TITLE PAGE

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Protocol Title: A Phase 3, Randomized, Double-blind, Active-Comparator-Controlled Clinical Study of Adjuvant MK-7684A (Vibostolimab with Pembrolizumab) Versus Adjuvant Pembrolizumab in Participants with High-risk Stage II-IV Melanoma (KEYVIBE-010)

Protocol Number: 010-04

Compound Number: MK-7684A

Sponsor Name: Merck Sharp & Dohme LLC

(hereafter called the Sponsor or MSD)

Legal Registered Address:

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Regulatory Agency Identifying Number(s):

NCT	05665595
EU CT	2022-501417-31
EudraCT	Not Applicable
JRCT	2031230099
WHO	Not Applicable
UTN	Not Applicable
IND	161,909

Approval Date: 27 June 2024

Sponsor Signatory

Typed Name: Title:	Date

Protocol-specific Sponsor contact information can be found in the Investigator Study File Binder (or equivalent).

Investigator Signatory

I agree to conduct this clinical study in accordance with the design outlined in this protocol and to abide by all provisions of this protocol.

Typed Name: Title:	Date

DOCUMENT HISTORY

Document	Date of Issue	Overall Rationale
Amendment 4	27-JUN-2024	Based on recommendations of the eDMC to discontinue the experimental arm (MK-7684A) following an interim review of the data showed no benefit over the comparator arm of pembrolizumab monotherapy.
Amendment 3	20-DEC-2023	To update futility analysis strategy and enrollment duration. The number of events required for IA1 has been changed to have an earlier futility analysis to prevent potential unnecessary exposure of study participants to study intervention (MK-7684A).
Amendment 2	15-MAR-2023	To address comments from the EU on inclusion of adolescents
Amendment 1	17-NOV-2022	Extended safety monitoring per Agency feedback
Original Protocol	15-SEP-2022	Not applicable

PROTOCOL AMENDMENT SUMMARY OF CHANGES

Amendment: 04

Overall Rationale for the Amendment:

Based on recommendations of the eDMC to discontinue the experimental arm (MK-7684A) following an interim review of the data showed no benefit over the comparator arm of pembrolizumab monotherapy.

Summary of Changes Table

Section Number and Name	Description of Change	Brief Rationale
Primary Reason for Amendment		
Section 1.1, Synopsis	Overall Design: Text added stating per Amendment 04, following an interim review of data by eDMC that showed no benefit over the comparator arm (pembrolizumab monotherapy), the experimental arm (MK-7684A) will be discontinued and ongoing participants will be offered the comparator treatment of pembrolizumab monotherapy, for up to 17 cycles of study treatment or until disease progression, whichever occurs first.	The experimental arm (MK-7684A) is discontinued based on the recommendations of the eDMC following an interim review of new data that showed no benefit over the comparator arm of pembrolizumab monotherapy.

Section Number and Name	Description of Change	Brief Rationale
Additional Changes		
Title Page	JRCT number added.	To provide new information.
Document History	Date for approval of Amendment 2 corrected from MAR 13 to MAR 15, 2023.	To correct the date for Amendment 2.
Section 1.1, Synopsis	Intervention Groups and Duration: Text added regarding the discontinuation of the experimental arm (MK-7684A) and ongoing participants moved to pembrolizumab monotherapy, for up to 17 cycles of study treatment or until disease progression, whichever occurs first.	See rationale for Section 1.1, discontinuation of experimental arm.
	Intervention Groups and Duration chart: added text to the Arm A heading stating discontinued as of Amendment 04.	See rationale for Section 1.1, discontinuation of experimental arm.
	Intervention Groups and Duration chart: for Arm B, clarified pembrolizumab monotherapy regimen is for up to 17 cycles or until discontinuation, whichever occurs first.	See rationale for Section 1.1, discontinuation of experimental arm.
	Duration of Participation: Clarified that pembrolizumab monotherapy will continue for up to 17 cycles of study treatment or until one of the conditions for discontinuation is met, whichever occurs first.	See rationale for Section 1.1, discontinuation of experimental arm.
	Duration of Participation: Text added stating no data collection is required for Efficacy Follow-up Visit.	See rationale for Section 1.1, discontinuation of experimental arm.

Section Number and Name	Description of Change	Brief Rationale
Section 1.2, Schema	Text added regarding the discontinuation of the experimental arm (MK-7684A) following eDMC interim review and ongoing participants moved to pembrolizumab monotherapy for the remainder of the study.	See rationale for Section 1.1, discontinuation of experimental arm.
	Figure 1: Age-related symbols corrected in the Key Eligibility Criteria note.	To correct erroneous information.
	Figure 1: Non-binding futility timings and number updated.	To align with current enrolment projections.
Section 1.3, Schedule of Activities	Text added regarding the discontinuation of the experimental arm (MK-7684A) following eDMC interim review and ongoing participants moved to pembrolizumab monotherapy for the remainder of the study, and added a reference to the new Schedule of Activities (SoA).	See rationale for Section 1.1, discontinuation of experimental arm.
Section 1.3.1, Schedule of Activities (Original Protocol to Protocol Amendment 03)	Added parenthetical, (Original protocol to Protocol Amendment 03), to section heading and SoA title.	See rationale for Section 1.1, discontinuation of experimental arm.
	Tumor Scan row: Note added to confirm imaging requirements for participants with primary neck lesions; subsequently, dashed arrow from C1 through DMFS Follow-up removed, and X marker added to DMFS Follow-up column.	To confirm neck imaging is only required for participants with a primary lesion on the head or neck at all protocol-specified time points.
Section 1.3.2, Schedule of Activities (Protocol Amendment 04)	New section added to provide SoA following Protocol Amendment 04 approval.	See rationale for Section 1.1, discontinuation of experimental arm.
Section 2.1, Study Rationale	Text added regarding the discontinuation of the experimental arm (MK-7684A) following eDMC interim review and ongoing participants moved to pembrolizumab monotherapy for the remainder of the study.	See rationale for Section 1.1, discontinuation of experimental arm.
Section 4.1, Overall Design	Text added stating per Amendment 04, following an interim review of data by eDMC that showed no benefit over the comparator arm (pembrolizumab monotherapy), the experimental arm (MK-7684A) will be discontinued and all ongoing participants on treatment will move to the comparator arm (Arm B: pembrolizumab monotherapy) for the remainder of the study.	See rationale for Section 1.1, discontinuation of experimental arm.
Section 4.4, Beginning and End-of-Study Definition	Text updated to provide maximum duration on study (including follow-up) and to reference Section 1.1, Synopsis, for duration information.	To provide clear estimates for expected study duration.
	Text added confirming the end of the study will be defined as when all participants have discontinued treatment and have completed the safety follow-up requirements.	See rationale for Section 1.1, discontinuation of experimental arm.

Section Number and Name	Description of Change	Brief Rationale
Section 4.4.1, Clinical Criteria for Early Study Termination	Text added stating the reason for the discontinuation of the experimental arm (MK-7684A) per eDMC recommendations.	See rationale for Section 1.1, discontinuation of experimental arm.
	Text added confirming the end of the study will be defined as when all participants have discontinued treatment and have completed the safety follow-up requirements.	See rationale for Section 1.1, discontinuation of experimental arm.
Section 6, Study Intervention	Text added stating that any reports of supply complaints or temperature excursions should be sent to a specified mailbox.	To ensure study intervention issues are reported correctly.
Section 6.1, Study Intervention(s) Administered	Text added regarding the discontinuation of the experimental arm (MK-7684A) and ongoing participants moved to pembrolizumab monotherapy, for up to 17 cycles of study treatment or until disease progression, whichever occurs first.	See rationale for Section 1.1, discontinuation of experimental arm.
	Table 3: Experimental Arm and Comparator Arm updated to reflect discontinuation of experimental arm and duration of pembrolizumab monotherapy.	See rationale for Section 1.1, discontinuation of experimental arm.
	Table 3: Footnote added stating that commercially available supplies, in terms of unit dose strength or formulation, may vary depending on market availability.	To ensure compliance with local prescribing information for commercial supplies.
Section 6.1.1, Treatment	Text added regarding the discontinuation of the experimental arm (MK-7684A) and ongoing participants moved to pembrolizumab monotherapy, for up to 17 cycles of study treatment or until disease progression, whichever occurs first.	See rationale for Section 1.1, discontinuation of experimental arm.
	Text added that Sponsor should be consulted if the investigator wishes benefitting participants to continue MK-7684A treatment.	See rationale for Section 1.1, discontinuation of experimental arm.
Section 6.3.1, Intervention Assignment	Text added regarding the discontinuation of the experimental arm (MK-7684A) and ongoing participants moved to pembrolizumab monotherapy, for up to 17 cycles of study treatment or until disease progression, whichever occurs first.	See rationale for Section 1.1, discontinuation of experimental arm.
	Text added that Sponsor should be consulted if the investigator wishes benefitting participants to continue MK-7684A treatment.	See rationale for Section 1.1, discontinuation of experimental arm.
Section 6.3.3, Blinding	Text added to state that following eDMC interim review of data, all participants have been unblinded.	See rationale for Section 1.1, discontinuation of experimental arm.
Section 6.5, Concomitant Therapy	Removed repetitive text.	See rationale for Section 1.2, Key Eligibility Criteria footnote.
Section 7.1, Discontinuation of Study Intervention	Text added regarding the discontinuation of the experimental arm (MK-7684A) and ongoing participants moving to pembrolizumab monotherapy with a reference to Section 1.3.2 (SoA).	See rationale for Section 1.1, discontinuation of experimental arm.

Section Number and Name	Description of Change	Brief Rationale
Section 7.2, Participant Withdrawal From the Study	Text added stating that participants who complete or discontinue study intervention and have completed safety follow-up will be considered to have completed the study. This also applies to participants in efficacy follow-up.	See rationale for Section 1.1, discontinuation of experimental arm.
Section 8.1.9, Study Intervention Administration	Text added regarding the discontinuation of the experimental arm (MK-7684A) and ongoing participants moved to pembrolizumab monotherapy for the remainder of the study (a total of 17 cycles of study treatment or until disease progression, whichever occurs first).	See rationale for Section 1.1, discontinuation of experimental arm.
	Text added that Sponsor should be consulted if the investigator wishes benefitting participants to continue MK-7684A treatment.	See rationale for Section 1.1, discontinuation of experimental arm.
Section 8.1.9.1, Timing of Dose Administration	Text added referencing Section 1.3.2 (SoA).	See rationale for Section 1.1, discontinuation of experimental arm.
Section 8.1.10, Discontinuation and Withdrawal	Text added referencing Section 1.3.2 (SoA).	See rationale for Section 1.1, discontinuation of experimental arm.
Section 8.1.11, Participant Blinding/Unblinding	Text added stating that the treatment arms have been unblinded, per the eDMC recommendation to discontinue the experimental arm (MK-7684A).	See rationale for Section 1.1, discontinuation of experimental arm.
Section 8.2.1, Tumor Imaging and Assessment of Disease	Text added to confirm imaging requirements for participants with primary neck lesions.	See rationale for Section 1.3, Tumor Scans for neck imaging.
	Text added to reference to Section 1.3.2 (SoA).	See rationale for Section 1.1, discontinuation of experimental arm.
Section 8.2.1.2, Tumor Scans During the Study	Text added to reference Section 1.3.2 (SoA) and state that no further scans are required in follow-up.	See rationale for Section 1.1, discontinuation of experimental arm.
Section 8.2.1.3, End-of-treatment and Follow-up Tumor Scans	Text added to reference Section 1.3.2 (SoA) and state that no further scans are required in follow-up.	See rationale for Section 1.1, discontinuation of experimental arm.
Section 8.2.2, Patient-reported Outcomes	Text added to reference Section 1.3.2 (SoA) and state that no further PROs are required.	See rationale for Section 1.1, discontinuation of experimental arm.
Section 8.3, Safety Assessments	Text added to reference Section 1.3.2 (SoA).	See rationale for Section 1.1, discontinuation of experimental arm.
Section 8.4.3, Follow-up of AE, SAE, and Other Reportable Safety Event Information	Text revised to state that all nonserious AEs are not required to be followed until the outcome of the event is known but every effort should be made to capture this information.	To provide flexibility to investigators when a patient has withdrawn consent or has been lost to follow-up.
Section 8.4.4, Regulatory Reporting Requirements for SAE	Text added to align with EU requirements for reporting SUSARs.	To comply with EU regulatory requirements.

Section Number and Name	Description of Change	Brief Rationale
Section 8.6, Pharmacokinetics	Text added to reference Section 1.3.2 (SoA) and state that no further PK/ADA samples are required.	See rationale for Section 1.1, discontinuation of experimental arm.
Section 8.8, Biomarkers	Text added to reference Section 1.3.2 (SoA) and state that no further biomarker samples are required.	See rationale for Section 1.1, discontinuation of experimental arm.
Section 8.11.4.2, Efficacy Follow-up Visits	Text added to reference Section 1.3.2 (SoA) and state that no further Efficacy Follow-up Visits are required.	See rationale for Section 1.1, discontinuation of experimental arm.
Section 8.11.4.3, DMFS Follow-up Visits	Text added to reference Section 1.3.2 (SoA) and state that no further DMFS Follow-up Visits are required.	See rationale for Section 1.1, discontinuation of experimental arm.
Section 8.11.4.4, Survival Follow-up Contacts	Text added to reference Section 1.3.2 (SoA) and state that no further Survival Follow-up Contact are required.	See rationale for Section 1.1, discontinuation of experimental arm.
Section 9, Statistical Analysis Plan	Text added regarding the discontinuation of the experimental arm (MK-7684A) following eDMC interim review and ongoing participants moved to pembrolizumab monotherapy for the remainder of the study.	See rationale for Section 1.1, discontinuation of experimental arm.
Section 9.1, Statistical Analysis Plan Summary	Text updated with approximate timings on IA2, IA3, IA4, IA5, and FA. Statistical assumptions were not changed.	See rationale for Section 1.2, futility timing.
Section 9.2, Responsibility for Analyses/In-house Blinding	Text added to state that following eDMC review of the data at IA1, no additional efficacy and PRO data analysis will be conducted at subsequent IAs and that information regarding planned IAs in Section 9 is being retained for historical purposes.	See rationale for Section 1.1, discontinuation of experimental arm.
Section 9.7.1, Interim Analyses	Table 11 updated with approximate timings on IA2, IA3, IA4, IA5, and FA. Statistical assumptions were not changed.	See rationale for Section 1.2, futility timing.
Section 10.1.1, Code of Conduct for Clinical Trials	Text added to reference to EU 536/2014 regulation.	See rationale for Section 8.4.4.
Section 10.1.3, Data Protection	Text added regarding EU global privacy statement.	See rationale for Section 8.4.4.
Section 10.7.6, Italy	Section removed as requirements for Italy are stated in Section 10.7.11 (previously 10.7.12).	To remove duplicate text.
Throughout document	Treatment arm has been changed to experimental arm.	To be consistent with updated treatment arms listed in Study Interventions table.
	Minor administrative, formatting, grammatical, and/or typographical changes were made throughout the document.	To ensure clarity and accurate interpretation of the intent of the protocol.

TABLE OF CONTENTS

LIST OF TABLES

LIST OF FIGURES

1 PROTOCOL SUMMARY

1.1 Synopsis

Protocol Title: A Phase 3, Randomized, Double-blind, Active-Comparator-Controlled Clinical Study of Adjuvant MK-7684A (Vibostolimab with Pembrolizumab) Versus Adjuvant Pembrolizumab in Participants with High-risk Stage II-IV Melanoma (KEYVIBE-010)

Short Title: Adjuvant MK-7684A vs Pembrolizumab for Resected High-Risk Melanoma

Acronym: KEYVIBE-010

Hypotheses, Objectives, and Endpoints:

Hypotheses are aligned with objectives in the Objectives and Endpoints table.

In individuals with high-risk resected Stage IIB, IIC, III or IV melanoma:

Primary Objective	**Primary Endpoint**
To compare MK-7684A to pembrolizumab with respect to RFS Hypothesis (H1): MK-7684A is superior to pembrolizumab with respect to RFS as assessed by investigator.	RFS: time from randomization to any recurrence (local, locoregional, regional or distant) as assessed by investigator, or death due to any cause, whichever occurs first.
Secondary Objectives	**Secondary Endpoints**
To compare MK-7684A to pembrolizumab with respect to DMFS. Hypothesis (H2): MK-7684A is superior to pembrolizumab with respect to DMFS as assessed by investigator.	DMFS: The time from randomization to appearance of a distant metastasis as assessed by investigator or death due to any cause, whichever occurs first. A distant metastasis refers to cancer that has spread from the original (primary) tumor to distant organs or distant lymph nodes.
To compare MK-7684A to pembrolizumab with respect to OS. Hypothesis (H3): MK-7684A is superior to pembrolizumab with respect to overall survival.	OS: The time from randomization to death due to any cause.
To evaluate the safety and tolerability of MK-7684A and pembrolizumab	Adverse event Study intervention discontinuation due to AEs

To evaluate MK-7684A to pembrolizumab with respect to mean change from baseline in global health status/QoL, physical functioning, and role functioning using the EORTC QLQ-C30	Change in score from baseline evaluated by: Global health status/QoL score (Items 29 and 30) Physical functioning score (Items 1-5) Role functioning score (Items 6 and 7)

Overall Design:

Protocol Amendment 04 implementation: based on recommendations of the eDMC following an interim review of the data that showed no benefit over the comparator arm of pembrolizumab monotherapy, the experimental arm (Arm A: MK-7684A) will be discontinued and all ongoing participants on treatment will move to the comparator arm (Arm B: pembrolizumab monotherapy) for the remainder of the study (a total of 17 cycles of study treatment or until disease progression, whichever occurs first).

Study Phase	Phase 3
Primary Purpose	Treatment
Indication	Malignant melanoma
Population	Adult and adolescent participants (≥12 years old and ≥40 kg) with high-risk (Stage IIb-IV) resected melanoma
Study Type	Interventional
Intervention Model	Parallel This is a multi site study.
Type of Control	Active Control Without Placebo
Study Blinding	Double-blind with in-house blinding
Blinding Roles	Participants or Subjects Investigator Sponsor
Estimated Duration of Study	The Sponsor estimates that the study will require approximately 8 years from the time the first participant (or their legally acceptable representative) provides documented informed consent until the last participant's last study-related contact.

Number of Participants:

Approximately 1,560 participants will be randomized in the study.

Intervention Groups and Duration:

Protocol Amendment 04 implementation: All active participants in the experimental arm (Arm A: MK-7684A) will be moved to the comparator arm (Arm B: pembrolizumab monotherapy) for the remainder of the study (a total of 17 cycles of study treatment or until disease progression, whichever occurs first).

Arm Name	**Intervention Name**	**Unit Dose Strength(s)**	**Dosage Level(s)**	**Route of Administration**	**Regimen/ Treatment Period/ Vaccination Regimen**	**Use**
Arm A (Protocol Amendment 04: Arm A discontinued)	MK-7684A	MK-7684 200 mg + pembrolizumab 200 mg/ 20 mL vial	200 mg / 200 mg	IV Infusion	Q3W (Day 1 of each cycle) for 17 cycles or until discon-tinuation criteria are met	Test Product
Arm B	Pembrolizumab	25 mg/mL	Adults: 200 mg Adolescents ≥40 kg: 2 mg/kg (up to max of 200 mg)	IV Infusion	Q3W (Day 1 of each cycle) for 17 cycles or until discon-tinuation criteria are met, whichever occurs first	Comparator

IV=intravenous; Q3W=every 3 weeks.
MK-7684A is a coformulation of vibostolimab (MK-7684) with pembrolizumab.

Total Number of Intervention Groups/Arms	2
Duration of Participation	Each participant will participate in the study from the time the participant provides documented informed consent through the final protocol-specified contact. After a screening phase of up to 28 days, each participant will be assigned to receive study intervention for up to 17 cycles or until one of the conditions for discontinuation of study intervention is met, whichever occurs first. After the end of treatment, each participant will be followed for the occurrence of AEs and spontaneously reported pregnancy. Participants who discontinue for reasons other than disease recurrence will have posttreatment follow-up for disease status until any of the conditions for discontinuation of Efficacy Follow-up are met. Participants who discontinue for reasons other than confirmed metastatic disease recurrence will be followed for disease status until metastatic disease recurrence is confirmed (radiographically and/or by examination with subsequent biopsy). Participants who initiate a nonstudy anticancer treatment for melanoma will have posttreatment DMFS follow-up until metastatic disease recurrence is documented. All participants will be followed for OS until death, withdrawal of consent, or the end of the study. Protocol Amendment 04 implementation: no data collection for efficacy follow-up will be required.

Study Governance Committees:

Executive Oversight Committee	Yes
Data Monitoring Committee	Yes
Clinical Adjudication Committee	No

Study governance considerations are outlined in Appendix 1.

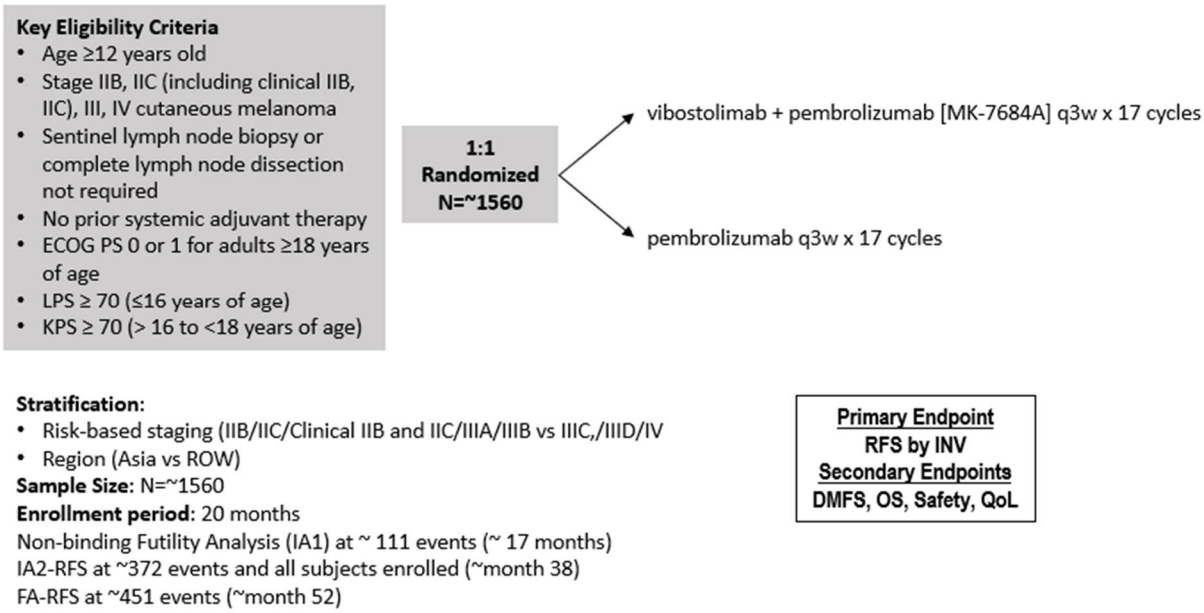
Study Accepts Healthy Participants: No

A list of abbreviations is in Appendix 11.

1.2 Schema

The study design is depicted in Figure 1. Protocol Amendment 04 implementation: Following eDMC interim review of the data, the experimental arm (Arm A: MK-7684A) will be discontinued and all ongoing participants will move to the comparator arm (Arm B: pembrolizumab monotherapy) for the remainder of the study.

Figure 1 Study Design



DMFS=distant metastasis-free survival; ECOG=Eastern Cooperative Oncology Group; IA=Interim Analysis; INV=investigator; KPS=Karnofsky performance status; LPS=Lansky play-performance scale; OS=overall survival; QoL=quality of life; RFS=recurrence-free survival; ROW=rest of world.

1.3 Schedule of Activities

See Appendix 7 for country-specific requirements. Table 1 documents the Schedule of Activities up to Protocol Amendment 03.

Protocol Amendment 04 implementation: Following eDMC interim review of the data, the experimental arm (Arm A: MK-7684A) will be discontinued and all ongoing participants will move to the comparator arm (Arm B: pembrolizumab monotherapy) for the remainder of the study. Refer to Table 2 for Schedule of Activities to be implement following approval of Protocol Amendment 04.

1.3.1 Schedule of Activities (Original Protocol through Protocol Amendment 03)

Table 1 Schedule of Activities (Original protocol through Protocol Amendment 03)

Study Period	**Screening**	**Treatment (3-Week Cycles for up to 17 Cycles)**			**EOT**	**Posttreatment**				**Notes**
Visit Number/Title	**Screening**	**C1**	**C2 and Even # Cycles**	**C3 and Odd # Cycles**	**Discon**	**Safety Follow-up**	**Efficacy Follow-up**	**DMFS Follow-up**	**Survival Follow-up**	**All assessments should be performed before treatment administration unless otherwise indicated.**
Cycle Day	**Up to 28 days before first dose**	**1**	**1**	**1**	**At Discon**	**30 days and 90 days from last dose**	**Per Imaging Schedule**	**Per Imaging Schedule**	**Q12W**	
Scheduled Days	**-28 to -1**	**+3**	**±3**	**±3**	**+7**	**+7**			**±14**	
Administrative Procedures										
Informed Consent/Assent	X									
Informed Consent/Assent for FBR	X									Participant may participate in main study without providing FBR consent. For country-specific criteria, refer to Appendix 7.
Inclusion/Exclusion Criteria	X									
Participant ID Card Issued	X	X								Add the randomization number at the time of randomization.
Medical History and Demographics	X									
Disease History	X									

Study Period	**Screening**	**Treatment (3-Week Cycles for up to 17 Cycles)**			**EOT**	**Posttreatment**				**Notes**
Visit Number/Title	**Screening**	**C1**	**C2 and Even # Cycles**	**C3 and Odd # Cycles**	**Discon**	**Safety Follow-up**	**Efficacy Follow-up**	**DMFS Follow-up**	**Survival Follow-up**	**All assessments should be performed before treatment administration unless otherwise indicated.**
Cycle Day	**Up to 28 days before first dose**	**1**	**1**	**1**	**At Discon**	**30 days and 90 days from last dose**	**Per Imaging Schedule**	**Per Imaging Schedule**	**Q12W**	
Scheduled Days	**-28 to -1**	**+3**	**±3**	**±3**	**+7**	**+7**			**±14**	
Prior/Concomitant Medication Review	X	X	X	X	X	X				Record medication(s) administered within 28 days before the start of study intervention, during the study, and through the Safety Follow-up Visit. Concomitant medications for an SAE administered after the Safety Follow-up Visit should be recorded.
Randomization		X								
Poststudy Anticancer Therapy Status						X	X	X	X	
Vital Status	←---→								X	On Sponsor request, participants may be contacted for survival information at any time during the study.
Study Intervention Administration										
Blinded Study Intervention Administration (MK-7684A or pembrolizumab)		X	X	X						

Study Period	**Screening**	**Treatment (3-Week Cycles for up to 17 Cycles)**			**EOT**	**Posttreatment**				**Notes**
Visit Number/Title	**Screening**	**C1**	**C2 and Even # Cycles**	**C3 and Odd # Cycles**	**Discon**	**Safety Follow-up**	**Efficacy Follow-up**	**DMFS Follow-up**	**Survival Follow-up**	**All assessments should be performed before treatment administration unless otherwise indicated.**
Cycle Day	**Up to 28 days before first dose**	**1**	**1**	**1**	**At Discon**	**30 days and 90 days from last dose**	**Per Imaging Schedule**	**Per Imaging Schedule**	**Q12W**	
Scheduled Days	**-28 to -1**	**+3**	**±3**	**±3**	**+7**	**+7**			**±14**	
Efficacy Procedures										
Tumor Scan (Neck, Chest, Abdomen, and Pelvis)	X	◄----------				----------►		X	X*	Perform at the EOT Visit and 12 weeks (±7 days) from date of randomization, then Q12W (±7 days) for 2 years after randomization, then Q6M (±14 days) through Year 4, then once at 5 years (±28 days) after date of randomization. NECK CT is required only for participants with primary tumors of the head and neck and during the study if clinically indicated. * Radiographic imaging in Survival Follow-up may be performed as clinically indicated, per local standard of care, or following new anticancer therapy imaging schedule. Refer to the Site Imaging Manual for details.
Brain Scan	X	As clinically indicated								
Bone Scan	As clinically indicated									
Pathology Report	X	Recurrence only								
Lesion Photograph		Recurrence only								Submit diagnostic photograph for cutaneous recurrence if possible.
Safety Procedures										
Full Physical Examination	X				X					
Height	X	X*	X*	X*	X*	X*				*Pediatric participants only.
Weight	X	X	X	X	X	X				

Study Period	**Screening**	**Treatment (3-Week Cycles for up to 17 Cycles)**			**EOT**	**Posttreatment**				**Notes**
Visit Number/Title	**Screening**	**C1**	**C2 and Even # Cycles**	**C3 and Odd # Cycles**	**Discon**	**Safety Follow-up**	**Efficacy Follow-up**	**DMFS Follow-up**	**Survival Follow-up**	**All assessments should be performed before treatment administration unless otherwise indicated.**
Cycle Day	**Up to 28 days before first dose**	**1**	**1**	**1**	**At Discon**	**30 days and 90 days from last dose**	**Per Imaging Schedule**	**Per Imaging Schedule**	**Q12W**	
Scheduled Days	**-28 to -1**	**+3**	**±3**	**±3**	**+7**	**+7**			**±14**	
Directed Physical Examination		X	X	X		X	X*	X*		The investigator or qualified designee should conduct a visual inspection of local recurrence and palpation of regional lymph nodes to assess regional recurrence. *During follow-up, if a clinic visit is not feasible, a physical examination will not be collected.
Vital Signs (temperature, heart rate, respiratory rate, and blood pressure)	X	X	X	X	X	X				
12-lead ECG	X									A 6-lead ECG is allowed per institutional standard.
Age-appropriate Performance Scale (Lansky/Karnofsky/ECOG)	X*		X	X	X	X				*Screening assessment to be performed within 7 days of C1D1. ≤16 years of age: Lansky; >16 to <18 years of age: Karnofsky; ≥18 years of age: ECOG
AE/SAE Review	X	X	X	X	X	X				Refer to Section 8.4.1 for the duration of AE reporting.
Laboratory Assessments										Laboratory samples should be taken and reviewed pre-dose at each time point indicated.
Hematology/Chemistry	X		X	X	X	X				Screening samples to be taken within 7 days of first dose of study intervention. See Appendix 2 for further details.
Urine Testing (urinalysis or dipstick)	X		X		X	X				Screening samples to be taken within 7 days of first dose of study intervention. See Appendix 2 for further details.

Study Period	**Screening**	**Treatment (3-Week Cycles for up to 17 Cycles)**			**EOT**	**Posttreatment**				**Notes**
Visit Number/Title	**Screening**	**C1**	**C2 and Even # Cycles**	**C3 and Odd # Cycles**	**Discon**	**Safety Follow-up**	**Efficacy Follow-up**	**DMFS Follow-up**	**Survival Follow-up**	**All assessments should be performed before treatment administration unless otherwise indicated.**
Cycle Day	**Up to 28 days before first dose**	**1**	**1**	**1**	**At Discon**	**30 days and 90 days from last dose**	**Per Imaging Schedule**	**Per Imaging Schedule**	**Q12W**	
Scheduled Days	**-28 to -1**	**+3**	**±3**	**±3**	**+7**	**+7**			**±14**	
Coagulation Tests (PT/INR and aPTT/PTT)	X									Perform within 7 days before first dose of study intervention. Consider more frequent testing for participants receiving anticoagulants. See Appendix 2 for further details.
T3/T4/TSH	X		X		X	X				Screening samples to be taken within 7 days of first dose of study intervention. See Appendix 2 for further details.
LDH	X	Recurrence only								Screening samples to be taken within 7 days of first dose of study intervention. See Appendix 2 for further details.
Urine or Serum Pregnancy Test (WOCBP only)	X	X	X	X	X	X*				WOCBP require a negative test within 24 hours (for a urine test) or 72 hours (for a serum test) within C1D1 and before each subsequent dose of study intervention. *Repeat at 120 days from last dose of study intervention. See Section 8.3.5 for pregnancy testing requirements.
HIV, Hepatitis B and Hepatitis C Testing	X*									*Only if required per Section 5.1 and/or Appendix 7. See Appendix 2 for further details.

