Official Protocol Title:	A Phase II Clinical Trial to Study the Efficacy and Safety of Pembrolizumab (MK-3475) and Pembrolizumab in Combination with Other Investigational Agents in Subjects with High-risk Non-muscle Invasive Bladder Cancer (NMIBC) Unresponsive to Bacillus Calmette-Guerin (BCG) Therapy
NCT number:	NCT02625961
Document Date:	26-Feb-2025

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TITLE:

A Phase II Clinical Trial to Study the Efficacy and Safety of Pembrolizumab (MK-3475) and Pembrolizumab in Combination with Other Investigational Agents in Subjects with High-risk Non-muscle Invasive Bladder Cancer (NMIBC) Unresponsive to Bacillus Calmette-Guerin (BCG) Therapy

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DOCUMENT HISTORY

Document	Date of Issue	Overall Rationale
Amendment 12	26-FEB-2025	The Sponsor has decided to discontinue treatment with vibostolimab/MK-7684A based on lack of efficacy observed in other studies. The favezelimab/MK-4280A program will be discontinued based on Sponsor prioritization strategy. The decision to deprioritize the favezelimab/MK-4280A program was made after a thorough evaluation of the data from the clinical program.
Amendment 11	26-JAN-2024	To address a health authority request.
Amendment 10	29-AUG-2023	To add country-specific appendices for Italy and Finland, and utDNA for biomarker. Additional clarifications throughout the document were made.
Amendment 09	21-SEP-2022	Global: Based on the results of KEYNOTE-057 from Cohort A, pembrolizumab was approved by the FDA in JAN-2020 for the treatment of patients with BCG-unresponsive NMIBC with CIS +/- papillary tumors who are considered ineligible or elected not to undergo radical cystectomy. However, initial efficacy and long-term durability is modest, and novel combinations that will improve on monotherapy efficacy are needed. Hence, a new signal-finding cohort (Cohort C) has been added to KEYNOTE-057 to evaluate the efficacy and safety of coformulations of pembrolizumab (MK-7684A and MK-4280A) in patients with BCG-unresponsive NMIBC with CIS +/- papillary tumors.
Amendment 08	02-JUL-2021	Global: To update the dose modification and toxicity management guidelines for immune-related adverse events (irAEs). Additional minor clarifications and updates were made.

Document	Date of Issue	Overall Rationale
Amendment 07	19-JUN-2018	United Kingdom: Deleted the following text in Section 7.1.5.3.1 that introduced a conflict in the reporting of adverse events (AEs)/serious adverse events (SAEs) for pembrolizumab "All AEs that occur prior to the Safety Follow-up Visit should be recorded. Subjects with an AE of Grade >1 will be followed until the resolution of the AE to Grade 0-1 or until the beginning of a new anticancer therapy, whichever occurs first. SAEs that occur within 90 days of the end of treatment or before initiation of a new anticancer treatment should also be followed and recorded regardless of causality. SAEs that occur within 90 days of the end of treatment or before initiation of a new anticancer therapy should also be followed and recorded regardless of causality." Additional minor clarifications and updates were made.
Amendment 06	18-JUN-2018	Global: Deleted the following text in Section 7.1.5.3.1 that introduced a conflict in the reporting of AEs/SAEs for pembrolizumab "All AEs that occur prior to the Safety Follow-up Visit should be recorded. Subjects with an AE of Grade >1 will be followed until the resolution of the AE to Grade 0-1 or until the beginning of a new anticancer therapy, whichever occurs first. SAEs that occur within 90 days of the end of treatment or before initiation of a new anticancer treatment should also be followed and recorded regardless of causality. SAEs that occur within 90 days of the end of treatment or before initiation of a new anticancer therapy should also be followed and recorded regardless of causality." Additional minor clarifications and updates were made.
Amendment 05	01-DEC-2017	United Kingdom: Multiple programmed cell death 1/ligand 1 (PD-1/PD-L1) inhibitors have now demonstrated efficacy across PD-L1 expression subgroups in the second-line post-platinum setting and in the first-line for cisplatin-ineligible subjects. Therefore, consistent with the all-comer treatment paradigm established in urothelial cancer, analyses based on PD-L1 expression were moved from primary to secondary objectives. Consistent results have been seen for pharmacokinetic (PK) and antidrug antibodies (ADA) across multiple indications including urothelial carcinoma; therefore, blood samples for PK and ADA were no longer collected and PK/ADA Exploratory Objective was removed. Additional minor clarifications and updates were made.

Document	Date of Issue	Overall Rationale
Amendment 04	01-DEC-2017	Global: Multiple PD-1/PD-L1 inhibitors have now demonstrated efficacy across PD-L1 expression subgroups in the second-line post-platinum setting and in the first-line for cisplatin-ineligible subjects. Therefore, consistent with the all-comer treatment paradigm established in urothelial cancer, analyses based on PD-L1 expression were moved from primary to secondary objectives. Consistent results have been seen for PK and ADA across multiple indications including urothelial carcinoma; therefore, blood samples for PK and ADA were no longer collected and PK/ADA Exploratory Objective was removed. Additional minor clarifications and updates were made.
Amendment 03	17-JUL-2016	United Kingdom: In inclusion criterion 4, removed 2 prior cystoscopy/transurethral resection of the bladder tumor (TURBT) requirement and requesting visually complete resection with 1 prior cystoscopy, and in inclusion criterion 5, adequate Bacillus Calmette-Guérin (BCG) therapy definition was revised to no longer associate the second course of induction/maintenance BCG to diagnosis date and BCG-unresponsive-definition was extended for recurrent high-risk, non-muscle invasive bladder cancer (HR NMIBC) from 6 to 9 months from last BCG instillation. These changes were made to better align with current global standards of care for cystoscopy/TURBT and BCG treatment for this patient population.
Amendment 02	08-JUL-2016	Global: In inclusion criterion 4, removed 2 prior cystoscopy/TURBT requirement and requesting visually complete resection with 1 prior cystoscopy, and in inclusion criterion 5, adequate BCG therapy definition was revised to no longer associate the second course of induction/maintenance BCG to diagnosis date and BCG-unresponsive definition was extended for recurrent HR NMIBC from 6 to 9 months from last BCG instillation. These changes were made to better align with current global standards of care for cystoscopy/TURBT and BCG treatment for this patient population.

Document	Date of Issue	Overall Rationale
Amendment 01	17-MAR-2016	United Kingdom: Added that live vaccines should not be used for 120 days after the last dose of MK-3475 is administered, and monthly pregnancy testing is required for UK subjects as stipulated in Clinical Trials Facilitation Group (CTFG) guidance.
Original Protocol	14-SEP-2015	Not applicable

PROTOCOL AMENDMENT SUMMARY OF CHANGES

Amendment: 12

Overall Rationale for the Amendment:

The Sponsor has decided to discontinue treatment with vibostolimab/MK-7684A based on lack of efficacy observed in other studies.

The favezelimab/MK-4280A program will be discontinued based on Sponsor prioritization strategy. The decision to deprioritize the favezelimab/MK-4280A program was made after a thorough evaluation of the data from the clinical program.

Summary of Changes Table

Section Number and Name	Description of Change	Brief Rationale
Primary Reason for Amendment		
Section 1.0, Trial Summary	Participants receiving vibostolimab/MK-7684A will be transitioned to pembrolizumab. Participants receiving favezelimab/MK-4280A may continue on study therapy until study completion or may transition to pembrolizumab.	The Sponsor has decided to discontinue treatment with vibostolimab/MK-7684A based on lack of efficacy observed in other studies. The favezelimab/MK-4280A program will be discontinued based on Sponsor prioritization strategy. The decision to deprioritize the favezelimab/MK-4280A program was made after a thorough evaluation of the data from the clinical program.

Section Number and Name	Description of Change	Brief Rationale
Additional Changes		
Title Page	jRCT added	Per Japan regulatory request.
Section 1.0, Trial Summary	The following summary text was added: Four Phase 3 studies met prespecified futility criteria for OS or RFS: MK-7684A-003 in metastatic NSCLC with PD-L1 TPS ≥50% CCI [redacted] MK-7684A-007 in metastatic NSCLC with PD-L1 TPS ≥1% CCI [redacted] MK-7684A-008 in ES-SCLC (OS HR, 1.26; 95% CI, 1.00-1.59; presented at Society for Immunotherapy of Cancer 2024), and MK-7684A-010 in adjuvant melanoma (RFS HR, 1.25; 95% CI, 0.87-1.80; presented at Society for Melanoma Research 2024) (data on file). Overall, the lack of efficacy observed with MK-7684A rendered the risk-benefit balance unfavorable, so treatment with this investigational therapy was stopped in all studies. At implementation of Amendment 12 or upon receipt of investigator letter detailing discontinuation of the vibostolimab/MK-7684A and favezelimab/MK-4280A clinical programs, the following changes apply. The changes listed below supersede any protocol content/instructions from previous amendments. For All Cohorts: • This study is closed to enrollment. This study has enrolled 296 participants. • CCI [redacted] • Participants currently in the efficacy Follow-up Phase or Survival Follow-up are considered to have completed the study and therefore should obtain disease assessments and further oncological care as per local SOC. No further data will be collected. For Cohort C: • Biomarker Future Biomedical Research samples will no longer be collected. • Participants receiving vibostolimab/MK-7684A will be transitioned to pembrolizumab or may discontinue treatment at the discretion of the investigator. • Participants receiving favezelimab/MK-4280A may continue on study therapy until study completion or may transition to pembrolizumab or discontinue treatment at the discretion of the investigator. • Pembrolizumab may be sourced locally or centrally.	Refer to rationale for Section 1.0 above for the discontinuation of the vibostolimab/MK-7684A and favezelimab/MK-4280A clinical program(s).

Section Number and Name	Description of Change	Brief Rationale
	• Participants who have access to pembrolizumab monotherapy as SOC should be considered for discontinuation from the study. Those benefiting from pembrolizumab, but unable to access it as SOC outside the study, may continue treatment until discontinuation criteria are met. The last required study visit will be the Safety Follow-up Visit and they will be followed for the mandatory safety reporting period (90 days postdose). • Laboratory procedures/assessments as listed in the Trial Flow Chart (Section 6.1) should be completed per local SOC. • Imaging, urine cytology, and surgical pathology samples will no longer be submitted to the central vendor nor read by BICR. However, for participants who are still on study treatment disease assessments will continue per local SOC schedule and local SOC method of assessment. All imaging and samples as well as relevant objectives and endpoints will be assessed locally. • Participants who complete study treatment or otherwise meet EOT criteria will be discontinued from the study after the safety reporting period (90 days postdose) (Section 7.2). • When an extension study becomes available, participants receiving treatment may consent to enroll in an extension study or else will be discontinued from the trial and treated per local SOC. o Participation in this study is ended when the participant is consented for an extension study or discontinued from the trial. o This study ends when the last participant completes the last study-related contact, withdraws consent, or is lost to follow-up (Section 5.10), or the last participant on active treatment is consented in an extension study, whichever comes first. o For participants who enter an extension study, all AEs, SAEs, and other reportable safety events must be reported by the investigator in this protocol (parent study) from the time of randomization up to the time of providing documented informed consent for an extension study. Note: Once consented to an extension study, safety events, including those considered related to study intervention, will be collected as instructed in the extension study.	

Section Number and Name	Description of Change	Brief Rationale
	• The prespecified analyses of the study described in the statistical analysis plan (SAP) will not be performed. Selected analyses of efficacy and safety endpoints of exploratory nature only will be performed at the end of the study. Long-term efficacy/survival data will no longer be collected. Existing protocol content is retained for historical reference.	
Section 2.0, Trial Design Section 3.0, Objective(s) & Hypothesis(es) Section 4.0, Background & Rationale Section 5.0, Methodology Section 6.0, Trial Flow Chart Section 7.0, Trial Procedures Section 8.0, Statistical Analysis Plan Section 9.0, Labeling, Packaging, Storage and Return of Clinical Supplies Section 10.0, Administrative and Regulatory Details Section 12.0, Appendices	Text introduced to reference changes in Section 1.0.	Refer to rationale for Section 1.0 for the discontinuation of the vibostolimab/MK-7684A and favezelimab/MK-4280A clinical program(s).
Section 5.2, Trial Treatment(s)	Table 2: Added a pembrolizumab row to allow Cohort C participants to transition to pembrolizumab monotherapy with local or central sourcing.	Refer to rationale for Section 1.0 for the discontinuation of the vibostolimab/MK-7684A and favezelimab/MK-4280A clinical program(s).
Section 7.1.2.12, Biomarkers	Corrected SoA to Trial Flow Chart (Section 6.1).	The term SoA does not correctly identify the intended table in this older protocol.
Section 7.1.5.3.3, Survival Follow-up	Corrected NIMBC to NMIBC.	NIMBC is a typo.

Section Number and Name	Description of Change	Brief Rationale
Section 7.2.3, Time Period and Frequency for Collecting AE, SAE, and Other Reportable Safety Event Information	Added periods and duration for potential DILI/DILI reporting.	To maintain continued regulatory reporting compliance in alignment with new Health Authority DILI reporting requirements.
Section 7.2.3, Time Period and Frequency for Collecting AE, SAE, and Other Reportable Safety Event Information	Removed Immediate Reporting of Adverse Events to the Sponsor heading and created new Section 7.2.3 heading to group reporting information.	To accommodate new DILI language, see rationale for Section 7.2.3 above.
Section 7.2.3.1, Serious Adverse Events	Added potential DILI/DILI to definition of SAE.	See rationale for Section 7.2.3.
Section 7.2.3.1, Serious Adverse Events	Renumbered former Section 7.2.4.1 to Section 7.2.3.1.	See rationale for Section 7.2.3.
Section 7.2.3.2, Reporting of Pregnancy and Lactation to the Sponsor	Renumbered former Section 7.2.3 to current Section 7.2.3.2.	Renumbering due to addition of new Section 7.2.3.
Section 7.2.3.3, Events of Clinical Interest	ECI updated to include potential DILI injury/DILI injury, with associated reporting requirements.	See rationale for Section 7.2.3.
Section 7.2.3.3, Events of Clinical Interest	Renumbered former Section 7.2.4.2 to Section 7.2.3.3.	See rationale for Section 7.2.3.
Section 7.2.3.4, Protocol-Specific Exceptions to Serious Adverse Event Reporting	Renumbered former Section 7.2.4.3 to Section 7.2.3.4.	See rationale for Section 7.2.3.
Section 7.2.4, Evaluating Adverse Events	Renumbered former Section 7.2.5 to Section 7.2.4.	See rationale for Section 7.2.3.
Section 7.2.5, Follow-up of AE, SAE, and Other Reportable Safety Event Information	New section added to include potential DILI/DILI as reportable events.	See rationale for Section 7.2.3.
Section 12.4, Abbreviations	Added missing and new abbreviations to the list of abbreviations.	For clarity and accuracy of understanding text.

1.0 TRIAL SUMMARY

Four Phase 3 studies met prespecified futility criteria for OS or RFS: MK-7684A-003 in metastatic NSCLC with PD-L1 TPS ≥50% CCI [redacted] MK-7684A-007 in metastatic NSCLC with PD-L1 TPS ≥1% CCI [redacted], MK-7684A-008 in ES-SCLC (OS HR, 1.26; 95% CI, 1.00-1.59; presented at Society for Immunotherapy of Cancer 2024), and MK-7684A-010 in adjuvant melanoma (RFS HR, 1.25; 95% CI, 0.87-1.80; presented at Society for Melanoma Research 2024) (data on file). Overall, the lack of efficacy observed with MK-7684A rendered the risk-benefit balance unfavorable, so treatment with this investigational therapy was stopped in all studies.

At implementation of Amendment 12 or upon receipt of investigator letter detailing discontinuation of the vibostolimab/MK-7684A and favezelimab/MK-4280A clinical programs, the following changes apply. The changes listed below supersede any protocol content/instructions from previous amendments.

For All Cohorts:

- This study is closed to enrollment. This study has enrolled 296 participants.
- CCI [redacted]
- Participants currently in the efficacy Follow-up Phase or Survival Follow-up are considered to have completed the study and therefore should obtain disease assessments and further oncological care as per local SOC. No further data will be collected.

For Cohort C:

- Biomarker Future Biomedical Research samples will no longer be collected.
- Participants receiving vibostolimab/MK-7684A will be transitioned to pembrolizumab or may discontinue treatment at the discretion of the investigator.
- Participants receiving favezelimab/MK-4280A may continue on study therapy until study completion or may transition to pembrolizumab or discontinue treatment at the discretion of the investigator.
- Pembrolizumab may be sourced locally or centrally.
- Participants who have access to pembrolizumab monotherapy as SOC should be considered for discontinuation from the study. Those benefiting from pembrolizumab, but unable to access it as SOC outside the study, may continue treatment until discontinuation criteria are met. The last required study visit will be the Safety Follow-up Visit and they will be followed for the mandatory safety reporting period (90 days postdose).

- Laboratory procedures/assessments as listed in the Trial Flow Chart (Section 6.1) should be completed per local SOC.

- Imaging, urine cytology, and surgical pathology samples will no longer be submitted to the central vendor nor read by BICR. However, for participants who are still on study treatment disease assessments will continue per local SOC schedule and local SOC method of assessment. All imaging and samples as well as relevant objectives and endpoints will be assessed locally.

- Participants who complete study treatment or otherwise meet EOT criteria will be discontinued from the study after the safety reporting period (90 days postdose) (Section 7.2).

- When an extension study becomes available, participants receiving treatment may consent to enroll in an extension study or else will be discontinued from the trial and treated per local SOC.

  - Participation in this study is ended when the participant is consented for an extension study or discontinued from the trial.

  - This study ends when the last participant completes the last study-related contact, withdraws consent, or is lost to follow-up (Section 5.10), or the last participant on active treatment is consented in an extension study, whichever comes first.

  - For participants who enter an extension study, all AEs, SAEs, and other reportable safety events must be reported by the investigator in this protocol (parent study) from the time of randomization up to the time of providing documented informed consent for an extension study. Note: Once consented to an extension study, safety events, including those considered related to study intervention, will be collected as instructed in the extension study.

- The prespecified analyses of the study described in the statistical analysis plan (SAP) will not be performed. Selected analyses of efficacy and safety endpoints of exploratory nature only will be performed at the end of the study. Long-term efficacy/survival data will no longer be collected.

Existing protocol content is retained for historical reference.

Abbreviated Title	Pembrolizumab (MK-3475), and pembrolizumab in combination with other investigational agents in high-risk NMIBC patients unresponsive to BCG
Trial Phase	Phase II
Clinical Indication	High-risk, non-muscle invasive bladder cancer (NMIBC)
Trial Type	Interventional
Type of control	No treatment control
Route of administration	Intravenous
Trial Blinding	Unblinded Open-label
Treatment Groups	Pembrolizumab (MK-3475) 200 mg every 3 weeks (Q3W) MK-7684A – Coformulation of 200 mg vibostolimab (MK-7684) and 200 mg pembrolizumab Q3W MK-4280A – Coformulation of 800 mg favezelimab (MK-4280) and 200 mg pembrolizumab Q3W
Number of trial subjects	Approximately 320 subjects will be enrolled.
Estimated duration of trial	The Sponsor estimates that the trial will require approximately CCI from the time the first subject (or their legally acceptable representative) provides documented informed consent until the last subject's last study-related contact.
Duration of Participation	Subjects will participate in the trial from the time the subject provides documented informed consent through the final contact. After a screening phase of approximately 28 days, subjects in Cohorts A and B will receive pembrolizumab, and after a screening phase of approximately 42 days, subjects in Cohort C Arm 1 will receive MK-7684A and Arm 2 will receive MK-4280A. Subjects will be treated with pembrolizumab, MK-7684A, or MK-4280A for up to 35 administrations (approximately 2 years). Subjects who complete study treatment will continue into the posttreatment tumor assessment period for an additional 3 years. The final evaluation in the tumor assessment period of 5 years will be Week 264. CCI Subjects who do not complete up to 35 administrations (approximately 2 years) of study treatment and discontinue for reasons other than pathology-confirmed persistent high-risk disease, high-risk recurrence, or disease progression will continue to have posttreatment tumor assessments until disease progression is documented, initiation of a non-study cancer treatment, withdrawal of consent, becomes lost to follow-up, or follow-up for a maximum of 5 years, whichever occurs first. Subjects who discontinue study treatment for pathology-confirmed persistent high-risk disease, high-risk recurrence, or disease progression will not continue to have study defined posttreatment tumor assessments and will instead enter Survival Follow-up. All subjects will be followed for overall survival and bladder status until death, withdrawal of consent, or the end of the study for a total duration of up to 5 years.

