumab SC 1,200 mg coformulated with rHuPH20 (2,000 units/mL) Q4W was expected to provide noninferior geometric mean exposures after the first dose and at steady state relative to nivolumab 3 mg/kg IV Q2W while not exceeding exposures (C_{avgd28} and C_{minss}) predicted for nivolumab 10 mg/kg IV Q2W.

Nivolumab SC 600 mg coformulated with rHuPH20 (2,000 units/mL) Q2W was selected because it was expected to have a linear exposure profile (ie, ~ 50% lower C_{max} and AUC) after the first dose to that of nivolumab SC 1,200 mg coformulated with rHuPH20 (2,000 units/mL) Q4W. This alternative posology was evaluated in CA2098KX to potentially provide SC dosing optionality for patients and prescribers.

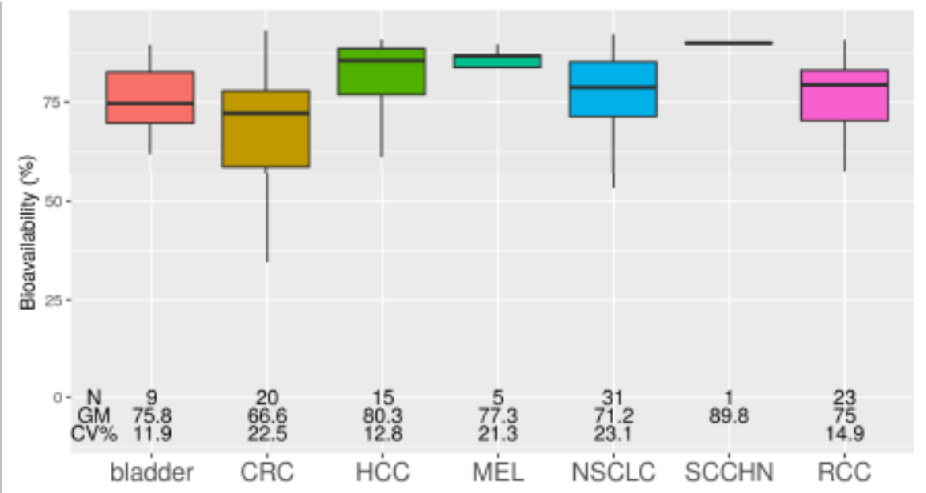
Nivolumab SC 900 mg coformulated with rHuPH20 (2,000 units/mL) Q3W was selected by linear interpolation given the known linear PK exhibited by nivolumab, as previously discussed at the June 9, 2023 MIDD meeting with FDA. A Q3W nivolumab SC dosing regimen would provide additional optionality for patients and prescribers to enable use in combination with partner therapies dosed at a Q3W cadence such as chemotherapy.

The FDA's Assessment:

FDA agrees with the Applicant's proposed SC dosage of 1200 mg nivolumab with 20000 units/mL (5 mL) hyaluronidase Q4W. The primary exposure endpoints (C_{avgd28} and C_{minss}) with the lower boundary of 90% CI of the GMR between 1200 mg SC Q4W and 3 mg/kg IV Q2W met the prespecified margin of not less than 0.8 in the pivotal study CA20967T.

The Applicant proposes the nivolumab/hyaluronidase SC dosages of 1200 mg Q4W and alternative dosages of 600 mg Q2W and 900 mg Q3W for the proposed adult indications requested in BLA 761381 and BLA 761429 that were previously approved for nivolumab IV dosages of 3 mg/kg IV Q2W, 240 mg Q2W and 480 mg Q4W. This proposal is supported by the observed data showing no statistically significant ($p > 0.05$) difference detected in nivolumab bioavailability across different tumor types including metastatic NSCLC, advanced or metastatic RCC, unresectable or metastatic melanoma, HCC, metastatic CRC (MSI-H or dMMR) or mUC after nivolumab SC administration (Figure 4). It is anticipated that nivolumab PK exposures are comparable in other tumor types after SC administration as seen after IV administration.

Figure 4: Nivolumab Bioavailability Across Different Tumor Types in Study CA2098KX



Source: population PK Study Report - CA2098KX, Figure 5.3.2-1, page 58

The proposed alternative dosages for nivolumab SC administration are 600 nivolumab/10000 units hyaluronidase Q2W and 900 mg nivolumab/15000 units hyaluronidase Q3W. These dosages are supported by modeling and simulation showing their comparable exposures to the dosage of 1200 mg nivolumab/20000 units hyaluronidase SC Q4W with less fluctuation and below safety margin established by nivolumab IV.

Table 9: Nivolumab Exposures with Different Dosages Predicted by Modeling and Simulation

GeoMean (CV%)	1200 mg Q4W	900 mg Q3W	600 mg Q2W
C _{avg,ss}	182 (44)	182 (44)	182 (44)
C _{max,ss}	230 (39)	214 (40)	199 (42)
C _{min,ss}	126 (51)	141 (49)	157 (47)

Source: Nivolumab SC simulation and bridging report (Table 5.1.2-1).

6.2.2.2. Therapeutic Individualization

The Applicant's Position:

The impact of intrinsic and extrinsic factors on nivolumab IV PK have been previously characterized in subjects with advanced solid tumors.⁷ There were no significant intrinsic and extrinsic factors identified that required a nivolumab dose adjustment or therapeutic individualization. The covariates age, sex, race, renal function, baseline LDH, PS, PD-L1 expression, tumor size and immunogenicity were evaluated previously and not determined to be clinically relevant predictors of nivolumab CL (the magnitude of the effect on CL was < 20%).

In the CA2098KX popPK analysis, the effect of baseline body weight, eGFR, PS, and sex on nivolumab CL were consistent with the nivolumab IV popPK analysis. The only covariate retained on the nivolumab SC absorption PK parameters was the effect of sex on F; however, the effect was not statistically significant as the 95% CI included the null value. Females only had ~10% lower bioavailability than males; therefore, the effect was not considered to have any clinically meaningful impact.⁴

In the analysis in the 2L RCC setting for CA20967T, the impact of PS, sex, eGFR, and baseline body weight (which were significant predictors on nivolumab CL in the previous nivolumab final model) were evaluated and found to be consistent with the prior analysis.³ No new covariate effects were identified.

The FDA's Assessment:

FDA agrees with the Applicant's position that no dose adjustment is recommended for nivolumab SC dosages based on intrinsic factors including body weight, sex, age, race, baseline LDH, PD-L1 expression, solid tumor type, tumor size, renal impairment, or hepatic impairment as for nivolumab IV formulation. The population PK analysis of CA20967T reported that eGFR, PS and sex on nivolumab clearance (CL) and baseline body weight on central volume of distribution (VC) were statistically significant covariates (95% CI did not include null value) (Figure 5 and Figure 6); however, the magnitude of the effect was <20% and not expected to be clinically meaningful and sex effects on exposure metrics were also not considered clinically important based on a flat exposure-response relationship for efficacy and safety of nivolumab.

Figure 5: Covariate Effects on Final Nivolumab Population Pharmacokinetic Model in Study CA2098KX

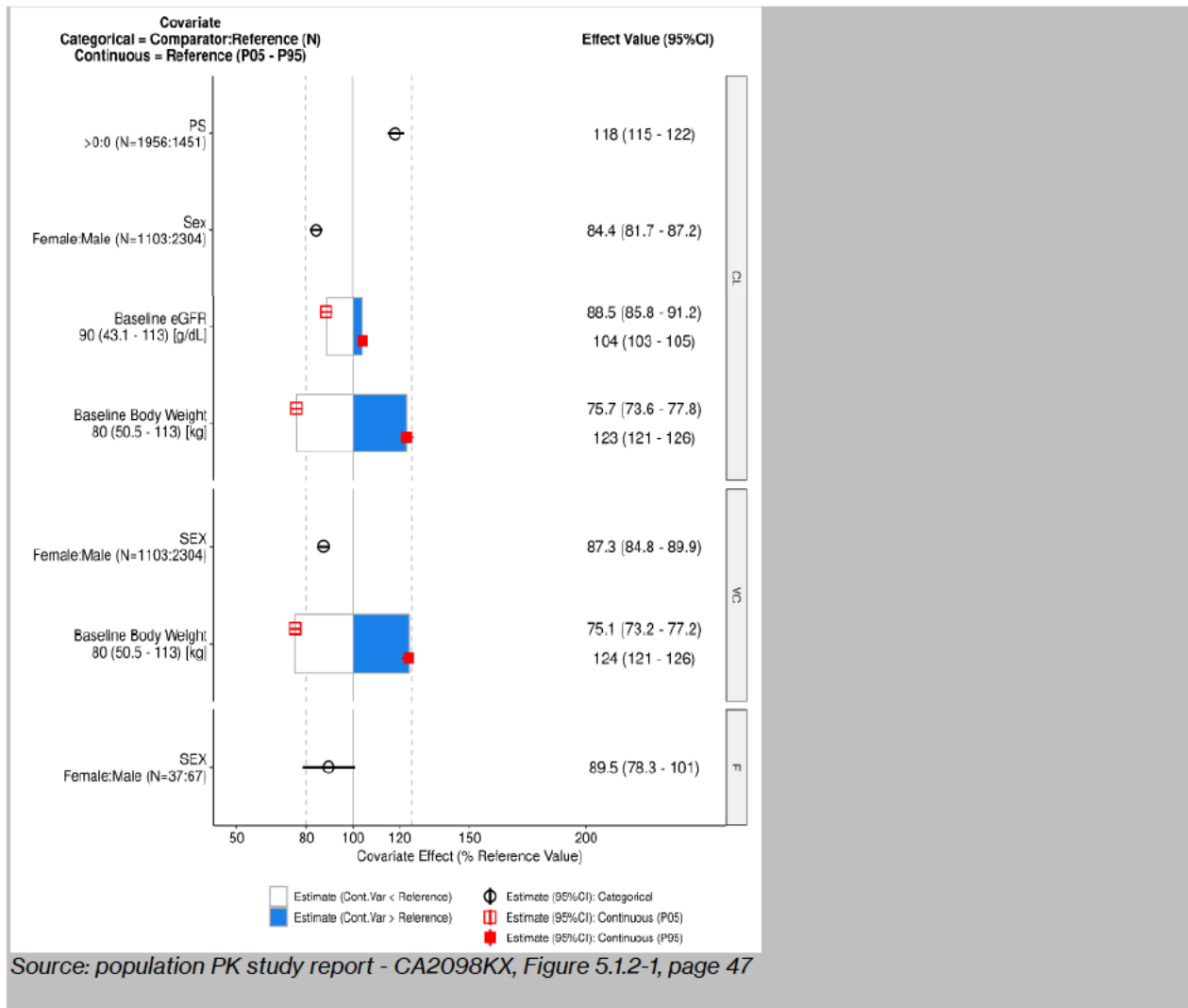
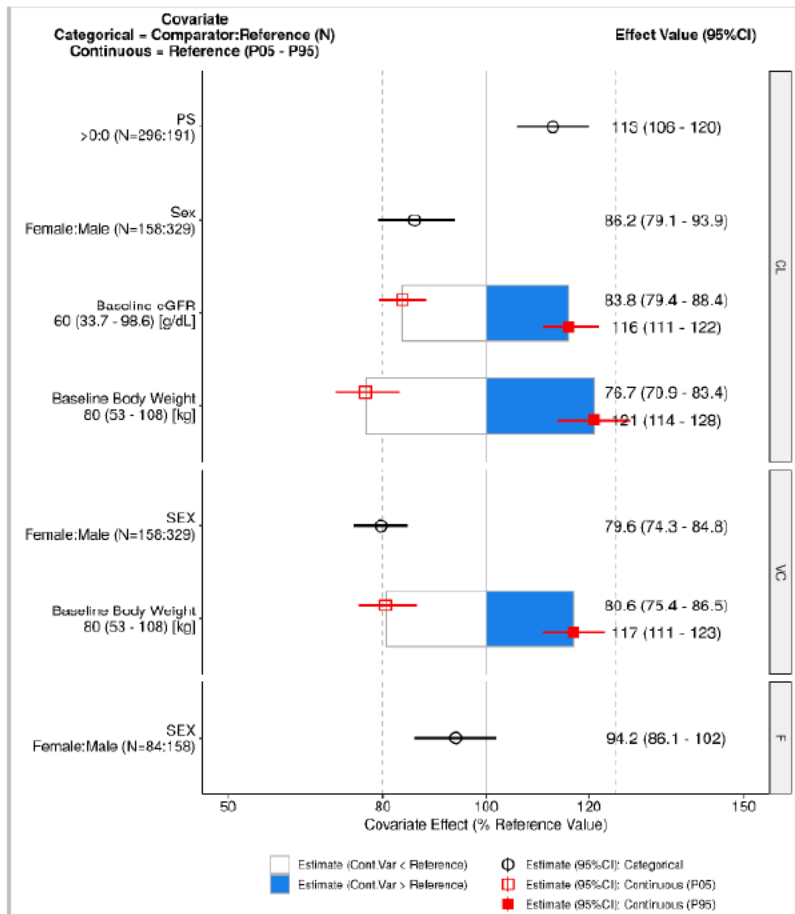


Figure 6: Covariate Effects on Final Nivolumab Population Pharmacokinetic Model in Study CA20967T



Source: population PK study report - CA20967T, Figure 5.1.1-1, page 42

6.2.2.3. Outstanding Issues

The Applicant's Position:

Not applicable.

The FDA's Assessment:

There are no outstanding issues.

6.3. Comprehensive Clinical Pharmacology Review

6.3.1. General Pharmacology and Pharmacokinetic Characteristics

Data:

Table 10: Applicant - General Pharmacology and Pharmacokinetic Characteristics

Physicochemical Properties	
Chemical structure and	<u>Nivolumab</u> Chemical structure: Nivolumab is a soluble protein consisting of 4 polypeptide chains,

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molecular weight	which include 2 identical heavy chains and 2 identical light chains and is a human IgG4 monoclonal antibody directed against the PD-1 receptor. Molecular weight: 146,221 daltons (143,619.17 daltons, protein portion) <u>rHuPH20</u> Chemical structure: rHuPH20 is the active ingredient in the approved product HYLENEX®. It is a neutral pH-active human hyaluronidase that is a glycosylated single-chain protein with up to 447 amino acids. rHuPH20 depolymerizes hyaluronan under physiologic conditions and acts as a spreading factor in vivo. Molecular weight: 51 kDa with glycosylation increasing the molecular weight to 60-65 kDa.
Administration, formulation type, strengths	<u>Subcutaneous administration, Solution for injection</u> Nivolumab 600 mg co-formulated with rHuPH20 10,000 units (Q2W) Nivolumab 900 mg co-formulated with rHuPH20 15,000 units (Q3W) Nivolumab 1,200 mg co-formulated with rHuPH20 20,000 units (Q4W)
Pharmacology	
Mechanism of Action	Binding of the PD-1 ligands, PD-L1 and PD-L2, to the PD-1 receptor found on T cells, inhibits T-cell proliferation and cytokine production. Upregulation of PD-1 ligands occurs in some tumors and signaling through this pathway can contribute to inhibition of active T-cell immune surveillance of tumors. Nivolumab is a human immunoglobulin G4 (IgG4) monoclonal antibody that binds to the PD-1 receptor and blocks its interaction with PD-L1 and PD-L2, releasing PD-1 pathway-mediated inhibition of the immune response, including the anti-tumor immune response. In syngeneic mouse tumor models, blocking PD-1 activity resulted in decreased tumor growth. Hyaluronan is a polysaccharide found in the extracellular matrix of the subcutaneous tissue. It is depolymerized by the naturally occurring enzyme hyaluronidase. Unlike the stable structural components of the interstitial matrix, hyaluronan has a half-life of approximately 0.5 days. Hyaluronidase increases permeability of the subcutaneous tissue by temporarily depolymerizing hyaluronan. In the doses administered, hyaluronidase in OPDIVO SC acts locally. The effects of hyaluronidase are reversible, and permeability of the subcutaneous tissue is restored within 24 to 48 hours.
Pharmacodynamics	Increases in peripheral pharmacodynamic biomarkers (PD-1 receptor occupancy [RO], IFNγ and IFNγ-inducible chemokines) demonstrate immune activation post nivolumab treatment. On-treatment level of RO demonstrates extent of target engagement as measured by PD-1 RO assay to determine the degree of saturation on peripheral effector T-cells by nivolumab treatment. Similarly, levels of IFNγ and IFNγ-inducible chemokines reflect cytotoxic cytokine production primarily by activated T cells post nivolumab treatment. In CA20967T, we characterized biomarker measures from periphery with endpoint measurement of changes from baseline in these peripheral pharmacodynamic biomarkers to demonstrate comparable biological activity of nivolumab SC against nivolumab IV.
General Information	
Bioanalysis	Nivolumab IV and or SC serum concentrations were determined using the validated ECL immunoassay (Method ICD 416). 2 historical IV monotherapy studies included in the CA2098KX popPK analysis were analyzed for nivolumab serum concentrations by either cross-validated ELISA methods TLIAM 0082 or ICD 316.
Dose or exposure range tested in clinical trials	Nivolumab IV: 3 mg/kg Q2W Nivolumab SC: single dose 720 mg and 960 mg $\pm$ rHuPH20; 600 mg + rHuPH20 Q2W; 1,200 mg + rHuPH20 Q4W
Max Tolerated Dose	MTD was not reached with nivolumab SC.
Exposures at Proposed Dose	Based on CA2098KX, nivolumab PK following 600 mg Q2W (Part E) was relatively similar to that of 1,200 mg Q4W when considering differences in dose and schedule as well as

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Regimen	expected accumulation with Q2W dosing. Based on CA20967T, PK noninferiority was met for the co-primary endpoints Cavgd28 and Cminss for nivolumab SC 1,200 mg Q4W vs nivolumab IV 3 mg/kg Q2W. Based on the bridging/simulation analyses, the exposure measures for the below proposed dosages of nivolumab SC were non-inferior to nivolumab IV 480 mg Q4W and/or 360 mg Q3W and/or 240 mg Q2W for each indication assessed: • nivolumab SC 600 mg + rHuPH20 10,000 units (Q2W) • nivolumab SC 900 mg + rHuPH20 15,000 units (Q3W) • nivolumab SC 1,200mg + rHuPH20 20,000 Units (Q4W)
Absorption	The model estimated typical values of absorption rate constant and bioavailability for nivolumab SC in CA20967T are 0.0123 hr ⁻¹ (or 0.295 Day ⁻¹) and 0.788 (or 78.8%), respectively. Peak concentrations occurred by around 6 days.
Distribution	The geometric mean volume of distribution at steady state and coefficient of variation (CV%) for nivolumab SC in CA20967T is 6.32 L (21.3%).
Elimination: Terminal half-life and CL	Nivolumab clearance decreases over time, with a geometric mean maximal reduction from baseline values (CV%) of 24.6% (15.8%) resulting in a geometric mean steady-state clearance (CLss) (CV%) of 7.18 mL/h (52.3%) in patients with RCC in CA20967T. The decrease in CLss is not considered clinically relevant. The geometric mean (CV%) elimination half-life (t _{1/2}) is 26.5 days (32.1%).
Immuno-genicity	Based on CA20967T, the incidence of treatment emergent anti-nivolumab antibodies was higher for nivolumab SC (46 subjects or 22.8%) than for nivolumab IV (15 subjects or 7.0%). Anti-rHuPH20 antibodies developed in 8.8% of subjects, which is consistent with the known ADA incidence for this hyaluronidase. In the nivolumab SC arm, 2 subjects developed neutralizing antibodies to nivolumab, and 5 subjects developed neutralizing antibodies to rHuPH20 whereas neutralizing antibodies were not observed in the nivolumab IV arm. Based on CA2098KX, positive ADAs for nivolumab SC were reported in the dose cohorts evaluated in the study; however, ADAs were not associated with an effect on PK, efficacy or safety, and no neutralizing antibodies were detected. The sample sizes in the study were small; however, the ADA profile of nivolumab SC appeared consistent with the known ADA profile of nivolumab IV observed across the historical clinical development program. In both CA20967T and CA2098KX, there was no meaningful impact of ADAs on either nivolumab SC absorption PK parameters or exposures nor was there an apparent impact of positive ADAs on efficacy and the development of select AEs (hypersensitivity reaction/anaphylaxis/injection or infusion-related reaction).

The Applicant's Position:

The clinical pharmacology and PK of nivolumab SC is well characterized.

The FDA's Assessment:

FDA generally agrees with the Applicant's position on clinical pharmacology and nivolumab PK characterization after SC administration in the dose finding Study CA2098KX and the pivotal Study CA20967T.

Study CA2098KX

This is a Phase 1/2 PK multi-tumor study of nivolumab SC monotherapy with the objective to describe the PK of nivolumab for SC administration and to evaluate the PK of nivolumab SC 600 mg Q2W co-formulated with hyaluronidase. The study reported that the geometric mean nivolumab exposures increased with increasing SC doses (720 mg, 960 mg and 1200 mg) in the first cycle. The exposures of 600 mg Q2W dosing regimen had comparable

overall exposure to the 1200 mg Q4W dosing regimen when comparing both treatments over four weeks.

In part A and part B, SC nivolumab was administered in the abdomen only. In part C, part D and part E, SC nivolumab was administered in the abdomen or in the thigh. The total dose of nivolumab with hyaluronidase was administered as a single SC injection, while nivolumab alone SC was administered as 1 to 4 injections. Group 2 and Group 4 under part B received nivolumab without hyaluronidase by SC injection using a syringe pump over approximately 30 minutes. All other groups in Parts A-E received nivolumab with hyaluronidase by injection via syringe manually over approximately 2-5 minutes, with part E patients receiving the coformulation of nivolumab and hyaluronidase premixed in one vial. Across the doses tested, the SC formulation of nivolumab with hyaluronidase greatly reduced the mean administration time to < 5 min compared with the standard 30- or 60-min infusion of nivolumab IV. The exposure parameters are reported as in Table 11.

Table 11: Summary Statistics for PK Parameters - Evaluable PK Subjects - CA2098KX

Parameter Statistic	Treatment					
	PART A (GRP 1)	PART B (GRP 2)	PART B (GRP 3)	PART B (GRP 4)	PART D	PART E
C _{MAX} (ng/mL) GEO.MEAN [N] (GEO.%CV)	54.8 [22] (51)	56.6 [18] (34)	81.4 [10] (41)	63.9 [17] (30)	106 [34] (46)	57.8 [36] (31)
T _{MAX} (h) MEDIAN [N] (MIN-T _{MAX})	167 [22] (47.0 - 357)	167 [18] (50.1 - 339)	141 [10] (47.2 - 333)	168 [17] (139 - 355)	130 [34] (44.5 - 317)	130 [36] (45.2 - 337)
AUC (TAU) (h*ng/mL) GEO.MEAN [N] (GEO.%CV)	24908 [20] (53)	27909 [16] (36)	40264 [10] (45)	32702 [13] (31)	53561 [33] (40)	15857 [35] (30)
C _{TAU} (ng/mL) GEO.MEAN [N] (GEO.%CV)	22.2 [20] (86)	26.9 [16] (65)	39.2 [10] (67)	34.8 [13] (41)	54.4 [33] (49)	43.6 [35] (36)

Source: Table 9.2-1 of the CA2098KX primary CSR, page 127

Note: The PK values for nivolumab (SC) – only Cycle 1 are presented.

PART A - GRP 1: nivolumab SC 720 mg + rHuPH20 2000 units/mL

PART B - GRP 2: nivolumab SC 720 mg

PART B - GRP 3: nivolumab SC 960 mg + rHuPH20 2000 units/mL

PART B - GRP 4: nivolumab SC 960 mg

PART D: nivolumab SC 1,200 mg + rHuPH20 2000 units/mL

PART E: nivolumab SC 600 mg co-formulated with rHuPH20 2000 units/mL

Study CA20967T

This is a pivotal noninferiority trial of nivolumab SC versus nivolumab IV in patients with advanced or metastatic ccRCC who have received prior systemic therapy. The popPK analysis showed that the nivolumab exposure measures with nivolumab 1200 mg SC Q4W were not less than that with nivolumab 3 mg/kg IV Q2W (Table 12).

The popPK model from previous studies with IV nivolumab was updated to add the absorption process of the SC nivolumab. The PK of nivolumab was generally characterized using a two-compartment model with first order absorption estimated from results of the dose-finding study CA2098KX and first order elimination. The estimation was based on the

results obtained from the study to assess a dose range of 600 mg to 1200 mg administered in the thigh and abdomen.

Table 12: Statistical Analyses of Nivolumab SC and Nivolumab IV PK Co-primary Endpoints – with Stratification Factors from IRT (ie, weight category [< 80 kg or ≥ 80 kg] and IMDC risk Group [favorable, intermediate, or poor]) - PK Evaluable Patients - CA20967T

PK parameter = Cavgd28 (µg/mL)								
TREATMENT AND COMPARISON	N	On Natural Logarithmic Scale				On Original Scale		
		ADJUSTED MEAN	ADJUSTED MEAN DIF	STANDARD ERROR	90% CI	ADJUSTED GEO MEAN	ADJUSTED GMR	90% CI
SC	242	4.349		0.0225	(4.312, 4.386)	77.373		(74.555, 80.297)
IV	245	3.608		0.0220	(3.571, 3.644)	36.875		(35.565, 38.235)
SC vs. IV			0.741	0.0288	(0.694, 0.789)		2.098	(2.001, 2.200)
PK parameter = Cminss (µg/mL)								
TREATMENT AND COMPARISON	N	On Natural Logarithmic Scale				On Original Scale		
		ADJUSTED MEAN	ADJUSTED MEAN DIF	STANDARD ERROR	90% CI	ADJUSTED GEO MEAN	ADJUSTED GMR	90% CI
SC	242	4.806		0.0394	(4.741, 4.871)	122.227		(114.552, 130.416)
IV	245	4.233		0.0384	(4.169, 4.296)	68.901		(64.676, 73.402)
SC vs. IV			0.573	0.0504	(0.490, 0.656)		1.774	(1.633, 1.927)
MODEL INFORMATION								
Estimation Method		- REML						
Residual Variance Method		- Profile						
Fixed Effects SE Method		- Model-Based						
Degrees of Freedom Method		- Residual						
Fixed Effects		- Weight categorization (CRF), IMDC risk group (CRF) and treatment						

Source: Table 9.1.1-1 of the CA20967T primary CSR, page 140

Note: Nivolumab exposure measures were estimated from the popPK analysis.

Impact of Immunogenicity on PK

The immunogenicity assays used for study CA20967T have adequate drug tolerance and can reliably detect the ADA and Nab to nivolumab. All study samples contain drug concentrations lower than the drug tolerance of 800 µg/mL for ADA and 200 µg/mL for NAb (Table 12). The presence of nivolumab in the ADA samples does not interfere with the detection of ADA or NAb.

Table 13: Summary of Key Assay Characteristics Related to Current Immunogenicity Assessment

Assays	ADA assay	NAb assay
Validation report number	JRY2	RFDW2
Method	Electrochemiluminescence (ECL) Immunoassay (Ligand binding assay)	Cell-based functional chemiluminescence assay
Positive control (PC)	100.0 ng/mL	5,000 ng/mL (LPC) and 20,000 ng/mL (HPC)

Drug tolerance	800 µg/mL of nivolumab at 100 ng/mL of PC	up to 200 µg/mL at 8.65 µg/mL PC
% of samples with observed drug concentration > drug tolerance	0%	0%

In study CA20967T, a numerically higher incidence of ADA against nivolumab in the SC arm was observed (23%, 46/202) when compared to the IV arm (7%, 15/215) (Table 14). The median time to the first detection of ADA against nivolumab was 4.1 weeks versus 4.9 weeks, in the SC arm and IV arm respectively. The median duration of persistence of ADA against nivolumab was longer in SC arm (11.9 weeks) than in IV arm (5.6 weeks). Refer to section 8.2.4 for safety results from study CA20967T and section 8.2.5 for safety results from study CA2098KX.

Table 14: Immunogenicity Assessments Summary - All Immunogenicity Evaluable Patients with Baseline and at Least One Post-Baseline Assessment for ADA against Nivolumab- CA20967T

ADA Status (%)	Arm A (Nivo SC)		Arm B (Nivo IV)
	Nivolumab N = 202	rHuPH20 N = 215	Nivolumab N = 215
BASELINE ADA POSITIVE	12 (5.9)	20 (9.3)	9 (4.2)
ADA POSITIVE	46 (22.8)	19 (8.8)	15 (7.0)
PERSISTENT POSITIVE (PP)	2 (1.0)	7 (3.3)	0
NOT PP - LAST SAMPLE POSITIVE	17 (8.4)	11 (5.1)	6 (2.8)
OTHER POSITIVE	27 (13.4)	1 (0.5)	9 (4.2)
NEUTRALIZING POSITIVE	2 (1.0)	5 (2.3)	0
ADA NEGATIVE	155 (76.7)	196 (91.2)	200 (93.0)
N.A.	1 (0.5)	0	0

Source: Table 11.1.1-1 of the CA20967T Primary CSR, page 151

Note:

Post-baseline assessments are assessments reported after initiation of treatment.

Baseline ADA Positive: A patient with pretreatment baseline ADA-positive sample.

ADA Positive: A patient with at least one ADA-positive sample post treatment relative to baseline (ADA negative at baseline or ADA titer to be at least 4-fold or greater [$\geq$] than baseline positive titer) at any time after initiation of treatment.

Subject (b) (6) in nivolumab SC arm had post-baseline positive ADA but was not included in this table due to missing baseline sample.

Persistent Positive (PP): ADA-positive sample at 2 or more consecutive time points, where the first and last ADA-positive samples are at least 16 weeks apart.

Not PP-Last Sample Positive: Not persistent but with ADA-positive sample at the last sampling time point.

Other Positive: Not persistent but some ADA-positive samples with the last sample being negative.

Neutralizing Positive: At least one ADA-positive sample with NAb detected post-baseline.

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Subject (b) (6) was not included in the "Neutralizing Positive" category for rHuPH20 due to the subject's "ADA Negative" status.

ADA Negative: A patient with only ADA-negative sample after initiation of treatment

N.A.: Subject (b) (6), baseline nivolumab ADA sample was positive with titer as 8, but the titer for the post-baseline positive ADA sample could not be determined due to insufficient quantity, resulting in an undetermined ADA status.

FDA conducted an analysis of immunogenicity impact on PK by assigning missing ADA baseline as ADA baseline negative and yielded a similar incidence of ADA of 25% (56/226) in SC arm and 8.2% in IV arm (Table 15).

Table 15: Summary of Clinical Study CA20967T, Including Immunogenicity Results and C_{trough}

Study	CA20967T	
Route of administration	SC	IV
Recommended dose regimen	1200 mg co-formulated with rHuPH20 20,000 units Q4W	3 mg/kg Q2W
Treatment duration (planned)	Patients received treatment until progression, unacceptable toxicity, withdrawal of consent, completion of 2 years (104 weeks) of treatment, death, or the end of study, whichever occurs first.	
Treatment duration (actual) [Median (min, max)] ^a	6.6 (0.0, 22.4) months	7.7 (0.0, 24.0) months
PK sampling ^b	Predose at Day 1 of Cycles (Q4W) 1, 2, 3, 4, 5, 9, 13, 21, and 25; a postdose at Day 4, 8, 15, 22 of Cycles 1; Follow-up	Predose at Day 1 of Cycles (Q2W) 1, 2, 3, 5, 7, 9, 17, 25, 33, 41, and 49; a postdose at end of infusion, Day 8 of Cycles 1 and 2; Follow-up
ADA sampling ^b	Predose at Day 1 of Cycles (Q4W) 1, 2, 3, 5, 9, 13, 21, and 25; Follow-up	Predose at Day 1 of Cycles (Q2W) 1, 3, 5, 9, 17, 25, 33, 41, and 49; Follow-up
No. of patients received treatment ^c	247	245
Applicant reported ADA incidence ^d	ADA against nivolumab: 23% (46/202) ADA against rHuPH20: 8.8% (19/215)	7.0% (15/215)
Applicant reported Nab incidence ^d	Nab against nivolumab: 4.3% (2/46) Nab against rHuPH20: 26% (5/19)	0% (0/15)
ADA incidence ^e per FDA analysis	ADA against nivolumab: 25% (56/226)	8.2% (19/233)

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	ADA against rHuPH20: 8.8% (20/228)							
NAb incidence ^e (among ADA+) per FDA analysis	Nab against nivolumab: 3.6% (2/56) Nab against rHuPH20: 25% (5/20)				0% (0/19)			
Nivolumab concentration (µg/mL); Arithmetic mean ± SD of C _{trough}								
Applicant analysis of C _{trough} ^f	SC				IV			
	Predose	Week	n	Mean ± SD	Predose	Week	n	Mean ± SD
	C2D1	4	213	61.3 ± 30.9	C3D1	4	212	33.4 ± 11.4
	C3D1	8	192	95.6 ± 45.8	C5D1	8	205	54.92 ± 19.2
	C5D1	16	158	136.9 ± 63.3	C9D1	16	157	70.5 ± 24.2
	C9D1	24	89	161.7 ± 80.2	C17D1	32	102	83.9 ± 36.1
	C13D1	36	35	190.5 ± 92.1	C25D1	48	50	91.5 ± 38.1
	C21D1	60	4	153.3 ± 64.4	C33D1	64	18	83.9 ± 36.1
					C41D1	80	8	93.7 ± 25.2
Source: FDA analysis								
^{a, c} Table 6.1-2 (page 79) in the CSR of Study CA20967T								
^b Table 9.5.1-1 and 9.5.1-2 (page 92-94) in the protocol of Study CA20967T								
^d Table 11.1.1-1 (page 151) in the CSR of Study CA20967T								
^e ADA incidence from an independent analysis using an internal analysis tool. (See the SPO folder for analysis of nivolumab , and the SPO folder for analysis of hyaluronidase). NAb incidence represents the fraction of ADA+ subjects who are NAb positive.								
^f C _{trough} of a given cycle was calculated using the ADPC dataset.								

Compared to the patients with ADA negative, C_{trough} was 24-32% lower in ADA positive patients in SC arm at up to 3 out of 7 timepoints and at follow up 1 with time-matched ADA and PK data; C_{trough} was 38-55% lower in ADA positive patients in IV arm at up to 2 out of 7 timepoints with time-matched ADA and PK data (Table 16 and Figure 5).

Table 16: Comparison of Nivolumab Trough Concentration by ADA Status at Each Visit for Study CA20967T (FDA's Analysis)

Arm	Timepoint (CycleDay / Week)	Geometric mean concentration (µg/mL)				ADA+ to ADA- ratio	
		ADA+ group	N	ADA- group	N	GMR	90% CI
	C2D1/W4	42.03	43	55.18	142	0.762	(0.624, 0.930) ^c
	C3D1/W8	59.65	23	87.45	152	0.682	(0.550, 0.847) ^c

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SC nivolumab + rHuPH20	C5D1/W16	92.59	9	123.57	138	0.749	(0.568, 0.989) ^c
	C9D1/W32	121.79	5	144.95	82	0.840	(0.555, 1.272)
	FOLLOW UP 1 ^a	13.74	6	78.11	48	0.176	(0.078, 0.395) ^c
	FOLLOW UP 2 ^a	3.82	3	12.52	30	0.305	(0.054, 1.711)
IV nivolumab	C3D1/W4	19.98	12	32.31	186	0.618	(0.521, 0.734) ^c
	C5D1/W8	22.61	7	50.32	183	0.449	(0.309, 0.653) ^c
	C91/W16	56.71	2	64.02	142	0.886	(0.474, 1.656)
	C17D1/W32	100.00	1	76.68	99	1.304	NA
	FOLLOW UP 1 ^b	2.77	2	30.22	57	0.092	(0.041, 0.207) ^c
	FOLLOW UP 2 ^b	0.56	1	5.28	31	0.106	NA

Source: FDA analysis

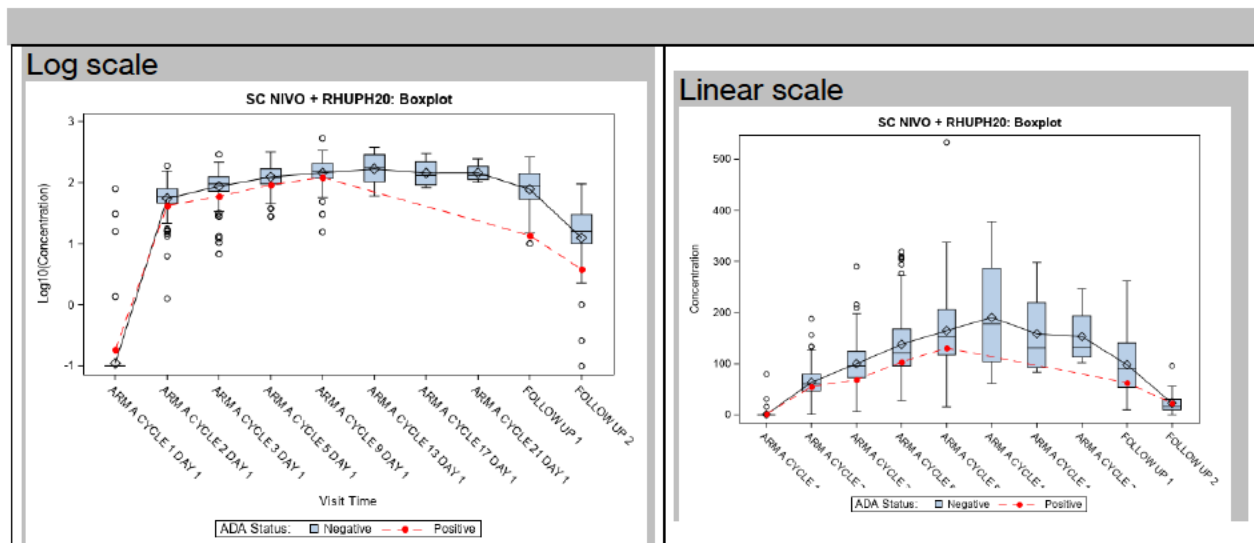
^a Follow-up Visit 1 should occur 30 days from the last dose (± 7 days) or can be performed on the date of discontinuation if that date is greater than 30 days from the last dose.

^b Follow-up Visit 2 occurs approximately 100 days (± 7 days) from last dose of study medication. Cited from Page 32 of the CSR.

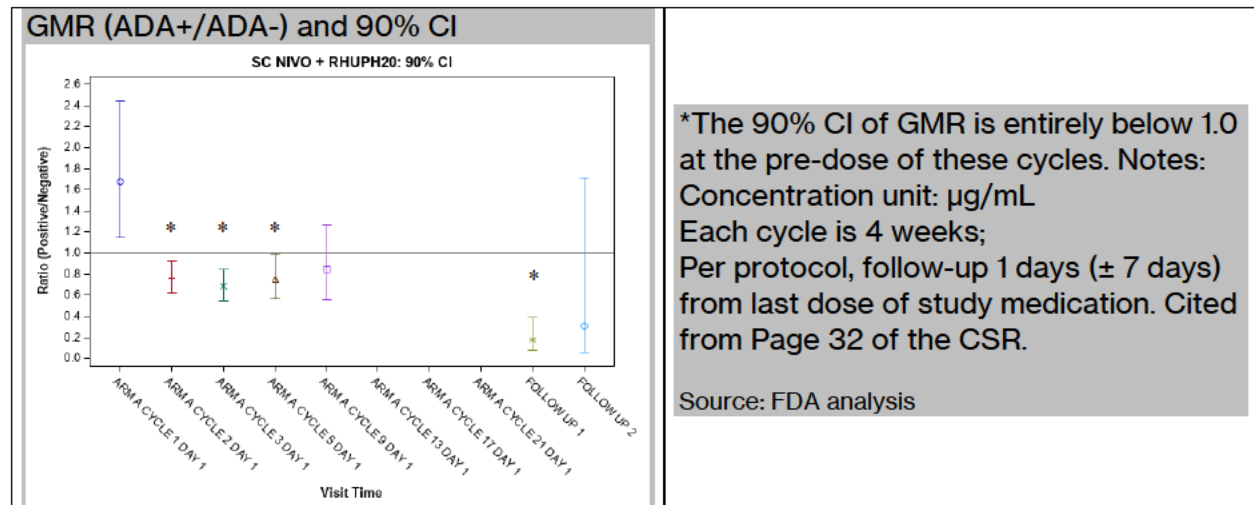
^c The 90% CI of GMR is entirely below 1.0 at the pre-dose of these cycles.

Three panels in Figure 7 represent the boxplot of nivolumab concentration in the SC arm in logarithmic scale and in linear scale, and the 90% CI of GMR of nivolumab concentration (ADA+ to ADA- ratio). Note that there were no patients with positive ADA status in Cycle 13, 17 and 21.

Figure 7: Comparison of Nivolumab Concentration Over Time in ADA+ and ADA- Samples During the Treatment Period in The SC Nivolumab Treatment Arm in Study CA20967T (FDA's Analysis)

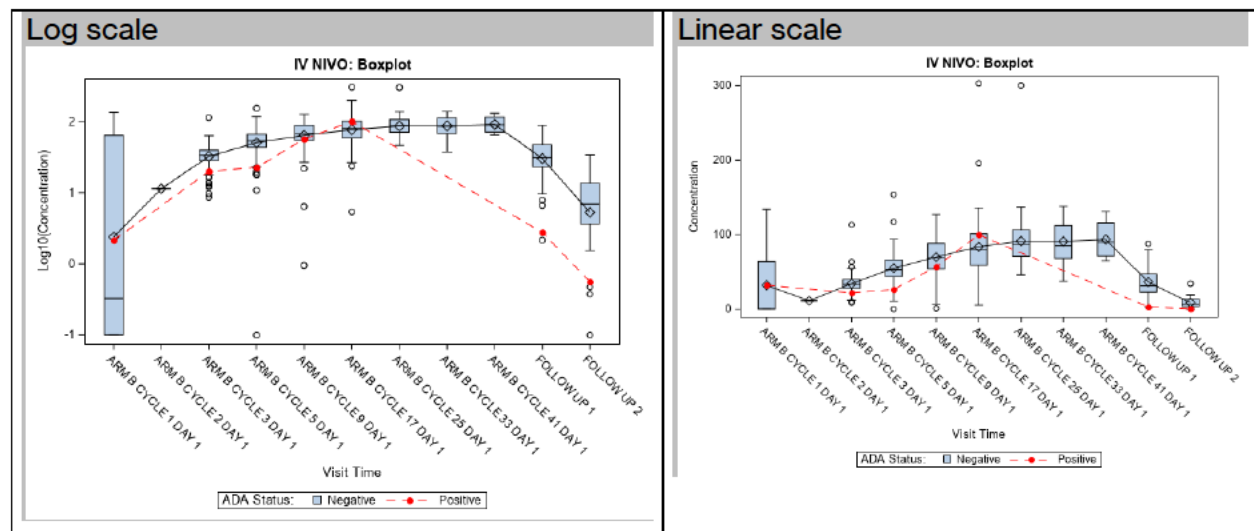


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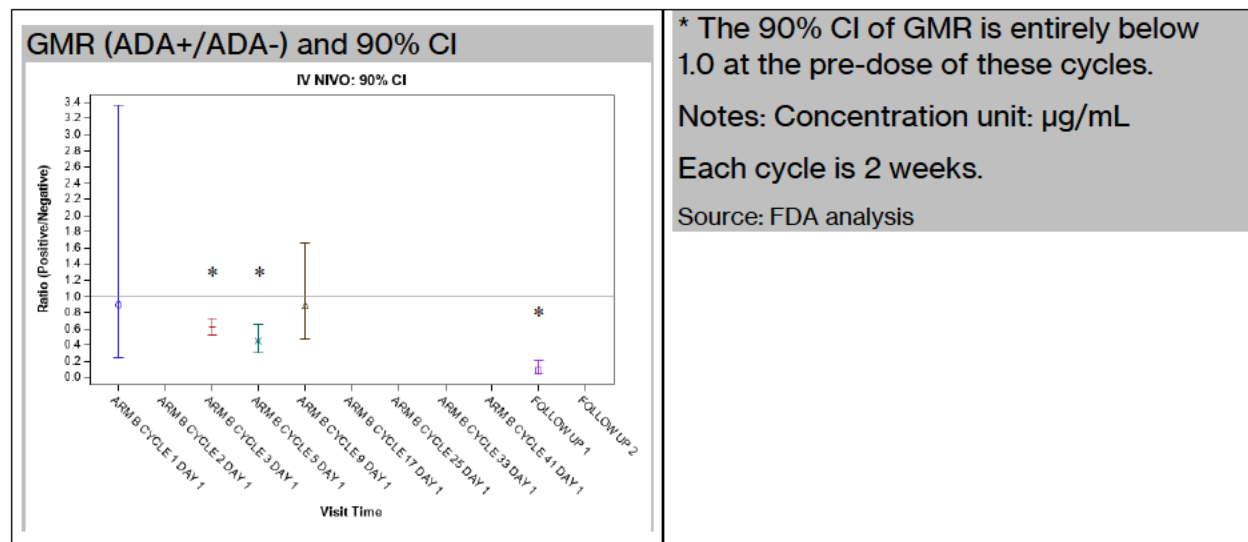


Three panels in Figure 8 represent the boxplot of nivolumab concentration in the IV arm in logarithmic scale and in linear scale, and the 90% CI of GMR of nivolumab concentration (ADA+ to ADA- ratio). Note that there were no patients with positive ADA status in Cycle 25, 33 and 41.