Study Period	**Screening**	**Treatment (3-Week Cycles for up to 17 Cycles)**			**EOT**	**Posttreatment**				**Notes**
Visit Number/Title	**Screening**	**C1**	**C2 and Even # Cycles**	**C3 and Odd # Cycles**	**Discon**	**Safety Follow-up**	**Efficacy Follow-up**	**DMFS Follow-up**	**Survival Follow-up**	**All assessments should be performed before treatment administration unless otherwise indicated.**
Cycle Day	**Up to 28 days before first dose**	**1**	**1**	**1**	**At Discon**	**30 days and 90 days from last dose**	**Per Imaging Schedule**	**Per Imaging Schedule**	**Q12W**	
Scheduled Days	**-28 to -1**	**+3**	**±3**	**±3**	**+7**	**+7**			**±14**	
Patient-reported Outcomes Assessments										Administer PROs in the order shown before performing any other procedures, assessments, or treatment.
EORTC QLQ-C30		X		X*	X	X	X#	X#		*Cycles 5, 9, 13, and 17 Administered to adults (≥18 years of age at screening) only. #During follow-up, if a clinic visit is not feasible, PROs will not be collected
EQ-5D-5L		X		X*	X	X	X#	X#		*Cycles 5, 9, 13, and 17 # During follow-up, if a clinic visit is not feasible, PRO will not be collected
Pharmacokinetics/ Pharmacodynamics/ Biomarkers										
Blood collection for PK		X	X			X				Predose (within 24 hours before study intervention infusion): Cycles 1, 2, 4, 8, 12 and 16 Postdose (within 10 minutes after end of infusion): Cycles 1 and 8
Blood collection for ADA		X	X			X				Predose (within 24 hours before study intervention infusion): Cycles 1, 2, 4, 8, 12 and 16

Study Period	**Screening**	**Treatment (3-Week Cycles for up to 17 Cycles)**			**EOT**	**Posttreatment**				**Notes**
Visit Number/Title	**Screening**	**C1**	**C2 and Even # Cycles**	**C3 and Odd # Cycles**	**Discon**	**Safety Follow-up**	**Efficacy Follow-up**	**DMFS Follow-up**	**Survival Follow-up**	**All assessments should be performed before treatment administration unless otherwise indicated.**
Cycle Day	**Up to 28 days before first dose**	**1**	**1**	**1**	**At Discon**	**30 days and 90 days from last dose**	**Per Imaging Schedule**	**Per Imaging Schedule**	**Q12W**	
Scheduled Days	**-28 to -1**	**+3**	**±3**	**±3**	**+7**	**+7**			**±14**	
Archival and/or Newly Obtained Tissue Collection	X	Submission of tumor tissue is optional for recurrence								At Screening: Submit archival or fresh tumor sample if sufficient tumor tissue is available. At Recurrence (optional): Submit fresh tumor sample. See Procedure Manual for details.
Blood for Genetic Analysis		X								Collect predose. See Section 8.8.1 for additional information.
Blood for ctDNA Analysis		X	X*	X**	X		X***	X***		Collect predose on C1D1. *Collect predose on Day 1 for even cycles: C2 and C4 **Collect predose on Day 1 for odd cycles: C3, C5, C9, C13, and C17 ***During follow-up, if a clinic visit is not feasible, blood for ctDNA will not be collected.

ADA=antidrug antibodies; AE=adverse event; aPTT=activated partial thromboplastin time; C=cycle; ctDNA=circulating tumor DNA; D=day; Discon=discontinuation; DMFS=distant metastasis-free survival; ECG=electrocardiogram; ECOG=Eastern Cooperative Oncology Group; EORTC QLQ=European Organization for Research and Treatment of Cancer Quality of Life Questionnaire; EOT=end of treatment; EQ-5D-5L=EuroQoL 5 dimensions-5 levels; FBR=future biomedical research; HIV=human immunodeficiency virus; ID=identification; LDH=lactate dehydrogenase; PK=pharmacokinetics; PRO=patient-reported outcome; PT/INR=prothrombin time/international normalized ratio; PTT=partial thromboplastin time; Q12W=every 12 weeks; Q6M=every 6 months; SAE=serious adverse event; T3=triiodothyronine; T4=thyroxine; TSH=thyroid-stimulating hormone; WOCBP=woman of childbearing potential.

1.3.2 Schedule of Activities (Protocol Amendment 04)

Table 2 Schedule of Activities (Protocol Amendment 04)

Study Period	Treatment (3-Week Cycles for up to 17 Cycles)		EOT	Posttreatment	Notes
Visit Number/Title	**C2 and Even # Cycles**	**C3 and Odd # Cycles**	**Discon**	**Safety Follow-up**	**All assessments should be performed before treatment administration unless otherwise indicated. Participants who complete or discontinue study intervention and have completed safety follow-up will be considered to have completed the study. This also applies to participants in efficacy follow-up.**
Cycle Day	**1**	**1**	**At Discon**	**30 days and 90 days from last dose**	
Scheduled Days	**±3**	**±3**	**+7**	**+7**	
Administrative Procedures					
Informed Consent/Assent	X				Reconsent with revised informed consent form.
Prior/Concomitant Medication Review	X	X	X	X	Record medication(s) administered through to the Safety Follow-up Visit. Concomitant medications for an SAE administered after the Safety Follow-up Visit should be recorded.
Study Intervention Administration					
Pembrolizumab administration	X	X			Participants may receive a total of 17 cycles of study treatment.
Efficacy Procedures					
Tumor Scan (Neck, Chest, Abdomen, and Pelvis)	Q12W or per local standard-of-care				NECK CT is required only for participants with primary tumors of the head and neck and during the study if clinically indicated. On-treatment scans required to confirm if recurrence occurs (treatment discontinuation criteria).
Safety Procedures					
Full Physical Examination			X		
Weight	X	X	X	X	
Vital Signs (temperature, heart rate, respiratory rate, and blood pressure)	X	X	X	X	
12-lead ECG					A 6-lead ECG is allowed per institutional standard.
Age-appropriate Performance Scale (Lansky/Karnofsky/ECOG)	X	X	X	X	≤16 years of age: Lansky; >16 to <18 years of age: Karnofsky; ≥18 years of age: ECOG
AE/SAE Review	X	X	X	X	Refer to Section 8.4.1 for the duration of AE reporting.

Study Period	Treatment (3-Week Cycles for up to 17 Cycles)		EOT	Posttreatment	Notes
Visit Number/Title	**C2 and Even # Cycles**	**C3 and Odd # Cycles**	**Discon**	**Safety Follow-up**	**All assessments should be performed before treatment administration unless otherwise indicated.**
Cycle Day	**1**	**1**	**At Discon**	**30 days and 90 days from last dose**	**Participants who complete or discontinue study intervention and have completed safety follow-up will be considered to have completed the study. This also applies to participants in efficacy follow-up.**
Scheduled Days	**±3**	**±3**	**+7**	**+7**	
Laboratory Assessments					Laboratory samples should be taken and reviewed pre-dose at each time point indicated.
Hematology/Chemistry	X	X	X	X	See Appendix 2 for further details.
Urine Testing (urinalysis or dipstick)	X		X	X	See Appendix 2 for further details.
T3/T4/TSH	X		X	X	See Appendix 2 for further details.
Urine or Serum Pregnancy Test (WOCBP only)	X	X	X	X*	*Repeat at 120 days from last dose of study intervention. See Section 8.3.5 for pregnancy testing requirements.

AE=adverse event; C=cycle; D=day; Discon=discontinuation; ECG=electrocardiogram; ECOG=Eastern Cooperative Oncology Group; EOT=end of treatment; Q12W=every 12 weeks; SAE=serious adverse event; SOC=standard-of-care; T3=triiodothyronine; T4=thyroxine; TSH=thyroid-stimulating hormone; WOCBP=woman of childbearing potential.

2 INTRODUCTION

2.1 Study Rationale

Melanoma is a malignant tumor that arises from melanocytes that accounts for less than 2% of skin cancers, though 90% of deaths due to cutaneous tumors are associated with melanoma [Garbe, C., et al 2012] [American Cancer Society 2014]. Worldwide, about 324,635 individuals were diagnosed with melanoma in 2021, and in the US an estimated 99,780 new cases of melanoma will be diagnosed and 7,650 will die of their melanoma in 2022. The risk of melanoma increases with age, with the median age of diagnosis of 61 years [American Cancer Society 2014]. However, melanoma is not uncommon among individuals younger than 30 years and is the second most diagnosed cancer (after lymphomas) among adolescents and young adults [Weir, H. K., et al 2011]. Most patients with melanoma (84%) are initially diagnosed with localized disease, whereas 9% have regional disease, and 4% have metastatic disease at diagnosis [National Cancer Institute 2017].

Standard treatment for localized melanoma is surgical resection. For patients with Stage III or IV resectable disease, systemic adjuvant therapy has been established as a standard of care option for appropriate patients after resection, with NCCN-recommended regimens including nivolumab, pembrolizumab, and dabrafenib/trametinib (for melanoma with BRAF V600-activating mutation). For patients with Stage IIB or IIC disease, systemic therapy with pembrolizumab is an accepted standard of care option. For patients with Stage I and IIA disease, standard of care management after resection is observation [National Comprehensive Cancer Network 2022].

The US FDA, EMA and other worldwide health authorities have approved the use of pembrolizumab for the adjuvant treatment of adult and pediatric (12 years and older) patients with Stage IIB, IIC, or III melanoma following complete resection. KEYNOTE-054 showed that adjuvant pembrolizumab treatment of patients with Stage III disease resulted in a statistically significant and clinically meaningful improvement in RFS compared with placebo (HR=0.57 [98.4% CI: 0.43, 0.74]; $p<0.0001$) with a median duration of follow-up of 15 months. KEYNOTE-716 further established the role of pembrolizumab therapy in the treatment of adjuvant melanoma by demonstrating that in patients with Stage IIB and IIC melanoma in the adjuvant setting, pembrolizumab provided a statistically significant and clinically meaningful 35% reduction in the risk of disease recurrence or death in the pembrolizumab group compared with the placebo group (HR=0.65 [95% CI: 0.46, 0.92]; $p=0.00658$). KEYNOTE-716 also showed that adjuvant pembrolizumab significantly improved DMFS compared with placebo (HR=0.64 [95% CI: 0.47, 0.88]) [Long, G. V., et al 2022].

Before the approval of adjuvant anti-PD-1 therapies, the 5-year survival rate for patients with localized disease at diagnosis was 99% (~ 83% for Stage IIB and IIC), regional disease was 63% and distant disease was 20%, demonstrating an unmet need for new therapeutic options [National Cancer Institute 2017] [Gershenwald, J. E., et al 2017]. While adjuvant anti-PD-1 monotherapies have showed an improvement in RFS and DMFS in patients with high-risk disease, anti-PD-1 based combination therapies may be able to further improve these outcomes.

Protocol Amendment 04 implementation: Following eDMC interim review of the data, the experimental arm (Arm A: MK-7684A) will be discontinued and all ongoing participants will move to the comparator arm (Arm B: pembrolizumab monotherapy) for the remainder of the study.

2.1.1 Preliminary Data for Coformulation of Vibostolimab with Pembrolizumab (MK-7684A) in Melanoma

The combination of vibostolimab (MK-7684) with pembrolizumab as a fixed dose coformulation (MK-7684A) is under evaluation in several ongoing studies, including studies in participants with melanoma.

KEYMAKER-U02 is an ongoing platform study evaluating investigational agents with or without pembrolizumab and pembrolizumab alone in participants with melanoma.
A summary of the existing efficacy and safety data from the KEYMAKER-U02 substudies evaluating MK-7684 with pembrolizumab (either sequentially administered or as MK-7684A) in participants with melanoma (substudies KEYMAKER-02B and KEYMAKER-02C) is provided below. Together, these studies show proof-of-concept for the evaluation of MK-7684A in this Phase 3 study.

2.1.1.1 Substudy KEYMAKER-02B

Substudy KEYMAKER-02B is evaluating various agents combined with pembrolizumab (including vibostolimab with pembrolizumab) compared with pembrolizumab alone in participants with first-line advanced melanoma.

As of 07-APR-2022, 42 participants had been treated with the combination of vibostolimab (200 mg Q3W) and pembrolizumab (200 mg Q3W), and 21 participants had been treated with pembrolizumab alone.

Among evaluable participants with on-study imaging, the ORR as assessed by the investigator was 40.0% for participants receiving the combination of MK-7684 and pembrolizumab versus 29.4% for participants receiving single-agent pembrolizumab. The median progression free survival for the combination of MK-7684 and pembrolizumab was 15.1 months (95% CI: 6.2, NR), whereas the median progression free survival for pembrolizumab alone was 4.2 months (95% CI: 4.1, NR). Review of the safety data as of 15-FEB-2022 for participants treated with the combination of vibostolimab with pembrolizumab in KEYMAKER-02B demonstrates a well-tolerated and manageable safety profile generally similar to that of pembrolizumab monotherapy.

2.1.1.2 Substudy KEYMAKER-02C

Substudy KEYMAKER-02C is evaluating various agents (including vibostolimab) in the neoadjuvant setting followed by adjuvant pembrolizumab in participants with clinically detectable and resectable Stage IIIB-IIID melanoma.

As of 21-MAR-2022, 26 participants receiving vibostolimab (200 mg Q3W) and pembrolizumab, and 15 participants receiving pembrolizumab alone were evaluable for a response. The pathologic response in the combination arm versus the pembrolizumab arm are as follows:

pCR: 46.2% (12 of 26) vs. 40% (6 of 15)

near pCR: 19.2% (5 of 26) vs. 6.7% (1 of 15)

major pPR: 65.4% (17 of 26) vs. 46.7% (7 of 15)

pPR: 11.5% (3 of 26) vs. 13.3% (2 of 15)

pNR: 23.1% (6 of 26) vs. 40% (6 of 15).

A review of the safety data as of 07-FEB-2022 identified no new safety signals from participants treated with vibostolimab in combination with pembrolizumab in this study.

2.2 Background

Refer to the IB and approved labeling for detailed background information on MK-7684A and pembrolizumab.

2.2.1 Pharmaceutical and Therapeutic Background

2.2.1.1 MK-7684A

MK-7684A is a fixed dose coformulation of vibostolimab (MK-7684) with pembrolizumab.

MK-7684 is a humanized, antagonistic IgG1 mAb that binds to the immune checkpoint receptor, TIGIT, and blocks the interaction between TIGIT and its ligands. TIGIT is one of multiple immune checkpoint molecules that maintains immune homeostasis and prevent uncontrolled immune activation. TIGIT competes with the activating receptor CD226 for its ligands, CD155/PVR/Necl5/Tage4 and CD112/PVRL-2, which are expressed on antigen-presenting cells. Binding of TIGIT to its ligands negatively modulates T-cell activity.

The mechanism of TIGIT-mediated T-cell inhibition is not completely understood. Some reports showed that TIGIT knockdown increases T-cell proliferation and effector cytokine production [Zhang, T., et al 2014] and that anti TIGIT antibodies characterized as agonists can decrease T-cell activation [Lozano, E., et al 2012]. Some reports have also showed that TIGIT may inhibit T-cell activation by opposing the CD226-mediated positive signal through ligand competition or heterodimerization with CD226 [Levin, S. D., et al 2011] [Johnston, R. J., et al 2014]. Importantly, it has been shown both in vitro and in vivo, that CD226 knockdown or blockade (with an antagonist antibody) eliminates the positive impact of TIGIT antagonism [Levin, S. D., et al 2011] [Johnston, R. J., et al 2014].

In a variety of mouse and human tumor models, TIGIT is highly expressed on CD4+ and CD8+ TIL and its expression has been correlated with CD8+ T-cell infiltration [Johnston, R. J., et al 2014] [Chauvin, J. M., et al 2015]. Coordinated TIGIT and PD-1 blockade results in increased proliferation, cytokine production, and degranulation of CD8+ human TIL from melanoma [Chauvin, J. M., et al 2015].

As of 06-JAN-2022, safety data were available for a total of 462 participants treated with either vibostolimab monotherapy (n=68), vibostolimab in combination with pembrolizumab administered sequentially (n=293), or as the coformulated product, MK-7684A (n=51), vibostolimab, pembrolizumab, pemetrexed, and carboplatin combination therapy (n=10), or MK-7684, pembrolizumab, carboplatin or cisplatin, and etoposide combination therapy (n=40) as part of Study MK-7684-001.

Of the 462 participants treated in Study MK-7684-001, 338 (73.2%) experienced at least 1 AE that was considered by the investigator to be related to study treatment. Of the 338 participants who experienced DRAEs in this study, most were of Grade 1 or 2 severity; 15.4% experienced 1 or more DRAEs of Grade 3 severity, 4.8% experienced 1 or more DRAEs of Grade 4 severity (decreased neutrophil count [n=13], lipase increased [n=6], decreased white blood cell count [n=3], and acute kidney injury, depression and neutropenia [n=1 each]), and 0.2% experienced 1 or more DRAEs of Grade 5 severity (pneumonitis [n=1]). The most common DRAEs were pruritus (21.0%), rash (18.4%), fatigue (17.1%), and nausea (11.9%) [IB Edition 10 2022].

2.2.1.2 Pembrolizumab

Pembrolizumab is a potent humanized IgG4 mAb with high specificity of binding to the PD-1 receptor, thus inhibiting its interaction with PD-L1 and PD-L2. Based on preclinical in vitro data, pembrolizumab has high affinity and potent receptor blocking activity for PD-1. Pembrolizumab has an acceptable preclinical safety profile and is in clinical development as an IV immunotherapy for advanced malignancies. KEYTRUDA® (pembrolizumab) is indicated for the treatment of patients across several indications.

The importance of intact immune surveillance function in controlling outgrowth of neoplastic transformations has been known for decades [Disis, M. L. 2010]. Accumulating evidence shows a correlation between tumor-infiltrating lymphocytes in cancer tissue and favorable prognosis in various malignancies. In particular, the presence of CD8+ T-cells and the ratio of CD8+ effector T-cells/FoxP3+ T-regs correlates with improved prognosis and long-term survival in solid malignancies, such as ovarian, colorectal, and pancreatic cancer; hepatocellular carcinoma; malignant melanoma; and renal cell carcinoma. Tumor-infiltrating lymphocytes can be expanded ex vivo and reinfused, inducing durable objective tumor responses in cancers such as melanoma [Dudley, M. E., et al 2005] [Hunder, N. N., et al 2008].

The PD-1 receptor-ligand interaction is a major pathway hijacked by tumors to suppress immune control. The normal function of PD-1, expressed on the cell surface of activated T-cells under healthy conditions, is to down-modulate unwanted or excessive immune responses, including autoimmune reactions. PD-1 (encoded by the gene Pdcd1) is an Ig

superfamily member related to CD28 and CTLA-4 that has been shown to negatively regulate antigen receptor signaling on engagement of its ligands (PD-L1 and/or PD-L2) [Greenwald, R. J., et al 2005] [Okazaki, T., et al 2001].

The structure of murine PD-1 has been resolved [Zhang, X., et al 2004]. PD-1 and its family members are type I transmembrane glycoproteins containing an IgV–type domain responsible for ligand binding and a cytoplasmic tail responsible for the binding of signaling molecules. The cytoplasmic tail of PD-1 contains 2 tyrosine-based signaling motifs, an immunoreceptor tyrosine-based inhibition motif, and an immunoreceptor tyrosine-based switch motif. After T-cell stimulation, PD-1 recruits the tyrosine phosphatases, SHP-1 and SHP-2, to the immunoreceptor tyrosine-based switch motif within its cytoplasmic tail, leading to the dephosphorylation of effector molecules such as CD3ζ, PKCθ, and ZAP70, which are involved in the CD3 T-cell signaling cascade [Okazaki, T., et al 2001] [Chemnitz, J. M., et al 2004] [Sheppard, K-A, et al 2004] [Riley, J. L. 2009]. The mechanism by which PD-1 down-modulates T-cell responses is similar to, but distinct from, that of CTLA-4, because both molecules regulate an overlapping set of signaling proteins [Parry, R. V., et al 2005] [Francisco, L. M., et al 2010].

2.3 Benefit/Risk Assessment

It cannot be guaranteed that participants in clinical studies will directly benefit from treatment during participation, as clinical studies are designed to provide information about the safety and effectiveness of an investigational medicine.

Pembrolizumab monotherapy has shown activity for the adjuvant treatment of Stage II-III melanoma and has received regulatory approvals for this indication. Pembrolizumab has also shown an RFS benefit in participants with Stage IV disease in the SWOG1404/ KEYNOTE-053 study, and nivolumab has shown activity in this disease stage in the CheckMate-238 study, which led to regulatory approval in resected Stage IV melanoma. Both drugs are recommended by NCCN guidelines as options for adjuvant use after successful metastasis-directed therapy [National Comprehensive Cancer Network 2022].

The existing data suggest that blockade of TIGIT with vibostolimab offers a new immunological mechanism, which has been shown to enhance the activity of pembrolizumab in preclinical and early clinical observations. Review of safety data for vibostolimab in combination with pembrolizumab has not identified any new risks not previously identified for pembrolizumab monotherapy, and the severity and management of immune-mediated events with the combination is consistent with the established profile of pembrolizumab monotherapy. The combination of vibostolimab and pembrolizumab (as coformulated MK-7684A) may achieve increased therapeutic efficacy with minimal added toxicity over pembrolizumab monotherapy and preliminary data observed in KEYMAKER-02B and KEYMAKER-02C support this.

Additional details regarding specific benefits and risks for participants participating in this clinical study may be found in the accompanying MK-7684A and pembrolizumab IBs and informed consent documents.

3 HYPOTHESES, OBJECTIVES, AND ENDPOINTS

Hypotheses are aligned with objectives in the Objectives and Endpoints table.

In individuals with high-risk resected Stage IIB, IIC, III or IV melanoma:

Primary Objective	**Primary Endpoint**
To compare MK-7684A to pembrolizumab with respect to RFS Hypothesis (H1): MK-7684A is superior to pembrolizumab with respect to RFS as assessed by investigator.	RFS: time from randomization to any recurrence (local, locoregional, regional or distant) as assessed by investigator, or death due to any cause, whichever occurs first.
Secondary Objectives	**Secondary Endpoints**
To compare MK-7684A to pembrolizumab with respect to DMFS. Hypothesis (H2): MK-7684A is superior to pembrolizumab with respect to DMFS as assessed by investigator.	DMFS: The time from randomization to appearance of a distant metastasis as assessed by investigator or death due to any cause, whichever occurs first. A distant metastasis refers to cancer that has spread from the original (primary) tumor to distant organs or distant lymph nodes.
To compare MK-7684A to pembrolizumab with respect to OS. Hypothesis (H3): MK-7684A is superior to pembrolizumab with respect to overall survival.	OS: The time from randomization to death due to any cause.
To evaluate the safety and tolerability of MK-7684A and pembrolizumab	Adverse event Study intervention discontinuation due to AEs
To evaluate MK-7684A to pembrolizumab with respect to mean change from baseline in global health status/QoL, physical functioning, and role functioning using the EORTC QLQ-C30	Change in score from baseline evaluated by: Global health status/QoL score (Items 29 and 30) Physical functioning score (Items 1-5) Role functioning score (Items 6 and 7)

Tertiary/Exploratory Objectives	Tertiary/Exploratory Endpoints
To evaluate the TTST in both treatment arms.	TTST: the time from randomization to the date of first subsequent therapy (eg, surgical procedure, radiation therapy, antineoplastic therapy) or death due to any cause, whichever occurs first.
To evaluate the PRFS2 in both treatment arms.	PRFS2: the time from randomization to the earliest of the following: (1) date of first disease progression per RECIST 1.1 beyond the initial unresectable disease recurrence; (2) date of second recurrence in participants without evidence of disease after a surgical procedure of a resectable first recurrence; or (3) death due to any cause.
To evaluate MK-7684A to pembrolizumab with respect to mean change from baseline in the EuroQoL EQ-5D-5L VAS score	Change from baseline in the EQ-5D-5L VAS
To evaluate the PK profile of vibostolimab and pembrolizumab when administered as coformulated MK-7684A	PK parameters (C_{max}, C_{trough}) for vibostolimab PK parameters (C_{max}, C_{trough}) for pembrolizumab
To evaluate the immunogenicity of vibostolimab and pembrolizumab when administered as coformulated MK-7684A	ADA incidence for vibostolimab ADA incidence for pembrolizumab
To identify molecular (genomic, metabolic, and/or proteomic) biomarkers that may be indicative of clinical response/resistance, safety, pharmacodynamic activity, and/or the mechanism of action of MK-7684A	Molecular (genomic, metabolic and/or proteomic) determinants of response or resistance to treatments, using blood and/or tumor tissue

4 STUDY DESIGN

4.1 Overall Design

Protocol Amendment 04 implementation: based on recommendations of the eDMC following an interim review of the data that showed no benefit over the comparator arm of pembrolizumab monotherapy, the experimental arm (Arm A: MK-7684A) will be discontinued and all ongoing participants on treatment will move to the comparator arm (Arm B: pembrolizumab monotherapy) for the remainder of the study.

This is a Phase 3, randomized, double-blind, active-controlled, parallel-group, multicenter, efficacy and safety study of adjuvant MK-7684A (Arm A) versus adjuvant pembrolizumab (Arm B) in approximately 1,560 participants 12 years of age and older (and weighing at least 40 kg if <18 years of age) with resected high-risk (Stage IIB-IV per AJCC eighth edition including clinical Stage II) melanoma (Appendix 8). Enrollment of participants with Stage IIIA disease will be capped at approximately 10% of total enrollment. Participants must not have received any prior systemic therapy for their melanoma beyond surgical resection. The study design is shown in Figure 1.

Eligible participants will be randomized 1:1 to receive treatment with either MK-7684A or pembrolizumab. Randomization will be stratified according to the participant's disease risk (IIB/IIC/clinical IIB and IIC/IIIA/IIIB vs IIIC/IIID/IV) and by geographic region (Asia vs ROW). Crossover from one intervention arm to the other is not permitted.

Participants will receive treatment for up to 17 cycles of either MK-7684A or pembrolizumab or until one of the criteria for discontinuation of study intervention is met (Section 7.1). Participants will undergo imaging including neck/chest/abdomen/pelvis CT and/or MRI when clinically indicated at the timepoints described in the SoA. Participants will be followed after discontinuation of study intervention for disease recurrence and survival as described in Section 8.11.4. Protocol Amendment 04 implementation: All active participants in the experimental arm (Arm A: MK-7684A) will be moved to the comparator arm (Arm B: pembrolizumab monotherapy) for the remainder of the study (a total of 17 cycles of study treatment or until disease progression, whichever occurs first) [see Section 6.3.1].

The primary endpoint of the study is RFS, and key secondary endpoints include DMFS and OS. Distant metastasis refers to cancer that has spread from the primary tumor and beyond local or nearby tissues and regional lymph nodes to distant organs or nonregional lymph nodes.

Adverse events will be monitored throughout the study and graded in severity according to the guidelines outlined in the NCI CTCAE v5.0 (Appendix 3.5). Each participant will be monitored for AEs and SAEs (refer to Section 8.4.1 for details).

Results of the futility and interim analyses will be reviewed by an eDMC, which will make recommendations to the Sponsor to continue, modify, or end the study according with the plan described in Sections 4.4.1, 9.7, and 10.1.4.

Specific procedures to be performed during the study, including prescribed times and associated visit windows, are outlined in Section 1.3 of the SoA. Details of each procedure are provided in Section 8.

4.2 Scientific Rationale for Study Design

This study is being conducted to compare the efficacy and safety of adjuvant MK-7684A with adjuvant pembrolizumab monotherapy in participants with high-risk Stage II-IV melanoma in a randomized, double blinded fashion.

4.2.1 Rationale for Endpoints

4.2.1.1 Efficacy Endpoints

This study will use RFS based on recurrence as assessed by the investigator as the primary endpoint. RFS is an acceptable measure of clinical benefit for a randomized study in melanoma that demonstrates superiority of a new antineoplastic therapy especially if the magnitude of the effect is large and the therapy has an acceptable risk/benefit profile [Food and Drug Administration 2018].

Investigator-identified recurrence will be used to make treatment decisions as well as for efficacy analyses where specified.

New incident cases of melanoma will be distinguished from recurrences by a local pathologist. A pathologist will review skin lesion biopsy specimens and resection samples to identify if an intraepidermal component exists in the sample. If an intraepidermal component does exist, it is consistent with a new primary melanoma as opposed to a regional (in-transit) or distant metastatic recurrence. Refer to Appendix 9 for details regarding Guidance for Distinguishing Primary Cutaneous Melanomas from Cutaneous Metastases of Melanoma. New incident cases of melanoma and second cancer diagnoses are not counted as events for recurrence-free survival. A central imaging vendor will be used to collect, clean, and hold tumor imaging for potential retrospective analysis.

4.2.1.2 Safety Endpoints

See Appendix 7 for country-specific requirements.

Safety parameters frequently used for evaluating investigational-systemic anticancer treatments are included as safety endpoints including, but not limited to, the incidence of, causality, and outcome of AEs/SAEs, and changes in vital signs and laboratory values. AEs will be assessed as defined by CTCAE, Version 5.0.

4.2.1.3 Patient-reported Outcomes

Symptomatic improvement is considered a clinical benefit and accepted by health authorities as additional evidence of the risk-benefit profile of any new study intervention. In this study, HRQoL and disease-related symptoms will be investigated via the following assessment tools: EORTC QLQ-C30 questionnaires. Health utilities will be evaluated using the

EQ-5D-5L PRO instrument. These measures are not pure efficacy or safety endpoints because they are affected by both disease progression and treatment tolerability.

4.2.1.4 EORTC QLQ-C30

EORTC QLQ-C30 is a psychometrically and clinically validated instrument appropriate for assessing HRQoL in oncology studies [Aaronson, N. K., et al 1993]. The EORTC QLQ-C30 is the most widely used cancer-specific HRQoL instrument, which contains 30 items and measures 5 functional dimensions (physical, role, emotional, cognitive and social), 3 symptom items (fatigue, nausea/vomiting, and pain), 6 single items (dyspnea, sleep disturbance, appetite loss, constipation, diarrhea, and financial impact), and a global health and QoL scale [Aaronson, N. K., et al 1993]. For the global health status or QoL and function scales, a higher value indicates a better level of function; for symptom scales and items, a higher value indicates increased severity of symptoms. Change from baseline in global health status/QoL, physical functioning, and role functioning scales of the EORTC QLQ-C30, will be evaluated as secondary objectives.

4.2.1.5 EQ-5D-5L

The EQ-5D-5L is a standardized instrument for use as a measure of health outcome and will provide data to develop health utilities for use in health economic analyses [Rabin, R. and de Charro, F. 2001]. The 5 health state dimensions in the EQ-5D-5L include the following: Mobility, Self-Care, Usual Activities, Pain/Discomfort, and Anxiety/Depression. Each dimension is rated on a 5-point scale from 1 (no problem) to 5 (unable to/extreme problems). The EQ-5D-5L also includes a graded (0 to 100) vertical visual analog scale on which the participant rates his or her general state of health at the time of the assessment. This instrument has been used extensively in cancer studies and published results from these studies support its validity and reliability [Pickard, A. S., et al 2007].

4.2.1.6 Planned Exploratory Biomarker Research

See Appendix 7 for country-specific requirements.

The mechanism of action of many antitumor agents is not completely understood and much remains to be learned regarding how best to leverage new drugs in treating patients. Thus, to aid future patients, it is important to investigate the determinants of response or resistance to cancer treatments administered, as well as determinants of AEs in the course of our clinical studies. These efforts may identify novel predictive/pharmacodynamic biomarkers and generate information that may better guide single-agent and combination therapy with antineoplastic drugs. To identify novel biomarkers, biospecimens (ie, blood components, tumor material) will be collected to support analyses of cellular components (eg, protein,

DNA, RNA, metabolites) and other circulating molecules. Investigations may include, but are not limited to:

Germline (blood) genetic analyses (eg, SNP analyses, whole exome sequencing, whole genome sequencing)

This research may evaluate whether genetic variation within a clinical study population correlates with response to the treatment(s) under evaluation. If genetic variation is found to predict efficacy or AEs, the data might inform optimal use of therapies in the patient population. Furthermore, it is important to evaluate germline DNA variation across the genome to interpret tumor-specific DNA mutations. Finally, MSI may be evaluated as this is an important biomarker for some cancers (ie, colorectal cancer).

Genetic (DNA) analyses from tumor

The application of new technologies, such as next generation sequencing, has provided scientists the opportunity to identify tumor-specific DNA changes (ie, mutations, methylation status, microsatellite instability). Key molecular changes of interest to immuno-oncology drug development include the mutational burden of tumors and the clonality of T-cells in the tumor microenvironment. Increased mutational burden (sometimes called a 'hyper-mutated' state) may generate neoantigen presentation in the tumor microenvironment. To conduct this type of research, it is important to identify tumor-specific mutations that occur across all genes in the tumor genome. Thus, genome-wide approaches may be used for this effort. Note that to understand tumor-specific mutations, it is necessary to compare the tumor genome with the germline genome. Microsatellite instability may also be evaluated as this is an important biomarker for some cancers (ie, colorectal cancer). Circulating tumor DNA and/or RNA may also be evaluated from blood samples.

Tumor and/or blood RNA analyses

Both genome-wide and targeted mRNA expression profiling and sequencing in tumor tissue and/or in blood may be performed to define gene signatures that correlate to clinical response to treatment with antitumor therapies. Specific gene sets (ie, those capturing interferon-gamma transcriptional pathways) may be evaluated and new signatures may be identified. Individual genes may also be evaluated (eg, IL-10). MicroRNA profiling may also be pursued as well as exosomal profiling.

Proteomics and IHC using blood and/or tumor

Tumor and/or blood samples from this study may undergo proteomic analyses (eg, PD-L1 IHC). Therefore, tumor tissue may be subjected to proteomic analyses using a variety of platforms that could include, but are not limited to, immunoassays and liquid chromatography/mass spectrometry. This approach could identify novel protein biomarkers that could aid in patient selection for antitumor therapy.

Other blood-derived biomarkers

In addition to expression on the tumor tissue, PD-L1 and other tumor derived proteins can be shed from tumor and released into the blood. Assays such as ELISA measure such proteins in serum. Correlation of expression with response to pembrolizumab therapy may identify new approaches for predictive biomarkers in blood, representing a major advance from today's reliance on assessing tumor biomarkers. This research would serve to develop such assays for future clinical use.

Other molecular changes of interest include the subtype of T-cells in the tumor microenvironment. The T-cell repertoire from tumor tissue and blood components may be evaluated.

4.2.1.7 Future Biomedical Research

The Sponsor will conduct FBR on specimens for which consent was provided during this study. This research may include genetic analyses (DNA), gene expression profiling (RNA), proteomics, metabolomics (serum, plasma), and/or the measurement of other analytes, depending on which specimens are consented for FBR.