A list of abbreviations used in this document can be found in Appendix 12.4.

2.0 TRIAL DESIGN

Changes that apply as of Amendment 12 are listed in Section 1.0 and supersede any protocol content/instructions from previous amendments. Existing protocol content in this section is retained for historical reference.

2.1 Trial Design

This is a multisite, open-label trial of pembrolizumab (MK-3475; Cohorts A and B) and MK-7684A or MK-4280A (Cohort C) in subjects with high-risk non-muscle invasive bladder cancer (NMIBC) unresponsive to Bacillus Calmette-Guérin (BCG) who are considered ineligible for radical cystectomy or have elected not to undergo the procedure, to be conducted in conformance with Good Clinical Practices (GCP). Cohorts A and B are single-arm, and Cohort C has 2 treatment arms.

> ***High-Risk NMIBC,*** *according to the International Bladder Cancer Group (IBCG), is defined as any of the 3 characteristics: High Grade Ta, T1, and/or carcinoma-in-situ (CIS).*

Approximately 260 subjects with high-risk NMIBC may be enrolled into Cohorts A and B of this study, with 130 subjects in each cohort. In Amendment 09, KEYNOTE-057 was updated to include a signal-finding cohort (Cohort C) that will enroll an additional 60 subjects.

Subjects must have disease that is unresponsive to adequate BCG therapy as defined in Section 5.1.2.

Subjects may have received other intravesical or systemic therapies (excluding antiprogrammed cell death ligand 1 [anti-PD-1/PD-L1] agents) for NMIBC after receiving their last BCG instillation as long as they have met the aforementioned criteria for BCG unresponsive disease. Subjects who are BCG intolerant also may be included in the trial only if they meet the criteria for adequate BCG therapy.

Prior to enrollment, subjects will have undergone recent cystoscopic procedure(s) and complete transurethral resection of bladder tumor (TURBT) to remove all resectable disease (Ta and T1 components) and assure the absence of muscle invasive disease. Residual CIS (Tis components) not amenable to complete resection is acceptable. The most recent cystoscopy must have been performed within 12 weeks from starting trial treatment with pembrolizumab, MK-7684A, or MK-4280A. Subjects with T1 disease must have undergone restaging TURBT procedure within 12 weeks prior to randomization to ensure complete resection of all T1 disease. Subjects must not have undergone any intervening intravesical chemotherapy (except a single dose of intravesical chemotherapy at the time of most recent cystoscopy/TURBT) or immunotherapy from the time of most recent cystoscopy/TURBT to starting trial treatment. At screening, subjects will provide a urine cytology specimen and either fresh or archival formalin-fixed paraffin embedded (FFPE preferred) tumor biopsies

for central pathology review to confirm grade, and stage of disease, and assure a diagnosis of high-risk NMIBC and the absence of muscle invasion or any metastatic disease. This same tissue will be centrally reviewed for PD-L1 determination by immunohistochemistry (IHC).

For Cohorts A and B, eligible subjects will be placed into a cohort based on the pathology characteristics of the centrally assessed tissue submitted during screening:

- Cohort A – with CIS at baseline (CIS only, Ta+CIS, or T1+CIS); or
- Cohort B – without CIS at baseline (High Grade Ta or Any Grade T1).

Enrollment for Cohorts A and B will be complete at the time Cohort C enrollment begins. After confirmation of high-risk NMIBC of the centrally assessed tissue submitted during screening, eligible subjects will be placed into Cohort C and randomly assigned to either Arm 1 or Arm 2.

- Cohort C - with CIS at baseline (CIS only, Ta+CIS, or T1+CIS)

Subjects must have been considered by the treating urologist/physician ineligible for radical cystectomy or have elected not to undergo the procedure after appropriate counseling for cystectomy as a standard of care. For Cohorts A and B, subjects will receive pembrolizumab 200 mg Q3W regardless of PD-L1 status. For Cohort C, subjects will be randomly assigned to receive either MK-7684A (coformulation of vibostolimab [MK-7684] and pembrolizumab) or MK-4280A (coformulation of favezelimab [MK-4280] and pembrolizumab) regardless of PD-L1 status.

Subjects will undergo tumor evaluation with cystoscopy and urine cytology every 12 weeks (± 2 weeks) for the first 2 years, then every 24 weeks (± 2 weeks) thereafter for a total duration of up to 5 years. The final evaluation in the posttreatment tumor assessment period of 5 years will be Week 264. TURBT/biopsies will be performed during the cystoscopy if there is visible evidence of tumor. If cystoscopy is normal and urine cytology is subsquently positive or suspicious of high-risk NMIBC, the subject should be scheduled expeditiously for a repeat cystoscopy with random biopsies (see Table 5). For Cohort C subjects, in addition to tumor evaluation with urine cytology and cystoscopy, random biopsies (R-biopsies) are required at the Week 48 (Month 12) time point. R-biopsies should be obtained of the trigone, bladder dome, right, left, anterior, and posterior bladder walls, as well as biopsy of the prostatic urethra in males.

In addition, subjects will be evaluated with cross-sectional imaging CTU of the abdomen and pelvis every 24 weeks (± 2 weeks) for the first 2 years and yearly (52 ±4 weeks) thereafter. CTU will be performed at this specified interval to assess for the presence of extra-vesical metastatic or nodal disease and urothelial lesions in the upper urinary tract. If clinically indicated per Table 5, CTU will be performed more frequently if there is evidence of recurrence on cystoscopy or pathology or by urine cytology. All imaging obtained during the study will be submitted for an independent central radiology review to evaluate for the presence of extra-vesical disease.

Subjects with an abnormal cystoscopy where malignant/suspicious lesions are visualized on cystoscopy regardless of central laboratory assessed negative urine cytology (ie, "negative for high grade urothelial carcinoma" or "atypical urothelial carcinoma") will undergo TURBT/biopsy of the target malignant/suspicious lesion(s) and evaluation of extra-vesical disease with CTU.

Subjects with a normal cystoscopy where there are no malignant/suspicious lesions visualized on cystoscopy, but have a central laboratory assessed urine cytology result of "high grade urothelial carcinoma present" or "suspicious for high grade urothelial carcinoma" will undergo serial biopsies of the normal-looking mucosa (R-biopsies). R-biopsies should be obtained of the trigone, bladder dome, right, left, anterior, and posterior bladder walls, as well as biopsy of the prostatic urethra in males. These subjects will also undergo evaluation of extra-vesical disease with CTU.

Subjects with a normal cystoscopy where there are no malignant/suspicious lesions visualized on cystoscopy and without a centrally assessed urine cytology result of "high grade urothelial carcinoma present" or "suspicious for high grade urothelial carcinoma" will not undergo biopsies and will be considered disease-free (refer to Figure 4 and Figure 5). No CTU studies to evaluate extra-vesical disease will be performed unless otherwise part of the scheduled follow-up per protocol.

Subjects with central pathology-confirmed low grade Ta recurrence at any time during the study will be permitted to undergo a repeat TURBT and remain on trial treatment.

Adverse events will be monitored throughout the trial and graded in severity according to the guidelines outlined in the National Cancer Institute (NCI) Common Terminology Criteria for Adverse Events (CTCAE) Version 4.0. Refer to Appendix 12.6 for details.

For subjects in Cohort A and B, treatment with pembrolizumab will continue until the subject has central pathology-confirmed persistent or recurrent high-risk NMIBC, or progressive disease by central pathology and/or radiology review at any time during the study. For subjects in Cohort C, study treatment will continue until the subject has central pathology-confirmed persistent or recurrent CIS or high grade Ta at the 24-week efficacy review or thereafter. Subjects with central pathology-confirmed T1 or disease progression to T2 or worse at any time will be discontinued from the study treatment for all cohorts. It should be noted that the development of high grade disease involving the upper tract will constitute recurrence of high-risk disease necessitating discontinuation from the study for all cohorts.

In the absence of disease persistence/recurrence or progression, treatment with pembrolizumab, MK-7684A, or MK-4280A will continue as described above until unacceptable AE(s), intercurrent illness that prevents further administration of treatment, the investigator's decision to withdraw the subject, the subject withdraws consent, pregnancy of the subject, noncompliance with trial treatment or procedure requirements, completion of 35 administrations (approximately 2 years) of treatment with pembrolizumab, MK-7684A, MK-4280A, or administrative reasons (refer to Section 5.8.1).

After 18 months of trial treatment, subjects without any evidence of disease at 2 or more consecutive evaluation visits may consider stopping trial treatment.

After the end of trial treatment subjects will be followed for 30 days for AE monitoring. AEs and events of clinical interest (ECI) will be collected for 30 days, and SAEs will be collected for 90 days following cessation of trial treatment or until the subject initiates new anticancer therapy, whichever occurs first.

Subjects who discontinue treatment for reasons other than persistence or recurrence of high-risk NMIBC or disease progression will have posttreatment follow-up for disease status until disease progression, initiating a non-study cancer treatment, withdrawing consent, death, or becoming lost to follow-up, for a total duration of up to 5 years (Week 264). During this period, subjects will continue study-related disease assessments including radiographic imaging (CTU), cystoscopy (with biopsy/TURBT as applicable per Table 5), and urine cytology per schedule. All subjects will be followed for overall survival and bladder status until death, withdrawal of consent, or the end of the trial, whichever occurs first, for a total duration of up to 5 years.

The primary objective of this study is to evaluate the anti-tumor activity of pembrolizumab (Cohorts A and B), MK-7684A (Cohort C Arm 1), and MK-4280A (Cohort C Arm 2) in subjects with high-risk NMIBC who are unresponsive to BCG therapy and are considered ineligible for cystectomy or have elected not to undergo the procedure. Efficacy evaluations will be based on outcomes measures of cystoscopy, urine cytology, TURBT/biopsies and CTU.

The full analysis set (FAS) population will serve as the primary population for the analyses of efficacy data in this trial. The FAS population consists of all enrolled subjects who receive at least one dose of trial treatment and have a baseline evaluation consisting of pre-enrollment cystoscopy, TURBT/biopsy, urine cytology, and baseline CTU imaging. The FAS population will be analyzed separately by cohort. For Cohort A, an interim analysis (IA) is planned to assess the proof-of-concept (POC) and the study may be modified or stopped due to lack of clinical activity. The All Patients as Treated (APaT) population will be used for safety analyses.

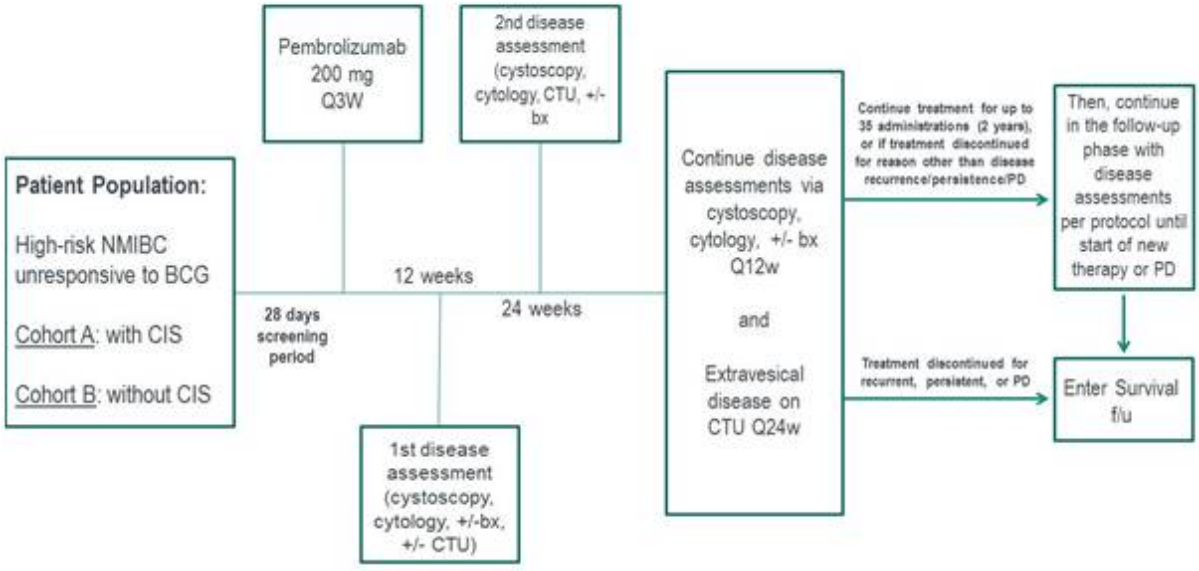
Participation in this trial and subsequent cohort assignment will be dependent on supplying tumor tissue from recent TURBT/biopsies and CTU images for central independent radiology review.

Specific procedures to be performed during the trial, as well as their prescribed times and associated visit windows, are outlined in the Trial Flow Chart - Section 6.0. Details of each procedure are provided in Section 7.0 – Trial Procedures.

2.2 Trial Diagram

The trial design is depicted in Figure 1 for Cohorts A and B, and in Figure 2 for Cohort C.

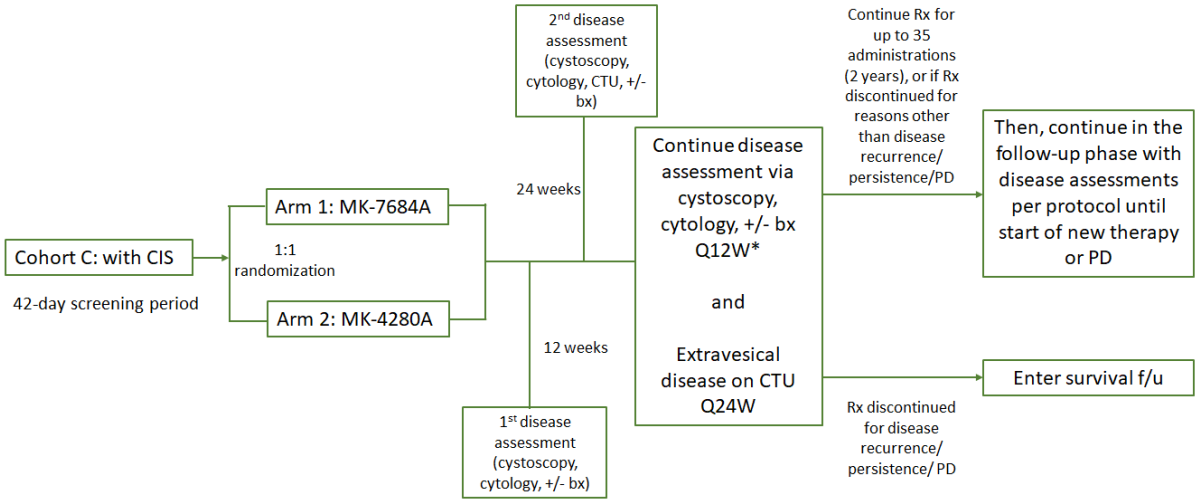
Figure 1 Trial Diagram – Cohorts A and B



BCG = Bacillus Calmette-Guérin; CIS = carcinoma-in-situ; CT = computed tomography; CTU = computed tomography urography; bx = biopsy; f/u = follow-up; NMIBC = non-muscle invasive bladder cancer; PD = progressive disease; Q12W = every 12 weeks; Q24W = every 24 weeks; Rx = treatment; TURBT = transurethral resection of bladder tumor.

- Note: Subjects will undergo first tumor evaluation with cystoscopy, urine cytology, and biopsy (if applicable) at Week 12 and every 12 weeks thereafter for up to 35 administrations (2 years). Subjects who have persistent high-risk disease for Cohort A at 12-week assessment or recurrent high-risk NMIBC or progressive disease at any time point for Cohorts A and B will be discontinued from study treatment. Subjects who discontinue treatment for reasons other than persistent or recurrent high-risk NMIBC or progressive disease will continue study-related disease assessments including cystoscopy (with TURBT/biopsies as applicable), urine cytology, and CTU imaging on schedule. Further assessments are described in Section 7.1 – Trial Procedures.

Figure 2 Trial Diagram – Cohort C



CIS = carcinoma-in-situ; CT = computed tomography; CTU = computed tomography urography; bx = biopsy; f/u = follow-up; NMIBC = non-muscle invasive bladder cancer; PD = progressive disease; Q12W = every 12 weeks; Q24W = every 24 weeks; Rx = treatment; TURBT = transurethral resection of bladder tumor.

MK-7684A: Coformulation of 200 mg vibostolimab (MK-7684) and 200 mg pembrolizumab

MK-4280A: Coformulation of 800 mg favezelimab (MK-4280) and 200 mg pembrolizumab

- Note: Subjects will undergo first tumor evaluation with cystoscopy, urine cytology, and biopsy (if applicable) at Week 12 and Q12W thereafter for up to 35 administrations (approximately 2 years). Cohort C subjects who have ≥T1 disease at any time point or have high grade Ta or CIS at 24-week assessment or thereafter will be discontinued from study treatment. *Cohort C subjects will also undergo random biopsies at Week 48 (Month 12). Subjects who discontinue treatment for reasons other than persistent or recurrent high-risk NMIBC or progressive disease at any time point will continue study-related disease assessments including cystoscopy (with TURBT/biopsies as applicable), urine cytology, and CTU imaging on schedule. Further assessments are described in Section 7.1 – Trial Procedures.

3.0 OBJECTIVE(S) & HYPOTHESIS(ES)

Changes that apply as of Amendment 12 are listed in Section 1.0 and supersede any protocol content/instructions from previous amendments. Existing protocol content in this section is retained for historical reference.

For the purposes of this trial, the term study population is defined as subjects with high-risk NMIBC who are unresponsive to BCG and are either ineligible for radical cystectomy or elect not to undergo the procedure. The study population is the sum of Cohorts A, B, and C subjects irrespective of PD-L1 status. All objectives for this trial described in the following sections are inclusive of the study population as defined unless specified otherwise.

3.1 Primary Objective(s) & Hypothesis(es)

Cohort A – Subjects with CIS at baseline (CIS only, Ta+CIS, or T1+CIS)

- Primary Objective: To evaluate anti-tumor activity of pembrolizumab by evaluating the absence of **high-risk NMIBC or progressive disease**, as determined by cystoscopy, cytology, biopsy (if applicable), and radiologic imaging by central pathology and radiology review.

- Hypothesis: Intravenous administration of single agent pembrolizumab) to subjects with high-risk NMIBC and underlying CIS at baseline who are unresponsive to BCG, and either are ineligible for radical cystectomy or elect not to undergo the procedure, will result in a complete response (CR) rate in high-risk NMIBC that CCI [redacted]

Cohort B – Subjects without CIS at baseline (High Grade Ta or Any Grade T1)

- Primary Objective: To evaluate anti-tumor activity of pembrolizumab by evaluating the absence of **high-risk NMIBC or progressive disease**, as determined by cystoscopy, cytology, biopsy (if applicable), and radiologic imaging by central pathology and radiology review.

- Hypothesis: Intravenous administration of single agent pembrolizumab to subjects will result in a 12-month **disease-free survival** (DFS) rate of high-risk NMIBC that is greater than 20%.

  The study is considered to have met its primary objective if the primary hypothesis for either Cohort A or Cohort B is successful. Details of the multiplicity strategy among the primary and secondary hypotheses within each cohort are given in Section 8.8 – Multiplicity.

Cohort C – Subjects with CIS at baseline (CIS only, Ta+CIS, or T1+CIS)

- Primary Objective: To evaluate anti-tumor activity of MK-7684A and MK-4280A by 12-month complete response (CR) rate of **high-risk NMIBC**, as determined by cystoscopy, cytology, biopsy, and radiologic imaging by central pathology and radiology review.

- Hypothesis: There is no formal hypothesis testing for Cohort C.