Figure 8: Comparison of Nivolumab Concentration Over Time in ADA+ and ADA- Samples During the Treatment Period in the IV Nivolumab Treatment Arm in Study CA20967T (FDA's Analysis)



BLA Multi-disciplinary Review and Evaluation {BLA 761381 and BLA 761429}
OPDIVO (nivolumab and hyaluronidase - nvhy) injection, for subcutaneous use

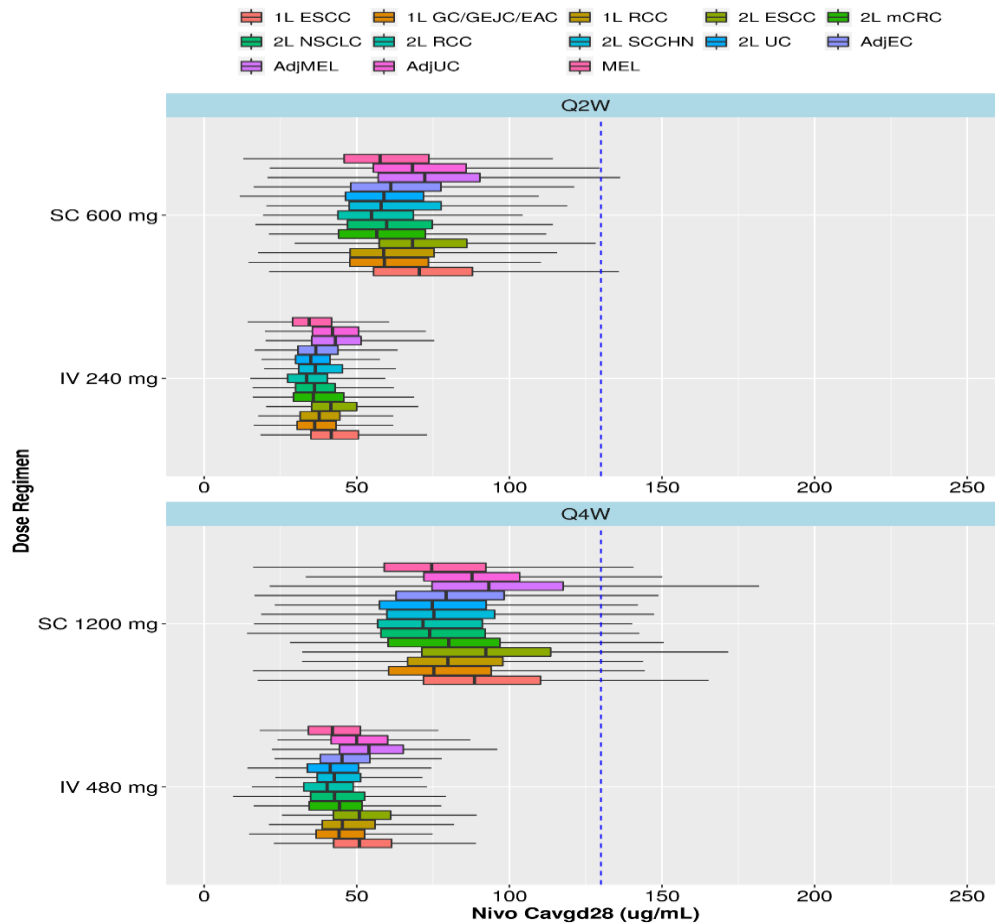


6.3.2. Clinical Pharmacology Questions

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

Data:

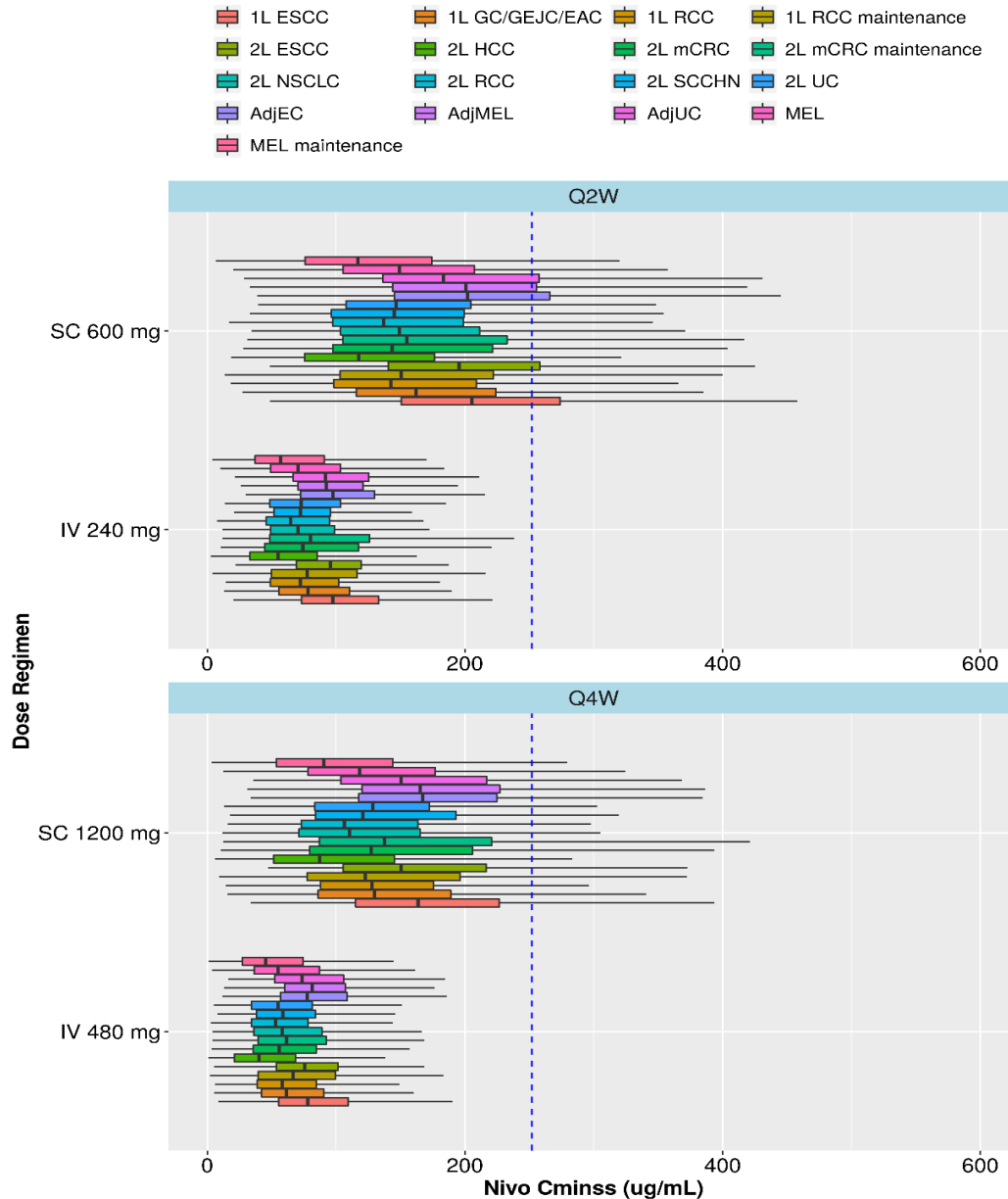
Figure 9: Applicant - Comparison of Simulated Cavgd28 Between IV and SC Administration Across Solid Tumor Indications (Q2W and Q4W)



Note: For illustration purposes the blue dashed line indicates nivolumab simulated median Cavgd28 of 130 ug/mL at 10 mg/kg IV Q2W in subjects with 2L RCC.

The boxplots are drawn by a bold middle line (median), lower (Q1) and upper (Q3) hinges (25th and 75th percentiles), and lower (Q1-1.5*IQR) and upper (Q3+1.5*IQR) whiskers. IQR = Q3-Q1.

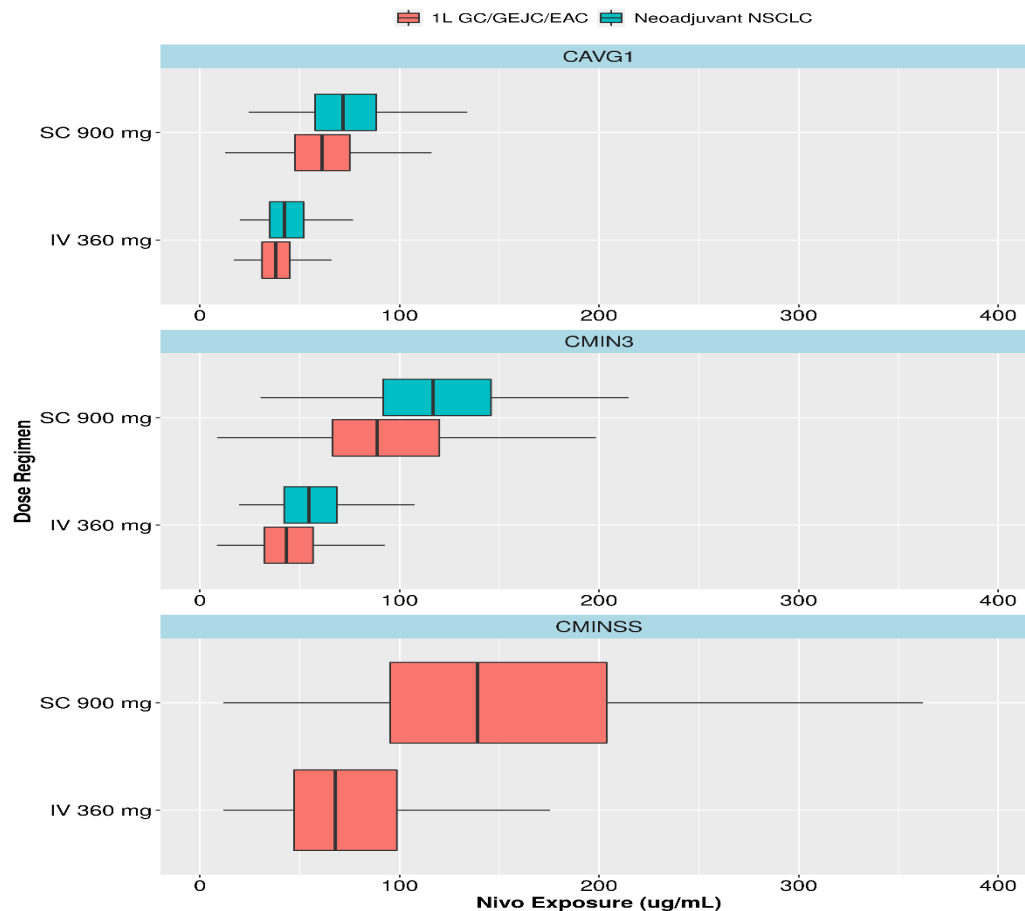
Figure 10: Applicant - Comparison of Simulated Cminss Between IV and SC Administration Across Solid Tumor Indications (Q2W and Q4W)



Note: For illustration purpose, the blue dashed line indicates nivolumab simulated median Cminss of 252 $\mu\text{g/mL}$ at 10 mg/kg IV Q2W in subjects with 2L RCC.

The boxplots are drawn by a bold middle line (median), lower (Q1) and upper (Q3) hinges (25th and 75th percentiles), and lower ($Q1-1.5*IQR$) and upper ($Q3+1.5*IQR$) whiskers. $IQR = Q3-Q1$.

Figure 11: Applicant - Simulated Exposure Comparison Between IV and SC Administration for Neoadjuvant Treatment of NSCLC and 1L GC/GEJC/EAC (Q3W)



Note: The boxplots are drawn by a bold middle line (median), lower (Q1) and upper (Q3) hinges (25th and 75th percentiles), and lower (Q1-1.5*IQR) and upper (Q3+1.5*IQR) whiskers. IQR = Q3-Q1.

The Applicant's Position:

Yes, the clinical pharmacology package for nivolumab SC for the treatment of 2L ccRCC based on CA20967T and for the treatment of multiple other adult solid tumor indications based on simulation-based bridging analyses, provides supportive evidence of effectiveness.

In CA20967T, nivolumab SC 1,200 mg co-formulated with 2,000 Units/mL of rHuPH20 and given Q4W demonstrated PK (co-primary endpoints of Cavgd28 and Cminss) and efficacy (key secondary endpoint of ORR by BICR) noninferiority compared to nivolumab IV 3 mg/kg Q2W (Table 4 and Table 27).

Simulation-based PK analyses were then used to bridge from 1,200 mg SC Q4W to alternative posologies of 600 mg Q2W and 900 mg Q3W in 2L ccRCC patients in

CA20967T. The geometric mean ratios for nivolumab SC 600 mg Q2W relative to nivolumab IV 3 mg/kg Q2W for Cavgd28 and Cminss were 1.64 and 2.20, respectively, and Cavgss was the same (182 µg/mL) for both regimens. The geometric means of eight exposure measures (Cavg1, Cmax1, Cmin1, Cavgd84, Cmind84, Cmaxd84, Cmaxss, and Cminss) for the 900 mg Q3W dosing regimen were in between those for the 1,200 mg Q4W and 600 mg Q2W regimens. Cavgss was the same (182 µg/mL) for all three regimens. The difference in the geometric means of exposure measures for nivolumab SC 900 mg Q3W and 1,200 mg Q4W were within 20% of one another with the exception of Cmax1, which was 24.7% lower for 900 mg Q3W. These differences are not expected to be clinically meaningful.

Subsequently, simulation-based PK analyses were used to bridge from approved nivolumab IV dosing regimens and indications (monotherapy, monotherapy maintenance after nivolumab plus ipilimumab, and in combination with chemotherapy or cabozantinib) to the nivolumab SC dosing regimens. The results from the analyses showed that across all solid tumor types evaluated (ie, melanoma, NSCLC, RCC, SCCHN, UC, mCRC, ESCC, GC, GEJC or EAC, and HCC), nivolumab SC dosing regimens (600 mg Q2W, 900 mg Q3W, and 1,200 mg Q4W) produced consistently higher first dose and steady-state exposures compared to those for the approved nivolumab IV dosing regimens (240 mg Q2W, 360 mg Q3W, and 480 mg Q4W) while also maintaining geometric mean exposures below those for nivolumab IV 10 mg/kg Q2W, a regimen shown to be safe and tolerable in clinical studies⁸ and used regularly to define the exposure safety margins for nivolumab (Figure 9, Figure 10, and Figure 11).⁹ Noninferiority was defined as a GMR of >1.0 and was met as follows:

- 600 mg SC Q2W vs 240 mg IV Q2W: The simulated GMRs (SC vs IV) ranged from 1.55 to 1.68 for Cavgd28 and 1.98 to 2.20 for Cminss.
- 900 mg SC Q3W vs 360 mg IV Q3W: The simulated GMRs (SC vs IV) were 1.66 and 2.11 for Cavg1 and Cmin3, respectively, in subjects with early-stage NSCLC. For subjects with 1L GC/GEJC/EAC, the GMRs (SC vs IV) were 1.56 and 2.06 for Cavg1 and Cminss, respectively.
- 1,200 mg SC Q4W vs 480 mg IV Q4W: The simulated GMRs (SC vs IV) ranged from 1.68 to 1.82 for Cavgd28 and 1.96 to 2.37 for Cminss.

The FDA's Assessment:

FDA agrees with the Applicant's position that the clinical pharmacology program for nivolumab SC for the treatment of multiple adult solid tumor indications based on study CA20967T and simulation-based bridging analyses, provides supportive evidence of effectiveness.

For simulation-based PK analyses to bridge between 1200 mg SC Q4W to alternative posologies of 600 mg Q2W and 900 mg Q3W, refer to section 19.4.0.

Efficacy was the secondary endpoint for study CA20967T including ORR and descriptive assessments of time to event endpoints. Overall, there is limited data based on the limited

number of dose regimens, follow-up time and number of patients in the study to characterize the exposure-efficacy relationship in patients treated with SC nivolumab 1200 mg Q4W. Previous studies conducted with nivolumab IV have shown a flat exposure-response relationship for both efficacy and safety over the dose range of 0.1-20 mg/kg. Refer to section 8.1 for details supporting efficacy.

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

The Applicant's Position:

Yes, nivolumab SC 1,200 mg co-formulated with rHuPH20 Q4W, and/or 900 mg co-formulated with rHuPH20 Q3W, and/or 600 mg co-formulated with rHuPH20 Q2W is appropriate for patients with melanoma, NSCLC, RCC, SCCHN, UC, CRC, HCC, EC, GC, GEJC, and EAC. The proposed nivolumab SC dosing regimens are supported by observed efficacy, safety, and PK data, and simulation-based bridging analyses.

The recommended dosing regimens of nivolumab SC 1,200 mg co-formulated with rHuPH20 Q4W, 900 mg co-formulated with rHuPH20 Q3W, and 600 mg co-formulated with rHuPH20 Q2W were supported by the totality of clinical data and pharmacometric analyses from patients with ccRCC in CA20967T, supportive PK and safety data from patients with advanced solid tumors in CA2098KX, simulation-based PK bridging analyses (posology and other solid tumor indications), and the collective clinical experience with nivolumab administered as monotherapy/monotherapy maintenance and in combination with chemotherapy/cabozantinib for the treatment of cancer.

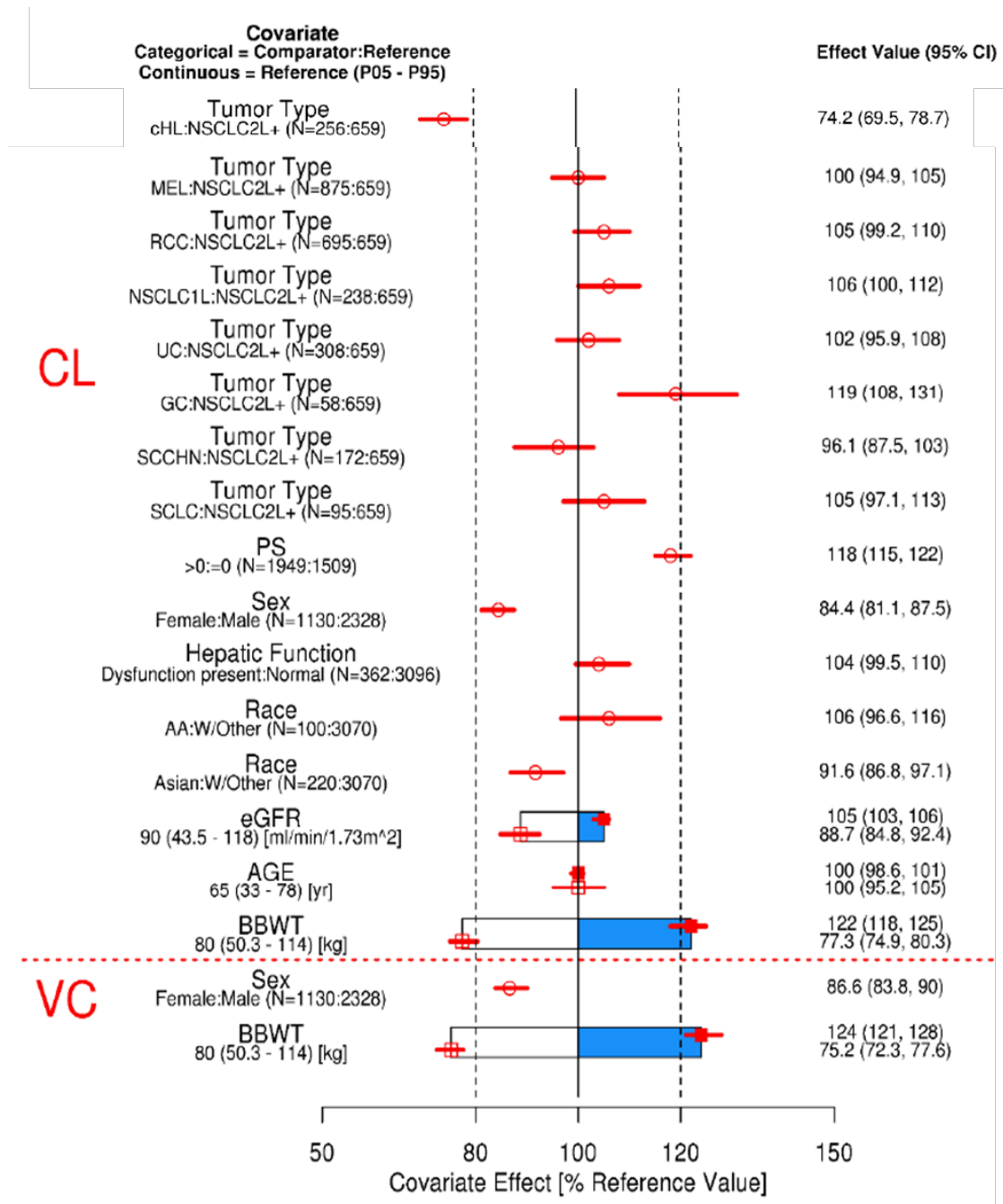
The FDA's Assessment:

FDA agrees with the Applicant's position that the SC nivolumab 1200 mg Q4W, 900 mg Q3W and 600 mg Q2W dosing regimens are appropriate for the general population for the proposed indications in BLA 761381 and BLA 761429 because the active ingredient nivolumab is the same for the SC formulation and the approved IV nivolumab formulation intended for the same populations. The PK of nivolumab was primarily characterized via studies conducted for nivolumab IV administration. The pivotal study CA20967T supporting the SC formulation demonstrated that the exposure of nivolumab SC at 1200 mg Q4W is not less than that of IV at 3 mg/kg Q2W in the ccRcc population and below safety margin established by nivolumab IV. The dose-finding study CA2098KX showed no statistically significant ($p > 0.05$) difference detected in nivolumab bioavailability across different tumor types in patients with different solid tumor types. Refer to Figure 2 in section 6.2.2.1. Nivolumab IV population PK analysis reported ([Figure 12](#)) that the effect of tumor type on nivolumab CL include:

- CL in patients with UC, NSCLC 1L, SCCHN, SCLC, melanoma, and RCC was similar to that in patients with NSCLC 2L+,
- CL in patients with GC was higher (~19 %) compared to NSCLC 2L+ patients,
- CL in patients with cHL was lower (~26 %) than that of NSCLC 2L+ patients.

The observed differences in nivolumab clearance among the tumor types are not considered clinically meaningful based on a flat exposure-response relationship for efficacy and safety of nivolumab.

Figure 12: Covariate Effects on PK Model Parameters (Full PPK Model)



Source: BLA 125554, Nivolumab Population Pharmacokinetic Analysis in Patients with Multiple Tumor Types,

Figure 5.1.1.2-1, page 56

Note 1: Categorical covariate effects (95% CI) are represented by open symbols (horizontal lines).

Note 2: Continuous covariate effects (95% CI) at the 5th/95th percentiles of the covariate are represented by the end of horizontal boxes (horizontal lines). Open/shaded area of boxes represents the range of covariate effects from the median to the 5th/95th percentile of the covariate.

Note 3: Reference patient is white/others male age=65 yr, PS=0, eGFR= 90 ml/min/1.73m² and body weight=80 kg, patient with normal hepatic function with NSCLC2L+. Parameter estimate in reference patient is considered as 100% (vertical solid line) and dashed vertical lines are at 80% and 120% of this value.

Note 4: Open circles estimate (95% CI) categorical; open boxes estimate (95% CI) continuous (P05); closed red boxes estimate (95% CI) continuous (P95); closed blue boxes estimate (continuous values > reference)

6.3.2.3 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.)?

The Applicant's Position:

No, an alternative dosing regimen or management strategy is not required for subpopulations based on intrinsic patient factors. There were no significant intrinsic or extrinsic factors (covariates) identified that required a nivolumab SC dose adjustment as discussed in the Appendix.

The FDA's Assessment:

FDA agrees with the Applicant's position that no dose adjustment is recommended for nivolumab SC based on the intrinsic factors including body weight, sex, age, race, baseline LDH, PD-L1 expression, solid tumor type, tumor size, renal impairment, or hepatic impairment. The population PK analysis of CA20967T showed that the effect of eGFR, PS and sex on nivolumab clearance (CL) and baseline body weight on central volume of distribution (VC) were statistically significant (95% CI did not include null value); however, the magnitude of the effect was <20% and not expected to be clinically meaningful and sex effects on exposure metrics were also not considered clinically important based on a flat exposure-response relationship for efficacy and safety of nivolumab. Exposure of nivolumab SC at 1200 mg Q4W has been demonstrated to be not less than that of the nivolumab IV 3 mg/kg Q2W and below the safety margin established by nivolumab IV.

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

The Applicant's Position:

No, as nivolumab SC is not administered orally, there is no potential for a food-drug interaction. In addition, based on the available data for nivolumab IV, the potential for a drug-drug interaction when nivolumab SC is administered as monotherapy, monotherapy maintenance, or in combination with chemotherapy or cabozantinib is low given that nivolumab likely degrades through catabolic pathways.

The FDA's Assessment:

FDA agrees with the Applicant's position that the potential of nivolumab drug-drug interactions with chemotherapy or cabozantinib in the approved combination therapies is low.

X

X

Primary Reviewer

Team Leader

7 Sources of Clinical Data

7.1. Table of Clinical Studies

Data:

Table 17: Applicant - Listing of Clinical Studies by the Sponsor Relevant to this BLA

Study	Design <i>Primary Objective</i>	Population	Dose/Schedule	No Subjects Planned/ Treated (N)	LPLV
<i>Pivotal Phase 3 Study to Support PK and Efficacy Non-inferiority, and Safety</i>					
CA20967T IND No.: 150,904 NCT0481 0078 Countries: 17 Number of sites: 73	Phase 3, open-label, randomized, noninferiority study of SC formulation of nivolumab versus IV nivolumab <i>Demonstrate PK noninferiority of nivolumab SC vs nivolumab IV administration</i>	Subjects with advanced or metastatic ccRCC who have evidence of progression after having received no more than 2 prior systemic treatment regimens	<u>Arm A:</u> nivo SC 1,200 mg coformulated with rHuPH20 Q4W ^a <u>Arm B:</u> IV nivo 3 mg/kg Q2W	454 / 492	24- Jul- 2023
<i>Supportive Phase 1/2 Study to Support Clinical Pharmacology, Safety and Efficacy</i>					
CA2098KX^b IND No.: 138,302 NCT03656718 Countries: 11 Number of sites: 21	Phase 1/2 open-label, multicenter, randomized study of nivolumab SC administered with and without rHuPH20 subcutaneously <u>Parts A-D:</u> Describe the PK of nivolumab administered subcutaneously, with or without rHuPH20 <u>Part E:</u> Evaluate the PK of nivolumab SC 600 mg Q2W co-formulated with rHuPH20	<u>Parts A-D:</u> ^c metastatic NSCLC; advanced or metastatic RCC; unresectable or metastatic melanoma; HCC; or metastatic CRC (MSI-H or dMMR). <u>Part E:</u> above tumors plus subjects with mUC	<u>Parts A and B:</u> <u>1. Single nivo SC dose (ie, 1 cycle):</u> Part A (Group 1): nivo SC 720 mg + rHuPH20 Part B (Group 2): nivo SC 720 mg Part B (Group 3): nivo SC 960 mg + rHuPH20 Part B (Group 4): nivo SC 960 mg 2. Four weeks after above mentioned single nivo SC dosing, subjects in Parts A and B received nivo IV 480 mg Q4W. 3. Four weeks after last nivo IV dose subjects in Parts A and B switch to Part C. <u>4. Part C^d:</u> nivo SC 1,200 mg + rHuPH20 Q4W. <u>Part D</u> (Group 5): ^d nivo SC 1,200 mg + rHuPH20 Q4W. <u>Part E</u> (Group 6): nivo SC 600 mg coformulated ^a with rHuPH20 Q2W.	137 / 139	07- Sep- 2022

^a Nivolumab and rHuPH20 solutions are pre-mixed in 1 vial when they are coformulated.

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- b In CA2098KX, all subjects that met inclusion/exclusion criteria were assigned a randomization number. Only subjects in Part B Groups 2 and 4 were randomized between the two treatment groups.
- c In CA2098KX, for Part B, other solid tumor types were permitted where PK was well characterized and discussed with the Sponsor.
- d Any ongoing subject on nivolumab SC + rHuPH20 treatment was permitted to switch over to nivolumab coformulated with rHuPH20 drug product. Nivolumab and rHuPH20 solutions are pre-mixed in 1 vial when they are coformulated.

The Applicant's Position:

Results from CA20967T¹⁰ demonstrate PK (Cavgd28 and Cminss) and efficacy (ORR) non-inferiority of nivolumab SC to nivolumab IV administration and provide evidence for a consistent benefit/risk profile of nivolumab SC to nivolumab IV with supportive PK, safety, and efficacy data from CA2098KX.

The FDA's Assessment:

FDA agrees with the Applicant's description of Study CA20967T and Study CA2098KX. The review of PK and efficacy data to support the approval of nivolumab SC was primarily based on the evaluation of data from Study CA20967T. Data from Study CA2098KX demonstrated no statistically significant difference detected in nivolumab bioavailability across different tumor types (metastatic NSCLC, advanced or metastatic RCC, unresectable or metastatic melanoma, HCC, metastatic CRC [MSI-H or dMMR], or metastatic UC) after nivolumab SC administration. In addition, dose selection of nivolumab SC of 1200 mg Q4W was also supported by exposure data from Study CA209025 (CheckMate 025).

Assessment of the benefit/risk profile of nivolumab SC is provided in Section 8.4.

8 Statistical and Clinical Evaluation

8.1. Review of Relevant Individual Trials Used to Support Efficacy

8.1.1. Pivotal Phase 3 Study CA20967T

Trial Design

The Applicant's Description:

Figure 13: Applicant - CA20967T Study Design Schematic

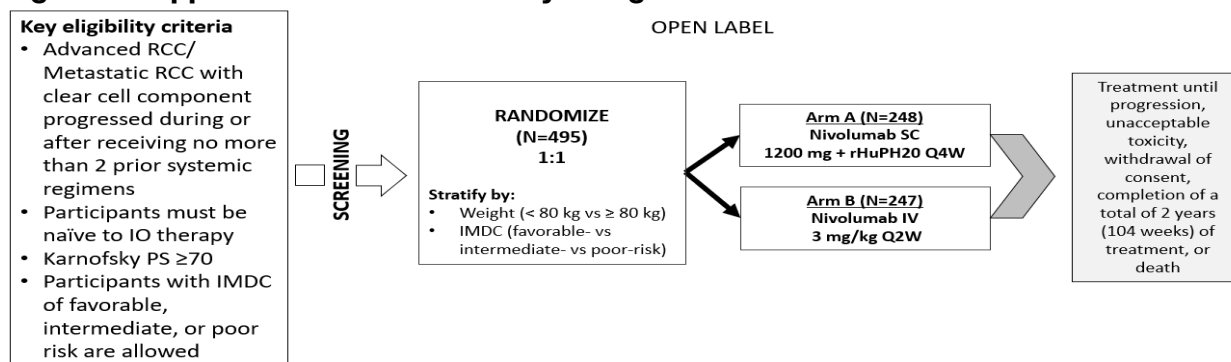


Table 18: Applicant - CA20967T Study Design Details

Design Aspect	Description
Phase 3	Multicenter, randomized, open-label study evaluating PK and efficacy noninferiority of nivolumab SC vs nivolumab IV and safety and tolerability of nivolumab SC.
Study enrollment	Eligible subjects were randomized 1:1 using an IRT system. Subjects were stratified by weight (< 80 kg vs ≥ 80 kg) and IMDC (favorable vs intermediate vs poor-risk disease) to either the nivolumab SC arm (Arm A) or nivolumab IV arm (Arm B).
Dose selection	Refer to Section 6.2.2.
Dose modification/ discontinuation	Delays of doses of nivolumab SC or nivolumab IV were permitted for any AE, laboratory abnormality, or intercurrent illness which, in the judgment of the investigator, warranted delaying the dose of study medication. Treatment discontinuation was permitted at the participant's request to stop study treatment, upon any clinical AE, laboratory abnormality or intercurrent illness which, in the opinion of the investigator, indicated that continued participation in the study was not in the best interest of the participant, termination of the study by the Sponsor, or loss of ability of a subject to freely provide consent through imprisonment or involuntary incarceration for treatment of either a psychiatric or physical illness.
Treatment compliance	Treatment compliance was periodically monitored by drug accountability, medical record, and eCRF.
Subject completion, discontinuation, or withdrawal	Treatment continued until disease progression as assessed by the investigator, unacceptable toxicity, withdrawal of consent, completion of 2 years (104 weeks) of treatment, death, study termination by the Sponsor, of the end of the study, whichever occurred first.
Concurrent medications	All medications (prescriptions and OTC medications) continued at the start of the study or started during the study and different from the study treatment were documented in the concomitant therapy section of the CRF.
Study Committees	The following committees ensured the integrity of the study: DMC performed a periodic review of safety on a specified timeframe.

Design Aspect	Description
	• Radiographic Review Committee (and imaging plan) received images which were assessed by BICR for the determination of the secondary endpoints (ORR, DCR, TTR, DOR, and PFS). • Study Steering Committee provided scientific advice on the development of this interventional study and provided guidance on protocol conduct or design established to provide overall supervision of the trial conduct.

The FDA's Assessment:

FDA agrees with the Applicant's description of the study design for Study CA20967T.

Eligibility Criteria

The Applicant's Description:

Adult (≥ 18 years) male and female subjects with advanced or metastatic ccRCC who had received no more than 2 prior systemic regimens, were naïve to checkpoint inhibitor therapy, and had evidence of intolerance or progression on or after the last treatment regimen received and within 6 months prior to randomization.

Key inclusion criteria included subjects with histological confirmation of RCC with a clear cell component, including subjects who may also have sarcomatoid features, with advanced (not amenable to curative surgery or radiation therapy) or metastatic disease (Stage IV) [AJCC, 8th edition]. Measurable disease, as defined by RECIST v1.1 criteria within 28 days prior to randomization in the primary study was required. A Karnofsky performance status ≥ 70 was required for all subjects at screening.

The FDA's Assessment:

FDA generally agrees with the Applicant's description of Study CA20967T. It is notable, however, that eligible patients were naïve to checkpoint inhibitor (CPI) therapy, which is not consistent with current US practice, which generally includes combination therapy with a Tyrosine kinase inhibitor (TKI) and anti-PD-1 antibody or single agent TKI. However, enrollment of CPI naïve patients with advanced or metastatic ccRCC who have been previously treated with no more than two prior systemic therapies was considered acceptable for the purposes of demonstrating PK and efficacy noninferiority between the subcutaneous formulation of nivolumab to the intravenous formulation of nivolumab and because no new efficacy claims were proposed based on the results of Study CA20967T (and a checkpoint inhibitor would be appropriate in patients not previously exposed to a CPI).

Study Endpoints

The Applicant's Description:

Table 19: Applicant - Key Endpoints for Nivolumab SC (CA20967T)

Primary Endpoints	Description
Cavgd28 and Cminss	The co-primary endpoints were derived from all PK evaluable subjects using popPK analysis. Cavgd28 was defined as the time-averaged serum nivolumab

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	concentration over the first 28 days of treatment. Cminss was defined as the trough serum nivolumab concentration at steady state. Noninferiority was to be met for both PK co-primary endpoints before noninferiority for the powered key secondary endpoint of ORR by BICR could be assessed.
Secondary Endpoints	Description
ORR by BICR	ORR was defined as the number of subjects with a confirmed best response of CR or PR, both by BICR, divided by the number of randomized subjects. BOR was defined as the best response designation, as determined by BICR, recorded between the date of randomization and the date of radiographically documented progression per RECIST v1.1 or the date of subsequent anticancer therapy (including on-treatment palliative therapy), whichever occurred first. ORR by BICR with a minimum of 6 months follow-up was the powered key secondary endpoint.
Cmind28, Cmax1, Cmaxss, Cavgss, and Ctrough at Week 17 (observed)	The following were derived from PK-evaluable subjects using popPK analysis. • Cmind28: trough nivolumab serum concentration at Day 28 • Cmax1: peak serum nivolumab concentration after the first dose • Cmaxss: peak serum nivolumab concentration at steady state • Cavgss: time-averaged nivolumab serum concentration at steady state Ctrough at Week 17 was obtained from PK-evaluable subjects using observed data.
Incidence of AEs, SAEs, AEs leading to discontinuation, deaths, and laboratory abnormalities	AEs were coded using MedDRA (most recent version of dictionary at the time of the DBL was used. AE results were graded for severity using the NCI CTCAE (version 5). On study lab parameters including hematology, chemistry, liver function, and renal function were summarized using worst grade NCI CTCAE per subject.
DCR by BICR, DOR by BICR, TTR by BICR, PFS by BICR, OS	• DCR was defined as the number of subjects with a BOR of CR, PR, or SD, per RECIST v1.1 as per BICR, divided by the number of randomized subjects. • DOR by BICR was defined as the time between the date of first CR to the date of the first documented tumor progression as determined by investigator (per RECIST v1.1), or death due to any cause, whichever occurs first. • TTR was defined as the time from randomization to the date of the first confirmed CR or PR as determined by BICR. DOR and TTR were evaluated for responders (confirmed CR or PR) only. • PFS was defined as the time from randomization to the date of the first documented tumor progression as determined by BICR (per RECIST v1.1) or death due to any cause. • OS was defined as the time from randomization to the date of death. A participant who had not died was censored at last known date alive.
Incidence of anaphylactic, hypersensitivity, and systemic infusion reactions/systemic injection reactions. Incidence of local injection- or infusion-site reactions	Study specific OESI, include: • anaphylactic, hypersensitivity, and systemic infusion or injection reactions, as AEs within the Broad SMQ of Anaphylactic Reaction • administration-site reactions (ie, infusion- or injection-site erythema/swelling/pruritis/pain)
Incidence of anti-nivolumab antibodies	Number (%) of subjects for the following parameters based on Evaluable Subjects: • Baseline ADA-positive

and neutralizing
antibodies

- ADA-positive
 - Persistent positive
 - Not PP-Last Sample Positive
 - Other positive
 - Neutralizing Positive (if applicable)
- ADA-negative

The FDA's Assessment:

FDA agrees with the Applicant's description of the study endpoints for Study CA20967T.

Statistical Analysis Plan and Amendments

The Applicant's Description:

The SAP was submitted to the FDA and finalized prior to the primary DBL of CA20967T, at which time the Applicant was unblinded to treatment randomization assignment.

Analysis Populations and Estimands

The PK population was defined as all treated participants with available PK serum time-concentration data. The PK evaluable population was a subset of PK population who had adequate dosing and nivolumab serum concentration time data for estimation of at least 1 PK endpoint. The co-primary endpoints (Cavgd28 and Cminss) were derived for all PK-evaluable participants using popPK analysis.

Table 20: Applicant - Estimands for PK Co-Primary Endpoints

Estimand Attribute	Definition	
Intercurrent Events	Event	Strategy
	Start of subsequent surgery or subsequent radiotherapy, partial infusion, concomitant medication	Treatment policy strategy: the occurrence of ICE is considered irrelevant, and information after ICE will be used.
	Start of subsequent systemic therapy	Hypothetical strategy: the clinical question of interest is about the PK parameter values had the ICE not occurred. However, due to the occurrence of the ICE, data collected afterwards may be confounded by the ICE, so PK samples collected in follow-up visits after ICE will be excluded from the popPK model. As long as the participant has at least one PK concentration available at the earlier timepoints, PK parameters might be derived from the popPK model, assuming the PK profile of the participant after the ICE is best represented by the other participants who did not have such ICE.
	Treatment discontinuation, death	Hypothetical strategy: the clinical question of interest is about the PK parameter values had the ICEs not occurred. At times, due to the occurrence of the ICEs, PK samples won't be available afterwards except for follow-up visits, but as long as a participant has at least one PK concentration available at the earlier timepoints, PK parameters might be derived from the popPK model, assuming the PK profile of the participant after the ICEs is best represented by the

		other participants who did not have such ICEs. For example, PK parameter values after death might be derived using the popPK model.
Population-level Summary	Geometric mean ratio of test arm vs reference arm and 90% CI	

The all randomized population was defined as all participants who were randomized to any treatment group in the study. Efficacy analyses were based on the all randomized population.

Table 21: Applicant - Endpoints for ORR Key Secondary Endpoint

Estimand Attribute	Definition	
Intercurrent Events	Event	Strategy
	Start of subsequent therapy (including on-treatment palliative therapy)	While-on-treatment strategy: data are only included in the analysis and treatment effect prior to occurrence of ICE is of interest. Any data collected after the ICE would not be used in the analysis.
	Treatment discontinuation, randomized but not treated	Treatment policy: responses after ICE will be considered.
Population-level Summary	Relative risk of ORR of test arm vs reference arm and 95% CI	

Multiplicity Adjustments

Efficacy non-inferiority determined by assessment of ORR by BICR, with a minimum of 6 months of follow-up, of nivolumab SC compared with nivolumab IV was the key secondary endpoint tested in a hierarchical fashion to preserve overall experiment-wise Type I error rate. Non-inferiority must be met for both PK co-primary endpoints, before the key secondary endpoint of ORR by BICR could be assessed.

Non-inferiority Margins and Analyses for Non-inferiority

For PK co-primary endpoints, non-inferiority was defined as 0.8 or greater for the lower limit of 2-sided 90% CI of geometric mean ratio of SC to IV Cavgd28 and Cminss.¹¹ The value of 0.8 was selected to define PK noninferiority in CA20967T because it is the lower bound of the 2-sided 90% CI criterion (0.8 to 1.25) used to compare geometric mean ratios of PK exposure measures between two products in bioequivalence and biocomparability studies. The FDA had previously agreed to non-inferiority margin of 0.8.

Cavgd28 and Cminss derived from the popPK model from all PK evaluable participants were used for non-inferiority assessment. A linear fixed effect model with treatment and stratification factors as fixed effects were fitted to the log-transformed Cavgd28 and Cminss for use in estimation of effects and construction of CIs. To assess non-inferiority of nivolumab SC to nivolumab IV, point estimate and the 2-sided 90% CIs for treatment differences on the log scale were exponentiated to obtain estimates for ratio of geometric means and respective 90% CIs for Cavgd28 and Cminss on the original scale. Non-inferiority of nivolumab SC to nivolumab IV were concluded if the lower limit of the 2-sided

90% CIs for the ratio of geometric means for both nivolumab Cavgd28 and Cminss was not lower than 0.8.

For the key secondary endpoint of ORR by BICR, the assumed non-inferiority margin was defined using a 60% retention of ORR (nivolumab SC vs nivolumab IV). This non-inferiority margin was discussed with the FDA.

The non-inferiority hypothesis for ORR could be stated as:

$H_0: ORR_{SC} / ORR_{IV} < 60\%$

$H_1: ORR_{SC} / ORR_{IV} \geq 60\%$ (non-inferiority)

To declare non-inferiority, the lower bound of the 95% CI of the stratified Mantel-Haenszel estimate of the relative risk of ORR (nivolumab SC vs nivolumab IV) has to be ≥ 0.60 . The CI was based on the Robins, Breslow, and Greenland¹² variance estimate for $\log(\hat{\theta}_{MH})$.

Subgroup Analyses

The key secondary endpoint of ORR by BICR was assessed for the following pre-specified subgroups:

- Age categorization (< 65, ≥ 65 and < 75, ≥ 75)
- Sex at birth (Male vs. Female)
- Race (White, Black or African American, Asian, American Indian or Alaska Native, Native Hawaiian or Other Pacific Islander, Other)
- Ethnicity (Hispanic/Latino and Not Hispanic/Latino)
- Region (US and EU, Mexico and South America, Rest of the World)
- Weight categorization (< 80 kg, ≥ 80 kg)
- Karnofsky performance status (70, 80, 90, 100)
- IMDC risk group (favorable [score 0], intermediate [score 1-2], poor [score 3-6])
- Prior nephrectomy (Yes vs. No)
- Prior lines of therapies (1 vs 2)

SAP Amendment

Table 22: Applicant - SAP Amendment Summary

Version Number	Description of Key Changes
1.0 / 15-Apr-2021	Original issue
2.0 / 27-Jun-2023	• For PK secondary endpoints, removed Tmax1 and added Ctrough at week 17 (observed). • Added the tables for estimands for PK co-primary endpoints and ORR key secondary endpoint. • Replaced stratification factors per IRT with stratification factors per CRF in main analyses, with the rationale.

The FDA's Assessment:

FDA adds that the NI margin for the key secondary endpoint of ORR assessed by BICR was not based on the comparative result from a placebo controlled trial or meta-analysis. Therefore, the preservation of treatment effect is not well defined for this NI comparison, leading to difficult in interpreting the results of the non-inferiority test.

Protocol Amendments

The Applicant's Description:

Table 23: Applicant - Summary of the 2 Protocol Revisions for CA20967T

Document (Amendment) Date	Summary of Key Changes	Subjects Randomized Under Protocol Version
Original Protocol 21-Oct-2020	NA	0
Protocol Amendment 01 17-Mar-2021	- Added co-primary PK endpoints of Cavgd28 and Cminss. Added Cmind28 as a secondary endpoint. - Changed mandatory tumor tissue submission at screening to optional. - Added additional PK collection at Cycle 1 Day 4. - Clarified pregnancy testing timing and removed reporting and surveillance of female partners of male participants. - Added details regarding COVID-19 vaccine permissibility. - Specified blood creatinine assessment instead of serum creatinine.	0
Protocol Amendment 02 18-May-2023	- Added new secondary PK endpoint of nivolumab trough concentration at Week 17. - Clarified the criteria to discontinue regular (every 24 weeks) tumor assessments in participants at ≥ 2 years after randomization. Appendix 9 updated to consolidate country-specific differences in order to comply with EU-CTR requirements. - Updated end of study definition.	495

The FDA's Assessment:

FDA agrees with the Applicant's description of the protocol amendments for Study CA20967T. Amendments were submitted to FDA for review. The co-primary pharmacokinetic endpoints of time-averaged serum concentration over the first 28 days (Cavgd28) and trough serum concentration at steady-state (Cminss) were added with protocol amendment 1, which occurred prior to randomization of any patients. Protocol amendment 2 occurred after 495 patients had been randomized and this included a new secondary PK endpoint of nivolumab trough concentration at week 17. Given that all substantial changes to primary or key secondary endpoints occurred prior to randomization of patients, these amendments would not be expected to impact the integrity of the study.

8.1.2. Study Results from CA20967T

Compliance with Good Clinical Practices

The Applicant's Position:

The laws and regulatory requirements of all countries that had sites participating in this study were adhered to. This study was conducted in accordance with Good Clinical Practice, as defined by the International Council for Harmonisation and in accordance with the ethical principles underlying European Union Directive 2001/20/EC and the US Code of

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Federal Regulations, Title 21, Part 50 (21 CFR 50). The protocol, amendments, administrative letters, and subject informed consent form received IRB/IEC approval prior to implementation. The quality of data collected and analyzed was monitored according to BMS SOPs. No significant GCP deviations impacting the study or serious breaches were reported.

The FDA's Assessment:

FDA agrees with the Applicant's position. There is no evidence that compliance with good clinical practices was violated during the conduct of Study CA20967T. There were no major issues identified during the conduct of this study that impacted the data quality of data integrity.

Financial Disclosure

The Applicant's Position:

Financial interests or arrangements with clinical investigators disclosed (Appendix 19.1).

The FDA's Assessment:

The Applicant disclosed that one study investigator ((b) (6)) became an employee of BMS while the study was ongoing. The Applicant states in the Financial Disclosure for Study CA20967T that this sub-investigator became an employee of BMS on (b) (6), and stopped work at (b) (6).