Such research is for biomarker testing to address emergent questions not described elsewhere in the protocol and will only be conducted on specimens from appropriately consented participants. The objective of collecting/retaining specimens for FBR is to explore and identify biomarkers that inform the scientific understanding of diseases and/or their therapeutic treatments. The overarching goal is to use such information to develop safer, more effective drugs/vaccines, and/or to ensure that participants receive the correct dose of the correct drug/vaccine at the correct time. The details of FBR research are presented in Appendix 6.

4.2.2 Rationale for the Use of Comparator

Pembrolizumab has shown efficacy in Stage III melanoma in KEYNOTE-054 and in Stage IIB and IIC melanoma in KEYNOTE-716, and has received approval from global health authorities for the use in these patient populations. It is a recommended standard of care regimen by the NCCN guidelines [National Comprehensive Cancer Network 2022]. Pembrolizumab has also shown an RFS benefit in participants with Stage IV disease in the SWOG1404/KEYNOTE-053 study [Grossmann, K. F., et al 2021], and nivolumab has shown activity in this disease stage in the CheckMate-238 study, which led to regulatory approval in resected Stage IV melanoma. Both drugs are recommended by NCCN guidelines for adjuvant use after successful metastasis-directed therapy.

4.3 Justification for Dose

4.3.1 MK-7684A

MK-7684A is a single-use drug product vial containing a fixed dose combination of 200 mg vibostolimab and 200 mg pembrolizumab in a 20.0 mL fill volume. MK-7684A is to be

administered Q3W. The single coformulation vial could provide simplified preparation and reduced infusion times compared with separate formulations administered sequentially.

Based on the totality of available data, including preliminary clinical PK, pharmacodynamics, safety, and efficacy from Study MK-7684-001, the selected dose of vibostolimab is 200 mg Q3W.

Observed PK profiles of vibostolimab suggest that target-mediated drug disposition of vibostolimab is saturated at the 200 mg and 700 mg doses. Preliminary population PK analysis indicated that the PK of MK-7684 is generally consistent with that of other humanized mAbs, which typically have low CL and a limited Vc [Keizer,R.J., et al 2010] [Dostalek,M., et al 2012] [Dirks, N. L. and Meibohm, B 2010]. As with other mAbs, body weight was found to be related to vibostolimab CL and Vc parameters, but the relationship was weak for both parameters. As such, this supports that fixed dosing would provide better control of PK variability than body weight-based dosing [Hendrikx, J. J. M. A., et al 2017] [Bai,S., et al 2012]. In addition, observed PK parameters were generally similar across tumor types in Study MK-7684-001.

Available clinical safety data indicated that vibostolimab is tolerable at doses up to and including 700 mg, both when used as monotherapy and in combination with pembrolizumab. No DLTs were observed at any of the vibostolimab doses tested either as monotherapy or in combination with pembrolizumab during the dose escalation and confirmation portion of Study MK-7684-001, and the maximum tolerated dose was not reached.

Clinical activity was observed at the 200 mg and the 700 mg dose levels of vibostolimab both during the dose escalation and confirmation portion of Study MK-7684-001 in participants with advanced solid tumors of all types and during the dose-expansion portion, particularly in PD-1/PD-L1 inhibitor treatment-naïve participants with non–small cell lung cancer and cervical cancer, PD-L1+ ovarian cancer, and PD-L1+ gastric cancer treated with MK-7684 in combination with pembrolizumab.

The 200-mg and 700-mg doses were compared in a randomized, dose-expansion cohort of participants with anti-PD-1/PD-L1 treatment-naïve cervical cancer in MK-7684-001 Part B. Exploratory analysis of exposure versus best change in tumor size showed a flat relationship, suggesting that 200 mg is at the plateau of the exposure-efficacy relationship. The mean difference in target lesion percent change from baseline between the 200 mg and 700 mg groups for the first scan was -2.1% (95% CI: -21.2, 16.9) with 2-sided p-value of 0.824, and for best overall scan was -8.1% (95% CI: -31.1, 15) with 2-sided p-value of 0.488. Therefore, tumor size reduction showed no significant difference between the 2 dose groups.

Overall, the totality of data, including lack of a clinically meaningful effect of body weight on PK, consistency of PK across indications and a flat dose-exposure-tumor size response relationship support that a fixed dose of 200 mg q3w is the RP2D for MK-7684 in combination with 200 mg pembrolizumab. For more information, see the MK-7684 IB.

4.3.1.1 MK-7684A Dosing in Adolescents

The Sponsor proposes to use 200 mg Q3W of vibostolimab and 200 mg q3w of pembrolizumab in adolescent participants aged 12 to 18 years with body weight ≥40 kg, administered as coformulated MK-7684A. The adult recommended Phase 2 dose of vibostolimab is 200 mg Q3W, and 200 mg q3w is an approved dose of pembrolizumab in adults. Consistent with the analyses published recently by the FDA on oncology drugs [Food and Drug Administration 2019], a 40-kg body weight cutoff in adolescents is projected to yield exposures overlapping with adults at the same fixed dose for both vibostolimab and pembrolizumab.

A preliminary adult population PK model of vibostolimab has been developed based on available PK data in adult participants with solid tumors in Study MK-7684-001. A 2-compartment model structure with linear and saturable clearance was found to adequately describe the PK of vibostolimab. For description of PK in a pediatric population, the impact of body weight and age was added to the model based on a previous, widely cited pediatric PK model for mAbs by Robbie et al. [Robbie, G. J., et al 2012]. In this model, body weight was included as a covariate on the volume and clearance parameters using standard allometric coefficients. A function describing clearance maturation as estimated by Robbie et al. was used to account for the dependence of clearance on age, after consideration of allometric dependence on weight. Note, the corrected form of the Robbie et al. maturation factor as described by Basu et al. was used [Basu, S., et al 2020].

Concentration profiles of vibostolimab were simulated in 1000 adolescent pediatric patients and 1000 adult patients at a dose of 200 mg Q3W. Age and weight for adolescent simulations were obtained from an internal database of 109 adolescent patients between 12 and 18 years with body weight greater than 40 kg who have been treated to date with pembrolizumab. Distributions of Cycle 1 vibostolimab AUC, C_{max}, and C_{trough} in adolescents are expected to be comparable to the lowest body weight quartile of adults. Exposures in adolescents dosed at 200 mg Q3W are expected to be significantly lower than adult exposures at 700 mg Q3W, with established safety.

A pediatric population PK model for pembrolizumab was previously developed using data from pediatric participants in KEYNOTE-051 and adult participants with solid and heme malignancies [Modeling and Simulation Report: Extension... 2017]. Pembrolizumab concentration profiles at a fixed dose of 200 mg Q3W in 1000 adolescents with body weight greater than 40 kg (resampled from 109 adolescent participants treated with pembrolizumab) were simulated from this model. PK profiles at 200 mg Q3W in 2993 adults (from the reference pembrolizumab PK dataset based on studies KEYNOTE-001, KEYNOTE-002, KEYNOTE-006, KEYNOTE-010, and KEYNOTE-024) were simulated using the established reference pembrolizumab adult PK model. Distributions of Cycle 1 pembrolizumab AUC, C_{max}, and C_{trough} in adolescents are expected to be comparable to the lowest body weight quartile of adult exposures. Exposures in adolescents dosed at 200 mg Q3W are expected to be significantly lower than the adult exposures at 10 mg/kg Q2W with established safety.

In summary, the regimen of 200 mg vibostolimab + 200 mg pembrolizumab (given Q3W as coformulated MK-7684A) in adolescents >40 kg is projected to yield exposures that overlap significantly with adult exposures at the same dosing regimen.

4.3.2 Pembrolizumab

The planned dose of pembrolizumab for adults in this study is 200 mg Q3W. Based on the totality of data generated in the KEYTRUDA® development program, 200 mg Q3W is an appropriate dose of pembrolizumab for adults across all indications. As outlined below, this dose is justified by:

- Clinical data from 8 randomized studies in melanoma and non–small cell lung cancer indications demonstrating flat dose- and exposure-efficacy relationships from 2 mg/kg Q3W to 10 mg/kg Q2W representing an approximate 5- to 7.5-fold exposure range (refer to IB, Section 5.2.2)
- Population PK analysis showing that both fixed dosing and weight-based dosing provides similar control of PK variability with considerable overlap in the distributions of exposures, supporting suitability of 200 mg Q3W
- Clinical data showing meaningful improvement in benefit-risk including overall survival at 200 mg Q3W across multiple indications
- Pharmacology data showing full target saturation in both systemic circulation (inferred from PK data) and tumor (inferred from physiologically based PK analysis) at 200 mg Q3W

For adolescents ≥40 kg, the planned dose of pembrolizumab in this study is 2 mg/kg (up to a maximum of 200 mg).

A model-based PK bridging analysis, which included available pediatric PK data from the pembrolizumab pediatric study KEYNOTE-051, was conducted to determine the pediatric dose based on the approach of exposure matching with adults. This analysis showed that a dose of 2 mg/kg (up to 200 mg) Q3W in pediatric participants provided PK exposures similar to those achieved at 2 mg/kg (or 200 mg) Q3W in adults, and served as the basis for approval of a pediatric indication in cHL as well as MSI-H cancers in the US at a dose of 2 mg/kg (up to 200 mg) Q3W. In addition, the safety of this dose in pediatric participants is established based on data from KEYNOTE-051 [Geoerger, B., et al 2020]. The incidence of positive immunogenicity status after pembrolizumab treatment in pediatric participants (2.8%) was comparable with that in adults (2.1%) and had no impact on pembrolizumab exposure. Based on these results, the pediatric dose for evaluation in this study is 2 mg/kg Q3W (up to a maximum of 200 mg Q3W).

4.4 Beginning and End-of-Study Definition

The overall study begins when the first participant (or their legally acceptable representative) provides documented informed consent. The overall study ends when the last participant completes the last study-related contact, withdraws consent, or is lost to follow-up (Section 7.3). For purposes of analysis and reporting, the overall study ends when the

Sponsor receives the last laboratory test result or at the time of final contact with the last participant, whichever comes last.

If the study includes countries in the European Economic Area (EEA), the local start of the study in the EEA is defined as First Site Ready (FSR) in any Member State.

The Sponsor estimates that the maximum duration of the study from first participant entered through long-term follow-up will be 8 years (~5 years after study intervention has been completed) to attain the final assessment of the study (eg, to evaluate safety and/or long-term efficacy) for all evaluable participants. Refer to the Synopsis, Section 1.1, for the duration of participation of participants.

Protocol Amendment 04 implementation: The study will end when all participants discontinue from treatment and complete safety follow up.

4.4.1 Clinical Criteria for Early Study Termination

The clinical study may be terminated early if the extent (incidence and/or severity) of emerging effects/clinical endpoints is such that the risk/benefit ratio to the study population as a whole is unacceptable. In addition, further recruitment in the study or at (a) particular study site(s) may be stopped due to insufficient compliance with the protocol, GCP, and/or other applicable regulatory requirements, procedure-related problems or the number of discontinuations for administrative reasons is too high.

Based on recommendations of the eDMC to discontinue the experimental arm (MK-7684A) following an interim review of the data showed no benefit over the comparator arm of pembrolizumab monotherapy, the study will end when all participants discontinue from treatment and complete safety follow up.

5 STUDY POPULATION

As stated in the Code of Conduct for Clinical Trials (Appendix 1.1), this study includes participants of varying age (as applicable), race, ethnicity, and sex (as applicable). The collection and use of these demographic data will follow all local laws and participant confidentiality guidelines while supporting the study of the disease, its related factors, and the IMP under investigation.

Prospective approval of protocol deviations to recruitment and enrollment criteria, also known as protocol waivers or exemptions, is not permitted.

5.1 Inclusion Criteria

An individual is eligible for inclusion in the study if the individual meets all of the following criteria:

See Appendix 7 for country-specific requirements.

Type of Participant and Disease Characteristics

1. Has surgically resected and histologically/pathologically confirmed diagnosis of Stage IIB and IIC (pathological or clinical), III, or IV cutaneous melanoma per AJCC eighth edition guidelines (Appendix 8). Participants with BRAF-mutated melanoma are eligible to enroll.

- A therapeutic lymph node dissection defined as an anatomically complete lymphadenectomy of the involved nodal basin for macroscopic disease (clinically, radiographically or sonographically [if performed] detectable lymph nodes) is required (Appendix 10). SLN biopsy and CLND for microscopic disease, however, are not required.
- Participants with recurrent disease who had prior resection are allowed as long as all current disease has been resected.
- Melanoma of unknown primary is eligible.
- Stage IIIA disease will be capped at approximately 10% of total enrollment.

2. Has not received any prior systemic therapy for their melanoma beyond surgical resection.

   NOTE: In case of an indication for post lymph node dissection radiotherapy, this must have been completed within 13 weeks postsurgery and before treatment initiation. Radiotherapy may alter the process of wound healing. If the wound healing is not complete, the participant is not eligible.

3. No more than 12 weeks have elapsed between final surgical resection and randomization. Treatment should start only after adequate wound healing from the surgical procedure as assessed by the investigator. If there is a delay of ≤2 weeks exceeding 12 weeks due to unforeseen circumstances, the eligibility should be discussed with the Sponsor and the decision documented. A delay of up to 1 week for screening imaging requirements will be allowed if Sponsor has allowed up to 1 week extension between surgical resection and randomization.
   Note: Final surgical resection is defined in this protocol as complete resection of melanoma, and a SLN biopsy, if feasible. If the wide excision is followed by the SLN biopsy (ie, they are not performed at the same time), no more than 12 weeks may elapse between the 2 surgical procedures. If a second wide excision needs to be completed after SLN biopsy, this date will be used to calculate final surgical resection date.
4. Has no evidence of metastatic disease on imaging after resection as determined by investigator assessment. All suspicious lesions amenable to biopsy should be confirmed negative for malignancy.
5. Has an appropriate performance status as follows assessed within 7 days of C1D1:

- Adolescents ≤16 years of age: LPS score ≥70
- Adolescents >16 to <18 years of age: KPS score ≥70
- Adults ≥18 years of age: ECOG Performance Status of 0 or 1

Demographics

6. Is male or female, at least 12 years of age and weighs ≥40 kg if <18 years of age, at the time of providing documented informed consent/assent (unless local regulations and/or institutional policies do not allow for participants <18 years of age to participate; for those sites, the eligible population is ≥18 years of age).

Male Participants

No measures.

Female Participants

7. A female participant is eligible to participate if she is not pregnant or breastfeeding, and at least one of the following conditions applies:

- Not a WOCBP

OR

- A WOCBP and:
  - Uses a contraceptive method that is highly effective (with a failure rate of <1% per year), or be abstinent from heterosexual intercourse as their preferred and usual lifestyle (abstinent on a long-term and persistent basis), as described in Appendix 5 during the intervention period and for at least 120 days after the last dose of study intervention. The investigator should evaluate the potential for contraceptive method failure (ie, noncompliance, recently initiated) in relationship to the first dose of study intervention. Contraceptive use by women should be consistent with local regulations regarding the methods of contraception for those participating in clinical studies.
  - Has a negative highly sensitive pregnancy test within 72 hours (serum) or 24 hours (urine) before the first dose of study intervention. If a urine test cannot be confirmed as negative (eg, an ambiguous result), a serum pregnancy test is required. In such cases, the participant must be excluded from participation if the serum pregnancy result is positive. Additional requirements for pregnancy testing during and after study intervention are in Section 8.3.5.
  - Abstains from breastfeeding during the study intervention period and for at least 120 days after study intervention.
  - Medical history, menstrual history, and recent sexual activity has been reviewed by the investigator to decrease the risk for inclusion of a woman with an early undetected pregnancy.

Informed Consent

8. The participant (or legally acceptable representative) has provided documented informed consent/assent for the study and agrees to DMFS and OS data collection until these study endpoints are reached (maximum follow-up of approximately 8 years). The participant may also provide consent/assent for FBR; however, the participant may participate in the study without participating in FBR.

Additional Categories

9. Archival tumor tissue sample or newly obtained biopsy of a tumor lesion not previously irradiated has been provided. Details pertaining to tumor tissue submission can be found in the Laboratory Manual.
   Note: If a participant does not have tumor tissue available, a participant may be eligible for enrollment after notifying the Sponsor via email.
10. HIV-infected participants must have well controlled HIV on ART, defined as:
    a. Having a CD4+ T-cell count ≥350 cells/mm^3 at the time of screening.
    b. Having achieved and maintained virologic suppression defined as confirmed HIV RNA level below 50 or the LLOQ (below the limit of detection) using the locally available assay at the time of screening and for at least 12 weeks before screening.
    c. Have not had any AIDS-defining opportunistic infections within the past 12 months.

d. Have been on a stable ART regimen, without changes in drugs or dose modification, for at least 4 weeks before randomization and agree to continue ART throughout the study.

11. Adequate organ function as defined in the following table (Table 3). Specimens must be collected within 7 days before the first dose of study intervention.

Table 3 Adequate Organ Function Laboratory Values

System	Laboratory Value
Hematological	
ANC	≥1500/µL
Platelets	≥100 000/µL
Hemoglobin	≥9.0 g/dL or ≥5.6 mmol/L[a]
Renal	
Measured or calculated creatinine clearance OR GFR	≥30 mL/min ≥30 mL/min
Hepatic	
Total bilirubin	≤1.5 ×ULN OR direct bilirubin ≤ULN for participants with total bilirubin levels >1.5 × ULN
AST (SGOT) and ALT (SGPT)	≤2.5 × ULN
Coagulation	
INR OR PT aPTT	≤1.5 × ULN unless participant is receiving anticoagulant therapy as long as PT or PTT is within therapeutic range of intended use of anticoagulants

ALT (SGPT)=alanine aminotransferase (serum glutamic pyruvic transaminase); ANC=absolute neutrophil count; aPTT=activated partial thromboplastin time; AST (SGOT)=aspartate aminotransferase (serum glutamic oxaloacetic transaminase); GFR=glomerular filtration rate; INR=International normalized ratio; PT=prothrombin time; PTT=partial thromboplastin time; ULN=upper limit of normal.

[a] Criteria must be met without erythropoietin dependency and without packed red blood cell (pRBC) transfusion within last 2 weeks.

Note: This table includes eligibility-defining laboratory value requirements for treatment; laboratory value requirements should be adapted according to local regulations and guidelines for the administration of specific chemotherapies.

12. Participants who are HBsAg positive are eligible if they have received HBV antiviral therapy for at least 4 weeks, and have undetectable HBV viral load before randomization.

    Hepatitis B screening tests are not required unless:

    a. Known history of HBV infection

    b. As mandated by local health authority

13. Participants with history of HCV infection are eligible if HCV viral load is undetectable at screening.
    Note: Participants must have completed curative antiviral therapy at least 4 weeks before randomization.

Hepatitis C screening tests are not required unless:

a. Known history of HCV infection

b. As mandated by local health authority

5.2 Exclusion Criteria

The participant must be excluded from the study if the participant meets any of the following criteria:

See Appendix 7 for country-specific requirements.

Medical Conditions

1. Has severe hypersensitivity (≥Grade 3) to any of the study interventions or their excipients.
2. Has ocular, mucosal, or conjunctival melanoma.
3. Has a diagnosis of immunodeficiency or is receiving chronic systemic steroid therapy (in dosing exceeding 10 mg daily of prednisone equivalent) or any other form of immunosuppressive therapy within 7 days prior the first dose of study medication.
   Note: The use of inhaled or topical steroids and systemic steroids at physiologic doses (up to 5 mg/m^2/day prednisone equivalent with maximum dose of 10 mg daily) is allowed on study.
4. Has not adequately recovered from major surgical procedure or has ongoing surgical complications.

Prior/Concomitant Therapy

5. Has received prior radiotherapy within 2 weeks of start of study intervention or has had a history of radiation pneumonitis.

   NOTE: Participants must have recovered from all radiation-related toxicities and do not require corticosteroids.
6. Received prior anticancer therapy with an anti-PD-1, anti-PD-L1, anti-PD-L2 or anti-TIGIT agent, or with an agent directed to another stimulatory or coinhibitory T-cell receptor (eg, CTLA-4, OX-40, CD137).
7. Received a live or live attenuated vaccine within 30 days before the first dose of study intervention. Administration of killed vaccines is allowed.

   Refer to Section 6.5 for information on COVID-19 vaccines.

Prior/Concurrent Clinical Study Experience

8. Has received an investigational agent or has used an investigational device within 4 weeks before study intervention administration.

Diagnostic Assessments

9. History of (noninfectious) pneumonitis/interstitial lung disease that required steroids or has current pneumonitis/interstitial lung disease.
10. Known additional malignancy that is progressing or has required active treatment within the past 3 years.

    NOTE: Participants with basal cell carcinoma of the skin, squamous cell carcinoma of the skin, or carcinoma in situ, excluding carcinoma in situ of the bladder, that have undergone potentially curative therapy are not excluded. Participants with low-risk prostate cancer (T1-T2a, Gleason score ≤6, and PSA <10 ng/mL) either treated with definitive intent or untreated in active surveillance are not excluded. Participants with a history of nonulcerated cutaneous primary melanoma <1 mm in depth with no nodal involvement are allowed in this study.

    NOTE: Participants with a history of mucosal or uveal melanoma are excluded from this study.
11. History of CNS metastases and/or carcinomatous meningitis.
12. Active autoimmune disease that has required systemic treatment in the past 2 years. Replacement therapy (eg, thyroxine, insulin, or physiologic corticosteroid replacement therapy for adrenal or pituitary insufficiency) is allowed.
13. Active infection, requiring systemic therapy.
14. History or current evidence of any condition, therapy, laboratory abnormality, or other circumstance that might confound the results of the study or interfere with the participant's participation for the full duration of the study, such that it is not in the best interest of the participant to participate, in the opinion of the treating investigator.
15. Known psychiatric or substance abuse disorder that would interfere with the participant's ability to cooperate with the requirements of the study.

Other Exclusions

16. History of allogenic tissue/solid organ transplant.

5.3 Lifestyle Considerations

No restrictions are required.

5.3.1 Meals and Dietary Restrictions

Participants should maintain a normal diet unless modifications are required to manage an AE such as diarrhea, nausea, or vomiting.

5.4 Screen Failures

Screen failures are defined as participants who consent to participate in the clinical study, but are not subsequently randomized in the study. A minimal set of screen-failure information is

required to ensure transparent reporting of screen-failure participants to meet the CONSORT publishing requirements and to respond to queries from regulatory authorities. Minimal information includes demography, screen-failure details, eligibility criteria, and any AEs or SAEs meeting reporting requirements as outlined in the data entry guidelines.

Participants who fail screening may be rescreened for eligibility after consultation between the investigator and the Sponsor and written documentation of the collaborative decision on participant management.

5.5 Participant Replacement Strategy

A participant who discontinues from study intervention or withdraws from the study will not be replaced.

6 STUDY INTERVENTION

Study intervention is defined as any investigational intervention(s), marketed product(s), placebo, or medical device(s) intended to be administered to a study participant according to the study protocol.

Clinical supplies (study interventions provided by the Sponsor) will be packaged to support enrollment. Clinical supplies will be affixed with a clinical label in accordance with regulatory requirements.

Global clinical supply complaints and/or temperature excursions are to be reported to the Clinical Complaints Intake mailbox, via email to clinical.complaints.intake@MSD.com, within 1 business day of awareness.

6.1 Study Intervention(s) Administered

The study interventions to be used in this study are outlined in Table 4.

Protocol Amendment 04 implementation: All active participants in the experimental arm (Arm A: MK-7684A) will be moved to the comparator arm (Arm B: pembrolizumab monotherapy) for the remainder of the study (a total of 17 cycles of study treatment or until disease progression, whichever occurs first).

Table 4 Study Interventions

Arm Name	Arm Type	Intervention Name	Intervention Type	Dose Formulation	Unit Dose Strength(s)	Dosage Level(s)	Route of Administration	Regimen/ Treatment Period/ Vaccination Regimen	Use	IMP or NIMP/ AxMP	Sourcing
Arm A (Protocol Amendment 04: Arm A discontinued)	Experimental	MK-7684A	Biological/ Vaccine	Solution	MK-7684 200 mg + pembrolizumab 200 mg/ 20 mL vial	200 mg / 200 mg	IV Infusion	Q3W (Day 1 of each cycle) for 17 cycles or until discon-tinuation criteria are met	Test Product	IMP	Centrally by the Sponsor
Arm B	Active Comparator	Pembrolizumab	Biological/ Vaccine	Solution	25 mg/mL	Adults: 200 mg Adolescents ≥40 kg: 2 mg/kg (up to max of 200 mg)	IV Infusion	Q3W (Day 1 of each cycle) for 17 cycles or until discon-tinuation criteria are met, whichever occurs first	Comparator	IMP	Centrally by the Sponsor

EEA=European Economic Area; IMP=investigational medicinal product; IV=intravenous; max=maximum; NIMP/AxMP=noninvestigational/auxiliary medicinal product; Q3W=every 3 weeks.

For commercially available supplies, the unit dose strength or formulation may vary, depending on market availability.

The classification of IMP and NIMP/AxMP in this table is based on guidance issued by the European Commission and applies to countries in the EEA. Country differences with respect to the definition/classification of IMP and NIMP/AxMP may exist. In these circumstances, local legislation is followed.

All study interventions will be administered on an outpatient basis.

All products indicated in Table 4 will be provided centrally by the Sponsor or locally by the study site, subsidiary, or designee, depending on local country operational or regulatory requirements.

For any commercially available product that is provided by the study site, subsidiary, or designee, every attempt will be made to source these supplies from a single lot/batch number. The study site is responsible for recording the lot number, manufacturer, and expiry date for any locally purchased product as per local guidelines unless otherwise instructed by the Sponsor.

Refer to Section 8.1.9 for details regarding administration of the study intervention.

6.1.1 Treatment

The treatment of MK-7684A and pembrolizumab consists of up to 17 treatments administered Q3W or until discontinuation criteria are met. NOTE: The number of treatments is calculated starting with the first dose.

Protocol Amendment 04 implementation: All active participants in the experimental arm (Arm A: MK-7684A) will be moved to the comparator arm (Arm B: pembrolizumab monotherapy) for the remainder of the study (a total of 17 cycles of study treatment or until disease progression, whichever occurs first). NOTE: For study participants who, in the opinion of the study investigator, are benefitting from MK-7684A, the study investigator may request Sponsor consultation for continuation of treatment with MK-7684A.

6.2 Preparation/Handling/Storage/Accountability

6.2.1 Dose Preparation

Details on preparation and administration of MK-7684A and pembrolizumab are provided in the Pharmacy Manual.

The rationale for selection of doses to be used in this study is in Section 4.3.

6.2.2 Handling, Storage, and Accountability

The investigator or designee must confirm appropriate temperature conditions have been maintained during transit for all study intervention received, and any discrepancies are reported and resolved before use of the study intervention.

Only participants enrolled in the study may receive study intervention, and only authorized site staff may supply or administer study intervention. All study interventions must be stored in a secure, environmentally controlled, and monitored (manual or automated) area in accordance with the labeled storage conditions with access limited to the investigator and authorized site staff.

The investigator, institution, or the head of the medical institution (where applicable) is responsible for study intervention accountability, reconciliation, and record maintenance (ie, receipt, reconciliation, and final disposition records).

For all study sites, the local country Sponsor personnel or designee will provide appropriate documentation that must be completed for drug accountability and return, or local discard and destruction if appropriate. Where local discard and destruction is appropriate, the investigator is responsible for ensuring that a local discard/destruction procedure is documented.

The study site is responsible for recording the lot number, manufacturer, and expiry date for any locally purchased product (if applicable) as per local guidelines unless otherwise instructed by the Sponsor.

The investigator shall take responsibility for and shall take all steps to maintain appropriate records and ensure appropriate supply, storage, handling, distribution, and usage of study interventions in accordance with the protocol and any applicable laws and regulations.

6.3 Measures to Minimize Bias: Randomization and Blinding

6.3.1 Intervention Assignment

Intervention randomization will occur centrally using an IRT system. There are 2 study intervention arms. Participants will be assigned randomly in a 1:1 ratio to receive MK-7684A (Arm A) or pembrolizumab (Arm B), respectively.

Enrollment of participants with Stage IIIA disease will be capped at approximately 10% of total enrollment.

Protocol Amendment 04 implementation: All active participants in the experimental arm (Arm A: MK-7684A) will be moved to the comparator arm (Arm B: pembrolizumab monotherapy) for the remainder of the study. NOTE: For study participants who, in the opinion of the study investigator, are benefitting from MK-7684A, the study investigator may request Sponsor consultation for continuation of treatment with MK-7684A.

6.3.2 Stratification

Intervention randomization will be stratified according to the following factors:

1. Risk-based staging (IIB/IIC/clinical IIB and IIC/IIIA/IIIB vs IIIC/IIID/IV)
2. Region (Asia vs ROW)

Stratification by risk is based on the known differences in the risk of death, RFS, and DMFS between these groups as shown in KEYNOTE-054, KEYNOTE-716 and by others [Gershenwald, J. E., et al 2017a] [Eggermont, A. M. M., et al 2018] [Eggermont, A. M. M., et al 2021].

6.3.3 Blinding

A double-blinding technique with in-house blinding will be used. The participant, the investigator, and Sponsor personnel or delegate(s) who are involved in the study intervention administration or clinical evaluation of the participants are unaware of the intervention assignments.

Protocol Amendment 04 implementation: Following eDMC interim review of data, all participants have been unblinded.

6.4 Study Intervention Compliance

If there are interruptions in the study intervention schedule or infusion/injection was stopped, the details of and reason for any interruption or infusion/injection cessation of study intervention will be documented in the participant's medical record.

Refer to Section 6.6.1 for Dose Modification and Toxicity Management Guidelines for irAEs associated with pembrolizumab monotherapy, coformulations, or IO combinations and for other allowed dose interruptions.

Interruptions from the protocol-specified treatment plan require consultation between the investigator and the Sponsor and written documentation of the collaborative decision on participant management.

Participants will be dosed at the site, and they will receive study intervention directly from the investigator or designee, under medical supervision. The date and time of each dose administered in the clinic will be recorded in the source documents and recorded in the CRF. The dose of study intervention and study participant identification will be confirmed at the time of dosing by a member of the study site staff other than the person administering the study intervention.

6.5 Concomitant Therapy

If there is a clinical indication for any medications or vaccinations prohibited, the investigator must discuss any questions regarding this with the Sponsor's Clinical Director. The final decision on any supportive therapy or vaccination rests with the investigator and/or the participant's primary physician. However, the decision to continue the participant on study intervention requires the mutual agreement of the investigator and the Sponsor.

The following medications and vaccinations are prohibited during the study:

- Antineoplastic systemic therapy (including chemotherapy, biological therapy, immunotherapy, and targeted therapies) not specified in this protocol.

  NOTE: Topical anticancer agents to treat skin lesions (eg basal cell carcinoma or squamous cell carcinoma) are allowed (excluding skin metastases of melanoma).
- Investigational agents other than MK-7684A or pembrolizumab
- Radiation therapy

- Live or live attenuated vaccines within 30 days before the first dose of study intervention and while participating in the study, and for 30 days after the last dose of study intervention.

Note: Any licensed COVID-19 vaccine (including for Emergency Use) in a particular country is allowed in the study as long as they are mRNA vaccines, replication-incompetent adenoviral vaccines, or inactivated vaccines. These vaccines will be treated just as any other concomitant therapy. These vaccines should not be administered within 10 days of study treatment.

Investigational vaccines (ie, those not licensed or approved for Emergency Use) are not allowed.

NOTE: Seasonal flu vaccines are allowed in this study but should not be administered within 10 days of study treatment.

For country-specific criteria, refer to Appendix 7.

- Systemic glucocorticoids except when used for the following purposes:

  To modulate symptoms of an AE that is suspected to have an immunologic etiology

  For the prevention of emesis

  To premedicate for IV contrast allergies

  To treat asthma or COPD exacerbations (only short-term oral or IV use in doses >10 mg/day prednisone equivalent)

  For chronic systemic replacement not to exceed 10 mg/day prednisone equivalent for adults or 5 mg/m2/day (maximum of 10 mg/day) prednisone equivalent for pediatric participants (≥12 years old and <18 years old)
- Other glucocorticoid use except when used for the following purposes:

  For topical use or ocular use

  Intraarticular joint use

  For inhalation in the management of asthma or chronic obstructive pulmonary disease

If the investigator determines that a participant requires any of the following prohibited medications and vaccinations for any reason during the study, study intervention with MK-7684A or pembrolizumab must be discontinued.

Blood transfusions are allowed at any time during the study, except to meet eligibility criteria and in the 4 weeks before the first dose of pembrolizumab.

All treatments that the investigator considers necessary for a participant's welfare may be administered at the discretion of the investigator in keeping with the community standards of medical care.

All concomitant medication will be recorded on the eCRF including all prescription, OTC products, herbal supplements, and IV medications, and fluids. If changes occur during the

study period, documentation of drug dosage, frequency, route, and date should also be included on the eCRF. All concomitant medications received within 28 days before the first dose of study intervention and up to 90 days after the last dose of study intervention should be recorded. All concomitant medications administered during SAEs or ECIs are to be recorded. SAEs and ECIs are defined in Section 8.4.

6.5.1 Rescue Medications and Supportive Care

No rescue or supportive medications are specified for use in this study.

Participants should receive appropriate supportive care measures as deemed necessary by the treating investigator.

Suggested supportive care measures for the management of AEs with potential immunologic etiology are outlined along with the dose modification guidelines in Section 6.6.

6.6 Dose Modification

Any interruption of study intervention beyond 12 weeks, due to a non-immune AE, requires Sponsor consultation. Further details are provided in Section 7.1.