3.2 Secondary Objective(s) & Hypothesis(es)

Cohort A – Subjects with CIS at baseline (CIS only, Ta+CIS, T1+CIS)

1. Key Secondary Objective: To evaluate anti-tumor activity of pembrolizumab by CR rate of **any disease**.

   Hypothesis: Intravenous administration of single agent pembrolizumab will result in a CR rate of **any disease** that CCI [redacted]

2. Key Secondary Objective: To evaluate anti-tumor activity of pembrolizumab by Duration of Response (DOR) of **high-risk NMIBC** and **any disease** (responders only).

3. Secondary Objective: To evaluate anti-tumor activity of pembrolizumab in **PD-L1 positive subjects** by CR rate of **high-risk NMIBC** and **any disease**.

4. Secondary Objective: To evaluate anti-tumor activity of pembrolizumab in PD-L1 positive subjects by DOR of **high-risk NMIBC** and **any disease** (responders only).

5. Secondary Objective: To evaluate anti-tumor activity of pembrolizumab in the study population and **in PD-L1 positive subjects** by the following endpoints:

   a. DOR rate at specific time points (eg, at 6 months, 12 months, etc.) of both **high-risk NMIBC and any disease** (responders only);

   b. Progression free survival, to worsening of grade or stage or death;

   c. Progression free survival, to muscle invasive or metastatic disease or death; or

   d. Overall survival (OS).

Cohort B – Subjects without CIS at baseline (High Grade Ta or Any Grade T1)

6. Key Secondary Objective: To evaluate anti-tumor activity of pembrolizumab by DFS rate of **any disease.**

   Hypothesis: Intravenous administration of single agent pembrolizumab will result in a 12-month DFS rate of **any disease** that CCI [redacted]

7. Secondary Objective: To evaluate anti-tumor activity of pembrolizumab in **PD-L1 positive subjects** by 12-month DFS rate of **high-risk NMIBC** and **any disease**.

8. Secondary Objective: To evaluate anti-tumor activity of pembrolizumab in the study population and **in PD-L1 positive subjects** by the following endpoints:

    a. Overall DFS and 3-month/6-month DFS rates of **high-risk NMIBC** and **any disease**;

    b. Progression free survival, to worsening of grade or stage or death;

    c. Progression free survival, to muscle invasive or metastatic disease or death; or

    d. OS.

Cohort C – Subjects with CIS at baseline (CIS only, Ta+CIS, T1+CIS)

9. Secondary Objective: To evaluate anti-tumor activity of MK-7684A and MK-4280A in the study population by the following endpoints:

    a. DOR of **high-risk NMIBC** (responders only);

    b. CR rate at 3 months, CR rate at 6 months, and overall CR rate;

    c. Progression free survival, to worsening of grade or stage or death;

    d. Progression free survival, to muscle invasive or metastatic disease or death; or

    e. OS.

3.3 Exploratory Objectives

CCI

[redacted]

3.4 Safety Objective

1. Objective: To characterize the safety and tolerability of pembrolizumab, MK-7684A, and MK-4280A.

4.0 BACKGROUND & RATIONALE

Changes that apply as of Amendment 12 are listed in Section 1.0 and supersede any protocol content/instructions from previous amendments. Existing protocol content in this section is retained for historical reference.

4.1 Background

Pembrolizumab

Pembrolizumab is a potent humanized immunoglobulin G4 (IgG4) monoclonal antibody (mAb) with high specificity of binding to the PD-1 receptor, thus inhibiting its interaction with PD-L1 and programmed cell death ligand 2 (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 intravenous (IV) immunotherapy for advanced malignancies. Keytruda® (pembrolizumab) is indicated for the treatment of patients across many indications. For more details on specific indications, refer to the pembrolizumab Investigator's Brochure (IB).

MK-7684A

MK-7684A is a coformulation of vibostolimab (MK-7684) and pembrolizumab. MK-7684 is a humanized, antagonist mAb that binds to the immune checkpoint receptor, T-cell immunoglobulin and immunoreceptor tyrosine-based inhibitory motif (TIGIT), and blocks the interaction between TIGIT and its ligands. 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. For more details, refer to the MK-7684/MK-7684A IB.

MK-4280A

MK-4280A is a coformulation of favezelimab (MK-4280) and pembrolizumab. MK-4280 binds to the immune checkpoint receptor LAG-3 and blocks the interaction of LAG-3 with MHC Class II ligands. MK-4280 has also been shown to have an acceptable preclinical safety profile and is in clinical development as an IV immunotherapy for advanced malignancies. For more details, refer to the MK-4280/MK-4280A IB.

4.1.1 Pharmaceutical and Therapeutic Background

4.1.1.1 Pembrolizumab

Pembrolizumab (previously known as SCH 9000475) is a potent and highly selective humanized mAb of the IgG4/kappa isotype designed to directly block the interaction between PD-1 and its ligands, PD-L1 and PD-L2.

The importance of intact immune surveillance in controlling outgrowth of neoplastic transformation has been known for decades [1]. Accumulating evidence shows a correlation between tumor-infiltrating lymphocytes (TILs) in cancer tissue and favorable prognosis in various malignancies [2] [3] [4] [5] [6]. In particular, the presence of CD8+ T-cells and the ratio of CD8+ effector T-cells/FoxP3+ regulatory T-cells seems to correlate with improved prognosis and long-term survival in many solid tumors.

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, which has been shown to negatively regulate antigen receptor signaling on engagement of its ligands (PD-L1 and/or PD-L2) [7] [8]. The structure of murine PD-1 has been resolved [9]. PD-1 and family members are type I transmembrane glycoproteins containing an Ig Variable-type (V-type) domain responsible for ligand binding and a cytoplasmic tail, which is 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 (ITIM) and an immunoreceptor tyrosine-based switch motif (ITSM). Following T-cell stimulation, PD-1 recruits the tyrosine phosphatases SHP-1 and SHP-2 to the ITSM 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 [7] [10] [11] [12]. The mechanism by which PD-1 down modulates T-cell responses is similar to, but distinct from that of CTLA-4 as both molecules regulate an overlapping set of signaling proteins [13] [14]. PD-1 was shown to be expressed on activated lymphocytes including peripheral CD4+ and CD8+ T-cells, B-cells, T_{regs} and Natural Killer T (NKT) cells [15] [16]. Expression has also been shown during thymic development on CD4-CD8- (double negative) T-cells as well as subsets of macrophages and dendritic cells [17]. The ligands for PD-1 (PD-L1 and PD-L2) are constitutively expressed or can be induced in a variety of cell types, including non-hematopoietic tissues as well as in various tumors [18] [19] [20] [13]. Both ligands are type I transmembrane receptors containing both IgV- and IgC-like domains in the extracellular region and contain short cytoplasmic regions with no known signaling motifs. Binding of either PD-1 ligand to PD-1 inhibits T- cell activation triggered through the T-cell receptor. PD-L1 is expressed at low levels on various non-hematopoietic tissues, most notably on vascular endothelium, whereas PD-L2 protein is only detectably expressed on antigen-presenting cells found in lymphoid tissue or chronic inflammatory environments. PD-L2 is thought to control immune T-cell activation in lymphoid organs, whereas PD-L1 serves to dampen unwarranted T-cell function in peripheral tissues [13]. Although healthy organs express little (if any) PD-L1, a variety of cancers were demonstrated to express abundant levels of this T-cell inhibitor. PD-1 has been suggested to regulate tumor-specific T-cell expansion in subjects with melanoma (MEL) [21]. This suggests that the PD-1/PD-L1 pathway plays a critical role in tumor immune evasion and should be considered as an attractive target for therapeutic intervention.

4.1.1.2 MK-7684A

MK-7684A is a coformulation of 200 mg vibostolimab and 200 mg pembrolizumab.

Refer to Section 4.1.1.1 for pembrolizumab background information.

4.1.1.2.1 MK-7684

MK-7684 is a humanized, antagonist mAb that binds to the immune checkpoint receptor, TIGIT, and blocks the interaction between TIGIT and its ligands. This human IgG1 antibody is being developed as a cancer immunotherapeutic with a potential to be used as monotherapy or to be combined with pembrolizumab (a humanized anti-PD-1 receptor antibody) to increase benefit to patients with various tumor types.

TIGIT is an immunomodulatory receptor expressed primarily on activated CD4+ and CD8+ T-cells, NK cells, and NKT cells. Its structure reveals a single extracellular immunoglobulin domain, a transmembrane region, an immunoglobulin tail tyrosine-like phosphorylation motif, and an immunoreceptor tyrosine-based inhibitory motif.

TIGIT forms part of a costimulatory network that consists of a positive (CD226) and negative (TIGIT) immunomodulatory receptor on T-cells, and ligands (CD155 and CD112) expressed on tumor cells and antigen presenting cells [22]. Whereas, CD226 is widely expressed on most immune cells, TIGIT is highly expressed on memory T-cells, T_{regs}, NK cells, and NKT cells [23] [24]. CD155/PVR (poliovirus receptor) and CD112/PVRL-2 (poliovirus receptor-related 2) are 2 nectin family members that are widely expressed both on cells of the hematopoietic system and on fibroblasts and endothelial cells. Functionally, these receptor ligands are involved in cell adhesion and motility. CD155 is reported to be overexpressed in several tumor types, and has been found to be induced by Ras activation and genotoxic stress [25] [26] [27] [28] [29].

In addition, TIGIT is highly coexpressed with PD-1 on both CD4+ and CD8+ TILs including T_{regs}, in mouse and human tumors, and has been reported to be coexpressed with PD-1 and T-cell immunoglobulin and mucin domain containing-3 on the TILs with the most exhausted phenotype [30] [31]. Furthermore, enhanced anti-tumor efficacy is observed in preclinical models when an anti-TIGIT antibody is used with an anti-PD-1 antibody. Therefore, the Sponsor hypothesize that combining MK-7684 with pembrolizumab will offer substantially augmented anti-tumor efficacy.

4.1.1.3 MK-4280A

MK-4280A is a coformulation of 800 mg favezelimab with 200 mg pembrolizumab.

Refer to Section 4.1.1.1 for pembrolizumab background information.

4.1.1.3.1 MK-4280

LAG-3 is an inhibitory immune modulatory receptor that regulates effector T-cell homeostasis, proliferation, and activation, and has a role in the suppressor activity of T_{regs}

[32] [33] [34]. LAG-3 is expressed on activated CD8+ and CD4+ T-cells, T_{regs} and the T_r1 regulatory T-cell population, as well as on NKT and a subset of tolerogenic plasmacytoid dendritic cells [35] [36] [37]. Because of its proposed role on both effector T-cells and T_{regs}, LAG-3 is one of several immune checkpoint molecules where simultaneous blockade of both cell populations has the potential to enhance anti-tumor immunity [38].

LAG-3 is structurally related to CD4 and a member of the Ig superfamily. Like CD4, its ligand is MHC Class II molecules [39] [40]. Interaction with its ligand leads to dimerization and signal transduction resulting in altered T-cell activation. Following T-cell activation, LAG-3 is transiently expressed on the cell surface. A large proportion of LAG-3 molecules are found in intracellular stores and can be rapidly translocated to the cell membrane on T-cell activation [41]. LAG-3 expression is regulated at the cell surface by extracellular cleavage to yield a soluble form of LAG-3 (sLAG-3), which can be detected in serum [42]. Expression of LAG-3 is tightly regulated and represents a self-limiting mechanism to counter uncontrolled T-cell activity.

LAG-3 is commonly coexpressed with PD-1 on anergic/exhausted T-cells, and both in vitro and in vivo data indicate that dual blockade of LAG-3 and PD-1 can have a synergistic impact on reversing tumor-specific anergy [43] [44].

In samples collected from human patients, LAG-3 and PD-1 coexpression has been correlated with T-cell anergy/exhaustion. For example, tumor samples collected from patients with ovarian cancer contained NY ESO 1 specific CD8+ T-cells that coexpressed high levels of PD-1 and LAG-3 [44]. In vitro dual blockade of these 2 pathways was able to improve the T-cells' ability to produce IFNγ and proliferate, while blockade of either pathway on its own did not. Additionally, LAG-3 expression on T_{regs} has been shown to correlate with the production of cytokines traditionally thought to have an immunosuppressive role (eg, IL 10, TGF β1) [43]. LAG-3 expression has been identified on tumor-infiltrating T_{regs} in patients with head and neck squamous cell cancer and non–small cell lung cancer (NSCLC) as well as on tumor-infiltrating CD4+ Foxp3- (T_r1) cells in patients with CRC [45] [46] [47]. In the patients with CRC, the presence of these LAG-3+ T_r1 cells expressing IL 10 was associated with disease progression [48].

4.1.2 Preclinical and Clinical Trials

4.1.2.1 Pembrolizumab

Therapeutic studies in mouse models have shown that administration of antibodies blocking PD-1/PD-L1 interaction enhances infiltration of tumor-specific CD8+ T-cells and leads ultimately to tumor rejection, either as a monotherapy or in combination with other treatment modalities. Anti-mouse PD-1 or anti-mouse PD-L1 antibodies have demonstrated anti-tumor responses as a monotherapy in models of squamous cell carcinoma, pancreatic carcinoma, MEL and colorectal carcinoma. Blockade of the PD-1 pathway effectively promoted CD8+ T-cell infiltration into the tumor and the presence of IFNγ, granzyme B and perforin, indicating that the mechanism of action involved local infiltration and activation of effector T-cell function in vivo [49] [50] [51] [52] [53] [54]. Experiments have confirmed the in vivo

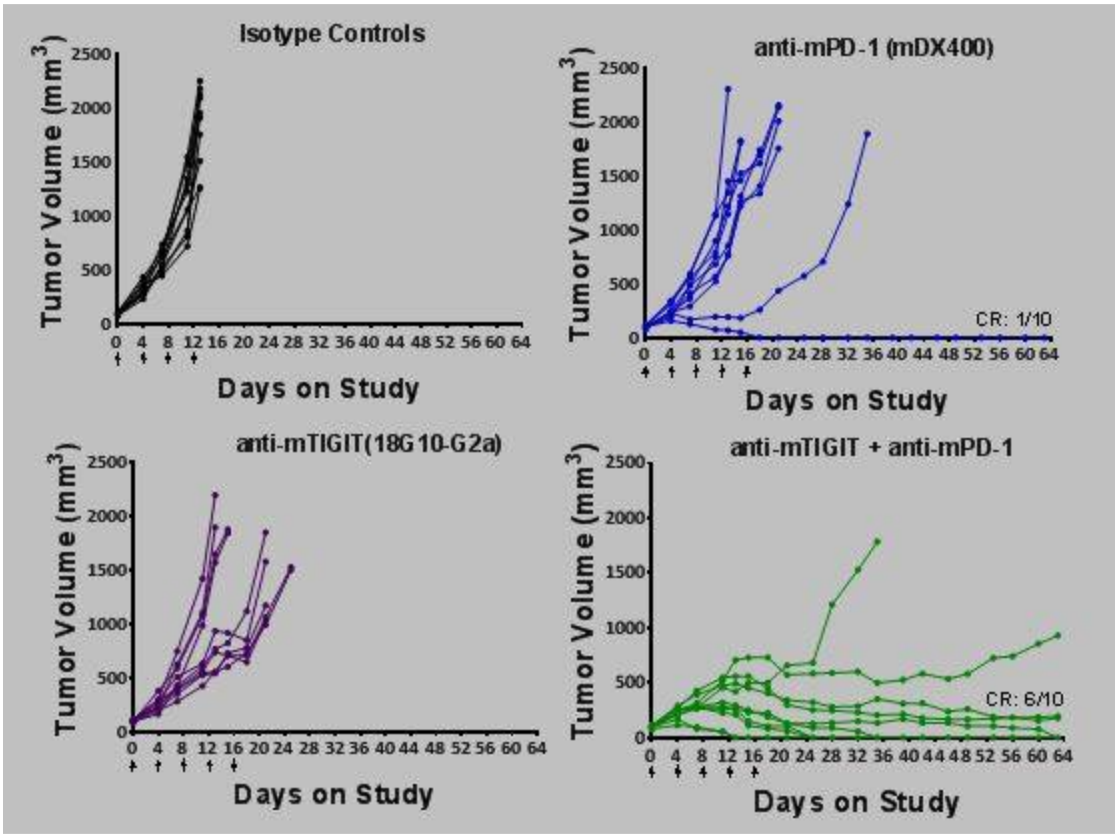
efficacy of PD-1 blockade as a monotherapy as well as in combination with chemotherapy in syngeneic mouse tumor models (see the pembrolizumab IB for more information).

4.1.2.2 MK-7684A

Evaluation of TIGIT modulation as an approach to enhance tumor immunity was prompted by preclinical observations showing that antagonizing TIGIT has potent immunostimulatory effects.

A representative study evaluating anti-TIGIT treatment as a single agent and in combination with anti-PD-1 (muDX400) therapy in the murine subcutaneous CT26-tumor-bearing model is shown in Figure 3. The CT26 colon carcinoma model has been classified as partially responsive to anti-PD-1 treatment with only partial tumor growth inhibition observed. CT26 model selection was based on baseline TIGIT protein surface expression on CD8+ and CD4+ TILs, baseline mRNA expression of CD155, and induction of TIGIT and CD155 expression in tumors after anti-PD-1 treatment. Combination treatment of 18G10-G2a with anti-PD-1 (mDX400) demonstrated significantly enhanced efficacy and survival as compared with anti-TIGIT and anti-PD-1 monotherapy treatments. Animals with CRs showed curative protection from tumor rechallenge, consistent with the development of immune memory (data not shown).

Figure 3 Anti-tumor Efficacy of Anti-TIGIT 18G10-IgG2a as a Single Agent and in Combination With Anti-PD-1 (muDX400) Therapy in the Murine Subcutaneous CT26 Colon Carcinoma-tumor Bearing Model



CR = complete response; Ig = immunoglobulin; PD-1 = programmed death 1; TIGIT = T-cell immunoglobulin and immunoreceptor tyrosine-based inhibitory motif.

CT26-tumor-bearing BALB/cAnN mice (mean tumor volume at start of treatment ~100 mm^3) were administered anti-TIGIT antibody (18G10-G2a) at a dose of 18 mg/kg and an anti-murine anti-PD-1 antibody (mDX400) at a dose of 10 mg/kg by intraperitoneal injection, every 4 days for 5 cycles. Tumor volume curves are presented for individual animals within each group (n=10/group).

These studies (and others) have demonstrated that anti-mouse TIGIT mAb treatment can augment anti-tumor T-cell responses and induce tumor rejection in several murine tumor models when used alone and in combination with an anti-mouse PD-1 mAb.

The results of studies using chimeric anti-mouse TIGIT mAbs on the IgG2a backbone revealed that administration of single agent anti-mouse TIGIT mAbs are efficacious in treating multiple established subcutaneous murine tumors and that combining anti-mouse TIGIT 18G10-G2a with anti-mouse PD-1 leads to enhanced combination benefit over either single agent alone.

See the MK-7684/MK-7684A and pembrolizumab IBs for more information.

Refer to Section 4.1.2.1 for details on pembrolizumab preclinical studies.

4.1.2.3 MK-4280A

In the literature there are reports of co-blockade of PD-1 and LAG-3 with blocking antibodies in syngeneic mouse tumor models. Co-blockade was reported to result in greater tumor inhibition over either single agent in the Sal1N fibrosarcoma and MC38 colon adenocarcinoma tumor models [55]. However, co-blockade had minor effect on the poorly immunogenic B16F10 melanoma model [56]. Blockade of LAG-3 alone had modest anti-tumor activity in the MBT-2 bladder syngeneic mouse tumor model, whereas co-blockade of LAG-3 and PD-1 (with 28G10-mG1) resulted in greater numbers of animals with CRs and fewer numbers of animals with progressive disease compared with murinized anti-PD-1 alone in 2 independent studies. Loss of drug exposures over the course of therapy, preferentially in the combination therapy group, may underestimate the combination anti-tumor benefit. Curative murinized anti-PD-1 therapy or murinized anti-PD-1 and anti-LAG-3 combination therapy resulted in the establishment of long-term immune memory to MBT-2 tumor rechallenge [57].

See the MK-4280/MK-4280A and pembrolizumab IBs for more information.

Refer to Section 4.1.2.1 for details on pembrolizumab preclinical studies.