This site (b) (4) had eight investigators who enrolled a total of (b) (4) patients, of whom (b) (4) were randomized (b) (4) on the SC arm; (b) (4) on the IV arm). Since the co-primary endpoints for this study were pharmacokinetic it is unlikely that bias was introduced that affected the interpretation of the primary endpoint. FDA reviewed the safety data for this site (b) (4) specifically and did not identify any notable differences that would be expected to impact FDA's overall impression of the safety data for Study CA20967T. FDA has concluded that it is unlikely that financial bias had an impact on the efficacy or safety findings from Study CA20967T.

There were no other investigators with disclosable financial interests.

Patient Disposition

Data:

BLA Multi-disciplinary Review and Evaluation {BLA 761381 and BLA 761429}
OPDIVO (nivolumab and hyaluronidase - nvhy) injection, for subcutaneous use

Table 24: Applicant - Subject Disposition - All Enrolled, Randomized, and Treated Subjects in CA20967T

All Enrolled Status (%)	Total N = 572		
ENROLLED	572	(100.0)	
RANDOMIZED	495	(86.5)	
NOT RANDOMIZED	77	(13.5)	
REASON NOT RANDOMIZED			
SUBJECT WITHDREW CONSENT	2	(0.3)	
DEATH	1	(0.2)	
SUBJECT NO LONGER MEETS STUDY CRITERIA	74	(12.9)	
NOT RANDOMIZED DUE TO COVID-19	0		
All Randomized Status (%)	Nivolumab SC N = 248	Nivolumab IV N = 247	Total N = 495
TREATED	247	(99.2)	492
NOT TREATED	1	(0.4)	3
REASON FOR NOT TREATED			
SUBJECT WITHDREW CONSENT	1	(0.4)	3
NOT TREATED DUE TO COVID-19	0	0	0
All Treated Status (%)	Nivolumab SC N = 247	Nivolumab IV N = 245	Total N = 492
ONGOING TREATMENT	87	(35.2)	173
COMPLETED TREATMENT	0	1	(0.2)
DISCONTINUED TREATMENT	160	(64.8)	318
REASON FOR DISCONTINUATION OF TREATMENT			
DEATH	1	(0.4)	1
POOR/NON-COMPLIANCE	0	1	(0.2)
SUBJECT NO LONGER MEETS STUDY CRITERIA	0	1	(0.2)
DISEASE PROGRESSION	109	(44.1)	219
STUDY DRUG TOXICITY	14	(5.7)	29
ADVERSE EVENT UNRELATED TO STUDY DRUG	20	(8.1)	34
OTHER	1	(0.4)	2
SUBJECT WITHDREW CONSENT	9	(3.6)	16
LOST TO FOLLOW-UP	0	1	(0.2)
ADMINISTRATIVE REASONS BY SPONSOR (CLOSURE OF RUSSIAN SITES)	6	(2.4)	14
DISCONTINUED TREATMENT DUE TO COVID-19	1	(0.4)	1
REASON FOR DISCONTINUATION OF TREATMENT DUE TO COVID-19			
ADVERSE EVENT UNRELATED TO STUDY DRUG	1	(0.4)	1
ONGOING STUDY	152	(61.5)	313
DISCONTINUED STUDY	95	(38.5)	179

Table 24: Applicant - Subject Disposition - All Enrolled, Randomized, and Treated Subjects in CA20967T

All Treated Status (%)	SC Nivolumab N = 247	IV Nivolumab N = 245	Total N = 492
REASON FOR DISCONTINUATION OF STUDY			
DEATH	72 (29.1)	59 (24.1)	131 (26.6)
LOST TO FOLLOW-UP	5 (2.0)	1 (0.4)	6 (1.2)
SUBJECT WITHDREW CONSENT	11 (4.5)	11 (4.5)	22 (4.5)
OTHER	0	4 (1.6)	4 (0.8)
ADMINISTRATIVE REASONS BY SPONSOR (CLOSURE OF RUSSIAN SITES)	7 (2.8)	9 (3.7)	16 (3.3)
DISCONTINUED STUDY DUE TO COVID-19	1 (0.4)	0	1 (0.2)
REASON FOR DISCONTINUATION OF STUDY DUE TO COVID-19			
DEATH	1 (0.4)	0	1 (0.2)

Dataset: ADSL

The Applicant's Position:

Subjects enrolled in CA20967T were largely representative of an mRCC US population. For CA20967T, the applicability of the global data to the US population and practice of medicine was evaluated in accordance with *ICH Topic E 5 (R1) Ethnic Factors in the Acceptability of Foreign Clinical Data, September 1998*. Diagnosis methods for RCC are similar between the US and the global sites. Moreover, there are no known differences in the etiology of RCC across the different regions or ethnicities. Importantly, race was not previously identified as a factor influencing nivolumab's clearance in a comprehensive pooled population pharmacokinetic analysis. For these reasons, the data from CA20967T is applicable to the US.

In CA20967T, 572 subjects were enrolled, 495 subjects were randomized, and 492 subjects were treated. The rates of subjects who discontinued treatment were comparable between the treatment arms, the most common reason for treatment discontinuation was disease progression, and the most common reason for study discontinuation was death Table 24.

The FDA's Assessment:

FDA agrees that patient disposition in this study was balanced across the treatment arms. There does not appear to be an imbalance in patient discontinuation from study treatment or withdrawal from the study. FDA notes, that there is underrepresentation of patients from racial and ethnic minority groups, specifically patients who identify as Black or African American (n=2, 0.4%) and Asian (n=4, 0.8%). While most U.S. patients with mRCC are Caucasian (~71%), the U.S. mRCC population includes patients who identify as African American (~7%), and Asian/Pacific Islanders (~6%) (Garcia et al, 2023).

FDA notes that although all patients enrolled to the study must have been previously treated and have received no more than two prior therapies, prior checkpoint inhibitor was not allowed. The preferred/recommended first-line therapy for patients with advanced or metastatic ccRCC includes a TKI in combination with an anti-PD(L)-1 inhibitor or combination CPI therapy, with other treatment options including single agent TKI. For patients who have not received an anti-PD(L)-1 inhibitor in the first-line setting, subsequent therapy includes an anti-PD(L)-1 therapy, including single agent nivolumab. Although patients in this study did not receive CPI in the first-line setting (as generally preferred in the US), FDA considers this patient population to be appropriate for a assessment of nivolumab SC and nivolumab IV (and CPI would be appropriate in patients who did not receive earlier checkpoint inhibition).

Protocol Violations/Deviations

Data:

Table 25: Applicant - Summary of Relevant Protocol Deviations in CA20967T

	Number of Subjects (%)		
	SC Nivolumab N = 248	IV Nivolumab N = 247	Total N = 495
SUBJECTS WITH AT LEAST ONE DEVIATION	1 (0.4)	1 (0.4)	2 (0.4)
AT ENTRANCE			
SUBJECT WITH BASELINE KPS < 70	0	0	0
SUBJECT WITHOUT SITES OF MEASURABLE DISEASES AT BASELINE	1 (0.4)	1 (0.4)	2 (0.4)
ON-TREATMENT DEVIATIONS			
SUBJECT WHO RECEIVED ANTI-CANCER THERAPY	0	0	0
SUBJECT TREATED DIFFERENTLY THAN AS RANDOMIZED	0	0	0

Datasets: ADSL, ADPD

The Applicant's Position:

IPDs are a subset of protocol deviations that may significantly impact the completeness, accuracy, and/or reliability of the study data or that may significantly affect a subject's rights, safety, or well-being. Monthly monitoring of protocol deviations was conducted and where appropriate additional follow-up and training was conducted with sites and site-facing roles. The Protocol Deviations Assessment Plan was utilized to assess the protocol deviations. The most noted deviation was out of window trial procedure. A review of the deviations determined there was no detriment to subject safety and no significant impact on the interpretability of study results.

RPDs are a subset of IPDs that could affect the interpretability of key study results; they are programmable deviations from the clinical database and are protocol specific. RPDs were reported in 1 subject in each arm and did not impact study data (Table 25).

The FDA's Assessment:

FDA reviewed the important protocol deviations and relevant protocol deviations reported in Appendices 2.2.1 and 2.2.2, respectively, of the Clinical Study Report for Study CA20967T. There was a total of two reported relevant protocol deviations in Study CA20967T, both relevant protocol deviations that included one patient on each treatment arm without sites of measurable disease at baseline. The protocol deviations reported for Study CA20967T do not raise any concerns regarding the overall conduct or quality of the study, study safety, or the clinical interpretation of data with respect to study endpoints.

Table of Demographic Characteristics

Data:

Table 26: Applicant - Key Demographic and Baseline Characteristics: All Randomized Subjects in CA20967T

	SC Nivolumab N = 248	IV Nivolumab N = 247	Total N = 495
AGE (YEARS)			
N	248	247	495
MEAN	63.6	64.1	63.8
MEDIAN	64.0	66.0	65.0

Table 26: Applicant - Key Demographic and Baseline Characteristics: All Randomized Subjects in CA20967T

	SC Nivolumab N = 248	IV Nivolumab N = 247	Total N = 495
MIN , MAX SD	35 , 93 10.5	20 , 87 10.2	20 , 93 10.3
SEX (%)			
MALE	164 (66.1)	171 (69.2)	335 (67.7)
FEMALE	84 (33.9)	76 (30.8)	160 (32.3)
RACE (%)			
WHITE	205 (82.7)	217 (87.9)	422 (85.3)
BLACK OR AFRICAN AMERICAN	0	2 (0.8)	2 (0.4)
ASIAN	3 (1.2)	1 (0.4)	4 (0.8)
AMERICAN INDIAN OR ALASKA NATIVE	2 (0.8)	3 (1.2)	5 (1.0)
OTHER	38 (15.3)	24 (9.7)	62 (12.5)
ETHNICITY (%)			
HISPANIC OR LATINO	93 (37.5)	84 (34.0)	177 (35.8)
NOT HISPANIC OR LATINO	80 (32.3)	83 (33.6)	163 (32.9)
NOT REPORTED	75 (30.2)	80 (32.4)	155 (31.3)
COUNTRY BY GEOGRAPHIC REGION (%)			
US AND EU	67 (27.0)	76 (30.8)	143 (28.9)
UNITED STATES OF AMERICA	2 (0.8)	6 (2.4)	8 (1.6)
MEXICO AND SOUTH AMERICA	159 (64.1)	148 (59.9)	307 (62.0)
REST OF THE WORLD	22 (8.9)	23 (9.3)	45 (9.1)
WEIGHT (KG)			
N	248	247	495
MEAN	77.84	77.77	77.80
MEDIAN	76.80	76.70	76.80
MIN, MAX	35.0, 152.6	47.5, 157.4	35.0, 157.4
SD	18.21	16.40	17.32
PRIOR NEPHRECTOMY (%)			
YES	203 (81.9)	205 (83.0)	408 (82.4)
NO	45 (18.1)	42 (17.0)	87 (17.6)
IMDC RISK GROUP (CRF) (%)			
FAVORABLE [SCORE 0]	48 (19.4)	57 (23.1)	105 (21.2)
INTERMEDIATE [SCORE 1-2]	158 (63.7)	147 (59.5)	305 (61.6)
POOR [SCORE 3-6]	42 (16.9)	43 (17.4)	85 (17.2)

Datasets: ADSL, ADDX

The Applicant's Position:

In all randomized subjects, demographics (age, gender, race, ethnicity) were generally balanced between treatment arms (Table 26). The median age of all randomized subjects was 65.0 years. Most subjects were male (67.7%) and white (85.3%). 28.9% of subjects were from US and EU, 62.0% from Mexico and South America, and 9.1% from the rest of the world.

The FDA's Assessment:

FDA agrees with the Applicant's assessment that demographic and baseline characteristics were generally well balanced across treatment arms. The median age of patients randomized to the nivolumab SC arm was 64 years, which is slightly lower than the median age at diagnosis for RCC (65 years) reported in the registry. This is also notable since study patients had to have at least one prior line of therapy. The majority of patients on the nivolumab SC (66.1%) and nivolumab IV (69.2%) arms were men. There was an

underrepresentation of patients that identify as either Asian (0.8%) or Black/African-American (0.4%), compared to the expected proportion of these patients groups reported in registry data (African American (~7%), and Asian/Pacific Islanders (~6%)) (Garcia et al, 2023).

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

Data: See Table 26.

The Applicant's Position:

Baseline disease characteristics were mostly comparable across arms. Stratification factors (IMDC risk classification and baseline weight) based on IRT were balanced between arms. The vast majority of the subjects had either clear cell type or clear cell component with sarcomatoid features at study entry. Subjects on the nivolumab SC arm had a slightly higher incidence of poor prognostic features compared with the nivolumab IV arm, with more subjects with Stage IV disease at baseline, more subjects with CNS metastasis at baseline, more subjects whose disease had sarcomatoid features, more subjects with 2 prior lines of therapy, and more subjects with a shorter time from diagnosis to first systemic therapy in the metastatic setting.

The FDA's Assessment:

FDA generally agrees. There was a lower proportion of patients with a favorable IMDC risk classification in the nivolumab SC arm relative to the nivolumab IV arm (19.4% vs 23.1%). There was also a greater proportion of patients in the nivolumab SC arm that had received 2 prior lines of therapy (10.9% vs 5.3%). This slight imbalance of poor prognostic features would be expected to favor the nivolumab IV arm, and not the investigational therapy (nivolumab SC).

Treatment Compliance, Concomitant Medications, and Rescue Medication Use

The Applicant's Position:

Treatment Compliance: Study drugs were administered via SC injection and IV infusion by trained medical personnel at each site. Treatment compliance was monitored by routine monitoring of clinical source documents and drug accountability, as well as the subject's medical record and CRF.

Concomitant Therapy: In the nivolumab SC arm, most subjects (81.8%) received concomitant non-study medications. Premedication with systematic corticosteroids was administered in 5 (2.0%) subjects in the nivolumab SC arm.

Rescue Medication Use: Not applicable.

The FDA's Assessment:

Treatment compliance: FDA agrees with the Applicant's assessment of treatment compliance. Per protocol study drugs on both arms were administered by trained medical

personnel at each site.

Concomitant Therapy: A total of 5 (2.0%) patients on the nivolumab SC arm and 9 (3.7%) patients on the nivolumab IV arm received pre-medication with systemic corticosteroids. Other concomitant medications received by patients on Study CA20967T were generally balanced across treatment arms. The most common concomitant medications received (>20%; SC vs. IV) were cardiovascular medications (67% vs. 73%), vaccines (61% vs. 60%), pain medications (52% vs. 47%), medications for gastroesophageal reflux disease (24% vs. 25%), antibiotics (22% vs. 27%), and diabetes medications (20% vs. 22%).

Rescue Medication Use: A total of 90 (36.4%) patients on the nivolumab SC arm (corticosteroids 98%; mycophenolate 1.2%; apremilast 0.8%; azathioprine 0.4%) and 97 (39.6%) patients on the nivolumab IV arm (corticosteroids 100%; apremilast 0.4%) received immune-modulating medications for a treatment emergent adverse event. See further discussion of IMAEs in the section evaluating Significant Adverse Events occurring on Study CA20967T.

Efficacy Results – Primary Endpoint (Including Sensitivity Analyses)

Data: Not applicable.

The Applicant's Position:

Not applicable. Primary endpoints in CA20967T were PK-related (see Section 6.2.1).

The FDA's Assessment:

See assessment of the primary endpoints for Study CA20967T in the Clinical Pharmacology Section 6.2.1. The study met the predefined acceptance margin for the pharmacokinetic co-primary endpoints, with the lower boundary of 90% confidence interval of geometric mean ratios not less than 0.8 for both serum nivolumab C_{avg} over 28 days and C_{min} at steady state.

Data Quality and Integrity

The Applicant's Position:

Data review and quality control checks were implemented by BMS and consisted of site monitoring visits guided by the SMP to review source documents against the CRF and data validation checks of the CRF and externally loaded data as per the established Data Review Plan. Data quality review was performed to ensure data completeness and data integrity. Any issues or findings were followed up for resolution during Data Quality Sub-team meetings and Data Review Meetings. The Vendor Data Quality Oversight Plan was used to ensure oversight of Data Management review performed by Accenture. In addition, a review of the database was performed by BMS Global Biometric and Data Sciences to enhance the quality and ensure completeness of the data. When the database was declared complete and accurate, the DBL Checklist was completed, which documented that all prerequisites for the DBL were achieved, and the database was locked.

The FDA's Assessment:

The data quality is generally acceptable. The FDA reviewer was able to reproduce the efficacy results based on the submitted AdaM and SDTM datasets for Study CA20967T.

Efficacy Results – Secondary and other relevant endpoints

Data:

Table 27: Applicant - Summary of Efficacy - All Randomized Subjects in CA20967T

	Nivo SC (N = 248)	Nivo IV (N = 247)
SECONDARY ENDPOINTS		
Confirmed BOR per BICR, n (%)		
CR	5 (2.0)	4 (1.6)
PR	55 (22.2)	41 (16.6)
SD	96 (38.7)	110 (44.5)
PD	62 (25.0)	66 (26.7)
UTD	30 (12.1)	26 (10.5)
ORR per BICR (CR + PR)^a		
n (%)	60 (24.2)	45 (18.2)
(95% CI)	(19.0, 30.0)	(13.6, 23.6)
Estimate of Objective Response Risk Ratio (95% CI) ^{b,c}		1.33 (0.94, 1.87)
Difference of ORR, % (95% CI) ^{b,d}	6 (-1.2, 13.1)	
DCR per BICR (CR + PR + SD)		
n (%)	156 (62.9)	155 (62.8)
(95% CI)	(56.6, 68.9)	(56.4, 68.8)
Estimate of Disease Control Risk Ratio (95% CI) ^{b,c}	1.01 (0.88, 1.15)	
Difference of DCR, % (95% CI) ^{b,d}	0.6 (-7.7, 8.9)	
TTR per BICR, months		
Median	3.70	3.68
Min, Max	1.7, 11.1	1.6, 11.3
Q1, Q3	1.92, 5.62	1.94, 5.52
Standard Deviation	2.51	2.35
DOR per BICR		
N events/N responders (%)	19/60 (31.7)	5/45 (11.1)
Median, months (95% CI) ^e	14.49 (7.52, N.A.)	N.A. (13.90, N.A.)
Min, Max (months) ^f	1.6+, 20.4+	1.6+, 20.2+
PFS per BICR (Primary Definition)		
Events, n (%)	152 (61.3)	147 (59.5)
Median, months (95% CI) ^e	7.23 (5.13, 7.49)	5.65 (5.29, 7.39)
HR (95% CI) ^g	1.06 (0.84, 1.34)	
6-month PFS Rates (95% CI)	50.8 (44.1, 57.2)	47.7 (40.9, 54.2)
OS		
Events, n (%)	73 (29.4)	61 (24.7)
Median, months (95% CI) ^e	N.A. (19.22, N.A.)	N.A. (22.57, N.A.)
HR (95% CI) ^g	1.25 (0.89, 1.77)	
6-month OS Rates (95% CI)	84.1 (78.8, 88.2)	87.9 (82.9, 91.5)

^a CR+PR, confidence interval based on the Clopper and Pearson method.

^b Stratified by weight categorization (< 80 kg vs ≥ 80 kg) and IMDC risk group (favorable vs intermediate vs poor) as entered into the CRF.

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- ^c Strata adjusted risk ratio (nivolumab SC over nivolumab IV) using Mantel-Haenszel method.
- ^d Strata adjusted difference in objective response rate or disease control rate (Arm A - Arm B) based on Cochran Mantel-Haenszel (CMH) method of weighting.
- ^e Median computed using Kaplan-Meier method.
- ^f Symbol + indicates a censored value.
- ^g Cox proportional hazard model, stratified by weight categorization (< 80 kg vs ≥ 80 kg) and IMDC risk group (favorable vs intermediate vs poor) as entered into the CRF. Hazard Ratio is nivolumab SC over nivolumab IV.

Datasets: ADSL, ADEFRESP, ADEFTTES

The Applicant's Position:

Results of the key secondary endpoint of ORR per BICR were noninferior for the comparison of nivolumab SC vs nivolumab IV in subjects with advanced or metastatic ccRCC who have received prior systemic therapy, meeting the key secondary endpoint (Table 27).

The FDA's Assessment:

As described in the previous section, there are difficulties in interpreting the results of the non-inferiority test of ORR given that the non-inferiority margin was not based on a comparative result from a historical trial.

In study CA20967T, responses were observed in 60 (24.2%; 95% CI: 19.0, 30.0) patients in the nivolumab SC arm and in 45 (18.2%; 95% CI: 13.6, 23.6) patients in the nivolumab IV arm. This response rate is similar to what has been reported previously in patients with previously treated RCC in CheckMate-025, which reported an ORR of 21.5% (95% CI: 17.6, 25.8). PD-L1 expression was not assessed on Study CA20967T. PD-L1 expression is not routinely used as a biomarker in RCC (Saliby et al, 2024).

FDA notes that the ORR assessed by investigator was 21.0% (95% CI: 16.1, 26.6) in the nivolumab SC arm and 21.5% (95% CI: 16.5%, 27.1%) in the nivolumab IV arm, with a risk ratio of 1.00 (95% CI: 0.92, 1.10). The concordance rate between BICR and investigator's assessments of whether a patient was a responder was 88% in the nivolumab SC arm and 89% in the nivolumab IV arm. The results of ORR assessed by investigator were generally consistent with those of ORR per BICR.

Dose/Dose Response

The Applicant's Position:

Nivolumab SC 1,200 mg Q4W was demonstrated to be noninferior to nivolumab IV 3 mg/kg Q2W based on results of key secondary endpoint ORR per BICR (24.2% [95% CI: 19.0, 30.0] and 18.2% [95% CI: 13.6, 23.6] in the nivolumab SC and nivolumab IV arms, respectively. ORR risk ratio was 1.33 [95% CI: 0.94, 1.87]). Other secondary efficacy endpoints (DCR, TTR, and PFS) were comparable between treatment regimens (Table 27).

The results from the simulation-based PK bridging analyses showed that across all solid tumor types evaluated (ie, melanoma, NSCLC, RCC, SCCHN, UC, mCRC, ESCC, GC, GEJC

or EAC, and HCC), nivolumab SC dosing regimens (600 mg Q2W, 900 mg Q3W, and 1,200 mg Q4W) produced consistently higher first dose and steady-state exposures compared to those for the approved nivolumab IV dosing regimens (240 mg Q2W, 360 mg Q3W, and 480 mg Q4W) while also maintaining geometric mean exposures below those for nivolumab IV 10 mg/kg Q2W, a regimen shown to be safe and tolerable in clinical studies and used regularly to define the exposure safety margins for nivolumab.

The FDA's Assessment:

FDA agrees with the Applicant's position regarding identification of the recommended dose of nivolumab SC. The 1200 mg dose of nivolumab SC was selected based on the exposure of this dose being not less than the exposure of nivolumab IV at a dose of a 3 mg/kg Q2W in CheckMate 025. The other dosage regimens for nivolumab SC (600 mg Q2W and 900 mg Q3W) were identified via modeling and simulation.

Durability of Response

Data:

Median DOR per BICR was 14.49 months (95% CI: 7.52, NA) in the nivolumab SC arm, and not reached (95% CI: 13.90, N.A.) in the nivolumab IV arm (Table 27). The upper bound of the 95% CI was not reached for either arm indicating that the DOR was immature at the current DBL and included heavy censoring due to ongoing follow-up.

The Applicant's Position:

DOR had few events and included heavy censoring due to ongoing follow-up at the time of primary analysis. In CA20967T, the DOR profile (both number of responses and longer follow-up) is expected to change with additional follow up. In CA209025 (nivolumab IV 3 mg/kg Q2W vs everolimus in 2L+ advanced ccRCC), with minimum follow-up of 87.7 months, the median DOR of confirmed response per investigator for nivolumab was 18.23 months (95% CI: 12.91, 25.79), suggesting that, while immature, the early trends seen in CA20967T are within expectations in this treatment setting.¹³

The FDA's Assessment:

FDA agrees with the Applicant's description of durability of response. FDA adds that 45% of the responders in the nivolumab SC arm achieved a durable response of at least 6 months and 58% of the responders in the nivolumab IV arm achieved a durable response of at least 6 months.

Persistence of Effect

Data:

In CA20967T (minimum follow-up of 8 months) the DCR for nivolumab SC was 62.9%, compared to 62.8% for nivolumab IV (Table 27). The median PFS per BICR (primary definition) for nivolumab SC was 7.23 months (95% CI: 5.13, 7.49) compared to 5.65 months (95% CI: 5.29, 7.39) for nivolumab IV. ORR by BICR was 24.2% (95% CI: 19.0, 30.0) for

nivolumab SC and 18.2% (95% CI: 13.6, 23.6) for nivolumab IV with median DOR per BICR of 14.49 months (95% CI: 7.52, NA) in nivolumab SC and not reached (95% CI: 13.90, N.A.) for nivolumab IV. Median OS was not reached for either arm. 6-month OS rates were 84.1% (95% CI: 78.8, 88.2) for nivolumab SC vs 87.9% (95% CI: 82.9, 91.5) for nivolumab IV.

The Applicant's Position:

DCR and PFS data indicate that nivolumab SC provides sustained disease control consistent to that of nivolumab IV. At the time of the primary analysis an upper bound for the 95% CI for DOR could not be estimated for either arm and there was heavy censoring due to ongoing follow-up, indicating that DOR was immature at the current DBL, and additional follow-up is needed, but early trends are consistent with previous observations of DOR in this treatment setting seen in CA209025.¹³

OS was also immature at the time of analysis. Only 29.4% of subjects in the nivolumab SC arm had an OS event, there was heavy censoring beyond 8 months due to ongoing follow-up, the median OS was not reached, nor was the upper bound of the 95% CI defined. However, the 6-month OS rates were similar between the arms. CA20967T is ongoing to follow-up for the longer-term efficacy and safety of nivolumab SC.

The FDA's Assessment:

FDA generally agrees with the descriptive efficacy results for the endpoints DCR, PFS, and OS presented in this section. FDA notes that the analyses of these endpoints are descriptive only and should be interpreted with caution. PFS with approximately 60% of events was similar. OS is too immature for analysis. Even with an updated OS analysis in the safety update (events in less than 40% patients), the KM curves generally remain together for the first 15 months. The updated HR of 1.19 came closer to unity compared to the earlier analysis (Table 27). Although there was some separation after 15 months, there was heavy censoring. The current median estimated OS in the SC arm was approximately 25 months which is consistent with the treatment effect for nivolumab observed in CHECKMATE-025.

Efficacy Results – Secondary or exploratory COA (PRO) endpoints

Data:

FKSI-19, which measures tumor-specific HRQoL in kidney cancer, completion rates were > 99% at baseline and ≥ 80% in both treatment arms at all on-treatment assessments through Week 81. Mean changes from baseline for FKSI-19 total scores were generally stable and similar between the nivolumab SC and nivolumab IV treatment arms throughout most on-treatment time points. Similar results were observed for the FKSI-19 subscales.

The EQ-5D-5L, which assesses health status and utility had similar completion rates to the FKSI-19. The mean changes from baseline in the VAS scores were generally small and positive and similar between nivolumab SC and nivolumab IV at most on-treatment timepoints. The utility index scales were generally stable and similar between treatment arms.

The Applicant's Position:

Clinical outcome assessment results in CA20967T were generally similar in the nivolumab SC and nivolumab IV treatment arms, maintaining baseline quality of life, as measured by the FSKI-19 and its subscales, as well as the EQ-5D-5L assessments.

The FDA's Assessment:

Participants were asked to complete the FSKI-19 and the EQ-5D-5L questionnaires in their preferred language via paper during screening and dosing visits and through Safety Follow-up Visits 1 and 2. Additionally, the EQ-5D-5L was captured during Survival Follow-up Visits by telephone administration.

FDA notes that although the completion rates (number of patients with valid questionnaire assessment / number of patients expected to have an assessment) of the PRO questionnaires were high in both arms as described by the Applicant, the available data rates (number of patients with valid questionnaire assessment / number of randomized patients) dropped below 50% after Week 29 in the nivolumab SC arm and after Week 33 in the nivolumab IV arm.

FDA reviewed the PRO results submitted by the Applicant but did not independently verify all the results. The PRO results from this study cannot support any efficacy claims as the PRO endpoints are exploratory.

Additional Analyses Conducted on the Individual Trial

The Applicant's Position:

Not applicable.

The FDA's Assessment:

See assessment of Subpopulations in section 8.1.6.

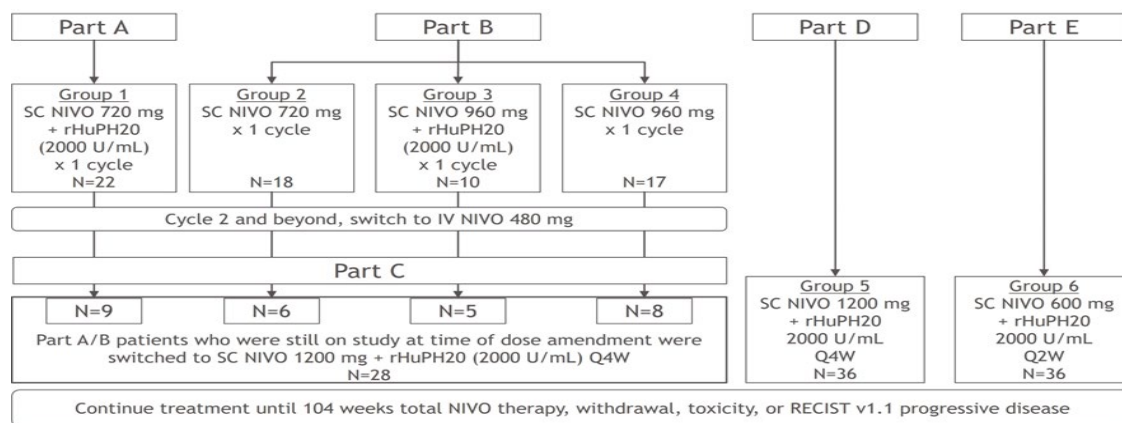
8.1.3. Supportive Phase 1/2 Study CA2098KX

Trial Design

The Applicant's Description:

CA2098KX¹⁴ is supportive, providing evidence of the comparability of the PK, safety, and tolerability of nivolumab SC (BMS-986298) with a permeation enhancer, rHuPH20, to that of nivolumab IV.

Figure 14: Applicant - CA2098KX Study Design Schematic



Actual enrollment: The first 10 subjects were assigned to Group 3. The next 35 subjects were randomized 1:1 into Group 2 (n = 18) and Group 4 (n = 17).

Crossover into Part C and dosing in Part D (Group 5) occurred after the nivolumab SC (BMS-986298) dosing regimen was identified from analysis of PK data from Parts A & B. At the time of Protocol Amendment 04, enrollment for Part D has completed and actual enrollment was 36 subjects.

Group 2 and Group 4 received nivolumab SC (BMS-986298) by syringe pump without rHuPH20.

Any ongoing subjects on nivolumab SC + rHuPH20 treatment may switch over to nivolumab coformulated with rHuPH20 drug product.

Table 28: Applicant - CA2098KX Study Design Details

Design Aspect	Description
Phase 1/2 design	Multicenter, randomized, open-label Phase 1/2 study that evaluated the PK, safety, and tolerability of nivolumab SC administered with and without rHuPH20 subcutaneously. The study was divided into the following periods: Screening period; Treatment period consisting of Part A, Part B, Part C, Part D, and Part E; and a Safety Follow-up period. Note: only results from Parts D and E are described in this document.
Study enrollment	Participants meeting inclusion/exclusion criteria (enrolled) were assigned randomization number. Only participants in Part B Groups 2 and 4 were randomized between the two treatment groups.
Eligibility criteria	Men and women ≥ 18 years of age at the time of informed consent with histologic or cytologic confirmation of advanced (metastatic and/or unresectable) solid tumors. With the exception of melanoma which does not require previous systemic therapy, all other tumor types including NSCLC, RCC, HCC, CRC, and UC required at least 1 or 2 prior systemic anti-cancer therapies in this study. Subjects needed to have measurable disease per RECIST v1.1 criteria, and an ECOG PS of 0 or 1. Prior radiotherapy was required to be completed at least 2 weeks prior to study treatment initiation.
Dose	<u>In Parts A and B</u> , subjects were allocated into 1 of 4 groups (Groups 1-4) and treated with either 720 mg or 960 mg nivolumab SC with or without rHuPH20 administered manually by syringe or syringe pump. 22 subjects were allocated to Part A. <u>In Part B</u> , the first 10 subjects were assigned to Group 3; the next 35 subjects were randomized 1:1 into Group 2 and Group 4. An initial nivolumab SC dose of 720 mg with rHuPH20 used in Part A, Group 1, was selected to provide PK similar to a nivolumab IV 480 mg flat dose on the basis that the mean population bioavailability of monoclonal antibodies following SC administration is ~75% of that achieved with IV administration. The same 720 mg nivolumab SC dose without rHuPH20 was used in Part B, Group 2.

BLA Multi-disciplinary Review and Evaluation {BLA 761381 and BLA 761429}
OPDIVO (nivolumab and hyaluronidase - nvhy) injection, for subcutaneous use

Design Aspect	Description
	Based on the bioavailability models and preliminary PK analyses from Part A, a single SC dose of 960 mg was tested in Part B in groups 3 and 4 to acquire additional nivolumab SC PK data. Four weeks after a single nivolumab SC dose (dose-finding), all subjects in Parts A and B received nivolumab IV 480 mg Q4W until progression (per RECIST v1.1), unacceptable toxicity, withdrawal of consent, completion of 104 weeks of treatment, crossover to 1,200 mg nivolumab SC with rHuPH20 Q4W dosing in Part C, or study termination by the sponsor, whichever occurred first. Subjects in Parts A and B who were still on study at the time of the dose amendment were switched to nivolumab SC 1,200 mg with rHuPH20 (2000 units/mL) Q4W manually by syringe in Part C. In Part D, subjects were treated with 1,200 mg nivolumab SC with rHuPH20 (2000 units/mL) Q4W manually by syringe (Group 5). In Part E, subjects were treated with 600 mg nivolumab SC coformulated with rHuPH20 (2000 units/mL) Q2W manually by syringe (Group 6). The 600 mg Q2W regimen was expected to have a linear exposure profile (ie, ~50% lower Cmax and AUCtau) to that of the 1,200 mg Q4W regimen assessed in previous cohorts.
Dose modification/discontinuation	Dose delay of nivolumab was permitted for any AE, laboratory abnormality, or intercurrent illness which, in the judgement of the investigator, warranted delaying the dose of study medication. Nivolumab discontinuation was permitted for any AE, laboratory abnormality, or intercurrent illness which, in the judgment of the investigator, presented a substantial clinical risk to the participant with continued dosing.
Treatment compliance	Treatment compliance was periodically monitored by drug accountability, medical record, and eCRF.
Subject completion, discontinuation, or withdrawal	Dosing in Parts A through E continued until RECIST v1.1 progression, unacceptable toxicity, withdrawal of consent, completion of 104 weeks of total nivolumab treatment (IV and SC), death, or study termination by the Sponsor.
Concurrent medications	All medications (prescriptions or OTC medications) continued at the start of the study or started during the study and different from the study treatment were to be documented in the concomitant therapy section of the eCRF.
Study Committees	No committees were used in this study.

The FDA's Assessment:

FDA agrees with the Applicant's assessment. The Applicant submitted efficacy data from Part D and Part E of Study CA2098KX. In Part D patients were administered nivolumab SC 1200 mg with rHuPH20 (2000 units/mL) Q4W. In Part E patients were administered with nivolumab SC 600 mg with rHuPH20 (2000 units/mL) Q2W.

Study Endpoints

The Applicant's Description:

Table 29: Applicant - Key Endpoints for Nivolumab SC (CA2098KX)

Primary Endpoints	Description
Serum nivolumab (Parts A, B, D, and E): Cmax, Tmax, AUC(TAU),	PK parameters of nivolumab were derived from serum concentration versus time measurements. Individual subject PK parameter values were derived by

Table 29: Applicant - Key Endpoints for Nivolumab SC (CA2098KX)

Ctau Serum nivolumab Part C: Ctrough	non-compartmental, and if appropriate, population PK methods by a validated PK analysis program using actual times.
Secondary Endpoints	Description
Incidences of AEs, TRAEs, SAEs, TRSAEs, AEs/TRAEs leading to discontinuation, deaths, and laboratory abnormalities.	Analysis of all safety data will follow the BMS guideline of analysis of safety data. The evaluation of safety is based on clinical AEs, vital signs, and clinical laboratory results reported during the study.
Incidence of AEs in the broad SMQ of Anaphylactic Reaction and incidence of events within the hypersensitivity /infusion reaction	Incidence of AEs in the broad SMQ of Anaphylactic Reaction occurring within 2 days after study drug administration Incidence of events within the hypersensitivity/infusion reaction select AE category occurring within 2 days after study drug administration.
Incidence of anti-nivolumab antibodies and neutralizing antibodies	ADA incidence is defined as the proportion of the study population found to have seroconverted or boosted their pre-existing ADA during the study period.
Exploratory Endpoints	Description
ORR, PFS, and OS	ORR was defined as the number of assigned/randomized and treated subjects who achieve a best response of CR or PR based on investigator assessments (using RECIST v1.1 criteria) divided by the number of all assigned/randomized and treated subjects. PFS was defined as the time between the date of first dose and the date of first documented tumor progression, based on investigator assessments (per RECIST v1.1 criteria), or death due to any cause, whichever occurs first. OS was defined as the time from first dose to the date of death from any cause. For subjects that are alive, their survival time was censored at the date of last contact date (or "last known alive date"). OS was censored at the date of first dose for subjects who were treated but had no follow-up.
Including, but not limited to: summary measures of change (or % change) from baseline in various biomarkers and molecular characteristics of the tumor	Subject listings of PD-L1 expression in all treated subjects with available PD-L1 data.
Incidence of anti-rHuPH20 antibodies and neutralizing antibodies	Percentage of subjects who develop anti-rHuPH20 antibodies and neutralizing antibodies
Patient experience and preference questionnaire	The core questionnaire contained items assessing patient perceptions regarding the convenience and acceptability of the mode of administration, treatment related symptoms, and satisfaction with treatment. The questionnaire was administered immediately following completion of the injection or infusion on Day 1 of treatment Cycle 1 and Cycle 2 in Part A and Part B, and on Day 1 Cycle 1 of Part C, Part D, and Part E.

The FDA's Assessment:

FDA agrees with the Applicant's description of the key endpoints for Study CA2098KX.

Statistical Analysis Plan

The Applicant's Description:

Table 30: Applicant - SAP Amendment Summary

Version Number	Description of Key Changes
1.0 / 08-May-2019	Original issue
2.0 / 31-Mar-2020	Changes were made to accommodate the changes in protocol version 3, namely, to increase the participant number in Part D and to identify the dose of nivolumab SC to be used for Parts C and D.
3.0 / 22-Jun-2021	Changes were made to accommodate the changes in protocol version 4; namely, to update the total participant number and schedule of analyses to account for addition of Part E.

SAP version 3 was submitted to the FDA on 10-Aug-2021 in sequence 0058. There have been five DBLs. Interim analyses 1 and 2 occurred under the first version of the SAP. Interim analyses 3 and 4 occurred under the second version of the SAP. Interim analyses 5 (primary analysis) occurred under the third version of the SAP.

There was no hypothesis testing associated with the primary PK assessment. The analyses of the primary PK endpoints were based on the evaluable PK subjects population. For PK subjects, a given PK parameter is derived if adequate PK profiles is available for deriving the parameter of interest.

The analysis populations defined in the SAP are as follows:

- *All Enrolled Subjects*: all subjects who signed an informed consent form and registered into the IRT. This is the dataset for disposition.
- *All Randomized Subjects*: all subjects randomized to any treatment arm in the study. In this study all subjects that met inclusion/exclusion criteria were assigned a randomization number. However, only subjects in Part B Groups 2 and 4 were randomized between the two treatment groups.
- *All Treated Subjects*: all subjects who received at least 1 dose of nivolumab. This is the dataset for exposure, safety, PRO and efficacy analyses.
- *PK Subjects*: All treated subjects with available PK data.
- *Evaluable PK Subjects*: The Evaluable PK Subjects population is a subset of the PK Subjects Population. The Evaluable PK Subjects population includes:
 - All treated subjects with available PK data and with adequate PK profiles for accurate estimation of PK parameters.

All available derived PK parameter values will be included in the PK data set and reported, but only subjects in the Evaluable PK Subjects population will be included in the summary statistics and statistical analysis.

- *Immunogenicity Evaluable Subjects*: All treated subjects who have a baseline and at least 1 post-baseline immunogenicity assessment.

Using these analysis populations, five interim analyses (interim analysis #5 was the primary analysis) have been conducted:

- **Interim analysis #1** was conducted after all subjects had been enrolled in Part A and completed cycle 1 (Nivolumab SC + rHuPH20). The following data were reported:
 - Pre-treatment data from all enrolled subjects in Part A.
 - All available data on study population, extent of exposure, previous and concomitant medications and safety from all treated subjects in Part A.
- **Interim analysis #2** was conducted once 10 subjects had been enrolled in Part B group 3 and completed cycle 1 (Nivolumab SC + rHuPH20). The following data were reported:
 - Pre-treatment data from all enrolled subjects in Part A and Part B group 3.
 - All available data on study population, extent of exposure, previous and concomitant medications, safety, PK and immunogenicity of nivolumab from all treated subjects in Part A and Part B group 3.
 - All available data on Patient Reported Outcome from all treated subjects in Part A.
- **Interim analysis #3** was conducted when the first 10 subjects in Part D completed the single dose of subcutaneous nivolumab. All subjects enrolled in all Parts of the study up to the lock were analyzed. The following data were reported:
 - Pre-treatment data from all enrolled subjects in Parts A, B, C and D.
 - All available data on study population, extent of exposure, previous and concomitant medications, safety and PK from all treated subjects in Parts A, B, C and D.
 - All available data on Patient Reported Outcome from all treated subjects in Parts A, B, C and D.
- **Interim analysis #4** was conducted when all subjects in Part D completed the single dose of nivolumab SC. All subjects enrolled in all Parts of the study up to the lock were analyzed. The following data were reported:
 - Pre-treatment data from all enrolled subjects in Parts A, B, C and D
 - All available data on study population, extent of exposure, previous and concomitant medications, safety, PK and immunogenicity of nivolumab from all treated subjects in Parts A, B, C and D.
 - All available data on Patient Reported Outcome from all treated subjects in Parts A, B, C, and D.
- **Interim analysis #5** (primary analysis) was conducted when all participants in Part E completed a minimum of 6 months of follow-up from first dose date. All participants enrolled in all Parts of the study up to the data cutoff date were analyzed. The following data were reported:
 - Pre-treatment data from all enrolled subjects in Parts A, B, C, D, and E.
 - All available data on study population, extent of exposure, previous and concomitant medications, efficacy, safety, PK and immunogenicity of nivolumab from all treated subjects in Parts A, B, C, D and E.

- All available data on Patient Reported Outcomes from all treated subjects in Parts A, B, C, D, and E.

The FDA's Assessment:

FDA agrees with the Applicant's description of the Statistical Analysis Plan.

Protocol Amendments

The Applicant's Description:

Table 31: Applicant - Summary of the 5 Global Protocol Revisions for CA2098KX

Document (Amendment) Date	Key Changes in Study Design	Subjects Randomized/Assigned at time of Protocol Amendment
Revised Protocol 01 05-Jul-2018	• Nivolumab SC (b) (4) drug substance was removed from the study. • Subjects in Part D were to receive nivolumab SC + rHuPH20 manually by syringe beginning at Cycle 1. • Procedures and inclusion criteria updated to include assessment of tumor PD-L1 expression measured by immunohistochemistry prior to treatment and to require results for subjects in Part A to be available prior to opening Part B for enrollment. • Additional biomarker and pharmacodynamic assessments added.	0
Revised Protocol 02 11-Dec-2018	• Assignment (n = 10) / randomization (n = 20) of subjects in Part B after dosing in Part A. • Inclusion/Exclusion criteria was only assessed during screening visit. • Requirement for exclusion of subjects based on positive urine screen for drugs of abuse was removed. • In Part B, other solid tumor types may be considered for enrollment at the discretion of the Medical Monitor. • Frequency of scans for response/survival follow-up was updated. • Timing, method, and type of tumor tissue specimens from biopsy was defined, including exceptions for subjects who had a biopsy in the preceding 12 months. • Criteria was added to the following sections that took into account anticipated compromise of baseline liver function in subjects with HCC: ○ Inclusion/exclusion criteria ○ Criteria for dose delay, dose resumption, and dose discontinuation ○ Management of hepatic AEs ○ Drug-induced liver injury • Evaluable PK subjects population was further characterized and defined what was considered an inadequate PK profile.	2 subjects randomized/assigned Part A: 2

BLA Multi-disciplinary Review and Evaluation {BLA 761381 and BLA 761429}
OPDIVO (nivolumab and hyaluronidase - nvhy) injection, for subcutaneous use

	Reference to number of interim analyses was removed to allow for greater flexibility to add additional analyses if necessary.	
Revised Protocol 03 25-Oct-2019	Updated to increase subject number in Part D, and to identify the dose of nivolumab SC to be used for Parts C and D.	67 subjects randomized/assigned Part A: 22 Part B: 45
Revised Protocol 04 02-Apr-2021	- Added information on safety reporting related to SARS-CoV-2 and COVID-19 eligibility and vaccine guidance. Added SARS-CoV-2 baseline serology collections for Part E subjects. - Added screening procedural outline specific for Part E and updates to add on-treatment and follow-up procedures for Part E. Added relevant information specific to Part E and described rHuPH20 to be introduced to Part E subjects. - Updated secondary endpoints to include TRAEs, TRSAEs and TRAEs leading to discontinuation. - Updated inclusion criteria related to tumor types, tumor tissue collection, PD-L1 expression, and reproductive status/contraceptive requirements for females. - Modified for clarity and added precision estimates for PK endpoint in Part E. - Added information about IA 5, to occur when all subjects in Part E have completed a minimum of 6 months of follow-up from first dose date.	103 subjects randomized/assigned Part A: 22 Part B: 45 Part D: 36
Revised Protocol 05 08-Sep-2021	- Additional PK sampling for Part E added. - Exclusion criteria updated per MHRA request.	103 subjects randomized/assigned Part A: 22 Part B: 45 Part D: 36

The FDA's Assessment:

FDA agrees with the Applicant's summary of the protocol amendments. The amended protocols were submitted to the FDA for review.