6.6.1 Immune-Related Events and Dose Modification (Withhold, Treat, Discontinue)

Dose Modification and Toxicity Management for Immune-related AEs Associated with Pembrolizumab Monotherapy, Coformulations or IO Combinations

AEs associated with pembrolizumab monotherapy, coformulation, or IO combination exposure may represent an immune-related response. These irAEs may occur shortly after the first dose or several months after the last dose of pembrolizumab monotherapy, coformulation, or IO combination treatment and may affect more than one body system simultaneously. Therefore, early recognition and initiation of treatment is critical to reduce complications. Based on existing clinical study data, most irAEs were reversible and could be managed with interruptions of pembrolizumab monotherapy, coformulation, or IO combination administration of corticosteroids and/or other supportive care. For suspected irAEs, ensure adequate evaluation to confirm etiology or exclude other causes. Additional procedures or tests such as bronchoscopy, endoscopy, skin biopsy may be included as part of the evaluation.

Attribution of Toxicity:

When study interventions are administered in combination, attribution of an adverse event to a single component is likely to be difficult. Therefore, while the investigator may attribute a toxicity event to pembrolizumab monotherapy, coformulations, or IO combinations, pembrolizumab monotherapy, coformulations, or IO combinations must be held according to the criteria in the Dose Modification and Toxicity Management Guidelines for Immune-Related Adverse Events.

Holding Study Interventions:

When study interventions are administered in combination and if the AE is considered immune-related, pembrolizumab monotherapy, coformulations, or IO combinations should be held according to recommended Dose Modification criteria.

If the toxicity does not resolve or the criteria for resuming treatment are not met, the participant must be discontinued from pembrolizumab monotherapy, coformulations, or IO combinations.

Restarting Study Interventions:

Participants may restart pembrolizumab monotherapy, coformulations, or IO combinations as described below:

If the toxicities do resolve and conditions are aligned with what is defined in the Dose Modification and Toxicity Management Guidelines for irAEs, pembrolizumab monotherapy, coformulations, or IO combinations may be restarted at the discretion of the investigator.

Dose Modification and Toxicity Management Guidelines for irAEs associated with pembrolizumab monotherapy, coformulations, or IO combinations are provided in Table 5.

Table 5 Dose Modification and Toxicity Management Guidelines for Immune-related Adverse Events Associated With Pembrolizumab Monotherapy, Coformulations, or IO Combinations

General instructions:

1. Severe and life-threatening irAEs should be treated with IV corticosteroids followed by oral steroids. Other immunosuppressive treatment should begin if the irAEs are not controlled by corticosteroids.
2. Pembrolizumab monotherapy, coformulations, or IO combinations must be permanently discontinued if the irAE does not resolve or the corticosteroid dose is not ≤10 mg/day within 12 weeks of the last treatment.
3. The corticosteroid taper should begin when the irAE is ≤ Grade 1 and continue at least 4 weeks.
4. If pembrolizumab monotherapy, coformulations, or IO combinations have been withheld, treatment may resume after the irAE decreased to ≤ Grade 1 after corticosteroid taper.

irAEs	Toxicity Grade (CTCAE v5.0)	Action With Pembrolizumab Monotherapy, Coformulations, or IO Combinations	Corticosteroid and/or Other Therapies	Monitoring and Follow-up
Pneumonitis	Grade 2	Withhold	• Administer corticosteroids (initial dose of 1 to 2 mg/kg prednisone or equivalent) followed by taper • Add prophylactic antibiotics for opportunistic infections	• Monitor participants for signs and symptoms of pneumonitis • Evaluate participants with suspected pneumonitis with radiographic imaging and initiate corticosteroid treatment
	Recurrent Grade 2, or Grade 3 or 4	Permanently discontinue		
Diarrhea/Colitis	Grade 2 or 3	Withhold	• Administer corticosteroids (initial dose of 1 to 2 mg/kg prednisone or equivalent) followed by taper	• Monitor participants for signs and symptoms of enterocolitis (ie, diarrhea, abdominal pain, blood or mucus in stool with or without fever) and of bowel perforation (ie, peritoneal signs and ileus) • Participants with ≥Grade 2 diarrhea suspecting colitis should consider GI consultation and performing endoscopy to rule out colitis • Participants with diarrhea/colitis should be advised to drink liberal quantities of clear fluids. If sufficient oral fluid intake is not feasible, fluid and electrolytes should be substituted via IV infusion
	Recurrent Grade 3 or Grade 4	Permanently discontinue		

irAEs	Toxicity Grade (CTCAE v5.0)	Action With Pembrolizumab Monotherapy, Coformulations, or IO Combinations	Corticosteroid and/or Other Therapies	Monitoring and Follow-up
AST or ALT Elevation or Increased Bilirubin	Grade 2[a]	Withhold	• Administer corticosteroids (initial dose of 0.5 to 1 mg/kg prednisone or equivalent) followed by taper	• Monitor with liver function tests (consider weekly or more frequently until liver enzyme value returned to baseline or is stable)
	Grade 3[b] or 4[c]	Permanently discontinue	• Administer corticosteroids (initial dose of 1 to 2 mg/kg prednisone or equivalent) followed by taper	
T1DM or Hyperglycemia	New onset T1DM or Grade 3 or 4 hyperglycemia associated with evidence of β-cell failure	Withhold[d]	• Initiate insulin replacement therapy for participants with T1DM • Administer antihyperglycemic in participants with hyperglycemia	• Monitor participants for hyperglycemia or other signs and symptoms of diabetes
Hypophysitis	Grade 2	Withhold	• Administer corticosteroids and initiate hormonal replacements as clinically indicated	• Monitor for signs and symptoms of hypophysitis (including hypopituitarism and adrenal insufficiency)
	Grade 3 or 4	Withhold or permanently discontinue[d]		
Hyperthyroidism	Grade 2	Continue	• Treat with nonselective beta-blockers (eg, propranolol) or thionamides as appropriate	• Monitor for signs and symptoms of thyroid disorders
	Grade 3 or 4	Withhold or permanently discontinue[d]		
Hypothyroidism	Grade 2	Continue	• Initiate thyroid replacement hormones (eg, levothyroxine or liothyronine) per standard of care	• Monitor for signs and symptoms of thyroid disorders
	Grade 3 or 4	Withhold or permanently discontinue[d]		
Nephritis: grading according to increased creatinine or acute kidney injury	Grade 2	Withhold	• Administer corticosteroids (prednisone 1 to 2 mg/kg or equivalent) followed by taper	• Monitor changes of renal function
	Grade 3 or 4	Permanently discontinue		
Neurological Toxicities	Grade 2	Withhold	• Based on severity of AE administer corticosteroids	• Ensure adequate evaluation to confirm etiology and/or exclude other causes
	Grade 3 or 4	Permanently discontinue		

irAEs	Toxicity Grade (CTCAE v5.0)	Action With Pembrolizumab Monotherapy, Coformulations, or IO Combinations	Corticosteroid and/or Other Therapies	Monitoring and Follow-up
Myocarditis	Asymptomatic cardiac enzyme elevation with clinical suspicion of myocarditis (which was previously myocarditis Grade 1 using CTCAE v4.0)	Withhold	• Based on severity of AE administer corticosteroids	• Ensure adequate evaluation to confirm etiology and/or exclude other causes
	Grade 2, 3 or 4	Permanently discontinue		
Exfoliative Dermatologic Conditions	Suspected SJS, TEN, or DRESS	Withhold	• Based on severity of AE administer corticosteroids	• Ensure adequate evaluation to confirm etiology or exclude other causes
	Confirmed SJS, TEN, or DRESS	Permanently discontinue		
All Other irAEs	Persistent Grade 2	Withhold	• Based on severity of AE administer corticosteroids	• Ensure adequate evaluation to confirm etiology or exclude other causes
	Grade 3	Withhold or discontinue based on the event[e]		
	Recurrent Grade 3 or Grade 4	Permanently discontinue		

AE(s)=adverse event(s); ALT=alanine aminotransferase; AST=aspartate aminotransferase; CTCAE=Common Terminology Criteria for Adverse Events; DRESS=Drug Rash with Eosinophilia and Systemic Symptom; GI=gastrointestinal; IO=immuno-oncology; ir=immune related; IV=intravenous; SJS=Stevens-Johnson Syndrome; T1DM=type 1 diabetes mellitus; TEN=Toxic Epidermal Necrolysis; ULN=upper limit of normal.

Note: Non-irAE will be managed as appropriate, following clinical practice recommendations.

[a] AST/ALT: >3.0 to 5.0 × ULN if baseline normal; >3.0 to 5.0 × baseline, if baseline abnormal; bilirubin:>1.5 to 3.0 × ULN if baseline normal; >1.5 to 3.0 × baseline if baseline abnormal

[b] AST/ALT: >5.0 to 20.0 × ULN, if baseline normal; >5.0 to 20.0 × baseline, if baseline abnormal; bilirubin:>3.0 to 10.0 × ULN if baseline normal; >3.0 to 10.0 × baseline if baseline abnormal

[c] AST/ALT: >20.0 × ULN, if baseline normal; >20.0 × baseline, if baseline abnormal; bilirubin: >10.0 × ULN if baseline normal; >10.0 × baseline if baseline abnormal

[d] The decision to withhold or permanently discontinue pembrolizumab monotherapy, coformulations, or IO combinations is at the discretion of the investigator or treating physician. If control achieved or ≤ Grade 2, pembrolizumab monotherapy, coformulations, or IO combinations may be resumed.

[e] Events that require discontinuation include, but are not limited to encephalitis and other clinically important irAEs (eg, vasculitis and sclerosing cholangitis)

Dose Modification and Toxicity Management of Infusion Reactions Related to Pembrolizumab Monotherapy, Coformulations (MK-7684A), or IO Combinations

Pembrolizumab monotherapy, coformulations (MK-7684A), or IO combinations may cause severe or life-threatening infusion reactions including severe hypersensitivity or anaphylaxis. Signs and symptoms usually develop during or shortly after drug infusion and generally resolve completely within 24 hours of completion of infusion. Dose modification and toxicity management guidelines on pembrolizumab monotherapy, coformulations (MK-7684A), or IO combinations associated infusion reactions are provided in Table 6.

Table 6 Pembrolizumab Monotherapy, Coformulations (MK-7684A), or IO Combinations Infusion Reaction Dose Modification and Treatment Guidelines

NCI CTCAE Grade	Treatment	Premedication at Subsequent Dosing
Grade 1 Mild reaction; infusion interruption not indicated; intervention not indicated	Increase monitoring of vital signs as medically indicated until the participant is deemed medically stable in the opinion of the investigator	None
Grade 2 Requires therapy or infusion interruption but responds promptly to symptomatic treatment (eg, antihistamines, NSAIDs, narcotics, IV fluids); prophylactic medications indicated for ≤24 h	Stop Infusion Additional appropriate medical therapy may include but is not limited to: IV fluids Antihistamines NSAIDs Acetaminophen Narcotics Increase monitoring of vital signs as medically indicated until the participant is deemed medically stable in the opinion of the investigator. If symptoms resolve within 1 hour of stopping drug infusion, the infusion may be restarted at 50% of the original infusion rate (eg, from 100 mL/h to 50 mL/h). Otherwise, dosing will be held until symptoms resolve and the participant should be premedicated for the next scheduled dose. Participants who develop Grade 2 toxicity despite adequate premedication should be permanently discontinued from further study intervention.	Participant may be premedicated 1.5 h (±30 min) prior to infusion of study intervention with: Diphenhydramine 50 mg po (or equivalent dose of antihistamine). Acetaminophen 500 to 1000 mg po (or equivalent dose of analgesic).

NCI CTCAE Grade	Treatment	Premedication at Subsequent Dosing
Grades 3 or 4 Grade 3: Prolonged (ie, not rapidly responsive to symptomatic medication and/or brief interruption of infusion); recurrence of symptoms after initial improvement; hospitalization indicated for other clinical sequelae (eg, renal impairment, pulmonary infiltrates) Grade 4: Life-threatening; pressor or ventilatory support indicated	Stop Infusion. Additional appropriate medical therapy may include but is not limited to: Epinephrine** IV fluids Antihistamines NSAIDs Acetaminophen Narcotics Oxygen Pressors Corticosteroids Increase monitoring of vital signs as medically indicated until the participant is deemed medically stable in the opinion of the investigator. Hospitalization may be indicated. **In cases of anaphylaxis, epinephrine should be used immediately. Participant is permanently discontinued from further study intervention.	No subsequent dosing
CTCAE=Common Terminology Criteria for Adverse Events; h=hour; IV=intravenous; NCI=National Cancer Institute; NSAIDs=nonsteroidal anti-inflammatory drugs. Note: Appropriate resuscitation equipment should be available at the bedside and a physician readily available during the period of drug administration. For further information, please refer to the CTCAE v5.0 at http://ctep.cancer.gov		

Other Allowed Dose Interruption for Pembrolizumab Monotherapy, Coformulations, or IO Combinations

Pembrolizumab monotherapy, coformulations, or IO combinations may be interrupted for situations other than treatment-related AEs such as medical or surgical events and/or unforeseen circumstances not related to study intervention. However, study intervention is to be restarted within 3 weeks (21 days) of the originally scheduled dose and within <6 weeks (42 days) of the previously administered dose, unless otherwise discussed with the Sponsor. The reason for study intervention interruption is to be documented in the participant's study record.

6.7 Intervention After the End of the Study

There is no study-specified intervention after the end of the study.

6.8 Clinical Supplies Disclosure

The emergency unblinding call center will use the intervention/randomization schedule for the study to unblind participants and to unmask study intervention identity. The emergency unblinding call center should only be used in cases of emergency (see Section 8.1.11). If the emergency unblinding call center is not available for a given site in this study, the central electronic intervention randomization system (IRT) should be used to unblind participants

and to unmask study intervention identity. The Sponsor will not provide random code/disclosure envelopes or lists with the clinical supplies.

6.9 Standard Policies

Not applicable.

7 DISCONTINUATION OF STUDY INTERVENTION AND PARTICIPANT WITHDRAWAL

7.1 Discontinuation of Study Intervention

Discontinuation of study intervention does not represent withdrawal from the study.

As certain data on clinical events beyond study intervention discontinuation may be important to the study, they must be collected through the participant's last scheduled follow-up, even if the participant has discontinued study intervention. Therefore, all participants who discontinue study intervention before completion of the protocol-specified treatment period will still continue to be monitored in this study and participate in the study visits and procedures as specified in Section 1.3 and Section 8.11.3 unless the participant has withdrawn from the study (Section 7.2).

Participants may discontinue study intervention at any time for any reason or be discontinued from the study intervention at the discretion of the investigator should any untoward effect occur. In addition, a participant may be discontinued from study intervention by the investigator or the Sponsor if study intervention is inappropriate, the study plan is violated, or for administrative and/or other safety reasons.

A participant must be discontinued from study intervention, but continue to be monitored in the study for any of the following reasons:

- The participant or participant's legally acceptable representative requests to discontinue study intervention.

  NOTE: See Appendix 7 for country-specific requirements.
- Any prolonged interruption of study intervention beyond the permitted periods, for irAE management or other allowed dose interruptions, as noted in Section 6.6.1, require Sponsor consultation prior to restarting treatment. If treatment will not be restarted, the participant will continue to be monitored in the study and the reason for discontinuation of study intervention will be recorded in the medical record.
- The participant has a medical condition or personal circumstance which, in the opinion of the investigator and/or Sponsor, placed the participant at unnecessary risk from continued administration of study intervention.
- The participant has a confirmed positive serum pregnancy test.
- Confirmed disease recurrence identified by investigator radiographically and/or by examination (with subsequent biopsy).
- Any progression or recurrence of malignancy, or any occurrence of another malignancy that requires active treatment.

  Exceptions to secondary malignancy include basal cell carcinoma of the skin, squamous cell carcinoma of the skin, new nonulcerated primary melanoma <1 mm in depth with no nodal involvement, or carcinoma in situ (excluding carcinoma in situ of the bladder) that have undergone potentially curative therapy. Exceptions should be discussed with the Sponsor before continuing therapy or remaining in follow-up.

Diagnosis of a new primary melanoma ≥1 mm or <1 mm with ulceration will result in discontinuation of therapy.

- Initiation of new anticancer treatment.
- Any prohibited medication as listed in Section 6.5 is deemed necessary by the investigator/treating physician.
- Any study intervention-related toxicity specified as a reason for permanent discontinuation as defined in the guidelines for dose modification due to AEs in Section 6.6.

For participants who are discontinued from study intervention, but continue to be monitored in the study, all visits and procedures, as outlined in the SoA, should be completed.

Discontinuation from study intervention is "permanent." Once a participant is discontinued from study intervention, they shall not be allowed to restart study intervention.

Protocol Amendment 04 implementation: due to discontinuation of the experimental arm (Arm A: MK-7684A) and participants moving to the comparator arm (Arm B: pembrolizumab monotherapy), the visits and procedures outlined in Section 1.3.2 (Amendment 04 SoA) should be followed.

7.2 Participant Withdrawal From the Study

A participant must be withdrawn from the study if the participant or participant's legally acceptable representative withdraws consent from the study.

If a participant withdraws from the study, they will no longer receive study intervention or be followed at scheduled protocol visits.

Specific details regarding procedures to be performed at the time of withdrawal from the study, as well as specific details regarding withdrawal from FBR, are outlined in Section 8.9. The procedures to be performed should a participant repeatedly fail to return for scheduled visits and/or if the study site is unable to contact the participant are outlined in Section 7.3.

Protocol Amendment 04 implementation: Participants who complete or discontinue study intervention and have completed safety follow-up will be considered to have completed the study. This also applies to participants in efficacy follow-up.

7.3 Lost to Follow-up

If a participant fails to return to the clinic for a required study visit and/or if the site is unable to contact the participant, the following procedures are to be performed:

- The site must attempt to contact the participant and reschedule the missed visit. If the participant is contacted, the participant should be counseled on the importance of maintaining the protocol-specified visit schedule.

- The investigator or designee must make every effort to regain contact with the participant at each missed visit (eg, telephone calls and/or a certified letter to the participant's last known mailing address or locally equivalent methods). These contact attempts should be documented in the participant's medical record.

NOTE: A participant is not considered lost to follow-up until the last scheduled visit for the individual participant. The missing data for the participant will be managed via the prespecified statistical data handling and analysis guidelines.

8 STUDY ASSESSMENTS AND PROCEDURES

- Study procedures and their timing are summarized in the SoA.
- Adherence to the study design requirements, including those specified in the SoA, is essential and required for study conduct.
- The investigator is responsible for ensuring that procedures are conducted by appropriately qualified (by education, training, and experience) staff. Delegation of study-site personnel responsibilities will be documented in the Investigator Trial File Binder (or equivalent).
- All study-related medical decisions must be made by an investigator who is a qualified physician.
- All screening evaluations must be completed and reviewed to confirm that potential participants meet all eligibility criteria. The investigator will maintain a screening log to record details of all participants screened and to confirm eligibility or record reasons for screening failure, as applicable.
- Procedures conducted as part of the participant's routine clinical management (eg, blood count) and obtained before providing document informed consent may be used for screening or baseline purposes provided the procedures meet the protocol-specified criteria and were performed within the time frame defined in the SoA.
- Additional evaluations/testing may be deemed necessary by the investigator and or the Sponsor for reasons related to participant safety. In some cases, such evaluation/testing may be potentially sensitive in nature (eg, HIV, hepatitis C), and thus local regulations may require that additional informed consent be obtained from the participant. In these cases, such evaluations/testing will be performed in accordance with those regulations.

8.1 Administrative and General Procedures

8.1.1 Informed Consent

The investigator or medically qualified designee (consistent with local requirements) must obtain documented informed consent from each potential participant (or their legally acceptable representative) prior to participating in this clinical study or FBR. If there are changes to the participant's status during the study (eg, health or age of majority requirements), the investigator or medically qualified designee must ensure the appropriate documented informed consent is in place.

8.1.1.1 General Informed Consent

Informed consent given by the participant or their legally acceptable representative must be documented on a consent form. The form must include the study protocol number, study protocol title, dated signature, and agreement of the participant (or his/her legally acceptable representative) and of the person conducting the consent discussion.

A copy of the signed and dated informed consent form should be given to the participant (or their legally acceptable representative) before participation in the study.

The initial ICF, any subsequent revised ICF, and any written information provided to the participant must receive the IRB/IEC's approval/favorable opinion in advance of use. The participant or his/her legally acceptable representative should be informed in a timely manner if new information becomes available that may be relevant to the participant's willingness to continue participation in the study. The communication of this information will be provided and documented via a revised consent form or addendum to the original consent form that captures the participant's or the participant's legally acceptable representative's dated signature.

Specifics about the study and the study population are to be included in the study informed consent form.

Informed consent will adhere to IRB/IEC requirements, applicable laws and regulations, and Sponsor requirements.

8.1.1.2 Consent and Collection of Specimens for Future Biomedical Research

The investigator or medically qualified designee will explain the FBR consent to the participant, or the participant's legally acceptable representative, answer all of his/her questions, and obtain documented informed consent before performing any procedure related to FBR. A copy of the informed consent will be given to the participant before performing any procedure related to FBR.

8.1.2 Inclusion/Exclusion Criteria

All inclusion and exclusion criteria will be reviewed by the investigator, who is a qualified physician, to ensure that the participant qualifies for the study.

8.1.3 Participant Identification Card

All participants will be given a participant identification card identifying them as participants in a research study. The card will contain study-site contact information (including direct telephone numbers) to be used in the event of an emergency. The investigator or qualified designee will provide the participant with a participant identification card immediately after the participant provides documented informed consent. At the time of intervention randomization, site personnel will add the treatment/randomization number to the participant identification card.

The participant ID card also contains contact information for the emergency unblinding call center so that a health care provider can obtain information about study intervention in emergency situations where the investigator is not available.

8.1.4 Medical History

A medical history will be obtained by the investigator or qualified designee. The medical history will collect all active conditions and any condition diagnosed within the prior 10 years that the investigator considers to be clinically important. Details regarding the

disease for which the participant has enrolled in this study will be recorded separately and not listed as medical history.

If a medical condition is diagnosed at the time of screening due to the physical examination, laboratory tests, radiologic assessment, other assessment, and/or a combination of these evaluations, the medical condition is to be recorded as a baseline condition along with the participant's other medical history unless due to any protocol-specified intervention (eg, procedure, washout, or run-in treatment including placebo run-in).

8.1.5 Melanoma Disease History

A history of the participant's melanoma will be obtained by the investigator or qualified designee. Details of their condition including disease stage, date of initial diagnosis, date of resection, date of SLN and CLND (if performed), date of any upstaging and other relevant information regarding their melanoma including details on any prior radiation therapy received will be recorded. If a participant previously underwent genomic profiling for their melanoma, these data may be provided.

8.1.6 Prior and Concomitant Medications Review

8.1.6.1 Prior Medications

The investigator or qualified designee will review prior medication use, including any protocol-specified washout requirement, and record prior medication taken by the participant within 28 days before starting the study. Treatment for the disease for which the participant has enrolled in this study will be recorded separately and not listed as a prior medication.

8.1.6.2 Concomitant Medications

The investigator or qualified designee will record medication, if any, taken by the participant during the study through the Safety Follow-up Visit. All medications related to reportable SAEs and ECIs should be recorded.

8.1.7 Assignment of Screening Number

All consented participants will be given a unique screening number that will be used to identify the participant for all procedures that occur before randomization. Each participant will be assigned only 1 screening number. Screening numbers must not be reused for different participants.

Any participant who is screened multiple times will retain the original screening number assigned at the initial Screening Visit. Specific details on the screening/rescreening visit requirements are in Section 8.11.1.

8.1.8 Assignment of Treatment/Randomization Number

All eligible participants will be randomly allocated and will receive a treatment/randomization number. The treatment/randomization number identifies the

participant for all procedures occurring after treatment randomization. Once a treatment/randomization number is assigned to a participant, it can never be reassigned to another participant.

A single participant cannot be assigned more than 1 treatment/randomization number.

8.1.9 Study Intervention Administration

Study intervention will be administered by the investigator and/or study staff according to the specifications within the Pharmacy Manual. All study interventions will be administered on an outpatient basis.

If an adolescent <18 years of age at randomization becomes ≥18 years of age during the study, they will continue to receive the adolescent dosing to which they were randomized for the duration of the study.

Protocol Amendment 04 implementation: All active participants in the experimental arm (Arm A: MK-7684A) will be moved to the comparator arm (Arm B: pembrolizumab monotherapy) for the remainder of the study (a total of 17 cycles of study treatment or until disease progression, whichever occurs first). NOTE: For study participants who, in the opinion of the study investigator, are benefitting from MK-7684A, the study investigator may request Sponsor consultation for continuation of treatment with MK-7684A.

8.1.9.1 Timing of Dose Administration

Study intervention is to be administered at the study visits outlined in the SoA. Cycle 1 study intervention should begin within 3 days of randomization. For all subsequent cycles, study intervention may be administered up to 3 days before or after the scheduled day of administration. Participants will continue receiving study intervention until one of the criteria for treatment discontinuation are met (Section 7.1) or until they complete the entire course of treatment as outlined in the SoA.

Protocol Amendment 04 implementation: the visits and procedures for all active participants outlined in Section 1.3.2 should be followed.

8.1.10 Discontinuation and Withdrawal

Participants who discontinue study intervention before completion of the treatment period should be encouraged to continue to be followed for all remaining study visits as outlined in the SoA and Section 8.11.3.

Participants who withdraw from the study should be encouraged to complete all applicable activities scheduled for the Safety Follow-up Visit at the time of withdrawal. Any AEs that are present at the time of withdrawal should be followed in accordance with the safety requirements outlined in Section 8.4.

Protocol Amendment 04 implementation: the visits and procedures for all active participants outlined in Section 1.3.2 should be followed.

8.1.10.1 Withdrawal From Future Biomedical Research

Participants may withdraw their consent for FBR. Participants may withdraw consent at any time by contacting the study investigator. If medical records for the study are still available, the investigator will contact the Sponsor using the designated mailbox (clinical.specimen.management@MSD.com). Subsequently, the participant's consent for FBR will be withdrawn. A letter will be sent from the Sponsor to the investigator confirming the withdrawal. It is the responsibility of the investigator to inform the participant of completion of withdrawal. Any analyses in progress at the time of request for withdrawal or already performed before the request being received by the Sponsor will continue to be used as part of the overall research study data and results. No new analyses would be generated after the request is received.

If the medical records for the study are no longer available (eg, if the investigator is no longer required by regulatory authorities to retain the study records) or the specimens have been completely anonymized, there will no longer be a link between the participant's personal information and their specimens. In this situation, the request for specimen withdrawal cannot be processed.

8.1.11 Participant Blinding/Unblinding

STUDY INTERVENTION IDENTIFICATION INFORMATION IS TO BE UNMASKED ONLY IF NECESSARY FOR THE WELFARE OF THE PARTICIPANT. EVERY EFFORT SHOULD BE MADE NOT TO UNBLIND.

For emergency situations where the investigator or medically qualified designee (consistent with local requirements) needs to identify the intervention used by a participant and/or the dosage administered, he/she will contact the emergency unblinding call center by telephone and make a request for emergency unblinding. As requested by the investigator or medically qualified designee, the emergency unblinding call center will provide the information to him/her promptly and report unblinding to the Sponsor. Before contacting the emergency unblinding call center to request unblinding of a participant's intervention assignment, the investigator who is a qualified physician should make reasonable attempts to enter the toxicity grade of the AEs observed, the relation to study intervention, the reason thereof, etc, in the medical record. If it is not possible to record this assessment in the medical record before the unblinding, the unblinding should not be delayed.

If unblinding has occurred, the circumstances around the unblinding (eg, date, reason, and person performing the unblinding) must be documented promptly, and the Sponsor Clinical Director notified as soon as possible.

Once an emergency unblinding has taken place, the investigator, site personnel, and Sponsor personnel may be unblinded so that the appropriate follow-up medical care can be provided to the participant.

Participants whose treatment assignment has been unblinded by the investigator or medically qualified designee and/or nonstudy treating physician should continue to be monitored in the study.

Additionally, the investigator or medically qualified designee must go into the IRT system and perform the unblind in the IRT system to update drug disposition. If the emergency unblinding call center is not available for a given site in this study, the IRT system should be used for emergency unblinding if this is required for participant safety.

At the end of the study, random code/disclosure envelopes or lists and unblinding logs are to be returned to the Sponsor or designee.

Protocol Amendment 04 implementation: treatment arms have been unblinded as per the recommendation by the eDMC to discontinue the experimental arm (MK-7684A).

8.1.12 Calibration of Equipment

The investigator or qualified designee has the responsibility to ensure that any device or instrument used for a clinical evaluation/test during a clinical study that provides information about inclusion/exclusion criteria and/or safety or efficacy parameters shall be suitably calibrated and/or maintained to ensure that the data obtained are reliable and/or reproducible. Documentation of equipment calibration must be retained as source documentation at the study site.

8.1.13 Tumor Tissue for Biomarker Status

During the screening period, a tumor sample for each participant is required, if available, and is to be:

- A newly obtained biopsy of a tumor lesion, which was not previously irradiated

Or

- An archival tumor tissue sample if a new biopsy is unavailable (depending on protocol requirements)

At the time of recurrence, the participant may provide an optional fresh tumor sample.

FFPE tissue blocks are preferred to slides. Newly obtained biopsies are preferred to archived tissue.

Details pertaining to tumor tissue submission can be found in the Laboratory Manual.

See Appendix 7 for country-specific requirements.

8.1.14 Elevated Transaminases With Treated HBV or HCV

Participants who were treated for HBV or HCV, enrolled in the study, and present with elevated transaminases according to the criteria below should be evaluated for viral hepatitis exacerbation/reactivation.

- If baseline AST/ALT <2×ULN and an increase of AST/ALT ≥5×ULN
- If baseline AST/ALT ≥2×ULN and an increase of AST/ALT >3 × baseline level

- AST/ALT >500 U/L regardless of baseline

Viral load testing and additional hepatitis serologies should be included as required.

8.2 Efficacy/Immunogenicity Assessments

8.2.1 Tumor Imaging and Assessment of Disease

Throughout this section, the term 'scan' refers to any medical imaging data used to assess tumor burden and may include cross-sectional imaging (such as CT or MRI), medical photography, or other methods as specified in this protocol.

The process for scan collection and transmission to the iCRO can be found in the SIM. Tumor scans by CT are strongly preferred. For the abdomen and pelvis, contrast-enhanced MRI may be used when CT with iodinated contrast is contraindicated, or when mandated by local practice. The same scan technique should be used in a participant throughout the study to optimize the reproducibility of the assessment of existing and new tumor burden and improve the accuracy of the response assessment based on scans.

Note: For the purposes of assessing tumor scans, the term "investigator" refers to the local investigator at the site and/or the radiological reviewer at the site or at an offsite facility.

For participants with primary tumors of the head and neck, neck imaging is required at time points indicated in the SoA.

If brain scans are performed, magnetic resonance imaging is preferred; however, CT imaging will be acceptable, if MRI is medically contraindicated.

Bone scans may be performed to evaluate bone metastases. Any supplemental scans performed to support a positive or negative bone scan, such as plain X-rays acquired for correlation, should also be submitted to the iCRO.

Participant eligibility will be determined using investigator assessment. All scheduled scans for each participant will be submitted to the iCRO. In addition, unscheduled scans to determine disease progression and scans obtained for other reasons but show disease recurrence are to be submitted to the iCRO.

See Appendix 7 for country-specific requirements.

Protocol Amendment 04 implementation: the visits and procedures for all active participants outlined in Section 1.3.2 should be followed.

8.2.1.1 Initial Tumor Scans

Initial tumor scans and brain scan at Screening must be performed within 28 days before the date of randomization. The investigator must review the Screening scans to confirm the participant has no evidence of disease at study entry.

The screening scans must be submitted to the iCRO for potential retrospective review.

Tumor scans and brain scans performed as part of routine clinical management are acceptable for screening if they are of acceptable diagnostic quality and performed within 28 days of randomization.

8.2.1.2 Tumor Scans During the Study

The first on-study scan should be performed at 12 weeks (±7 days) from the date of randomization. Subsequent tumor scans should be performed every 12 weeks (±7 days) or more frequently if clinically indicated. After 2 years, participants will have scans performed Q6M (±14 days) through 4 years after date of randomization, and then once at 5 years (±28 days) from date of randomization. Scan timing should follow calendar days and should not be adjusted for delays in cycle starts.

Protocol Amendment 04 implementation: the visits and procedures for all active participants outlined in Section 1.3.2 should be followed. No scans are required in follow-up.

8.2.1.3 End-of-treatment and Follow-up Tumor Scans

If participants discontinue study intervention, tumor scans should be performed at the time of discontinuation (±4 week window) unless previous scans were obtained within 4 weeks of discontinuation. If participants discontinue study intervention due to a documented DMFS event, this is the final required tumor scan.

If participants discontinue study intervention without a documented DMFS event, every effort is to be made to monitor disease status by acquiring tumor scans using the same schedule calculated from the date of randomization (refer to Section 8.2.1.2).

Scans are to be continued until one of the following conditions are met:

- DMFS event
- Pregnancy
- Participant enters Survival Follow-up
- Death
- Withdrawal of consent
- The end of the study

Protocol Amendment 04 implementation: the visits and procedures for all active participants outlined in Section 1.3.2 should be followed. No scans are required in follow-up.

8.2.1.4 RECIST 1.1 Assessment of Disease

The principles of RECIST 1.1 regarding the development of a new lesion(s) will guide the radiographic determination of RFS and DMFS events as assessed by the investigator.

RECIST 1.1 will additionally be used in the assessment of tumor response for evaluation of PRFS2. Although RECIST 1.1 references a maximum of 5 target lesions in total and 2 per

organ, this protocol allows a maximum of 10 target lesions in total and 5 per organ, if clinically relevant to enable a broader sampling of tumor burden.