4.1.3 Ongoing Clinical Trials

Refer to the respective IBs for pembrolizumab, MK-7684A, and MK-4280A for clinical data regarding ongoing urothelial carcinoma trials, as well as other indications, including melanoma, NSCLC, head and neck, and hematologic malignancies.

4.2 Rationale

4.2.1 Rationale for the Trial and Selected Subject Population

Bladder cancer represents 4.4% of all new cancer diagnoses in the US; it is the fourth most common cancer in men, the tenth most common in women, and the tenth leading cause of cancer death overall. Bladder cancer accounts for an estimated 550,000 new cases and an estimated 200,000 deaths worldwide, and in the US alone there are an estimated 81,180 new cases and an estimated 17,100 deaths each year [58] [59]. Bladder cancer is more common in men than women; global incidence of bladder cancer among men and women is 32.4 and 8.0 per 100,000 person-years, respectively. Incidence in Non-Hispanic white, Non-Hispanic black, Non-Hispanic Asian/Pacific Islander, Non-Hispanic American Indian/Alaska Native, and Hispanic men is 38.5, 18.9, 15.3, 21.6, and 17.6, per 100,000 person-years, respectively. Bladder cancer becomes more common with age, with the highest incidence rates reported in people aged 65-74 years [59].

As well as age, smoking, occupational exposure to carcinogens, certain medical treatments (including pelvic radiation and cyclophosphamide), and genetic predisposition are risk factors for bladder cancer [60] [61] [62] [63] [64] [65] [61]. Notably, bladder cancer is associated with the highest cost per patient from diagnosis to death of all malignancies, largely owing to the frequent procedures required for disease monitoring and treatment [66].

Bladder cancer can be categorized as NMIBC, which represents 75% of primary diagnoses and is characterized by frequent recurrence and high morbidity but a low-risk of mortality, or muscle invasive bladder cancer, which represents the other 25% of primary diagnoses and is potentially lethal in approximately 50% of patients [67].

NMIBC is stratified as low, intermediate, and high-risk, according to the IBCG classification, with high-risk being defined as the presence of any High Grade, T1 or CIS. High-risk NMIBC affects 25,000 patients each year [68].

Progression to metastatic disease occurs in 20-30% of these individuals with death due to bladder cancer in nearly all of these patients [69] [70] [71] [72].

Standard therapy for high-risk NMIBC patients includes TURBT augmented by intravesical administration of BCG [73] [74]. BCG is a bovine mycoplasma derived agent which creates a profound immunologic/inflammatory reaction in the bladder epithelium, and thereby, reduces tumor recurrences. While BCG therapy is successful at preventing early tumor recurrences, most patients do not maintain sustained remissions [75] [76].

With 5-year follow-up, recurrent bladder tumors requiring repetitive TURBT and further cystoscopic surveillance are observed in 66% of patients. For post-BCG tumor recurrences, a second 6-week course of BCG may be administered at the discretion of the treating urologist if a significant disease-free interval was observed between the initial BCG instillation and the tumor recurrence. Ultimately, however, failure of BCG to prevent tumor recurrences presents a significant clinical challenge particularly in the BCG-refractory population where 5-year rates of progression to muscle invasive stage are observed in 58% of patients. Progression to metastatic disease occurs in 20-30% of these individuals with death due to bladder cancer in nearly all of these patients [69] [70] [71] [72].

Given the high-rate of progression to muscle invasive stages, both the American Urological Association (AUA) and the European Association of Urology have advocated for cystectomy as a standard option for BCG-refractory urothelial carcinoma (UC) patients [77] [78]. However, due to the 28% morbidity and 3% mortality rates associated with cystectomy, many patients either have comorbidities precluding surgical intervention or electively seek non-surgical alternative therapy options [79].

Additional intravesical therapy with non-BCG agents has been extensively evaluated both in the front-line and post-BCG settings [74] [80]. While 6-month CR rates have been encouraging once therapy is stopped 1-year relapse free survival rates have only been sustained in 10-15% of patients.

Recently, novel immune checkpoint inhibitors have been developed which block both the PD-1 and/or PD-L1 mediated pathways. In normal physiology, the PD-1/PD-L1 pathway functions to dampen inflammatory immune responses as a checkpoint balance preventing unregulated destructive inflammation. In UC, expression of PD-1 by TILs has been observed in 96% of muscle invasive UC patients undergoing cystectomy, with moderate or marked expression seen in 43% of patients. In small studies of NMIBC patients at least 30% of patients express PD-1 with an association noted between PD-1 expression and prior BCG

therapy. Additional studies have demonstrated marked expression of PD-L1 within 69% of post-BCG relapsed urothelial cancer tumors compared with 19% of BCG-naïve tumors from the same patients. Collectively, the data implicates the PD-1/PD-L1 pathway as key resistance mechanism to traditional BCG therapy [81].

In summary, a strong rationale exists to study pembrolizumab in patients with NMIBC unresponsive to BCG, based on the following:

- NMIBC represents a population amenable to immunotherapies;
- A public workshop held by the Food and Drug Administration (FDA) and AUA recognized BCG unresponsive NMIBC as an important unmet medical need for development of new therapies, as these patients have few available non-surgical options [82];
- Expression of PD-L1 is frequent in bladder cancer;
- Activation of the PD-1/PD-L1 pathway could be implicated in resistance to BCG therapy;
- Pembrolizumab has shown significant activity in a pre-treated population with metastatic urinary tract cancer [83].

Furthermore, in melanoma patients, disease burden was shown to be an independent prognostic factor in patients treated with pembrolizumab [84]. A somewhat analogous pattern is being observed in the metastatic urinary tract cancer cohort of KEYNOTE-012, though small numbers preclude assessment of any statistical significance.

Subjects with NMIBC, with smaller disease burden compared with patients with metastatic bladder cancer may attain even a greater benefit from immunotherapy with pembrolizumab.

Between 09-DEC-2015 and 01-APR-2018, of the 334 subjects screened in KEYNOTE-057, 101 subjects were enrolled in Cohort A and received at least one dose of pembrolizumab and included in the safety analysis. Of these 101 subjects, 96 subjects were included in the efficacy analysis. Median follow-up was 36.4 months (interquartile range: 32.0-40.7). Thirty-nine (41%; 95% CI 30.7–51.1) of 96 subjects with BCG-unresponsive carcinoma-in-situ of the bladder with or without papillary tumors had a CR at 3 months. Pembrolizumab monotherapy was tolerable and has shown promising anti-tumor activity in patients with BCG-unresponsive non-muscle invasive bladder cancer who declined or were ineligible for radical cystectomy. Based on these results, pembrolizumab received FDA approval for use in patients with BCG-unresponsive CIS tumors. Despite the modest efficacy, the 12-month CR rate was 19% (18/96) and thus there still remains a significant unmet need for therapies with longer duration of response.

Besides PD-1/PD-L1, there are other checkpoint molecules such as TIGIT and LAG3 that contribute to resistance to treatment in many cancers including UC. There is no clinical data available demonstrating efficacy of anti-TIGIT or anti-LAG3 with or without

anti-PD-1/PD-L1 inhibitors in bladder cancer; however, there has been recent literature evaluating the expression of many checkpoint molecules in bladder cancer. Compared with healthy donors, increased peripheral blood total NK cells, and higher TIGIT expression on NK, CD4+ and CD8+ T-cells were seen in NMIBC patients (26 prior BCG treated and 12 BCG-naïve). There was no difference in expression between responders and non-responders [85]. Similarly, stromal expression of LAG-3 has been shown to correlate with poor prognosis in mUC and expression in immune cell subsets tends to correlate with PD-1 expression [86]. Thus, TIGIT and/or LAG3 could potentially enhance the activity of anti-PD-1/PD-L1 pathways and will be explored in combination with pembrolizumab (coformulations).

Clinical data from the MK-7684-001 study suggests that vibostolimab demonstrates greatest activity in combination with pembrolizumab in subjects with advanced solid tumors. Activity appears to enrich in tumors that are IO responsive, such as bladder cancer and in biomarker groups consistent with the mechanism of action, including tumors expressing PD-L1 and those with immune infiltrate based on presence of CD4/CD8 cells or expression of an IFN-γ signature [87]. Based on responsiveness to immune checkpoints and biomarker expression of PD-L1, TIGIT, LAG3 and other markers of immune infiltration, and unmet medical need, it is expected that MK-7684A and MK-4280A will have an enhanced efficacy compared with pembrolizumab monotherapy alone. Coformulations of pembrolizumab with anti-TIGIT and anti-LAG3 inhibitors have the potential to build on the efficacy of pembrolizumab monotherapy with minimal added toxicity and thus offer an effective bladder sparing non-surgical treatment option.

4.2.2 Rationale for Dose Selection/Regimen/Modification

4.2.2.1 Rationale for Pembrolizumab Dose Selection/Regimen/Modification

The planned dose of pembrolizumab for this trial is 200 mg Q3W. Based on the totality of data generated in the Keytruda® development program, 200 mg Q3W is the 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 NSCLC indications demonstrating flat dose- and exposure-efficacy relationships from 2 mg/kg Q3W to 10 mg/kg every 2 weeks (Q2W) representing an approximate 5- to 7.5-fold exposure range (refer to pembrolizumab IB for additional details),

- Population pharmacokinetics (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 OS at 200 mg Q3W across multiple indications, and

- Pharmacology data showing full target saturation in both systemic circulation (inferred from PK data) and tumor (inferred from physiologically based PK [PB/PK] analysis) at 200 mg Q3W.

Traditionally, treatments for NMIBC have been delivered intravesically. However, given that the mechanism of action of pembrolizumab is by systemic activation of the immune system, intravenous administration is pertinent in this disease setting.

The dose modification algorithm for pembrolizumab will follow the FDA-approved scheme detailed in Section 5.2.1.

4.2.2.2 Rationale for MK-7684A Dose Selection/Regimen/Modification

MK-7684A is a single-use drug product vial containing a fixed-dose combination of 200 mg MK-7684 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. Study MK-7684-001 is evaluating the safety and PK biocomparability of this coformulated product to that of the sequential administration of MK-7684 and pembrolizumab.

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

Observed PK profiles of MK-7684 suggest that target-mediated clearance of MK-7684 is saturated at the 200/210 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 clearance and a limited central volume of distribution (Vc) [88] [89] [90]. As with other mAbs, body weight was found to be related to MK-7684 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 [91] [92]. In addition, observed PK parameters were generally similar across tumor types in Study MK-7684-001.

Available clinical safety data indicated that MK-7684 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 MK-7684 doses tested either as monotherapy or in combination with pembrolizumab during the dose escalation and confirmation portion of Study MK-7684-001, and the MTD was not reached.

Clinical activity was observed at the 200/210 mg and the 700 mg dose levels of MK-7684 both during the dose escalation and confirmation portion of Study MK-7684-001 in subjects with advanced solid tumors of all types and during the dose expansion portion, particularly in PD-1/PD-L1 inhibitor treatment-naïve subjects with NSCLC, cervical cancer, and PD-L1-positive ovarian and gastric cancer treated with MK-7684 in combination with pembrolizumab.

The 200 mg and 700 mg doses were compared in a randomized dose finding cohort of subjects 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 (based on preliminary data from 63 subjects) shows a flat relationship, suggesting that 200 mg is at the plateau of the exposure-efficacy relationship. CCI

[redacted]

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.

Based on available safety data and the results of preliminary population PK analysis, the Sponsor considers MK-7684A to be sufficiently comparable to sequentially administered vibostolimab and pembrolizumab to warrant further testing of MK-7684A in future studies.

4.2.2.3 Rationale for MK-4280A Dose Selection/Regimen/Modification

The planned dose of favezelimab in this study is 800 mg Q3W. Preliminary PK data from subjects treated in MK-4280-001 study receiving favezelimab alone and in combination with pembrolizumab in advanced solid tumors at doses from 7 mg to 800 mg showed that serum favezelimab exposures increased in a dose-dependent manner.

Preliminary PK profiles of favezelimab exposures suggest that target receptor-mediated clearance (reflecting target engagement of membrane LAG-3) of favezelimab was more likely to stay saturated at ≥700 mg dose compared with lower doses considering PK C_{trough} variability observed. Additionally, efficacy data from a randomized dose finding study in subjects with gastric cancer in MK-4280-001 suggested possible trend towards better efficacy at higher doses. Favezelimab given alone and in combination with pembrolizumab has been tolerable at all dose levels tested from 7 mg to 800 mg with no clear dose dependence in the type or frequency of AEs. For more detailed information, please refer to the MK-4280/MK-4280A IB. Therefore, based on the totality of preliminary data accumulated so far, a fixed-dose of 800 mg dose of favezelimab coformulated with 200 mg of pembrolizumab Q3W was selected for this trial.

4.2.3 Rationale for Endpoints

4.2.3.1 Efficacy Endpoints

4.2.3.1.1 Primary

Complete response rate and disease-free survival of high-risk NMIBC

The primary efficacy objective of this trial is to evaluate the anti-tumor activity of pembrolizumab, MK-7684A, and MK-4280A in subjects with high-risk NMIBC who are unresponsive to BCG, and who are considered either medically ineligible for cystectomy or have elected not to undergo the procedure. CR for subjects in Cohort A, DFS of high-risk NMIBC at 12-months for subjects in Cohort B, and CR at 12-months for subjects in Cohort C, as assessed by central pathology and radiology review, will be used as the primary efficacy endpoints.

Complete response in CIS and the 12-month DFS rate for (non-CIS) high-risk NMIBC are considered important endpoints in a single-arm study in this patient population with high unmet medical need and lack of non-surgical treatment options. The CR at 12 months in CIS allows to capture the durability of initial response that will aid in future clinical development with coformulations. Duration of response is the key differentiating factor for the coformulations, and subjects are expected to have a 12-month CR rate of at least 19% as seen with pembrolizumab monotherapy in Cohort A of KEYNOTE-057. In NMIBC, high-risk recurrences (including high grade Ta, low/high grade T1 and Tis) define treatment failure and dictate need for an alternative therapy. Low grade Ta recurrences are a biologically distinct entity, with lower rates of recurrence, progression, and death, as reported in several studies [93] [94] [95] [96] [97]. Subjects who experience low grade recurrences of Ta undergo repeat TURBTs and continue on the same therapy. Subjects who experience high-risk recurrences are at a greater risk for progression to muscle invasive disease, metastatic disease and death related to the disease. Patients who develop high grade urothelial carcinoma involving the upper tract will be considered to have had a high-risk recurrence and will be taken off study, and these events will be counted as such in the efficacy analyses.

While presence of CIS is a poor prognostic factor in treatment-naïve patients receiving BCG, it is not known if subjects with CIS will respond differently to anti-PD-1 blockage with pembrolizumab. Subjects will be assigned as follows:

Cohort A – with CIS at baseline (CIS only, Ta+CIS or T1+CIS); or

Cohort B – without CIS at baseline (High Grade Ta or Any Grade T1)

Cohort C – with CIS at baseline (CIS only, Ta+CIS or T1+CIS)

As of Amendment 09, enrollment in Cohorts A and B has been completed; additional subjects will be enrolled into Cohort C.

4.2.3.1.2 Secondary

Complete response or disease-free survival of any disease

Complete response (Cohorts A and C) and disease-free survival rate at 12 months (Cohort B) are considered valid endpoints in this patient population with high unmet medical need and lack of efficacious non-surgical treatment options, as defined in the FDA/AUA public workshop. Complete response (Cohorts A and C) and disease-free survival (Cohort B) of any disease will be key secondary endpoints.

Duration of response

Results observed with pembrolizumab in bladder and other cancers have shown extended durations of response not typically observed with existing agents. DOR has been recognized as an important goal and is cited as one of the primary reasons for the use of, for example, IL-2 in renal cell carcinoma.

PD-L1 Expression

PD-L1 expression in tumor tissue will be characterized by IHC using the PD-L1 IHC 22C3 pharmDx to examine the relationship between tumor PD-L1 expression and response to treatment with pembrolizumab. Pembrolizumab was approved by the FDA in 3 indications (first-line and second-line locally advanced/metastatic UC and high-risk NMIBC) regardless of PD-L1 status.

Overall survival

OS is the gold standard endpoint to demonstrate efficacy of an antineoplastic therapy.

Progression free survival

PFS either by grade/stage or PFS to muscle invasive or metastatic disease may be an acceptable scientific endpoint in a population.

Dates of progression will be determined by a composite assessment of cystoscopy/pathology and radiographic imaging. Central radiologists and pathologists will read the images and the pathology specimens to minimize bias in the response assessments.

4.2.3.1.3 Exploratory

4.2.3.1.3.1 Patient-reported Outcomes (For Cohorts A and B only)

The eEQ-5D, FACT-Bl, and CLSS are not pure efficacy or safety endpoints because they are affected by both disease progression and treatment tolerability. A description of these protocol-required assessments is notated below and must be completed by the subject as indicated Section 6.0 - Trial Flow Chart and in chronological order as specified below:

eEQ-5D

The eEQ-5D is a standardized instrument for use as a measure of health outcome. The eEQ-5D will provide data for use in economic models and analyses including developing health utilities or QALYs. The 5 health state dimensions in this instrument include the following: mobility, self-care, usual activities, pain/discomfort, and anxiety/depression [72]. Each dimension is rated on a 3-point scale from 1 (extreme problem) to 3 (no problem). The eEQ-5D also includes a graded (0 to 100) vertical visual analog scale on which the subject rates his or her general state of health at the time of the assessment.

FACT-Bl

The Functional Assessment of Chronic Illness Therapy (FACIT) is a general collection of quality-of-life questionnaires which are focused on the management of chronic illness. Included in these questionnaires are the Functional Assessment of Cancer Therapy (FACT) assessments, of which the FACT-Bl focuses specifically on subjects with bladder cancer. This questionnaire is a collection of items divided into 4 categories: physical well-being, social/family well-being, emotional well-being and functional well-being. These questionnaires are considered appropriate for use in subjects with any form of cancer and have also been used and validated in other chronic illnesses.

Core Lower Urinary Tract Symptom Score

The Core Lower Urinary Tract Symptom Score (CLSS) is a questionnaire measuring 10 symptoms (daytime frequency, nocturia, urgency, urgency incontinence, stress incontinence, slow urinary stream, straining, feeling of incomplete emptying, bladder pain, and urethral pain) rated on a point scale.

4.2.3.2 Safety Endpoints

The primary safety objective of this trial is to characterize the safety and tolerability of pembrolizumab, MK-7684A, and MK-4280A in subjects with high-risk NMIBC who are unresponsive to BCG. The primary safety analysis will be based on subjects who experienced toxicities as defined by CTCAE criteria. Safety will be assessed by quantifying the toxicities and grades experienced by subjects who have received pembrolizumab, MK-7684A, or MK-4280A, including SAEs and ECIs.

Safety will be assessed by reported adverse experiences using CTCAE, Version 4.0. Refer to Appendix 12.6 for details. The attribution to drug, time of onset, duration of the event, its resolution, and any concomitant medications administered will be recorded. AEs will be analyzed including, but not limited to, all AEs, SAEs, fatal AEs, and laboratory changes. These are routine safety parameters collected and analyzed in Phase II/III oncology trials. Furthermore, specific irAEs will be collected as described in Section 5.6 – Rescue Medications & Supportive Care.

4.2.3.3 Planned Exploratory Biomarker Research

Introduction: Cancer immunotherapies represent an important and novel class of anti-tumor agents. However, the mechanism of action of these exciting new therapies 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 immunotherapy and other treatments administered, as well as determinants of adverse events in the course of our clinical trials. These efforts may identify novel predictive/pharmacodynamic biomarkers and generate information that may better guide single agent and combination therapy with immune-oncology 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 (e.g., SNP analyses, whole exome sequencing, whole genome sequencing): This research may evaluate whether genetic variation within a clinical trial population correlates with response to the treatment(s) under evaluation. If genetic variation is found to predict efficacy or adverse events, 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, microsatellite instability (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 contributing towards the development/progression of cancer and/or driving response to therapy. Key molecular changes of interest to immune-oncology drug development include the mutational burden of tumors and the clonality of T-cells in the tumor microenvironment. Increased mutational burden (sometimes referred to as a 'hyper-mutated' state) may generate neo-antigen 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. MSI 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 pembrolizumab or other immunotherapies. Pembrolizumab induces a response in tumors that likely reflects an inflamed/ immune phenotype. Specific immune-related gene sets (such as those capturing interferon-gamma transcriptional pathways) may be evaluated and new signatures may be identified. Individual genes related to the immune system may also be evaluated (e.g., IL-10). MicroRNA profiling may also be pursued as well as exosomal profiling.