8.1.4. Study Results from Phase 1/2 Study CA2098KX Compliance with Good Clinical Practices

The Applicant's Position:

The laws and regulatory requirements of all countries that had sites participating in this study were adhered to. This study was conducted in accordance with Good Clinical Practice, as defined by the International Council for Harmonisation and in accordance with the ethical principles underlying European Union Directive 2001/20/EC and the US Code of Federal Regulations, Title 21, Part 50 (21 CFR 50).

The protocol, amendments, and subject informed consent received appropriate approval by the IRB/IEC prior to initiation of study at the site. This study was conducted in accordance with GCP by qualified investigators using a single protocol to promote consistency across sites. Measures to minimize bias included aspects of the study design, data validation, and

the use of third parties for critical activities.

The FDA's Assessment:

FDA agrees with the Applicant's position. There is no evidence that compliance with good clinical practices was violated during the conduct of Study CA2098KX.

Financial Disclosure

The Applicant's Position:

Refer to Section 19.1.

The FDA's Assessment:

Of the 316 investigators identified that participated in Study CA2098KX, there were none with financial disclosures to report. Additional information is presented in Appendix 19.2.

Patient Disposition

Data:

193 subjects were enrolled, and 139 subjects were treated across 21 sites in 11 countries. 36 subjects were enrolled in both Part D and Part E. The most frequent reason for subjects not completing study treatment was disease progression: 20 (55.6%) subjects in Part D, and 14 (38.9%) subjects in Part E.

The Applicant's Position:

The subjects enrolled in CA2098KX are reflective of the inclusion/exclusion criteria for populations with solid tumors.

The FDA's Assessment:

FDA generally agrees with the data presented by the Applicant. A total of 20 (56%) patients in Part D and 14 (39%) in part E discontinued due to disease progression. The reason for discontinuation was not reported for 7 (19%) patients in Part D and 14 (39%) patients in Part E. A total of 4 (11%) of patients in Part D and 1 (2.8%) in Part E discontinued due to AE attributed to study drug toxicity.

Protocol Violations/Deviations

Data:

IPDs are a subset of protocol deviations that may significantly impact the completeness, accuracy, and/or reliability of the study data or that may significantly affect a subject's rights, safety, or well-being. Routine monitoring of protocol deviations was conducted and where appropriate additional follow-up and training was conducted with sites and site-facing roles.

The Protocol Deviations Assessment Plan was utilized to assess the protocol deviations. The most noted IPD was failure or delay in obtaining consent for updated Informed Consent versions. Review of the deviations determined that there was no detriment to subject safety and no significant impact on the interpretability of study results.

RPDs are important protocol deviations that could affect the interpretability of key study results, are programmable deviations from clinical database, and are protocol-specific. RPDs were reported for 1 subject each in Part D and Part E. Both subjects missed at least one inclusion or exclusion criterion.

The Applicant's Position:

Reported deviations (IPDs and RPDs) did not impact the interpretability of study results.

The FDA's Assessment:

FDA reviewed the important protocol deviations and relevant protocol deviations. With respect to relevant protocol deviations, there was one patient in Part D who missed at least one inclusion criteria and there was also one patient in Part E who missed at least one inclusion criteria. The protocol deviations reported for Study CA2098KX do not raise any concerns regarding the overall conduct or quality of the study, study safety, or the clinical interpretation of data with respect to study endpoints.

Table of Demographic Characteristics

Data:

Table 32: Applicant - Key Demographic and Baseline Characteristics - All Treated Subjects CA2098KX (Parts D and E)

	Part D (n = 36)	Part E (n = 36)
Age		
Mean	64.6	63.6
Median	69.0	64.0
Min, Max	24, 93	37, 80
Q1, Q3	59, 73	58, 73
SD	13.0	11.0
Sex (%)		
Male	26 (72.2)	27 (75.0)
Female	10 (27.8)	9 (25.0)
Race		
White	31 (86.1)	34 (94.4)
Black or African American	1 (2.8)	0
Asian	1 (2.8)	1 (2.8)
American Indian or Alaska Native	0	0
Native Hawaiian or Other Pacific Islander	0	0
Other	3 (8.3)	1 (2.8)
Weight (kg)		
Mean	80.4	75.9
Median	80.7	73.5
Min, Max	48 ,133	44 ,121
Q1, Q3	65 , 91	67 , 89
SD	19.6	17.4
Tumor type		
Colorectal Cancer (MSI-H)	7 (19.4)	4 (11.1)

Table 32: Applicant - Key Demographic and Baseline Characteristics - All Treated Subjects CA2098KX (Parts D and E)

	Part D (n = 36)	Part E (n = 36)
Gastric Cancer	0	0
Head and Neck Cancer	0	0
Hepatocellular Carcinoma	6 (16.7)	7 (19.4)
Melanoma	3 (8.3)	0
Non-small Cell Lung Carcinoma	11 (30.6)	10 (27.8)
Renal Cell Carcinoma	9 (25.0)	6 (16.7)
Urothelial Cancer	0	9 (25.0)
Prior lines of therapies		
Adjuvant therapy	2 (5.6)	3 (8.3)
0	5 (13.9)	0
1	24 (66.7)	22 (61.1)
2	4 (11.1)	8 (22.2)
≥ 3	1 (2.8)	3 (8.3)
Performance Status (ECOG) (%)		
0	13 (36.1)	13 (36.1)
1	23 (63.9)	23 (63.9)

Dataset: ADSL

The Applicant's Position:

Demographics for subjects in Parts D and E were generally representative of the populations studied in CA2098KX (Table 32).

The FDA's Assessment:

FDA agrees with the data presented in Table 32. The median age of patients was 69 and 64 years old in Part D and Part E of the Study CA2098KX. The majority of patients in both Part D and Part E were male. There was underrepresentation of traditionally underrepresented minorities in Study CA2098KX.

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

Data: See Table 32.

The Applicant's Position:

Baseline characteristics for subjects in Parts D and E were generally representative of the populations studied in CA2098KX.

The FDA's Assessment:

Tumor types represented in Study CA2098KX were tumor types that are generally responsive to immune checkpoint inhibition including hepatocellular carcinoma, melanoma, non-small cell lung cancer, renal cell carcinoma, urothelial cancer, and microsatellite instability high colorectal cancer. In Part D and Part E, a total of 24 (67%) and 22 (61%) had received 1 prior line of therapy, respectively. A total of 5 (14%) of patients in Part D and 11 (34%) patients on Part E had received at least 2 prior therapies.

In Part D, a total of 3 (17%) had PD-L1 expression of $\geq 1\%$ and a total of 2 (12%) patients with PD-L1 expression of $\geq 50\%$ (Dako PharmDx 28-8 assay). In Part E, a total of 1 (10%) had PD-L1 expression of $\geq 1\%$ and no patients had PD-L1 expression of $\geq 50\%$ (Dako PharmDx 28-8 assay). Part D and Part E included 7 (19%) patients and 4 (11%) patients with MSI-H colorectal cancer, respectively. No patients received a prior immune-checkpoint inhibitor.

Treatment Compliance, Concomitant Medications, and Rescue Medication Use

The Applicant's Position:

Treatment Compliance: Nivolumab was administered by IV or SC by trained medical personnel at each site. Treatment compliance was monitored by routine monitoring of clinical source documentation and drug accountability, as well as the subject's medical record and CRF. Majority of subjects received 90 to 110% of the planned dose intensity, none had a relative dose intensity $\geq 110\%$.

Concomitant Therapy: Concomitant medications were recorded at baseline and throughout the treatment phase of the study in the appropriate section of the eCRF. All medications (prescriptions or OTC medications) continued at the start of the study or started during the study and different from the study treatment were documented in the concomitant therapy section of the eCRF.

Rescue Medication Use: Not applicable.

The FDA's Assessment:

Treatment Compliance: FDA generally agrees with the Applicant's position. In Part D a total of 35 (97%) patients received 90 to 110% of the planned dose intensity and in Part E a total of 32 (89%) patients received 90 to 110% of the planned dose intensity.

Concomitant Therapy: FDA agrees with the Applicant's description.

Rescue Medication Use: Immune-modulating medications were received by 13 (36%) patients in Part D and 15 (42%) patients in Part E. These proportions are similar to those reported for patients on the nivolumab SC arm of the pivotal study CA20967T.

Efficacy Results – Primary Endpoint (Including Sensitivity Analyses)

The Applicant's Position:

Not applicable. The primary endpoints in CA2098KX were PK-related and are discussed in Section 6.2.1.

The FDA's Assessment:

See Clinical Pharmacology assessment of pharmacokinetic primary endpoints from Study CA2098KX in Section 6.2.1.

Data Quality and Integrity

The Applicant's Position:

Data cleaning and quality control checks were implemented by BMS and consisted of site monitoring visits guided by the SMP to review source documents against the eCRF and data validation checks of the eCRF and externally loaded data. Data quality review was performed to ensure data completeness, accuracy, and integrity. Any issues or findings were followed up for resolution during Data Quality Sub-team meetings and Data Review Meetings. The Vendor Data Quality Oversight Plan was used to ensure oversight of Data Management review performed by Accenture. In addition, a review of the database was performed by BMS GBDS to enhance the quality and ensure completeness of the data, and the BMS RAVE Clinical database was audited prior to the data cutoff. When the database was declared complete and accurate, the Database Lock Checklist was completed, which documented that all prerequisites for the DBL were achieved, and the database was locked.

The FDA's Assessment:

FDA agrees with the Applicant's position. FDA review did not uncover any data integrity issues. FDA agrees that the submission was complete and of adequate quality.

Efficacy Results – Secondary and other relevant endpoints

Data:

Table 33: Applicant - Efficacy Summary (Exploratory Endpoints) - All Treated Subjects in Parts D and E of CA2098KX

	Part D N = 36 Nivolumab SC 1,200 mg + rHuPH20 2000 U/mL Q4W	Part E N = 36 Nivolumab SC 600 mg + rHuPH20 2000 U/mL Q2W
BOR per Investigator^a, n (%)		
Complete Response	0	0
Partial Response	9 (25.0)	9 ^c (25.0)
Stable Disease	11 (30.6)	10 (27.8)
Progressive Disease	14 (38.9)	13 (36.1)
Unable to Determine	2 (5.6)	4 (11.1)
Death prior to disease assessment	1 (2.8)	4 (11.1)
Other	1 (2.8)	0
ORR per Investigator^a	9/36 (25.0)	9/36 (25.0)
ORR ^b (95% CI), %	(12.1, 42.2)	(12.1, 42.2)
PFS per Investigator		
Median (95% CI), months	4.14 (2.66, 8.05)	6.16 (2.79, 8.15)
6-month	40.0 (24.0, 55.5)	52.9 (35.1, 67.9)
12-month	31.2 (16.8, 46.7)	N.A
OS		
Events, n (%)	19/36	14/36
Median OS (95% CI), months	23.10 (13.96, N.A)	9.59 (6.08, N.A)

Table 33: Applicant - Efficacy Summary (Exploratory Endpoints) - All Treated Subjects in Parts D and E of CA2098KX

	Part D N = 36 Nivolumab SC 1,200 mg + rHuPH20 2000 U/mL Q4W	Part E N = 36 Nivolumab SC 600 mg + rHuPH20 2000 U/mL Q2W
6-month	77.8 (60.4, 88.2)	68.7 (50.6, 81.3)
12-month	69.0 (51.0, 81.5)	N.A

^a Per RECIST 1.1 Response Criteria

^b CR+PR, confidence interval based on the Clopper and Pearson method.

N.A: Not Available: minimum follow up not reached or all observations censored at timepoint of interest. PFS/OS based on Kaplan-Meier Estimates. Participants who did not progress or have complete response but had partial response might be represented by stable disease.

^c 3 of the 9 subjects in Part E were unconfirmed partial responders.

Datasets: ADSL, ADEFTTES, ADRS

The Applicant's Position:

Efficacy endpoints were exploratory in CA2098KX. Due to the sequencing of SC and IV nivolumab regimens administered in Parts A, B, and C of CA2098KX, efficacy results are only presented for Parts D and E since these subjects received only nivolumab SC without any intervening nivolumab IV. Efficacy endpoints including ORR, PFS, and OS obtained for Parts D and E are within the expected range in this advanced multi tumor setting previously studied with nivolumab IV. Minimum follow-up for OS (time from last subject's first dose date to clinical cut-off date [07-Sep-2022]) was 24.4 and 6.0 months for Parts D and E, respectively.

Key efficacy findings (Table 33):

- At DBL, the reported investigator-assessed ORR by RECIST was 25.0% (95% CI: 12.1, 42.2) in Part D and 25.0% (95% CI: 12.1, 42.2) for Part E. Best overall response reported no CR in either Part D or E.
- The investigator-assessed median PFS was 4.14 months (95% CI: 2.66, 8.05) for Part D and 6.16 months (95% CI: 2.79, 8.15) for Part E.
- Median OS was 23.10 months (95% CI: 13.96, N/A) for Part D and 9.59 months (95% CI: 6.08, N/A) for Part E.

The FDA's Assessment:

As stated by the Applicant, efficacy endpoints in Study CA2098KX were exploratory. As observed in Table 32, the tumor types represented in Part D and Part E varied as did line of therapy. FDA agrees that the ORR reported is within what is expected for nivolumab in advanced solid tumors (with the majority of patients in 2nd-line or later) where there has been some enrichment for tumor types more likely to respond to immune checkpoint inhibition. Responses (Investigator-accessed RECIST v.1.1) were observed across a variety of advanced solid tumor types in both Part D and Part E.

Dose/Dose Response

The Applicant's Position:

Not applicable. CA2098KX was utilized to select the dose based on comparable exposure to the nivolumab IV dose and was not designed to select the dose based on efficacy.

The FDA's Assessment:

See Clinical Pharmacology assessment of pharmacokinetic primary endpoints from Study CA2098KX in Section 6.2.1.

Durability of Response

Data:

Median combined PFS across Parts D and E was 4.57 months (95% CI: 2.83, 6.57). Median PFS for each cohort separately was 4.14 months (95% CI: 2.66, 8.05) for Part D and 6.16 months (95% CI: 2.79, 8.15) for Part E (Table 33). OS rate at 6 months for Parts D and E were 77.8% (95% CI: 60.4%, 88.2%) and 68.7% (95% CI: 50.6%, 81.3%), respectively.

The Applicant's Position:

PFS for either treatment regimen (1,200 mg Q4W or 600 mg Q2W) was within the expected range for nivolumab in this advanced multi tumor setting based on previous studies with nivolumab IV. Tumor types accounting for $\geq 10\%$ of patients in either Part D or E included CRC MSI-H, HCC, NSCLC, RCC and UC. Historical trials of nivolumab monotherapy in these tumor types and the reported mPFS were CheckMate-142 (CRC MSI-H/dMMR)¹⁵ with a mPFS 14.3 months (95% CI: 4.30, NE); CheckMate-040 (HCC post sorafenib) with a mPFS 2.83 months (95% CI: 2.63, 4.04);¹⁶ Pooled CheckMate-017 and CheckMate-057 (2L NSCLC) with a mPFS 2.56 (95% CI: 2.20, 3.48);¹⁷ CheckMate-025 (2L RCC) with a mPFS 4.6 (95% CI: 3.7, 5.4);¹⁸ and CheckMate-275 (UC) with a mPFS 2.00 months (95% CI: 1.87, 2.63).¹⁹

The FDA's Assessment

FDA considers time-to-event endpoints in single-arm studies to be uninterpretable.

Persistence of Effect

The Applicant's Position:

The efficacy analysis for CA2098KX was exploratory, with a minimum follow up of 24.4 months and 6.0 months for Parts D and E, respectively. Efficacy endpoints including ORR, PFS and OS obtained from these two cohorts treated exclusively with nivolumab SC are within the expected range in this advanced multi tumor setting previously studied with nivolumab IV. The study is ongoing to follow subjects for up to two years post last treatment to assess the longer-term efficacy and safety of nivolumab.

The FDA's Assessment:

[FDA will complete this section.]

Efficacy Results – Secondary or exploratory COA (PRO) endpoints

Data:

Of those patients who completed the PEPQ and experienced both SC and IV administration (Part C), a higher proportion of patients stated a preference for SC administration over IV administration of nivolumab (71% vs 10%).²⁰ Across all Parts, patients stated they were very satisfied with how nivolumab SC was administered (78-100%) and reported minimal pain/discomfort associated with SC injection (0.0-1.3 out of 10). Additionally, most patients reported that the injection time was less than expected or was acceptable. These results are limited by the small number of questionnaire respondents.

The Applicant's Position:

PROs did not report negative impacts from SC administration, and data collected from Part C suggest preference for SC over IV.

The FDA's Assessment:

FDA considers the PRO results exploratory only.

Additional Analyses Conducted on the Individual Trial

The Applicant's Position:

Not applicable.

The FDA's Assessment:

Not applicable.

8.1.5. Integrated Review of Effectiveness

The FDA's Assessment:

The Applicant's claims of the effectiveness of nivolumab with nivolumab SC for the requested indications is supported by the results of Study CA20967T. Study CA20967T compared nivolumab SC (n=248) with nivolumab IV (n=247) in adult patients with advanced or metastatic ccRCC who are naïve to therapy targeting T-cell co-stimulation or checkpoint pathways, and have received no more than 2 prior systemic regimens. The results of Study CA20967T demonstrated pharmacokinetic noninferiority of nivolumab SC to nivolumab IV. Noninferiority of nivolumab SC to nivolumab IV was concluded with Cavgd28 GMR (90% CI) of 2.098 (2.001, 2.200) and Cminss GMR (90% CI) of 1.774 (1.633, 1.927) as the lower bounds of the 2-sided 90% CIs for both endpoints were above 0.8. The effectiveness of nivolumab SC was also supported by the key secondary endpoint of ORR by BICR according to RECIST 1.1. Noninferiority of the key secondary endpoint was demonstrated with an ORR of 24.2% (95% CI: 19.0, 30.0) for nivolumab plus hyaluronidase SC, and 18.2% (95% CI: 13.6, 23.6) for nivolumab IV. The stratified Mantel-Haenszel estimate of the ORR RR was 1.33 (95% CI: 0.94, 1.87). However, the non-inferiority margin was not based on a comparative result from a historical trial, and therefore the preservation of treatment effect is not well defined for this comparison and the results of the non-inferiority test are difficult to interpret.

Overall, results from Study CA20967T demonstrate effectiveness of nivolumab SC as measured by pharmacokinetic noninferiority and further supported by the results of the key secondary endpoint of ORR by BICR according to RECIST 1.1.

8.1.6. Assessment of Efficacy Across Trials

Primary Endpoints

The Applicant's Position:

Not applicable. The primary endpoints for CA20967T and CA2098KX were PK-related.

The FDA's Assessment:

FDA generally agrees with the Applicant's position. The primary endpoints for CA20967T and CA2098KX were PK-related and are discussed in Section 6.2.1.

Secondary and Other Endpoints

The Applicant's Position:

The multi-tumor, multi-cohort, non-randomized efficacy endpoints of ORR, PFS and OS from CA2098KX are consistent with and supportive of the conclusion of non-inferiority for nivolumab SC vs IV in CA20967T.

The FDA's Assessment:

The primary pharmacokinetic endpoints in Study CA20967T were supported by the key secondary endpoint of ORR by BICR according to RECIST 1.1 which is discussed above in Section 8.1.2 and 8.1.5.

In Study CA2098KX, the response rate reported is within what is expected for nivolumab in advanced solid tumors (with the majority of patients in 2nd-line or later) where there has been some enrichment for tumor types more likely to respond to immune checkpoint inhibition. Responses (Investigator-assessed RECIST v.1.1) were observed across a variety of advanced solid tumor types in both Part D and Part E.

Subpopulations

The Applicant's Position:

Based on the data from CA20967T and CA2098KX, no sub populations were identified with a differentiated efficacy profile.

The FDA's Assessment:

An exploratory analysis of nivolumab ADA-positive patients in Study CA20967T showed a numerically lower ORR (BICR) than nivolumab ADA-negative patients in both the nivolumab SC arm and the nivolumab IV arm. In the nivolumab SC arm 15.2% (7 of 46; 95% CI: 6.3, 28.9) of nivolumab ADA-positive patients and 27.7% (43 of 155; 95% CI: 20.9, 35.5) of nivolumab ADA-negative patients had an objective response by BICR according to RECIST v1.1. In the nivolumab IV arm no (0 of 15; 95% CI: 0.0, 21.8) nivolumab ADA-positive patients and 20.5% (41 of 200; 95% CI: 15.1, 26.8) of nivolumab ADA-negative patients had an

objective response by BICR according to RECIST v1.1. This analysis was exploratory and results should be interpreted with caution.

Additional Efficacy Considerations

The FDA's Assessment:

Study CA20967T met its primary objectives to demonstrate comparability of the PK co-primary endpoints and comparable anti-tumor activity between nivolumab SC and nivolumab IV. Although there were a very small number of patients enrolled to the study that identify as racial or ethnic minorities, it is unlikely that there would be a differential effect based on race or ethnicity in the analysis of the primary study endpoints and no clinically significant difference has been observed to date. Substantial evidence of effectiveness has been demonstrated for nivolumab IV across tumor types and among patients from various racial and ethnic demographic subgroups.

8.1.7. Integrated Assessment of Effectiveness

The Applicant's Position:

The submitted data from studies CA20967T and CA2098KX meet the statutory evidentiary standard for substantial evidence of effectiveness. The data support the proposed indications as stated in Section 2.

Nivolumab SC demonstrated noninferiority to nivolumab IV in the ORR by BICR key secondary endpoint in CA20967T, with consistent data across DCR, TTR, and PFS. This conclusion is supported by the exploratory efficacy endpoints ORR, PFS, and OS in CA2098KX which are consistent with the historical efficacy profile of nivolumab IV.

CA20967T was a large, adequately-powered clinical trial. The key efficacy secondary endpoint showed that based on ORR per BICR, nivolumab SC is noninferior to nivolumab IV for subjects with advanced or metastatic clear cell RCC who have received prior systemic therapy. Other secondary efficacy endpoints that were well characterized at this primary analysis (DCR, TTR, and PFS) were comparable between treatment regimens, and support the conclusion based on the co-primary PK endpoints and key efficacy endpoint.

Data from CA2098KX provide further supportive evidence of the efficacy of nivolumab SC. Exploratory efficacy endpoints including ORR, PFS, and OS obtained for Parts D and E treated exclusively with nivolumab SC, are within the expected range in this advanced multi tumor setting previously studied with nivolumab IV.

The FDA's Assessment:

FDA agrees that the submitted data meet the statutory evidentiary standard for substantial evidence of effectiveness. Study CA20967T was a multi-regional, randomized, open-label study to compare the pharmacokinetics, efficacy, and safety of nivolumab SC to nivolumab IV in adult patients with advanced or metastatic ccRCC who are naïve to therapy targeting T-cell co-stimulation or checkpoint pathways, and have received no more than 2 prior systemic regimens.

In Study CA20967T, substantial evidence of effectiveness for all of the proposed adult indications (Section 2.1) for nivolumab SC was established based on the comparability of pharmacokinetic parameters and the key secondary endpoint for efficacy. The comparison of nivolumab SC to nivolumab IV met the predefined acceptance margin for pharmacokinetic primary endpoints, with the lower boundary of 90% confidence interval of geometric mean ratios of not less than 0.8 for both serum nivolumab Cavg over 28 days and Cmin at steady state. In Study CA20967T, there was no notable difference between the nivolumab SC arm and the nivolumab IV arm in the key secondary endpoint of ORR by BICR according to RECIST 1.1, which provided supporting evidence for the effectiveness of nivolumab SC.

8.2. Review of Safety

Data: See Table 39 and Table 50.

The Applicant's Position:

The overall safety profile of nivolumab demonstrated in studies CA20967T and CA2098KX indicated that nivolumab SC was safe and well-tolerated. AEs reported in SC dose regimens were consistent with the known AE profile of nivolumab IV. Local injection site reactions were reported but were mild to moderate (Grade 1-2). No new safety signals or safety concerns were identified, and the safety profile was manageable based on the already established management guidelines. The addition of rHuPH20 had no impact on the overall safety profile of nivolumab SC as compared to nivolumab IV.

The FDA's Assessment:

The data supporting FDA's assessment of the safety of nivolumab SC is based primarily on the safety population from Study CA20967T which was a global, open-label, randomized, noninferiority study of nivolumab SC (n=247) versus nivolumab IV (n=245) in adult patients with advanced or metastatic ccRCC who are naïve to therapy targeting T-cell co-stimulation or checkpoint pathways, and have received no more than 2 prior systemic regimens. Supportive data came from Study CA2098KX which was a multicenter, randomized, open-label, Phase 1/2 study that evaluated the PK, safety, and tolerability of nivolumab SC in patients with hepatocellular carcinoma, melanoma, non-small cell lung cancer, renal cell carcinoma, urothelial cancer, and MSI-High colorectal cancer. In addition, based on the demonstration of PK comparability safety of nivolumab SC is further supported by the demonstration of safety of nivolumab IV in the pivotal trials that support the current IV indications for nivolumab.

The safety profile, including common treatment emergent AEs, Grade 3 or 4 AEs; SAEs, AEs leading to death; and AEs resulting in treatment delay, injection/infusion interruption, or treatment discontinuation; immune-mediated adverse events (IMAEs); and other events of special interest (OESI) was generally consistent with the established and well characterized safety profile of nivolumab IV. The notable exception is the presence of injection-site

reactions which occurred in 20 (8%) patients in the nivolumab SC arm of Study CA20967T and were generally mild (i.e., Grade 1 or 2).

8.2.1. Safety Review Approach

The Applicant's Position:

The primary safety analysis group relevant to the proposed indications consists of 247 subjects treated with nivolumab SC in the pivotal study, CA20967T (Table 34). Safety results from pivotal study, CA20967T, are presented in Section 8.2.4.

Additional supportive data is provided for subjects with various solid tumors in CA2098KX Part D (N=36) and Part E (N=36). In Parts A-C of CA2098KX, subjects alternated between SC and IV nivolumab, preventing clear causality attribution for AEs to any particular route of administration. Safety results from supportive study, CA2098KX, are presented in Section 8.2.5.

The FDA's Assessment:

The FDA safety review focused on analyses of the incidence of key treatment-emergent adverse event (AE) categories including common AEs, Grade 3 or 4 AEs; SAEs, AEs leading to death; and AEs resulting in treatment delay, injection/infusion interruption, or treatment discontinuation; immune-mediated adverse events (IMAEs); other events of special interest (OESI); injection-site reactions; and infusion reactions. IMAEs were defined as AEs consistent with an immune-mediated mechanism or immune-mediated component for which non-inflammatory etiologies (e.g., infection or tumor progression) have been ruled out. IMAEs could include events with an alternate etiology which were exacerbated by the induction of autoimmunity. These analyses were limited to subjects who received immune-modulating medication (e.g., corticosteroids) for treatment of the event, with the exception of endocrine events, which were included in the analysis regardless of treatment since these events are often managed without immunosuppression.

FDA agreed previously to this definition of IMAEs in the Pre-BLA meeting. It is a reasonable, but conservative, definition of IMAEs that is likely to include events that are true immune-mediated events, with a plausible likelihood of being attributed to PD-1 inhibition on either of the treatment arms. It is possible that the incidence of IMAEs may be even higher if a less stringent definition were used, but one would run the risk of capturing events that were not true IMAEs.

The Applicant described IMAEs as either endocrine and non-endocrine events. Non-endocrine IMAEs included pneumonitis, diarrhea/colitis, hepatitis, nephritis and renal dysfunction, rash, and hypersensitivity. Endocrine IMAEs included adrenal insufficiency, hypothyroidism/thyroiditis, hypothyroidism, thyroiditis, hyperthyroidism, diabetes mellitus, and hypophysitis. Other events were included as IMAEs if they met the following criteria:

- Events occurring within 100 days of the last dose,
- Events regardless of causality,

- Events that were treated with immune modulating medication, with the exception of endocrine events (adrenal insufficiency, hypothyroidism/thyroiditis, hypothyroidism, thyroiditis, hyperthyroidism, diabetes mellitus, and hypophysitis), which were included in the analysis regardless of treatment since these events are often managed without immunosuppression.
- Events with no clear alternate etiology based on investigator assessment, or with an immune mediated component.

OESIs consisted of a list of PTs grouped by category, including: myositis/rhabdomyolysis, myocarditis, demyelination, Guillain-Barre syndrome, pancreatitis, uveitis, encephalitis, myasthenic syndrome, and graft versus host disease.

8.2.2. Review of the Safety Database

Overall Exposure

Data:

Table 34: Applicant - Safety Population

Clinical Trials		Nivolumab SC	Nivolumab IV
CA20967T		247	245
CA2098KX	Part D	36	N/A
	Part E	36	N/A

Table 35: Applicant - Duration of Study Therapy - All Treated Subjects in CA20967T

	Nivo SC N = 247	Nivo IV N = 245
DURATION OF THERAPY (MONTHS)		
MEAN (MIN, MAX)	7.31 (0.0, 22.4)	8.23 (0.0, 24.0)
MEDIAN	6.60	7.69
> 3 MONTHS (%)	176 (71.3)	190 (77.6)
> 6 MONTHS (%)	129 (52.2)	144 (58.8)
> 9 MONTHS (%)	85 (34.4)	105 (42.9)
> 12 MONTHS (%)	49 (19.8)	57 (23.3)

Datasets: ADSL, ADEXS

Table 36: Applicant - Duration of Study Therapy - All Treated Subjects in Parts D and E in CA2098KX

	PART D - GRP 5 N = 36	PART E - GRP 6 N = 36
DURATION OF THERAPY (MONTHS)		
MEAN (SD)	8.08 (8.160)	4.93 (3.111)
MEDIAN (MIN, MAX)	4.63 (0.0, 24.0)	4.60 (0.5, 10.2)
> 3 MONTHS (%)	23 (63.9)	23 (63.9)
> 6 MONTHS (%)	14 (38.9)	15 (41.7)
> 9 MONTHS (%)	11 (30.6)	4 (11.1)
> 12 MONTHS (%)	9 (25.0)	0

Datasets: ADSL, ADEXS

Table 37: Applicant - Cumulative Dose and Relative Dose Intensity, All Treated Subjects in CA20967T

BLA Multi-disciplinary Review and Evaluation {BLA 761381 and BLA 761429}
OPDIVO (nivolumab and hyaluronidase - nvhy) injection, for subcutaneous use

	Nivo SC N = 247	Nivo IV N = 245
NUMBER OF DOSES RECEIVED		
MEAN (SD)	8.6 (5.8)	17.7 (12.1)
MEDIAN (MIN - MAX)	8.0 (1 - 25)	17.0 (1 - 52)
CUMULATIVE DOSE (MG)		
MEAN (SD)	10338.462 (6990.640)	
MEDIAN (MIN - MAX)	9600.000 (1200.00 - 30000.00)	
CUMULATIVE DOSE (MG/KG)		
MEAN (SD)		53.191 (36.174)
MEDIAN (MIN - MAX)		50.681 (3.00 - 156.41)
RELATIVE DOSE INTENSITY (%)		
>= 110%	0	0
90% TO < 110%	223 (90.3)	194 (79.2)
70% TO < 90%	19 (7.7)	44 (18.0)
50% TO < 70%	4 (1.6)	7 (2.9)
< 50%	1 (0.4)	0

Datasets: ADSL, ADEXS

Table 38: Applicant - Cumulative Dose and Relative Dose Intensity, All Treated Subjects in Parts D and E in CA2098KX

	PART D N = 36	PART E N = 36
NUMBER OF DOSES RECEIVED (NIVOLUMAB SC)		
MEAN (SD)	9.6 (8.7)	11.0 (6.2)
MEDIAN (MIN - MAX)	6.0 (1 - 26)	10.5 (2 - 23)
CUMULATIVE DOSE FOR NIVOLUMAB SC DOSE (MG)		
MEAN (SD)	11466.7 (10415.8)	6616.7 (3722.2)
MEDIAN (MIN - MAX)	7200.0 (1200 - 31200)	6300.0 (1200 - 13800)
RELATIVE DOSE INTENSITY FOR NIVOLUMAB SC (%)		
>= 110%	0	0
>= 90% - < 110%	35 (97.2)	32 (88.9)
>= 70% - < 90%	0	4 (11.1)
>= 50% - < 70%	1 (2.8)	0
< 50%	0	0
DURATION OF SC INJECTION (MIN)		
N*	341	392
MEAN (SD)	4.7 (1.3)	4.5 (0.9)
MEDIAN (MIN - MAX)	5.0 (3 - 14)	5.0 (1 - 11)

Datasets: ADSL, ADEXS

The Applicant's Position:

The overall exposure to nivolumab SC in studies CA20967T and CA2098KX is considered adequate to support characterization of the safety profile in the intended patient population (Table 35 and Table 36). Nivolumab SC was well tolerated, with a majority of treated subjects receiving 90% to < 110% of the planned dose intensity (Table 37 and Table 38).

The FDA's Assessment:

FDA agrees that the overall exposure to nivolumab SC in studies CA20967T and CA2098KX is adequate to support characterization of the safety profile in the intended patient population. Relative dose-intensity in Study CA20967T was higher in the SC arm relative to the IV arm. A total of 223 (90.3%) and 194 (79.2%) patients in the nivolumab SC

arm and the nivolumab IV arm, respectively, received at least 90% of the planned dose intensity.

Relevant characteristics of the safety population:

The Applicant's Position:

See Table **26** and Table **32**.

The FDA's Assessment:

There were 1 of 248 (0.4%) patients randomized to the SC arm and 2 of 247 (0.8%) patients randomized to the IV arm who withdrew consent prior to initiation of study treatment. In Study CA20967T, there was a lower proportion of patients with a favorable IMDC risk classification in the nivolumab SC arm relative to the nivolumab IV arm (19.4% vs 23.1%). There was a greater proportion of patients in the nivolumab SC arm that had received 2 prior lines of therapy (10.9% vs 5.3%). There was also a slightly higher proportion of patients diagnosed with clear cell RCC with sarcomatoid features in the nivolumab SC arm relative to the nivolumab IV arm (6.0% vs. 2.4%). These imbalances between the treatment arms are not particularly concerning since these factors would have been expected to favor the control arm (nivolumab IV) and not the investigational therapy (nivolumab SC).

There was only minimal representation of underrepresented minorities on both Study CA20967T and Study CA2098KX, with the exception of the Hispanic or Latino population which was represented on Study CA20967T. On Study CA20967T, a total of 93 (38%) and 84 (34%) patients on the nivolumab SC and nivolumab IV arms, respectively, identified as Hispanic or Latino.

Adequacy of the safety database:

The Applicant's Position:

The size of the CA20967T safety database and duration of follow-up are considered adequate to provide a reasonable estimate of adverse reactions that may occur with nivolumab SC co-formulated with rHuPH20. Additionally, there are safety data from supportive Phase 1/2 study, CA2098KX, across doses, regimens and malignancies. Safety data from CA20967T and CA2098KX were consistent with the known safety profile of nivolumab IV; there were no new safety findings or safety signals (Table 39 and Table 50).

Together, data from CA20967T with supportive data from CA2098KX allows a thorough assessment of the safety profile of nivolumab SC co-formulated with rHuPH20 in the intended patient population. Characterization of common AEs and SAEs, and informing labeling and risk management strategies was based on CA20967T.

The FDA's Assessment:

FDA agrees that the safety database supporting the application is adequate in size with sufficient duration of treatment with the investigational regimen at the proposed dose for a thorough assessment of adverse events. Notably, by nature of the study design, there was more frequent (2x) safety monitoring in the IV arm with physical exam/labs every 2 weeks

relative to the SC arm with physical exam/labs every 4 weeks. This differential monitoring of safety does not preclude an assessment of the safety of SC nivolumab, but it should be taken into consideration when making any comparisons regarding the tolerability of the respective formulations.

8.2.3. Adequacy of Applicant's Clinical Safety Assessments

Issues Regarding Data Integrity and Submission Quality

The Applicant's Position:

See Section 0 and Section 8.1.4. The quality of data collected and analyzed was monitored according to BMS standard operating procedures. No issues with data quality and integrity have been identified.

The FDA's Assessment:

The submission contained all required components for summaries and raw data. The overall quality and integrity of the application was adequate for a comprehensive safety review to be completed. The review did not uncover any data integrity issues related to safety.

Categorization of Adverse Event

The Applicant's Position:

AEs were categorized by SOC and PT using MedDRA; version 26.0 in CA20967T and version 25.1 in CA2098KX. AEs were categorized by severity grade using NCI CTCAE version 5.0 for both CA20967T and CA2098KX.

The FDA's Assessment:

FDA agrees with the Applicant's description of the methods used for coding, categorizing, and grading AEs and the procedures for interrogating the safety data for pre-specified IMAE. FDA described the assessment and agreed with the definition and categorization of AEs, IMAEs and OESIs in Section 8.2.1.

Routine Clinical Tests

The Applicant's Position:

Standard laboratory tests (eg, liver, hepatic, renal, thyroid, metabolic) and pregnancy tests were conducted at screening as well as visits during treatment and follow-up. Laboratory tests were graded using the NCI CTCAE, version 5.0.

The FDA's Assessment:

FDA reviewed the study protocol for the routine clinical and laboratory assessments obtained during Study CA20967T. The safety monitoring employed during Study CA20967T is adequate and consistent with the safety monitoring of patients receiving standard of care immune checkpoint inhibitor therapy for advanced or metastatic ccRCC. A targeted physical examination with measurement of vital signs, performance status, and assessment of signs and symptoms was performed at each visit for treatment administration. AE's were assessed continuously using NCI CTCAE v5 and recorded at each visit with patients followed for at least 100 days after discontinuation of study

treatment. Clinical laboratory assessments were performed on site or with local laboratory testing within 72 hours prior to each dose.

Notably, on Arm A treatment (nivolumab SC) was administered every 28 days and on Arm B IV treatment (nivolumab IV) was administered every 14 days. Based upon the fact that targeted physical exams and clinical laboratory assessments occurred twice as frequently on the nivolumab IV arm relative to the nivolumab SC arm, it is plausible that this could have led to the identification of more AEs on the nivolumab IV arm if there is a relation between more frequent AE assessment and identification of adverse events. While FDA is able to adequately assess the safety of the SC formulation of nivolumab, due to this imbalance in safety assessments across arms, one should exercise caution when making comparisons regarding the safety of one formulation relative to the other.

8.2.4. Safety Results from Pivotal Study CA20967T

Table 39: Applicant - Summary of Safety - All Treated Subjects in CA20967T

Safety Parameters	Number of Subjects (%)			
	Nivo SC (N = 247)	Nivo IV (N = 245)		
Deaths (Any Time)	73 (29.6)	60 (24.5)		
Primary Reason for Death				
Disease	53 (21.5)	48 (19.6)		
Study Drug Toxicity	3 (1.2)	1 (0.4)		
Cardiovascular disease	4 (1.6)	3 (1.2)		
Unknown	1 (0.4)	3 (1.2)		
Other ^a	12 (4.9)	5 (2.0)		
Deaths within 30 days of last dose	15 (6.1)	9 (3.7)		
Primary Reason for Death				
Disease	7 (2.8)	7 (2.9)		
Cardiovascular Disease	3 (1.2)	1 (0.4)		
Other	5 (2.0)	1 (0.4)		
Deaths within 100 days of last dose	47 (19.0)	35 (14.3)		
Primary Reason for Death				
Disease	31 (12.6)	27 (11.0)		
Study Drug Toxicity	2 (0.8)	1 (0.4)		
Cardiovascular Disease	3 (1.2)	2 (0.8)		
Unknown	1 (0.4)	0		
Other	10 (4.0)	5 (2.0)		
	Any Grade	Grade 3-4	Any Grade	Grade 3-4
All-causality SAEs	69 (27.9)	52 (21.1)	71 (29.0)	56 (22.9)
≥ 1% of Subjects in Any Treatment Arm, by PT				
Malignant neoplasm progression	7 (2.8)	3 (1.2)	7 (2.9)	1 (0.4)
Pleural effusion	4 (1.6)	4 (1.6)	1 (0.4)	1 (0.4)
Pneumonitis	4 (1.6)	4 (1.6)	1 (0.4)	1 (0.4)
Hyperglycaemia	3 (1.2)	3 (1.2)	1 (0.4)	1 (0.4)
Hyperkalaemia	3 (1.2)	3 (1.2)	0	0
Hyponatraemia	0	0	3 (1.2)	3 (1.2)
Diarrhoea	3 (1.2)	1 (0.4)	1 (0.4)	1 (0.4)
Urinary tract infection	1 (0.4)	1 (0.4)	3 (1.2)	3 (1.2)
Spinal cord compression	1 (0.4)	1 (0.4)	3 (1.2)	3 (1.2)

Table 39: Applicant - Summary of Safety - All Treated Subjects in CA20967T

Safety Parameters	Number of Subjects (%)			
	Nivo SC (N = 247)		Nivo IV (N = 245)	
Anaemia	2 (0.8)	2 (0.8)	4 (1.6)	3 (1.2)
Femur fracture	0	0	4 (1.6)	3 (1.2)
Pulmonary embolism	0	0	4 (1.6)	3 (1.2)
Drug-related SAEs	17 (6.9)	16 (6.5)	17 (6.9)	16 (6.5)
≥ 1% of Subjects in Any Treatment Arm, by PT				
Pneumonitis	4 (1.6)	4 (1.6)	1 (0.4)	1 (0.4)
All-causality AEs leading to DC	25 (10.1)	18 (7.3)	29 (11.8)	21 (8.6)
≥ 1% of Subjects in Any Treatment Arm, by PT				
Pneumonitis	5 (2.0)	1 (0.4)	1 (0.4)	0
Drug-related AEs leading to DC	10 (4.0)	6 (2.4)	12 (4.9)	9 (3.7)
≥ 2% of Subjects in Any Treatment Arm, by PT				
Pneumonitis	5 (2.0)	1 (0.4)	1 (0.4)	0
All-causality AEs	230 (93.1)	87 (35.2)	229 (93.5)	100 (40.8)
≥ 10% of Subjects in Any Treatment Arm, by PT				
Diarrhoea	24 (9.7)	1 (0.4)	33 (13.5)	1 (0.4)
Asthenia	32 (13.0)	4 (1.6)	23 (9.4)	3 (1.2)
Hyperglycaemia	23 (9.3)	6 (2.4)	32 (13.1)	5 (2.0)
Decreased appetite	22 (8.9)	0	28 (11.4)	2 (0.8)
Arthralgia	29 (11.7)	1 (0.4)	39 (15.9)	1 (0.4)
Back pain	19 (7.7)	2 (0.8)	27 (11.0)	4 (1.6)
COVID-19	20 (8.1)	0	29 (11.8)	2 (0.8)
Pruritus	40 (16.2)	1 (0.4)	52 (21.2)	0
Blood creatinine increased	27 (10.9)	1 (0.4)	40 (16.3)	0
Anaemia	54 (21.9)	14 (5.7)	63 (25.7)	21 (8.6)
Cough	27 (10.9)	0	28 (11.4)	0
Hypothyroidism	24 (9.7)	0	30 (12.2)	0
Fatigue	19 (7.7)	2 (0.8)	39 (15.9)	5 (2.0)
Drug-related AEs	146 (59.1)	24 (9.7)	158 (64.5)	36 (14.7)
≥ 5% Drug-related AEs in Any Treatment				
Pruritus	37 (15.0)	1 (0.4)	48 (19.6)	0
Hypothyroidism	22 (8.9)	0	24 (9.8)	0
Rash	16 (6.5)	1 (0.4)	18 (7.3)	2 (0.8)
Asthenia	14 (5.7)	1 (0.4)	9 (3.7)	2 (0.8)
Diarrhea	13 (5.3)	0	12 (4.9)	1 (0.4)
Fatigue	10 (4.0)	0	27 (11.0)	2 (0.8)
Arthralgia	10 (4.0)	0	22 (9.0)	1 (0.4)
Anaemia	6 (2.4)	1 (0.4)	13 (5.3)	3 (1.2)
Blood thyroid stimulating hormone increased	6 (2.4)	0	13 (5.3)	0
All-causality Select AEs by Category				
Skin	64 (25.9)	4 (1.6)	74 (30.2)	3 (1.2)
Endocrine	40 (16.2)	6 (2.4)	52 (21.2)	3 (1.2)
Gastrointestinal	26 (10.5)	1 (0.4)	34 (13.9)	1 (0.4)
Hepatic	40 (16.2)	11 (4.5)	50 (20.4)	12 (4.9)
Renal	29 (11.7)	4 (1.6)	44 (18.0)	1 (0.4)
Pulmonary	13 (5.3)	4 (1.6)	9 (3.7)	3 (1.2)
Hypersensitivity/Infusion Reactions	3 (1.2)	1 (0.4)	9 (3.7)	0
Drug-related Select AEs by Category				
Skin	57 (23.1)	4 (1.6)	65 (26.5)	3 (1.2)
Endocrine	31 (12.6)	2 (0.8)	44 (18.0)	3 (1.2)

Table 39: Applicant - Summary of Safety - All Treated Subjects in CA20967T

Safety Parameters	Number of Subjects (%)			
	Nivo SC (N = 247)		Nivo IV (N = 245)	
Gastrointestinal	15 (6.1)	0	13 (5.3)	1 (0.4)
Hepatic	20 (8.1)	5 (2.0)	27 (11.0)	9 (3.7)
Pulmonary	13 (5.3)	4 (1.6)	8 (3.3)	2 (0.8)
Renal	7 (2.8)	0	12 (4.9)	0
Hypersensitivity/Infusion Reactions	1 (0.4)	1 (0.4)	6 (2.4)	0
Drug-related Local Site Reactions within 100 Days of Last Dose^b	17 (6.9)		5 (2.0)	
≥ 2 subjects AEs in Any Treatment				
Injection site erythema	5 (2.0)	0	0	0
Application site pain	2 (0.8)	0	0	0
Injection site edema	2 (0.8)	0	0	0
Infusion related reaction	0	0	5 (2.0)	0
AEs in the Broad SMQ of Anaphylactic Reactions within 100 days of last dose	90 (36.4)		106 (43.3)	
≥ 5% AEs in Any Treatment				
Pruritus	41 (16.6)	1 (0.4)	52 (21.2)	0
Cough	27 (10.9)	0	29 (11.8)	0
Rash	20 (8.1)	1 (0.4)	20 (8.2)	2 (0.8)
Dyspnoea	11 (4.5)	5 (2.0)	18 (7.3)	1 (0.4)
All-causality Non-endocrine IMAEs within 100 days of last dose where Immune Modulating Medication was Initiated by Category				
Rash	17 (6.9)	2 (0.8)	12 (4.9)	3 (1.2)
Diarrhea/Colitis	7 (2.8)	1 (0.4)	5 (2.0)	0
Hepatitis	6 (2.4)	4 (1.6)	14 (5.7)	9 (3.7)
Pneumonitis	7 (2.8)	2 (0.8)	7 (2.9)	2 (0.8)
Nephritis and Renal Dysfunction	3 (1.2)	0	2 (0.8)	0
Hypersensitivity	1 (0.4)	0	2 (0.8)	0
All-causality Endocrine IMAEs within 100 days of last dose by Category				
Hypothyroidism/Thyroiditis	24 (9.7)	0	25 (10.2)	0
Hyperthyroidism	2 (0.8)	0	11 (4.5)	0
Adrenal Insufficiency	5 (2.0)	2 (0.8)	2 (0.8)	0
Diabetes Mellitus	1 (0.4)	1 (0.4)	1 (0.4)	1 (0.4)
Hypophysitis	0	0	3 (1.2)	2 (0.8)
All-causality OESIs within 100 days of last dose by Category				
Myositis/Rhabdomyolysis	0	0	2 (0.8)	2 (0.8)
Uveitis	1 (0.4)	1 (0.4)	0	0
Myocarditis	1 (0.4)	1 (0.4)	0	0
Pancreatitis	1 (0.4)	1 (0.4)	1 (0.4)	0

MedDRA Version 26.0. CTC Version 5.0.