8.2.2 Patient-reported Outcomes

The EQ-5D-5L and EORTC QLQ-C30 questionnaires will be administered by trained site personnel and completed electronically by participants in the following order: EORTC QLQ-C30 first, then EQ-5D-5L. The questionnaires should be administered before dosing at the visits indicated in the SoA.

The EORTC QLQ-C30 will be administered only to adults (≥18 years of age) since the questionnaire is not validated in pediatric populations. The EQ-5D-5L will be administered to all study participants since it is considered acceptable to use for persons 12 years of age and older.

It is best practice and strongly recommended that ePROs are administered to randomized participants before drug administration, AE evaluation, and disease status notification. If the participant does not complete the ePROs at a scheduled time point, the MISS_MODE form must be completed to capture the reason the assessment was not performed.

Protocol Amendment 04 implementation: the visits and procedures for all active participants outlined in Section 1.3.2 should be followed. No further PRO assessments are required.

8.3 Safety Assessments

Details regarding specific safety procedures/assessments to be performed in this study are provided. The total amount of blood/tissue to be drawn/collected over the course of the study (from prestudy to poststudy visits), including approximate blood/tissue volumes drawn/collected by visit and by sample type per participant, can be found in the Study Procedures Manual.

Planned time points for all safety assessments are provided in the SoA.

Protocol Amendment 04 implementation: the visits and procedures for all active participants outlined in Section 1.3.2 should be followed.

8.3.1 Physical Examinations

Physical examinations will be conducted by an investigator or medically qualified designee (consistent with local requirements) per institutional standard. Investigators should pay special attention to clinical signs related to previous serious illnesses.

The investigator or qualified designee should conduct a visual inspection of local recurrence and palpation of regional lymph nodes to assess regional recurrence. Photographs of new skin lesions not visualized on imaging should be obtained and submitted to imaging vendor.

8.3.1.1 Full Physical Examination

The investigator or qualified designee will perform a full physical examination when described in the SoA. Clinically significant abnormal findings at Screening should be recorded as medical history. After the first dose of study intervention, new clinically significant abnormal findings should be recorded as AEs.

8.3.1.2 Directed Physical Examination

For all visits that do not require a full physical examination as defined in the SoA, the investigator or qualified designee will perform a directed physical examination as clinically indicated.

After the first dose of study intervention, new clinically significant abnormal findings should be recorded as AEs.

8.3.2 Vital Signs

- Temperature, pulse rate, respiratory rate, and blood pressure will be assessed.
- Blood pressure and pulse measurements will be assessed with a completely automated device. Manual techniques will be used only if an automated device is not available.
- Blood pressure and pulse measurements should be preceded by at least 5 minutes of rest for the participant in a quiet setting without distractions.

Height and weight will also be recorded as indicated in the SoA. For adult participants, height will be measured only at Screening whereas for pediatric participants height will be measured at every cycle as indicated in the SoA.

8.3.3 Electrocardiograms

Single 12-lead ECG will be obtained and reviewed by an investigator or medically qualified designee (consistent with local requirements) at Screening using an ECG machine that automatically calculates the HR and measures PR, QRS, QT, and QTc intervals. Clinically significant abnormal findings at Screening should be recorded as medical history. Additional timepoints may be performed as clinically necessary.

NOTE: A 6-lead ECG is allowed per institutional standard.

8.3.4 Clinical Safety Laboratory Assessments

Refer to Appendix 2 for the list of clinical laboratory tests to be performed and to the SoA for the timing and frequency.

- The investigator or medically qualified designee (consistent with local requirements) must review the laboratory report, document this review, and record any clinically relevant changes occurring during the study in the AE section of the CRF. The laboratory reports must be filed with the source documents. Clinically significant abnormal

laboratory findings are those which are not associated with the underlying disease, unless judged by the investigator to be more severe than expected for the participant's condition.

- All protocol-required laboratory assessments, as defined in Appendix 2, must be conducted in accordance with the Laboratory Manual and the SoA.
- If laboratory values from nonprotocol-specified laboratory assessments performed at the institution's local laboratory require a change in study participant management or are considered clinically significant by the investigator (eg, SAE or AE or dose modification), then the results must be recorded in the appropriate CRF (eg, SLAB).
- For any laboratory tests with values considered clinically significantly abnormal during participation in the study or within 90 days after the last dose of study intervention, every attempt should be made to perform repeat assessments until the values return to normal or baseline or if a new baseline is established as determined by the investigator.

Details regarding specific laboratory procedures/assessments to be performed in this study are provided below. The total amount of blood/tissue to be drawn/collected over the course of the study (from prestudy to poststudy visits), including approximate blood/tissue volumes drawn/collected by visit and by sample type per participant can be found in the Study Procedures Manual. Refer to the SoA for the timing of laboratory assessments.

Repeat or unscheduled samples may be taken for safety reasons or for technical issues with the samples.

8.3.4.1 Laboratory Safety Evaluations (Hematology, Chemistry and Urinalysis)

Details regarding specific laboratory procedures/assessments to be performed in this study are provided below. The total amount of blood/tissue to be drawn/collected over the course of the study (from prestudy to poststudy visits), including approximate blood/tissue volumes drawn/collected by visit and by sample type per participant can be found in the Laboratory Manual. Refer to the Study Flow Chart (Section 1.3) for the timing of laboratory assessments.

Laboratory tests for hematology, chemistry, and urinalysis are specified in Appendix 2.

8.3.5 Pregnancy Testing

- Pregnancy testing:
  - Pregnancy testing requirements for study inclusion are described in Section 5.1.
  - Pregnancy testing (urine and/or serum) should be conducted at least monthly as described in the SoA during study intervention.
  - Pregnancy testing (urine and/or serum) should be conducted as per the SoA for the time required to eliminate systemic exposure after the last dose of study intervention and should correspond with the time frame for participant's contraception as noted in Section 5.1. The length of time required to continue pregnancy testing for each study intervention is:
    - Pembrolizumab: 120 days

- MK-7684A: 120 days

- Additional serum or urine pregnancy tests may be performed, as determined necessary by the investigator or required by local regulation, to establish the absence of pregnancy at any time during the participant's participation in the study.

8.3.6 Performance Assessments

8.3.6.1 Karnofsky Performance Status

The KPS is a standard way of measuring the ability of cancer patients to perform ordinary tasks, with scores ranging from 0% to 100%. A higher score means the patient is better able to perform daily activities. The KPS will be assessed as specified in the SoA (Section 1.3) for participants >16 and <18 years of age.

8.3.6.2 Eastern Cooperative Oncology Group Performance Status

The ECOG Performance Status is standardized criteria to measure how cancer impacts level of functioning (performance status) in terms of ability to care for oneself, daily activity, and physical ability (walking, working, etc) with grades 0 to 5.

The ECOG status will be assessed as specified in the SoA (Section 1.3) for participants ≥18 years of age.

8.3.6.3 Lansky Play-Performance Scale

The LPS score is a standard way of measuring the functionality of pediatric participants up to and including the age of 16. The LPS is rated by parents based on their child's activity over the past week. Parents fill out the assessment based on the directions on the form, and the form is readministered over time to assess for changes in performance status. A higher score means the child is functioning better. The LPS will be assessed as specified in the SoA (Section 1.3).

8.4 Adverse Events, Serious Adverse Events, and Other Reportable Safety Events

The definitions of an AE or SAE, as well as the method of recording, evaluating, and assessing causality of AE and SAE and the procedures for completing and transmitting AE, SAE, and other reportable safety event reports can be found in Appendix 3.

Progression of the cancer under study is not considered an AE as described in Section 8.4.6 and Appendix 3.

Adverse events, SAEs, and other reportable safety events will be reported by the participant (or, when appropriate, by a caregiver, surrogate, or the participant’s legally authorized representative).

The investigator and any designees are responsible for detecting, documenting, and reporting events that meet the definition of an AE or SAE as well as other reportable safety events.

Investigators need to document if an SAE was associated with a medication error, misuse, or abuse.

Investigators remain responsible for following up AEs, SAEs, and other reportable safety events for outcome according to Section 8.4.3. The investigator, who is a qualified physician, will assess events that meet the definition of an AE or SAE as well as other reportable safety events with respect to seriousness, intensity/toxicity, and causality.

8.4.1 Time Period and Frequency for Collecting AE, SAE, and Other Reportable Safety Event Information

All AEs, SAEs, and other reportable safety events that occur after the participant provides documented informed consent, but before intervention randomization, must be reported by the investigator if the participant is receiving placebo run-in or other run-in treatment, if the event cause the participant to be excluded from the study, or is the result of a protocol-specified intervention, including, but not limited to washout or discontinuation of usual therapy, diet, or a procedure.

- All AEs, from the time of intervention randomization through 90 days after cessation of study intervention or 30 days after cessation of study intervention if the participant initiates new anticancer therapy, whichever is earlier, must be reported by the investigator.
- All pregnancies and exposure during breastfeeding, from the time of intervention randomization through the time required to eliminate systemic exposure after cessation of study intervention as described in Sections 5.1 and 8.3.5, or 120 days after cessation of study intervention if the participant initiates new anticancer therapy must be reported by the investigator.
- Additionally, any SAE brought to the attention of an investigator at any time outside the time specified above must be reported immediately to the Sponsor if the event is considered related to study intervention.

Investigators are not obligated to actively seek AEs or SAEs or other reportable safety events in former study participants. However, if the investigator learns of any SAE, including a death, at any time after a participant has been discharged from the study, and the investigator considers the event to be reasonably related to the study intervention or study participation, the investigator must promptly notify the Sponsor.

All initial and follow-up AEs, SAEs, and other reportable safety events will be recorded and reported to the Sponsor or designee within the time frames as indicated in Table 7.

Exception: A positive pregnancy test at the time of initial screening is not a reportable event unless the participant has received study intervention.

Table 7 Reporting Periods and Time Frames for Adverse Events and Other Reportable Safety Events

Type of Event	**Reporting Period:** Consent to Randomization/ Allocation	**Reporting Period:** Randomization/ Allocation Through Protocol-specified Follow-up Period	**Reporting Period:** After the Protocol-specified Follow-up Period	Time Frame to Report Event and Follow-up Information to Sponsor
NSAE	Report if: – due to protocol-specified intervention – causes exclusion – participant is receiving placebo run-in or other run-in treatment	Report all	Not required	Per data entry guidelines
SAE	Report if: – due to protocol-specified intervention – causes exclusion – participant is receiving placebo run-in or other run-in treatment	Report all	Report if: – drug/vaccine related. (Follow ongoing to outcome)	Within 24 hours of learning of event
Pregnancy/Lactation Exposure	Report if: – participant has been exposed to any protocol-specified intervention (eg, procedure, washout, or run-in treatment including placebo run-in) Exception: A positive pregnancy test at the time of initial screening is not a reportable event.	Report all	Previously reported – Follow to completion/ termination; report outcome	Within 24 hours of learning of event
ECI (requiring regulatory reporting)	Report if: – due to intervention – causes exclusion	Report – potential DILI – requiring regulatory reporting	Not required	Within 24 hours of learning of event
ECI (does not require regulatory reporting)	Report if: – due to intervention – causes exclusion	Report – non-DILI ECIs and those not requiring regulatory reporting	Not required	Within 5 calendar days of learning of event
New Cancer (that is not the cancer under study)	Report if: – due to intervention – causes exclusion	Report all	Not required	Within 5 calendar days of learning of event (unless SAE)

Type of Event	**Reporting Period:** Consent to Randomization/ Allocation	**Reporting Period:** Randomization/ Allocation Through Protocol-specified Follow-up Period	**Reporting Period:** After the Protocol-specified Follow-up Period	Time Frame to Report Event and Follow-up Information to Sponsor
Overdose	Report if: – receiving placebo run-in or other run-in medication	Report all	Not required	Within 5 calendar days of learning of event (unless SAE)
DILI=drug-induced liver injury; ECI=event of clinical interest; NSAE=nonserious adverse event; SAE=serious adverse event.				

8.4.2 Method of Detecting AEs, SAEs, and Other Reportable Safety Events

Care will be taken not to introduce bias when detecting AEs and/or SAEs and other reportable safety events. Open-ended and nonleading verbal questioning of the participant is the preferred method to inquire about AE occurrence.

8.4.3 Follow-up of AE, SAE, and Other Reportable Safety Event Information

After the initial AE/SAE report, the investigator is required to proactively follow each participant at subsequent visits/contacts. SAEs and other reportable safety events, including pregnancy and exposure during breastfeeding, ECIs, cancer, and overdose will be followed until resolution, stabilization, until the event is otherwise explained, or the participant is lost to follow-up (as defined in Section 7.3). The investigator will also make every attempt to follow nonserious AEs that occur in randomized participants for outcome. Further information on follow-up procedures is given in Appendix 3.

8.4.4 Regulatory Reporting Requirements for SAE

Prompt notification (within 24 hours) by the investigator to the Sponsor of SAE is essential so that legal obligations and ethical responsibilities toward the safety of participants and the safety of a study intervention under clinical investigation are met.

The Sponsor has a legal responsibility to notify both the local regulatory authority and other regulatory agencies about the safety of a study intervention under clinical investigation. The Sponsor will comply with country-specific regulatory requirements and global laws and regulations relating to safety reporting to regulatory authorities, IRB/IECs, and investigators.

Investigator safety reports must be prepared for SUSARs according to local regulatory requirements and Sponsor policy and forwarded to investigators as necessary.

An investigator who receives an investigator safety report describing an SAE or other specific safety information (eg, summary or listing of SAEs) from the Sponsor will file it along with the IB and will notify the IRB/IEC, if appropriate according to local requirements.

Note: To meet EU CTR requirements, the Sponsor will report SUSARs to the Eudravigilance database via E2B(R3) electronic ICSR form in compliance with CTR 536/2014.

8.4.5 Pregnancy and Exposure During Breastfeeding

Although pregnancy and infant exposure during breastfeeding are not considered AEs, any pregnancy or infant exposure during breastfeeding in a participant (spontaneously reported to the investigator or their designee) that occurs during the study are reportable to the Sponsor.

All reported pregnancies must be followed to the completion/termination of the pregnancy.

Any pregnancy complication will be reported as an AE or SAE.

The medical reason (example: maternal health or fetal disease) for an elective termination of a pregnancy will be reported as an AE or SAE. Prenatal testing showing fetus will be born with severe abnormalities/congenital anomalies that leads to an elective termination of a pregnancy will be reported as an SAE for the fetus.

Pregnancy outcomes of ectopic pregnancy, spontaneous abortion, missed abortion, benign hydatidiform mole, blighted ovum, fetal death, intrauterine death, miscarriage, and stillbirth must be reported as serious events (Important Medical Events). If the pregnancy continues to term, the outcome (health of infant) must also be reported.

8.4.6 Disease-related Events and/or Disease-related Outcomes Not Qualifying as AEs or SAEs

Efficacy endpoints as outlined in this section will not be reported to the Sponsor as described in Section 8.4.1.

Specifically, the suspected/actual events covered in this exception include any event that is disease progression of the cancer under study.

The Sponsor will ensure that unblinded aggregated efficacy endpoint events and safety data are monitored to safeguard the participants in the study.

8.4.7 Events of Clinical Interest

Selected serious and nonserious AEs are also known as ECIs and must be reported to the Sponsor.

Events of clinical interest for this study include:

1. Potential DILI events defined as an elevated AST or ALT laboratory value that is greater than or equal to 3× the ULN and an elevated total bilirubin laboratory value that is greater than or equal to 2× the ULN and, at the same time, an alkaline phosphatase laboratory value that is less than 2× the ULN, as determined by way of protocol-specified laboratory testing or unscheduled laboratory testing.*

   *NOTE: These criteria are based on available regulatory guidance documents. The purpose of the criteria is to specify a threshold of abnormal hepatic tests that may require an additional evaluation for an underlying etiology. The study-site guidance for

assessment and follow up of these criteria can be found in the Investigator Study File Binder (or equivalent).

8.5 Treatment of Overdose

For purposes of this study, an overdose will be defined as any dose exceeding the prescribed dose for MK-7684A by 3 times (ie, 300%) or the prescribed dose for pembrolizumab by 5 times. No specific information is available on the treatment of overdose of MK-7684A or pembrolizumab. In the event of overdose, the participant should be observed closely for signs of toxicity. Appropriate supportive treatment should be provided if clinically indicated.

8.6 Pharmacokinetics

Protocol Amendment 04 implementation: the visits and procedures for all active participants outlined in Section 1.3.2 should be followed. No further PK/ADA samples are required.

8.6.1 Blood Collection for Pharmacokinetics Analysis

Samples for PK analysis will be collected as described in the SoA. Sample collection, storage, and shipment instructions for PK samples will be provided in the Laboratory Manual.

8.7 Pharmacodynamics

Pharmacodynamic parameters will not be evaluated in this study.

8.8 Biomarkers

To identify novel biomarkers, the following biospecimens to support exploratory analyses of cellular components (eg, protein, RNA, DNA, metabolites) and other circulating molecules will be collected from all participants as specified in the SoA:

- Blood for Genetic Analysis
- Blood for ctDNA Analysis
- Tumor Tissue

For country-specific information, refer to Appendix 7

Sample collection, storage, and shipment instructions for the exploratory biomarker specimens will be in the Laboratory Manual.

Protocol Amendment 04 implementation: the visits and procedures for all active participants outlined in Section 1.3.2 should be followed. No further biomarker samples are required.

8.8.1 Planned Genetic Analysis Sample Collection

The planned genetic analysis sample should be drawn for planned analysis of the association between genetic variants in DNA and drug response. This sample will not be collected at the

site if there is either a local law or regulation prohibiting collection, or if the IRB/IEC does not approve the collection of the sample for these purposes. If the sample is collected, leftover extracted DNA will be stored for FBR if the participant provides documented informed consent for FBR. If the planned genetic analysis is not approved, but FBR is approved and consent is given, this sample will be collected for the purpose of FBR.

The planned genetic analysis sample should be obtained pre-dose on Day 1 but may be collected at the next scheduled blood draw, if needed. Sample collection, storage, and shipment instructions for planned genetic analysis samples will be in the Operations/Laboratory Manual.

8.9 Future Biomedical Research Sample Collection

If the participant provides documented informed consent for FBR, the following specimens will be obtained as part of FBR:

- Leftover samples listed in Section 8.8 (including any extracted material from samples)

8.10 Medical Resource Utilization and Health Economics

Medical resource utilization and health economics data, associated with medical encounters, will be collected in the CRF by the investigator and study-site personnel for all participants throughout the study. Protocol-mandated procedures, tests, and encounters are excluded.

All-cause hospitalizations and emergency department visits must be reported in the eCRF, from the time of treatment randomization through 90 days after cessation of study intervention, or 30 days after cessation of study intervention, if the participant initiates new anticancer therapy, whichever is earlier.

8.11 Visit Requirements

Visit requirements are outlined in Section 1.3. Specific procedure-related details are provided in Section 8.

8.11.1 Screening

Documented informed consent must be provided before performing any protocol-specific procedure. Results of a test performed before the participant signing consent as part of routine clinical management are acceptable in lieu of a screening test if performed within the specified time frame.

Screening procedures are to be completed within 28 days before the first dose of study intervention except for the following:

- Archival tumor tissue sample should be from <5 years before Screening.
- Laboratory tests and performance status are to be performed within 7 days before the first dose of study intervention.

- For women of childbearing potential, a urine or serum pregnancy test will be performed within 24 or 72 hours, respectively, before the first dose of study intervention. If urine pregnancy results cannot be confirmed as negative, a serum pregnancy test will be required (performed by the local study-site laboratory).

Participants may be rescreened after initially failing to meet the inclusion/exclusion criteria. Results from assessments during the initial screening period are acceptable in lieu of a repeat screening test if performed within the specified time frame and the corresponding inclusion/exclusion criteria is met. Participants who are rescreened will retain their original screening number.

8.11.2 Treatment Period Visits

Visit requirements are outlined in the SoA (Section 1.3). Specific procedure-related details are provided in Section 8.1.

8.11.3 Participants Discontinued From Study Intervention but Continuing to be Monitored in the Study

Discontinuation of treatment does not represent withdrawal from the study.

When a participant discontinues study intervention, procedures for discontinuation will be performed.

The discontinuation visit should occur at the time study intervention is discontinued for any reason. If the discontinuation visit occurs 90 days from the last dose of study intervention, at the time of the mandatory Safety Follow-up Visit, the discontinuation visit procedures and any additional safety follow-up procedures should be performed. Visit requirements are outlined in Section 1.3. Additional details regarding participant withdrawal and discontinuation are presented in Section 7.

8.11.4 Posttreatment Visit

8.11.4.1 Safety Follow-up Visit

The mandatory Safety Follow-up Visits should be conducted approximately 30 days and 90 days after the last dose of study intervention or before initiation of a new anticancer treatment, whichever comes first.

8.11.4.2 Efficacy Follow-up Visits

Participants who complete study intervention or who discontinue study intervention for a reason other than disease recurrence will begin Efficacy Follow-up and should be assessed according to the SoA to monitor disease status. Every effort should be made to collect information regarding disease status until disease recurrence, pregnancy, withdrawal of consent, death, or the end of the study. Information regarding poststudy anticancer treatment will be collected if new treatment is initiated. After disease recurrence is documented, participants will continue to be monitored for DMFS according to the SoA.

Protocol Amendment 04 implementation: the visits and procedures for all active participants outlined in Section 1.3.2 should be followed. Efficacy Follow-up Visits are not required.

8.11.4.3 DMFS Follow-up Visits

If participants discontinue study intervention without a documented DMFS event, every effort is to be made to monitor disease status by acquiring tumor scans using the same schedule calculated from the date of randomization. Participants will be assessed approximately every 12 weeks to review disease status, recent imaging, and current therapy until participants develop distant metastatic recurrence. Site investigator must collect and review copy of imaging reports, photographs and pathology reports (including imaging and biopsy/pathology assessment conducted external to site) to update disease status. A central imaging vendor will be used to collect, clean, and hold tumor imaging obtained during DMFS follow-up for possible analysis by Blinded Independent Central Review. If a participant refuses any further contact, or if a participant is discontinued from the study, the participant can authorize their site investigator to provide updated information about their tumor, anticancer treatment, well-being and overall status updates on their behalf. Radiographic imaging in the DMFS follow-up should be performed as described in the SoA and investigator assessments should be reported to the Sponsor. Information regarding poststudy anticancer treatment will be collected if new treatment is initiated.

At the time of recurrence, the participant may provide an optional fresh tumor sample.

Once participants complete all Efficacy Follow-up and DMFS follow-up visits and/or will not have further efficacy assessments, they must enter Survival Follow-up.

Protocol Amendment 04 implementation: the visits and procedures for all active participants outlined in Section 1.3.2 should be followed. DMFS Follow-up Visits are not required.

8.11.4.4 Survival Follow-up Contacts

Participant Survival Follow-up status will be assessed approximately every 12 weeks to assess for survival status until death, withdrawal of consent, or the end of the study, whichever occurs first. The collection of survival includes disease status (recurrence, progression, or new malignancy) if available or not already collected in imaging scans; record of further anticancer therapies and the outcomes in accordance with local regulations and participant consent.

The first survival follow-up assessment should be scheduled as described below:

- For participants who discontinue treatment intervention and who will not enter Efficacy Follow-up, the first survival follow-up contact will be scheduled 12 weeks after the Discontinuation Visit and/or Safety Follow-up Visit (whichever is last).
- For participants who completed assessments in Efficacy Follow-up, the first survival follow-up contact will be scheduled 12 weeks after the last efficacy assessment follow-up visit has been performed.

In the event that a participant refuses any further contact, or if a participant is discontinued from the study, the participant can authorize their site investigator to provide updated information about their tumor, anticancer treatment, well-being, and overall status updates on their behalf.

Protocol Amendment 04 implementation: the visits and procedures for all active participants outlined in Section 1.3.2 should be followed. No Survival Follow-up Contact is required.

8.11.5 Vital Status

To ensure current and complete survival information (vital status) is available at the time of database locks, updated vital status may be requested during the study by the Sponsor. For example, updated vital status may be requested before but not limited to, an eDMC review, interim and/or final analysis. Upon Sponsor notification, all participants who do not/will not have a scheduled study visit or study contact during the Sponsor-defined period will be contacted for their vital status.

Protocol Amendment 04 implementation: the visits and procedures for all active participants outlined in Section 1.3.2 should be followed. No further contact is required for Vital Status.

9 STATISTICAL ANALYSIS PLAN

This section outlines the statistical analysis strategy and procedures for the study. If, after the study has begun, changes are made to primary and/or key secondary hypotheses, or the statistical methods related to those hypotheses, then the protocol will be amended (consistent with ICH Guideline E-9). Changes to exploratory or other nonconfirmatory analyses made after the protocol has been finalized, but before the conduct of any analysis, will be documented in a sSAP and referenced in the CSR for the study. Separate analysis plans may be developed for PK/modeling analysis, biomarker analysis, and genetic data analysis. Post hoc exploratory analyses will be clearly identified in the CSR. The PRO analysis plan will also be included in the sSAP.

Protocol Amendment 04 implementation: Following eDMC interim review of the data, the experimental arm (Arm A: MK-7684A) will be discontinued and all ongoing participants will move to the comparator arm (Arm B: pembrolizumab monotherapy) for the remainder of the study.

9.1 Statistical Analysis Plan Summary

Key elements of the SAP are summarized below. The comprehensive plan is provided in Section 9.2 – Responsibility for Analyses/In-house Blinding through Section 9.12 – Extent of Exposure.

Study Design Overview	A Phase 3, Randomized, Double-blind, Active-Comparator-Controlled Clinical Study of Adjuvant MK-7684A (Vibostolimab with Pembrolizumab) Versus Adjuvant Pembrolizumab in Participants with High-risk Stage II-IV Melanoma (KEYVIBE-010)
Treatment Assignment	Approximately 1560 participants will be randomized in about 20 months (double-blind) in a 1:1 ratio between 2 treatment arms: • Arm A: MK-7684A as adjuvant therapy or • Arm B: Pembrolizumab as adjuvant therapy. Stratification factors are: • Risk-based Stage (IIB/IIC/clinical IIB and IIC/IIIA/IIIB vs IIIC/IIID/IV) • Region (Asia or ROW)
Analysis Populations	Efficacy: ITT Safety: APaT PRO: PRO FAS
Primary Endpoint	Recurrence-free survival
Key Secondary Endpoint(s)	• DMFS • OS
Statistical Methods for Key Efficacy Analyses	The primary hypothesis (RFS) and key secondary hypothesis (DMFS and OS) will be evaluated by comparing MK-7684A to pembrolizumab using a stratified log-rank test. The HR will be estimated using a stratified Cox regression model. Event rates over time will be estimated within each treatment group using the Kaplan-Meier method.
Statistical Methods for Key Safety Analyses	For analyses in which 95% CIs will be provided for differences between treatment groups in the percentage of participants with events, these analyses will be performed using the Miettinen and Nurminen method [Miettinen, O. and Nurminen, M. 1985].

Interim Analyses	**Efficacy** Five efficacy IAs and a final analysis are planned in this study. Results will be reviewed by an eDMC. Details are provided in Section 9.7 –Interim Analyses. Interim Analysis 1 (IA1): Timing: to be performed when ~ 111 RFS events have been observed, about 17 months after the first participant is randomized Primary purpose: nonbinding futility analysis of RFS Interim Analysis 2 (IA2): Timing: to be performed when ~ 372 RFS events have been observed, about 38 months after the first participant is randomized Primary purpose: efficacy analysis of RFS, DMFS, and OS Interim Analysis 3 (IA3): Timing: to be performed when ~ 451 RFS events have been observed, about 52 months after the first participant is randomized Primary purpose: efficacy analysis of RFS, DMFS, and OS Interim Analysis 4 (IA4): Timing: to be performed when ~ 355 DMFS events have been observed, about 68 months after the first participant is randomized Primary purpose: efficacy analysis of DMFS and OS Interim Analysis 5 (IA5): Timing: to be performed when ~ 218 OS events have been observed, about 80 months after the first participant is randomized Primary purpose: efficacy analysis of OS Final analysis (FA): Timing: to be performed when ~ 247 OS events have been observed, or 92 months after the first participant is randomized, whichever occurs first. Primary purpose: efficacy analysis of OS **Safety** The eDMC will review safety data periodically in the study. Safety analyses will also be performed at the time of interim efficacy analyses. Details will be specified in the DMC charter.
Multiplicity	The overall Type-I error rate over the 1 primary and 2 secondary efficacy hypotheses will be strongly controlled at 2.5% (one-sided) using a step-down approach of Maurer and Bretz [Maurer, W. and Bretz, F. 2013], with alpha passing from RFS to DMFS to OS.
Sample Size and Power	The planned sample size is approximately 1560 participants. There will be ~ 451 events at the RFS final analysis. The study has 91% power for detecting a HR of 0.73 at a one-sided 2.5% alpha level. It is estimated that there will be ~ 355 events at the DMFS final analysis (ie, IA4 of the study). With 355 DMFS events, the study has ~ 83% power for detecting a HR of 0.73 at a one-sided 2.5% alpha level. There will be ~ 247 deaths at the OS final analysis. With 247 deaths, the study has ~ 64% power for detecting a HR of 0.74 at a one-sided 2.5% alpha level.

9.2 Responsibility for Analyses/In-house Blinding

The statistical analysis of the data obtained from this study will be the responsibility of the Clinical Biostatistics Department of the Sponsor.

This study will be conducted as a double-blind study under in-house blinding procedures. The official, final database will not be unblinded until medical/scientific review has been performed, protocol deviations have been identified, and data have been declared final and complete.

The Sponsor will generate the randomized allocation schedule(s) for study treatment assignment for this protocol, and the randomization will be implemented in an IVRS.

Blinding issues with respect to planned IAs are described in Section 9.7 – Interim Analyses.

Protocol Amendment 04: Following eDMC review of the data at IA1, no additional efficacy data analysis will be conducted at subsequent IAs; information regarding planned IAs in Section 9 is being retained for historical purposes. No PRO analysis will be conducted.

9.3 Hypotheses/Estimation

Objectives and hypotheses of the study are stated in Section 3 – Hypotheses, Objectives, and Endpoints.

9.4 Analysis Endpoints

Efficacy and safety endpoints that will be evaluated are listed below.

9.4.1 Efficacy Endpoints

9.4.1.1 Primary Efficacy Endpoint

Recurrence-free Survival (RFS)

RFS is defined as the time from randomization to any recurrence (local, locoregional, regional or distant) as assessed by the investigator, or death due to any cause, whichever occurs first. New incident cases of melanoma and second cancer diagnoses are not counted as events for RFS. See Section 9.6.1 – Statistical Methods for Efficacy Analyses for the definition of censoring.

9.4.1.2 Secondary Efficacy Endpoints

Distant Metastasis-free Survival

DMFS is defined as the time from randomization to the first diagnosis of a distant metastasis, or death due to any cause, whichever occurs first. Distant metastasis refers to cancer that has spread from the original (primary) tumor and beyond local tissues and lymph nodes to distant organs or distant lymph nodes.

Overall Survival

OS is defined as the time from randomization to death due to any cause.

9.4.1.3 Exploratory Endpoints

Time to Subsequent Therapy

TTST is defined as time from randomization to the date of first subsequent therapy (eg, surgical procedure, radiation therapy, antineoplastic therapy), or death due to any cause, whichever occurs first.

Progression/Recurrence-free Survival 2

PRFS2 is defined as the time between the date of randomization and the earliest of the following:

- Date of first disease progression per RECIST1.1 beyond the initial unresectable disease recurrence (unresectable local-regional disease recurrence or unresectable distant metastatic disease recurrence);
- Date of second recurrence in participants without evidence of disease after surgical procedure of a resectable first recurrence (resectable local-regional recurrences or resectable distant metastatic disease recurrence);
- Date of death.

9.4.2 Safety Endpoints

Safety measurements are described in Section 4.2.1 – Rationale for Endpoints and Section 8.3 – Safety Assessments.

9.4.3 PRO Endpoints

The following secondary PRO endpoints will be evaluated:

- Change from baseline in EORTC QLQ-C30 global health status/QoL score, physical functioning score, and role functioning score

Exploratory PRO endpoints as described in Section 4.2.1.3 will be evaluated. Details will be provided in the sSAP.

9.5 Analysis Populations

9.5.1 Efficacy Analysis Population

The ITT population will serve as the population for primary efficacy analyses. All randomized participants will be included in this population. Participants will be included in the treatment group to which they are randomized.

Details on the approach to handling missing data are provided in Section 9.6 – Statistical Methods.

9.5.2 Safety Analysis Population

Safety analyses will be conducted in the APaT population, which consists of all randomized participants who received at least one dose of study intervention. Participants will be included in the treatment group corresponding to the study treatment they actually received for the analysis of safety data using the APaT population. For most participants this will be the treatment group to which they are randomized. Participants who take incorrect study treatment for the entire treatment period will be included in the treatment group corresponding to the study treatment actually received. Any participant who receives the incorrect study treatment for one cycle, but receives the correct treatment for all other cycles, will be analyzed according to the randomized treatment group and a narrative will be provided for any events that occur during the cycle for which the participant is incorrectly dosed.

At least one laboratory or vital sign measurement obtained after at least one dose of study treatment is required for inclusion in the analysis of each specific parameter. To assess change from baseline, a baseline measurement is also required.

9.5.3 PRO Analysis Population

The PRO analyses are based on the PRO FAS population, defined as all randomized participants who have at least one PRO assessment available for the specific endpoint and have received at least one dose of study treatment. Participants will be analyzed in the treatment group to which they are randomized. The PRO FAS population will be limited to participants ≥18 years of age for analysis of the EORTC QLQ-C30.