Proteomics and IHC using blood or tumor: Tumor and/or blood samples from this study may undergo proteomic analyses (e.g., PD-L1 IHC). PD-L1 protein level in tumor sections, assessed by IHC, has been shown to correlate with response to pembrolizumab in patients with NSCLC, and an in vitro diagnostic device has been developed for use with pembrolizumab in NSCLC. Preliminary data indicate that this association may also be true in additional cancer types (ie, triple-negative breast cancer [TNBC], head and neck, and gastric). Additional tumor or blood-derived proteins may also correlate with response to pembrolizumab. Therefore, tumor tissue may be subjected to proteomic analyses using a variety of platforms that could include, but are not limited to, immunoassays, liquid chromatography/mass spectrometry. This approach could identify novel protein biomarkers that could aid in patient selection for pembrolizumab, MK-7684A, and MK-4280A therapies.

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 enzyme-linked immunoassay 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.

PD-L1 IHC results from subjects with NSCLC, head and neck squamous cell carcinoma, cervical cancer, and esophageal squamous cell carcinoma treated with pembrolizumab, and TNBC treated with pembrolizumab plus chemotherapy, have shown that pre-treatment PD-L1 expression was a statistically significant predictor of response. The correlation of efficacy to PD-L1 expression in multiple tumor types indicates the value of this predictive biomarker for pembrolizumab. Therefore, at screening, subjects will be required to provide archival tumor tissue of sufficient quality to support the secondary, and exploratory objectives for this trial.

In addition, subjects will be required to provide tumor biopsies and urine samples obtained during the course of the trial to the central laboratory to assess for disease recurrence or progression and/or re-assess biomarker status.

Subjects will be enrolled onto this trial irrespective of PD-L1 expression (including subjects whose tumors do not express PD-L1). Archived tumor tissue specimens for study entry confirmation of NMIBC from recent cystoscopy/TURBTs will additionally be used for

determination of PD-L1 status using PD-L1 IHC 22C3 pharmDx to support the PD-L1 analysis of secondary and planned exploratory endpoints for this trial.

No relationship between candidate biomarkers and response to pembrolizumab in bladder cancer was found through analysis of data outside this trial (eg, in KEYNOTE-012, KEYNOTE-045, KEYNOTE-052 and other internal initiatives). The Sponsor does not intend to limit enrollment only to biomarker positive subjects at this point and will continue to monitor other ongoing studies (eg, KEYNOTE-676) in bladder cancer with pembrolizumab, MK-7684A, or MK-4280A.

4.2.4 Rationale for Interim Analysis (Cohort A Only)

A proof-of-concept IA (POC IA) will be conducted for the endpoint of 12-week rate of complete response of high-risk NMIBC in the first 20 patients (irrespective of PD-L1 biomarker status) who are enrolled onto Cohort A of this study. Cohort A has been chosen for the POC IA because these patients will begin treatment on study with active disease present in the bladder, such that responses can be observed directly thus enabling direct observation of clinical activity with pembrolizumab.

For the POC IA, efficacy will be determined as complete response defined as the complete cystoscopic resolution of high-risk non-muscle invasive bladder cancer at the time of the 12-week assessment. If sufficient complete responses are observed, the study will continue enrollment.

Because recurrences of high-risk disease would be expected to increase over time, the target response rate for the POC IA will be set at 35% or greater (a higher rate than that of the overall hypothesis for the study, 20%). Sufficient clinical responses must be observed such that the upper bound of the 95% confidence interval (CI) of the complete response rate, assessed by the binomial exact method, must be 35% or greater. For a sample size of 20 patients, at least 3 patients with complete responses must be observed for the study to continue under the current study design. Only subjects with at least one post-baseline disease evaluation in Cohort A are considered as available for the IA.

When the first 50 evaluable patients reach and complete the 24-week evaluation, a second evaluation will be performed wherein the durability of complete responses will be assessed.

To minimize the risk that patients might be exposed to an ineffective treatment, in particular PD-L1 negative patients, the following contingency plan with respect to the POC IA and its outcome(s) has been made:

- If insufficient complete responses (<3) are observed among the first 20 subjects in Cohort A, the study will be closed to enrollment of PD-L1 negative subjects, and a second POC IA will be conducted for the first 20 PD-L1 positive subjects who reach the 12-week assessment and are available for IA in Cohort A. If there are sufficient complete responses in PD-L1 positive subjects, the study will remain open to PD-L1 positive patients only, and the durability assessment will be performed when there are 50 PD-L1 positive subjects who have reached and completed the 24-week

assessment. If there is insufficient activity among the PD-L1 positive group, the study will be closed.

It is anticipated that the enrollment rates to Cohort A and Cohort B will be similar. However, if Cohort B enrolls more quickly such that 75 Cohort B subjects have been enrolled before the POC IA has begun in Cohort A, enrollment onto Cohort B will be temporarily halted until the POC IA has begun.

The results of the POC IA will be reported to an independent, external Data Monitoring Committee. The Data Monitoring Committee (DMC) will review interim trial results, consider the overall risk and benefit to trial subjects, and recommend if the trial should continue in accordance with the protocol. In order for this group to provide timely advice, PD-L1 status and clinical responses will be tracked by the study team in real time.

There is no planned IA for efficacy for Cohorts B and C. The internal Data Monitoring Committee will review ongoing safety and efficacy data, consider the overall risk and benefit to trial subjects, and recommend if the trial should continue in accordance with the protocol.

4.2.4.1 Future Biomedical Research

The Sponsor will conduct Future Biomedical Research on specimens collected for future biomedical research during this clinical trial. This research may include genetic analyses (DNA), gene expression profiling (RNA), proteomics, metabolomics (serum, plasma) and/or the measurement of other analytes.

Such research is for biomarker testing to address emergent questions not described elsewhere in the protocol (as part of the main trial) and will only be conducted on specimens from appropriately consented subjects. The objective of collecting specimens for Future Biomedical Research is to explore and identify biomarkers that inform the scientific understanding of diseases and/or their therapeutic treatments. For instance, exploratory pharmacogenetic (PGt) studies may be performed if significant Pharmacokinetic/Pharmacodynamic (PK/PD) relationships are observed or adverse events are identified. Genomic markers of disease may also be investigated. Such retrospective pharmacogenetic studies will be conducted with appropriate biostatistical design and analysis and compared to PK/PD results or clinical outcomes. Any significant PGt relationships to outcome would require validation in future clinical trials. The overarching goal is to use such information to develop safer, more effective drugs/vaccines, and/or to ensure that subjects receive the correct dose of the correct drug/vaccine at the correct time. The details of this Future Biomedical Research are presented in Appendix 12.2 - Collection and Management of Specimens for Future Biomedical Research. Additional informational material for institutional review boards/ethics committees (IRBs/ERCs) and investigational site staff is provided in Appendix 12.3.

4.3 Benefit/Risk

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

There is currently no standard non-surgical treatment for patients with NMIBC after BCG failure. The standard of care in this patient population is radical cystectomy, a procedure with significant associated morbidity and mortality. Pembrolizumab has shown some efficacy in heavily pre-treated metastatic bladder cancer and results of the current study has demonstrated efficacy in patients with BCG unresponsive CIS ± papillary tumors (Cohort A) who declined or ineligible for radical cystectomy. Findings in the bladder cancer POC cohort suggested that subjects with smaller disease burden could be experiencing a greater benefit from therapy, a finding that has been observed in the larger melanoma cohort within the pembrolizumab program. Based on these results, pembrolizumab received FDA approval for use in patients with BCG unresponsive CIS tumors.

Evaluating pembrolizumab, MK-7684A, and MK-4280A in subjects with NMIBC who are unresponsive to BCG, and either are ineligible for surgery, or have elected not to undergo the procedure, represents the opportunity to study the benefits of these agents in a population with high unmet need, and relatively small tumor burden.

The available clinical data on MK-4280 in combination with pembrolizumab has shown promising early efficacy results in patients with advanced NSCLC, gastric cancer, as well as in the first-line for melanoma patients and provides rationale to further evaluate this combination in other indications such as urothelial carcinoma. Currently, there is no data available with MK-4280 alone or in combination with pembrolizumab in the urothelial carcinoma population. However, the safety profile of the combination in other indications suggests that it is generally tolerable, with a safety profile similar to that of pembrolizumab monotherapy in prior studies. It is therefore hypothesized that the coformulation of MK-4280 and pembrolizumab (MK-4280A) will provide an efficacy advantage over pembrolizumab alone, without negatively impacting the safety of the patients being treated with this combination. Additional details regarding specific benefits and risks for subjects participating in this clinical study may be found in the accompanying IB and informed consent documents.

Early phase studies have shown promising results with the combination of MK-7684 and pembrolizumab in PD-1/PD-L1-treatment-naïve NSCLC and PD-L1 positive cervical cancer. The safety data for this combination in these early phase studies is similar to that with pembrolizumab monotherapy in prior studies, and the combination has been generally tolerable. The promising efficacy data as well as the safety profile of this combination support the hypothesis that the coformulation of MK-7684 and pembrolizumab (MK-7684A) will provide an efficacy advantage over pembrolizumab alone, without negatively impacting the safety of the patients being treated with this combination. Additional details regarding specific benefits and risks for subjects participating in this clinical study may be found in the accompanying IB and informed consent documents.

5.0 METHODOLOGY

Changes that apply as of Amendment 12 are listed in Section 1.0 and supersede any protocol content/instructions from previous amendments. Existing protocol content in this section is retained for historical reference.

5.1 Entry Criteria

5.1.1 Diagnosis/Condition for Entry into the Trial

Male and female subjects with high-risk NMIBC of at least 18 years of age who are unresponsive to BCG, and are ineligible for radical cystectomy/elected not to undergo the procedure will be enrolled in this trial.

5.1.2 Subject Inclusion Criteria

1. In order to be eligible for participation in this trial, the subject must: be willing and able to provide documented informed consent/assent for the trial. The subject may also provide consent/assent for Future Biomedical Research. However, the subject may participate in the main trial without participating in Future Biomedical Research.

2. Be ≥18 years of age on day of providing documented informed consent.

3. Have a histologically-confirmed diagnosis of high-risk non-muscle invasive (T1, High Grade Ta and/or CIS) transitional cell carcinoma of the bladder. Subjects with tumors of mixed transitional/non-transitional cell histology are allowed, but transitional cell carcinoma must be the predominant histology. Subjects with predominant or exclusively non-transitional cell histology are not allowed. Confirmation of histology, grade and stage will be performed by central review and must be completed during the screening period and prior to enrollment. Subjects with CIS must have CIS present on the tumor sample from the most recent cystoscopy/TURBT. Confirmation of T1 stage tumor requires the presence of detrusor muscle. The tumor samples submitted for central review must be from the most recent TURBT/biopsy available prior to randomization and include both the diagnostic and restaging TURBT/biopsy as applicable.

4. In subjects who have papillary tumors (Ta and T1), a complete TURBT must have been performed, as characterized by:

    - Attainment of a visually complete resection of all papillary tumors (Ta and T1)

    - Residual CIS not amenable to complete resection is allowed.

    - The most recent cystoscopy/TURBT must have been performed within 12 weeks of randomization.

- For Cohort C, subjects with T1 disease should have undergone a restaging TURBT procedure within 12 weeks prior to randomization to confirm complete resection and that the subject continues to meet eligibility criteria.

    - If restaging TURBT is performed within 12 weeks prior to randomization and the absence of muscle invasive tumor (≥T2) is confirmed by central pathology review, subjects are still eligible even if first TURBT was performed >12 weeks prior to randomization.

    - Tissue resected during restaging TURBT must be sent to central pathology lab for tumor histology evaluation with results confirming eligibility prior to randomization.

5. Have been treated with adequate BCG therapy and have developed **high-risk NMIBC that is unresponsive to BCG therapy**.

    - ***Adequate BCG therapy*** *must include:*

        - An induction course with at least 5 instillations of BCG (adequate induction) and

        - At least 7 instillations of BCG within 9 months of the first instillation of adequate induction course).

    - ***For Cohorts A and B, BCG unresponsive high-risk NMIBC*** *is defined as:*

        - Stage progression at 3 months (±4 weeks) despite adequate induction therapy (eg, Ta to T1, or CIS to T1; note: adequate induction therapy only, defined above, is required in this case); or

        - High grade T1 disease at the first evaluation after adequate BCG induction or

        - Persistent high-risk NMIBC at 6 months (±4 weeks) after adequate BCG; or

        - Recurrent high-risk NMIBC within 9 months of the last BCG instillation despite having received adequate BCG.

            Note: The last BCG instillation must have been within 9 months of the most recent HR NMIBC recurrence with which the subject enrolled on study.

    - ***For*** **Cohort C,** ***BCG unresponsive high-risk NMIBC*** *is defined as:*

        - Persistent or recurrent CIS alone or with Ta/T1 within 12 months of completion of adequate BCG therapy.

            Note: Stage progression (eg, CIS ± Ta to CIS + T1) at 3 months (±4 weeks) despite adequate induction therapy as defined above are eligible.

Note: The NMIBC recurrence with which the subject was deemed BCG-unresponsive does not have to be the most recent recurrence with which the subject enrolls into the study.

6. Have elected not to undergo, or are considered ineligible for radical cystectomy, as determined by the treating physician. Reasons for ineligibility or refusal of radical cystectomy should be discussed with the subject as part of the informed consent process and should be captured on the appropriate case report form. Ineligibility factors for radical cystectomy may include, but are not limited to:

   - Cardiovascular disease (eg, recent acute coronary syndrome, arrhythmia, heart failure)
   - Chronic obstructive pulmonary disease that would preclude a safe surgical procedure, as determined by the treating physician
   - Poor performance status (eg, ECOG >2)
   - Prior major abdominal and pelvic surgery that would preclude a safe surgical procedure, as determined by the treating physician

7. Have provided tissue for biomarker analysis from the most recent cystoscopy/TURBT procedures from which tumor sample is available. If submitting unstained cut slides, freshly cut slides should be submitted to the testing laboratory within 14 days from when the slides are cut. See Section 7.1.2 for an explanation.

   Note: It is preferred that the sample for PD-L1 analysis is taken from the most recent TURBT (ie, the same time point submitted for histology review). However, if there is not sufficient tissue, a sample can be provided from an earlier TURBT taken within 12 weeks before first dose of study treatment.

8. Have a performance status of 0, 1 or 2 on the Eastern Cooperative Oncology Group (ECOG) Performance Scale, as assessed within 28 days prior to treatment initiation. A maximum of 5% of subjects with ECOG 2 status will be enrolled into the study (for Cohorts A and B only).

9. Have adequate organ function as defined in Table 1. All screening labs should be performed within 28 days prior to treatment initiation.

   - *Subjects may not have received transfusion of packed red blood cells (PRBCs) or platelets within 4 weeks prior to screening.*

Table 1 Adequate Organ Function Laboratory Values

System	Laboratory Value
Hematological	
Absolute neutrophil count (ANC)	≥1,500/mcL
Platelets	≥100,000/mcL – without recent transfusion
Hemoglobin	≥9 g/dL or ≥5.6 mmol/L – without recent transfusion
Renal	
Measured or calculated creatinine clearance **OR** GFR	≥30 mL/min **OR** GFR ≥30 mL/min
Hepatic	
Total bilirubin	≤1.5xULN **OR** Direct bilirubin ≤ULN for subjects with total bilirubin levels >1.5xULN
AST (SGOT) and ALT (SGPT)	≤2.5xULN
Coagulation	
International Normalized Ratio (INR) or Prothrombin Time (PT) Activated Partial Thromboplastin Time (aPTT)	≤1.5xULN unless subject is receiving anticoagulant therapy as long as PT or PTT is within therapeutic range of intended use of anticoagulants
GFR = glomerular filtration rate; PTT = partial thromboplastin time; ULN = upper limit of normal	

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

    - Is not a WOCBP

      OR

    - Is a WOCBP and using a contraceptive method that is highly effective (with a failure rate of <1% per year), with low user dependency, or be abstinent from heterosexual intercourse as their preferred and usual lifestyle (abstinent on a long-term and persistent basis), as described in Appendix 12.9 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.

    - A WOCBP must have a negative highly sensitive pregnancy test (urine or serum as required by local regulations) within 24 hours for urine or within 72 hours for serum 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 subject must be excluded from participation if the serum pregnancy result is positive.

- Additional requirements for pregnancy testing during and after study intervention are located in Section 7.1.3.1.1.

- The investigator is responsible for review of medical history, menstrual history, and recent sexual activity to decrease the risk for inclusion of a woman with an early undetected pregnancy.

- Contraceptive use by females should be consistent with local regulations regarding the methods of contraception for those participating in clinical studies. If the contraception requirements in the local label for any of the study drugs is more stringent than the requirements above, the local label requirements should be followed.

5.1.3 Subject Exclusion Criteria

The subject must be excluded from participating in the trial if the subject:

1. Has centrally assessed muscle invasive (ie, T2, T3, T4) locally advanced non-resectable or metastatic urothelial carcinoma.

2. Has centrally assessed concurrent extra-vesical (ie, urethra, ureter or renal pelvis) non-muscle invasive transitional cell carcinoma of the urothelium.

3. Is currently participating and receiving study therapy or has participated in a study of an investigational agent and received study therapy or used an investigational device within 4 weeks of the first dose of treatment.

4. Has undergone any intervening intravesical chemotherapy or immunotherapy from the time of most recent cystoscopy/TURBT to starting trial treatment. (Note: A single dose of intravesical treatment given as part of the most recent cystoscopy/TURBT, during the screening period, such as with chemotherapy as per local/regional practices, is acceptable.)

5. Has had prior chemotherapy, targeted small molecule therapy, or radiation therapy within 2 weeks prior to Cycle 1, Day 1 or who has not recovered (ie, ≤Grade 1 or at baseline) from adverse events due to a previously administered agent.

    - *Subjects with ≤Grade 2 neuropathy or ≤Grade 2 alopecia are an exception to this criterion and may qualify for the study.*

    - *If subject has undergone major surgery, they must have recovered adequately from the toxicity and/or complications from the intervention prior to starting therapy.*

6. Has a known additional malignancy that has had progression or has required active treatment in the last 3 years. Exceptions include basal cell carcinoma of the skin, squamous cell carcinoma of the skin that has undergone potentially curative therapy or in situ cervical cancer. A history of prostate cancer that was treated with definitive intent

(surgically or through radiation therapy) is acceptable, provided that the following criteria are met: Stage T2N0M0 or lower with a Gleason score ≤7 and prostatic-specific antigen (PSA) undetectable for at least 1 year while off androgen deprivation therapy that was either treated with definitive intent or untreated in active surveillance that has been stable for the past year prior to study allocation.

7. Has present or progressive accumulation of pleural, ascitic, or pericardial fluid requiring drainage or diuretic drugs (exception for use in hypertension) within 2 weeks before randomization/study allocation for Cohort C.

8. Has severe hypersensitivity (≥Grade 3) to pembrolizumab (all cohorts), MK-7684A (Cohort C Arm 1), MK-4280A (Cohort C Arm 2), and/or any of their excipients.

9. Has an active autoimmune disease that has required systemic treatment in past 2 years (ie, with use of disease modifying agents, corticosteroids or immunosuppressive drugs). Replacement therapy (eg, thyroxine, insulin, or physiologic corticosteroid replacement therapy for adrenal or pituitary insufficiency, etc) is not considered a form of systemic treatment.

10. 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 to the first dose of the study intervention. The use of physiologic doses of corticosteroids may be approved after consultation with the Sponsor.

11. Has a history of (noninfectious) pneumonitis/interstitial lung disease that required steroids or has current pneumonitis.

12. Has an active infection requiring systemic therapy, including active or intractable UTI in the last month.

13. Has a history or current evidence of any condition, therapy, or laboratory abnormality that might confound the results of the trial, interfere with the subject's participation for the full duration of the trial, or is not in the best interest of the subject to participate, in the opinion of the treating investigator.

14. Has a known psychiatric or substance abuse disorder that would interfere with the subject's ability to cooperate with the requirements of the trial.