Note: Includes events reported between first dose and 30 days after last dose of study therapy except otherwise indicated.

a Other reasons for death (any time):

- Nivo SC: hip fracture related complications, suicide, diabetic ketoacidosis, shortness of breath, acute respiratory failure, left lung base pneumonia, multi-organ failure, COVID-related pneumonia, intraparenchymal hemorrhage, delirium, acute respiratory insufficiency, hyperkalemia

- Nivo IV: perforation of thin intestinal, acute diverticulitis, upper GI bleeding, kidney failure, multi-organ failure

b Local injection- or infusion-site reactions AEs include PTs under SOC of "General disorders and administration site conditions" which contain the words of "Administration site", "Injection site", "Puncture site", "Infusion site", and PTs under SOC of "Injury, poisoning and procedural complications" which contains

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the words "Injection related reaction" or "Infusion related reaction." For CA20967T, PTs containing the word "Application site" have also been included since the events were reported in reference to local injection reactions.

Datasets: ADSL, ADAE, ADAEIMM, ADAEQ

Deaths

Data: Refer to Table 39.

The Applicant's Position:

The majority of deaths in both treatment arms were reported as due to progressive disease. Deaths attributed to study drug toxicity by the investigator were reported in 3 subjects in the nivolumab SC arm (myocarditis, myasthenia, colitis complications) and 1 subject in the nivolumab IV arm (immune-mediated pneumonitis and pneumocystis jirovecii bronchopneumonia, and disease progression). Deaths reported as due to cardiovascular disease occurred in 4 subjects in the nivolumab SC arm and 3 subjects in the nivolumab IV arm; all were assessed as not related to study drug. The increased incidence of deaths in the nivolumab SC arm was largely driven by deaths in the 'other' category, which were all considered not related to the study drug per investigator, but to underlying disease conditions and/or comorbidities.

The FDA's Assessment:

There was a total of 24 (10%) and 14 (6%) patients on the SC and IV arms, respectively, who had fatal adverse events within 100 days of treatment discontinuation (Table 40). FDA reviewed all these narratives and there was a clear immune-related etiology in 3 (1.2%) cases on the SC arm and 1 (0.4%) case on the IV arm. This included single events of colitis, immune-mediated lung disease/pneumonia (PJP), and myositis on the SC arm; and an event of myocarditis on the IV arm. In a total of 9 (3.6%) and 5 (2.0%) of cases on the SC and IV arms, respectively, the fatal event was likely due progressive disease. Among the remaining events, there was no clear pattern, and most of the events were among those commonly observed in patients with cancer. The narratives for deaths other than malignant neoplasm are summarized below in Table 41.

Table 40: Summary of Grade 5 TEAEs (Excluding Malignant Neoplasm)

	Nivolumab with Hyaluronidase (SC) N=247; n (%)	Nivolumab (IV) N=245; n (%)
Fatal AEs within 100 Days (Excluding Malignant Neoplasm)	24 (10)	14 (6)
Fatal AEs with Immune-Mediated Etiology		
Colitis	1 (0.4)	0
Immune-Mediated Lung Disease/Pneumonia (PJP)	0	1 (0.4)
Myositis	1 (0.4)	0
Myocarditis	1 (0.4)	0
Other Fatal AEs		
Acute Respiratory Failure	1 (0.4)	0

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Cancer Pain	0	1 (0.4)
Cardiac Arrest/Cardio-respiratory Arrest/Myocardial Infarction	3 (1.2)	2 (0.8)
Cardiovascular Insufficiency	1 (0.4)	0
Completed Suicide	1 (0.4)	0
Covid-19 Pneumonia	1 (0.4)	0
Delirium/Aspiration Pneumonia	1 (0.4)	0
Diabetic Ketoacidosis	1 (0.4)	0
Diarrhea	1 (0.4)	0
Diverticulitis	0	1 (0.4)
Dyspnea	1 (0.4)	0
Embolism	0	1 (0.4)
Hyperkalemia	1 (0.4)	0
Intestinal Perforation	0	1 (0.4)
Multiple Organ Dysfunction Syndrome	2 (0.8)	2 (0.8)
Pleural Effusion	2 (0.8)	0
Pneumonia	1 (0.4)	0
Renal Failure	0	1 (0.4)
Respiratory Failure/Respiratory Disorder	3(1.2)	3 (1.2)
Unknown	1 (0.4)	0
Upper Gastrointestinal Hemorrhage	0	1 (0.4)

Table 41: Narratives for deaths excluding malignant neoplasm

Subject ID	Sex/Age	Treatment (SC vs. IV)	Preferred Term of AE	FDA Reviewer Comment	Days After Last Dose
(b) (6)	M/82	SC	Colitis	On Day 45, the subject was diagnosed with Grade 4 colitis. On Day 47, CT scan confirmed the presence of colonic perforation. On Day 57, the subject died due to colitis. <i>Reviewer Comment: Due to the timing and nature of this event it is likely that this event may be treatment related.</i>	56

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(b) (6)	M/73	SC	Myositis	On Day 41, the subject was hospitalized with Grade 3 muscular weakness that included both myasthenia and generalized myositis as well as symptomatic atrioventricular block. He continued to experience palpable ptosis with fatigability and ophthalmoparesis. On Day 59, the subject died due to myopathy and respiratory failure. <i>Reviewer Comment: Due to the timing and nature of this event it is likely that this event may be treatment related.</i>	32
(b) (6)	M/74	SC	Myocarditis	On Day 77 ((b) (6)), the subject was hospitalized due to Grade 4 myocarditis. On Day 86, the study therapy was discontinued due to myocarditis with the last dose of nivolumab and rHuPH20 received on Day 59. On Day 191, the subject's condition continued to deteriorate and died due to myocarditis. <i>Reviewer Comment: Due to the timing and nature of this event it is likely that this event may be treatment related.</i>	132

Death occurred outside of the protocol-defined 90-day safety follow-up window, but the AE began prior the end of that window

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(b) (6)	M/75	SC	Sudden Death	Sudden death, stated as due to cardiovascular disease, occurred 18 days after the 1st nivolumab (SC) dose. <i>Reviewer Comment: It is likely that this event was not treatment related, but details of this case were not sufficient to rule out any treatment related cause.</i>	18
(b) (6)	M/81	SC	Acute Myocardial Infarction	On Day 124 ((b) (6)), 23 days after the 3rd nivolumab dose (SC), the subject died due to acute myocardial infarction.	23
(b) (6)	M/69	SC	Cardio-respiratory Arrest	On Day 56, the subject died of cardio-respiratory arrest.	27
(b) (6)	F/71	SC	Cardio-respiratory Arrest	Deteriorating condition. On Day 578, 87 days after the 18th nivolumab (SC) dose, the subject died due to cardio-respiratory arrest. <i>Reviewer Comment: With the deteriorating condition of the patient, this is plausibly due to disease progression, but minimal details provided.</i>	87
(b) (6)	M/85	SC	Covid-19 Pneumonia	On Day 68, the subject died due to COVID-19 pneumonia.	38
(b) (6)	M/80	SC	Delirium/Aspiration Pneumonia	Patient died due to aspiration pneumonia exacerbated by his altered mental status.	29
(b) (6)	F/47	SC	Diabetic Ketoacidosis	On Day 31, the study therapy was discontinued due to diabetic ketoacidosis, with last dose of nivolumab. On the same day (Day 31), the subject died due to diabetic ketoacidosis	30

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(b) (6)	M/56	SC	Hyperkalemia	On Day 161, the subject died from a cardiac event preceded and plausibly caused by hyperkalemia. As per death certificate, the direct cause of death was severe hyperkalemia.	34
(b) (6)	F/77	SC	Pneumonia	On Day 326, the subject was diagnosed with pneumonia and secondary septic shock. On Day 326, the subject died due to pneumonia and septic shock.	67
(b) (6)	F/55	SC	Respiratory Failure	Lung metastases present at baseline. On Day 15, the subject was diagnosed with Grade 4 toxicity to various agents (opiate intoxication) with positive naloxone test. On Day 17, the subject died due to respiratory failure.	16
(b) (6)	M/85	SC	Respiratory Failure	On Day 72, the subject died due to respiratory failure and cardiac arrest secondary to disease progression. <i>Reviewer Comment: The cause of respiratory failure is likely related to disease progression, but not enough detail is provided to rule out any drug-related causes.</i>	17

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(b) (6)	F/42	SC	Acute Respiratory Failure	There was an increase in the number and size of nodules and pulmonary masses on both sides. On Day 170, 84 days after the 2nd (last) nivolumab (SC) dose, the subject had acute respiratory failure. The subject experienced a gradual deterioration in symptoms over the course of several days, with the emergence of sputum in blood. <i>Reviewer Comment: Likely due to disease progression.</i>	84
(b) (6)	F/70	SC	Cardiovascular Insufficiency	Patient declining with widely metastatic disease. On Day 265, 49 days after the last dose of nivolumab SC, the subject died due to cardiovascular insufficiency with the narrative stating that death was due to disease progression. <i>Reviewer Comment: Likely due to disease progression.</i>	49
(b) (6)	M/57	SC	Diarrhea	Stated cause of death was disease progression.	59

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(b) (6)	F/66	SC	Dyspnea	At baseline, disease was present in the mediastinum, lung, kidney, and lymph node. Subject hospitalized due to dyspnea (Grade 3). CT of chest ruled out pneumonitis and the breathing difficulty was assessed as related to oncologic diagnosis. Condition declined with findings of disease progression. The stated cause of death was dyspnea caused by generalized illness. <i>Reviewer Comment: Likely due to disease progression.</i>	28
(b) (6)	M/51	SC	Multiple Organ Dysfunction Syndrome	Patient declining clinically at Day 126. On day 158, 46 days after the last dose of nivolumab, the patient passed with the stated cause of death as multiple organ dysfunction syndrome due to disease progression. <i>Reviewer Comment: Likely due to disease progression.</i>	46
(b) (6)	M/65	SC	Multiple Organ Dysfunction Syndrome	At baseline the disease was present at lung, pleura, chest wall, soft tissue, liver, kidney and adrenal gland. The subject developed sustained and irreversible clinical decline from Day 22. On Day 34, 33 days after the last dose of nivolumab SC, the subject died at home due to multiple organ dysfunction assessed as unrelated to study therapy. <i>Reviewer Comment: Likely due to disease progression.</i>	33

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(b) (6)	M/78	SC	Pleural Effusion	On Day 253, the subject died of disease progression, 78 days, after last dose of nivolumab infusion. <i>Reviewer Comment: Likely due to disease progression.</i>	78
(b) (6)	F/64	SC	Pleural Effusion	On Day 61, 32 days after 2nd nivolumab (SC) dose, the subject died due to pleural effusion caused by disease progression. <i>Reviewer Comment: Likely due to disease progression.</i>	32
(b) (6)	M/62	SC	Respiratory Failure	On Day 78, 41 days after the last nivolumab (SC) administration, the subject was hospitalized with Grade 4 respiratory failure secondary to progression of renal carcinoma. On Day 83, the subject died of acute respiratory insufficiency secondary to disease progression. <i>Reviewer Comment: Likely due to disease progression.</i>	52
(b) (6)	M/40	SC	Completed Suicide	At study baseline, disease was present in the mediastinum, lung, adrenal gland, liver, lymph node and peritoneum. The subject had ongoing events of abdominal pain and peripheral edema. On Day 100, 13 days after the 4th nivolumab (SC) dose, the subject completed suicide.	13

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(b) (6)	M/61	IV	Pneumocystis Jirovecii Pneumonia/ Immune-mediated Lung Disease	On Day 200, 37 days after the last dose of nivolumab IV, the subject died due to Pneumocystis jirovecii pneumonia, immune mediated pneumonitis and disease progression.	37
(b) (6)	F/74	IV	Cardiac Arrest	On Day 17, 2 days after the 2nd nivolumab IV dose, the subject was hospitalized due to Grade 4 cardiac arrest and passed the following day (Day 18). It was unknown if an autopsy was performed.	3
(b) (6)	M/74	IV	Cardio-respiratory Arrest/Acute Respiratory Failure	On Day 146, 19 days after the last nivolumab IV dose, the subject developed worsening of condition due to Grade 3 serious acute respiratory failure in the context of increased paraneoplastic left pleural effusion. The subject's general condition declined and on Day 163, 36 days after the 10th nivolumab IV dose, the subject died with cause of death stated as cardiorespiratory arrest and acute respiratory failure.	36
(b) (6)	F/81	IV	Multiorgan Failure/Hypovolemic Shock Secondary to Diverticulitis	On Day 284, CT scan showed evidence of acute diverticulitis complicated by abscess. On Day 299, the subject experienced poor general condition, shallow respiration, and the subject died due to multiple organ failure and hypovolemic shock secondary to diverticulosis.	39

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 OPDIVO (nivolumab and hyaluronidase - nvhy) injection, for subcutaneous use

(b) (6)	M/42	IV	Embolism	On Day 9, the subject was diagnosed with Grade 2 embolism that worsened to Grade 3 on Day 21. On Day 53, 38 days after the 2nd nivolumab IV dose the subject continued with embolism and also had an intracavitary thrombus in the right atrium. He had sudden death due to seizure (probably related to disease progression/ stroke) and embolism.	38
(b) (6)	M/71	IV	Intestinal Perforation	On Day 111, 25 days after the 5th nivolumab IV dose, the subject was hospitalized with Grade 3 intestinal perforation associated with abdominal pain. On Day 126, 40 days after the 5th nivolumab IV infusion, the event of intestinal perforation worsened and the subject passed. <i>Reviewer Comment: Based upon the details provided this event does not appear to be from an immune-mediated etiology and the investigator assessed this event as unrelated to nivolumab IV.</i>	40

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 OPDIVO (nivolumab and hyaluronidase - nvhy) injection, for subcutaneous use

(b) (6)	M/77	IV	Multiple Organ Dysfunction Syndrome	On Day 211, 45 days after the 12th nivolumab (IV) dose, the subject was diagnosed with multiple organ dysfunction syndrome and passed. It is unknown if an autopsy was performed. <i>Reviewer Comment: The event was assessed by the investigator as unrelated to nivolumab IV, but there was insufficient information to assess attribution.</i>	45
(b) (6)	M/69	IV	Renal Failure	On Day 225 ((b) (6)), 35 days after the 13th nivolumab (IV) dose (last), the subject was hospitalized with Grade 4 acute kidney injury (not related) associated with pain. CT scan showed the presence of retro-tumoral hematoma. On Day 239, 49 days after the 13th nivolumab (IV) dose (last), the subject died due to renal failure. <i>Reviewer Comment: This event is plausibly due to the underlying disease.</i>	49
(b) (6)	M/73	IV	Respiratory Disorder	On Day 36 ((b) (6)), 7 days after the 3rd nivolumab (IV) infusion, the subject was diagnosed with Grade 4, respiratory disorder associated with dyspnea. The subject's clinical findings revealed disease progression. On Day 46, 17 days after the 3rd nivolumab IV infusion, the subject died due to disease progression and respiratory dysfunction.	17

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OPDIVO (nivolumab and hyaluronidase - nvhy) injection, for subcutaneous use

(b) (6)	M/51	IV	Cancer Pain/Disease Progression	On Day 144, 86 days after the 5th nivolumab (IV) dose, the subject experienced Grade 3 cancer pain. On Day 160, the subject died due to disease progression and cancer pain. <i>Reviewer Comment: Likely due to disease progression.</i>	102
(b) (6)	M/60	IV	Multiple Organ Dysfunction Syndrome	On Day 100, 85 days after the 2nd nivolumab IV dose, the subject died of multiple organ dysfunction syndrome secondary to disease progression. <i>Reviewer Comment: Likely due to disease progression.</i>	85
(b) (6)	M/79	IV	Respiratory Failure	On Day 116, 31 days after the 7th nivolumab IV dose, the subject died due to serious respiratory failure secondary to progression of the underlying disease. <i>Reviewer Comment: Likely due to disease progression.</i>	31
(b) (6)	M/58	IV	Respiratory Failure	On Day 150, 58 days after the 7th nivolumab infusion, the subject was hospitalized and subsequently died due to respiratory failure secondary to disease progression. <i>Reviewer Comment: Likely due to disease progression.</i>	58

(b) (6)	M/57	IV	Upper Gastrointestinal Hemorrhage	On Day 95, 14 days after the 6th nivolumab (IV) dose, the subject was hospitalized with Grade 4 upper gastrointestinal hemorrhage, due to duodenal infiltration of kidney tumor. On Day 223, the subject died due to upper gastrointestinal hemorrhage and anemia. The subject also had back pain, and oedema peripheral at the time of death. <i>Reviewer Comment: Likely due to disease progression.</i>	26
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Serious Adverse Events

Data: Refer to Table 39.

The Applicant's Position:

Among all treated subjects, the overall frequencies of all-causality and drug-related SAEs (any grade and Grade 3-4) within 30 days of last dose were comparable between the nivolumab SC and nivolumab IV treatment arms.

The FDA's Assessment:

FDA agrees with the Applicant's assessment. A similar frequency of any grade SAEs within 30 days of the last dose was observed in both the SC and IV treatment arms. The most common SAEs (>1%) on the SC arm (excluding malignant neoplasm progression) included pleural effusion (1.6%), pneumonitis (1.6%), hyperglycemia (1.2%), hypercalcemia (1.2%), hemorrhage (1.2%), and diarrhea (1.2%).

Dropouts and/or Discontinuations Due to Adverse Effects

Data: Refer to Table 39.

The Applicant's Position:

The overall frequencies of all causality and drug-related AEs leading to discontinuation (any grade and Grade 3-4) within 30 days of last dose were comparable between the nivolumab SC and nivolumab IV treatment arms.

The FDA's Assessment:

FDA agrees with the Applicant's assessment. FDA analysis of the safety dataset for Study CA20967T identified 25 (10%) patients in the SC arm and 29 (12%) patients in the IV arm who experienced AEs (within 30 days of the last dose) that resulted in treatment

discontinuation. The most frequently reported AEs (>0.5%) leading to treatment discontinuation (excluding malignant neoplasm progression) in the SC arm were pneumonitis (2.0%), dyspnea (0.8%), fatigue (0.8%), and muscular weakness (0.8%) in the SC arm. The most frequently reported AEs (>0.5%) leading to treatment discontinuation in the IV arm were pneumonitis (0.8%), fatigue (0.8%), aspartate aminotransferase increased (0.8%), myositis (0.8%), and spinal cord compression (0.8%).

Dose Interruption/Reduction Due to Adverse Effects

Data: Dose reductions were not permitted in CA20967T.

Most subjects received all doses of study medications without an infusion/injection interruption or dose delay. The number of subjects with at least one dose delay due to an AE (all causality) was less in the nivolumab SC arm (85 subjects, 34.4%) than the nivolumab IV arm (116 subjects, 47.3%); most frequently due to:

- Nivolumab SC: COVID-19 (4.5%), blood creatinine increased (2.8%), anemia (2.4%), and hyperglycemia, diarrhea, and pneumonitis (2.0% each).
- Nivolumab IV: COVID-19 (9.4%), anemia (4.5%), ALT increased, and AST increased (2.9%, each), diarrhea, hyperglycemia, asthenia, and fatigue (2.4%, each), and pneumonitis and rash (2.0%, each).

The number of subjects with at least one dose delay due to an AE (drug-related) was less in the nivolumab SC arm (36 subjects, 14.6%) than the nivolumab IV arm (62 subjects, 25.3%), most frequently due to:

- Nivolumab SC: pneumonitis (2.0%), blood creatinine increased and diarrhea (1.6%, each), and anemia (1.2%).
- Nivolumab IV: ALT increased (2.4%), AST increased, pneumonitis, fatigue, and rash (2.0% each), blood creatinine increased, and hyperglycemia (1.6%, each), diarrhea, hypothyroidism, and anemia (1.2%, each).

The Applicant's Position:

Frequencies of all causality and drug-related AEs leading to dose delay (any grade and Grade 3-4) within 30 days of last dose were comparable between treatment arms.

The FDA's Assessment:

FDA generally agrees with the Applicant's assessment. The most common (>1%) AEs leading to dose interruption are included in Table 42. As stated by the Applicant, the number of patients with at least one dose delay due to an AE was less in the nivolumab SC arm relative to the nivolumab IV arm. Adverse events leading to dose interruptions occurred in 85 patients (34%) in the nivolumab SC arm and 116 patients (47%) in the nivolumab IV arm. It is plausible that this difference is at least partially attributable to the fact that the IV arm treatment was administered twice as frequently (Q2W cycles) as the SC arm (Q4W cycles). This more frequent dosing along with more frequent physical exam and clinical laboratory assessments would allow for more opportunities for dose interruption on the IV arm relative to the SC arm. FDA notes small numerical differences in the incidences of AEs leading to treatment interruption between the arms, including a noticeable difference in the incidence of COVID-19 infection leading to dose interruption between the arms. This difference may be due to a higher frequency of healthcare visits resulting in a higher risk of

acquiring COVID-19 infection due to the more frequent dosing regimen on the nivolumab IV arm.

Table 42: AEs Leading to Dose Interruption

	NIVOLUMAB SC N = 247; n (%)	NIVOLUMAB IV N = 245; n (%)
AEs Leading to Dose Interruption	85 (34)	116 (47)
Covid-19	11 (4.5)	23 (9)
Blood Creatinine Increased	7 (2.8)	4 (1.6)
Anemia	6 (2.4)	11 (4.5)
Diarrhea (GT)	6 (2.4)	6 (2.4)
Fatigue (GT)	6 (2.4)	12 (4.9)
Hemorrhage (GT)	5 (2.0)	3 (1.2)
Hyperglycemia	5 (2.0)	6 (2.4)
Pneumonitis (GT)	5 (2.0)	6 (2.4)
Rash (GT)	4 (1.6)	6 (2.4)
Decreased Appetite	3 (1.2)	1 (0.4)
Hypoalbuminemia	3 (1.2)	1 (0.4)
Aspartate Aminotransferase Increased	2 (0.8)	7 (2.9)
Cough (GT)	2 (0.8)	4 (1.6)
Hypothyroidism (GT)	2 (0.8)	3 (1.2)
Musculoskeletal Pain (GT)	2 (0.8)	8 (3.3)
Pneumonia (GT)	2 (0.8)	3 (1.2)
Respiratory Tract Infection	2 (0.8)	3 (1.2)
Alanine Aminotransferase Increased	1 (0.4)	7 (2.9)
Blood Bilirubin Increased	1 (0.4)	3 (1.2)
Urinary Tract Infection (GT)	1 (0.4)	4 (1.6)
Femur Fracture	0 (0)	3 (1.2)
Platelet Count Decreased	0 (0)	3 (1.2)

Significant Adverse Events

Data: See Table 39 for IMAEs and OESIs reported in CA20967T.

The Applicant's Position:

Local site reactions: Local site reactions were all Grade 1-2 (Table 39). Injection site erythema was the most frequently reported injection-site reaction (5 [2.0%] subjects) in the nivolumab SC arm. Infusion related reaction (5 [2.0%] subjects) was the most frequently reported in the nivolumab IV arm.

IMAEs: Overall, the majority of IMAEs were Grade 1-2 (Table 39). Across IMAE categories,

the majority of events were manageable using the established management algorithms, with resolution reported as occurring when IMMs (mostly systemic corticosteroids) were administered. Some endocrine IMAEs were not considered resolved due to the continuing need for hormone replacement therapy.

OESIs: Among all treated subjects, OESIs (regardless of causality or IMM treatment, with extended follow-up) were infrequent (<1%), and most events were reported as resolved by the time of DBL. The most frequently reported OESIs (any grade) are shown in Table 39.

The FDA's Assessment:

Local site reactions: FDA generally agrees with the Applicant's assessment of local site reactions as depicted in Table 39. A total of 20 (8%) of patients on the SC arm experienced local site reactions using a FDA compiled list of preferred terms: injection site erythema (2.4%), application site pain (0.8%), injection site edema (0.8%), injection site pain (0.8%), injection site reaction (0.8%) administration site pain (0.4%), application site erythema (0.4%), application site rash (0.4%), infusion site reaction (0.4%), injection site discoloration (0.4%), injection site inflammation, (0.4%), injection site pruritis (0.4%), and puncture site erythema (0.4%). There were no local site reactions on the IV arm. A total of 5 (2.0) patients on the IV experienced infusion reactions. There were no infusion reactions experienced on the SC arm.

IMAEs: FDA agrees with the Applicant's assessment that the majority of the IMAEs were Grades 1 or 2. The incidence and severity of the grouped terms of IMAEs were similar in the SC and IV arms, but with the caveat that there was more frequent monitoring on the IV arm (See Table 43). The most frequently reported grouped terms for IMAEs of any grade were similar across treatment arms. The most frequently reported grouped terms for IMAEs of any grade for the SC arm included hypothyroidism/thyroiditis (10%) and rash (7%). The most frequently reported grouped terms for IMAEs of any grade for the IV arm included hypothyroidism/ thyroiditis (10%), hepatitis (6%), and rash (4.9%) (See Table 44).

It is notable that this definition of IMAEs was limited to those AEs consistent with an immune-mediated mechanism or immune-mediated component for which non-inflammatory etiologies have been ruled out. IMAEs could include events with an alternate etiology which were exacerbated by the induction of autoimmunity. Further, these analyses were limited to patients who received immune-modulating medication (e.g., corticosteroids) for treatment of the event, with the exception of endocrine events, which were included in the analysis regardless of treatment since these events are often managed without immunosuppression.

FDA previously agreed to this definition of IMAE during the pre-BLA meeting. FDA agrees that this definition of IMAEs is a reasonable, but conservative, definition of IMAEs that is likely to identify events that are true immune-mediated events, but could potentially underestimate the incidence, particularly in cases where assessment of an immune-mediated event may be confounded by other possible non-inflammatory etiologies. It is possible that the incidence of IMAEs reported may be higher if a less stringent definition were used, but one would run the risk of capturing events that were not true IMAEs. Even if

a less stringent definition were used, such as “TEAEs requiring immune-modulating medication,” the proportion of patients with such TEAEs remained similar across treatment arms. For example, FDA’s assessment of rescue medications identified a total of 90 (36.4%) patients on the nivolumab SC arm and 97 (39.6%) patients on the nivolumab IV arm who received immune-modulating medications for a treatment-emergent adverse event.

The management algorithms for IMAEs on Study CA20967T were consistent with generally accepted guidelines for the management of toxicities associated with immune checkpoint inhibitors (e.g., ASCO Guideline for the Management of Immune-Related Adverse Events in Patients treated with immune checkpoint inhibitor therapy). FDA agrees with the Applicant’s assessment that IMAEs were generally manageable with accepted management algorithms. The proportion of patients on the nivolumab SC arm requiring dose-delays due to IMAEs in the predefined categories was low (Table 43).

OESIs: FDA agrees with the Applicant’s assessment that OESIs were infrequent (<1%). Notably, there was a fatal event of myocarditis on the nivolumab SC arm. Myocarditis is a labeled rare adverse event that occurs at an incidence of <1% in patients who received OPDIVO or OPDIVO in combination with ipilimumab. The incidence of myocarditis (0.4%) with nivolumab SC on Study CA20967T is consistent with what has been reported in labeling for OPDIVO (OPDIVO USPI).

Table 43: Summary of IMAEs

	Nivolumab with Hyaluronidase (SC) N=247; n (%)	Nivolumab (IV) N=245; n (%)
Non-Endocrine		
All-Grade IMAEs	38 (15)	37 (15)
Grade 3-4 IMAEs	9 (3.6)	14 (6)
Serious IMAEs	7 (2.8)	6 (2.4)
Pts with IMAEs leading to dose delays	18 (7)	22 (9)
Pts with IMAEs leading to treatment discontinuation	6 (2.4)	7 (2.9)
Endocrine		
All-Grade IMAEs	30 (12)	37 (15)
Grade 3-4 IMAEs	3 (1.2)	3 (1.2)
Serious IMAEs	2 (0.8)	3 (1.2)
Pts with IMAEs leading to dose delays	3 (1.2)	6 (2.4)

Pts with IMAEs leading to treatment discontinuation	1 (0.4)	2 (0.8)
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Table 44: IMAEs and OESIs (Grouped Terms)

	Nivolumab with Hyaluronidase (SC) N=247; n (%)		Nivolumab (IV) N=245; n (%)	
	Any Grade	Grade 3/4	Any Grade	Grade 3/4
Non-Endocrine (Grouped Terms)				
Rash	17 (7)	2 (0.8)	12 (4.9)	3 (1.2)
Diarrhea/Colitis	7 (2.8)	1 (0.4)	5 (2.0)	0
Pneumonitis	7 (2.8)	2 (0.8)	7 (2.9)	2 (0.8)
Hepatitis	6 (2.4)	4 (1.6)	14 (6)	9 (3.7)
Nephritis/Renal Dysfunction	3 (1.2)	0	2 (0.8)	0
Hypersensitivity	1 (0.4)	0	2 (0.8)	0
Endocrine (Grouped Terms)				
Hypothyroidism/Thyroiditis	24 (10)	0	25 (10)	0
Adrenal Insufficiency	5 (2.0)	2 (0.8)	2 (0.8)	0
Hyperthyroidism	2 (0.8)	0	11 (4.5)	0
Diabetes Mellitus	1 (0.4)	1 (0.4)	1 (0.4)	1 (0.4)
Hypophysitis	0	0	3 (1.2)	2 (0.8)
Other Events of Special Interest				
Myositis	0	0	2 (0.8)	2 (0.8)
Myocarditis	1 (0.4)	1 (0.4)	0	0
Pancreatitis	1 (0.4)	1 (0.4)	1 (0.4)	0
Uveitis	1 (0.4)	1 (0.4)	0	0

Treatment Emergent Adverse Events and Adverse Reactions

Data:

Table 45: Applicant - Adverse Reactions in ≥ 5% of Patients Receiving Nivolumab SC - CA20967T

Adverse Reaction	Nivolumab SC (n=247)		Nivolumab IV (n = 245)	
	All Grades (%)	Grades 3-4 (%)	All Grades (%)	Grades 3-4 (%)
General				
Fatigue ^a	20	2.4	25	3.3
Injection site reaction ^b	7	0	0	0
Edema	6	0.4	11	0.8
Musculoskeletal and Connective Tissue				
Musculoskeletal pain	20	1.2	29	2.4
Arthralgia	12	0.4	16	0.4

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Adverse Reaction	Nivolumab SC (n=247)		Nivolumab IV (n = 245)	
	All Grades (%)	Grades 3-4 (%)	All Grades (%)	Grades 3-4 (%)
Skin and Subcutaneous Tissue				
Pruritus	16	0.4	21	0
Rash ^c	13	1.2	12	1.2
Gastrointestinal				
Diarrhea	10	0.4	14	0.4
Abdominal pain ^d	10	0	9	0.4
Nausea	8	0	9	0
Constipation	8	0	6	0
Vomiting	6	0.4	4.9	0
Respiratory, Thoracic, and Mediastinal				
Cough	11	0	11	0
Endocrine				
Hypothyroidism ^e	10	0	12	0
Metabolism and Nutrition				
Hyperglycemia	9	2.4	13	2.0
Decreased appetite	9	0	11	0.8

^a Includes asthenia.

^b Includes injection site erythema, application site pain, injection site pain, application site erythema, application site rash, injection site discoloration, injection site inflammation, and injection site pruritus.

^c Includes erythematous rash, macular rash, maculopapular rash, papular rash, vesicular rash, dermatitis, and acneiform dermatitis.

^d Includes abdominal discomfort, lower abdominal pain, and upper abdominal pain.

^e Includes autoimmune hypothyroidism, central hypothyroidism, and primary hypothyroidism.

Dataset: ADSL, ADAE

Clinically important adverse reactions (< 5% of patients who received nivolumab SC: Cardiac: myocarditis, Respiratory, thoracic, and mediastinal: pneumonitis, dyspnea; Endocrine: adrenal insufficiency, hyperthyroidism, thyroiditis; Gastrointestinal: colitis, pancreatitis; Hepatobiliary: hepatitis; Nervous system: peripheral neuropathy; Skin and subcutaneous tissue: psoriasis, erythema; Musculoskeletal and connective tissue: arthritis; Blood and lymphatic system: eosinophilia; Eye disorders: uveitis; and Immune system: hypersensitivity.

The Applicant's Position:

The overall safety profile of nivolumab SC was consistent with the safety profile of nivolumab IV in adult patients with advanced or metastatic ccRCC and other tumor types where nivolumab monotherapy was studied. No new safety signals or safety concerns were identified. The safety profile was manageable based on the already established management guidelines.

The FDA's Assessment:

FDA generally agrees with the Applicant's assessment. FDA analysis of TEAEs included the use of internally standardized grouped terms to evaluate the frequency of clinically related adverse events. The most frequently reported (≥5% on any arm) adverse events are listed in Table 46. The most common (≥20% incidence) any grade TEAEs in the SC arm were musculoskeletal pain (31%) and fatigue (20%). The most common any grade TEAEs in the

IV arm were musculoskeletal pain (39%), fatigue (25%), and pruritis (21%). The most common ($\geq 2\%$ incidence) Grade 3 or 4 TEAEs in the SC arm were fatigue (2.4%), hyperglycemia (2.4%), hyperkalemia (2.4%), and dyspnea (2.0%). The most common Grade 3 or 4 TEAEs in the IV arm were fatigue (3.3%), musculoskeletal pain (3.3%), hypercalcemia (2.9%), hemorrhage (2.0%), hyperglycemia (2.0%), and hyponatremia (2.0%). While the overall incidence of Grade 3 or 4 TEAEs was numerically higher in the IV arm, it is plausible that the more frequent monitoring in the IV arm may have contributed to this observed difference. Overall, the TEAEs reported were similar in both the nivolumab SC and nivolumab IV arms and generally consistent with the known safety profile of nivolumab as described in the USPI for Opdivo.

Table 46: Treatment Emergent Adverse Events Reported in $\geq 5\%$ of Patients

	NIVOLUMAB SC N = 247		NIVOLUMAB IV N = 245	
	All grades n (%)	Grades 3-4 n (%)	All grades n (%)	Grades 3-4 n (%)
Patients with TEAEs	230 (93)	87 (35)	229 (93)	100 (41)
Gastrointestinal Disorders				
Diarrhea (GT)	26 (11)	1 (0.4)	34 (14)	1 (0.4)
Abdominal Pain (GT)	24 (10)	0 (0.0)	24 (10)	1 (0.4)
Nausea	20 (8)	0 (0.0)	22 (9)	0 (0.0)
Constipation	19 (8)	0 (0.0)	15 (6)	0 (0.0)
Vomiting (GT)	15 (6)	1 (0.4)	12 (4.9)	0 (0.0)
Vascular Disorders				
Hemorrhage (GT)	13 (5)	3 (1.2)	21 (9)	5 (2.0)
Hypertension (GT)	11 (4.5)	3 (1.2)	20 (8)	4 (1.6)
General Disorders And Administration Site Conditions				
Fatigue (GT)	49 (20)	6 (2.4)	61 (25)	8 (3.3)
Edema (GT)	13 (5)	1 (0.4)	27 (11)	2 (0.8)
Pyrexia (GT)	7 (2.8)	0 (0.0)	13 (5)	0 (0.0)
Musculoskeletal And Connective Tissue Disorders				
Musculoskeletal Pain (GT)	77 (31)	4 (1.6)	95 (39)	8 (3.3)
Metabolism And Nutrition Disorders				
Hyperglycemia	23 (9)	6 (2.4)	32 (13)	5 (2.0)
Decreased Appetite	22 (9)	0 (0.0)	28 (11)	2 (0.8)
Hyperkalemia	17 (7)	6 (2.4)	21 (9)	1 (0.4)

	NIVOLUMAB SC N = 247		NIVOLUMAB IV N = 245	
	All grades n (%)	Grades 3-4 n (%)	All grades n (%)	Grades 3-4 n (%)
Hypercalcemia	11 (4.5)	4 (1.6)	16 (7)	7 (2.9)
Hyponatremia	4 (1.6)	0 (0.0)	16 (7)	5 (2.0)
Infections And Infestations				
Covid-19	20 (8)	0 (0.0)	29 (12)	2 (0.8)
Skin And Subcutaneous Tissue Disorders				
Pruritus	40 (16)	1 (0.4)	52 (21)	0 (0.0)
Rash (GT)	36 (15)	3 (1.2)	32 (13)	3 (1.2)
Endocrine Disorders				
Hypothyroidism (GT)	30 (12)	0 (0.0)	42 (17)	0 (0.0)
Investigations				
Blood Creatinine Increased	27 (11)	1 (0.4)	40 (16)	0 (0.0)
Blood Alkaline Phosphatase Increased	14 (6)	3 (1.2)	12 (4.9)	4 (1.6)
Alanine Aminotransferase Increased	13 (5)	1 (0.4)	18 (7)	3 (1.2)
Aspartate Aminotransferase Increased	13 (5)	1 (0.4)	23 (9)	3 (1.2)
Weight Decreased	11 (4.5)	0 (0.0)	19 (8)	3 (1.2)
Blood And Lymphatic System Disorders				
Anemia	54 (22)	14 (6)	63 (26)	21 (9)
Respiratory, Thoracic And Mediastinal Disorders				
Cough (GT)	27 (11)	0 (0.0)	28 (11)	0 (0.0)
Dyspnea (GT)	12 (4.9)	5 (2.0)	21 (9)	1 (0.4)
Nervous System Disorders				
Headache (GT)	10 (4.0)	1 (0.4)	22 (9)	2 (0.8)
Dizziness (GT)	7 (2.8)	0 (0.0)	13 (5)	0 (0.0)

Group Headache (GT) includes PT terms HEADACHE,
Group Dyspnoea (GT) includes PT terms DYSPNOEA, DYSPNOEA EXERTIONAL,
Group Haemorrhage (GT) includes PT terms HAEMATURIA, UPPER GASTROINTESTINAL HAEMORRHAGE,
LOWER GASTROINTESTINAL HAEMORRHAGE, HAEMOPTYSIS, EPISTAXIS, VAGINAL HAEMORRHAGE,
TUMOUR HAEMORRHAGE, HAEMORRHAGE INTRACRANIAL, HAEMORRHOIDAL HAEMORRHAGE,
HAEMORRHAGE,

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Group Hypertension (GT) includes PT terms HYPERTENSION, BLOOD PRESSURE INCREASED,
Group Fatigue (GT) includes PT terms FATIGUE, ASTHENIA,
Group Oedema (GT) includes PT terms OEDEMA PERIPHERAL, GENERALISED OEDEMA, PENILE OEDEMA, LOCALISED OEDEMA, FACE OEDEMA,
Group Diarrhoea (GT) includes PT terms DIARRHOEA, COLITIS, ENTERITIS, ENTEROCOLITIS,
Group Musculoskeletal Pain (GT) includes PT terms ARTHRALGIA, BACK PAIN, SPINAL PAIN, MUSCULOSKELETAL PAIN, NON-CARDIAC CHEST PAIN, BONE PAIN, NECK PAIN, MUSCULOSKELETAL CHEST PAIN, MYALGIA, ARTHRITIS, PAIN IN EXTREMITY, MUSCULOSKELETAL STIFFNESS, MUSCULOSKELETAL DISCOMFORT,
Group Rash (GT) includes PT terms RASH, DERMATITIS ACNEIFORM, RASH MACULO-PAPULAR, ERYTHEMA MULTIFORME, ECZEMA, RASH PAPULAR, RASH ERYTHEMATOUS, DERMATITIS, SKIN EXFOLIATION, RASH MACULAR, PALMAR-PLANTAR ERYTHRODYSAESTHESIA SYNDROME, RASH PRURITIC, DERMATITIS BULLOUS,
Group Abdominal Pain (GT) includes PT terms ABDOMINAL PAIN, ABDOMINAL PAIN LOWER, ABDOMINAL PAIN UPPER, ABDOMINAL DISCOMFORT, EPIGASTRIC DISCOMFORT, HEPATIC PAIN,
Group Vomiting (GT) includes PT terms VOMITING,
Group Dizziness (GT) includes PT terms VERTIGO, DIZZINESS, DIZZINESS POSTURAL,
Group Cough (GT) includes PT terms COUGH,
Group Pyrexia (GT) includes PT terms PYREXIA, HYPERPYREXIA, HYPERTHERMIA,
Group Hypothyroidism (GT) includes PT terms HYPOTHYROIDISM, BLOOD THYROID STIMULATING HORMONE INCREASED,

Laboratory Findings

Data:

Table 47: Applicant - Laboratory Values Worsening from Baseline^a ≥ 20% of Patients on Nivolumab SC - CA20967T

Laboratory Abnormality	Nivolumab SC		Nivolumab IV	
	All Grades (%)	Grades 3-4 (%)	All Grades (%)	Grades 3-4 (%)
Hematology				
Anemia	46	7	48	9
Lymphopenia	36	6	45	9
Chemistry				
Increased creatinine	38	1.3	43	0.4
Hyponatremia	34	2.6	40	2.5
Hyperkalemia	34	3.0	45	2.9
Increased alkaline phosphatase	32	2.1	33	2.0
Hypercalcemia	29	2.1	31	4.1
Increased albumin	25	1.7	35	0.4
Increased ALT	21	1.3	26	4.1

a Each test incidence is based on the number of patients who had both baseline and at least one on-study laboratory measurement available: Nivolumab SC group (range: 232 to 235 patients) and Nivolumab IV group (range: 240 to 244 patients).

Dataset: ADSL, ADZL

The Applicant's Position:

The majority of laboratory abnormalities (hematology, liver tests, kidney function tests, thyroid function tests, and electrolytes) were Grade 1-2. The percentage of subjects with laboratory tests that worsened to Grade 3 or 4 relative to baseline was low (Table 47).

The FDA's Assessment:

FDA agrees with the Applicant's assessment that the majority of laboratory abnormalities were Grade 1 or 2. There was a numerically higher number of laboratory abnormality events on the IV arm, but it is possible that this difference is at least partially attributable to the fact that labs were performed twice as frequently on the nivolumab IV arm (i.e., with every Q2W cycle) than on the nivolumab SC arm (i.e., with every Q4W cycle).

Table 48: Study CA20967T - Laboratory Values Worsening from Baseline ($\geq 20\%$ in Patients Receiving Nivolumab SC)

Laboratory Abnormality ¹	Nivolumab SC N=247		Nivolumab IV N=245	
	All Grades (%)	Grades 3-4 (%)	All Grades (%)	Grades 3-4 (%)
Hematology				
Hemoglobin decreased	46	7	48	9
Lymphocytes decreased	36	6	45	9
Chemistry				
Creatinine increased	38	1.3	43	0.4
Sodium decreased	34	2.6	40	2.5
Potassium increased	34	3.0	45	2.9
Alkaline phosphatase increased	32	2.1	33	2.0
Calcium increased	29	2.1	31	4.1
Albumin decreased	25	1.7	35	0.4
ALT increased	21	1.3	26	4.1

- Each test incidence is based on the number of patients who had both baseline and at least one on-study laboratory measurement available: Nivolumab SC group (range: 232 to 235 patients) and Nivolumab IV group (range: 240 to 244 patients).

Vital Signs

Data: Vital signs were monitored and recorded at the site per institutional standard of care during screening and treatment visits. These assessments were intended to be used as safety monitoring by the treating physician.

The Applicant's Position:

Nivolumab SC did not appear to have clinically meaningful adverse effects on subject vital

signs during the study.

The FDA's Assessment:

Per protocol body temperature, blood pressure, and heart rate were assessed pre-dose during every cycle. FDA agrees that there did not appear to be clinically meaningful adverse effects on patient vital signs during the study.

Electrocardiograms (ECGs)

The Applicant's Position:

ECG testing was conducted at Screening as a part of eligibility assessments for study participation. Routine ECG testing (as part of study safety assessments) was not performed during the on-treatment and follow-up visits.

The FDA's Assessment:

ECG testing was performed at screening within 14 days prior to randomization but was not performed during the course of the study during the on-treatment and follow-up visits. ECG testing has been conducted previously in studies of nivolumab IV.

QT

The Applicant's Position: Not applicable.

The FDA's Assessment:

Study CA20967T was not designed to formally assess ECG interval, rate, rhythm, or morphology. ECG was performed at baseline and then only as clinically indicated. The effect of nivolumab on QT interval has been assessed in studies of nivolumab IV.

Immunogenicity

Data:

Table 49: Applicant - ADA Assessments - CA20967T - All Immunogenicity Evaluable Subjects with Baseline and at Least One Post-Baseline Assessment

ADA Status (%)	Arm A		Arm B
	Nivolumab SC N = 202	rHuPH20 N = 215	Nivolumab IV N = 215
BASELINE ADA POSITIVE	12 (5.9)	20 (9.3)	9 (4.2)
ADA POSITIVE	46 (22.8)	19 (8.8)	15 (7.0)
PERSISTENT POSITIVE (PP)	2 (1.0)	7 (3.3)	0
NOT PP - LAST SAMPLE POSITIVE	17 (8.4)	11 (5.1)	6 (2.8)
OTHER POSITIVE	27 (13.4)	1 (0.5)	9 (4.2)
NEUTRALIZING POSITIVE	2 (1.0)	5 (2.3)	0
ADA NEGATIVE	155 (76.7)	196 (91.2)	200 (93.0)
N.A.	1 (0.5)	0	0

Note: Post-baseline assessments are assessments reported after initiation of treatment.