9.6 Statistical Methods

Statistical testing and inference for safety analyses are described in Section 9.6.2. Efficacy results that will be deemed to be statistically significant after consideration of the Type-I error control strategy are described in Section 9.8. Nominal p-values may be computed for other efficacy analyses, but should be interpreted with caution due to potential issues of multiplicity, sample size, etc.

9.6.1 Statistical Methods for Efficacy Analyses

This section describes the statistical methods that address the primary and secondary objectives. Methods related to the tertiary objectives addressing PROs and other exploratory endpoints (eg, TTST) will be described in the sSAP.

The stratification factors used for randomization (see Section 6.3.2) will be applied to all stratified analyses, in particular, the stratified log-rank test, stratified Cox model. If there are small strata, for the purpose of analysis, strata will be combined to ensure sufficient number of participants, responses and events in each stratum. Details regarding the pooling strategy will be prespecified in a future sSAP amendment before the database lock for the first analysis when each applicable endpoint will be analyzed.

9.6.1.1 Recurrence-free Survival

The nonparametric Kaplan-Meier method will be used to estimate the RFS curve in each treatment group. The treatment difference in RFS will be assessed by the stratified log-rank test (based on the stratification factors defined in Section 6.3.2). A stratified Cox proportional hazard model with Efron's method of tie handling will be used to assess the magnitude of the treatment difference (ie, HR) between the treatment arms. The HR and its 95% CI from the stratified Cox model with Efron's method of tie handling and with a single treatment covariate will be reported. Kaplan-Meier estimates and the corresponding 95% CIs at specific follow-up timepoints will be provided for RFS. The stratification factors used for randomization (see Section 6.3.2 – Stratification) will be applied to both the stratified log-rank test and the stratified Cox model.

Since disease assessment is performed periodically, events such as disease recurrence and metastatic disease recurrence can occur any time in the time interval between the last assessment where the event was not documented and the assessment when the event is documented. For the primary analysis, the true date of the event will be approximated by the date of the first assessment at which event is objectively documented. Participants who do not experience a first recurrence event will be censored at the last disease assessment.

To evaluate the robustness of the RFS endpoint, a sensitivity analysis with a different set of censoring rules will be performed. For the sensitivity analysis, the true date of the event will be approximated by the date of the first assessment at which event is objectively documented, after ≤1 missed disease assessment and before new anticancer therapy is initiated, if any. Participants who experience a first recurrence immediately after ≥2 consecutive missed disease assessments or after new anticancer therapy is initiated will be censored at the last disease assessment before the earlier date of the ≥2 consecutive missed disease assessment or date the new anticancer therapy is initiated. Participants who do not experience a first recurrence event will be censored at the last disease assessment before new anticancer therapy is initiated, if any. The censoring rules for primary and sensitivity analyses of RFS are summarized in Table 8.

Table 8 Censoring Rules for Primary and Sensitivity Analyses of Recurrence-free Survival

Situation	Primary Analysis	Sensitivity Analysis
Recurrence or death documented after ≤1 missed disease assessment, and before new anticancer therapy, if any	Event at earliest date of documented recurrence or death	Event at earliest date of documented recurrence or death
Recurrence or death documented immediately after ≥2 consecutive missed disease assessments or after new anticancer therapy, if any	Event at earliest date of documented recurrence or death	Censored at last disease assessment before the earlier date of ≥2 consecutive missed disease assessment and new anticancer therapy, if any
No recurrence and no death; and new anticancer treatment is not initiated	Censored at last disease assessment	Censored at last disease assessment
No recurrence and no death; new anticancer treatment is initiated	Censored at last disease assessment	Censored at last disease assessment before new anticancer treatment

As indicated in Section 9.4.1.1, new primary melanomas will not be counted as RFS events for the primary RFS analysis. A sensitivity analysis to include new primary melanomas as RFS events will be performed to assess the robustness of the RFS endpoint.

Additional supportive unstratified analyses may also be provided. Further details of RFS sensitivity analyses will be described in the sSAP.

9.6.1.2 Distant Metastases-free Survival

The nonparametric Kaplan-Meier method will be used to estimate the survival curves. The treatment difference in risk for metastatic disease will be assessed by the stratified log-rank test. A stratified Cox proportional hazard model with Efron's method of tie handling will be used to assess the magnitude of the treatment difference (ie, the HR). The HR and its 95% CI from the stratified Cox model with a single treatment covariate will be reported. The stratification factors used for randomization (see Section 6.3.2 – Stratification) will be applied, as stratification factors used for analysis, to both the stratified log-rank test and the stratified Cox model. Participants without documented metastatic disease diagnosis (and alive) will be censored at the date of their last disease assessment.

Additional supportive unstratified analyses may also be provided. Further details of DMFS sensitivity analyses will be described in the sSAP as needed.

9.6.1.3 Overall Survival

The nonparametric Kaplan-Meier method will be used to estimate the survival curves. The treatment difference in survival will be assessed by the stratified log-rank test. A stratified Cox proportional hazard model with Efron's method of tie handling will be used to assess the magnitude of the treatment difference (ie, the HR). The HR and its 95% CI from the stratified Cox model with a single treatment covariate will be reported. The stratification factors used for randomization (see Section 6.3.2 – Stratification) will be applied, as stratification factors used for analysis, to both the stratified log-rank test and the stratified Cox model. Kaplan-Meier estimates and the corresponding 95% CIs at specific follow-up timepoints will be provided for OS. Participants without documented death at the time of the analysis will be censored at the date of the last follow-up.

Additional supportive unstratified analyses may also be provided. Further details of OS sensitivity analyses will be described in the sSAP as needed.

9.6.1.4 Summary of Statistical Methods for Efficacy

Table 9 summarizes the primary analysis approach for primary and secondary efficacy endpoints. Sensitivity analysis methods are described above for each endpoint as applicable.

Methods related to exploratory objectives (and supportive analyses including TTST and PRFS2) will be described in the sSAP.

The strategy to address multiplicity issues concerning multiple efficacy endpoints, multiple populations, and interim analyses is described in Section 9.7 – Interim Analyses and in Section 9.8 – Multiplicity.

Table 9 Analysis Strategy for Key Efficacy Endpoints

Endpoint/Variable (Description, Time Point)	Statistical Method[a]	Analysis Population	Missing Data Approach
Primary Hypothesis 1			
RFS	Test: Stratified log-rank test Estimation: Stratified Cox model with Efron's tie handling method	ITT	See Table 8 for censoring rules
Secondary Hypothesis 2			
DMFS	Test: Stratified log-rank test Estimation: Stratified Cox model with Efron's tie handling method	ITT	Censored at last known disease evaluation
Secondary Hypothesis 3			
OS	Test: Stratified log-rank test Estimation: Stratified Cox model with Efron's tie handling method	ITT	Censored at last known alive date

DMFS=distant metastasis free survival; ITT=intent-to-treat: OS=overall survival; RFS=recurrence-free survival.
[a] Statistical models are described in further details in the text. For stratified analyses, the stratification factors used for randomization will be used as stratification factors for analysis.

9.6.2 Statistical Methods for Safety Analyses

9.6.2.1 Overall Safety Assessment

The overall safety evaluation will include a summary by treatment group of the number and percentage of participants with at least one AE, a drug-related AE, a serious AE, a serious drug-related AE, a Grade 3 to 5 AE, a discontinuation from study intervention due to an AE, and an AE resulting in death. Point estimates and 95% CIs for the differences between treatment groups in the percentages of participants with the event will be provided based on the criteria described below.

Point estimate and 95% CIs for the difference between treatment groups in the percentage of participants with specific AEs will be provided if at least 10% of participants in any treatment group report the event. The threshold of at least 10% of participants was chosen because the population enrolled in this study is in critical condition and usually experiences various AEs of similar types regardless of treatment; events reported less frequently than 10% of participants would obscure the assessment of the overall safety profile and add little to the interpretation of potentially meaningful treatment differences. In addition, difference in the percentage of participants with specific Grade 3 to 5 AEs (≥5% of participants in 1 of the treatment groups) and SAEs (≥5% of participants in 1 of the treatment groups) will also be summarized by point estimate and 95% CIs.

CIs for the differences between treatment group will be provided using the Miettinen and Nurminen method [Miettinen, O. and Nurminen, M. 1985]. Because many 95% CIs may be provided without adjustment for multiplicity, the CIs should be regarded as a helpful descriptive measure to be used in safety review, not as a formal method for assessing the statistical significance of the between-group differences. Table 10 summarizes the analysis strategy for safety endpoints in this study.

Table 10 Analysis Strategy for Safety Parameters

Analysis Part	Safety Endpoint	Descriptive Statistics	95% Between-group CI (Graphical Display)
Overall Safety Assessment	Specific AEs (incidence ≥10% of participants in one of the treatment groups)	X	X
	Specific Grade 3-5 AE (incidence ≥5% of participants in one of the treatment groups)	X	X
	Specific serious AE (incidence ≥5% of participants in one of the treatment groups)	X	X
	Any AE	X	-
	Any Grade 3-5 AE	X	-
	Any serious AE	X	-
	Any drug-related AE	X	-
	Any serious and drug-related AE	X	-
	Any Grade 3-5 and drug-related AE	X	-
	Discontinuation study treatment due to AE	X	-
	AE that resulted in death	X	-
	AE that led to dose interruption	X	-
	Specific AEs, SOCs (incidence < 10% of participants in all of the treatment groups)	X	-
	Change from Baseline Results (laboratory test result toxicity shift, vital signs)	X	-
Assessment of safety topics of special interest	Pembrolizumab AEOSI	X	-

AE=adverse event; AEOSI=adverse event(s) of special interest; CI=confidence interval; SOC=system organ class.

9.6.2.2 Assessment of Safety Topics of Special Interest

AEs that are immune-mediated or potentially immune-mediated will be evaluated separately. These events have been characterized consistently throughout the pembrolizumab clinical

development program. Point estimates and 95% CIs for between-group difference is not expected to add value to the safety evaluation, and hence only number and percentage of participants with such pembrolizumab AEOSI will be provided, as well as the number and percentage of participants with corticosteroids administration to treat an AEOSI. Summary statistics will be provided for the analysis of time from first dose to the onset of an AEOSI.

9.6.3 Statistical Methods for Patient-Reported Outcome Analyses

The time point for the mean change from baseline will be determined based on blinded data review before the database lock for any PRO analysis and documented in the sSAP.

To assess the treatment effects on the PRO score change from baseline in the EORTC QLQ-C30 global health status/QoL, physical functioning, and role functioning, and the EQ-5D-5L VAS outcome, mixed model repeated measures will be applied [Verbeke, G. and Molenberghs, G. 2009], with the change from baseline in the PRO score as the response variable, treatment, time as fixed effects, baseline endpoint score, and stratification factors used for randomization (Section 6.3.2) as covariates.

The treatment difference in terms of LS mean change from baseline will be estimated from this model together with 95% CI. Model-based LS mean with 95% CI will be provided by treatment group for PRO scores at baseline and postbaseline time point.

Additional details for the PRO analyses will be described in the sSAP.

9.6.4 Summaries of Demographic and Baseline Characteristics

The comparability of the treatment groups for each relevant demographic and baseline characteristic will be assessed by the use of tables and/or graphs. No statistical hypothesis tests will be performed on these characteristics. The number and percentage of participants screened and randomized and the primary reasons for screening failure and discontinuation will be displayed. Demographic variables, baseline characteristics, primary and secondary diagnoses, and prior and concomitant therapies will be summarized by treatment either by descriptive statistics or categorical tables.

9.7 Interim Analyses

Study enrollment may be ongoing at the time of IA1 (Table 11). Blinding to treatment assignment will be maintained at all investigational sites. The results of IAs will not be shared with the investigators before the completion of the study. Participant-level unblinding will be restricted to an internal unblinded (or external, as appropriate) statistician and scientific programmer performing the IA, who will have no other responsibilities associated with the study.

An eDMC will serve as the primary reviewer of the results of the IA (analyses) of the study and will make recommendations for discontinuation of the study or protocol modifications to an executive committee of the Sponsor. If the eDMC recommends modifications to the design of the protocol or discontinuation of the study, this executive committee (and potentially other limited Sponsor personnel) may be unblinded to results at the treatment-

level results to act on these recommendations. The extent to which individuals are unblinded with respect to results of IAs will be documented by the unblinded statistician. Additional logistic details will be provided in the eDMC charter.

Treatment-level results from the IA will be provided to the eDMC by the unblinded statistician. Before final study unblinding, the unblinded statistician will not be involved in any discussions regarding modifications to the protocol, statistical methods, identification of protocol deviations, or data validation efforts after the IAs.

9.7.1 Efficacy Interim Analyses

Five interim analyses are planned in addition to the final analysis for this study. For the interim and final analyses, all randomized participants will be included. Results of the interim analyses will be reviewed by the eDMC. Details of the boundaries for establishing statistical significance concerning efficacy are discussed further in Section 9.8 – Multiplicity.

The analyses planned, endpoints evaluated, and drivers of timing are summarized in Table 11.

Table 11 Analyses Planned, Endpoints Evaluated, and Drivers of Timing

Analyses	Key Endpoints	Timing	Estimated Time After First Participant Randomized	Primary Purpose of Analysis
IA1	RFS	~ 111 RFS events observed	~ 17 months	RFS Nonbinding futility IA
IA2	RFS, DMFS[a], OS[a]	(1) enrollment is completed, and (2) ~ 372 RFS events observed	~ 38 months	RFS IA DMFS IA OS IA
IA3	RFS, DMFS[a], OS[a]	~ 451 RFS events observed	~ 52 months	RFS FA DMFS IA OS IA
IA4	DMFS, OS	~ 355 DMFS events observed	~ 68 months	DMFS FA OS IA
IA5	OS	~ 218 OS events observed	~ 80 months	OS IA
FA	OS	(1) 96 months after the first participant randomized, or (2) ~ 247 OS events observed, whichever occurs earlier	~ 92 months	OS FA

DMFS=distant metastasis-free survival; FA=final analysis; IA=interim analysis; OS=overall survival; RFS=recurrence-free survival.
[a] DMFS/OS will be tested only if RFS is positive based on the multiplicity strategy defined in Section 9.8.

9.7.2 Safety Interim Analyses

The eDMC will be responsible for periodic interim safety reviews as specified in the eDMC charter. Interim safety analyses will also be performed at the time of interim efficacy analyses. Details will be specified in the DMC charter.

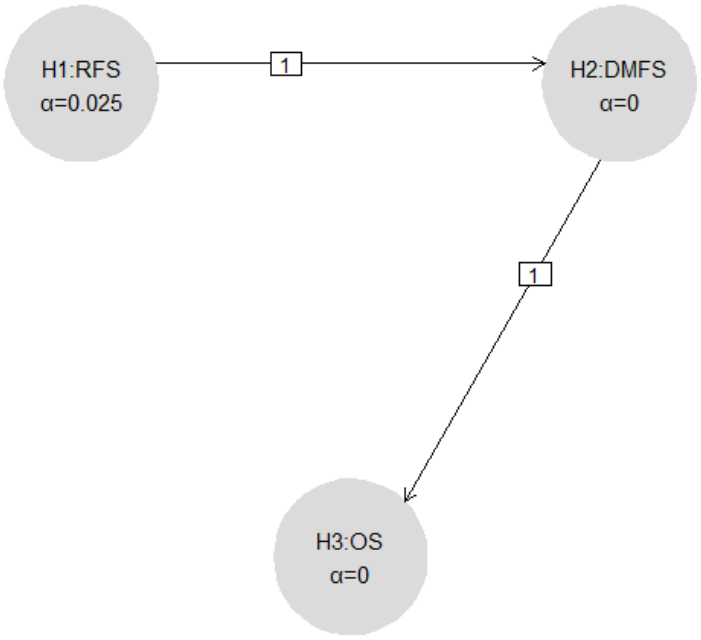
9.8 Multiplicity

The multiplicity strategy specified in this section will be applied to the primary hypothesis and 2 secondary hypotheses. The primary hypothesis tests the superiority of MK-7684A to pembrolizumab with respect to RFS. The 2 secondary hypotheses test the superiority of MK-7684A to pembrolizumab with respect to DMFS and OS. The overall Type-I error among the 3 hypotheses is strongly controlled at 2.5% (one-sided), with 2.5% initially allocated to the RFS hypothesis. The study will be considered a success if RFS is shown to be statistically significant at either an interim analysis or the final analysis under multiplicity control.

The study uses the graphical method of Maurer and Bretz [Maurer, W. and Bretz, F. 2013] to control multiplicity for multiple hypotheses as well as interim analyses. According to this approach, when a particular null hypothesis is rejected, the alpha allocated to that hypothesis can be reallocated to other hypothesis tests.

Figure 2 shows that the initial one-sided α allocation is assigned to the RFS hypothesis. Should the RFS comparison be statistically significant, the 2.5% alpha will be reallocated to the DMFS comparison. Should the DMFS comparison be statistically significant, the 2.5% alpha will be reallocated to the OS comparison.

Figure 2 Multiplicity Graph for Type-I Error Control of Study Hypotheses



DMFS=distant metastasis-free survival; H=hypothesis; OS=overall survival; RFS=recurrence-free survival.
Note: DMFS will only be tested if RFS null hypothesis is rejected at one-sided α = 0.025. OS will only be tested if both DMFS and OS null hypothesis are rejected at one-sided α = 0.025.

9.8.1 Recurrence-free Survival

The first interim analysis is to perform an RFS-based nonbinding futility check when ~111 RFS events have been observed. IA1 is estimated to occur at ~ 17 months after the first participant is randomized. Table 12 shows the probability of continuing study based on different assumptions for true HR for RFS. In addition, safety and efficacy data in all subjects will also be reviewed by eDMC as part of the totality of the data in order for eDMC to make any recommendation of potential modifications of study conduct.

Table 12 Probability of Continuing Study Based on Different Assumptions for True HR of RFS at IA1

Futility Bar of Observed HR	**True HR of RFS**	**Probability of Observing a HR<0.95[a] and Continuing Study**
0.95	0.63	98.5%
0.95	0.73	91.7%
0.95	0.83	76.2%
0.95	0.93	54.5%
0.95	1.03	33.5%
0.95	1.13	18.0%
0.95	1.23	8.7%
0.95	1.33	3.8%

HR=hazard ratio; RFS=recurrence-free survival.
[a] Assuming ~ 111 RFS events have occurred among randomized participants

The study initially allocates $\alpha = 2.5\%$, one-sided to test RFS. Table 13 shows the boundary properties for the interim efficacy analyses, which were derived using a Lan-DeMets alpha-spending function approximating O'Brien-Fleming bounds. Note that the final row indicates the total power to reject the null hypothesis for RFS.

If the actual number of RFS events at the interim and final analyses differs from those specified in the table, the bounds will be updated using this spending function evaluated at the observed information fraction (fraction of observed over expected final events) at each analysis.

Table 13 Boundary Properties for Planned Analyses of the RFS Analyses Based on α = 0.025

Analysis	Value	Efficacy
IA 2: 82%[a]	Z[b]	2.2103
N: 1560	p (1-sided)[b]	0.0135
Events: 372	HR[c] at bound	0.7950
Month: 37.3	P(Cross)[d] if HR=1	0.0135
	P(Cross)[d] if HR=0.73	0.7922
Final (IA3)	Z[b]	2.0317
N: 1560	p (1-sided)[b]	0.0211
Events: 451	HR[c] at bound	0.8258
Month: 51.3	P(Cross)[d] if HR=1	0.0250
	P(Cross)[d] if HR=0.73	0.9095

HR=hazard ratio; IA=interim analysis; N=number; RFS=recurrence-free survival.
[a] Percentage of total number of events expected at final analysis
[b] Boundary values for statistical significance
[c] HR at bound is the approximate HR required to reach an efficacy bound
[d] Probability of crossing boundary for statistical significance

9.8.2 Distant Metastases-free Survival

The study initially allocates α = 0.0 to test DMFS. If the null hypothesis for RFS is rejected, α = 0.025, one-sided is fully reallocated to DMFS hypothesis testing.

Table 14 shows the boundary properties for the interim analysis and final analysis, which were derived using a Lan-DeMets alpha-spending function approximating O'Brien-Fleming bounds. Note that the final row indicates the total power to reject the null hypothesis for DMFS.

If the actual number of DMFS events at the interim and final analyses differs from those specified in the table, the bounds will be updated using this spending function evaluated at the observed information fraction (fraction of observed over expected final events) at each analysis.

Table 14 Efficacy Boundaries and Properties for the DMFS Analyses

Analysis	Value	Efficacy
IA 2: 73%[a]	Z[b]	2.3779
N: 1560	p (1-sided)[b]	0.0087
Events: 259	HR[c] at bound	0.7441
Month: 37.3	P(Cross)[d] if HR=1	0.0087
	P(Cross)[d] if HR=0.73	0.5589
IA 3: 90%[a]	Z[b]	2.1612
N: 1560	p (1-sided)[b]	0.0153
Events: 318	HR[c] at bound	0.7846
Month: 51.3	P(Cross)[d] if HR=1	0.0179
	P(Cross)[d] if HR=0.73	0.7492
Final (IA4)	Z[b]	2.0686
N: 1560	p (1-sided)[b]	0.0193
Events: 355	HR[c] at bound	0.8027
Month: 67.4	P(Cross)[d] if HR=1	0.0250
	P(Cross)[d] if HR=0.73	0.8293

DMFS=distant metastasis-free survival; HR=hazard ratio; IA=interim analysis; N=number.
[a] Percentage of total number of events expected at final analysis
[b] Boundary values for statistical significance
[c] HR at bound is the approximate HR required to reach an efficacy bound
[d] Probability of crossing boundary for statistical significance

9.8.3 Overall Survival

The study initially allocates $\alpha = 0$, to test OS. If the null hypothesis for DMFS is rejected then $\alpha = 0.025$, one-sided is fully reallocated to OS hypothesis testing. Table 15 shows the boundary properties for the planned interim and final analysis, which were derived using a Lan-DeMets alpha-spending function approximating O'Brien-Fleming bounds. Note that the final row indicates the total power to reject the null hypothesis for OS.

If the actual number of OS events at the interim and final analyses differs from those specified in the table, the bounds will be updated using this spending function evaluated at the observed information fraction (fraction of observed over expected final events) at each analysis.

Table 15 Efficacy Boundaries and Properties for the OS Analyses

Analysis	Value	Efficacy
IA 2: 38%[a]	Z[b]	3.4483
N: 1560	p (1-sided)[b]	0.0003
Events: 94	HR[c] at bound	0.4909
Month: 37.3	P(Cross)[d] if HR=1	0.0003
	P(Cross)[d] if HR=0.74	0.0233
IA 3: 56%[a]	Z[b]	2.7824
N: 1560	p (1-sided)[b]	0.0027
Events: 139	HR[c] at bound	0.6233
Month: 51.3	P(Cross)[d] if HR=1	0.0028
	P(Cross)[d] if HR=0.74	0.1574
IA 4: 75%[a]	Z[b]	2.3794
N: 1560	p (1-sided)[b]	0.0087
Events: 185	HR[c] at bound	0.7044
Month: 67.2	P(Cross)[d] if HR=1	0.0096
	P(Cross)[d] if HR=0.74	0.3762
IA 5: 88%[a]	Z[b]	2.1975
N: 1560	p (1-sided)[b]	0.0140
Events: 218	HR[c] at bound	0.7423
Month: 79.7	P(Cross)[d] if HR=1	0.0170
	P(Cross)[d] if HR=0.74	0.5275
Final	Z[b]	2.0674
N: 1560	p (1-sided)[b]	0.0194
Events: 247	HR[c] at bound	0.7685
Month: 91.8	P(Cross)[d] if HR=1	0.0250
	P(Cross)[d] if HR=0.74	0.6410

HR=hazard ratio; IA=interim analysis; N=number; OS=overall survival.
[a] Percentage of total number of events expected at final analysis
[b] Boundary values for statistical significance
[c] HR at bound is the approximate HR required to reach an efficacy bound
[d] Probability of crossing boundary for statistical significance

9.8.4 Safety Analyses

The eDMC has responsibility for assessment of overall risk/benefit. When prompted by safety concerns, the eDMC can request corresponding efficacy data. External DMC review of efficacy data to assess the overall risk/benefit to study participants will not require a multiplicity adjustment typically associated with a planned interim efficacy analysis; however, to account for any multiplicity concerns raised by the eDMC review of unplanned efficacy data prompted by safety concerns, a sensitivity analysis for RFS adopting a conservative multiplicity adjustment will be prespecified in the sSAP. This analysis will be performed if efficacy data is requested by the eDMC during a safety evaluation to assess risk/benefit.

9.9 Sample Size and Power Calculations

The study will randomize approximately 1560 participants in a 1:1 ratio between MK-7684A adjuvant treatment and pembrolizumab adjuvant treatment. RFS is the primary endpoint for the study, with DMFS and OS as the key secondary endpoints.

9.9.1 Recurrence-free Survival

RFS is the primary endpoint. The final analysis of RFS is event-driven and will be conducted after approximately 451 RFS events have been observed, unless the study is terminated early. It may occur at ~ 52 months after the first participant is randomized (depending on enrollment rate and event accumulation rate).

With an alpha of 2.5% (one-sided) and sample size of 1560, the study has an overall ~ 91% power for RFS, assuming the true HR (MK-7684A vs. pembrolizumab) is 0.73. These calculations are based on the following assumptions: (1) RFS follows an “cure” model with a long-term RFS for pembrolizumab monotherapy of 56% and the 18-month RFS estimated to be 77%; (2) an enrollment period of 20 months and at least 32 months follow-up; and (3) a monthly drop-out rate of 0.4%.

9.9.2 Distant Metastases-free Survival

DMFS is a secondary endpoint. The final analysis of DMFS is event-driven and will be conducted after approximately 355 DMFS events have been observed, unless the study is terminated early. It may occur at ~ 68 months after the first participant is randomized (depending on enrollment rate and event accumulation rate).

Should the comparisons of RFS be statistically significant, an alpha of 2.5% (one-sided) will be available for testing DMFS. With a sample size of 1560, the study has ~ 83% power for DMFS, assuming the true HR (MK-7684A vs. pembrolizumab) is 0.73. These calculations are based on the following assumptions: (1) DMFS follows an “cure” model with a long-term DMFS for pembrolizumab monotherapy of 68% and the 18-month DMFS estimated to be 84%; (2) an enrollment period of 20 months and at least 48 months follow-up; and (3) a monthly drop-out rate of 0.4%.

9.9.3 Overall Survival

OS is a secondary endpoint. The final analysis of OS is event and calendar driven. It will be conducted (1) ~ 96 months after the first participant randomized, or (2) ~ 247 OS events observed, whichever occurs earlier.

Should the comparisons of both RFS and DMFS be statistically significant, an alpha of 2.5% (one-sided) will be available for testing OS. With a sample size of 1560, the study has ~ 64% power for OS, assuming the true HR (MK-7684A vs. pembrolizumab) is 0.74. These calculations are based on the following assumptions: (1) OS follows an exponential distribution for pembrolizumab monotherapy with the 40-month OS estimated to be 89%; (2) an enrollment period of 20 months and at least 72 months follow-up; and (3) a monthly drop-out rate of 0.4%.

The sample size and power calculations were performed in the software R (package "gsDesign").

9.10 Subgroup Analyses

To determine whether the treatment effect is consistent across various subgroups, the estimate of the between-group treatment effect (with a nominal 95% CI) for the primary and key secondary endpoints will be estimated and plotted within each category of the following classification variables:

- Age (<65 years versus ≥65 years)
- Sex (male versus female)
- Race (white versus nonwhite)
- ECOG Performance Status (0 versus 1) or equivalent KPS (for adolescents >16 to <18 years of age) or LPS status (for adolescents ≤16 years of age) (70/80 versus 90/100)
- Region (Asia versus ROW)
- Risk-based Stage (IIB/IIC/clinical IIB and IIC/IIIA/IIIB vs IIIC/IIID/IV)

The consistency of the treatment effect will be assessed using descriptive statistics for each category of the subgroup variables listed above. If the number of participants in a category of a subgroup variable is less than 5% of the ITT population, the subgroup analysis will not be performed for this category of the subgroup variable, and this subgroup variable will not be displayed in the forest plot. The subgroup analyses for RFS, DMFS, and OS will be conducted using an unstratified Cox model.

9.11 Compliance (Medication Adherence)

Drug accountability data for study treatment will be collected during the study. Any deviation from protocol-directed administration will be reported.

9.12 Extent of Exposure

The extent of exposure will be summarized as duration of treatment in number of cycles or administrations as appropriate. Summary statistics will be provided on the Extent of Exposure for the APaT population.

10 SUPPORTING DOCUMENTATION AND OPERATIONAL CONSIDERATIONS

10.1 Appendix 1: Regulatory, Ethical, and Study Oversight Considerations

10.1.1 Code of Conduct for Clinical Trials

Merck Sharp & Dohme LLC, Rahway, NJ, USA (MSD)

I. Introduction

A. Purpose

Merck Sharp & Dohme LLC, Rahway, NJ, USA (MSD), through its subsidiaries, conducts clinical trials worldwide to evaluate the safety and effectiveness of our products. As such, we are committed to designing, planning, conducting, analyzing, and reporting these trials in compliance with the highest ethical and scientific standards. Protection of participants in clinical trials is the overriding concern in the design and conduct of clinical trials. In all cases, MSD clinical trials will be conducted in compliance with MSD's global standards, local and/or national regulations (including all applicable data protection laws and regulations), Regulation (EU) 536/2014, the International Council for Harmonisation Good Clinical Practice (ICH GCP) E6 and ICH General Considerations for Clinical Studies E8, and in accordance with the ethical principles that have their origin in the Declaration of Helsinki.

B. Scope

Highest ethical and scientific standards shall be endorsed for all clinical interventional investigations sponsored by MSD irrespective of the party (parties) employed for their execution (e.g., contract research organizations, collaborative research efforts). This Code is not intended to apply to trials that are observational in nature, or which are retrospective. Further, this Code does not apply to investigator-initiated trials, which are not under the full control of MSD.

II. Scientific Issues

A. Trial Conduct

1. Trial Design

Except for pilot or estimation trials, clinical trial protocols will be hypothesis-driven to assess safety, efficacy, and/or pharmacokinetic or pharmacodynamic indices of MSD or comparator products. Alternatively, MSD may conduct outcomes research trials, trials to assess or validate various endpoint measures, or trials to determine patient preferences, etc.

The design (i.e., participant population, duration, statistical power) must be adequate to address the specific purpose of the trial and shall respect the data protection rights of all participants, trial site staff and, where applicable, third parties. Input may be considered from a broad range of stakeholders, including patient advocacy groups/patients representing the trial population, caregivers, and

healthcare providers to ensure operational feasibility. Trial design also includes proactive identification of critical to quality factors utilizing a risk-based approach. Plans are then developed to assess and mitigate risks to those factors as appropriate during the trial. All trial protocols are and will be assessed for the need and capability to enroll underrepresented groups. Participants must meet protocol entry criteria to be enrolled in the trial.

2. Site Selection

MSD's clinical trials are conducted globally in many different countries and in diverse populations, including people of varying age, race, ethnicity, gender, and accounting for other potential disease related factors. MSD selects investigative sites based on medical expertise, access to appropriate participants, adequacy of facilities and staff, previous performance in clinical trials, as well as budgetary considerations. Prior to trial initiation, sites are evaluated by MSD personnel (or individuals acting on behalf of MSD) to assess the ability to successfully conduct the trial. Individuals involved in trial conduct receive training commensurate with their role prior to their becoming involved in the trial.

Where appropriate, and in accordance with regulatory authority guidance, MSD will make concerted efforts to raise awareness of clinical trial opportunities in various communities. MSD will seek to engage underrepresented groups and those disproportionately impacted by the disease under study. MSD will support clinical trial investigators to enroll underrepresented groups and expand access to those who will ultimately use the products under investigation.

3. Site Monitoring/Scientific Integrity

Investigative trial sites are monitored to assess compliance with the trial protocol and Good Clinical Practice (GCP). MSD reviews clinical data for accuracy, completeness, and consistency. Data are verified versus source documentation according to standard operating procedures. Per MSD policies and procedures, if potential fraud, scientific/research misconduct, privacy incidents/breaches or Clinical Trial-related Significant Quality Issues are reported, such matters are investigated. When necessary, appropriate corrective and/or preventative actions are defined and regulatory authorities and/or ethics review committees are notified.

B. Publication and Authorship

Regardless of trial outcome, MSD commits to publish the primary and secondary results of its registered trials of marketed products in which treatment is assigned, according to the pre-specified plans for data analysis. To the extent scientifically appropriate, MSD seeks to publish the results of other analyses it conducts that are important to patients, physicians, and payers. Some early phase or pilot trials are intended to be hypothesis generating rather than hypothesis testing; in such cases, publication of results may not be appropriate since the trial may be underpowered and the analyses complicated by statistical issues such as multiplicity.

MSD's policy on authorship is consistent with the recommendations published by the International Committee of Medical Journal Editors (ICMJE). In summary, authorship should reflect significant contribution to the design and conduct of the trial, performance or interpretation of the analysis, and/or writing of the manuscript. All named authors must be able to defend the trial results and conclusions. MSD funding of a trial will be acknowledged in publications.

III. Participant Protection

A. Regulatory Authority and Ethics Committee Review (Institutional Review Board [IRB]/Independent Ethics Committee [IEC])

All protocols and protocol amendments will be submitted by MSD for regulatory authority acceptance/authorization prior to implementation of the trial or amendment, in compliance with local and/or national regulations.

The protocol, protocol amendment(s), informed consent form, investigator's brochure, and other relevant trial documents must be reviewed and approved by an IRB/IEC before being implemented at each site, in compliance with local and/or national regulations and ICH Guidelines. Changes to the protocol that are required urgently to eliminate an immediate hazard and to protect participant safety may be enacted in anticipation of ethics committee approval. MSD will inform regulatory authorities of such new measures to protect participant safety, in compliance with local and/or national regulations.