15. Is pregnant or breastfeeding, or expecting to conceive within the projected duration of the trial, starting with the screening visit through 120 days after the last dose of trial treatment.

16. Has received prior therapy with an anti-PD-1, anti-PD-L1, anti-PD-L2 agent, or with an agent directed to another coinhibitory T-cell receptor (eg, CTLA-4, OX-40, CD137).

17. Has received previous treatment with another agent targeting the TIGIT and/or LAG3 receptor pathway (Cohort C only).

18. Has a known history of Human Immunodeficiency Virus (HIV) (HIV-1/2 antibodies). No HIV testing is required unless mandated by local health authority.

    Note (for Cohort C): HIV-infected subjects who have well controlled HIV on ART are eligible, defined as:

    - Subjects on ART must have a CD4+ T-cell count >350 cells/mm^3 at the time of Screening.
    - Subjects on ART must have 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.
    - It is advised that subjects must not have had any AIDS-defining opportunistic infections within the past 12 months.
    - Subjects on ART must have been on a stable regimen, without changes in drugs or dose modification, for at least 4 weeks before study entry (randomization/allocation).

19. Has known active Hepatitis B (eg, HBsAg reactive) or Hepatitis C (eg, HCV RNA [qualitative] is detected).

    Note (for Cohort C): Subjects who are HBsAg positive are eligible if they have received HBV antiviral therapy for at least 4 weeks and have undetectable HBV viral load prior to randomization. Subjects should remain on antiviral therapy throughout study intervention and follow local guidelines for HBV antiviral therapy postcompletion of study intervention.

    No testing for Hepatitis B and Hepatitis C is required unless mandated by local health authority.

20. Has received a live virus vaccine within 30 days of planned start of trial treatment. Refer to Section 5.5.2 for information on COVID-19 vaccines.

21. Has had an allogeneic tissue/solid organ transplant.

5.2 Trial Treatment(s)

The treatment to be used in this trial is outlined below in Table 2.

Table 2 Trial Treatment

Arm Name	Arm Type	Intervention Name	Intervention Type	Dose Formulation	Unit Dose Strength(s)	Dosage Level(s)	Route of Adminis-tration	Regimen/ Treatment Period/ Vaccination Regimen	Use	IMP or NIMP/ AxMP	Sourcing
Cohorts A and B	Experimental	Pembrolizumab	Biological/ Vaccine	Solution for Infusion	25 mg/mL	200 mg	IV infusion	Q3W; Day 1 of each cycle	Test Product	IMP	Centrally by Sponsor
Cohort C Arm 1	Experimental	MK-7684A	Biological/ Vaccine	Solution for Infusion	MK-7684 200 mg + pembrolizumab 200 mg/ 20 mL vial	200 mg/ 200 mg	IV Infusion	Q3W; Day 1 of each cycle	Test Product	IMP	Centrally by Sponsor
Cohort C Arm 2	Experimental	MK-4280A	Biological/ Vaccine	Solution for Infusion	MK-4280 20 mg/mL + pembrolizumab 5 mg/mL	800 mg/ 200 mg	IV Infusion	Q3W; Day 1 of each cycle	Test Product	IMP	Centrally by Sponsor
Cohort C Arms 1 and 2	Experimental	Pembrolizumab	Biological/ Vaccine	Solution for Infusion	25 mg/mL	200 mg	IV infusion	Q3W; Day 1 of each cycle	Test Product	IMP	Centrally by Sponsor or Locally

IMP = investigational medicinal product; IV = intravenous; NIMP/AxMP = noninvestigational/auxiliary medicinal product; Q3W = every 3 weeks.

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 European Economic Area (EEA). Country differences with respect to the definition/classification of IMP and NIMP/AxMP may exist. In these circumstances, local legislation is followed.

Trial treatment should begin on the day of randomization or as close as possible to the date on which the subject is allocated/assigned.

All supplies indicated in Table 2 above will be provided centrally by the Sponsor or locally by the trial site, subsidiary or designee, depending on local country operational or regulatory requirements.

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 trial treatments in accordance with the protocol and any applicable laws and regulations.

5.2.1 Dose Modification (Escalation/Titration/Other)

5.2.1.1 Dose Selection (Preparation)

The rationale for selection of doses to be used in this trial is provided in Section 4.0 – Background & Rationale. There are no specific calculations or evaluations required to be performed in order to administer the proper dose to each subject.

5.2.1.2 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 subject must be discontinued from pembrolizumab monotherapy, coformulations, or IO combinations.

Restarting Study Interventions:

Subjects 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 3.

Table 3 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 (CTCAEv4.0)	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 1-2 mg/kg prednisone or equivalent) followed by taper	• Monitor subjects for signs and symptoms of pneumonitis • Evaluate subjects with suspected pneumonitis with radiographic imaging and initiate corticosteroid treatment • Add prophylactic antibiotics for opportunistic infections
	Recurrent Grade 2 or Grade 3 or 4	Permanently discontinue		
Diarrhea / Colitis	Grade 2 or 3	Withhold	• Administer corticosteroids (initial dose of 1-2 mg/kg prednisone or equivalent) followed by taper	• Monitor subjects 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) • subjects with ≥Grade 2 diarrhea suspecting colitis should consider GI consultation and performing endoscopy to rule out colitis • subjects 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 (CTCAEv4.0)	Action With Pembrolizumab Monotherapy, Coformulations or IO Combinations	Corticosteroid and/or Other Therapies	Monitoring and Follow-up
AST / ALT Elevation or Increased Bilirubin	Grade 2	Withhold	• Administer corticosteroids (initial dose of 0.5-1 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 or 4	Permanently discontinue	• Administer corticosteroids (initial dose of 1-2 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 [a]	• Initiate insulin replacement therapy for subjects with T1DM • Administer anti-hyperglycemic in subjects with hyperglycemia	• Monitor subjects 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 [a]		
Hyperthyroidism	Grade 2	Continue	• Treat with non-selective beta-blockers (eg, propranolol) or thionamides as appropriate	• Monitor for signs and symptoms of thyroid disorders
	Grade 3 or 4	Withhold or Permanently discontinue [a]		

irAEs	Toxicity Grade (CTCAEv4.0)	Action With Pembrolizumab Monotherapy, Coformulations or IO Combinations	Corticosteroid and/or Other Therapies	Monitoring and Follow-up
Hypothyroidism	Grade 2-4	Continue	• Initiate thyroid replacement hormones (eg, levothyroxine or liothyronine) per standard of care	• Monitor for signs and symptoms of thyroid disorders
Nephritis and renal dysfunction	Grade 2	Withhold	• Administer corticosteroids (prednisone 1-2 mg/kg or equivalent) followed by taper	• Monitor changes of renal function
	Grade 3 or 4	Permanently discontinue		
Myocarditis	Grade 1	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		
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 [b]		
	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] 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.

[b] Events that require discontinuation include, but are not limited to: Guillain-Barre Syndrome, encephalitis, myelitis, DRESS, SJS, TEN and other clinically important irAEs (eg, vasculitis and sclerosing cholangitis).

Dose Modification and Toxicity Management of Infusion Reactions Related to Pembrolizumab Monotherapy or Coformulations (MK-7684A or MK-4280A)

Pembrolizumab monotherapy, coformulations (MK-7684A or MK-4280A) 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 MK-4280A) associated infusion reaction are provided in Table 4.

Table 4 Pembrolizumab Monotherapy or Coformulations (MK-7684A or MK-4280A) 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 subject 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 hrs	**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 subject 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 (e.g. from 100 mL/hr to 50 mL/hr). Otherwise, dosing will be held until symptoms resolve and the subject should be premedicated for the next scheduled dose. Subjects who develop Grade 2 toxicity despite adequate premedication should be permanently discontinued from further study drug treatment.	Subject may be premedicated 1.5h (± 30 minutes) prior to infusion of pembrolizumab with: • Diphenhydramine 50 mg po (or equivalent dose of antihistamine). • Acetaminophen 500-1000 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 following 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 subject is deemed medically stable in the opinion of the investigator. Hospitalization may be indicated. **In cases of anaphylaxis, epinephrine should be used immediately. **Subject is permanently discontinued from further study drug treatment.**	No subsequent dosing
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 Common Terminology Criteria for Adverse Events v4.0 (CTCAE) at http://ctep.cancer.gov		

Other Allowed Dose Interruption for Pembrolizumab Monotherapy or Coformulations (MK-7684A or MK-4280A)

Pembrolizumab monotherapy or coformulations 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 of the originally scheduled dose and within 6 weeks of the previously administered dose, unless otherwise discussed with the Sponsor. The reason for study intervention interruption is to be documented in the subject's study record.

5.2.2 Timing of Dose Administration

Subjects will be considered enrolled in this trial when the unique allocation number is assigned to each subject by the interactive voice response system (IVRS). Once the subject is enrolled, trial treatment should be administered on Day 1 of each cycle after all procedures/assessments have been completed as detailed in Section 6.0 – Trial Flow Chart. Trial treatment may be administered up to 3 days before or after the scheduled Day 1 of each

cycle due to administrative reasons. Trial treatments will be administered on an outpatient basis unless the subject is hospitalized for an unrelated reason.

Pembrolizumab 200 mg for subjects in Cohorts A and B, and MK-7684A, or MK-4280A for subjects in Cohort C, will be administered as a 30-minute IV infusion Q3W. Sites should make every effort to target infusion timing to be as close to 30 minutes as possible. However, given the variability of infusion pumps from site to site, a window of -5 minutes and +10 minutes is permitted (ie, infusion time is 30 minutes: -5 min/+10 min).

The Pharmacy Manual contains specific instructions for pembrolizumab, MK-7684A, and MK-4280A dose calculation, reconstitution, preparation of the infusion fluid, and administration.

5.2.3 Treatment After Disease Recurrence

Immunotherapeutic agents such as pembrolizumab, MK-7684A, and MK-4280A may produce anti-tumor effects by potentiating endogenous cancer-specific immune responses. The response patterns seen with such an approach may extend beyond the typical time course of responses seen with cytotoxic agents and can manifest as a clinical response after an initial increase in tumor burden or even the appearance of new lesions.

In trials of pembrolizumab in metastatic disease, this has led to the treatment paradigm of continuing therapy beyond initial radiologic progression – provided the subjects meet specific criteria and the investigator believes the subject is deriving benefit from pembrolizumab therapy.

NMIBC patients receiving BCG therapy who experience persistent disease at 6-month cystoscopy, recurrent high-risk disease within the first 6 months or local progression (by grade or stage) are considered treatment-refractory, and thus discontinue BCG therapy. Patients with low grade Ta recurrences undergo repeat TURBT and continue on therapy. Low grade Ta relapses are biologically distinct entity from high-risk relapses.

While BCG, pembrolizumab, MK-7684A, and MK-4280A have very distinct mechanisms of action, within the spectrum of all anti-tumor therapies, both target the same cancer hallmark – the ability to evade the immune system. Similar paradigms will therefore be applied.

Subjects who have persistent, recurrent, or progressive high-risk NMIBC (by grade or stage), confirmed extra-vesical disease by CTU imaging, and/or are clinically unstable at any time point or as specified in the protocol should discontinue trial treatment.

Subjects who have, on central pathology review, low grade Ta recurrences may undergo TURBT and continue in the trial receiving pembrolizumab, MK-7684A, or MK-4280A treatment (Table 5).

The decision to continue trial treatment after the first evidence of recurrence by cystoscopy and local pathology is at the investigator's discretion based on the clinical status of the subject. CTU imaging of the abdomen and pelvis assuring the absence of extra-vesical

disease will be required. Subjects may receive trial treatment for up to one additional cycle, while waiting for central pathology confirmation if they are clinically stable as defined by the following criteria:

- Absence of signs and symptoms (including worsening of laboratory values) indicating disease progression
- No decline in ECOG performance status
- Absence of rapid progression of disease.

Table 5 Assessment and Treatment after First Evidence of Recurrence

	Clinically Stable*		
	Cystoscopy	**Imaging**	**Treatment**
Evidence of LOWGRADE Ta recurrence by cystoscopy and local pathology	Resection of all visible lesions by TURBT. Repeat cystoscopy/ TURBT and cytology in 12 weeks.	Evaluation for extra-vesical disease with CTU of the abdomen and pelvis.	Continue trial treatment at the investigator's discretion, to be confirmed by central pathology and local radiology review.
First evidence of HIGH-RISK (High Grade Ta, Any grade T1, or CIS) recurrence by cystoscopy and local pathology (Cohorts A and B)	Resection of all visible 'papillary' lesions by TURBT. Directed biopsies of 'flat' lesions are acceptable. Repeat cystoscopy and urine cytology per standard of care.	Evaluation for extra-vesical disease with CTU of the abdomen and pelvis.	Continue trial treatment (upon receipt of local pathology report confirming high-risk NMIBC recurrence) for up to one additional cycle at the investigator's discretion and upon consultation with the Sponsor while awaiting central pathology and local radiology review. Consider discontinuation of trial treatment and radical cystectomy.
For Cohort C: First evidence of T1 at any time or HIGH-RISK (High Grade Ta, or CIS) at 24-week or thereafter by cystoscopy and local pathology	Resection of all visible 'papillary' lesions by TURBT. Directed biopsies of 'flat' lesions are acceptable. Repeat cystoscopy and urine cytology per standard of care.	Evaluation for extra-vesical disease with CTU of the abdomen and pelvis.	Continue trial treatment (upon receipt of local pathology report confirming high-risk NMIBC recurrence) for up to one additional cycle at the investigator's discretion and upon consultation with the Sponsor while awaiting central pathology and local radiology review. Consider discontinuation of trial treatment and radical cystectomy.

	Clinically Stable*		
	Cystoscopy	**Imaging**	**Treatment**
Evidence of recurrence by CYTOLOGY only**, with negative cystoscopy	Random biopsies of normal-looking bladder urothelium. Biopsies of the trigone, bladder dome, left, right, anterior and posterior walls, and the prostatic urethra (for males) should be performed.	Evaluation for extra-vesical disease with CTU of the abdomen and pelvis.	Random (r-) biopsies should be scheduled and performed prior to the next scheduled efficacy assessment. Continue trial treatment while awaiting central pathology and local radiology review.
*If subjects are clinically unstable, they will not remain on treatment. **Evidence of recurrence by CYTOLOGY only is defined as central pathology urine cytology outcome reported as 'High Grade Urothelial Carcinoma' or 'Suspicious for High Grade Urothelial Carcinoma.'			

5.2.4 Trial Blinding/Masking

This is an open-label trial; therefore, the Sponsor, investigator and subject will know the treatment administered.

Clinical outcome and subject-level PD-L1 biomarker results will not be masked in the database to the study team at the Sponsor.

5.3 Randomization or Treatment Allocation

Randomization/allocation will occur centrally using an interactive voice response system/ integrated web response system (IVRS/IWRS). Subjects in Cohort A and B will be assigned to pembrolizumab by non-random assignment in an unblinded fashion. Subjects in Cohort C will be randomly assigned in 1:1 ratio to receive either MK-7684A or MK-4280A in an unblinded fashion.

5.4 Stratification

No stratification based on age, sex or other characteristics will be used in this trial.

5.5 Concomitant Medications/Vaccinations (Allowed & Prohibited)

Medications or vaccinations specifically prohibited in the exclusion criteria are not allowed during the ongoing trial. If there is a clinical indication for any medication or vaccination specifically prohibited during the trial, discontinuation from trial therapy or vaccination may be required. The investigator should discuss any questions regarding this with the Sponsor Clinical Director. The final decision on any supportive therapy or vaccination rests with the investigator and/or the subject's primary physician. However, the decision to continue the subject on trial therapy or vaccination schedule requires the mutual agreement of the investigator, the Sponsor and the subject.

5.5.1 Acceptable Concomitant Medications

All treatments that the investigator considers necessary for a subject'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 case report form (CRF) including all prescription, over-the-counter (OTC), herbal supplements, and IV medications and fluids. If changes occur during the trial period, documentation of drug dosage, frequency, route, and date may also be included on the CRF.

All concomitant medications received within 30 days before the first dose of trial treatment and 30 days after the last dose of trial treatment should be recorded. Concomitant medications administered after 30 days after the last dose of trial treatment should be recorded for SAEs and ECIs as defined in Section 7.2 – Assessing and Recording Adverse Events.

5.5.2 Prohibited Concomitant Medications

Subjects are prohibited from receiving the following therapies during the screening and treatment phase of this trial:

- Antineoplastic chemotherapy or biological therapy (systemic or intravesical)

  Note: A single dose of intravesical treatment given as part of the most recent cystoscopy/TURBT, during the screening period, such as with chemotherapy as per local/regional practices, is acceptable.

- Immunotherapy not specified in this protocol

- Investigational agents other than pembrolizumab, MK-7684A, and MK-4280A

- Radiation therapy

- Live vaccines within 30 days prior to the first dose of trial treatment and while participating in the trial. Examples of live vaccines include, but are not limited to, the following: measles, mumps, rubella, chicken pox, yellow fever, rabies, BCG, and oral typhoid vaccine. Seasonal influenza vaccines for injection are generally killed virus vaccines and are allowed; however intranasal influenza vaccines (eg, Flu-Mist®) are live attenuated vaccines, and are not allowed. See Appendix 12.8 for country-specific requirements.

  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.

- Systemic glucocorticoids are permitted only for the following purposes:
  - To modulate symptoms of an AE that is suspected to have an immunologic etiology.
  - As needed for the prevention of emesis.
  - Premedication for IV contrast allergies.
  - Short-term oral or IV use in doses >10 mg/day prednisone equivalent for chronic obstructive pulmonary disease exacerbations.
  - For chronic systemic replacement not to exceed 10 mg/day prednisone equivalent.
  - In addition, the following glucocorticoid use is allowed:
  - For topical use or ocular use.
  - Intraarticular joint use.
  - For inhalation in the management of asthma or chronic obstructive pulmonary disease.

Subjects who, in the assessment by the investigator, require the use of any of the aforementioned treatments for clinical management should be discontinued from the study treatment. Subjects may receive other medications that the investigator deems to be medically necessary.

The Exclusion Criteria (Section 5.1.3) describes other medications which are prohibited in this trial.

There are no prohibited medications during the Posttreatment Follow-up Phase.

5.6 Rescue Medications & Supportive Care

5.6.1 Supportive Care

Subjects 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 5.2.1.2 (Table 3). Where appropriate, these guidelines include the use of oral or IV treatment with corticosteroids, as well as additional anti-inflammatory agents if symptoms do not improve with administration of corticosteroids. Note that several courses of steroid tapering may be necessary, as symptoms may worsen when the steroid dose is decreased. For each disorder, attempts should be made to rule out other causes, such as metastatic disease or bacterial or viral infection, which might require additional supportive care. The treatment guidelines are intended to be applied when the investigator determines the events to be related to pembrolizumab, MK-7684A, or MK-4280A.

Note: If after the evaluation of the event, it is determined not to be related to pembrolizumab, MK-7684A, or MK-4280A, the investigator does not need to follow the treatment guidance. Refer to Table 3 in Section 5.2.1.2 for guidelines regarding dose modification and supportive care.

It may be necessary to perform conditional procedures such as bronchoscopy, endoscopy, or skin photography as part of evaluation of the event.

5.7 Diet/Activity/Other Considerations

5.7.1 Diet

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

5.8 Subject Withdrawal/Discontinuation Criteria

5.8.1 Discontinuation of Treatment

Discontinuation of treatment does not represent withdrawal from the trial.

As certain data on clinical events beyond treatment discontinuation may be important to the study, they must be collected through the subject's last scheduled follow-up, even if the subject has discontinued treatment. Therefore, all subjects who discontinue trial treatment prior to completion of the study will still continue to participate in the trial as specified in Section 6.0 – Trial Flow Chart and Section 7.1.5.3 – Posttreatment Visits.

Subjects may discontinue treatment at any time for any reason or be dropped from treatment at the discretion of the investigator should any untoward effect occur. In addition, a subject may be discontinued from treatment by the investigator or the Sponsor if treatment is inappropriate, the trial plan is violated, or for administrative and/or other safety reasons. Specific details regarding procedures to be performed at treatment discontinuation are provided in Section 7.1.4 – Other Procedures.