Baseline ADA Positive: A subject with baseline ADA-positive sample;

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OPDIVO (nivolumab and hyaluronidase - nvhy) injection, for subcutaneous use

ADA Positive: A subject with at least one ADA-positive sample relative to baseline (ADA negative at baseline or ADA titer to be at least 4-fold or greater [$\geq$] than baseline positive titer) at any time after initiation of treatment;

Persistent Positive: ADA-positive sample at 2 or more consecutive time points, where the first and last ADA-positive samples are at least 16 weeks apart;

Not PP-Last Sample Positive: Not persistent but with ADA-positive sample at the last sampling time point;

Other Positive: Not persistent but some ADA-positive samples with the last sample being negative;

Neutralizing Positive: At least one ADA-positive sample with neutralizing antibodies detected post-baseline;

ADA Negative: A subject with only ADA-negative sample after initiation of treatment.

N.A.: A subject with positive samples at baseline and after initiation of treatment, but either of those having missing titer.

Datasets: ADISL, ADIS

The Applicant's Position:

The percentage of subjects with anti-nivolumab ADA at baseline was 5.9% and 4.2% in the nivolumab SC and nivolumab IV arms, respectively (Table 49). The incidence of anti-nivolumab antibodies developing after the start of treatment was higher for nivolumab SC (22.8%) than for nivolumab IV (7.0%).

9.3% of subjects in the nivolumab SC arm had anti-rHuPH20 antibodies at baseline. Anti-rHuPH20 antibodies developed after the start of nivolumab SC treatment in 8.8% of subjects in the nivolumab SC arm, which is consistent with the known ADA incidence for rHuPH20.²¹

Less than 5% of subjects receiving nivolumab SC were persistent positive for anti-nivolumab antibodies (N = 2; 1.0%) and for anti-rHuPH20 antibodies (N = 7; 3.3%); Table 49. Neutralizing antibodies to nivolumab and to rHuPH20 developed separately in 2 (1.0%) and 5 (2.3%) subjects, respectively, in the nivolumab SC arm. No neutralizing antibodies developed in the nivolumab IV arm.

There was no observed effect of anti-nivolumab and anti-rHuPH20 antibodies on the safety of the nivolumab SC or nivolumab IV regimens. Of treated subjects evaluable for nivolumab ADA, no hypersensitivity/infusion reaction select AEs were reported in nivolumab ADA positive subjects in either treatment arm. Hypersensitivity/infusion reaction select AEs were reported in 1.3% and 4.0% of nivolumab ADA negative subjects in the nivolumab SC and nivolumab IV treatment arms, respectively. Of treated subjects evaluable for rHuPH20 ADA, no hypersensitivity/infusion reaction select AEs were reported in rHuPH20 ADA positive subjects. Hypersensitivity/infusion reaction select AEs were reported in 1.5% of rHuPH20 ADA negative subjects in the nivolumab SC treatment arm.

No cases of anaphylactic reactions were reported in either treatment arm. Most AEs in the broad SMQ of anaphylactic reaction were non-serious and mild to moderate (Grade 1-2) in severity. A few symptoms (regardless of causality), such as erythema, rash, and pruritis were reported during the treatment period, which may be indicative of hypersensitivity reactions; however, these events were either isolated, or the rates were lower in the nivolumab ADA positive subjects compared with the nivolumab ADA negative subjects in both arms. A few events captured under the broad SMQ were not reported in relation to anaphylactic reactions but in relation to other conditions; however, these events were included, considering the Broad SMQ search strategy.

Of all treated subjects evaluable for ADA in the nivolumab SC arm, local site reaction AEs were reported in a greater proportion of ADA positive subjects compared to ADA negative subjects, were all Grade 1-2 and were reported as resolved.

The FDA's Assessment:

There were no infusion-related reactions reported on the nivolumab SC arm for Study CA20967T. There was also no identifiable trend of AEs in the broad SMQ of anaphylactic reaction occurrence with respect to ADA incidence. On the nivolumab SC arm, AEs in the broad SMQ of anaphylactic reaction occurred in 17 (37%) nivolumab ADA-positive patients and 61 (39.4%) nivolumab ADA-negative patients. On the nivolumab SC arm, AEs in the broad SMQ of anaphylactic reaction occurred in 9 (47%) rHuPH20 ADA-positive patients and 74 (39%) rHuPH20 ADA-negative patients.

There was a greater proportion of ADA-positive patients who experienced injection site reactions on the nivolumab SC arm for Study CA20967T. For patients in which nivolumab ADA status is known on the nivolumab SC arm, injection site reactions occurred in 7 (15%) nivolumab ADA-positive patients and 10 (7%) nivolumab ADA-negative patients. For patients in which rHuPH20 ADA status is known on the nivolumab SC arm, injection site reactions occurred in 5 (26%) rHuPH20 ADA-positive patients and 13 (7%) rHuPH20 ADA-negative patients

8.2.5. Safety Results from Supportive Study CA2098KX

Table 50: Applicant - Safety Summary - All Treated Subjects - CA2098KX (Parts D, E)

	Number of Subjects (%)	
	Part D, GRP 5 Nivolumab SC 1,200 mg + rHuPH20 2000 Units/mL ^a N = 36	Part E, GRP 6 Nivolumab SC 600 mg coformulated with rHuPH20 2000 units/mL ^b N = 36
Deaths	19 (52.8)	14 (38.9)
Primary Reason		
Disease	16 (44.4)	11 (30.6)
Study Drug Toxicity	0	0
Unknown	1 (2.8)	2 (5.6)
Other ^c	2 (5.6)	1 (2.8)
Deaths within 30 days of last dose	1 (2.8)	1 (2.8)
Primary Reason		
Disease	0	1 (2.8)
Study Drug Toxicity	0	0
Unknown	0	0
Other ^c	1 (2.8)	0
Deaths within 100 days of last dose	6 (16.7)	11 (30.6)
Primary Reason		
Disease	4 (11.1)	8 (22.2)
Study Drug Toxicity	0	0
Unknown	0	2 (5.6)
Other ^c	2 (5.6)	1 (2.8)

Table 50: Applicant - Safety Summary - All Treated Subjects - CA2098KX (Parts D, E)

	Adverse Event Grades			Any Grade	Grade 3-4	Grade 5
	Any Grade	Grade 3-4	Grade 5			
All-causality SAE	19 (52.8)	13 (36.1)	4 (11.1)	21 (58.3)	10 (27.8)	7 (19.4)
Drug-related SAE	3 (8.3)	3 (8.3)	0	1 (2.8)	1 (2.8)	0
Drug-related AEs leading to DC	4 (11.1)	3 (8.3)	0	1 (2.8)	1 (2.8)	0
All-Causality AEs	36 (100.0)	17 (47.2)	4 (11.1)	36 (100.0)	13 (36.1)	7 (19.4)
Drug-related AEs	27 (75.0)	6 (16.7)	0	28 (77.8)	4 (11.1)	0
≥ 2 subjects in any treatment group						
Fatigue	6 (16.7)	0	0	5 (13.9)	0	0
Injection site erythema	6 (16.7)	0	0	1 (2.8)	0	0
Injection site reaction	3 (8.3)	0	0	10 (27.8)	0	0
Pruritus	5 (13.9)	0	0	8 (22.2)	0	0
Rash	3 (8.3)	1 (2.8)	0	4 (11.1)	0	0
Rash erythematous	2 (5.6)	0	0	0	0	0
Dry skin	1 (2.8)	0	0	2 (5.6)	0	0
Blood creatinine increased	1 (2.8)	0	0	5 (13.9)	0	0
Hypothyroidism	8 (22.2)	0	0	6 (16.7)	0	0
Hyperthyroidism	6 (16.7)	0	0	1 (2.8)	0	0
ALT increased	3 (8.3)	2 (5.6)	0	3 (8.3)	1 (2.8)	0
AST increased	2 (5.6)	1 (2.8)	0	3 (8.3)	1 (2.8)	0
Lipase increased	2 (5.6)	2 (5.6)	0	0	0	0
Arthralgia	3 (8.3)	0	0	4 (11.1)	0	0
Musculoskeletal pain	0	0	0	3 (8.3)	0	0
Cough	2 (5.6)	0	0	1 (2.8)	0	0
Dry mouth	0	0	0	3 (8.3)	0	0
Diarrhoea	1 (2.8)	0	0	2 (5.6)	0	0
Adrenal insufficiency	0	0	0	2 (5.6)	0	0
Any Drug-related local site reactions	10 (27.8)	0	0	12 (33.3)	0	0
Injection site erythema	6 (16.7)	0	0	1 (2.8)	0	0
Injection site reaction	3 (8.3)	0	0	10 (27.8)	0	0
Injection site pain	1 (2.8)	0	0	0	0	0
Injection site pruritus	1 (2.8)	0	0	0	0	0
Injection related reaction	1 (2.8)	0	0	1 (2.8)	0	0
Injection site haematoma	0	0	0	1 (2.8)	0	0
All-causality Select AEs within 30 days of last dose						
Endocrine	10 (27.8)	0	0	9 (25.0)	0	0
Gastrointestinal	4 (11.1)	0	0	6 (16.7)	0	0
Hepatic	6 (16.7)	4 (11.1)	0	9 (25.0)	4 (11.1)	0

Table 50: Applicant - Safety Summary - All Treated Subjects - CA2098KX (Parts D, E)

Pulmonary	0	0	0	0	0	0
Renal	4 (11.1)	0	0	7 (19.4)	0	0
Skin	12 (33.3)	3 (8.3)	0	12 (33.3)	0	0
Hypersensitivity/ Infusion reaction	1 (2.8)	0	0	0	0	0
Drug-related Select AEs within 30 days of last dose						
Endocrine	10 (27.8)	0	0	8 (22.2)	0	0
Gastrointestinal	1 (2.8)	0	0	2 (5.6)	0	0
Hepatic	4 (11.1)	3 (8.3)	0	5 (13.9)	2 (5.6)	0
Renal	1 (2.8)	0	0	5 (13.9)	0	0
Skin	11 (30.6)	3 (8.3)	0	11 (30.6)	0	0
All-causality Endocrine IMAEs						
Adrenal insufficiency	0	0	0	2 (5.6)	0	0
Hypothyroidism	8 (22.2)	0	0	6 (16.7)	0	0
Diabetes mellitus	1 (2.8)	0	0	0	0	0
Hyperthyroidism	5 (13.9)	0	0	1 (2.8)	0	0
All-causality Non-Endocrine IMAEs						
Hepatitis	1 (2.8)	1 (2.8)	0	1 (2.8)	1 (2.8)	0
Nephritis and renal dysfunction	0	0	0	1 (2.8)	0	0
Rash	5 (13.9)	2 (5.6)	0	2 (5.6)	0	0

- ^a Subjects in Part D initially received nivolumab SC coadministered with rHuPH20 by injection via syringe. Afterwards, any ongoing subject was allowed to switch over to nivolumab SC coformulated with rHuPH20, with nivolumab SC and rHuPH20 solutions premixed in one vial.
- ^b Subjects in Part E received the coformulation of nivolumab SC and rHuPH20 premixed in one vial and administered by injection via syringe.
- ^c The verbatim terms reported for the 'other' reasons for death were as follows: perforated viscus and respiratory infection due to Covid-19 in Part D Group 5; cerebral ischemic infarction in Part E Group 6.
- Notes: All events are within 100 days of the last dose of study drug, unless otherwise indicated.
Local site reactions included general disorders and administration site conditions which contained the words of "Administration site", "Injection site", or "Puncture site", also included the SOC of "Injury, poisoning and procedural complications" which contained the words "Injection related reaction".
MedDRA version 25.1; CTC Version 5.0.
Datasets: ADSL, ADAE, ADAEIMM

Deaths

Data: Refer to Table 50.

The Applicant's Position:

The most frequently reported cause of death was disease progression (16 [44.4%] subjects in Part D and 11 [30.6%] subjects in Part E). No death was reported due to study drug toxicity in Parts D or E. All deaths under the category of 'other' were not related to study drug.

The FDA's Assessment:

After review of the case narratives, FDA agrees with the Applicant's assessment that no deaths attributable to treatment with nivolumab SC occurred on Study CA2098KX.

Serious Adverse Events

Data: Refer to Table 50.

The Applicant's Position:

The overall incidence of SAEs was consistent with the historical safety profile of nivolumab IV.

The FDA's Assessment:

FDA agrees with the Applicant's assessment. The observed frequency of any grade SAEs within 30 days of the last dose is generally consistent with the historical safety profile of nivolumab IV. The most common SAEs (>1 patient) in Part D (excluding malignant neoplasm progression) included rash (6%). The most common SAEs (>1 patient) in Part E (excluding malignant neoplasm progression) included Covid-19 (6%) and dyspnea (6%).

Dropouts and/or Discontinuations Due to Adverse Effects

Data: Refer to Table 50.

The Applicant's Position:

The overall incidence of dropouts and discontinuations due to AEs were consistent with the historical profile of nivolumab IV.

The FDA's Assessment:

FDA agrees that the overall incidence of dropouts and discontinuations due to AEs was generally consistent with the historical safety profile of nivolumab IV. Excluding malignant neoplasm progression, there were 7 (19%) AEs leading to treatment discontinuation in Part D and 4 (11%) AEs leading to treatment discontinuation in Part E. Preferred terms for treatment discontinuation in Part D included ALT increased (6%), AST increased (2.8%), COVID-19 (2.8%), dysphagia (2.8%), fatigue (2.8%), hemorrhage (2.8%), lipase increased (2.8%), musculoskeletal pain (2.8%), rash (2.8%), and vulvitis (2.8%). Preferred terms for treatment discontinuation in Part E included musculoskeletal pain (2.8%), ascites (2.8%), GGT increased (2.8%), and general physical health deterioration (2.8%). The singular reported event of vulvitis, while not specifically identified in labeling for Opdivo, has been described in case reports with nivolumab IV (labeling does clearly identify that immune reaction can occur at any site).

Dose Interruption/Reduction Due to Adverse Effects

Data:

Dose reductions were not permitted in CA2098KX.

The most frequently reported any grade AEs leading to dose delay (within 30 days of last dose) were:

- Nivo SC: COVID-19 (4.5%), blood creatinine increased (2.8%), anemia (2.4%), and hyperglycemia, diarrhea, and pneumonitis (2.0% each).
- Nivo IV: COVID-19 (9.4%), anemia (4.5%), ALT increased, and AST increased (2.9% each), diarrhea, hyperglycemia, asthenia, and fatigue (2.4% each), and pneumonitis and rash (2.0% each).

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OPDIVO (nivolumab and hyaluronidase - nvhy) injection, for subcutaneous use

The most frequently reported any grade drug-related AEs leading to dose delay (within 30 days of last dose) were:

- Nivo SC: pneumonitis (2.0%), blood creatinine increased and diarrhea (1.6% each), and anemia (1.2%).
- Nivo IV: ALT increased (2.4%), AST increased, pneumonitis, fatigue, and rash (2.0% each), blood creatinine increased, and hyperglycemia (1.6% each), diarrhea, hypothyroidism, and anemia (1.2% each).

The Applicant's Position:

The frequency of AEs leading dose delay with nivolumab SC were consistent with those observed with nivolumab IV.

The FDA's Assessment:

The data presented by the Applicant appears incorrect as they appear to represent the results from Study CA20967T. The most common any grade AEs leading to dose delay in Study CA2098KX are included in Table 51 below. With the exception of rash, all events occurred in only one patient each and there was no identifiable pattern of toxicity beyond what has been described previously with nivolumab IV.

Table 51: AEs Leading to Dose Delay on Study CA2098KX

	PART D N = 36 N (%)	PART E N = 36 N (%)
Action taken for treatment drug - drug interrupted - due to AEs	10 (28)	16 (44)
Rash (GT)	2 (6)	0 (0)
Arrhythmia (GT)	1 (2.8)	0 (0)
Breast Cancer	1 (2.8)	0 (0)
Diabetes Mellitus	1 (2.8)	0 (0)
Diarrhea (GT)	1 (2.8)	0 (0)
Dysphagia	1 (2.8)	0 (0)
Hemianopia	1 (2.8)	0 (0)
Hepatic Cytolysis	1 (2.8)	0 (0)
Hyperglycemia	1 (2.8)	0 (0)
Hyperthyroidism	1 (2.8)	0 (0)
Musculoskeletal Pain (GT)	1 (2.8)	0 (0)
Blood Creatinine Increased	0 (0)	3 (8)
Covid-19	0 (0)	3 (8)

BLA Multi-disciplinary Review and Evaluation {BLA 761381 and BLA 761429}
OPDIVO (nivolumab and hyaluronidase - nvhy) injection, for subcutaneous use

	PART D N = 36 N (%)	PART E N = 36 N (%)
Alanine Aminotransferase Increased	0 (0)	2 (6)
Aspartate Aminotransferase Increased	0 (0)	2 (6)
Acute Kidney Injury (GT)	0 (0)	1 (2.8)
Anemia	0 (0)	1 (2.8)
Anal Abscess	0 (0)	1 (2.8)
Blood Alkaline Phosphatase Increased	0 (0)	1 (2.8)
Blood Urea Increased	0 (0)	1 (2.8)
Confusional State	0 (0)	1 (2.8)
Covid-19 Pneumonia	0 (0)	1 (2.8)
Epilepsy	0 (0)	1 (2.8)
Fatigue (GT)	0 (0)	1 (2.8)
Glucocorticoid Deficiency	0 (0)	1 (2.8)
Hypothyroidism (GT)	0 (0)	1 (2.8)
Inguinal Hernia	0 (0)	1 (2.8)
Nausea	0 (0)	1 (2.8)
Pyrexia (GT)	0 (0)	1 (2.8)
Tumor Fistulization	0 (0)	1 (2.8)

Group Hypothyroidism (GT) includes PT terms HYPOTHYROIDISM, BLOOD THYROID STIMULATING HORMONE INCREASED,
Group Fatigue (GT) includes PT terms FATIGUE, ASTHENIA,
Group Musculoskeletal Pain (GT) includes PT terms BACK PAIN, ARTHRALGIA, MUSCULOSKELETAL PAIN, MYALGIA, PAIN IN EXTREMITY, NON-CARDIAC CHEST PAIN, MUSCULOSKELETAL DISCOMFORT, NECK PAIN, BONE PAIN,
Group Diarrhoea (GT) includes PT terms DIARRHOEA,
Group Rash (GT) includes PT terms RASH, DERMATITIS ACNEIFORM, RASH PRURITIC, RASH ERYTHEMATOUS, RASH MACULO-PAPULAR, RASH PAPULAR, ECZEMA, PEMPHIGOID, DERMATITIS, VULVOVAGINAL RASH, RASH MACULAR,
Group Pyrexia (GT) includes PT terms PYREXIA,
Group Arrhythmia (GT) includes PT terms ATRIAL FIBRILLATION, ATRIOVENTRICULAR BLOCK FIRST DEGREE,
Group Acute Kidney Injury (GT) includes PT terms NEPHROPATHY TOXIC, ACUTE KIDNEY INJURY,
Source: ADSL (Subject-Level Analysis Dataset) - 2024-02-29, ADAE (Adverse Event Analysis Dataset) - 2024-02-29. Variables used: USUBJID, TR01AG1, SAFFL, TRTEM2FL, AEDECOD, ATOXGRN, AEACN, AEBODSYS, AESER

Significant Adverse Events

Data: See Table 50 for IMAEs reported in CA2098KX.

The Applicant's Position:

Local site reactions: The majority of local site reactions were Grade 1-2, with PT injection site erythema as the most frequently reported in Part D (6 [16.7%] subjects), and PT injection site reaction the most frequently reported in Part E (10 [27.8%] subjects).

IMAEs: Overall, the majority of IMAEs in both Part D and Part E were Grade 1-2 (Table 50).

OESIs: No OESI (all causality or drug-related) was reported in Parts D or E of CA2098KX.

The FDA's Assessment:

Local site reactions: Local injection site reactions of any grade occurred in 11 (31%) patients in Part D and in 12 (33%) patients in Part E of Study CA2098KX. All local injection site reactions were Grade 1 or 2. Preferred terms for local site reactions on Arm D included injection site erythema (17%), injection site reaction (8%), injection site pain (6%), injection site pruritis (2.8%), injection related reaction (2.8%). Preferred terms for local site reactions on Arm E included injection site reaction (28%), injection site erythema (2.8%), injection site hematoma (2.8%), and injection related reaction (2.8%).

IMAEs: The most frequently reported grouped terms for IMAEs of any grade for Part D included hypothyroidism (22%), hyperthyroidism (14%), and rash (14%). The most frequently reported grouped terms for IMAEs of any grade for Part E included hypothyroidism (17%) and rash (6%).

OESIs: No OESIs of any causality were reported in Part D or Part E of Study CA2098KX.

Treatment Emergent Adverse Events and Adverse Reactions

Data: Refer to Table 50

The Applicant's Position:

Overall, the safety profile of nivolumab SC was consistent with the known mechanism of action of nivolumab. Most AEs were low grade (Grades 1-2). No new types of clinically important events were identified, and the majority were manageable in the clinical setting with concomitant medications.

The FDA's Assessment:

All patients on either arm experienced at least one any grade TEAE. Grade 3 or 4 TEAEs occurred in 53% of patients in Part D and 42% of patients on Part E. The most common ($\geq 5\%$ incidence) Grade 3 or 4 TEAEs in Part D were rash (8%), ALT increased (6%), and lipase increased (6%). The most common ($\geq 5\%$ incidence) Grade 3 or 4 TEAEs in Part E were AST increased (8%), ALT increased (6%), and hemorrhage (6%). The types and frequencies of TEAEs reported is generally consistent with what has been reported previously for nivolumab IV, particularly given the size of the cohorts, the tumor types included (NSCLC, RCC, HCC, UC, and CRC), and the refractory disease setting (at least 1 or 2 prior systemic therapies).

Table 52: Summary of AEs for Study CA2098KX

	PART D N = 36 N (%)	PART E N = 36 N (%)
All-Grade TEAEs	36 (100)	36 (100)
Grade 3-5 TEAEs	19 (53)	15 (42)
Grade 3-4 TEAEs	19 (53)	15 (42)
Grade 3	12 (33)	13 (36)
Grade 4	7 (19)	2 (6)
Grade 5 (Deaths due to TEAEs)	0 (0.0)	0 (0.0)
Serious TEAEs (SAEs)	16 (44)	18 (50)
Action taken for treatment drug - drug withdrawn - due to AEs	9 (25)	4 (11)
Action taken for treatment drug - drug interrupted - due to AEs	10 (28)	16 (44)
Action taken for treatment drug - dose increased - due to AEs	1 (2.8)	0 (0.0)

Source: ADSL (Subject-Level Analysis Dataset) - 2024-02-29, ADAE (Adverse Event Analysis Dataset) - 2024-02-29. Variables used: USUBJID, TR01AG1, SAFFL, TRTEM2FL, ATOXGRN, AESER, AEACN

	PART D N = 36		PART E N = 36	
	All grades n (%)	Grades 3-4 n (%)	All grades n (%)	Grades 3-4 n (%)
Patients with TEAEs	36 (100)	19 (53)	36 (100)	15 (42)
General Disorders And Administration Site Conditions				
Fatigue (GT)	8 (22)	0 (0.0)	15 (42)	1 (2.8)
Injection Site Erythema	6 (17)	0 (0.0)	1 (2.8)	0 (0.0)
Edema (GT)	4 (11)	0 (0.0)	0 (0.0)	0 (0.0)
Injection Site Reaction	3 (8)	0 (0.0)	10 (28)	0 (0.0)

	PART D N = 36		PART E N = 36	
	All grades n (%)	Grades 3-4 n (%)	All grades n (%)	Grades 3-4 n (%)
Pyrexia (GT)	2 (6)	0 (0.0)	5 (14)	0 (0.0)
Musculoskeletal And Connective Tissue Disorders				
Musculoskeletal Pain (GT)	14 (39)	0 (0.0)	14 (39)	1 (2.8)
Gastrointestinal Disorders				
Abdominal Pain (GT)	5 (14)	1 (2.8)	9 (25)	0 (0.0)
Constipation	5 (14)	0 (0.0)	5 (14)	0 (0.0)
Diarrhea (GT)	4 (11)	0 (0.0)	6 (17)	0 (0.0)
Nausea	1 (2.8)	0 (0.0)	8 (22)	0 (0.0)
Dry Mouth	0 (0.0)	0 (0.0)	4 (11)	0 (0.0)
Infections And Infestations				
Urinary Tract Infection (GT)	7 (19)	1 (2.8)	2 (6)	0 (0.0)
Vascular Disorders				
Hemorrhage (GT)	6 (17)	2 (6)	4 (11)	2 (6)
Investigations				
ALT Increased	4 (11)	2 (6)	5 (14)	2 (6)
Blood Creatinine Increased	4 (11)	0 (0.0)	6 (17)	0 (0.0)
Lipase Increased	4 (11)	2 (6)	0 (0.0)	0 (0.0)
AST Increased	3 (8)	1 (2.8)	7 (19)	3 (8)
Skin And Subcutaneous Tissue Disorders				
Rash (GT)	8 (22)	3 (8)	9 (25)	0 (0.0)
Pruritus	6 (17)	0 (0.0)	9 (25)	0 (0.0)
Endocrine Disorders				
Hypothyroidism (GT)	7 (19)	0 (0.0)	8 (22)	0 (0.0)
Hyperthyroidism	6 (17)	0 (0.0)	1 (2.8)	0 (0.0)
Respiratory, Thoracic And Mediastinal Disorders				
Cough (GT)	4 (11)	0 (0.0)	3 (8)	0 (0.0)
Blood And Lymphatic System Disorders				
Anemia	3 (8)	1 (2.8)	7 (19)	4 (11)

Laboratory Findings

The Applicant's Position:

Abnormalities in hematology laboratory results, liver tests, kidney function tests, and electrolytes in nivolumab subjects were primarily Grade 1-2.

The FDA's Assessment:

FDA agrees with the Applicant's assessment. Laboratory abnormalities were mostly Grade 1 or Grade 2. Laboratory abnormalities of increased AST or ALT were similar to what has been described previously in the USPI for nivolumab IV.

Table 53: Laboratory Abnormalities Occurring in $\geq 20\%$ of Patients in Study CA2098KX

	PART D N = 36		PART E N = 36	
	Grades 1-4 n/N evaluable (%)	Grades 3-4 n/N evaluable (%)	Grades 1-4 n/N evaluable (%)	Grades 3-4 n/N evaluable (%)
HEMOGLOBIN (G/L) - Decreased	11/35 (31)	1/35 (2.9)	12/36 (33)	2/36 (6)
ALBUMIN, LOCAL LAB (G/L) - Decreased	10/35 (29)	1/35 (2.9)	4/9 (44)	1/9 (11)
LIPASE, TOTAL (COLORIMETRIC ASSAY) (U/L) - Increased	10/32 (31)	0/32 (0.0)	0/0 (0.0)	0/0 (0.0)
ALKALINE PHOSPHATASE (ALP), LOCAL LAB (U/L) - Increased	9/35 (26)	1/35 (2.9)	8/35 (23)	2/35 (6)
HYPONATREMIA (MMOL/L) - Decreased	9/35 (26)	1/35 (2.9)	12/36 (33)	1/36 (2.8)
SODIUM, LOCAL LAB (MMOL/L) - Decreased	9/35 (26)	1/35 (2.9)	12/36 (33)	1/36 (2.8)
CREATININE, LOCAL LAB (UMOL/L) - Increased	8/35 (23)	0/35 (0.0)	10/36 (28)	0/36 (0.0)
G-GLUTAMYL TRANSFERASE (GGT) (U/L) - Increased	8/35 (23)	1/35 (2.9)	2/4 (50)	2/4 (50)
ASPARTATE AMINOTRANSFERASE (AST), LOCAL LAB (U/L) - Increased	6/35 (17)	2/35 (6)	11/36 (31)	3/36 (8)

	PART D N = 36		PART E N = 36	
	Grades 1-4 n/N evaluable (%)	Grades 3-4 n/N evaluable (%)	Grades 1-4 n/N evaluable (%)	Grades 3-4 n/N evaluable (%)
LYMPHOCYTES (ABSOLUTE), LOCAL LAB (10 ⁹ /L) - Decreased	6/32 (19)	0/32 (0.0)	12/33 (36)	2/33 (6)
CALCIUM, CORRECTED, LOCAL LAB (MMOL/L) - Increased	5/20 (25)	0/20 (0.0)	2/14 (14)	0/14 (0.0)
LYMPHOCYTES (ABSOLUTE) (10 ⁹ /L) - Decreased	2/3 (67)	1/3 (33)	3/3 (100)	0/3 (0.0)
APTT (SEC) - Increased	1/4 (25)	0/4 (0.0)	1/8 (13)	0/8 (0.0)

Source: ADSL (Subject-Level Analysis Dataset) - 2024-02-29, ADLB (Lab Analysis Dataset IS Units) - 2024-02-29. Variables used: USUBJID, TR01AG1, SAFFL, PARAM, ABLFL, AVAL, ANRLO, ANRHI, ONTRT2FL, APEREDT, ADT, APERSDT, ADY, ATOXGRN

Vital Signs

Data:

Vital signs were monitored and recorded at the site per institutional standard of care during screening, and vital signs were monitored during treatment visits. These assessments were intended to be used as safety monitoring by the treating physician.

The Applicant's Position:

Nivolumab SC did not appear to have clinically meaningful adverse effects on subject vital signs during the study.

The FDA's Assessment:

Per protocol body temperature, blood pressure, and heart rate were assessed pre-dose during every cycle. FDA agrees that there did not appear to be clinically meaningful adverse effects on subject vital signs during the study.

Electrocardiograms

The Applicant's Position:

ECG testing was conducted at Screening as part of eligibility assessments for study participation. Routine ECG testing (as part of study safety assessments) was not performed during the on-treatment and follow-up visits.

The FDA's Assessment:

ECG testing was performed at screening within 14 days prior to randomization but was not performed during the course of the study during the on-treatment and follow-up visits. ECG testing has been conducted in prior studies of nivolumab IV.

QT

The Applicant's Position:

Not applicable.

The FDA's Assessment:

Study CA20967T was not designed to formally assess ECG interval, rate, rhythm, or morphology. ECG was performed at baseline and then only as clinically indicated. Assessments of QT interval have been conducted in prior studies of nivolumab IV.

Immunogenicity

Data:

Table 54: Applicant - ADA Assessments Summary by Original Treatment Allocation - Treated Subjects in Parts D and E with Baseline and at Least One Post-Baseline Assessment in CA2098KX

Subject ADA Status (%)	PART D - GRP 5 N = 36	PART E - GRP 6 N = 35
BASELINE ADA POSITIVE	1 (2.8)	1 (2.9)
ADA POSITIVE	4 (11.1)	10 (28.6)
PERSISTENT POSITIVE (PP)	1 (2.8)	0
NOT PP-LAST SAMPLE POSITIVE	1 (2.8)	2 (5.7)
OTHER POSITIVE	2 (5.6)	8 (22.9)
NEUTRALIZING POSITIVE	0	0
ADA NEGATIVE	32 (88.9)	25 (71.4)

Baseline ADA Positive: A subject with baseline ADA-positive sample;
ADA Positive: A subject with at least one ADA-positive sample relative to baseline (ADA negative at baseline or ADA titer to be at least 4-fold or greater ($\geq$) than baseline positive titer) at any time after initiation of treatment;
Persistent Positive (PP): ADA-positive sample at 2 or more consecutive timepoints, where the first and last ADA-positive samples are at least 16 weeks apart;
Not PP-Last Sample Positive: Not persistent but with ADA-positive sample at the last sampling timepoint;
Other Positive: Not persistent but some ADA-positive samples with the last sample being negative;
Neutralizing Positive: At least one ADA-positive sample with neutralizing antibodies detected post-baseline;
ADA Negative: A subject with no ADA-positive sample after initiation of treatment. Post-baseline assessments are assessments reported after initiation of treatment.
Participants without both baseline and post baseline results are excluded.
Datasets: *ADSL*, *ADYT*

The Applicant's Position:

Of the 36 nivolumab ADA evaluable subjects in Part D, 1 subject was nivolumab ADA positive at baseline, 4 subjects were ADA positive relative to baseline, and 1 subject was persistent positive and no subject was neutralizing ADA positive. ADA titers from positive subjects ranged from 2-16.

Of the 35 nivolumab ADA evaluable subjects in Part E, 1 subject was nivolumab ADA positive at baseline, 10 subjects were ADA positive relative to baseline, and no subject was persistent positive or neutralizing ADA positive. ADA titers from positive subjects ranged from 1-128.

No subject in the study developed neutralizing antibodies to nivolumab. Immunogenicity associated with nivolumab SC is infrequent.

Among the treated subjects across all parts (A-E) evaluable and positive for ADA (N=29), no subject was reported with hypersensitivity/infusion related reaction select AEs, compared with 5 of 108 (4.6%) in the nivolumab ADA-negative subgroup. Thus, the presence of nivolumab ADA did not appear to be associated with the occurrence of these events. Based on assessment of the occurrence of ADAs in relation to PFS, investigator assessed BOR, and OS, some subjects positive for nivolumab ADAs continued treatment with clinical benefit, and there was no apparent trend showing an effect of positive ADA on the efficacy of nivolumab.

The FDA's Assessment:

FDA agrees with the Applicant's assessment. There were no events of infusion-related reaction, bronchospasm, or hypersensitivity in nivolumab ADA-positive patients in Part D or Part E of Study CA2098KX. Immunogenicity based upon rHuPH20 ADA was not available as of database lock. See Section 8.2.4 for an assessment of the effect of rHuPH20 ADA status on the safety of nivolumab SC.

8.2.6. Analysis of Submission-Specific Safety Issues

8.2.6.1 Comparison with Broader Safety Experience

The Applicant's Position:

With the exception of local site reactions (Table 39 and Table 50), the safety profile reported with nivolumab SC was consistent with the known safety profile of nivolumab IV and was manageable based on already established management guidelines. No new safety signals were detected in either CA20967T or CA2098KX.

The FDA's Assessment:

FDA generally agrees with the Applicant's assessment. With the exception of local site reactions, there were no new safety signals identified in Study CA20967T or Study CA2098KX that have not been reported in the OPDIVO USPI or in the published literature of clinical trials or case series.

8.2.7. Clinical Outcome Assessment (COA) Analyses Informing Safety/Tolerability

Data:

The FACIT GP5, is an item in the FKSI-19 and assesses the extent of perceived bother due to symptomatic AEs. A majority of scores throughout most on-treatment time points were at Level 1 (no bother) with over 90% of subjects reporting Levels 1 through Level 3 (somewhat bother) in both arms.

The Applicant's Position:

In CA20967T, a review of the FACIT GP5 results did not identify a substantial difference in perceived bother from symptomatic AEs by patients, supporting that there was no suggestion of tolerability difference between nivolumab SC and nivolumab IV.

The FDA's Assessment:

There did not appear to be an appreciable difference in FACIT GP5 results as the study progressed. The proportion of patients indicating "Not at all" with respect to perceived bother from symptomatic AEs declined slightly as the study progressed. The majority of patients in the nivolumab SC arm continued to indicate either "Not at all" or "A little bit" with respect to perceived bother from symptomatic AEs even as the study progressed from baseline to week 105. The COA results are considered exploratory.

8.2.8. Safety Analyses by Demographic Subgroups

Data:

Table 55: Applicant - Drug-Related Adverse Events by Worst CTC Grade and by Age, Gender, Race, and Region - All Treated Subjects in CA20967T

	Nivo SC				Nivo IV			
	N	Any Grade	Grade 3-4	Grade 5	N	Any Grade	Grade 3-4	Grade 5
Total	247	146 (59.1)	24 (9.7)	0	245	158 (64.5)	36 (14.7)	0
By Age								
< 65 yrs	129	78 (60.5)	10 (7.8)	0	115	75 (65.2)	15 (13.0)	0
≥ 65 and < 75 yrs	84	46 (54.8)	8 (9.5)	0	97	61 (62.9)	15 (15.5)	0
≥ 75 and < 85 yrs	30	19 (63.3)	5 (16.7)	0	30	19 (63.3)	6 (20.0)	0
≥ 75 yrs	34	22 (64.7)	6 (17.6)	0	33	22 (66.7)	6 (18.2)	0
≥ 65 yrs	118	68 (57.6)	14 (11.9)	0	130	83 (63.8)	21 (16.2)	0
By Sex								
Male	163	101 (62.0)	17 (10.4)	0	171	107 (62.6)	28 (16.4)	0
Female	84	45 (53.6)	7 (8.3)	0	74	51 (68.9)	8 (10.8)	0
By Race								
White	204	121 (59.3)	23 (11.3)	0	215	139 (64.7)	31 (14.4)	0
Black or African American	0	0	0	0	2	1 (50.0)	0	0
Asian	3	1 (33.3)	0	0	1	1 (100.0)	0	0
Other	38	24 (63.2)	1 (2.6)	0	24	17 (70.8)	5 (20.8)	0
By Region								
US and EU	67	39 (58.2)	7 (10.4)	0	75	44 (58.7)	11 (14.7)	0
Mexico and South America	158	95 (60.1)	15 (9.5)	0	147	100 (68.0)	23 (15.6)	0
Rest of the World	22	12 (54.5)	2 (9.1)	0	23	14 (60.9)	2 (8.7)	0

MedDRA Version 26.0, CTC version 5.0; Includes events reported between first dose and 30 days after last dose of study therapy.

Datasets: ADSL, ADAE, ADSUB

The Applicant's Position:

None of the noted differences in demographic subgroups alters the overall benefit/risk profile of nivolumab SC.

For all treated subjects in the nivolumab SC arm of CA20967T, no major differences in drug-related AEs of Any Grade and Grade 3-4 were reported in older subjects compared

with younger subjects. No specific SOC/PT level patterns were identified. Across most age groups of Any Grade and Grade 3-4, AE rates were consistently lower in the nivolumab SC arm compared with the nivolumab IV arm. Rates of Grade 3-4 drug-related AEs were lower for males in the nivolumab SC arm compared with the nivolumab IV arm, while rates were comparable for females in the nivolumab SC and nivolumab IV arms. For subgroups based on race, most subjects were classified as "White". Very low sample sizes in other categories of race, such as "Black or African American", "Asian", and "Other", limit the interpretability of potential differences. Subgroup analyses by region shared similar patterns with those by reported in the overall study population.

Additional safety analyses were performed using the stratification factor of weight category (< 80 kg or ≥ 80 kg). In subjects < 80 kg and ≥ 80 kg, the overall frequencies of drug-related any-grade, Grade 3-4, and Grade 5 AEs within 30 days of last dose were mostly similar between the nivolumab SC and nivolumab IV treatment arms. At the SOC/PT level, no patterns or clusters were identified.

The FDA's Assessment:

FDA performed analyses by demographic subgroups using the safety population dataset to evaluate and confirm the safety profile of nivolumab SC across certain subgroups based on age, sex, race, ethnicity, and region. In general, both any grade and Grade ≥3 adverse events were similar across treatment arms for most demographic subgroups evaluated. Adverse events were similar in both elderly (≥ 65 years) and young (< 65 years) patients, but there was a greater proportion of very elderly (≥ 75 years) patients with Grade ≥3 adverse events on the nivolumab plus hyaluronidase SC arm relative to the nivolumab IV arm (55.9% vs. 39.4%). This was a small subset of patients and therefore interpretation is difficult.

Adverse events were similar in both females and males and there were no major differences across the treatment arms.

As there were very few patients in the American Indian or Alaskan Native, Asian, and Black or African American demographic subgroups, no conclusions can be drawn regarding the safety profile in these subgroups.

Adverse events were also similar with respect to ethnicity (Hispanic or Latino vs. Non-Hispanic or Latino). The proportion of patients with Any Grade or Grade 3 or 4 adverse events were also similar across the regions of the study.

Table 56: Safety Analyses by Demographic Subgroups

	Nivolumab plus Hyaluronidase SC			Nivolumab IV		
	N	Any Grade n (%)	Grade ≥3 n (%)	N	Any Grade n (%)	Grade ≥3 n (%)
Age						
< 65 years	129	120	48	115	107	49

BLA Multi-disciplinary Review and Evaluation {BLA 761381 and BLA 761429}
OPDIVO (nivolumab and hyaluronidase - nvhy) injection, for subcutaneous use

		(93.0)	(37.2)		(93.0)	(42.6)
≥ 65 years	118	110 (93.2)	49 (41.5)	130	122 (93.8)	57 (43.8)
≥ 75 years	34	32 (94.1)	19 (55.9)	33	32 (97.0)	13 (39.4)
Sex						
Female	84	78 (92.9)	35 (41.7)	74	70 (94.6)	28 (37.8)
Male	163	152 (93.3)	62 (38.0)	171	159 (93.0)	78 (45.6)
Race						
American Indian or Alaskan Native	2	2 (100)	1 (50.0)	3	3 (100)	2 (66.7)
Asian	3	3 (100)	1 (33.3)	1	1 (100)	1 (100)
Black or African American	0	0	0	2	2 (100)	1 (50.0)
White	204	189 (92.6)	81 (39.7)	215	200 (93.0)	92 (42.8)
Other	38	36 (94.7)	14 (36.8)	24	23 (95.8)	10 (41.7)
Ethnicity						
Hispanic or Latino	92	85 (92.4)	41 (44.6)	83	80 (96.4)	35 (42.2)
Non-Hispanic or Latino	80	73 (91.3)	27 (33.8)	82	71 (86.6)	33 (40.2)
Geographic Region						
EU and US	67	61 (91.0)	22 (32.8)	75	65 (86.7)	32 (42.7)
Mexico and South America	158	149 (94.3)	68 (43.0)	147	144 (98.0)	65 (44.2)
Rest of the World	22	20 (90.9)	7 (31.8)	23	20 (87.0)	9 (39.1)

8.2.9. Specific Safety Studies/Clinical Trials

The Applicant's Position:

Not applicable.

The FDA's Assessment:

Not applicable.

8.2.10. Additional Safety Explorations

Human Carcinogenicity or Tumor Development

The Applicant's Position:

No studies were conducted related to human carcinogenicity for nivo SC.

The FDA's Assessment:

Not applicable.

Human Reproduction and Pregnancy

The Applicant's Position:

In both CA20967T and CA2098KX, all pregnancy tests were negative during the study in all individuals of childbearing potential.

The FDA's Assessment:

FDA agrees with the Applicant's assessment. See Section 5.4 of the USPI for Opdivo for information on the potential for embryofetal toxicity with nivolumab.

Pediatrics and Assessment of Effects on Growth

The Applicant's Position:

Not applicable. No pediatric subjects were enrolled in either CA20967T or CA2098KX.

The FDA's Assessment:

FDA agrees with the Applicant's position.

Overdose, Drug Abuse Potential, Withdrawal, and Rebound

The Applicant's Position:

There is no information on overdose or drug abuse. No cases of withdrawal symptoms related to nivo SC were reported in CA20967T or CA2098KX.

The FDA's Assessment:

FDA agrees with the Applicant's position.

8.2.11. Safety in the Postmarket Setting

Safety Concerns Identified Through Postmarket Experience

The Applicant's Position:

Not applicable. Nivolumab SC is not currently marketed in any territory.

The FDA's Assessment:

Not applicable as nivolumab SC is not currently marketed.

Expectations on Safety in the Postmarket Setting

The Applicant's Position:

The safety profile of nivolumab SC has been analyzed and found to be comparable to an established standard of care, nivolumab IV, through the open-label studies CA20967T and CA2098KX. Further potential safety issues are not anticipated beyond the risks conveyed in the proposed labelling. BMS considers that the analysis of pregnancy cases in the Corporate Safety Database as part of routine PV actions will provide adequate monitoring of nivolumab SC safety in pregnancy. Periodic and cumulative reviews of safety data from pregnancy cases will continue to be provided in the nivolumab Development Safety Update Report, which describes the clinical trial experience of both the IV and SC formulations.

The FDA's Assessment:

Potential safety concerns are not expected beyond the risks reported in Study CA20967T, Study CA2098KX, and the extensive prior clinical experience with nivolumab IV formulation. Routine pharmacovigilance will be conducted by FDA to monitor for any unexpected adverse events.

8.2.12. Integrated Assessment of Safety

The Applicant's Position:

Pooled analyses were not conducted.

The FDA's Assessment:

The data supporting FDA's assessment of the safety of nivolumab SC is based primarily on the safety population from Study CA20967T which was a global, open-label, randomized, noninferiority study of SC formulation of nivolumab (n=247) versus IV nivolumab (n=245) in adult patients with advanced or metastatic ccRCC who are naïve to therapy targeting T-cell co-stimulation or checkpoint pathways, and have received no more than 2 prior systemic regimens. Supportive data came from Study CA2098KX which was a multicenter, randomized, open-label, Phase 1/2 study that evaluated the PK, safety, and tolerability of nivolumab SC in patients with hepatocellular carcinoma, melanoma, non-small cell lung cancer, renal cell carcinoma, urothelial cancer, and MSI-High colorectal cancer.

The safety profile, including treatment emergent common AEs, Grade 3 or 4 TEAEs; SAEs, TEAEs leading to death; and TEAEs resulting in treatment delay, injection/infusion interruption, or treatment discontinuation; immune-mediated adverse events (IMAEs); and other events of special interest (OESI) was generally consistent with the established and well characterized safety profile of nivolumab IV. The notable exception is the presence of injection-site reactions which occurred in 20 (8%) patients in the nivolumab SC arm of Study CA20967T and were generally mild (i.e., Grade 1 or 2).

Direct comparisons of the treatment arms on Study CA20967T, with respect to the frequency of TEAEs, are limited by the differences in monitoring across treatment arms (i.e., physical exams and laboratory assessments) with twice as frequent monitoring in the nivolumab IV arm due to the difference in dosing frequency across the treatment arms.

While direct comparisons are challenging due to the differences in monitoring, it is evident that nivolumab SC has an acceptable safety profile that is consistent with what has been described previously across studies of nivolumab IV.

SUMMARY AND CONCLUSIONS

8.3. Statistical Issues

The FDA's Assessment:

The efficacy assessment of Study CA20967T was based on a pre-specified comparison of ORR assessed by BICR between nivolumab SC and nivolumab IV arms. Although the Applicant used a non-inferiority test for this comparison, the non-inferiority margin was not based on a comparative result from a historical trial, and therefore the preservation of treatment effect is not well defined for this comparison and the results of the non-inferiority test are difficult to interpret. However, the pivotal study CA20967T showed no notable difference between the nivolumab SC arm and the nivolumab IV arm in terms of the clinical efficacy endpoints including ORR, PFS, and OS.