B. Safety

The guiding principle in decision-making in clinical trials is that participant welfare is of primary importance. Potential participants will be informed of the risks and benefits of, as well as alternatives to, trial participation. At a minimum, trial designs will take into account the local standard of care.

All participation in MSD clinical trials is voluntary. Participants enter the trial only after informed consent is obtained. Trial designs include procedures and systems for the identification, monitoring, and reporting of safety concerns. Participants may withdraw from an MSD trial at any time, without any influence on their access to, or receipt of, medical care that may otherwise be available to them.

During trial planning, the need for an independent Data Monitoring Committee (DMC) is assessed. DMC review of data accumulated during the conduct of the trial is integral to the well-being of trial participants.

C. Confidentiality

MSD is committed to safeguarding participant confidentiality, to the greatest extent possible, as well as all applicable data protection rights. Unless required by law, only the investigator, Sponsor (or individuals acting on behalf of MSD), ethics committee, and/or regulatory authorities will have access to confidential medical records that might identify the participant by name.

D. Genomic Research

Genomic research will only be conducted in accordance with a protocol and informed consent authorized by an ethics committee.

E. Trial Results

At the time of providing informed consent and in accordance with local laws and regulations, participants should be informed about the plans for availability of trial results.

IV. Financial Considerations

A. Payments to Investigators

Clinical trials are time- and labor-intensive. It is MSD's policy to compensate investigators (or the sponsoring institution) in a fair manner for the work performed in support of MSD trials. MSD does not pay incentives to enroll participants in its trials. However, when enrollment is particularly challenging, additional payments may be made to compensate for the time spent in extra recruiting efforts.

MSD does not pay for participant referrals. However, MSD may compensate referring physicians for time spent on medical record review and medical evaluation to identify potentially eligible participants.

B. Clinical Research Funding

Informed consent forms will disclose that the trial is sponsored by MSD, and that the investigator or sponsoring institution is being paid or provided a grant for performing the trial. However, the local ethics committee may wish to alter the wording of the disclosure statement to be consistent with financial practices at that institution. As noted above, all publications resulting from MSD trials will indicate MSD as a source of funding.

C. Funding for Travel and Other Requests

Funding of travel by investigators and support staff (e.g., to scientific meetings, investigator meetings, etc) will be consistent with local guidelines and practices.

V. Investigator Commitment

Investigators will be expected to review MSD's Code of Conduct as an appendix to the trial protocol, and in signing the protocol, agree to support these ethical and scientific standards.

See Appendix 7 for country-specific requirements.

10.1.2 Financial Disclosure

Financial disclosure requirements are outlined in the US Food and Drug Administration Regulations, Financial Disclosure by Clinical Investigators (21 CFR Part 54). It is the Sponsor's responsibility to determine, based on these regulations, whether a request for

financial disclosure information is required. It is the investigator's/subinvestigator's responsibility to comply with any such request.

The investigator/subinvestigator(s) agree, if requested by the Sponsor in accordance with 21 CFR Part 54, to provide their financial interests in and/or arrangements with the Sponsor to allow for the submission of complete and accurate certification and disclosure statements. The investigator/subinvestigator(s) further agree to provide this information on a Certification/Disclosure Form, frequently known as a financial disclosure form, provided by the Sponsor. The investigator/subinvestigator(s) also consent to the transmission of this information to the Sponsor in the United States for these purposes. This may involve the transmission of information to countries that do not have laws protecting personal data.

10.1.3 Data Protection

The Sponsor will conduct this study in compliance with all applicable data protection regulations.

Participants will be assigned a unique identifier by the Sponsor. Any participant records or datasets that are transferred to the Sponsor will contain the identifier only; participant names or any information that would make the participant identifiable will not be transferred.

The participant must be informed that their personal study-related data will be used by the Sponsor in accordance with local data protection law. The level of disclosure must also be explained to the participant.

The participant must be informed that their medical records may be examined by Clinical Quality Assurance auditors or other authorized personnel appointed by the Sponsor, by appropriate IRB/IEC members, and by inspectors from regulatory authorities.

The Sponsor has EU-approved Binding Corporate Rules since 2017, covering all aspects of its Global Privacy Program (Corporate Policy 20), and is self-certified pursuant to the EU-US Data Privacy Framework.

10.1.3.1 Confidentiality of Data

By signing this protocol, the investigator affirms to the Sponsor that information furnished to the investigator by the Sponsor will be maintained in confidence, and such information will be divulged to the IRB, IEC, or similar or expert committee, affiliated institution, and employees, only under an appropriate understanding of confidentiality with such board or committee, affiliated institution, and employees. Data generated by this study will be considered confidential by the investigator, except to the extent that it is included in a publication as provided in the Publications section of this protocol.

10.1.3.2 Confidentiality of Participant Records

By signing this protocol, the investigator agrees that the Sponsor (or Sponsor representative), IRB/IEC, or regulatory authority representatives may consult and/or copy study documents to verify worksheet/CRF data. By signing the consent form, the participant agrees to this

process. If study documents will be photocopied during the process of verifying worksheet/CRF information, the participant will be identified by unique code only; full names/initials will be masked before transmission to the Sponsor.

By signing this protocol, the investigator agrees to treat all participant data used and disclosed in connection with this study in accordance with all applicable privacy laws, rules, and regulations.

10.1.3.3 Confidentiality of IRB/IEC Information

The Sponsor is required to record the name and address of each IRB/IEC that reviews and approves this study. The Sponsor is also required to document that each IRB/IEC meets regulatory and ICH GCP requirements by requesting and maintaining records of the names and qualifications of the IRB/IEC members and to make these records available for regulatory agency review upon request by those agencies.

10.1.4 Committees Structure

10.1.4.1 Executive Oversight Committee

The EOC is comprised of members of Sponsor Senior Management. The EOC will receive and decide on any recommendations made by the DMC regarding the study.

10.1.4.2 External Data Monitoring Committee

To supplement the routine study monitoring outlined in this protocol, an external DMC will monitor the interim data from this study. The voting members of the committee are external to the Sponsor. The members of the DMC must not be involved with the study in any other way (eg, they cannot be study investigators) and must have no competing interests that could affect their roles with respect to the study.

The DMC will make recommendations to the EOC regarding steps to ensure both participant safety and the continued ethical integrity of the study. Also, the DMC will review interim study results, consider the overall risk and benefit to study participants (Section 9.7 - Interim Analyses) and recommend to the EOC whether the study should continue in accordance with the protocol.

Specific details regarding composition, responsibilities, and governance, including the roles and responsibilities of the various members and the Sponsor protocol team; meeting facilitation; the study governance structure; and requirements for and proper documentation of DMC reports, minutes, and recommendations will be described in the DMC charter that is reviewed and approved by all the DMC members.

10.1.4.3 Scientific Advisory Committee (SAC)

This study was developed in collaboration with a SAC. The SAC is comprised of both Sponsor and non-Sponsor scientific experts who provide scientific and strategic guidance on

various aspects of the clinical trial and/or development, which may include study design, interpretation of study results, and subsequent peer-reviewed scientific publications.

10.1.5 Publication Policy

The results of this study may be published or presented at scientific meetings. The Sponsor will comply with the requirements for publication of study results. In accordance with standard editorial and ethical practice, the Sponsor will generally support publication of multicenter studies only in their entirety and not as individual site data. In this case, a coordinating investigator will be designated by mutual agreement.

If publication activity is not directed by the Sponsor, the investigator agrees to submit all manuscripts or abstracts to the Sponsor before submission. This allows the Sponsor to protect proprietary information and to provide comments.

Authorship will be determined by mutual agreement and in line with ICMJE authorship requirements.

10.1.6 Compliance with Study Registration and Results Posting Requirements

Under the terms of the FDAAA of 2007 and the EMA clinical trials Regulation 536/2014, the Sponsor of the study is solely responsible for determining whether the study and its results are subject to the requirements for submission to http://www.clinicaltrials.gov, www.clinicaltrialsregister.eu, https://euclinicaltrials.eu, or other local registries. MSD, as Sponsor of this study, will review this protocol and submit the information necessary to fulfill these requirements. MSD entries are not limited to FDAAA or the EMA clinical trials Regulation 536/2014 mandated trials. Information posted will allow participants to identify potentially appropriate studies for their disease conditions and pursue participation by calling a central contact number for further information on appropriate study locations and study-site contact information.

By signing this protocol, the investigator acknowledges that the statutory obligations under FDAAA, the EMA clinical trials Regulation 536/2014, or other locally mandated registries are that of the Sponsor and agrees not to submit any information about this study or its results to those registries.

10.1.7 Compliance with Law, Audit, and Debarment

By signing this protocol, the investigator agrees to conduct the study in an efficient and diligent manner and in conformance with this protocol, generally accepted standards of GCP (eg, ICH GCP: Consolidated Guideline and other generally accepted standards of GCP), and all applicable federal, state, and local laws, rules, and regulations relating to the conduct of the clinical study.

The Code of Conduct, a collection of goals and considerations that govern the ethical and scientific conduct of clinical investigations sponsored by MSD, is provided in this appendix under the Code of Conduct for Clinical Trials.

The investigator agrees not to seek reimbursement from participants, their insurance providers, or from government programs for procedures included as part of the study reimbursed to the investigator by the Sponsor.

The investigator will promptly inform the Sponsor of any regulatory authority inspection conducted for this study.

The investigator agrees to provide the Sponsor with relevant information from inspection observations/findings to allow the Sponsor to assist in responding to any citations resulting from regulatory authority inspection and will provide the Sponsor with a copy of the proposed response for consultation before submission to the regulatory authority.

Persons debarred from conducting or working on clinical studies by any court or regulatory authority will not be allowed to conduct or work on this Sponsor's studies. The investigator will immediately disclose in writing to the Sponsor if any person who is involved in conducting the study is debarred or if any proceeding for debarment is pending or, to the best of the investigator's knowledge, threatened.

For investigators located in countries with serious breach reporting requirements, investigator will promptly report to the Sponsor any serious breach or suspected serious breach that occurs in compliance with those requirements. Unless more specifically defined in the applicable requirements, a serious breach is any breach of the applicable clinical trial regulation or of the clinical trial protocol which is likely to affect to a significant degree: (i) the safety or rights of a trial participant, or (ii) the reliability and robustness of the data generated in the clinical trial.

10.1.8 Data Quality Assurance

All participant data relating to the study will be recorded on printed or electronic CRF unless transmitted to the Sponsor or designee electronically (eg, laboratory data). The investigator or qualified designee is responsible for verifying that data entries are accurate and correct by physically or electronically signing the CRF.

Detailed information regarding Data Management procedures for this protocol will be provided separately.

The investigator must maintain accurate documentation (source data) that supports the information entered in the CRF.

The investigator must permit study-related monitoring, audits, IRB/IEC review, and regulatory agency inspections and provide direct access to source data documents.

Study documentation will be promptly and fully disclosed to the Sponsor by the investigator upon request and also shall be made available at the study site upon request for inspection, copying, review, and audit at reasonable times by representatives of the Sponsor or any regulatory authorities. The investigator agrees to promptly take any reasonable steps that are requested by the Sponsor or any regulatory authorities as a result of an audit or inspection to cure deficiencies in the study documentation and worksheets/CRFs.

The Sponsor or designee is responsible for the data management of this study including quality checking of the data.

Study monitors will perform ongoing source data review and verification to confirm that data entered into the CRF by authorized site personnel are accurate, complete, and verifiable from source documents; that the safety and rights of participants are being protected; and that the study is being conducted in accordance with the currently approved protocol and any other study agreements, ICH GCP, and all applicable regulatory requirements.

Records and documents, including participants' documented informed consent, pertaining to the conduct of this study must be retained by the investigator for 15 years after study completion unless local regulations or institutional policies require a longer retention period. No records may be destroyed during the retention period without the written approval of the Sponsor. No records may be transferred to another location or party without written notification to the Sponsor.

10.1.9 Source Documents

Source documents provide evidence for the existence of the participant and substantiate the integrity of the data collected. The investigator/institution should maintain adequate and accurate source documents and study records that include all pertinent observations on each of the site's participants. Source documents and data should be attributable, legible, contemporaneous, original, accurate, and complete. Changes to source data should be traceable, should not obscure the original entry, and should be explained if necessary (eg, via an audit trail). Source documents are filed at the investigator's site.

Data reported on the CRF or entered in the eCRF that are transcribed from source documents must be consistent with the source documents or the discrepancies must be explained. The investigator/institution may need to request previous medical records or transfer records, depending on the study. Also, current medical records must be available.

10.1.10 Study and Site Closure

The Sponsor or its designee may stop the study or study-site participation in the study for medical, safety, regulatory, administrative, or other reasons consistent with applicable laws, regulations, and GCP.

In the event the Sponsor prematurely terminates a particular study site, the Sponsor or designee will promptly notify that study site's IRB/IEC as specified by applicable regulatory requirement(s).

10.2 Appendix 2: Clinical Laboratory Tests

- The tests detailed in Table 16 will be performed by the local laboratory as indicated in the SoA. Results should be reviewed pre-dose at each time point indicated in the SoA.
- Protocol-specific requirements for inclusion or exclusion of participants are detailed in Section 5 of the protocol.
- Additional tests may be performed at any time during the study as determined necessary by the investigator or required by local regulations.

The investigator (or medically qualified designee) must document their review of each laboratory safety report.

Laboratory results that could unblind the study will not be reported to investigative sites or other blinded personnel until the study has been unblinded.

Table 16 Protocol-required Safety Laboratory Assessments

Laboratory Assessments	**Parameters**			
Hematology	Platelet Count RBC Count Hemoglobin Hematocrit	RBC Indices: MCV MCH Reticulocytes		WBC count with Differential[a]: Neutrophils Lymphocytes Monocytes Eosinophils Basophils
Chemistry	BUN[b]	Potassium	AST/SGOT	Total bilirubin (and direct bilirubin, if total bilirubin is above the ULN)
	Albumin	Carbon Dioxide (CO_2) or Bicarbonate[e]	Chloride	Phosphorous
	Creatinine, CrCl[c] or GFR[d]	Sodium	ALT/SGPT	Total Protein
	Glucose (fasting or nonfasting per institutional standard)	Calcium	Alkaline phosphatase	Magnesium
	LDH			
Routine Urinalysis	• Specific gravity • pH, glucose, protein, blood, ketones, by dipstick • Microscopic examination (if blood or protein is abnormal)			
Pregnancy Testing	• Highly sensitive serum and/or urine hCG pregnancy test (as needed for WOCBP)			

Laboratory Assessments	Parameters
Other Screening Tests	• Coagulation: PT/INR and aPTT/PTT • FSH (as needed in WONCBP only) • Thyroid: T3, T4 and TSH NOTE: Free T3/T4 is acceptable if total T3/T4 cannot be determined • Serology (HIV antibody, HBsAg and/or HBV DNA, and anti-HCV antibody and/or HCV RNA) if applicable (refer to Section 5.1 and Appendix 7)

ALT=alanine aminotransferase; aPTT=activated partial thromboplastin time; AST=aspartate aminotransferase; BUN=blood urea nitrogen; FSH=follicle-stimulating hormone; GFR=glomerular filtration rate; hCG=human chorionic gonadotropin; MCH=mean corpuscular hemoglobin; MCV=mean corpuscular volume; PTT=partial thromboplastin time; RBC=red blood cell; SGOT=serum glutamic oxaloacetic transaminase; SGPT=serum glutamic pyruvic transaminase; ULN=upper limit of normal; WOCBP=women of childbearing potential; WONCBP=women of nonchildbearing potential.

[a] Absolute or % acceptable per institutional standard.

[b] BUN is preferred, but if not available, then urea may be tested. Record either BUN or urea result, but not both.

[c] Creatinine clearance should be calculated using Cockcroft-Gault:
$\frac{(140\text{-age [years]}) \times \text{weight (kg)}}{\text{Serum creatinine (mg/dL)} \times 72}$ (×F)*
*where F = 0.85 for females and F = 1 for males

[d] To individualize GFR in units of mL/min, multiply the estimate of GFR by the participant's body surface area and divide by 1.73 m^2.

[e] Perform if considered local standard of care.

10.3 Appendix 3: Adverse Events: Definitions and Procedures for Recording, Evaluating, Follow-up, and Reporting

10.3.1 Definitions of Medication Error, Misuse, and Abuse

Medication error

This is an unintended failure in the drug treatment process that leads to or has the potential to lead to harm to the patient.

Misuse

This refers to situations where the medicinal product is intentionally and inappropriately used not in accordance with the terms of the product information.

Abuse

This corresponds to the persistent or sporadic intentional, excessive use of a medicinal product for a perceived psychological or physiological reward or desired nontherapeutic effect.

10.3.2 Definition of AE

AE definition

- An AE is any untoward medical occurrence in a clinical study participant, temporally associated with the use of study intervention, whether or not considered related to the study intervention.
- Note: An AE can therefore be any unfavorable and unintended sign (including an abnormal laboratory finding), symptom, or disease (new or exacerbated) temporally associated with the use of a study intervention.
- Note: For purposes of AE definition, study intervention includes any pharmaceutical product, biological product, vaccine, diagnostic agent, medical device, combination product, or protocol-specified procedure whether investigational or marketed (including placebo, active comparator product, or run-in intervention), manufactured by, licensed by, provided by, or distributed by the Sponsor for human use in this study.

Events meeting the AE definition

- Any abnormal laboratory test results (hematology, clinical chemistry, or urinalysis) or other safety assessments (eg, ECG, radiological scans, vital signs measurements), including those that worsen from baseline, considered clinically significant in the medical and scientific judgment of the investigator.
- Exacerbation of a chronic or intermittent preexisting condition including either an increase in frequency and/or intensity of the condition.
- New conditions detected or diagnosed after study intervention administration even though it may have been present before the start of the study.

- Signs, symptoms, or the clinical sequelae of a suspected drug-drug interaction.
- Signs, symptoms, or the clinical sequelae of a suspected overdose of either study intervention or a concomitant medication.
- For all reports of overdose (whether accidental or intentional) with an associated AE, the AE term should reflect the clinical symptoms or abnormal test result. An overdose without any associated clinical symptoms or abnormal laboratory results is reported using the terminology "accidental or intentional overdose without adverse effect."
- Any new cancer (that is not a condition of the study). Progression of the cancer under study is not a reportable event. Refer to Section 8.4.6 for additional details.

Events NOT meeting the AE definition

- Medical or surgical procedure (eg, endoscopy, appendectomy): the condition that leads to the procedure is the AE.
- Situations in which an untoward medical occurrence did not occur (social and/or convenience admission to a hospital).
- Anticipated day-to-day fluctuations of preexisting disease(s) or condition(s) present or detected at the start of the study that do not worsen.
- Surgical procedure(s) planned prior to informed consent to treat a preexisting condition that has not worsened.
- Refer to Section 8.4.6 for protocol-specific exceptions.

10.3.3 Definition of SAE

If an event is not an AE per definition above, then it cannot be an SAE even if serious conditions are met.

An SAE is defined as any untoward medical occurrence that, at any dose:

a. Results in death
b. Is life-threatening

   The term "life-threatening" in the definition of "serious" refers to an event in which the participant was at risk of death at the time of the event. It does not refer to an event, which hypothetically might have caused death, if it were more severe.
c. Requires inpatient hospitalization or prolongation of existing hospitalization

   Hospitalization is defined as an inpatient admission, regardless of length of stay, even if the hospitalization is a precautionary measure for continued observation. (Note: Hospitalization for an elective procedure to treat a preexisting condition that has not worsened is not an SAE.) A preexisting condition is a clinical condition that is diagnosed prior to the use of an MSD product and is documented in the participant's medical history.
d. Results in persistent or significant disability/incapacity

   The term disability means a substantial disruption of a person's ability to conduct normal life functions.

This definition is not intended to include experiences of relatively minor medical significance such as uncomplicated headache, nausea, vomiting, diarrhea, influenza, and accidental trauma (eg, sprained ankle) that may interfere with or prevent everyday life functions but do not constitute a substantial disruption.

e. Is a congenital anomaly/birth defect

   In offspring of participant taking the product regardless of time to diagnosis.

f. Other important medical events

   Medical or scientific judgment should be exercised in deciding whether SAE reporting is appropriate in other situations such as important medical events that may not be immediately life-threatening or result in death or hospitalization but may jeopardize the participant or may require medical or surgical intervention to prevent 1 of the other outcomes listed in the above definition. These events should usually be considered serious.

   Examples of such events include invasive or malignant cancers, intensive treatment in an emergency room or at home for allergic bronchospasm, blood dyscrasias, or convulsions that do not result in hospitalization, or development of drug dependency or drug abuse.

10.3.4 Additional Events Reported

Additional events that require reporting

In addition to the above criteria, AEs meeting either of the below criteria, although not serious per ICH definition, are reportable to the Sponsor.

- Is a new cancer (that is not the cancer under study) as noted in Section 8.4.1.
- Is associated with an overdose.

10.3.5 Recording AE and SAE

AE and SAE recording

- When an AE/SAE occurs, it is the responsibility of the investigator to review all documentation (eg, hospital progress notes, laboratory, and diagnostics reports) related to the event.
- The investigator will record all relevant AE/SAE information on the AE CRFs/worksheets at each examination.
- It is not acceptable for the investigator to send photocopies of the participant's medical records to the Sponsor in lieu of completion of the AE CRF page.
- There may be instances when copies of medical records for certain cases are requested by the Sponsor. In this case, all participant identifiers, with the exception of the participant number, will be blinded on the copies of the medical records before submission to the Sponsor.
- The investigator will attempt to establish a diagnosis of the event based on signs, symptoms, and/or other clinical information. In such cases, the diagnosis (not the individual signs/symptoms) will be documented as the AE/SAE.

Assessment of intensity/toxicity

- An event is defined as "serious" when it meets at least 1 of the predefined outcomes as described in the definition of an SAE, not when it is rated as severe.
- The investigator will make an assessment of intensity for each AE and SAE (and other reportable safety event) according to the NCI CTCAE, version 5.0. Any AE that changes CTCAE grade over the course of a given episode will have each change of grade recorded on the AE CRFs/worksheets.
  - Grade 1: Mild; asymptomatic or mild symptoms; clinical or diagnostic observations only; intervention not indicated.
  - Grade 2: Moderate; minimal, local or noninvasive intervention indicated; limiting age-appropriate instrumental ADL.
  - Grade 3: Severe or medically significant but not immediately life-threatening; hospitalization or prolongation of hospitalization indicated; disabling; limiting self-care ADL.
  - Grade 4: Life threatening consequences; urgent intervention indicated.
  - Grade 5: Death related to AE.

Assessment of causality

- Did the Sponsor's product cause the AE?
- The determination of the likelihood that the Sponsor's product caused the AE will be provided by an investigator who is a qualified physician. The investigator's signed/dated initials on the source document or worksheet that supports the causality noted on the AE form, ensures that a medically qualified assessment of causality was done. This initialed document must be retained for the required regulatory time frame. The criteria below are intended as reference guidelines to assist the investigator in assessing the likelihood of a relationship between the test product and the AE based upon the available information.
- **The following components are to be used to assess the relationship between the Sponsor's product and the AE; the greater the correlation with the components and their respective elements (in number and/or intensity), the more likely the Sponsor's product caused the AE:**
  - **Exposure:** Is there evidence that the participant was actually exposed to the Sponsor's product such as: reliable history, acceptable compliance assessment (pill count, diary, etc), expected pharmacologic effect, or measurement of drug/metabolite in bodily specimen?
  - **Time Course:** Did the AE follow in a reasonable temporal sequence from administration of the Sponsor's product? Is the time of onset of the AE compatible with a drug-induced effect (applies to studies with IMP)?
  - **Likely Cause:** Is the AE not reasonably explained by another etiology such as underlying disease, other drug(s)/vaccine(s), or other host or environmental factors.
  - **Dechallenge:** Was the Sponsor's product discontinued or dose/exposure/frequency reduced?
    - If yes, did the AE resolve or improve?

- If yes, this is a positive dechallenge.
- If no, this is a negative dechallenge.

(NOTE: This criterion is not applicable if: (1) the AE resulted in death or permanent disability; (2) the AE resolved/improved despite continuation of the Sponsor's product; (3) the study is a single-dose drug study; or (4) Sponsor's product(s) is/are only used 1 time.)

- Rechallenge: Was the participant re-exposed to the Sponsor's product in this study?
  - If yes, did the AE recur or worsen?
  - If yes, this is a positive rechallenge.
  - If no, this is a negative rechallenge.

(NOTE: This criterion is not applicable if: (1) the initial AE resulted in death or permanent disability, or (2) the study is a single-dose drug study; or (3) Sponsor's product(s) is/are used only 1 time.)

NOTE: IF A RECHALLENGE IS PLANNED FOR AN AE THAT WAS SERIOUS AND MAY HAVE BEEN CAUSED BY THE SPONSOR'S PRODUCT, OR IF RE-EXPOSURE TO THE SPONSOR'S PRODUCT POSES ADDITIONAL POTENTIAL SIGNIFICANT RISK TO THE PARTICIPANT THEN THE RECHALLENGE MUST BE APPROVED IN ADVANCE BY THE SPONSOR CLINICAL DIRECTOR AS PER DOSE MODIFICATION GUIDELINES IN THE PROTOCOL, AND IF REQUIRED, THE INIRB/IEC.

- **Consistency with study intervention profile:** Is the clinical/pathological presentation of the AE consistent with previous knowledge regarding the Sponsor's product or drug class pharmacology or toxicology?
- The assessment of relationship will be reported on the case report forms/worksheets by an investigator who is a qualified physician according to their best clinical judgment, including consideration of the above elements.
- Use the following scale of criteria as guidance (not all criteria must be present to be indicative of a Sponsor's product relationship).
  - Yes, there is a reasonable possibility of Sponsor's product relationship:
    - There is evidence of exposure to the Sponsor's product. The temporal sequence of the AE onset relative to the administration of the Sponsor's product is reasonable. The AE is more likely explained by the Sponsor's product than by another cause.
  - No, there is not a reasonable possibility of Sponsor's product relationship:
    - Participant did not receive the Sponsor's product OR temporal sequence of the AE onset relative to administration of the Sponsor's product is not reasonable OR the AE is more likely explained by another cause than the Sponsor's product. (Also entered for a participant with overdose without an associated AE.)
- The investigator must review and provide an assessment of causality for each AE/SAE and document this in the medical notes.

- There may be situations in which an SAE has occurred and the investigator has minimal information to include in the initial report to the Sponsor. However, it is very important that the investigator always make an assessment of causality for every event before the initial transmission of the SAE data to the Sponsor.
- The investigator may change their opinion of causality in light of follow-up information and send an SAE follow-up report with the updated causality assessment.
- The causality assessment is 1 of the criteria used when determining regulatory reporting requirements.
- For studies in which multiple agents are administered as part of a combination regimen, the investigator may attribute each AE causality to the combination regimen or to a single agent of the combination. In general, causality attribution should be assigned to the combination regimen (ie, to all agents in the regimen). However, causality attribution may be assigned to a single agent if in the investigator's opinion, there is sufficient data to support full attribution of the AE to the single agent.

Follow-up of AE and SAE

- The investigator is obligated to perform or arrange for the conduct of supplemental measurements and/or evaluations as medically indicated or as requested by Sponsor to elucidate the nature and/or causality of the AE or SAE as fully as possible. This may include additional laboratory tests or investigations, histopathological examinations, or consultation with other health care professionals.
- New or updated information will be recorded in the CRF.
- The investigator will submit any updated SAE data to the Sponsor within 24 hours of receipt of the information.

10.3.6 Reporting of AEs, SAEs, and Other Reportable Safety Events to the Sponsor

AE, SAE, and other reportable safety event reporting to Sponsor via electronic data collection tool

- The primary mechanism for reporting to the Sponsor will be the EDC tool.
  - Electronic reporting procedures can be found in the EDC data entry guidelines (or equivalent).
  - If the electronic system is unavailable for more than 24 hours, then the site will use the paper AE Reporting form.
  - Reference Section 8.4.1 for reporting time requirements.
- The site will enter the SAE data into the electronic system as soon as it becomes available.
- After the study is completed at a given site, the EDC tool will be taken off-line to prevent the entry of new data or changes to existing data.
- If a site receives a report of a new SAE from a study participant or receives updated data on a previously reported SAE after the EDC tool has been taken off-line, then the site can report this information on a paper SAE form or by telephone (see next section).

- Contacts for SAE reporting can be found in the Investigator Study File Binder (or equivalent).

SAE reporting to the Sponsor via paper CRF

- If the EDC tool is not operational, facsimile transmission or secure email of the SAE paper CRF is the preferred method to transmit this information to the Sponsor.
- In rare circumstances and in the absence of facsimile equipment, notification by telephone is acceptable with a copy of the SAE data collection tool sent by overnight mail or courier service.
- Initial notification via telephone does not replace the need for the investigator to complete and sign the SAE CRF pages within the designated reporting time frames.
- Contacts and instructions for SAE reporting and paper reporting procedures can be found in the Investigator Study File Binder (or equivalent).

10.4 Appendix 4: Medical Device and Drug–Device Combination Products: Product Quality Complaints/Malfunctions: Definitions, Recording, and Follow-up

Not applicable.

10.5 Appendix 5: Contraceptive Guidance

10.5.1 Definitions

Women of Childbearing Potential (WOCBP)

A woman is considered fertile following menarche and until becoming postmenopausal unless permanently sterile (see below):

If fertility is unclear (eg, amenorrhea in adolescents or athletes) and a menstrual cycle cannot be confirmed before first dose of study intervention, additional evaluation should be considered.

Women in the following categories are not considered WOCBP:

- Premenarchal
- Premenopausal female with 1 of the following:
  - Documented hysterectomy
  - Documented bilateral salpingectomy
  - Documented bilateral oophorectomy

For individuals with permanent infertility due to an alternate medical cause other than the above (eg, Mullerian agenesis, androgen insensitivity), investigator discretion should be applied to determining study entry.

Note: Documentation can come from the site personnel's review of the participant's medical records, medical examination, or medical history interview.

- Postmenopausal female
  - A postmenopausal state is defined as no menses for 12 months without an alternative medical cause.
    - A high FSH level in the postmenopausal range may be used to confirm a postmenopausal state in women not using hormonal contraception or HRT. However, in the absence of 12 months of amenorrhea, confirmation with 2 FSH measurements in the postmenopausal range is required.
  - Females on HRT and whose menopausal status is in doubt will be required to use one of the non-hormonal highly effective contraception methods if they wish to continue their HRT during the study. Otherwise, they must discontinue HRT to allow confirmation of postmenopausal status before study enrollment.

10.5.2 Contraceptive Requirements

Contraceptives allowed during the study include[a]:
Highly Effective Contraceptive Methods That Have Low User Dependency[b] *Failure rate of <1% per year when used consistently and correctly.*
• Progestogen-only subdermal contraceptive implant[c] • IUS[c,d] • Non-hormonal IUD • Bilateral tubal occlusion
• Azoospermic partner (vasectomized or secondary to medical cause) This is a highly effective contraception method provided that the partner is the sole male sexual partner of the WOCBP and the absence of sperm has been confirmed. If not, an additional highly effective method of contraception should be used. A spermatogenesis cycle is approximately 90 days. Note: Documentation of azoospermia for a male participant can come from the site personnel's review of the participant's medical records, medical examination, or medical history interview.
Highly Effective Contraceptive Methods That Are User Dependent[b] *Failure rate of <1% per year when used consistently and correctly***.**
• Combined (estrogen- and progestogen- containing) hormonal contraception[c] - Oral - Intravaginal - Transdermal - Injectable
• Progestogen-only hormonal contraception[c] - Oral - Injectable
Sexual Abstinence • Sexual abstinence is considered a highly effective method only if defined as refraining from heterosexual intercourse during the entire period of risk associated with the study intervention. The reliability of sexual abstinence needs to be evaluated in relation to the duration of the study and the preferred and usual lifestyle of the participant.
[a] Contraceptive use by men or women should be consistent with local regulations regarding the use of contraceptive methods for participants of clinical studies. [b] Typical use failure rates are higher than perfect-use failure rates (ie, when used consistently and correctly) [c] If locally required, in accordance with CTFG guidelines, acceptable hormonal contraceptives are limited to those which inhibit ovulation. [d] IUS is a progestin releasing IUD. Note: The following are not acceptable methods of contraception: - Periodic abstinence (calendar, symptothermal, post-ovulation methods), withdrawal (coitus interruptus), spermicides only, and LAM. - Male condom with cap, diaphragm, or sponge with spermicide. - Male and female condom should not be used together (due to risk of failure with friction).

10.6 Appendix 6: Collection and Management of Specimens for Future Biomedical Research

1. Definitions

a. Biomarker: A biological molecule found in blood, other body fluids, or tissues that is a sign of a normal or abnormal process or of a condition or disease. A biomarker may be used to see how well the body responds to a treatment for a disease or condition.[1]

b. Pharmacogenomics: The investigation of variations of DNA and RNA characteristics as related to drug/vaccine response.[2]

c. Pharmacogenetics: A subset of pharmacogenomics, pharmacogenetics is the influence of variations in DNA sequence on drug/vaccine response.[2]

d. DNA: Deoxyribonucleic acid.

e. RNA: Ribonucleic acid.

2. Scope of Future Biomedical Research[3, 4]

The specimens consented and/or collected in this study as outlined in Section 8.8 will be used in various experiments to understand:

- The biology of how drugs/vaccines work
- Biomarkers responsible for how a drug/vaccine enters and is removed by the body
- Other pathways with which drugs/vaccines may interact
- The biology of disease

The specimen(s) may be used for future assay development and/or drug/vaccine development.