A subject must be discontinued from treatment but continue to be monitored in the trial for any of the following reasons:

- The subject or subject's legally acceptable representative requests to discontinue treatment.
- The subject has a confirmed positive serum pregnancy test.
- Any progression or recurrence of another malignancy or any occurrence of another malignancy that requires active treatment.
- The subject has intercurrent illness that prevents further administration of treatment (other than another malignancy as noted above).

- The subject has evidence of the following as determined by central pathology and/or local radiology review:
  - Persistent high-risk disease at 12-week disease assessment for Cohorts A
  - High grade Ta or CIS at 24-week disease assessment or any timepoint thereafter for Cohort C
  - T1 at any disease assessment with or without presence of CIS for all Cohorts
  - High-risk recurrence at any time point for Cohorts A and B and after 24-week disease assessment for Cohort C

    Note: Subjects who develop high grade urothelial carcinoma involving the upper urinary tract will be considered to have developed recurrent high-risk NMIBC.
  - Disease progression (by grade or stage) at any time point
  - The subject has completed 35 administrations (2 years) of treatment with pembrolizumab, MK-7684A, or MK-4280A.

    Note: 35 administrations (2 years) of study medication is calculated from the date of first dose.
- The subject may discontinue if a minimum of 18 months of treatment is completed with pembrolizumab, MK-7684A, or MK-4280A and remains without evidence of disease at 2 or more consecutive evaluation visits.

  Note: 18 months of study medication is calculated from the date of first dose.

  Additional Note: Subjects should remain on study and will continue to have study- related disease assessments including cystoscopy and imaging on schedule.

For subjects who are discontinued from treatment but continue to be monitored in the trial, see Section 6.0 – Trial Flow Chart, and Section 7.1.5.3 – Posttreatment Visits for those procedures to be completed at each specified visit.

Subjects may be allowed to begin treatment again if deemed medically appropriate.

5.8.2 Withdrawal from the Trial

Subjects may withdraw from the trial at any time for any reason. If a subject withdraws from the trial, they will no longer receive treatment or be followed at scheduled protocol visits.

A subject must be withdrawn from the trial if:

- The subject or subject's legally acceptable representative withdraws consent from the trial.
- The subject is lost to follow-up.

Specific details regarding procedures to be performed at the time of withdrawal from the trial including specific details regarding withdrawal from Future Biomedical Research are outlined in Section 7.1.4 – Other Procedures.

5.9 Subject Replacement Strategy

A subject who discontinues from the trial will not be replaced.

5.10 Beginning and End of the Trial

The overall study begins when the first subject (or their legally acceptable representative) provides documented informed consent. The overall trial ends when the last subject is at least 6 months post their last study medication administration, discontinues from the trial or is lost to follow-up (ie, the subject is unable to be contacted by the investigator).

For the purposes of analysis and reporting, the overall study ends when the Sponsor receives the last laboratory result or at the time of final contact with the last subject, 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.

5.11 Clinical Criteria for Early Trial Termination

Early trial termination will be the result of the criteria specified below:

- Cohorts A and B may be stopped early for lack of proof-of-concept or safety based on the recommendation of the independent, external DMC. Cohort C will use the internal DMC and the cohort may be stopped early for lack of signal or safety based on their recommendations.
- Quality or quantity of data recording is inaccurate or incomplete
- Poor adherence to protocol and regulatory requirements
- Incidence or severity of adverse drug reaction in this or other studies indicates a potential health hazard to subjects
- Plans to modify or discontinue the development of the trial treatment

In the event of Sponsor decision to no longer supply trial treatment, ample notification will be provided so that appropriate adjustments to subject treatment can be made.

6.0 TRIAL FLOW CHART

Changes that apply as of Amendment 12 are listed in Section 1.0 and supersede any protocol content/instructions from previous amendments. Existing protocol content in this section is retained for historical reference.

6.1 Treatment and Follow-up Phase

Trial Period:	Screening Phase	Treatment Cycles[a]								End of Treatment	Posttreatment		
							To be repeated beyond Cycle 8						
Treatment Cycle/Title:	Screening (Visit 1)	1	2	3	4	5	6[a]	7[a]	8	Discon	Safety Follow-up Visit	Follow-up Phase[b]	Survival Follow-up[c]
Scheduling Window (Days)[d]:	-28 to -1 (Cohorts A and B) -42 to -1 (Cohort C)	+3[d]	± 3	± 3	± 3	± 3	± 3	± 3	± 3	At time of discon	30 days post last dose (± 3 days)	Every 12 weeks post discon (± 2 weeks)	Every 12 weeks (± 2 weeks)
Administrative Procedures													
Informed Consent	X[e]												
Informed Consent for Future Biomedical Research	X[f]												
Inclusion/Exclusion Criteria	X												
Subject Identification Card	X												
Demographics and Medical History	X												
Prior Cystoscopy/TURBT History[g]	X												
Prior and Concomitant Medication Review[h]	X	X	X	X	X	X	X	X	X	X	X		
Pembrolizumab / MK-7684A / MK-4280A Administration		X[d]	X	X	X	X	X	X	X				
Post-study Anticancer Therapy and Oncologic Surgery Status												X	X[c]
Survival and bladder Status[i]		←----------										----------→	X[c]
Clinical Procedures/Assessments													
Review Adverse Events[j]	X	X	X	X	X	X	X	X	X	X	X[k]	X[k]	

Trial Period:	Screening Phase	Treatment Cycles[a]								End of Treatment	Posttreatment		
							To be repeated beyond Cycle 8						
Treatment Cycle/Title:	Screening (Visit 1)	1	2	3	4	5	6[a]	7[a]	8	Discon	Safety Follow-up Visit	Follow-up Phase[b]	Survival Follow-up[c]
Scheduling Window (Days)[d]:	-28 to -1 (Cohorts A and B) -42 to -1 (Cohort C)	+3[d]	± 3	± 3	± 3	± 3	± 3	± 3	± 3	At time of discon	30 days post last dose (± 3 days)	Every 12 weeks post discon (± 2 weeks)	Every 12 weeks (± 2 weeks)
12-Lead Electrocardiogram (Locally performed)	X												
Full Physical Examination	X												
Directed Physical Examination		X	X	X	X	X	X	X	X	X			
Vital Signs, Height and Weight[l]	X	X	X	X	X	X	X	X	X	X	X	X	
ECOG Performance Status[m]	X	X	X	X	X	X	X	X	X	X	X	X	
Laboratory Procedures/Assessments: analysis performed by LOCAL laboratory													
Pregnancy Test – Urine or Serum hCG[n]	X	X	X	X	X	X	X	X	X	X	X		
PT/INR and aPTT[o]	X												
CBC with Differential[p]	X[q]		X	X	X	X	X[r]	X[r]	X[r]	X	X[s]		
Chemistry Panel[p]	X[q]		X	X	X	X	X[r]	X[r]	X[r]	X	X[s]		
Urinalysis[p]	X[q]		X		X		X		X[t]		X[s]		
T3, FT4 and TSH[p]	X[q]		X		X		X		X[t]		X[s]		
Laboratory Procedures/Assessments: analysis performed by CENTRAL laboratory													
Urine Cytology (central confirmation of disease)[u, bb]	X					X[bb]				X[dd]		X[u]	
Blood for Future Biomedical Research (for Cohorts A and B only)[v]		X											
Blood for ctDNA analysis (for Cohort C only)[w]		X	X	X		X[w]				X			

Trial Period:	Screening Phase	Treatment Cycles[a]								End of Treatment	Posttreatment		
Treatment Cycle/Title:	Screening (Visit 1)	1	2	3	4	5	To be repeated beyond Cycle 8: 6[a]	To be repeated beyond Cycle 8: 7[a]	8	Discon	Safety Follow-up Visit	Follow-up Phase[b]	Survival Follow-up[c]
Scheduling Window (Days)[d]:	-28 to -1 (Cohorts A and B) -42 to -1 (Cohort C)	+3[d]	± 3	± 3	± 3	± 3	± 3	± 3	± 3	At time of discon	30 days post last dose (± 3 days)	Every 12 weeks post discon (± 2 weeks)	Every 12 weeks (± 2 weeks)
Urine for utDNA analysis (for Cohort C only)[w]		X	X	X		X[w]				X			
Correlative Blood Samples (for Cohorts A and B only)		X[x,y]	X[y]	X[y]						X[y]			
Blood for Genetic Analysis[z]		X											
Efficacy Measurements													
Evaluation of extra-vesical disease (CTU)[aa]	X					X[aa]				X[dd]		X[aa]	
Cystoscopy[bb] (with TURBT/ biopsy[cc] if applicable)						X[bb]				X[dd]		X[bb]	
Random biopsy (for Cohort C only)[ee]		At Week 48 Efficacy Assessment Only											
Tumor Tissue Collection													
Archival/Newly Obtained Tissue Collection for Biomarker Analysis and NMIBC Analysis	X[ff]												
Patient-reported Outcomes (for Cohorts A and B only)													
EQ-5D		X[gg]	X[gg]	X[gg]	X[gg]		X[gg]		X[gg]	X[gg]	X		
FACT -Bl		X[gg]	X[gg]	X[gg]	X[gg]		X[gg]		X[ff]	X[gg]	X		
CLSS (Core Lower Urinary Tract Symptom Score)		X[gg]	X[gg]	X[gg]	X[gg]		X[gg]		X[gg]	X[gg]	X		

Trial Period:	Screening Phase	Treatment Cycles[a]								End of Treatment	Posttreatment		
							To be repeated beyond Cycle 8						
Treatment Cycle/Title:	Screening (Visit 1)	1	2	3	4	5	6[a]	7[a]	8	Discon	Safety Follow-up Visit	Follow-up Phase[b]	Survival Follow-up[c]
Scheduling Window (Days)[d]:	-28 to -1 (Cohorts A and B) -42 to -1 (Cohort C)	+3[d]	± 3	± 3	± 3	± 3	± 3	± 3	± 3	At time of discon	30 days post last dose (± 3 days)	Every 12 weeks post discon (± 2 weeks)	Every 12 weeks (±2 weeks)

a. In general, assessments/procedures (including imaging assessments) are to be performed prior to the first dose of treatment for each cycle unless otherwise specified. Treatment cycles are 3 weeks; If treatment is delayed, all procedures **except urine cytology, cystoscopy, and imaging** should be performed based on the new dosing schedule. **Urine cytology, cystoscopy, and imaging should be performed as previously scheduled and independent of other study procedures regardless of any treatment delays**. All even-numbered cycles after Cycle 6 follow the same procedure schedule with the exception of Cycle 8. All odd-numbered cycles after Cycle 7 follow the Cycle 7 procedure schedule.
b. Subjects who discontinue trial treatment for reasons other than persistence or recurrence of high-risk NMIBC or disease progression should remain on study and should continue study-related disease assessments including urine cytology, cystoscopy and imaging on schedule until (1) the start of new anticancer treatment, (2) disease progression as assessed by central pathology and radiology review, (3) death, (4) withdrawal of consent or (5) the end of the study, for a total duration of up to 5 years (Week 264), whichever occurs first. See Section 7.1.2for timing of urine cytology, cystoscopy and imaging assessments in the Follow-up Phase.
c. After the start of new anticancer treatment, documented disease progression by the central pathology and radiology review, or when subject has completed study treatment and Follow-up Phase, the subject should be contacted every 12 weeks (±2 weeks) to assess for survival and bladder status for a total duration of up to 5 years.
d. Site personnel will access IVRS prior to dosing on Cycle 1, Day 1 (C1, D1) to obtain the subject's randomization number. Cycle 1 treatment must be given within 3 days following randomization (+3 days). In general, the window for each visit is ±3 days unless otherwise noted.
e. Documented informed consent must be obtained prior to performing any protocol-specified procedure. Results of a test performed prior to the subject providing documented informed consent as part of routine clinical management are acceptable in lieu of a screening test if performed within the specified time frame (eg, within 28 days [for Cohorts A and B] and 42 days [for Cohort C]) prior to the first dose of trial treatment). Screening number will be assigned when subject has provided documented informed consent.
f. Providing documented informed consent for FBR sample is optional. Detailed instructions for the collection and management of specimens for FBR are provided in the Procedures Manual and Appendix 12.2.
g. The most recent cystoscopy/TURBT must have been performed within 12 weeks of starting trial treatment (C1, D1).
h. Prior medications – Record all medications taken within 30 days of the first dose of trial treatment. Concomitant medications – Enter new medications started during the trial through the Safety Follow-up Visit. Record all medications taken for AEs as defined in Section 7.2. See Appendix 12.8 for country-specific requirements.
i. After documented disease persistence, recurrence, or progression as assessed by the central pathology lab and/or local radiology review, or after the start of new anticancer treatment, contact should be made approximately every 12 weeks. Sponsor may request survival and bladder status updates at any time during the course of the study for a total duration of up to 5 years. Upon Sponsor notification, all subjects who do not/will not have a scheduled study visit or study contact during the Sponsor-defined time period will be contacted for their survival and bladder status (excluding subjects that have a death event previously recorded).
j. AEs and laboratory safety measurements will be graded per NCI CTCAE Version 4.0. All AEs, whether gradable by CTCAE or not, will also be evaluated for seriousness.
k. Record all AEs and ECIs occurring within 30 days after the last dose of trial treatment. Report all SAEs (related and unrelated to trial treatment) occurring up until 90 days after the last dose of trial treatment or the start of new anticancer treatment (including cystectomy), whichever comes first.
l. Vital signs to include temperature, pulse, respiratory rate, weight, and blood pressure. Height will be measured at screening only. Vital signs will be collected at screening, prior to the administration of each dose of trial treatment at every cycle, at treatment discontinuation, and at follow-up.
m. ECOG at screening to be performed within 28 days prior to Day 1 of trial treatment. ECOG performance status will also be performed prior to the administration of each dose of trial treatment at every cycle, at treatment discontinuation, and during Follow-up Phase.

Trial Period:	Screening Phase	Treatment Cycles[a]								End of Treatment	Posttreatment		
							To be repeated beyond Cycle 8						
Treatment Cycle/Title:	Screening (Visit 1)	1	2	3	4	5	6[a]	7[a]	8	Discon	Safety Follow-up Visit	Follow-up Phase[b]	Survival Follow-up[c]
Scheduling Window (Days)[d]:	-28 to -1 (Cohorts A and B) -42 to -1 (Cohort C)	+3[d]	± 3	± 3	± 3	± 3	± 3	± 3	± 3	At time of discon	30 days post last dose (± 3 days)	Every 12 weeks post discon (± 2 weeks)	Every 12 weeks (±2 weeks)

n. For women of childbearing potential, a urine pregnancy test should be performed within 72 hours prior to first dose of trial treatment. If urine pregnancy results are positive or cannot be confirmed as negative, a serum pregnancy test performed by the local study site laboratory will be required. Pregnancy tests (serum and/or urine tests) should be repeated if required by local guidelines. Pregnancy test for the ongoing subjects in Cohort B and for all subjects in Cohort C should be repeated on Day 1 of every cycle, at the time of treatment discontinuation, at the safety follow-up visit, and at least 120 days after the last dose of study intervention. See Section 7.1.3.1.1 for additional details and Appendix 12.8 for country-specific requirements.
o. Coagulation factors (PT/INR and aPTT) should be tested as part of the screening procedures performed within 28 days prior to the first dose of trial treatment (Cycle 1) for all subjects. Any subject receiving anticoagulant therapy should have coagulation factors monitored closely throughout the trial.
p. After Cycle 1, predose lab samples can be collected up to 72 hours before the scheduled timepoint.

q. Laboratory tests for screening are to be performed within 28 days prior to the first dose of trial treatment (C1, D1). For subjects with a baseline estimated creatinine clearance below the normal institutional laboratory range, a baseline-measured creatinine clearance should be performed. See Section 7.1.3 for details regarding laboratory tests. Refer to Section 12.8 for country-specific requirements.
r. CBC and Chemistry tests should be collected on Day 1 of every 3-week cycle after Cycle 8.
s. Unresolved abnormal labs that are drug-related AEs should be followed until resolution. Labs do not need to be repeated after the end of treatment if labs are within normal range.
t. Urinalysis and thyroid function tests (T3 or Free T3, FT4 and TSH) should be repeated every 2 cycles after Cycle 6 up to one year of treatment.
u. Specimens for urine cytology should be collected every 12 weeks post first dose of trial treatment (C1, D1). Voided urine samples should be collected prior to cystoscopy; alternatively, bladder washings can be collected at the time of cystoscopy. Urine cytology will be assessed by a central vendor as part of the evaluation for disease recurrence. First morning urine is not suitable because of the frequent presence of cytolysis. (See Procedures Manual.) The first on-treatment urine cytology specimen should be collected no sooner than 12 weeks post first dose of trial treatment (C1, D1) and may be collected within a window of up to 2 weeks afterwards (12 weeks +2 weeks), the same manner of timing of the first on-treatment cystoscopy. Subsequent samples are to be collected with a window of ±2 weeks.
v. Documented informed consent for FBR samples must be obtained before the DNA sample is collected. DNA sample for analysis should be obtained predose, on Day 1 (or with the next scheduled blood draw) as the last sample drawn, or at a later date as soon as documented informed consent is obtained. Detailed instructions for the collection and management of specimens for FBR are provided in the Procedures Manual and Appendix 12.2.
w. ctDNA/utDNA sample for analysis will be collected only for Cohort C and should be obtained at predose, on Day 1 (±7 days) of Cycles 1, 2, 3, 5 and every 12 weeks from Cycle 5 and thereafter, and at EOT. If a clinic visit is not feasible, blood for ctDNA/urine for utDNA will not be collected. Note, if C5 is delayed, blood for ctDNA and urine for utDNA at the first disease assessment timepoint (Week 12 from C1D1) and every 12 weeks from thereafter should be collected. No need to repeat collection at C5.
x. Blood for serum and blood for plasma correlative studies are to be collected only predose at Cycle 1 (See Procedures Manual.). Any leftover samples from the correlative blood studies will be stored for FBR if the subject (or their legally acceptable representative) provides documented informed consent for FBR.
y. Whole blood sample for RNA/DNA correlative studies should be collected predose at Cycles 1, 2, and 3, and again at treatment discontinuation. (See Procedures Manual.) Any leftover samples from the correlative blood studies will be stored for FBR if the subject (or their legally acceptable representative) provides documented informed consent for FBR.