8.4. Conclusions and Recommendations

The FDA's Assessment:

FDA concludes that Study CA20967T demonstrated that the comparison of nivolumab SC with nivolumab IV met the predefined acceptance margin for pharmacokinetic endpoints, with the lower boundary of 90% confidence interval of geometric mean ratios of not less than 0.8 for both serum nivolumab C_{avg} over 28 days and C_{min} at steady state. No notable differences were observed for the key secondary endpoint of ORR by BICR according to RECIST v1.1.

The safety profile reported for nivolumab SC was generally consistent with the known safety profile for nivolumab IV with the notable exception of injection-site reactions, which were associated with nivolumab SC treatment and generally mild. Overall the review team concludes that the data in BLA 761381 and BLA 761429 support a favorable benefit:risk assessment for nivolumab SC in the indicated population and recommends traditional approval for the following indications:

Renal Cell Carcinoma (RCC)

- adult patients with intermediate or poor risk advanced RCC, as a first-line treatment following combination treatment with ipilimumab.
 - Limitations of Use: OPDIVO QVANTIG is not indicated for the treatment of renal cell carcinoma in combination with ipilimumab.
- adult patients with advanced RCC, as a first-line treatment in combination with cabozantinib.
- adult patients with advanced RCC who have received prior anti-angiogenic therapy.

Melanoma

- adult patients with unresectable or metastatic melanoma.

- adult patients with unresectable or metastatic melanoma following combination treatment with intravenous nivolumab and ipilimumab.
 - Limitations of Use: OPDIVO QVANTIG is not indicated for the treatment of unresectable or metastatic melanoma in combination with ipilimumab.
- for the adjuvant treatment of adult patients with completely resected Stage IIB, Stage IIC, Stage III, or Stage IV melanoma.

Non-Small Cell Lung Cancer (NSCLC)

- adult patients with resectable (tumors ≥ 4 cm or node positive) NSCLC in the neoadjuvant setting, in combination with platinum-doublet chemotherapy.
- adult patients with resectable (tumors ≥ 4 cm or node positive) NSCLC and no known EGFR mutations or ALK rearrangements, for neoadjuvant treatment, in combination with platinum-doublet chemotherapy, followed by OPDIVO QVANTIG monotherapy as adjuvant treatment after surgery. (This indication was submitted as a Type 9 application under BLA 761429)
- adult patients with metastatic NSCLC and progression on or after platinum-based chemotherapy. Patients with EGFR or ALK genomic tumor aberrations should have disease progression on FDA-approved therapy for these aberrations prior to receiving OPDIVO QVANTIG.
 - Limitations of Use: OPDIVO QVANTIG is not indicated for the treatment of metastatic NSCLC in combination with ipilimumab.

Squamous Cell Carcinoma of the Head and Neck (SCCHN)

- adult patients with recurrent or metastatic SCCHN with disease progression on or after a platinum-based therapy.

Urothelial Carcinoma (UC)

- adjuvant treatment of adult patients with UC who are at high risk of recurrence after undergoing radical resection of UC.
- adult patients with unresectable or metastatic urothelial carcinoma, as first-line treatment in combination with cisplatin and gemcitabine. (This indication was submitted as a Type 9 application under BLA 761429)
- adult patients with locally advanced or metastatic UC who:
 - have disease progression during or following platinum-containing chemotherapy.
 - have disease progression within 12 months of neoadjuvant or adjuvant treatment with platinum-containing chemotherapy.

Colorectal Cancer

- adult patients with MSI-H or dMMR metastatic CRC that has progressed following treatment with a fluoropyridine, oxaliplatin, and irinotecan.

- Limitations of Use: OPDIVO QVANTIG is not indicated for the treatment of MSI-H or dMMR metastatic CRC in combination with ipilimumab.

Hepatocellular Carcinoma (HCC)

- adult patients with HCC previously treated with sorafenib and following combination treatment with ipilimumab.

Esophageal Cancer

- adult patients with completely resected esophageal or gastroesophageal junction cancer with residual pathologic disease, who have received neoadjuvant chemoradiotherapy (CRT).
- adult patients with unresectable advanced or metastatic esophageal squamous cell carcinoma as first-line treatment in combination with fluoropyrimidine- and platinum-containing chemotherapy.
 - Limitations of Use: OPDIVO QVANTIG is not indicated for the treatment of patients with unresectable advanced or metastatic ESCC in combination with ipilimumab.
- adult patients with unresectable advanced, recurrent or metastatic esophageal squamous cell carcinoma (ESCC) after prior fluoropyrimidine- and platinum-based chemotherapy.

8.4.1. Approach to Substantial Evidence of Effectiveness

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

1. Verbatim indication (enter approved indication if the application was approved and the Applicant's proposed indication if the application received a complete response): See review above.
2. SEE was established with (check one of the options for traditional or accelerated approval pathways and complete response not due to lack of demonstrating SEE)
 - a. Adequate and well-controlled clinical investigation(s):
 - i. ☐ Two or more adequate and well-controlled clinical investigations, OR
 - ii. ☐ One adequate and well-controlled clinical investigation with highly persuasive results that is considered to be the scientific equivalent of two clinical investigationsOR
 - b. ☒ One adequate and well-controlled clinical investigation and confirmatory evidence (refer to Section 1 above)OR

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

3. Complete response, if applicable

a. ☐ SEE was established

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

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

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

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

Primary Statistical Reviewer

Statistical Team Leader

Primary Clinical Reviewer

Clinical Team Leader

X

X

Primary Statistical Reviewer

Statistical Team Leader

X

X

Primary Clinical Reviewer

Clinical Team Leader

9 Advisory Committee Meeting and Other External Consultations

The FDA's Assessment:

The Division did not refer BLA 761381 or BLA 761429 to the Oncologic Drug Advisory Committee (ODAC) or seek input from Special Government Employees as no significant review issues were identified during the review of this application.

10 Pediatrics

The Applicant's Position:

The nivolumab SC agreed initial pediatric study plan, subject to PREA, is in accordance with section 505B(e) of the FD&C Act, as amended by FDASIA. PREA was further updated by FDARA, with respect to certain drugs intended for the treatment of an adult cancer and directed at a molecular target determined to be substantially relevant to the growth or progression of a pediatric cancer, and for which an original marketing application is submitted on or after August 18, 2020.

Therefore, the agreed iPSP for nivolumab SC is also in accordance with the *FDA Guidance for Industry, Pediatric Study Plans: Content of and Process for Submitting Initial Pediatric Study Plans and Amended Initial Pediatric Study Plans, July 2020*, as well as the *FDA Guidance for Industry FDARA Implementation Guidance for Pediatric Studies of Molecularly Targeted Oncology Drugs: Amendments to Sec. 505B of the FD&C Act, May 2021*.

The FDA's Assessment:

The Applicant's Agreed Initial Pediatric Study Plan for BLA 761381 included a proposal to address the FDARA provisions of PREA. The Applicant requested a partial waiver of submission of reports for the required molecularly targeted pediatric cancer investigation for nivolumab and hyaluronidase-nvhy in pediatric patients <12 years of age and a deferral of a molecularly targeted pediatric cancer investigation in pediatric patients 12 to <17 years of age. FDA review concluded that given the rarity of the cancer types in pediatric patients less than 12 years of age that benefit from nivolumab IV and that could potentially benefit from investigational treatment with nivolumab and hyaluronidase-nvhy, a partial waiver of this requirement in pediatric patients less than 12 year of age is reasonable. FDA review also concluded that a deferral would be granted for the study in patients 12 years and old.

Currently approved pediatric indications for nivolumab IV include: the treatment of pediatric patients (12 years and older) with unresectable or metastatic melanoma, as a single agent or in combination with ipilimumab; adjuvant treatment of pediatric patients 12 years and older with completely resected Stage IIB, Stage III, or Stage IV melanoma; and pediatric (12 years and older) patients with microsatellite instability-high (MSI-H) or mismatch repair deficient (dMMR) metastatic colorectal cancer that has progressed following treatment with a fluoropyrimidine, oxaliplatin, and irinotecan, as a single agent or in combination with ipilimumab.

The Applicant's obligations under section 505B(a)(1)(B) of the FD&C Act will be to submit reports from a molecularly targeted pediatric cancer investigation of nivolumab and hyaluronidase-nvhy gathered using appropriate formulations for each age group for which the study is required to assess the pharmacokinetics, dosing, and preliminary safety and efficacy of nivolumab co-formulated with hyaluronidase to BLA 761381. (b) (4)

For BLA 761429, the FDA waives the requirement for pediatric studies due to rarity of NSCLC and urothelial cancer in all pediatric age groups.

11 Labeling Recommendations

The Applicant's Position:

The clinical data provided in this BLA demonstrate the clinical benefit and safety of the use of nivolumab SC for the treatment of all indications listed in Section 2.

The FDA's Assessment: The proposed labeling submitted by the Applicant required extensive revision by the FDA. The Applicant's proposal to include only the information from the CHECKMATE-67T study is inadequate. Labeling must include complete and adequate safety and efficacy data to support all of the indications for the product, and CHECKMATE-67T enrolled only patients with advanced or metastatic clear cell renal cell carcinoma. FDA included supportive safety and efficacy data from the approved intravenous nivolumab labeling to support approval for the indications not studied in CHECKMATE-67T.

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

USPI Section	FDA Revision/Agreed-upon Labeling
Highlights	FDA included additional details in dosage and administration and adverse reactions for use as monotherapy and in combination with cabozantinib and in combination with chemotherapy. Limitations of use added (see Indications and Usage)
1 Indications and Usage	FDA revised (b) (4) to "monotherapy" because OPDIVO QVANTIG is a combination product containing nivolumab and hyaluronidase. FDA added "Limitations of Use" stating that OPDIVO QVANTIG is not indicated in combination with ipilimumab for all indications where Opdivo is approved for

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	combination use with ipilimumab.
2.1 Important Dosage and Administration Information	FDA added text: to reduce the risk of medication errors to describe switching between OPDIVO and OPDIVO QVANTIG
2.2 Recommended Dosage	FDA revised Tables 1 and 2 to separate monotherapy and combination therapy regimens
2.3 Preparation and Administration	FDA revised and re-ordered for clarity
5.1 Severe and Fatal Immune-Mediated Adverse Reactions	This section of the USPI follows the anti-PD-(L)1 harmonized format. FDA incorporated a description of the most severe adverse reactions (AR) in the intravenous nivolumab USPI at the beginning of each AR text and described ARs observed with OPDIVO QVANTIG, and with ARs observed with intravenous (IV) nivolumab in combination with cabozantinib and in combination with chemotherapy. The purpose of this format is to present a complete safety profile while avoiding copying the entire WARNINGS AND PRECAUTIONS section from the intravenous nivolumab USPI.
6.1 Clinical Trials Experience	Adverse Reactions of OPDIVO QVANTIG in Adult Patients with advanced renal cell carcinoma (RCC): text revised and edited for consistency with labeling regulations and guidances. This text described the safety observed in the CHECKMATE-67T study that enrolled patients with advanced or metastatic RCC. FDA included linkage statements and subheadings to support each of the indications in Section 1 and included the complete safety data from each pivotal trial supporting each indication from the IV nivolumab USPI.
6.2 Postmarketing Experience	FDA included postmarketing experience from IV nivolumab USPI
8.5 Geriatric Use	FDA added complete Geriatric Use data from IV nivolumab for each regimen pertinent to OPDIVO QVANTIG
12.3 Pharmacokinetics	The section describing the major outcome measure for the CHECKMATE-67T study as the comparison of the pharmacokinetics of OPDIVO QVANTIG to IV nivolumab was revised for clarity.
12.6 Immunogenicity	Section revised for clarity and to include full immunogenicity for IV nivolumab; ISR for ADA positive and negative described separately
13.1 Carcinogenesis,	Dose multiples for hyaluronidases revised for consistency

Mutagenesis, Impairment of Fertility	within USPI.
14 Clinical Studies	14.1 CHECKMATE-067T trial description and efficacy outcomes revised for clarity and brevity. Linkage statement included to introduce the efficacy data from IV nivolumab to further support the RCC indications. 14.2 – 14.12 Linkage statements were included to introduce the efficacy data from IV nivolumab to support all of the OPDIVO QVANTIG indications. Complete efficacy data from IV nivolumab were added.
Medication Guide	The Medication Guide was revised for consistency with the Prescribing Information.

12 Risk Evaluation and Mitigation Strategies (REMS)

The FDA's Assessment:

The clinical team determined a REMS for OPDIVO QVANTIG is not necessary to ensure the safe and effective use for the indicated populations given the consistency of the safety profile of the subcutaneous formulation with the safety profile observed with nivolumab IV. The medical community has experience with the management of adverse reactions associated with immune checkpoint inhibitor drugs. Recommendations for safe and effective use of OPDIVO QVANTIG are provided in the USPI as well as in the patient medication guide.

13 Postmarketing Requirements and Commitment

The FDA's Assessment:

Pediatrics

The following pediatric postmarketing requirement will be issued upon approval:

PMR 4762-1:

Conduct a molecularly targeted pediatric cancer investigation using an age-appropriate formulation of nivolumab and hyaluronidase-nvhy in pediatric patients 12 years of age and older.

Final Report Submission: 01/2025

Accelerated Approval

In addition to the pediatric PMR, Opdivo Qvantig will be subject to the AA PMRs for Opdivo for the HCC and MSI-H/dMMR CRC indications. BMS agreed to the following three PMRs (one for nivolumab for HCC, one for nivolumab for MSI-H/dMMR CRC, and one for nivolumab/ipilimumab combination for MSI-H/dMMR CRC). Although FDA generally has not

requested dataset submission in contemporaneous Accelerated Approval PMR language, these PMRs will reference dataset submission because they are *verbatim* (except for submission dates) from the respective Opdivo IV PMRs (PMR 3243-1, PMR 3449-1, PMR 3822-1). The FSRs referenced in these PMRs will be used to support the conversion of AA to regular approval for Opdivo Qvantig for the respective indications.

- Submit the final report demonstrating an improvement in overall survival from a multicenter, randomized trial to confirm the clinical benefit of nivolumab in combination with ipilimumab over standard therapy in patients with advanced hepatocellular carcinoma, that may inform product labeling. Submit the datasets with the final report.

Final Report Submission: 1/2025

- Submit the final report, including datasets, from trials conducted to verify and describe the clinical benefit of nivolumab 240 mg intravenously every two weeks in patients with microsatellite instability high or mismatch repair deficient metastatic colorectal cancer who have progressed following treatment with fluoropyrimidine, oxaliplatin and irinotecan, including at least 150 patients enrolled in BMS-initiated trials. In order to characterize response rate and duration, patients will be followed for at least 12 months from the onset of response.

Final Report Submission 11/2026

- Submit the final report, including datasets, from a randomized trial conducted to verify and describe the clinical benefit of nivolumab, administered in combination with ipilimumab, in patients with microsatellite instability-high or mismatch repair deficient metastatic colorectal cancer. The trial will be designed to demonstrate a clinically meaningful improvement in progression-free survival in patients randomized to receive nivolumab and ipilimumab as compared to patients randomized to receive nivolumab alone. In addition, the trial should evaluate for differences in overall survival between arms based on a pre-specified analysis. The analysis plan should describe the power for the overall survival analysis, as well as all assumptions made in determining the power.

Final Report Submission 11/2026

CMC

The CMC post-marketing commitment (PMC) listed below should be included in the action letter.

PMC 4762-2:

Establish and validate/qualify an appropriate method (existing or new), for determining the number and size of product-related visible particles in nivolumab subcutaneous injection drug product and implement the method for evaluation of visible particles in nivolumab subcutaneous injection drug product stability testing.

Final Report Submission: December 19, 2025

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 nivolumab IV in the indicated US patient populations and within racially and ethnically diverse patient populations in the US. No clinically significant differences in the pharmacokinetics of nivolumab have been observed based on race or age. Study CA20967t met its PK co-primary endpoints demonstrating PK comparability and no notable differences were observed for efficacy endpoints of ORR, PFS, or OS. FDA is not requesting a Diversity PMC.
☐ 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

14 Division Director (DHOT) (NME ONLY)

X

15 Division Director (OCP)

X

16 Division Director (OB)

X

17 Division Director (Clinical)

X

X

18 Appendices

18.1. Financial Disclosure

The Applicant's Position:

Financial interests or arrangements with clinical investigators have been disclosed in the table below. Financial disclosure information was collected and reported for the Investigators (Primary Investigators and Sub-investigators) participating in the CA20967T and CA2098KX clinical studies as recommended in the FDA Guidance for Clinical Investigators, Industry, and FDA Staff: *Financial Disclosure by Clinical Investigators*.

Covered Clinical Study (Name and/or Number): CA20967T

Was a list of clinical investigators provided:	Yes ☒	No ☐ (Request list from Applicant)
Total number of investigators identified: 463		
Number of investigators who are Sponsor employees (including both full-time and part-time employees): 1		
Number of investigators with disclosable financial interests/arrangements (Form FDA 3455): 0		
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: n/a Significant payments of other sorts: n/a Proprietary interest in the product tested held by investigator: n/a Significant equity interest held by investigator in study: n/a Sponsor of covered study: <u>n/a</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>7</u>		
Is an attachment provided with the reason:	Yes ☒	No ☐ (Request explanation from Applicant)

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

Covered Clinical Study (Name and/or Number): CA2098KX

Was a list of clinical investigators provided:	Yes ☒	No ☐ (Request list from Applicant)
Total number of investigators identified: <u>316</u>		
Number of investigators who are Sponsor employees (including both full-time and part-time employees): 0		
Number of investigators with disclosable financial interests/arrangements (Form FDA 3455): 0		
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: n/a Significant payments of other sorts: n/a Proprietary interest in the product tested held by investigator: n/a Significant equity interest held by investigator in study: n/a Sponsor of covered study: <u>n/a</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>4</u>		
Is an attachment provided with the reason:	Yes ☒	No ☐ (Request explanation from Applicant)

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

The FDA's Assessment:

Financial interests or arrangements with clinical investigators have been disclosed in the table for the two covered studies. No concerns were raised regarding the potential impact of financial arrangements between investigators and the Applicant on the interpretation of the study results.

18.2. Nonclinical Pharmacology/Toxicology

Data: See Section 5.

The Applicant's Position:

Not applicable.

The FDA's Assessment:

Not applicable.

18.3. References

- ¹ MacDonald D, Crosbie T, Christofides A, et al. A Canadian perspective on the subcutaneous administration of rituximab in non-Hodgkin lymphoma. *Curr Oncol* 2017;24:33-39.
- ² Jin J-F, Zhu L-L, Chen M, et al. The optimal choice of medication administration route regarding intravenous, intramuscular, and subcutaneous injection. *Patient Prefer Adherence* 2015;9:923-42.
- ³ Nivolumab Population Pharmacokinetic Analyses in Patients with Previously Treated Advanced or Metastatic RCC Following Intravenous or Subcutaneous Administration (Study CA20967T). Bristol-Myers Squibb Company; 2023. Document Control No: 930215259.
- ⁴ Population Pharmacokinetics of Nivolumab when Administered Subcutaneously in Subjects with Multiple Solid Tumors (Study CA2098kX). Bristol-Myers Squibb Company; 2023. Document Control No: 930211475.
- ⁵ Nivolumab Subcutaneous Simulation and Bridging Report for RCC and Multiple Solid Tumors. Bristol-Myers Squibb Company; 2024. Document Control No: 930217582.
- ⁶ Agrawal S, Feng Y, Roy A, et al. Nivolumab dose selection: challenges, opportunities, and lessons learned for cancer immunotherapy. *J Immunother Cancer* 2016;4:72.
- ⁷ Nivolumab population pharmacokinetic analysis in subjects with multiple tumor types. Bristol-Myers Squibb Company; 2016. Document Control No. 930103751.
- ⁸ Closeout Clinical Study Report for Study CA209003: A Phase 1, Open-label, multicenter, multidose escalation study of BMS-936558 (MDX-1106) in Subjects with Selected Advanced or Recurrent Malignancies. Bristol-Myers Squibb Company; 2021. Document Control No: 930175515.
- ⁹ Agrawal S, Feng Y, Roy A, Kollia G, and Lestini B. Nivolumab dose selection: challenges, opportunities, and lessons learned for cancer immunotherapy. *Journal for Immunotherapy of Cancer* 2016;4:72.
- ¹⁰ Primary Clinical Study Report for CA20967T: A Phase 3, Open-label, Randomized, Noninferiority Trial of Subcutaneous Formulation of Nivolumab in Participants with Advanced or Metastatic Clear Cell Renal Cell Carcinoma Who Have Received Prior Systemic Therapy. Bristol-Myers Squibb Company; 2023. Document Control No: 930214780.

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- 11 Mateos MV, Nahi H, Legiec W, et al. Subcutaneous versus intravenous daratumumab in patients with relapsed or refractory multiple myeloma (COLUMBA): a multicentre, open-label, non-inferiority, randomised, phase 3 trial. *Lancet Haematol* 2020;7:e370-e380.
- 12 Robins J, Breslow N, Greenland S. Estimators of the Mantel-Haenszel variance consistent in both sparse data and large-strata limiting models. *Biometrics* 1986;42:311-23.
- 13 Closeout Clinical Study Report for Study CA209025: A Randomized, Open-Label, Phase 3 Study of Nivolumab (BMS-936558) versus Everolimus in Subjects with Advanced or Metastatic Clear-Cell Renal Cell Carcinoma who have Received Prior Anti-Angiogenic Therapy. Bristol-Myers Squibb Company; 2022. Document Control No. 930183636.
- 14 Primary Clinical Study Report for CA2098KX: Phase 1/2 Pharmacokinetic Multi-tumor Study of Subcutaneous Formulation of Nivolumab Monotherapy. Bristol-Myers Squibb Company; 2023. Document Control No: 930209252.
- 15 Overman MJ, McDermott R, Leach J, et al. Nivolumab in patients with metastatic DNA mismatch repair-deficient or microsatellite instability-high colorectal cancer (CheckMate 142): an open-label, multicentre, phase 2 study. *Lancet Oncol* 2017;18:1182-91.
- 16 Addendum 03 for Interim Clinical Study Report for Study CA209040. A Phase 1/2 , Dose Escalation, Open-label, Non-comparative Study of Nivolumab or Nivolumab in Combination with Ipilimumab in Advanced Hepatocellular Carcinoma Subjects with or without Chronic Viral Hepatitis; and a Randomized, Open-label Study of Nivolumab vs Sorafenib in Advanced Hepatocellular Carcinoma Subjects who are Naive to Systemic Therapy. Bristol-Myers Squibb Company; 2018. Document Control No. 930128330.
- 17 Vokes EE, Ready N, Felip E, et al. Nivolumab versus docetaxel in previously treated advanced non-small cell lung cancer (CheckMate 017 and CheckMate 057): 3-year update and outcomes in patients with liver metastases. *Annals of Oncol* 2018;29:959-965.
- 18 Motzer RJ, Escudier B, McDermott S, et al. Nivolumab versus Everolimus in Advanced Renal-Cell Carcinoma. *N Engl J Med* 2015;373:1803-1813.
- 19 Sharma P, Retz M, Siefker-Radtke A, et al. Nivolumab in metastatic urothelial carcinoma after platinum therapy (CheckMate 275): a multicentre, single-arm, phase 2 trial. *Lancet Oncol* 2017;18:312-22.
- 20 Lonardi S, Bennett B, and Dixon M. Patient preference for subcutaneous nivolumab with/without recombinant human hyaluronidase PH20 versus intravenous nivolumab: an exploratory analysis of a phase 1/2 pharmacokinetic multi-tumor study. *ESMO Congress* 2022; September 9–13; Paris, France.
- 21 Recombinant Human Hyaluronidase PH20 (rHuPH20) Investigator’s Brochure Version 11.0. Halozyme, Inc; 2023. Document Control No. 930124324.

OCP Appendices (Technical documents supporting OCP recommendations)

Population PK Analysis

Executive Summary

The FDA's Assessment:

The PK of nivolumab was characterized by a two-compartment model with zero order infusion into the central compartment when administered by IV route and first order absorption from the extravascular compartment when administered via SC route and time-varying CL. This IV/SC popPK model was developed using data from 18 clinical studies of IV nivolumab and 1 Ph1/2 study of SC/IV nivolumab (CA2098KX). Population parameters of the IV/SC popPK model were re-estimated using Ph3 study CA20967T in RCC patients administered IV or SC nivolumab and individual exposure measures were predicted for statistical test. The non-inferiority of 1200 mg Q4W SC to 3 mg/kg Q2W IV was established for the primary and secondary PK endpoints.

The Ph1/2 study CA2098KX included multiple types of solid tumors and two SC dosages of nivolumab co-administered with rHuPH20 (i.e., 600 mg Q2W and 1200 mg Q4W) that showed similar bioavailability which is the basis for 1) evaluating exposure distribution in all approved solid tumor indications when nivolumab is administered via SC route, and 2) for evaluating alternative SC dosages.

To assess exposure distribution in solid tumor indications with SC nivolumab, the extravascular SC compartment of the IV/SC popPK model was inserted to the previously developed popPK models for IV nivolumab which showed exposures of SC nivolumab consistently higher than exposures of IV nivolumab. Extrapolation to alternative SC dosages (i.e., Q2W and Q3W) was based on bridging to the studied SC dosage of 1200 mg Q4W. Their AUC is expected to be comparable to that of Q4W but with smaller PK fluctuation within dosing interval. Additionally, the expected GMR for exposures between SC and IV of the same dosing intervals is also consistently above 1.

In conclusion, the proposed SC dosages for approved solid tumor indications are acceptable considering 1) PK non-inferiority between 1200 mg Q4W SC and 3 mg/kg Q2W IV, 2) PK comparability between 1200 mg Q4W SC and alternative SC dosages (900 mg Q3W and 600 mg Q2W) and larger expected GMR (>1) of SC to corresponding IV comparator of the same dosing interval, 3) Exposure distribution of SC despite a larger variability due to absorption and a higher ADA rate is expected to be above that of IV in all approved solid tumor indications.

PPK Assessment Summary

The Applicant's Position:

General Information - CA20967T	
Objectives of PPK Analysis	To characterize the PK parameters of nivolumab administered SC and IV in patients with 2L RCC using \$PRIOR subroutine in NONMEM.

		- To compare the predicted exposure measures for nivolumab 1,200 mg SC Q4W and nivolumab 3 mg/kg IV Q2W in patients with 2L RCC. - To assess the potential impact of development of anti-drug antibodies to nivolumab and to rHuPH20 on nivolumab PK parameters and predicted exposure measures for both nivolumab IV and SC in patients with 2L RCC. - To generate the co-primary endpoint nivolumab exposure measures (Cavgd28 and Cminss) to be used in the CA20967T noninferiority analysis.
Study Included		CA20967T
Dose(s) Included		Nivolumab SC 1,200 mg co-formulated with rHuPH20 20,000 units Q4W Nivolumab IV 3 mg/kg Q2W
Population Included		Adult subjects with 2L RCC
Population Characteristics (Error! Reference source not found.)	General	Nivolumab SC - Median (range) age: 64 (35, 93) years - Median (range) baseline body weight: 76.5 (35, 153) kg - Sex, n (%): 158 (65.3) males, 84 (34.7) females - Race, n (%): White: 199 (82.2), Black/African American: 0 (0), Asian: 3 (1.2), American Indian/Alaska Native 2 (0.8), Other: 38 (15.7) Nivolumab IV - Median (range) age: 66 (20, 87) years - Median (range) baseline body weight: 76.6 (47.5, 157) kg - Sex, n (%): 171 (69.8) males, 74 (30.2) females - Race, n (%): White: 215 (87.8), Black/African American: 2 (0.8), Asian: 1 (0.4), American Indian/Alaska Native 3 (1.2), Other: 23 (9.4)
	Organ Impairment	Renal function was defined based on eGFR. Nivolumab SC - Median (range) eGFR: 63.0 (24.4, 124) mL/min/1.73 m² Nivolumab IV - Median (range) eGFR: 60.6 (20.7, 118) mL/min/1.73 m²
	Pediatrics (if any)	NA
No. of Patients, PK Samples, and BLQ		487 subjects, 3734 samples (19 excluded as below LLOQ)
Sampling Schedule	Rich Sampling	Cycle = 28 days for SC and 14 days for IV SC Arm: Cycle 1 pre-dose, 72, 168, 336 and 504 hours. Predose at cycles 2, 3, 4, 5, 9, 13, 17, 21 and 25. Follow-up visits 1 and 2. IV Arm: Cycle 1 and 2 predose, EOI, and 168 hours. Predose at cycles 3, 5, 7, 9, 17, 25, 33, 41 and 49. Follow-up visits 1 and 2.
	ITT Population	NA

Covariates Evaluated	Static	Age, sex, race, baseline body weight, ECOG performance status, baseline eGFR	
	Time-varying	NA	
Final Model		Summary	Acceptability [FDA's comments]
Software and Version		The popPK analysis was performed using the NONMEM computer program (Version 7.4 ICON Development Solutions, Hanover, MD), compiled using GNU Fortran 7.5.0, Perl Speaks NONMEM (PsN version 4.9) may have been used as well. Diagnostic plots were prepared using the R software (Version 4.0.3 or higher, R Core Team, Vienna, Austria).	Yes
Model Structure		2-compartment model, with zero-order infusion into the central compartment when administered by IV route and first order absorption from the extravascular compartment when administered via SC route and time-varying CL	Yes
Model Parameter Estimates		Table below	Yes
Uncertainty and Variability (RSE, IIV, Shrinkage, Bootstrap)		Parameters were estimated with adequate precision (Table 2). RSE% values were <32% except for ZKA:F1. The condition number was 11.01, indicating the model was stable. The shrinkage values were around 10-37%, which were also reasonable.	Yes
BLQ for Parameter Accuracy		PK samples with BLQ were excluded from the PPK analysis. Exclusion of BLQ is not expected to impact PPK parameter estimates as only approximately 0.5% of total PK concentrations had BLQ.	Yes
GOF, VPC		Figures below	Yes
Significant Covariates and Clinical Relevance		Figure below eGFR, PS and sex on nivolumab CL and baseline body weight on VC were statistically significant covariates (95% CI did not include null value); however, the effects were not considered clinically relevant because the magnitude of the effect was < 20%. Females had a lower F than males, but the effect	

	was not statistically significant (95% CI included the null value).	
Labeling Language	Description	Acceptability [FDA's comments]
12.3 PK	(b) (4)	Yes. Recommended to use Vss from IV labeling given the estimate is considered to be more precisely estimated.

Table 1: Applicant – Summary of Covariates in the Population Pharmacokinetic Analysis Dataset by Administrative Route

	IV (N =245)	SC (N =242)	Overall (N =487)
Age (years)			
Mean (SD)	64.1 (10.1)	63.7 (10.5)	63.9 (10.3)
Median [Min, Max]	66 (20, 87)	64 (35, 93)	65 (20, 93)
Missing, n (%)	0 (0)	0 (0)	0 (0)
Baseline body weight (kg)			
Mean (SD)	77.7 (16.4)	77.7 (18.2)	77.7 (17.3)
Median [Min, Max]	76.6 (47.5, 157)	76.5 (35, 153)	76.5 (35, 157)
Missing, n (%)	0 (0)	0 (0)	0 (0)
Baseline albumin (g/dL)			
Mean (SD)	3.93 (0.498)	3.89 (0.551)	3.91 (0.525)
Median [Min, Max]	4 (2.36, 4.91)	3.97 (2.1, 5.1)	4 (2.1, 5.1)
Missing, n (%)	4 (1.63)	3 (1.24)	7 (1.44)
Baseline EGFR (mL/min/1.73 m ²)			
Mean (SD)	62.4 (19.8)	64.9 (19.9)	63.7 (19.9)
Median [Min, Max]	60.6 (20.7, 118)	63 (24.4, 124)	61.2 (20.7, 124)
Missing, n (%)	0 (0)	0 (0)	0 (0)
Sex, n (%)			
Female	74 (30.2)	84 (34.7)	158 (32.4)
Male	171 (69.8)	158 (65.3)	329 (67.6)

Missing	0 (0)	0 (0)	0 (0)
Race, n (%)			
American Indian/Alaska Native	3 (1.2)	2 (0.8)	5 (1.0)
Asian	1 (0.4)	3 (1.2)	4 (0.8)
Black/African American	2 (0.8)	0 (0)	2 (0.4)
Others	23 (9.4)	38 (15.7)	61 (12.5)
White	215 (87.8)	199 (82.2)	414 (85.0)
Missing	1 (0.4)	0 (0)	1 (0.2)
PS, n (%)			
0	91 (37.1)	100 (41.3)	191 (39.2)
1	137 (55.9)	126 (52.1)	263 (54.0)
2	17 (6.9)	16 (6.6)	33 (6.8)
3	0 (0)	0 (0)	0 (0)
Missing	0 (0)	0 (0)	0 (0)
ADA Nivo , n (%)			
Negative	200 (81.6)	155 (64.0)	355 (72.9)
Persistent Positive	0 (0)	2 (0.8)	2 (0.4)
Only The Last Sample Positive	6 (2.4)	17 (7.0)	23 (4.7)
Other Positive	9 (3.7)	27 (11.2)	36 (7.4)
Missing	30 (12.2)	41 (16.9)	71 (14.6)
ADA rHuPH20 , n (%)			
Negative	0 (0)	196 (81.0)	196 (40.2)
Persistent Positive	0 (0)	7 (2.9)	7 (1.4)
Only The Last Sample Positive	0 (0)	11 (4.5)	11 (2.3)
Other Positive	0 (0)	1 (0.4)	1 (0.2)
Missing	245 (100.0)	27 (11.2)	272 (55.9)

Table 2: Applicant - Parameter Estimates of the ~~Base~~-Final PopPK Model

Parameter [Units] ^{a,b}	Symbol	Estimate ^c	Standard Error (%RSE) ^d	95% CI ^{e,BS}
Fixed Effects				
CL_{0REF} [L/h]	q ₁	0.0108	1.63E-04 (1.51)	0.0107 - 0.0110
VC_{REF} [L]	q ₂	4.25	0.0318 (0.748)	4.23 - 4.26
Q_{REF} [L/h]	q ₃	0.0312	0.00101 (3.25)	0.0301 - 0.0318
VP_{REF} [L]	q ₄	2.67	0.0531 (1.99)	2.62 - 2.73
CL_{EMAX}	q ₅	-0.260	0.0148 (5.69)	-0.280 - -0.240
CL_{T50}	q ₆	1.41E+03	52.5 (3.73)	1.29E+03 - 1.52E+03
CL_{HILL}	q ₇	3.39	0.372 (11.0)	2.62 - 4.03
KA [1/hr]	q ₈	0.0123	4.47E-04 (3.62)	0.0118 - 0.0129
F_1	q ₉	0.788	0.0171 (2.17)	0.761 - 0.815
CL_{WTB}	q ₁₁	0.644	0.0975 (15.1)	0.439 - 0.834
CL_{GFR}	q ₁₂	0.306	0.0483 (15.8)	0.213 - 0.400
CL_{SEX}	q ₁₃	-0.149	0.0467 (31.3)	-0.234 - -0.0632
CL_{PS}	q ₁₄	0.122	0.0322 (26.3)	0.0618 - 0.184
VC_{WTB}	q ₁₅	0.525	0.0936 (17.8)	0.354 - 0.687
VC_{SEX}	q ₁₆	-0.228	0.0406 (17.8)	-0.298 - -0.165
$F1_{SEX}$	q ₁₉	0.942	0.0419 (4.44)	0.861 - 1.02

Table 2: Applicant - Parameter Estimates of the **Base-Final** PopPK Model

Parameter [Units] ^{a,b}	Symbol	Estimate ^c	Standard Error (%RSE) ^d	95% CI ^{e,BS}
$F1_{PS^f}$	q ₂₀	1.00		1.00 - 1.00
Random Effects				
ZCL [-]	w _{1,1}	0.135 (0.367)	0.00830 (6.16)	0.114 - 0.160
ZVC [-]	w _{2,2}	0.0827 (0.288)	0.00546 (6.60)	0.0729 - 0.0956
ZVP [-]	w _{3,3}	0.211 (0.459)	0.0225 (10.7)	0.168 - 0.331
ZEMAX [h]	w _{4,4}	0.0572 (0.239)	0.00602 (10.5)	0.0448 - 0.0711
ZKA	w _{5,5}	0.211 (0.459)	0.0400 (19.0)	0.116 - 0.331
F1	w _{6,6}	0.615 (0.784)	0.144 (23.4)	0.333 - 0.898
ZCL:ZVC	w _{1,2}	0.0395 (0.374)	0.00522 (13.2)	0.0324 - 0.0487
ZKA:F1	w _{5,6}	0.0744 (0.207)	0.0574 (77.2)	-0.0595 - 0.210
Residual Error				
Proportional [-]	q ₁₀	0.157	0.00241 (1.53)	0.145 - 0.169

Note 1: $CL0_{REF}$ is the typical value in a reference subject weighing 80 kg, EGFR of 90 mL/min/1.73 m², 65 year old male with PS = 0. VC_{REF} , Q_{REF} , and VP_{REF} are typical values in a reference subject weighing 80 kg. These reference values represent the approximate median values in the popPK analysis dataset used to establish the pre-specified model and also represent the approximate median values in the current popPK analysis dataset except for EGFR.

Note 2: ETA shrinkage (%): ETA_CL: 9.37; ETA_VC: 30.4; ETA_VP: 35.5; ETA_EMAX: 34.5; ETA_KA: 32.4; ETA_F: 36.6; EPS shrinkage (%): 17.0.

Note 3: Condition no: 11.01

^a Parameters with fixed values (not estimated) are denoted with a superscript 'f' after the names, with the fixed value given in the Estimate column

^b Random Effects and Residual Error parameter names containing a colon (:) denote correlated parameters

^c Random Effects and Residual Error parameter estimates are shown as *Variance (Standard Deviation)* for diagonal elements ($w_{i,i}$ or $s_{i,i}$) and *Covariance (Correlation)* for off-diagonal elements ($w_{i,j}$ or $s_{i,j}$)

^d RSE% is the relative standard error (Standard Error as a percentage of Estimate)

^e Confidence intervals of Random Effects and Residual Error parameters are for *Variance* or *Covariance*

^{BS} Confidence Interval values are taken from bootstrap calculations (992 successful out of a total of 1000)

Figure 1: Applicant – Observed Versus Predicted Population Average and Individual Concentration in the Final Population Pharmacokinetic Model by Administration Route

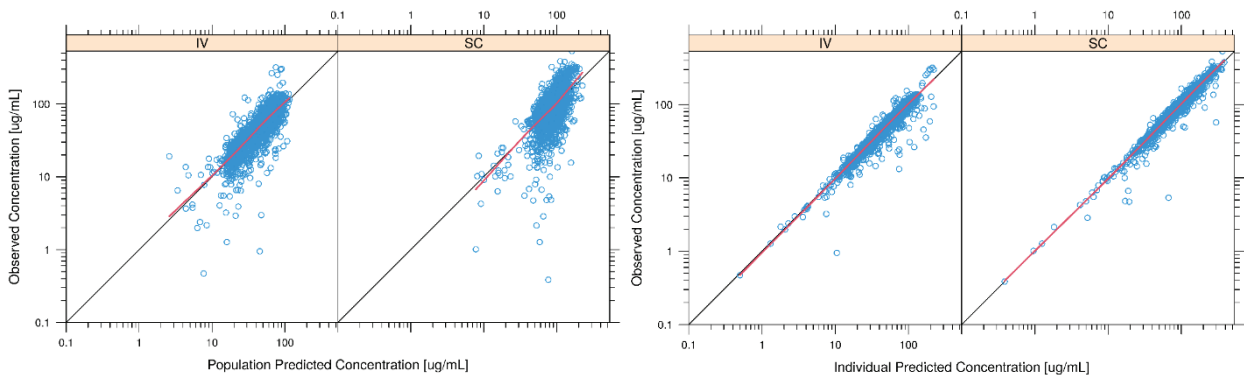


Figure 287: Applicant - CWRES versus Time after First Dose in the Final Population Pharmacokinetic Model by Administration Route

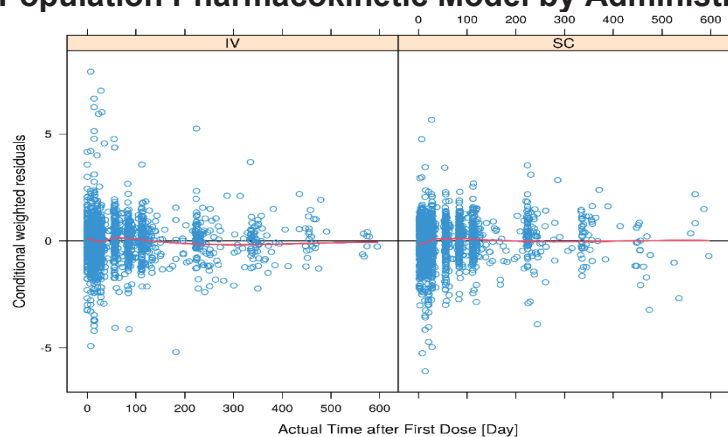
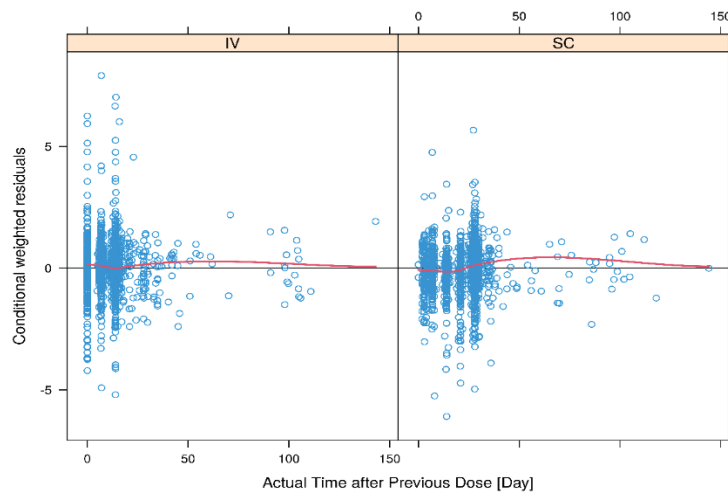


Figure 3: Applicant: - CWRES versus Time After Previous Dose in the Final Population Pharmacokinetic Model by Administration Route



Note: Solid red line represents locally weighted smooth line; solid black line represents line of identity.

Figure 4: Applicant – CWRES versus Population Predicted Concentration in the Final Population Pharmacokinetic Model by Administration Route

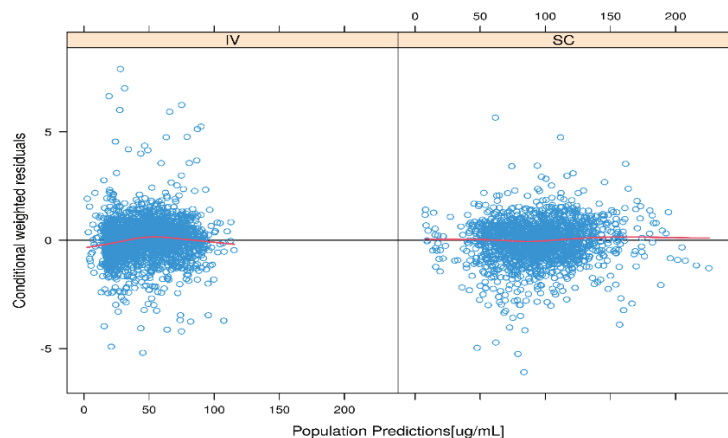


Figure 5: Applicant – Prediction-Corrected VPC of Trough Nivolumab Concentrations versus Actual Time after First Dose by Administration Route in the Final PopPK Model

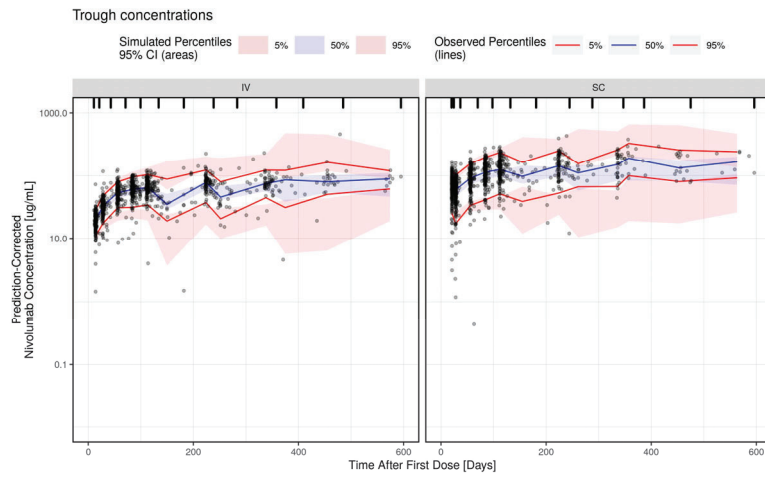


Figure 6: Applicant – Prediction Corrected VPC of Nivolumab Concentration versus Actual Time after Previous Dose by Administration Toure in the Final PopPK Model

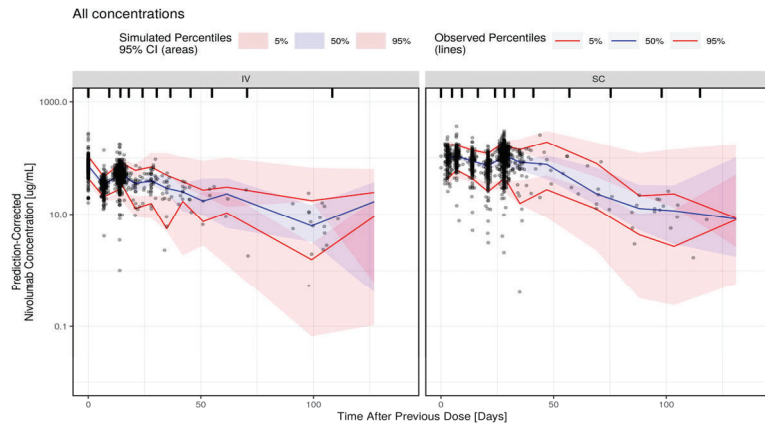
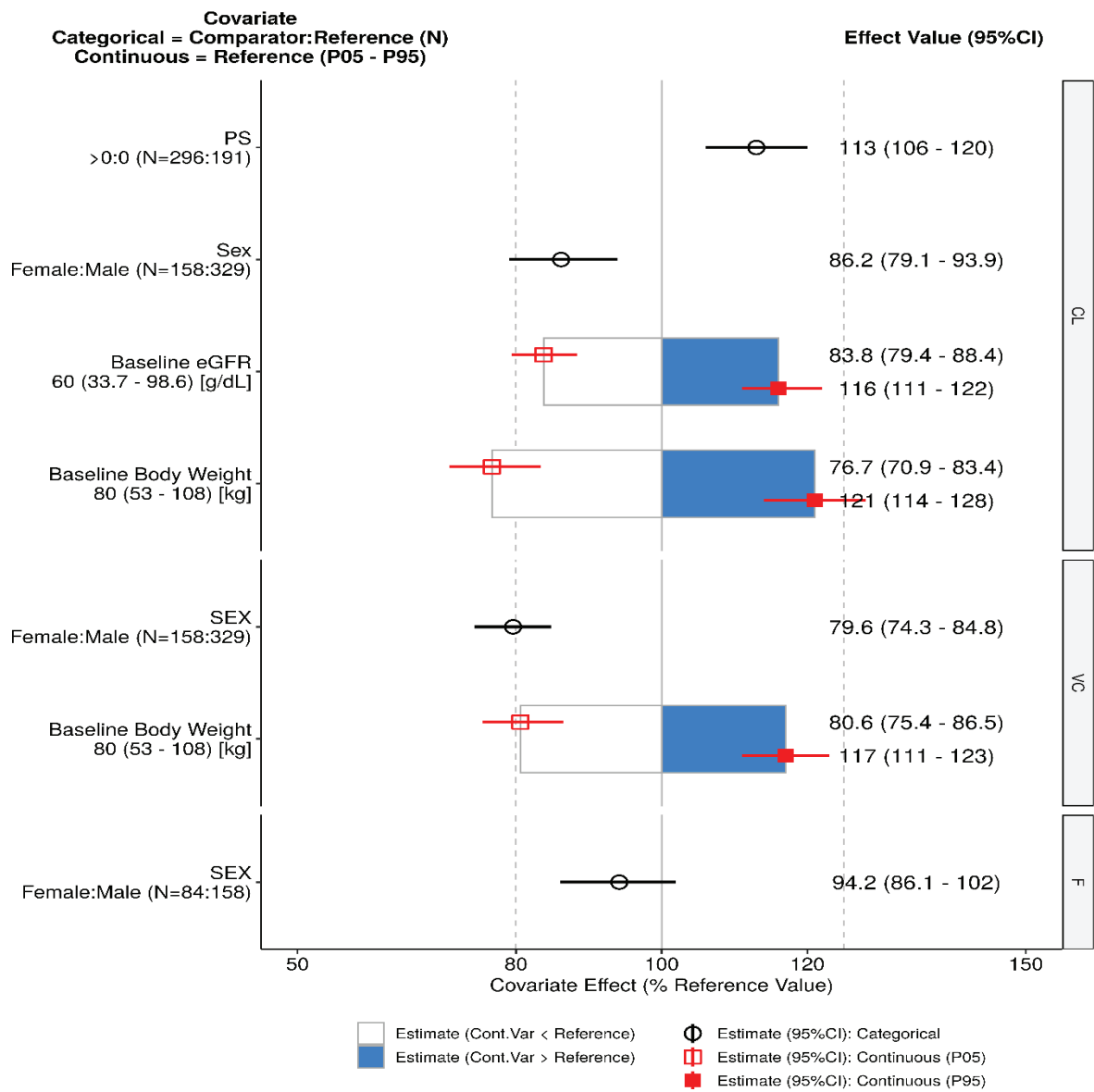


Figure 7: Applicant – Covariate Effects on Final Nivolumab PopPK Model



Note 1: Categorical covariate effects (95% CI) are represented by open symbols (horizontal lines).