It is now well recognized that information obtained from studying and testing clinical specimens offers unique opportunities to enhance our understanding of how individuals respond to drugs/vaccines, enhance our understanding of human disease, and ultimately improve public health through development of novel treatments targeted to populations with the greatest need. All specimens will be used by the Sponsor or those working for or with the Sponsor.

3. Summary of Procedures for Future Biomedical Research[3, 4]

a. Participants for Enrollment
All participants enrolled in the clinical study will be considered for enrollment in future biomedical research.

b. Informed Consent
Informed consent for specimens (ie, DNA, RNA, protein, etc) will be obtained during screening for protocol enrollment from all participants or legal guardians, at a study visit by the investigator or their designate. Informed consent for future biomedical research should be presented to the participants on the visit designated in the SoA. If delayed, present consent at next possible Participant Visit. Consent forms signed by the participant will be kept at the clinical study site under secure storage for regulatory reasons.

A template of each study site's approved informed consent will be stored in the Sponsor's clinical document repository.

c. eCRF Documentation for Future Biomedical Research Specimens
Documentation of participant consent for future biomedical research will be captured in the eCRFs. Any specimens for which such an informed consent cannot be verified will be destroyed.

d. Future Biomedical Research Specimen(s)
Collection of specimens for future biomedical research will be performed as outlined in the SoA. In general, if additional blood specimens are being collected for future biomedical research, these will usually be obtained at a time when the participant is having blood drawn for other study purposes.

4. Confidential Participant Information for Future Biomedical Research[3, 4]

In order to optimize the research that can be conducted with future biomedical research specimens, it is critical to link participants' clinical information with future test results. In fact, little or no research can be conducted without connecting the clinical study data to the specimen. The clinical data allow specific analyses to be conducted. Knowing participant characteristics like sex, age, medical history, and intervention outcomes is critical to understanding clinical context of analytical results.

To maintain privacy of information collected from specimens obtained for future biomedical research, the Sponsor has developed secure policies and procedures. All specimens will be single coded per ICH E15 guidelines as described below.

At the clinical study site, unique codes will be placed on the future biomedical research specimens. This code is a random number that does not contain any personally identifying information embedded within it. The link (or key) between participant identifiers and this unique code will be held at the study site. No personal identifiers will appear on the specimen tube.

5. Biorepository Specimen Usage[3, 4]

Specimens obtained for the Sponsor will be used for analyses using good scientific practices. Analyses using the future biomedical research specimens may be performed by the Sponsor, or an additional third party (eg, a university investigator) designated by the Sponsor. The investigator conducting the analysis will follow the Sponsor's privacy and confidentiality requirements. Any contracted third-party analyses will conform to the specific scope of analysis outlined in future biomedical research protocol and consent. Future biomedical research specimens remaining with the third party after specific analysis is performed will be reported to the Sponsor.

6. Withdrawal From Future Biomedical Research[3, 4]

Participants may withdraw their consent for FBR and ask that their biospecimens not be used for FBR. Participants may withdraw consent at any time by contacting the study investigator. If medical records for the study are still available, the investigator will contact the Sponsor using the designated mailbox (clinical.specimen.management@MSD.com). Subsequently, the participant's specimens will be flagged in the biorepository and restricted to study use only. If specimens were collected from study participants specifically for FBR, these specimens will be removed from the biorepository and destroyed. Documentation will be sent to the investigator confirming withdrawal and/or destruction, if applicable. It is the responsibility of the investigator to inform the participant of completion of the withdrawal and/or destruction,

if applicable. Any analyses in progress at the time of request for withdrawal/destruction or already performed before the request being received by the Sponsor will continue to be used as part of the overall research study data and results. No new analyses would be generated after the request is received.

If the medical records for the study are no longer available (eg, if the investigator is no longer required by regulatory authorities to retain the study records) or the specimens have been completely anonymized, there will no longer be a link between the participant's personal information and their specimens. In this situation, the request for withdrawal of consent and/or destruction cannot be processed.

7. **Retention of Specimens[3, 4]**
   Future biomedical research specimens will be stored in the biorepository for potential analysis for up to 20 years from the end of the study. Specimens may be stored for longer if a regulatory or governmental authority has active questions that are being answered. In this special circumstance, specimens will be stored until these questions have been adequately addressed.

   Specimens from the study site will be shipped to a central laboratory and then shipped to the Sponsor-designated biorepository. If a central laboratory is not used in a particular study, the study site will ship directly to the Sponsor-designated biorepository. The specimens will be stored under strict supervision in a limited access facility, which operates to assure the integrity of the specimens. Specimens will be destroyed according to Sponsor policies and procedures and this destruction will be documented in the biorepository database.

8. **Data Security[3, 4]**
   Databases containing specimen information and test results are accessible only to the authorized Sponsor representatives and the designated study administrator research personnel and/or collaborators. Database user authentication is highly secure, and is accomplished using network security policies and practices based on international standards to protect against unauthorized access.

9. **Reporting of Future Biomedical Research Data to Participants[3, 4]**
   No information obtained from exploratory laboratory studies will be reported to the participant, family, or physicians. Principle reasons not to inform or return results to the participant include lack of relevance to participant health, limitations of predictive capability, and concerns regarding misinterpretation.

   If important research findings are discovered, the Sponsor may publish results, present results in national meetings, and make results accessible on a public website in order to rapidly report this information to doctors and participants. Participants will not be identified by name in any published reports about this study or in any other scientific publication or presentation.

10. **Future Biomedical Research Study Population[3, 4]**
    Every effort will be made to recruit all participants diagnosed and treated on Sponsor clinical studies for future biomedical research.

11. Risks Versus Benefits of Future Biomedical Research[3, 4]

For future biomedical research, risks to the participant have been minimized and are described in the future biomedical research informed consent.

The Sponsor has developed strict security, policies, and procedures to address participant data privacy concerns. Data privacy risks are largely limited to rare situations involving possible breach of confidentiality. In this highly unlikely situation, there is risk that the information, like all medical information, may be misused.

12. Questions

Any questions related to the future biomedical research should be emailed directly to clinical.specimen.management@MSD.com.

13. References

1. National Cancer Institute [Internet]: Available from https://www.cancer.gov/publications/dictionaries/cancer-terms?cdrid=45618
2. International Council on Harmonisation [Internet]: E15: Definitions for Genomic Biomarkers, Pharmacogenomics, Pharmacogenetics, Genomic Data and Sample Coding Categories. Available from http://www.ich.org/products/guidelines/efficacy/efficacy-single/article/definitions-for-genomic-biomarkers-pharmacogenomics-pharmacogenetics-genomic-data-and-sample-cod.html
3. Industry Pharmacogenomics Working Group [Internet]: Understanding the Intent, Scope and Public Health Benefits of Exploratory Biomarker Research: A Guide for IRBs/IECs and Investigational Site Staff. Available at http://i-pwg.org/
4. Industry Pharmacogenomics Working Group [Internet]: Pharmacogenomics Informational Brochure for IRBs/IECs and Investigational Site Staff. Available at http://i-pwg.org/

10.7 Appendix 7: Country-specific Requirements

10.7.1 Argentina

Section 1.3 – Schedule of Activities

HBV, HCV, and HIV testing at screening is mandatory.

10.7.2 Austria

Section 5.1 Inclusion Criteria

Pediatric participants (<18 years of age) will not be enrolled in Austria.

10.7.3 Belgium

Section 5.1 Inclusion Criteria

Pediatric participants (<18 years of age) will not be enrolled in Belgium.

10.7.4 France

Section 5.1 Inclusion Criteria

Pediatric participants (<18 years of age) will not be enrolled in France.

10.7.5 United Kingdom

Section 5.1 Inclusion Criteria

Pediatric participants (<16 years of age) will not be enrolled in the United Kingdom.

Section 6.5 Concomitant Therapy

Listed below are specific concomitant therapies or vaccinations that are prohibited during the study (exceptions noted):

- Live vaccines must not be administered for 90 days after the last dose of study intervention. Refer to Section 6.5 for information on COVID-19 vaccines.

  NOTE: Any licensed COVID-19 vaccine (including for Emergency Use) in a particular country is allowed in the study as long as they are mRNA vaccines, replication-incompetent adenoviral vaccines, or inactivated vaccines. These vaccines will be treated just as any other concomitant therapy.

10.7.6 Ireland

Section 5.1 Inclusion Criteria

Pediatric participants (<18 years of age) will not be enrolled in Ireland.

Section 6.5 Concomitant Therapy

Listed below are specific concomitant therapies or vaccinations that are prohibited during the study (exceptions noted):

- Live vaccines must not be administered for 90 days after the last dose of study intervention. Refer to Section 6.5 for information on COVID-19 vaccines.

  NOTE: Any licensed COVID-19 vaccine (including for Emergency Use) in a particular country is allowed in the study as long as they are mRNA vaccines, replication-incompetent adenoviral vaccines, or inactivated vaccines. These vaccines will be treated just as any other concomitant therapy.

10.7.7 Germany

Throughout the Protocol:

Legally Acceptable Representative

Persons of legal age, who are incapable of comprehending the nature, significance and implications of the clinical study and of determining their will, are generally excluded from the participation in a clinical study at German sites as per AMG § 40b sentence 4 and 5.

Therefore all references to a participant's "legally acceptable representative" in the protocol are not applicable for participants in Germany.

Exclusion of minors as per German Drug Law (AMG) § 40b sentence 3

In compliance with German Drug Law no patients below the legal age of 18 will be enrolled in the study.

Exclusion of persons who per order of court or authorities have been accommodated in an institution as per German Drug Law (AMG) § 40a sentence 2

Persons, who have been committed to an institution by virtue of an order issued either by the judicial or the administrative authorities are excluded from participation in this clinical study in Germany.

Section 5.1 – Inclusion Criteria:

Inclusion Criterion 10: HIV testing is required at Screening for participants.

Inclusion Criteria 11 and 12: Hepatitis B and C testing is required at Screening for participants.

Explanation concerning inclusion of persons who may be dependent on the Sponsor or investigator according to GCP-V §7 sentence 3 no. 3

Relatives of Sponsor or investigators are not excluded from participation in this clinical study according to the inclusion and exclusion criteria. The Sponsor considers it unacceptable in oncology studies to deny the above patient group access to study therapies that may be superior to current standard care.

Section 8.2.1 Tumor Imaging and Assessment of Disease

The process for scan collection and transmission to the iCRO can be found in the SIM. Tumor scans by CT are strongly preferred. For the abdomen and pelvis, contrast-enhanced MRI may be used when CT with iodinated contrast is contraindicated, or when mandated by local practice. The same scan technique should be used in a participant throughout the study to optimize the reproducibility of the assessment of existing and new tumor burden and improve the accuracy of the response assessment based on scans.

CLARIFICATION

Per SIM Option 4, MRI is acceptable as replacement for CT if contraindicated medically and/or not aligned with local practice.

10.7.8 Poland

Section 5.1 Inclusion Criteria

Pediatric participants (<18 years of age) will not be enrolled in Poland.

10.7.9 Romania

Section 1.3 Schedule of Activities

HIV testing at screening is mandatory.

Hepatitis B and C testing at Screening is mandatory.

Section 5.1 – Inclusion Criteria

Inclusion Criteria 11 and 12: Hepatitis B and C testing is required at Screening for participants.

10.7.10 Spain

Section 5.1 Inclusion Criteria

Pediatric participants (<18 years of age) will not be enrolled in Spain.

10.7.11 Sweden

Section 4.2.1.2 Safety Endpoints

Safety parameters commonly used for evaluating investigational systemic anticancer treatments are included as safety endpoints including, but not limited to, the incidence of, causality, and outcome of AEs/SAEs; and changes in vital signs and laboratory values. Adverse events will be assessed as defined by CTCAE, v5.0.

Section 5.1 Inclusion Criteria

Pediatric participants (<18 years of age) will not be enrolled in Sweden.

Section 10.1 Appendix 1: Regulatory, Ethical, and Study Oversight Considerations

10.1.1 Code of Conduct for Clinical Trials

III. Participant Protection

A. Ethics Committee Review (IRB/IEC) and Health Authorities

The protocol, protocol amendments, ICF, Investigator Brochure, and other relevant documents must be submitted to and approved by the applicable Competent Authority and IRB/IEC before the study is initiated in accordance with EU Directive 2001/20/EC, Article 10 (a) and/or local requirements. Any amendments to the protocol will require IRB/IEC and Competent Authority approval before implementation of changes made to the study design, except for changes necessary to eliminate an immediate hazard to study participants [2001/20/EC, Article 10 (c)].

- Study and Site Closure

The Sponsor or its designee may stop the study or study site participation in the study for medical, safety, regulatory, administrative, or other reasons consistent with applicable laws, regulations, and GCP.

In the event the Sponsor prematurely terminates a particular study site, the Sponsor will promptly notify that study site's IRB/IEC.

In the EU [CT-1 (2010/C 82/01)], the Sponsor must send immediate end-of-study notification to the national competent authority and the Ethics Committee of the Member State concerned. The end-of-study notification must be sent within 15 days after the study is halted to clearly describe the reasons and follow-up measures, if any, taken for safety reasons. The 15-day notification applies only for early termination of the study. Otherwise the time window to send end-of-study notification is 90 days in the EU.

10.7.12 Italy

Section 1.3 – Schedule of Activities

HBV, HCV, and HIV testing at screening is mandatory.

Section 5.1 Inclusion Criteria

Pediatric participants (<18 years of age) will not be enrolled in Italy.

Section 5.2 – Exclusion Criteria

- Has a known history of HIV infection
- History of Hepatitis B (defined as HBsAg reactive) or known active Hepatitis C virus (defined as detectable HCV RNA [qualitative]) infection

10.7.13 South Africa

Section 1.3 – Schedule of Activities

HBV, HCV, and HIV testing at screening is mandatory.

Section 5.2 – Exclusion Criteria

- History of Hepatitis B (defined as HBsAg reactive) or known active Hepatitis C virus (defined as detectable HCV RNA [qualitative]) infection

10.7.14 China

Biomarker sample collection, testing and analysis as described in the following sections will be dependent on approval by the Human Genetic Resources Administration of China for participants enrolled in China:

Section 1.3 – Schedule of Activities

Section 4.2.1.6 – Planned Exploratory Biomarker Research

Section 5.1 – Inclusion Criteria

Section 5.2 – Exclusion Criteria

Section 8.1.13 – Tumor Tissue for Biomarker Status

Section 8.8 – Biomarkers

FBR will not be conducted in China.

10.7.15 Peru

Section 1.3 – Schedule of Activities

HBV, HCV, and HIV testing at Screening is mandatory.

10.7.16 Brazil

Section 5.1 Inclusion Criteria

Pediatric participants (<18 years of age) will not be enrolled in Brazil.

Section 1.3 – Schedule of Activities

FBR will not be conducted in Brazil.

Section 8.8 – Biomarkers

FBR will not be conducted in Brazil.

10.8 Appendix 8: Melanoma Staging

The AJCC has designated staging by TNM classification to define melanoma.

Staging tables are adapted from the AJCC, Eighth Edition. Refer to the AJCC guidelines for more information [Gershenwald, J. E., et al 2017b].

Staging tables are provided as follows:

[Table 17]	Melanoma T Category Definition
[Table 18]	Melanoma N Category Definition
[Table 19]	Melanoma M Category Definition
[Table 20]	AJCC Pathological (pTNM) Staging Groups
[Table 21]	AJCC Clinical Prognostic (cTNM) Staging Groups

Table 17 Melanoma T Category Definition

T-Stage	**T-Stage Definition (Thickness and Ulceration)**
TX	Primary tumor thickness cannot be assessed (ulceration status not applicable)
T0	No evidence of primary tumor (ulceration status not applicable)
Tis	Melanoma in situ (ulceration status not applicable)
T1	≤1.0 mm (ulceration status unknown or unspecified)
T1a	<0.8 mm without ulceration
T1b	<0.8 mm with ulceration or 0.8-1.0 mm with or without ulceration
T2	>1.0-2.0 mm (ulceration status unknown or unspecified)
T2a	>1.0-2.0 mm without ulceration
T2b	>1.0-2.0 mm with ulceration
T3	>2.0-4.0 mm (ulceration status unknown or unspecified)
T3a	>2.0-4.0 mm without ulceration
T3b	>2.0-4.0 mm with ulceration
T4	>4.0 mm (ulceration status unknown or unspecified)
T4a	>4.0 mm without ulceration
T4b	>4.0 mm with ulceration
AJCC = American Joint Committee on Cancer; T = primary tumor.	

Table 18 Melanoma N Category Definition

N Category	Number of Tumor-Involved Regional Lymph Nodes	Presence of In-transit, Satellite, and/or Microsatellite Metastases
NX	Regional Nodes not assessed (exception: pathological N category not required for T1 melanomas, use clinical N information)	No
N0	No regional metastases detected	No
N1	One tumor-involved node or any number of in-transit, satellite, and/or microsatellite metastases with no tumor-involved nodes	
N1a	One clinically occult (detected by SLN biopsy)	No
N1b	One clinically detected	No
N1c	No regional lymph node disease	Yes
N2	Two or 3 tumor-involved nodes or any number of in-transit, satellite, and/or microsatellite metastases with one tumor-involved node	
N2a	Two or 3 clinically occult (detected by SLN biopsy)	No
N2b	Two or 3, at least one of which was clinically detected	No
N2c	One clinically occult or clinically detected	Yes
N3	Four or more tumor-involved nodes or any number of in-transit, satellite, and/or microsatellite metastases with 2 or more tumor-involved nodes, or any number of matted nodes without or with in-transit, satellite, and/or microsatellite metastases	
N3a	Four or more clinically occult (detected by SLN biopsy)	No
N3b	Four or more, at least one of which was clinically detected, or the presence of any number of matted nodes	No
N3c	Two or more clinically occult or clinically detected and/or presence of any number of matted nodes	Yes

N = Regional Lymph Node

Table 19 Melanoma M Category Definition

M Category	**Anatomic Site**	**Lactate Dehydrogenase Level**
M0	No evidence of distant metastasis	Not applicable
M1	Evidence of distant metastasis	See below
M1a	Distant metastasis to skin, soft tissue including muscle, and/or nonregional lymph node	Not recorded or unspecified
M1a(0)		Not elevated
M1a(1)		Elevated
M1b	Distant metastasis to lung with or without M1a sites of disease	Not recorded or unspecified
M1b(0)		Not elevated
M1b(1)		Elevated
M1c	Distant metastasis to noncentral nervous system visceral sites with or without M1a or M1b sites of disease	Not recorded or unspecified
M1c(0)		Not elevated
M1c(1)		Elevated
M1d	Distant metastasis to CNS with or without M1a, M1b, or M1c sites of disease	Not recorded or unspecified
M1d(0)		Not elevated
M1d(1)		Elevated
M = Distant Metastasis		

Table 20 AJCC Pathological (pTNM) Staging Groups

Staging (AJCC Eighth Edition)			
0	Tis	N0	M0
IA	T1a	N0	M0
IA	T1b	N0	M0
IB	T2a	N0	M0
IIA	T2b	N0	M0
IIA	T3a	N0	M0
IIB	T3b	N0	M0
IIB	T4a	N0	M0
IIC	T4b	N0	M0
IIIB	T0	N1b, N1c	M0
IIIC	T0	N2b, N2c, N3b, N3c	M0
IIIA	T1a/b-T2a	N1a or N2a	M0
IIIB	T1a/b-t2a	N1b/c or N2b	M0
IIIB	T2b/T3a	N1a-N2b	M0
IIIC	T1a-T3a	N2c or N3a/b/c	M0
IIIC	T3b/T4a	Any N≥N1	M0
IIIC	T4b	N1a-N2c	M0
IIID	T4b	N3a/b/c	M0
IV	Any T, Tis	Any N	M1

M0 = No evidence of distant metastases; N0 = No regional metastasis detected including no tumor-involved nodes and no in-transit, satellite, and/or microsatellite metastasis.

Table 21 AJCC Clinical Prognostic (cTNM) Staging Groups

Staging (AJCC Eighth Edition)			
0	Tis	N0	M0
IA	T1a	N0	M0
IB	T1b	N0	M0
IB	T2a	N0	M0
IIA	T2b	N0	M0
IIA	T3a	N0	M0
IIB	T3b	N0	M0
IIB	T4a	N0	M0
IIC	T4b	N0	M0
III	Any T, Tis	≥N1	M0
IV	Any T	Any N	M1

M0 = No evidence of distant metastases; N0 = No regional metastasis detected including no tumor-involved nodes and no in-transit, satellite, and/or microsatellite metastasis.

10.9 Appendix 9: Guidance for Distinguishing Primary Cutaneous Melanomas from Cutaneous Metastases of Melanoma

If the diagnosis is made in the context of an appropriate clinical history, it is usually not difficult to establish a correct pathologic diagnosis of either primary cutaneous melanoma or cutaneous metastasis of melanoma. Occasionally it may be extremely difficult to definitively determine whether a melanoma is a primary tumor, or a metastasis based on pathological examination alone. This is particularly the case for a melanoma in the dermis that lacks an in situ component in the overlying epidermis. In many instances, such tumors represent a primary melanoma with regression of the superficial dermal and epidermal components. The pathologist should recognize this phenomenon by the presence of some subtle clues such as:

1. The presence of rare single atypical epidermal melanocytes,
2. Epidermal thinning with loss of rete ridges,
3. Fibrosis and vascular proliferation in the dermis overlying the lesion,
4. Defect in the band of superficial solar elastosis,
5. Bandlike lymphohistiocytic inflammatory cell infiltrate which usually includes numerous pigment-laden macrophages.

In cases where difficulty remains, it is prudent to examine microscopically additional tissue from the lesion, including further sections cut from the original and additional tissue blocks.

In some instances, it is impossible to be certain from the pathologic features alone whether a melanoma is primary or metastatic. In such cases, correlation with clinical information is essential, as this may provide further and critical clues (eg, a history of a pigmented plaque that disappeared over time leaving a lump in the dermis would be strong evidence in favor of a primary melanoma with a regressed superficial/epidermal component). Furthermore, some primary melanomas may arise in the dermis without origin from the epidermis, including some cases of desmoplastic melanoma, melanomas arising in congenital nevi and blue nevus-like melanoma. The presence of an associated, benign nevus component is evidence favoring that a lesion is a primary melanoma and not metastatic melanoma.

Some metastatic melanomas can show prominent epidermotropism, mimicking a primary tumor. In most epidermotropic melanomas the overlying junctional change does not extend beyond the dermal component. The presence of multiple foci of intralymphatic tumor may be a clue to recognizing epidermotropic melanoma.

Although the presence of subtle nuclear pleomorphism, occasional mitotic figures and an associated lymphoid infiltrate may provide pathologic clues to the correct diagnosis, correlation with clinical information is, as always, essential in reaching a final diagnosis [Gershenwald, J. E., et al 2017b] [Scolyer, R. A., et al 2020].

10.10 Appendix 10: Surgical Considerations

Recommendation for Surgical Management:

a. Wide excision with a 1-2 cm clinical margin surrounding the primary lesion or biopsy scar is recommended for entry on to this protocol. If the primary melanoma is completely resected within the wide excision margin, the resection is acceptable.
b. For lesions with Breslow's thickness >2 mm, a 2 cm minimum clinical margin is recommended when anatomically feasible. On other body sites with limited tissue availability a narrower margin is acceptable to avoid excessive morbidity.
c. For subungual melanoma, interphalangeal metacarpal/metatarsal-phalangeal amputation with histologically negative margins constitutes an adequate wide excision.
d. The specimen shall be excised to include skin and all subcutaneous tissue down to the muscular or deep fascia. Fascia may be included at the discretion of the operating surgeon.
e. The pathology report should report surgical margins and whether surgical resection margins are involved with the tumor, including close margin (eg, <1 mm between tumor and resection margin) and tumor abutting margin.

Closure of the defect (eg, primary advancement flap closure, split thickness skin graft, complex reconstruction) is at the discretion of the surgeon.

Therapeutic lymph node dissection for macroscopic disease

For this study a therapeutic axillary lymph node dissection is required for macroscopic disease (ie, clinically, radiographically, sonographically [if performed] detectable nodes).

Axillary Lymphadenectomy:

Axillary node dissection must include all involved nodes or at least 10 nodes are required for adequacy if this exceeds the number of involved nodes taken from Levels I and II and the Level III nodes. The boundaries of the dissection should include the axillary vein superiorly beginning at the thoracic outlet and coursing to the latissimus dorsi tendon. The lateral border of the dissection is the anterior edge of the latissimus dorsi muscle. The posterior boundary is the subscapular muscle. The anterior border of the resection is the pectoralis major group. The inferior boundary of the dissection should be the juncture of the latissimus dorsi and the serratus anterior muscles.

The contents within these boundaries should be completely removed with the exception of the long thoracic nerve and the thoracodorsal nerve, which should be identified during the dissection and preserved throughout. As stated, the pectoralis minor muscle may be divided or sacrificed with the specimen at the discretion of the surgeon. Care should be exercised that in the superior part of the dissection, the anterior pectoral nerve is not injured. The preferable approach to the axilla is through a horizontal incision in the line of the skin crease, 3 or 4 cm below the apex of the skin fold of the axilla.

Inguinal Lymphadenectomy:

A superficial femoral node dissection should be performed by excising all of the nodes inferior to the inguinal ligament and bounded by the medical border of the sartorius muscle in the lateral border of the adductor magnus muscle. The fatty and lymphatic tissues should be dissected carefully off the femoral vessels and nerves all the way up to the inguinal canal and for 3 cm superior to the inguinal ligament. The saphenous vein is resected to ensure complete excision of the lymph nodes. Transposition of the sartorius muscle should be considered (but is not mandatory) to cover the femoral vessels after complete lymphatic excision. Ideally, this area should be entered through a curvilinear incision staring laterally over the inguinal ligament and curving medially and inferiorly ending over the midpoint of the adductor magnus muscle. A minimum of 5 nodes must be resected for adequacy if this exceeds the detected number of involved nodes.

Deep Inguinal and External Iliac Node Dissection:

Deep inguinal and external iliac node dissection can be most easily approached by incising the abdominal wall musculature 3 or 4 cm superior to the inguinal ligament. This incision is taken down through the external oblique, internal oblique and transversus muscles, and the surgeon at that point stays extraperitoneally as in the approach to the iliac vessels for renal transplantation. With this approach, the external, internal and common iliac arteries are exposed and the lymphatics coursing among the iliac vessels are excised. A full ilioinguinal (deep) inguinal node dissection is advised in case of overt inguinal node- metastasis and when Cloquet’s node is positive.

(Modified) Radical Neck Dissection:

Classic or modified radical neck dissection must be performed for patients with melanoma of the head and neck and involved nodes. A minimum of 15 nodes must be resected for adequacy if this exceeds the detected number of involved nodes. Patients with melanoma located on the ear and anterior scalp and face require superficial parotidectomy along with a radical neck procedure. The boundaries of the radical neck dissection are inferiorly the clavicle; the mandible, the mastoid and the tail of the parotid gland superiorly; the anterior border of the trapezius muscle posteriorly and the strap muscle of the larynx anteriorly. The sternocleidomastoid muscle may be sacrificed or preserved at the surgeon's discretion. For posterior nodes, the radical neck incision must be extended posteriorly or a second incision must be made so that the suboccipital nodal group can be resected. For posterior neck dissection, surgical and pathological resection of at least 5 nodes are required for adequacy if this exceeds the detected number of involved nodes.

10.11 Appendix 11: Abbreviations

Abbreviation	Expanded Term
Ab	antibody
ADA	antidrug antibodies
AE	adverse event
AEOSI	adverse event of special interest
AJCC	American Joint Committee on Cancer
ALP	alkaline phosphatase
ALT	alanine aminotransferase
ANC	absolute neutrophil count
APaT	All Participants as Treated
ART	antiretroviral therapy
AST	aspartate aminotransferase
AUC	area under the curve
AxMP	auxiliary medicinal product
BCC	basal cell carcinoma
C	cycle
CD	cluster of differentiation
cHL	classical Hodgkin lymphoma
CI	confidence interval
CL	clearance
CLND	complete lymph node dissection
C_{max}	maximum plasma concentration
CNS	central nervous system
CONSORT	Consolidated Standards of Reporting Trials
COPD	chronic obstructive pulmonary disease
COVID-19	Coronavirus Disease 2019
CrCl	creatinine clearance
(e)CRF	(electronic) Case Report Form
CSR	clinical study report
CT	computed tomography
CTCAE	Common Terminology Criteria for Adverse Events
ctDNA	circulating tumor DNA
CTFG	Clinical Trial Facilitation Group
CTLA-4	cytotoxic T-lymphocyte-associated protein 4
C_{trough}	minimum plasma concentration
CYP	cytochrome P450
D	day
DILI	drug-induced liver injury
DLT	dose-limiting toxicity
(e)DMC	(external) Data Monitoring Committee
DMFS	distant metastasis-free survival
DNA	deoxyribonucleic acid
DRAE	drug-related adverse event

Abbreviation	Expanded Term
DRESS	drug rash with eosinophilia and systemic symptom
ECG	electrocardiogram
ECI	event of clinical interest
ECOG	Eastern Cooperative Oncology Group
EDC	electronic data capture
EEA	European Economic Area
ELISA	enzyme-linked immunosorbent assay
EMA	European Medicines Agency
EOC	Executive Oversight Committee
EORTC QLQ	European Organization for Research and Treatment of Cancer Quality of Life Questionnaire
EOT	end of treatment
EQ-5D-5L	EuroQoL 5 dimensions-5 levels
E-R	exposure response
EU	European Union
FAS	full analysis set
FBR	future biomedical research
FDA	Food and Drug Administration
FDAAA	Food and Drug Administration Amendments Acts
FFPE	formalin-fixed, paraffin embedded
FSH	follicle-stimulating hormone
FSR	first site ready
GCP	Good Clinical Practice
GFR	glomerular filtration rate
GI	gastrointestinal
H	hypothesis
HBsAg	hepatitis B surface antigen
HBV	hepatitis B virus
hCG	human chorionic gonadotropin
HCV	hepatitis C virus
HGRAC	Human Genetic Resources Administration of China
HIV	human immunodeficiency virus
HR	hazard ratio
HRT	hormone replacement therapy
HRQoL	health-related quality of life
IA(s)	interim analysis(ses)
IB	Investigator's Brochure
ICF	Informed Consent Form
ICH	International Council for Harmonisation of Technical Requirements for Pharmaceuticals for Human Use
ICMJE	International Committee of Medical Journal Editors
iCRO	imaging CRO
IEC	Independent Ethics Committee
Ig	immunoglobulin

Abbreviation	Expanded Term
IHC	immunohistochemistry
IL	interleukin
IMP	investigational medicinal product
IND	Investigational New Drug
IO	immune-oncology
irAEs	immune-related AEs
IRB	Institutional Review Board
IRT	interactive response technology
ITIM	immunoreceptor tyrosine-based inhibitory motif
ITT	intent-to-treat
IUD	intrauterine device
IUS	intrauterine hormone-releasing system
IV	intravenous
IVRS	interactive voice response system
IWRS	integrated web response system
KPS	Karnofsky performance status
LLOQ	lower limit of quantitation
LPLV	last patient last visit
LPS	Lansky play-performance scale
LS	least squares
M&N	Miettinen & Nurminen
mAb	monoclonal antibody
MedDRA	Medical Dictionary for Regulatory Activities
MRI	magnetic resonance imaging
mRNA	messenger RNA
MSI	microsatellite instability
MSI-H	microsatellite instability-high
NCCN	National Comprehensive Cancer Network
NCI	National Cancer Institute
NIMP	noninvestigational medicinal product
NR	not reached
NSAID	nonsteroidal anti-inflammatory drug
ORR	objective response rate
OS	overall survival
OTC	over-the-counter
pCR	pathological complete response
PD-1	programmed cell death 1 protein
PD-L1	programmed cell death ligand 1
PD-L2	programmed cell death ligand 2
PET	positron emission tomography
PK	pharmacokinetic
pNR	pathological no response
po	orally
pPR	pathological partial response

Abbreviation	Expanded Term
PRFS2	progression/recurrence-free survival 2
(e)PRO	(electronic) patient-reported outcome
PS	performance status
PSA	prostate-specific antigen
PVR	poliovirus receptor
QxM	every x months
QxW	every x weeks
QoL	quality of life
RECIST	Response Evaluation Criteria In Solid Tumors
RFS	recurrence-free survival
RNA	ribonucleic acid
ROW	rest of world
RP2D	recommended Phase 2 dose
SAC	Scientific Advisory Committee
SAE	serious adverse event
SAP	Statistical Analysis Plan
SCC	squamous cell carcinoma
SD	standard deviation
SGOT	serum glutamic oxaloacetic transaminase
SGPT	Serum glutamic pyruvic transaminase
SHP-1/2	Src homology region 2 domain-containing phosphatase 1/2
SIM	Site Imaging Manual
SJS	Stevens-Johnson Syndrome
SLN	sentinel lymph node
SNP	single nucleotide polymorphism
SoA	schedule of activities
sSAP	supplemental Statistical Analysis Plan
SUSAR	suspected unexpected serious adverse reaction
SWOG	Southwest Oncology Group
T1DM	type 1 diabetes mellitus
T3	triiodothyronine
T4	thyroxine
TEN	toxic epidermal necrolysis
TIGIT	T-cell immunoreceptor with Ig and ITIM domains
TIL	tumor-infiltrating lymphocyte
TSH	thyroid-stimulating hormone
TTST	time to subsequent therapy
ULN	upper limit of normal
US	United States
Vc	volume of the central compartment
VAS	Visual Analog Scale
WBC	white blood cell
WOCBP	woman/women of childbearing potential

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