Note 2: Continuous covariate effects (95% CI) at the 5th/95th percentiles of the covariate are represented by the end of horizontal boxes (horizontal lines). Open/shaded area of boxes represents the range of covariate effects from the median to the 5th/95th percentile of the covariate.

Note 3: Reference subject is a 65-year-old male, weighing 80 kg, with a normal PS status (PS = 0).

Baseline eGFR of 60 mL/min/1.73 m² was used in this plot as a median to represent the study distribution. VC_{REF} is typical value in a reference male subject weighing 80 kg. Parameter estimate in a reference subject is considered as 100% (vertical solid line) and dashed vertical lines are at 80% and 125% of this value.

General Information - CA2098KX		
Objectives of PPK Analysis		- To characterize the PK of nivolumab when administered subcutaneously - To evaluate covariates impacting nivolumab PK parameters
Studies Included		MDX1106-01 (CA209001), MDX1106-03 (CA209003), ONO-4538-01 (CA209005), CA209009, CA209010, CA209017, CA209025, CA209026, CA209032, CA209037, ONO-4538 (CA209051), CA209057, CA209063, CA209066, CA209067, CA209141, CA209275, CA2098KX
Dose(s) Included		Nivolumab IV 0.3, 1, 3, or 10 mg/kg for 1st dose, followed by additional re-treatment cycles; 0.1, 0.3, 1, 3, or 10 mg/kg Q2W; 1, 3, 10, and 20 mg/kg Q3W for 1st dose, followed by Q2W; 3 mg/kg Q2W; 0.3, 2 and 10 mg/kg Q3W Nivolumab SC 600 mg ± rHuPH20 Q2W Nivolumab SC 720 mg ± rHuPH20 Q4W Nivolumab SC 960 mg ± rHuPH20 Q4W Nivolumab SC 1,200 mg + rHuPH20 Q4W
Population Included		Adult subjects with solid tumors including NSCLC, MEL, RCC, SCLC, bladder, gastric, SCCHN, CRC, pancreatic cancer, prostate cancer, triple negative breast cancer
Population Characteristics (Table X)	General	Nivolumab SC - Median (range) age: 66.5 (24, 93) years - Median (range) baseline body weight: 77.3 (42, 133) kg - Sex, n (%): 37 (35.6) males, 67 (64.4) females - Race, n (%): White: 91 (87.5), Black/African American: 3 (2.9), Asian: 2 (1.9), Other: 8 (7.7) Nivolumab IV - Median (range) age: 62 (18, 90) years - Median (range) baseline body weight: 76.8 (34.1, 180) kg - Sex, n (%): 1066 (32.3) males, 2237 (67.7) females - Race, n (%): White: 2930 (88.7), Black/African American: 92 (2.8), Asian: 218 (6.6), Other: 57 (1.7)
	Organ Impairment	Renal function was defined based on eGFR. Nivolumab SC - Median (range) eGFR: 80.8 (32.4, 143) mL/min/1.73 m² Nivolumab IV - Median (range) eGFR: 82.6 (18.1, 191) mL/min/1.73 m²
	Pediatrics (if any)	NA
No. of Patients, PK Samples, and BLQ		3407 subjects, 18887 PK samples, 245 (1.3%) BLQ samples
Sampling Schedule	Rich Sampling	CA2098KX: Parts A and B: C1D1 predose, C1D2, C1D4 (±1 day), C1D8 (±2 days), C1D15 (±5 days), and C1D21 (±5 days) C2D1 predose and EOI, C2D15 (±5 days) C3D1 predose, C5D1 predose, C9D1 predose Predose every 6 cycles starting with C13D1 and first 2 follow-up visits FU1 and 2 Part C: C1D1, C2D1, C3D1, C5D1, and C9D1 predose Predose every 6 cycles starting with C13D1 and first 2 follow-up visits FU1 and 2

		Part D: C1D1 predose, C1D2, C1D4 (±1 day), C1D8 (±2 days), C1D15 (±5 days), and C1D21 (±5 days) C2D1 predose, C2D15 (±5 days) C3D1 predose, C5D1 predose, C9D1 predose Predose every 6 cycles starting with C13D1 and first 2 follow-up visits FU1 and 2 Part E: C1D1 predose, C1D2, C1D4 (±1 day), C1D8 (±2 days), C1D15 predose C2D1 and C2D15 predose C3D1 predose, C3D2, C3D4 (±1 day), C3D8 (±2 days), C3D15 C5D1, C9D1 Predose every 6 cycles starting with C13D1 and first 2 follow-up visits FU1 and 2	
	In ITT Population	NA	
Covariates Evaluated	Static	Age, baseline body weight, baseline eGFR, sex, race, ECOG Performance Status, tumor type, dose regimen	
	Time-varying	NA	
Final Model		Summary	Acceptability [FDA's comments]
Software and Version		The PPK analysis was performed using the nonlinear effects modeling (NONMEM 7.4) computer program, compiled using GNU Fortran 7.5.0, and all exploratory data analyses and presentations of data used R (version 4.0.3 or higher). The pcVPC were executed through PsN 4.9.0.	Yes
Model Structure		2-compartment model, with zero-order infusion into the central compartment when administered by the IV route and first order absorption from the extravascular compartment when administered by the SC route and time-varying CL	Yes
Model Parameter Estimates		See Table	Yes
Uncertainty and Variability (RSE, IIV, Shrinkage, Bootstrap)		Parameters were estimated with adequate precision (Table 4). RSE% values were <33%. The condition number was 49.78, indicating the model was stable. The shrinkage values were around 10-25%, except for ETA_EMAX (51.2%) and ETA_VP (44.3%). VP was well estimated with RSE% of 2.29%, and RSE% for CL _{E_{max}} was 7.78% with a point estimate of -0.263 (95% CI -0.303%- -0.223%), indicating a decrease in clearance with time.	Yes
BLQ for Parameter Accuracy		PK samples with BLQ were excluded from the PPK analysis. Exclusion of BLQ is not expected to impact PPK	Yes

	parameter estimates as only approximately 0.5% of total PK concentrations had BLQ.	
GOF, VPC	See Figures	Yes
Significant Covariates and Clinical Relevance	See Figure (The effect of baseline body weight, eGFR, PS and sex on nivolumab CL were statistically significant, but not clinically relevant (difference < 20%). The only covariate retained on the nivolumab SC absorption PK parameters was the effect of sex on F; however, the effect was not statistically significant as the 95% CI included the null value. Females only had ~10% lower bioavailability than males. The effect of sex was small and not considered to have any clinically meaningful impact. Regimen effect was tested as a covariate on F but was not found to be significant.)	Yes
Analysis Based on Simulation (optional)	NA	
Labeling Language	Description	Acceptability [FDA's comments]
12.3 PK	Not applicable	

Table 3: Applicant - Summary of Covariates in the PopPk Analysis Dataset by Administration Route

	IV (N = 3303)	SC (N = 104)	Overall (N = 3407)
Age (years)			
Mean (SD)	61.2 (11.2)	64.9 (11.4)	61.3 (11.2)
Median [Min, Max]	62 (18, 90)	66.5 (24, 93)	62 (18, 93)
Missing, n (%)	40 (1.21)	0 (0)	40 (1.17)
Baseline body weight (kg)			
Mean (SD)	78.3 (19.1)	77.5 (18.2)	78.3 (19)
Median [Min, Max]	76.8 (34.1, 180)	77.3 (42, 133)	76.8 (34.1, 180)
Missing, n (%)	1 (0.0303)	0 (0)	1 (0.0294)
Baseline albumin (g/dL)			
Mean (SD)	3.89 (0.504)	3.63 (0.542)	3.87 (0.509)
Median [Min, Max]	3.9 (1.4, 5.3)	3.66 (2.3, 4.7)	3.9 (1.4, 5.3)
Missing, n (%)	1351 (40.9)	0 (0)	1351 (39.7)
Baseline EGFR (mL/min/1.73 m ²)			
Mean (SD)	80.4 (22)	79.1 (22)	80.3 (22)
Median [Min, Max]	82.6 (18.1, 191)	80.8 (32.4, 143)	82.6 (18.1, 191)
Missing, n (%)	48 (1.45)	0 (0)	48 (1.41)
Sex, n (%)			
Female	2237 (67.7)	67 (64.4)	2304 (67.6)
Male	1066 (32.3)	37 (35.6)	1103 (32.4)
Race, n (%)			
Missing	6 (0.2)	0 (0)	6 (0.2)

Table 3: Applicant - Summary of Covariates in the PopPk Analysis Dataset by Administration Route

	IV (N = 3303)	SC (N = 104)	Overall (N = 3407)
White	2930 (88.7)	91 (87.5)	3021 (88.7)
Black/African American	92 (2.8)	3 (2.9)	95 (2.8)
Asian	218 (6.6)	2 (1.9)	220 (6.5)
Other	57 (1.7)	8 (7.7)	65 (1.9)
PS, n (%)			
0	1413 (42.8)	38 (36.5)	1451 (42.6)
1	1826 (55.3)	66 (63.5)	1892 (55.5)
2	61 (1.8)	0 (0)	61 (1.8)
Missing	3 (0.1)	0 (0)	3 (0.1)
Tumor type, n (%)			
NSCLC	1000 (30.3)	31 (29.8)	1031 (30.3)
MEL	875 (26.5)	5 (4.8)	880 (25.8)
Others ^a	102 (3.1)	35 (33.7)	137 (4.0)
RCC	695 (21.0)	23 (22.1)	718 (21.1)
SCLC	95 (2.9)	0 (0)	95 (2.8)
Bladder	306 (9.3)	9 (8.7)	315 (9.2)
Gastric	58 (1.8)	0 (0)	58 (1.7)
SCCHN	172 (5.2)	1 (1.0)	173 (5.1)
Dose regimen			
600 mg Q2W	0 (0)	36 (34.6)	36 (1.1)
1,200 mg Q4W	0 (0)	50 (48.1)	50 (1.5)
Other	3303 (100.0)	18 (17.3)	3321 (97.5)
Coadministration with rHuPH20			
Yes	0 (0)	104 (100.0)	104 (3.1)
No	3303 (100.0)	0 (0)	3303 (96.9)

^a Others includes: Colorectal Cancer, Pancreatic Cancer, Prostate cancer, Triple Negative Breast Cancer and Other. Other is 4 subjects from study CA209-005.

Table 4: Applicant - Parameter Estimates of the **Prior Final PopPK Model**

Name ^{a,b} [Units]	Symbol	Estimate ^c	Standard Error (RSE%) ^d	95% Confidence Interval ^e
Fixed Effects				
CL [L/h]	q ₁	0.0108	1.75E-4 (1.63)	0.0104 - 0.0111
VC [L]	q ₂	4.29	0.0334 (0.777)	4.23 - 4.36
Q [L/h]	q ₃	0.0312	0.00108 (3.46)	0.0291 - 0.0333
VP [L]	q ₄	2.73	0.0623 (2.29)	2.60 - 2.85
CL _{EMAX}	q ₅	-0.263	0.0204 (7.78)	-0.303 - -0.223
CL _{T50}	q ₆	1.53E+03	72.8 (4.76)	1.39E+03 - 1.67E+03
CL _{HILL}	q ₇	3.84	0.813 (21.2)	2.24 - 5.43
KA	q ₈	0.0129	6.15E-04 (4.77)	0.0117 - 0.0141
F1	q ₉	0.815	0.0291 (3.58)	0.758 - 0.872
CL _{WTB}	q ₁₂	0.607	0.0306 (5.04)	0.547 - 0.666
CL _{GFR}	q ₁₃	0.166	0.0210 (12.7)	0.125 - 0.207
CL _{SEX}	q ₁₄	-0.169	0.0165 (9.72)	-0.202 - -0.137
CL _{PS}	q ₁₅	0.169	0.0135 (7.98)	0.143 - 0.196
VC _{WTB}	q ₁₇	0.621	0.0297 (4.78)	0.563 - 0.680
VC _{SEX}	q ₁₈	-0.136	0.0147 (10.9)	-0.165 - -0.107
F1 _{SEX}	q ₂₆	0.895	0.0574 (6.41)	0.783 - 1.01

Table 4: Applicant - Parameter Estimates of the Prior Final PopPK Model

Name ^{a,b} [Units]	Symbol	Estimate ^c	Standard Error (RSE%) ^d	95% Confidence Interval ^e
$F1_{PS}^f$	q ₂₇	1.00		
Random Effects				
ZCL [-]	W _{1,1}	0.122 (0.349)	0.00579 (4.76)	0.110 - 0.133
ZVC [-]	W _{2,2}	0.0853 (0.292)	0.00711 (8.33)	0.0714 - 0.0993
ZVP [-]	W _{3,3}	0.212 (0.461)	0.0322 (15.2)	0.149 - 0.276
ZEMAX [h]	W _{4,4}	0.0537 (0.232)	0.00759 (14.1)	0.0388 - 0.0685
ZKA	W _{5,5}	0.132 (0.364)	0.0232 (17.5)	0.0869 - 0.178
F1	W _{6,6}	0.807 (0.898)	0.213 (26.4)	0.390 - 1.22
ZCL:ZVC	W _{1,2}	0.0402 (0.395)	0.00332 (8.24)	0.0337 - 0.0467
ZKA:F1	W _{5,6}	0.180 (0.551)	0.0588 (32.6)	0.0650 - 0.295
Residual Error				
Proportional [-]	q ₁₀	0.188	0.00281 (1.49)	0.183 - 0.194

Note: $CL0_{REF}$ is the typical value in a reference subject weighing 80 kg, EGFR of 90 mL/min/1.73 m², 65 year old male with PS = 0. VC_{REF} , Q_{REF} , and VP_{REF} are typical values in a reference subject weighing 80 kg. These reference values represent the approximate median values in the PPK analysis dataset.

Note1 : ETA shrinkage (%): ETA_CL: 12.3; ETA_VC: 22.3; ETA_VP: 44.3; ETA_EMAX: 51.2; ETA_KA: 20.1; ETA_F: 24.2; EPS shrinkage (%): 17.2.

Note 2: Between-subject variability in Q and VP and the covariance between Q and VP were fixed to the corresponding values as CL0 and VC.

^a Parameters with fixed values (not estimated) are denoted with a superscript 'f' after the names, with the fixed value given in the Estimate column

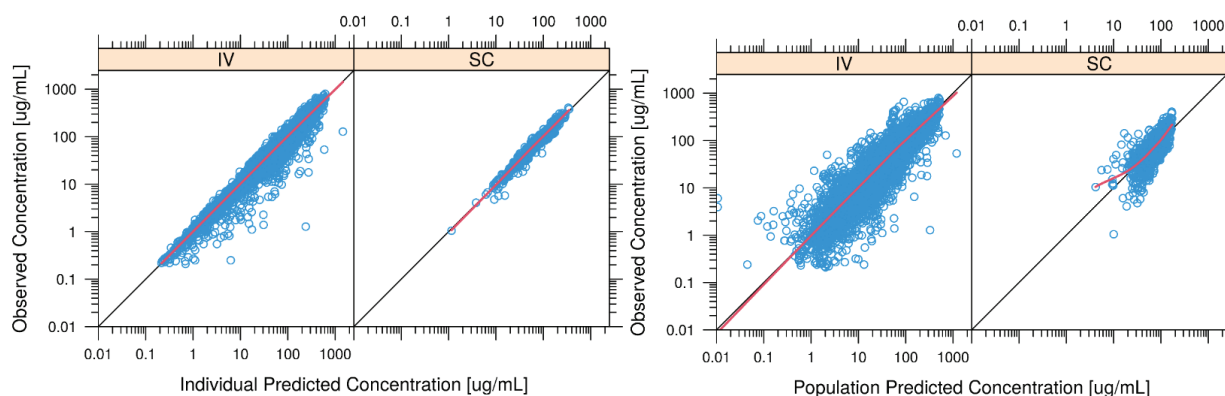
^b Random Effects and Residual Error parameter names containing a colon (:) denote correlated parameters.

^c Random Effects and Residual Error parameter estimates are shown as *Variance (Standard Deviation)* for diagonal elements ($w_{i,i}$ or $s_{i,i}$) and *Covariance (Correlation)* for off-diagonal elements ($w_{i,j}$ or $s_{i,j}$).

^d RSE% is the relative standard error (Standard Error as a percentage of Estimate).

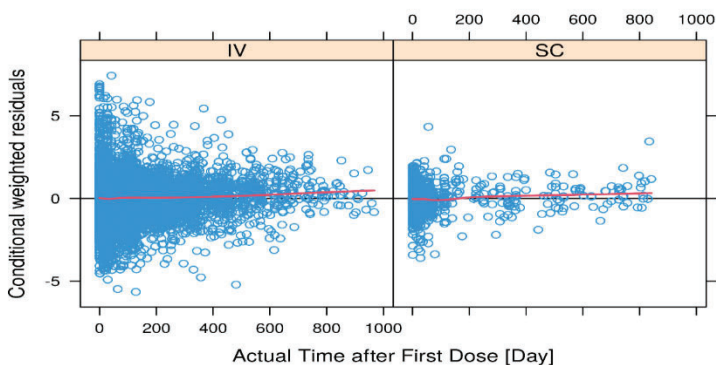
^e Confidence intervals of Random Effects and Residual Error parameters are for Variance or Covariance.

Figure 8: Applicant – Observed Versus Predicted Population Average and Individual Concentration in the Prior Population Pharmacokinetic Model by Administration Route



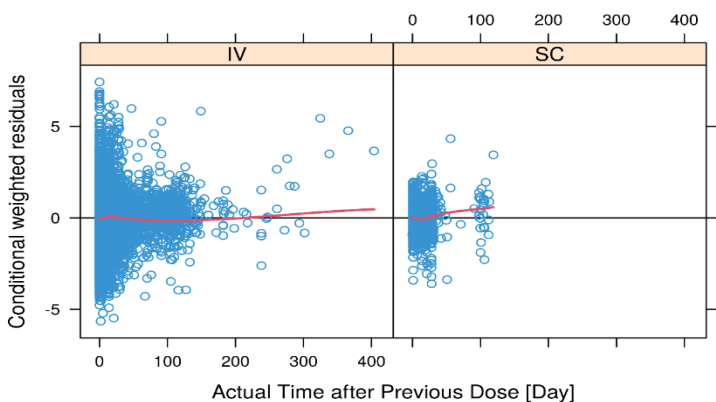
Note 1: Solid red line represents linear regression line. Solid black line represents line of identity

Figure 9: Applicant – CWRES Versus Time after First Dose in the Prior Final Population Pharmacokinetic Model by Administration Route



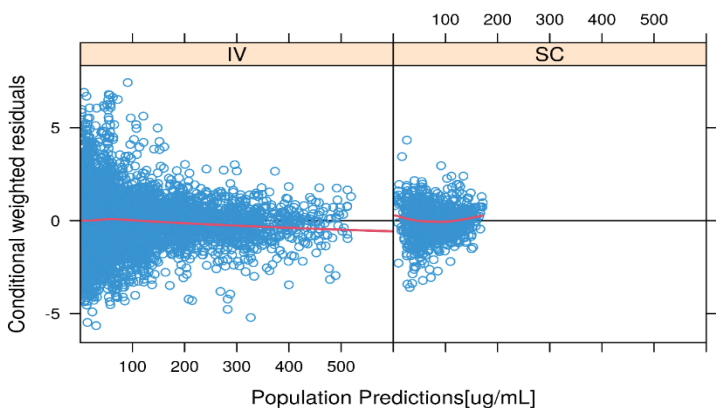
Note: Solid red line represents locally weighted smooth line; solid black line represents line of identity.

Figure 10: Applicant – CWRES Versus Time After Previous Dose in the Prior Final Population Pharmacokinetic Model by Administration Route



Note: Solid red line represents locally weighted smooth line; solid black line represents line of identity.

Figure 11: - Applicant – CWRES Versus Population Predicted Concentration in the Prior Final Population Pharmacokinetic Model by Administration Route



Note: Solid red line represents locally weighted smooth line; solid black line represents line of identity.

Figure 12: Applicant – Prediction-Corrected VPC of Trough Nivolumab Concentrations Versus Actual Time after First Dose by Administration Route in the Prior Final PopPK Model

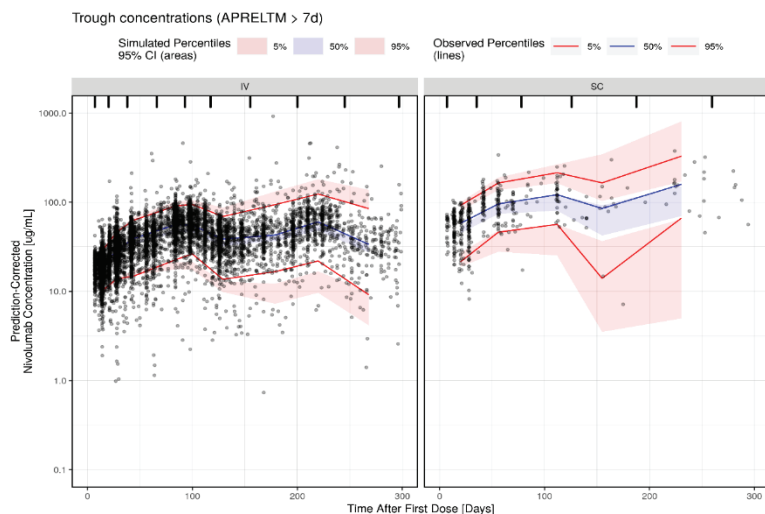


Figure 13: Applicant – Prediction-Corrected VPC of Nivolumab Concentrations Versus Actual Time after Previous Dose by Administration Route in the Prior Final PopPK Model

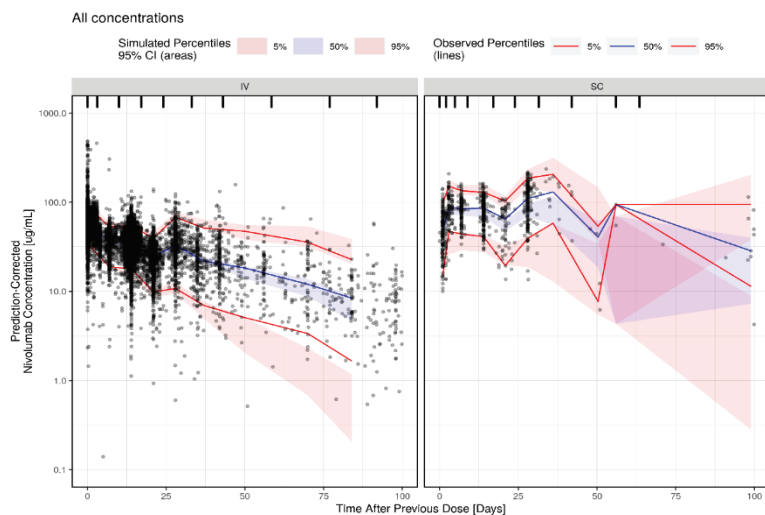
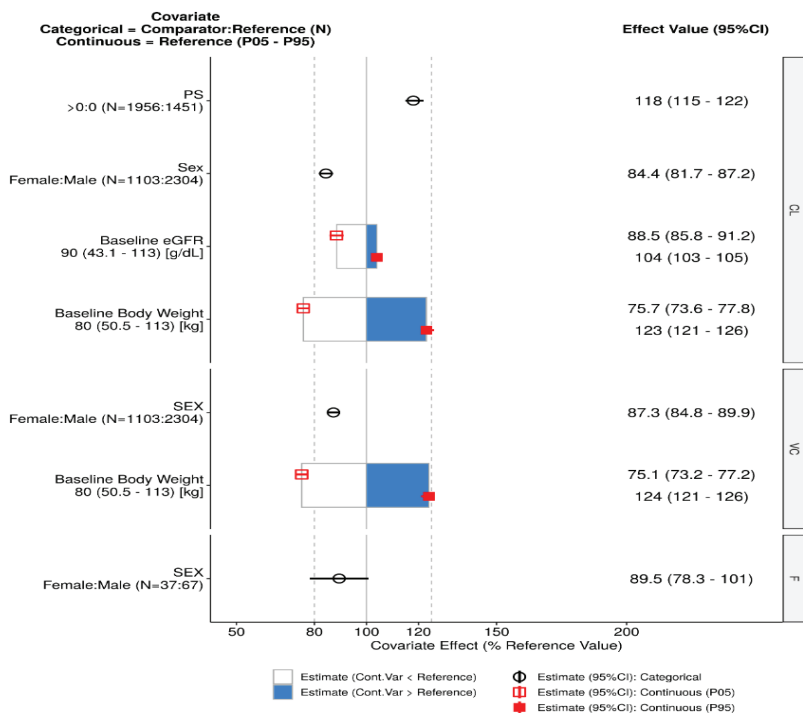


Figure 14: Applicant – Covariate Effects on Nivolumab Pharmacokinetic Parameters (Prior Final Model)



Note 1: Categorical covariate effects (95% CI) are represented by open symbols (horizontal lines).

Note 2: Continuous covariate effects (95% CI) at the 5th/95th percentiles of the covariate are represented by the end of horizontal boxes (horizontal lines). Open/shaded area of boxes represents the range of covariate effects from the median to the 5th/95th percentile of the covariate.

Note 3: Reference subject is a 65-year old white male, weighing 80 kg, with baseline eGFR of 90 mL/min/1.73 m², baseline ALB of 4 g/dL, baseline LDH (normalized to upper limit of normal) of 0.8, a normal PS status (PS = 0). VCREF is typical value in a reference subject weighing 80 kg. Parameter estimate in a reference subject is considered as 100% (vertical solid line) and dashed vertical lines are at 80% and 125% of this value.

The FDA's Assessment:

The population PK analysis is considered adequate to predict individual exposure estimates for non-inferiority test and be adapted for evaluation of exposure distribution in other approved solid tumors and extrapolation to alternative SC dosages.

PPK Review Issues

Evaluation of exposure distribution in other approved solid tumors and extrapolation to alternative SC dosages conducted by the Applicant were hereby provided for the completeness of the assessment.

Based on modeling and simulation, the exposures for 1200 mg Q4W and 600 mg Q2W SC are comparable across solid tumor indications and are consistently above the exposures of the IV dosages of corresponding dosing intervals (See Figures below).

For alternative SC dosages (i.e., 900 mg Q3W and 600 mg Q2W), the C_{avg,ss} is expected to be the same as the 1200 mg Q4W SC but with a smaller steady-state C_{max}:C_{min} ratio (

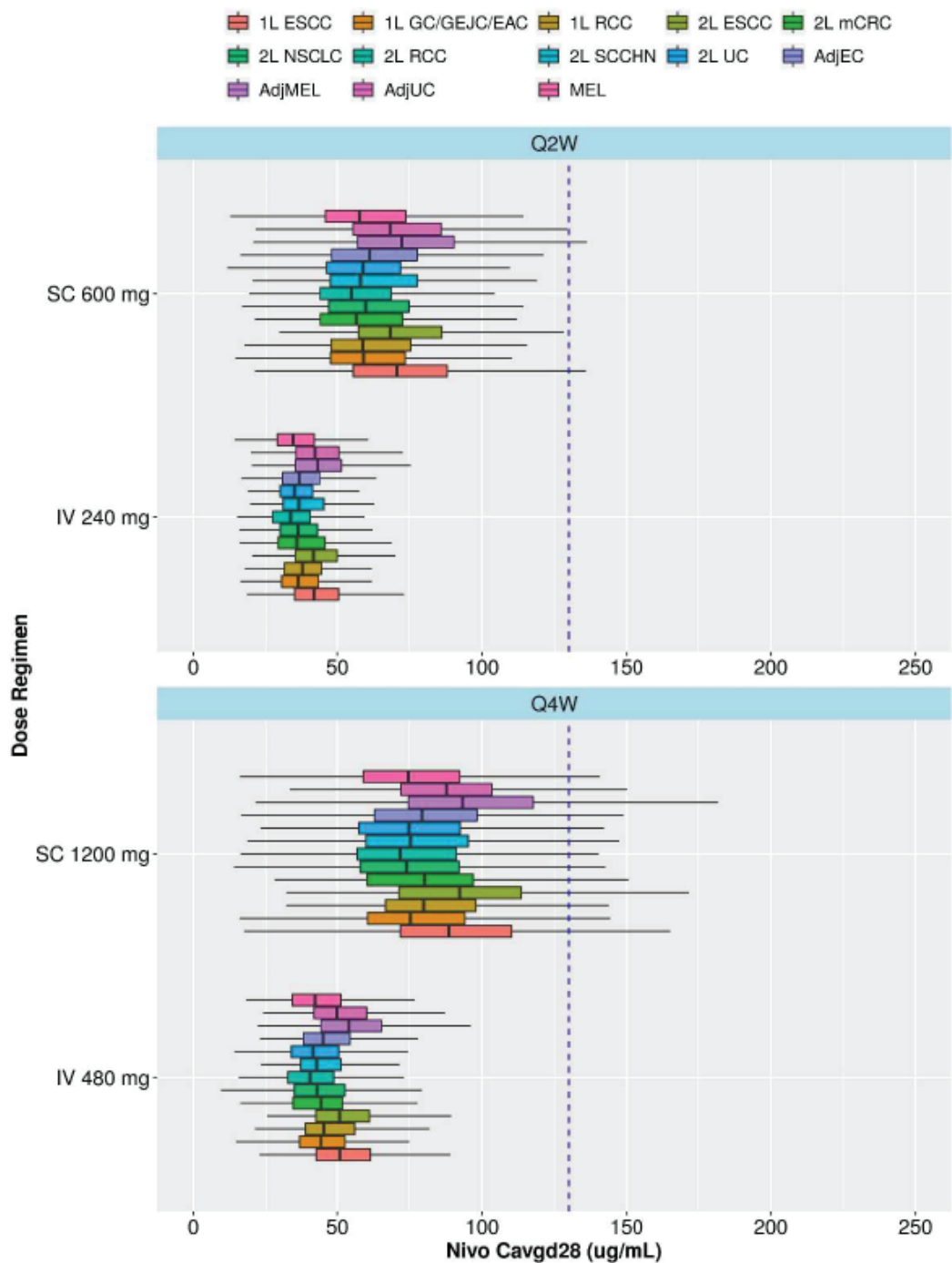
Figure 17: Predicted Geometric Mean Nivolumab Concentration-Time Profiles by SC Dosing Regimen (1200 mg Q4W, 900 mg Q3W and 600 mg Q2W) in Subjects with 2L RCC from CA20967T

). For the two PK primary endpoints, Cavgd28 can be compared between Q2W and Q4W while Cavgd84 is generated to compare with Q3W dosage, and Cmin,ss can be directly compared.

The bridging from 1200 mg Q4W SC to 600 mg Q2W SC was established first. Relative to 1200 mg Q4W SC, Cavgd28 decreased by 21% and Cmin,ss increased by 25% (Table 5). Given that there is sufficient GMR margin over 3 mg/kg Q2W IV, and the exposures of 600 mg Q2W are covered by the safety margin of 10 mg/kg Q2W IV, the exposure difference between 600 mg Q2W and 1200 mg Q4W SC for the primary PK endpoints is not considered clinically meaningful.

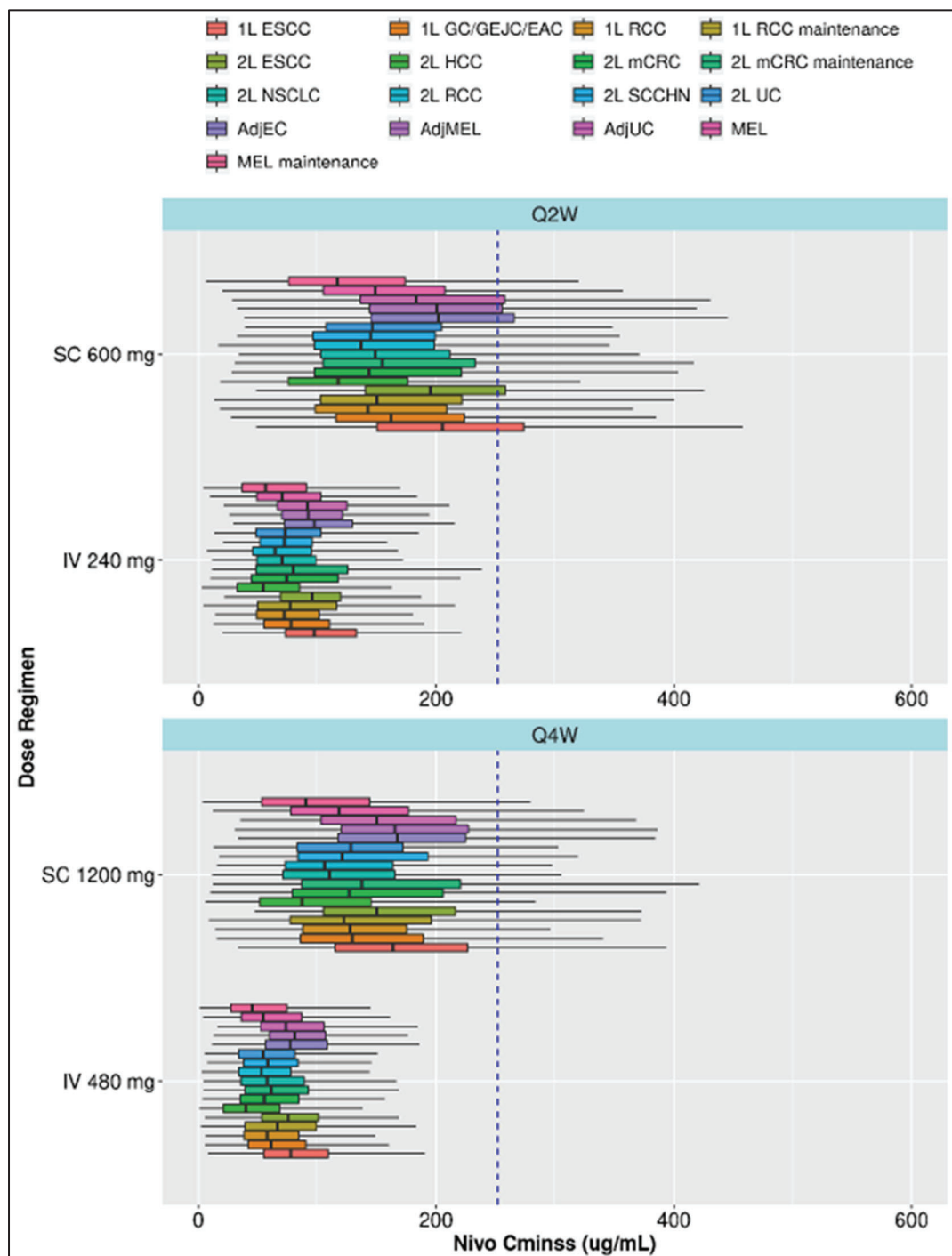
The bridging from 1200 mg Q4W SC to 900 mg Q3W SC is then regarded as an interpolation. PK profile of 900 mg Q3W SC is expected to be between PK profiles of 1200 mg Q4W and 600 mg Q2W. Relative to 1200 mg Q4W, Cavgd84 decreased by 4.5% and Cmin,ss increased by 12% (See Table).

Figure 15: Comparison of Simulated Cavg28 Between IV and SC Administration Across Solid Tumor Indications



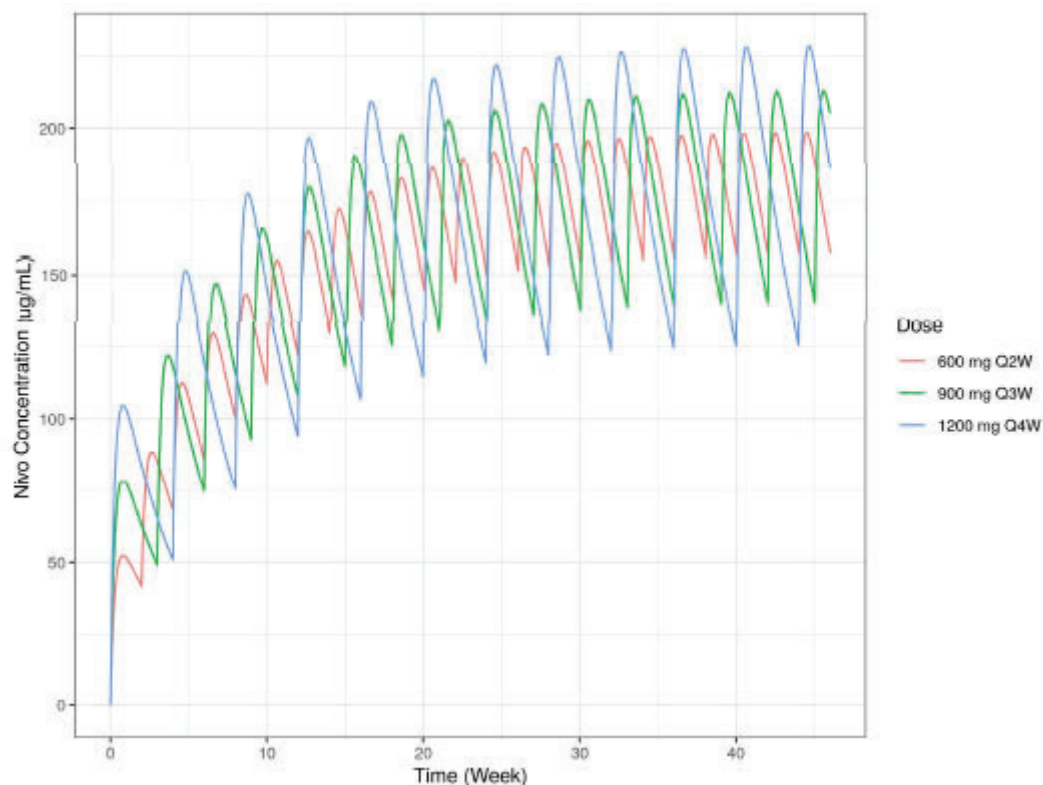
Source: Nivolumab SC simulation and bridging report (Figure 5.2-1). The blue dashed line indicates nivolumab simulated median Cavg28 of 130 $\mu\text{g/mL}$ at 10 mg/kg Q2W in subjects with 2L RCC.

Figure 16: Comparison of Simulated Cmin,ss Between IV and SC Administration Across Solid Tumor Indications



Source: Nivolumab SC simulation and bridging report (Figure 5.2-2). The blue dashed line indicates nivolumab simulated median Cminss of 252 $\mu\text{g/mL}$ at 10 mg/kg Q2W in subjects with 2L RCC.

Figure 17: Predicted Geometric Mean Nivolumab Concentration-Time Profiles by SC Dosing Regimen (1200 mg Q4W, 900 mg Q3W and 600 mg Q2W) in Subjects with 2L RCC from CA20967T



Source: Nivolumab SC simulation and bridging report (Figure 5.1.2-1).

Table 5. Predicted Geometric Means (CV%) of Nivolumab SC Exposures in 2L RCC Subjects from CA20967T by SC Dosing Regimen.

Exposure (µg/mL)	1200 mg Q4W SC	900 mg Q3W SC	600 mg Q2W SC	3 mg/kg Q2W IV	10 mg/kg Q2W IV	% Diff GM (900 mg Q3W relative to 1200 mg Q4W)	% Diff GM (600 mg Q2W relative to 1200 mg Q4W)
CAVG1	78.8(35.6)	63.9(34.8)	45.0(34.2)	29.8(24.8)	99.3(24.8)	-18.9	-42.9
CMAV1	108(32.7)	81.3(32.7)	54.2(32.7)	91.7(35.5)	247(33.9)	-24.7	-49.8
CMIN1	50.8(44.2)	49.0(40.7)	41.9(36.9)	19.6(28.6)	65.5(28.6)	-3.54	-17.5
CAVG28	78.8(35.6)	NE	62.0(34.9)	37.7(25.3)	126(25.3)	NE	-21.3
CMIN28	50.8(44.2)	NE	68.1(39.2)	31.9(29.6)	106(29.6)	NE	34.1
CAVG84	112(38.0)	107(37.7)	103(37.4)	NE	NE	-4.46	-8.04
CMAV84	180(35.5)	167(36.5)	156(37.7)	NE	NE	-7.22	-13.3
CMIN84	94.1(47.0)	107(44.7)	122(42.4)	NE	NE	13.7	29.6
CAVGSS	182(43.5)	182(43.5)	182(43.5)	92.5(34.4)	308(34.4)	0	0
CMAVSS	230(39.2)	214(40.4)	199(41.8)	160(27.6)	517(35.4)	-6.96	-13.5
CMINSS	126(51.0)	141(48.8)	157(46.6)	71.5(40.1)	238(40.1)	11.9	24.6

Source: Nivolumab SC simulation and bridging report (adapted from Figure 5.1.1-1 and Figure 5.1.2-1). NE: not evaluated.

Reviewer's Independent Analysis

None.

Exposure-Response Analysis

ER (efficacy) Executive Summary

The FDA's Assessment:

E-R analysis was not considered necessary for this application. Refer to clinical review regarding efficacy and safety evaluation between SC and IV arms.

ER (efficacy) Assessment Summary

The Applicant's Position:

Not applicable. ER analyses were not conducted for CA20967T or CA20987KX.

ER (safety) Executive Summary

The FDA's Assessment:

E-R analysis was not considered necessary for this application. Refer to clinical review regarding efficacy and safety evaluation between SC and IV arms.

ER (safety) Assessment Summary

The Applicant's Position:

Not applicable. ER analyses were not conducted for CA20967T or CA20987KX.

The FDA's Assessment:

None.

ER Review Issues

Not applicable.

Reviewer's Independent Analysis

None.

Overall benefit-risk evaluation based on E-R analyses

The Applicant's Position:

Not applicable. ER analyses were not conducted for CA20967T or CA20987KX.

The FDA's Assessment:

None

Additional Safety Analyses Conducted by FDA

The FDA's Assessment:

None.

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BLA 761381 and BLA 761429
Bristol-Myers Squibb Company
Original BLA and Type 9

Signatures

DISCIPLINE	REVIEWER	OFFICE/DIVISION	SECTIONS AUTHORED/ APPROVED	AUTHORED/ APPROVED
Nonclinical Reviewer/Leader	Matthew Thompson	Office of Oncologic Diseases/Division of Hematology Oncology Toxicology	Sections: 5	Select one: ☒ Authored ☒ Approved
	Signature: Matthew D. Thompson -S Digitally signed by Matthew D. Thompson -S Date: 2024.12.18 10:04:35 -05'00'			
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Medical Officer	Michael Fusco	Division of Oncology 3	Sections: 2, 3, 4, 7, 8, 9, 10.	Select one: ☒ Authored ☐ Approved
	Signature: Michael J. Fusco -S Digitally signed by Michael J. Fusco -S Date: 2024.12.19 14:41:20 -05'00'			
Medical Team Lead/Cross Discipline Team Lead	Jamie Brew	Division of Oncology 3	Sections: All	Select one: ☒ Authored ☒ Approved
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Division Director	Steven Lemery	Division of Oncology 3	Sections: All	Select one: ☐ Authored ☒ Approved
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