Trial Period:	Screening Phase	Treatment Cycles[a]								End of Treatment	Posttreatment		
							To be repeated beyond Cycle 8						
Treatment Cycle/Title:	Screening (Visit 1)	1	2	3	4	5	6[a]	7[a]	8	Discon	Safety Follow-up Visit	Follow-up Phase[b]	Survival Follow-up[c]
Scheduling Window (Days)[d]:	-28 to -1 (Cohorts A and B) -42 to -1 (Cohort C)	+3[d]	± 3	± 3	± 3	± 3	± 3	± 3	± 3	At time of discon	30 days post last dose (± 3 days)	Every 12 weeks post discon (± 2 weeks)	Every 12 weeks (±2 weeks)

z. This sample should be drawn for planned analysis of the association between genetic variants in DNA and drug response. If there is either a documented law or regulation prohibiting collection, or if the IRB/IEC does not approve the collection of the sample for these purposes, then this sample will not be collected at that site. If the sample is collected, leftover extracted DNA will be stored for FBR if the subject (or their legally acceptable representative) 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.

aa. Imaging timing is calculated from Cycle 1, Day 1. Timing should follow calendar days and should not be adjusted for delays in treatment. Evaluation of extra-vesical disease (CTU) will be performed at 24 weeks (±2 weeks) after first dose for the first 2 years. Subsequently, imaging will be performed yearly (52 weeks ±4 weeks) thereafter regardless of any treatment delays. See Section 7.1.2.9 for timing of imaging assessments during the Follow-up Phase.

bb. Cystoscopy and Urine Cytology timing is calculated from Cycle 1, Day 1. Timing should follow calendar days and should not be adjusted for delays in treatment. Cystoscopies and urine cytology will be performed every 12 weeks (±2 weeks) from the start of trial treatment (C1, D1) for the first 2 years, then every 24 weeks (±2 weeks) thereafter regardless of any treatment delays for a total duration of 5 years. The final evaluation in the posttreatment tumor assessment period of 5 years will be Week 264. Use of the same cystoscopy technique (white light or blue light) is required to be used in a subject throughout the trial. See Section 7.1.2.9 for timing of cystoscopy during the Follow-up Phase.

cc. Resection of all visible 'papillary' lesions by TURBT or directed biopsies of all visible 'flat' CIS lesions will be required on evidence of low grade Ta recurrence, and/or high-risk recurrence or progression by cystoscopy and pathology in accordance with Table 5. Random biopsies will be required if urine cytology is reported by central pathology laboratory as high grade urothelial carcinoma or suspicious for high grade urothelial carcinoma at any time point in accordance with Table 5. All TURBT/biopsy tissue at any time point must be sent to central laboratory for pathology review and biomarker testing (See Procedure Manual.).

dd. In subjects who discontinue trial treatment for reasons other than persistence or recurrence of high-risk NMIBC or disease progression, CTU, urine cytology, and cystoscopy should be performed at the time of treatment discontinuation (+2 weeks). If a previous CTU, urine cytology, and cystoscopy was obtained within 4 weeks prior to the date of discontinuation, then repeat assessments are not mandatory at treatment discontinuation.

ee. Random biopsies should be obtained of the trigone, bladder dome, right, left, anterior, and posterior bladder walls, as well as biopsy of the prostatic urethra in males.

ff. Baseline tumor tissue for biomarker analysis from archival TURBT or excisional biopsy/biopsies must be provided to the central vendor prior to randomization. Confirmation of high-risk NMIBC and presence of detrusor muscle (for invasive, tumors) must be confirmed by the central laboratory before enrollment. In addition, any tissue obtained during pembrolizumab, MK-7684A, or MK-4280A treatment obtained in accordance with Table 5 must be provided to the central vendor for pathology review and biomarker analysis. Detailed instructions for tissue collection, process and shipment are provided in the Procedures Manual. If the subject (or their legally acceptable representative) provides documented informed consent for FBR, any leftover tissue that would ordinarily be discarded at the end of the main study will be retained for FBR.

gg. Electronic patient-reported outcomes (ePROs) should be administered starting with EQ-5D, followed by FACT-Bl and CLSS. It is most relevant and strongly recommended that ePROs are administered prior to drug administration, AE evaluation, and disease status notification at Cycle 1, Cycle 2, Cycle 3, Cycle 4, and every 2 cycles thereafter (eg, Cycle 6, Cycle 8, Cycle 10) up to a year or End of Treatment, whichever comes first, and the 30-day posttreatment discontinuation follow-up visit. An exception to this recommendation may occur at the treatment discontinuation visit where patients may have already been notified of their disease status or an AE evaluation is known prior to them arriving to the clinic. If the subject does not complete the ePROs the MISS MODE form must be completed to capture the reason the assessment was not performed.

7.0 TRIAL PROCEDURES

Changes that apply as of Amendment 12 are listed in Section 1.0 and supersede any protocol content/instructions from previous amendments. Existing protocol content in this section is retained for historical reference.

7.1 Trial Procedures

The Trial Flow Chart - Section 6.0 summarizes the trial procedures to be performed at each visit. Individual trial procedures are described in detail below. It may be necessary to perform these procedures at unscheduled time points if deemed clinically necessary by the investigator.

Furthermore, additional evaluations/testing may be deemed necessary by the investigator and or the Sponsor for reasons related to subject safety. In some cases, such evaluation/testing may be potentially sensitive in nature (e.g., HIV, Hepatitis C, etc.), and thus local regulations may require that additional informed consent be obtained from the subject. In these cases, such evaluations/testing will be performed in accordance with those regulations.

7.1.1 Administrative Procedures

7.1.1.1 Informed Consent

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

7.1.1.1.1 General Informed Consent

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

A copy of the documented informed consent form should be given to the subject (or their legally acceptable representative) before participation in the study.

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

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

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

7.1.1.1.2 Consent and Collection of Specimens for Future Biomedical Research

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

7.1.1.2 Inclusion/Exclusion Criteria

All inclusion and exclusion criteria will be reviewed by the investigator or qualified designee to ensure that the subject qualifies for the trial.

7.1.1.3 Subject Identification Card

All subjects will be given a Subject Identification Card identifying them as subjects in a research trial. The card will contain trial site contact information (including direct telephone numbers) to be used in the event of an emergency. The investigator or qualified designee will provide the subject with a Subject Identification Card immediately after the subject provides documented informed consent.

The Subject Identification Card also contains contact information for the emergency call center so that a health care provider can obtain information about trial medication/vaccination in emergency situations where the investigator is not available.

7.1.1.4 Medical History

A medical history will be obtained by the investigator or qualified designee. Medical history will include all active conditions, and any condition diagnosed within the prior 10 years that are considered to be clinically significant by the investigator. Details regarding the subject's non-muscle invasive urothelial carcinoma will be recorded separately and not listed as medical history.

7.1.1.4.1 Prior History of Transurethral Resection of Bladder Tumor

Subjects with Ta or T1 disease must have undergone a visually complete TURBT prior to study entry. Residual CIS, therefore, not amenable to complete transurethral resection, is acceptable. The most recent cystoscopy must have been performed within 12 weeks of starting trial treatment. Results from most recent cystoscopy/TURBT should be entered in the clinical trial database (see data entry guidelines).

- Subjects will provide archival tumor tissue from prior TURBT for central pathology review to confirm high-risk NMIBC diagnosis and determine tumor(s) grade and/or stage for study entry. The local pathology report and all representative tissue from the most recent cystoscopy/TURBT must be sent to the central laboratory to ensure all materials are received and reviewed for confirmation of high-risk NMIBC. Central pathology review as part of the screening process will determine subject cohort determination.
    - Cohort A – CIS at baseline (CIS only, Ta+CIS, or T1+CIS).
    - Cohort B – without CIS at baseline (High Grade Ta or Any Grade T1).
    - Cohort C – CIS at baseline (CIS only, Ta+CIS, or T1+CIS).

7.1.1.5 Prior and Concomitant Medications Review

7.1.1.5.1 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 subject within 30 days before the first dose of trial treatment. Prior treatment for non-muscle invasive bladder cancer will be recorded separately and not listed as a prior medication.

7.1.1.5.2 Prior Treatment Details for Non-Muscle Invasive Bladder Cancer

The investigator or qualified designee will review all prior cancer treatments including systemic treatments, radiation and surgeries and record in the trial database. This will include detailed information about prior BCG usage, disease persistence or recurrence after BCG treatment and the time of disease recurrence from the initial induction dose of BCG. Reasons for subject ineligibility or refusal of radical cystectomy will also be recorded in the trial database**.**

7.1.1.5.3 Concomitant Medications

The investigator or qualified designee will record medication, if any, taken by the subject during the trial. All medications related to reportable SAEs and ECIs should be recorded as defined in Section 7.2 – Assessing and Recording of Adverse Events.

7.1.1.5.4 Survival and Bladder Status

The investigator or qualified designee will review all new anticancer therapy initiated after the last dose of trial treatment. If a subject initiates a new anticancer therapy within 30 days after the last dose of trial treatment, the 30-day Safety Follow-up Visit must occur before the start of the new therapy. Once new anticancer therapy has been initiated the subject will move into Survival Follow-up.

Details of the new anticancer therapy should be recorded in the trial database. This would include, but not be limited to, surgical procedures such as TURBT/biopsy and cystectomy, and oncologics and biologics such as additional BCG and systemic or intravesical chemotherapies.

7.1.1.6 Assignment of Screening Number

All consented subjects will be given a unique screening number that will be used to identify the subject for all procedures that occur prior to randomization or allocation. Each subject will be assigned only one screening number. Screening numbers must not be re-used for different subjects.

Any subject who is screened multiple times will retain the original screening number assigned at the initial screening visit.

Specific details on the screening visit requirements (screening/rescreening) are provided in Section 7.1.5.1.

7.1.1.7 Assignment of Randomization Number

All subjects will be initially allocated to either Cohort A (CIS only, Ta + CIS, or T1 + CIS) or Cohort B (without CIS, high grade Ta or any grade T1 only), and on completion of enrollment in Cohorts A and B subjects will be assigned to Cohort C (CIS only, Ta + CIS, or T1 + CIS) Arms 1 or 2 based on the baseline pathology characteristics of the centrally assessed tissue submitted during screening and will receive a randomization number prior to dosing on Cycle 1, Day 1.

Once a randomization number is assigned to a subject, it can never be re-assigned to another subject. A single subject cannot be assigned more than 1 randomization number. In addition, once the randomization number is assigned it cannot be modified.

Subjects in Cohort A and B will receive the same pembrolizumab 200 mg Q3W as trial treatment by non-random assignment in an unblinded fashion via IVRS. Subjects in Cohort C will receive either MK-7684A (Arm 1) or MK-4280A (Arm 2) randomly in 1:1 ratio as trial treatments in an unblinded fashion via IVRS.

7.1.1.8 Trial Compliance (Medication/Diet/Activity/Other)

If there are interruptions in the study intervention schedule, the details of and reason for any interruption of study intervention will be documented in the subject's medical record.

Refer to Section 5.2.1.2 – Immune-Related Events and Dose Modification (Withhold, Treat, Discontinue), for dose modification and toxicity management for irAEs associated with pembrolizumab, MK-7684A, and MK-4280A and for other allowed dose interruptions of pembrolizumab, MK-7684A, and MK-4280A.

7.1.2 Clinical Procedures/Assessments

7.1.2.1 Adverse Event Monitoring

The investigator or qualified designee will assess each subject to evaluate for potential new or worsening AEs as specified in Section 6.0 – Trial Flow Chart and more frequently if clinically indicated. Adverse events will be graded and recorded throughout the study and during the follow-up period according to NCI CTCAE Version 4.0 (Table 8). Toxicities will be characterized in terms regarding seriousness, causality, toxicity grading, and action taken with regard to trial treatment.

For subjects receiving treatment with pembrolizumab, MK-7684A, or MK-4280A all AEs of unknown etiology associated with pembrolizumab (MK-3475), MK-7684A, or MK-4280A exposure should be evaluated to determine if it is possibly an AE of a potentially immunologic etiology (termed irAEs). See Supportive Care Section 5.6.1 – Supportive Care regarding the identification, evaluation and management of potential irAEs.

Please refer to Section 7.2 – Assessing and recording Adverse Events for detailed information regarding the assessment and recording of AEs.

7.1.2.2 12-Lead Electrocardiogram

A standard 12-lead ECG will be performed using local standard procedures once at the screening visit as described in Section 6.0 – Trial Flow Chart. Clinically significant abnormal findings during screening should be recorded as medical history and clinically significant abnormal findings of any subsequent ECGs should be recorded as AEs.

7.1.2.3 Physical Examination

7.1.2.3.1 Full Physical Examination

The investigator or clinical designee will perform a complete physical examination during the screening period (see Section 6.0 – Trial Flow Chart). Clinically significant abnormal findings should be recorded as medical history.

7.1.2.3.2 Directed Physical Examination

The investigator or qualified designee will perform a directed physical examination as clinically indicated prior to dosing on Day 1 of each treatment cycle starting with Cycle 1. New clinically significant abnormal findings should be recorded as AEs.

7.1.2.4 Vital Signs

The investigator or qualified designee will take vital signs at screening, prior to the administration of each dose of trial treatment and at treatment discontinuation as specified in the Section 6.0 – Trial Flow Chart. Vital signs should include temperature, pulse, respiratory rate, weight and blood pressure. Height will be measured at screening only.

7.1.2.5 Eastern Cooperative Oncology Group Performance Scale

The investigator or qualified designee will assess ECOG status (see Appendix 12.5 – ECOG Performance Status) at screening (within ≤28 days prior the dosing on Day 1 Cycle 1) and prior to the dosing on Day 1 of each treatment cycle and discontinuation of trial treatment as specified in Section 6.0 – Trial Flow Chart.

7.1.2.6 Cystoscopy, Transurethral Resection of Bladder Tumor, and Biopsy

Subjects with high-risk NMIBC will have a history of cystoscopy, TURBT, and corresponding local pathology outcomes for tissue obtained in subjects' high-risk NMIBC history prior to screening and study entry. This history should be evaluated and fully documented in the electronic case report forms (eCRFs) as part of the screening evaluation and procedures.

Subjects must have had the most recent cystoscopy/TURBT performed within 12 weeks of the first dose of trial treatment where subjects with high grade Ta and/or T1 tumors must have visually complete resection of all papillary tumors. Subjects with CIS must have residual CIS not amendable to full resection at study entry. Subjects with T1 disease must have undergone restaging TURBT procedure within 12 weeks prior to randomization to ensure complete resection of all T1 disease. All tumor tissue resected at this most recent cystoscopy/TURBT/Biopsy/restaging TURBT will need to be obtained from the local laboratory and must be sent to the central laboratory for confirmation of high-risk NMIBC, absence of muscle invasive disease (for invasive tumors), and to identify the absence or presence of CIS prior to subject randomization and start of trial treatment to determine cohort allocation and eligibility, respectively.

Subjects allocated to study treatment will have cystoscopies performed every 12 weeks (± 2 weeks) from the start of trial treatment (C1, D1) for the first 2 years, then every 24 weeks (± 2 weeks) thereafter regardless of any treatment delays for a total duration of approximately 5 years. The final evaluation in the posttreatment tumor assessment period of 5 years will be Week 264.

A careful inspection of the whole urothelial lining in the bladder will be performed to check for tumors at each cystoscopy.

If cystoscopy shows evidence of recurrence or progression of disease at any time point, TURBT and/or biopsy will be required per Table 5 in Section 5.2.3 - Treatment After Disease Recurrence. For Cohort C subjects, R-biopsies are also required at the Week 48 (Month 12) time point. R-biopsies should be obtained of the trigone, bladder dome, right,

left, anterior, and posterior bladder walls, as well as biopsy of the prostatic urethra in males. All tumor tissue resected while the subject is in the study must be promptly sent to the central laboratory for the absence or presence of persistent, recurrent, or progressive disease. All papillary tumors should have detrusor muscle present to confirm absence or presence of locally advanced disease.

Cystoscopy should be performed per standard of care at the time points detailed in Section 6.0 - Trial Flow Chart. White light cystoscopy will be used, but fluorescence-guided cystoscopy (photodynamic diagnosis or blue light cystoscopy) may be substituted, if available. The treating urologist/surgeon will determine which cystoscopy technique subjects should undergo. Consistent use of the same technique within each individual subject will be required.

Refer to Section 6.0 - Trial Flow Chart for details of discontinuation requirements and Section 7.1.2.9 for details of posttreatment follow-up assessments.

7.1.2.7 Urine Cytology

Subjects must have a urine cytology collected as part of the screening procedures with a date of collection within the 28-day screening window. Once subjects start trial treatment, urine cytology will be performed every 12 weeks (±2 weeks) from the start of trial treatment (C1, D1) for the first 2 years, then every 24 weeks (±2 weeks) thereafter regardless of any treatment delays for a total duration of approximately 5 years. The final evaluation in the posttreatment tumor assessment period of 5 years will be Week 264.

The timing of the urine cytology collection is aligned with the timing of the cystoscopy procedure, and urine cytology should be collected prior to or at the time of each scheduled every 12-week cystoscopy.

Acceptable methods of collection for urine cytology assessments are as follows: voided urine, bladder washings, and catheterization.

All urine cytology specimens must be sent to the central laboratory for analysis. Urine cytology must be considered evaluable; if not, another sample must be collected and submitted as soon as possible to the central laboratory. When a centrally evaluated urine cytology is not available, a local result may be used, if available, for disease assessment outcome. Results will be reported by the central laboratory and site must record the results in the appropriate eCRF in a timely manner as part of the evaluation for disease recurrence.

If cystoscopy is normal and urine cytology is reported by the central laboratory as high grade urothelial carinoma or suspicious for high grade urothelial carinoma, subjects should be scheduled expeditiously for a repeat cystoscopy with random biopsies and CTU (see Table 5).

Refer to Section 6.0 - Trial Flow Chart for details of discontinuation requirements and Section 7.1.2.9 for details of posttreatment follow-up assessments.

7.1.2.8 Evaluation for Extra-vesical Disease

CTU imaging of the abdomen and pelvis for assessment of extra-vesical disease (ie, upper tract UC, and locally advanced or metastatic UC) will be performed as part of the screening evaluation. In collaboration with the Sponsor, an MRU may be utilized for assessment of extra-vesical disease at screening and on study disease assessment when a CTU is not possible to obtain. Rationale for MRU along with Sponsor's agreement for MRU will be documented on the Sponsor Consultation Form. Within the 28-day screening window for Cohort A & B and 42-day screening window for Cohort C, the central imaging vendor must review the screening CTU or MRU, wherever applicable, to confirm the absence of extra-vesical disease.

After randomization, timing of imaging assessments will be calculated starting at Cycle 1, Day 1 and subjects will be evaluated for presence of extra-vesical disease via CTU every 24 weeks (± 2 weeks) for the first 2 years, and yearly (52 weeks ± 4 weeks) thereafter. Imaging studies may be performed more frequently if clinically indicated (Table 5).

The process for CTU image acquisition and transmission to the central vendor can be found in the Site Imaging Manual. The Site Imaging Manual CTU guidelines must be followed for all protocol-required imaging CTU studies.

During study treatment, the local radiologist must read all obtained images to assess for the presence or absence of extra-vesical disease. The site must record the local radiologist results for all scheduled and unscheduled imaging on study in the appropriate eCRF in a timely manner as part of the evaluation for disease recurrence.

All imaging obtained on study must also be submitted for an independent central radiologist's review to assess the images for determination of extra-vesical disease.

Refer to Section 6.0 - Trial Flow Chart for details of discontinuation requirements and Section 7.1.2.9 for details of posttreatment follow-up assessments.

7.1.2.9 Follow-up Assessments

Subjects who discontinue treatment for reasons other than persistence or recurrence of high-risk NMIBC or disease progression will have posttreatment follow-up for disease status until disease progression, initiating a non-study cancer treatment, withdrawing consent, death, or becoming lost to follow-up. During this period, subjects will continue study-related disease assessments as described in Section 6.0 – Trial Flow Chart and below.

Follow-up visits are to be conducted every 12 weeks (± 2 weeks) and include assessments for any post-study anticancer therapy, AEs, vital signs, urine cytology, and ECOG status. In addition, evaluation for disease recurrence or progression via radiographic imaging (CTU), cystoscopy, and urine cytology will be performed as outlined below taking into consideration the time of treatment discontinuation.

Timing of Cystoscopy, Urine Cytology and Imaging in Follow-up

Subjects who complete 35 administrations (2 years) of trial treatment and remain free of high-risk disease should continue the below assessments for 3 additional years (for a total duration of approximately 5 years):

- CTU yearly (at 52 weeks ± 4 weeks)
- Cystoscopy and urine cytology every 24 weeks (± 2 weeks)

Subjects who discontinue trial treatment after 18 months due to continued response and have disease-free survival from high-risk NMIBC (as described in Section 5.8.1 – Discontinuation of Treatment) should continue the below assessments for an additional 3.5 years (for a total duration of approximately 5 years):

- CTU every 24 weeks (± 2 weeks) up to 2 years post start of study treatment (C1, D1); yearly thereafter (52 weeks ± 4 weeks)
- Cystoscopy and urine cytology every 12 weeks (± 2 weeks) up to 2 years post start of study treatment (C1, D1); and then every 24 weeks (± 2 weeks)

Subjects who discontinue trial treatment for reasons other than persistence or recurrence of high-risk NMIBC or disease progression should continue the below assessments for a total duration of approximately 5 years:

- CTU for evaluation of extra-vesical disease at the time of discontinuation
- CTU every 24 weeks (± 2 weeks) up to 2 years post start of study treatment (C1, D1); yearly thereafter (52 weeks ± 4 weeks)
- Cystoscopy and urine cytology every 12 weeks (± 2 weeks) up to 2 years post start of study treatment (C1, D1) dose; every 24 weeks (± 2 weeks)

Note: Consistent use of the same cystoscopic technique, including the use of white light or blue light cystoscopy, for each individual subject is required throughout the study including during follow-up.

The final evaluation in the posttreatment tumor assessment period of 5 years will be Week 264.

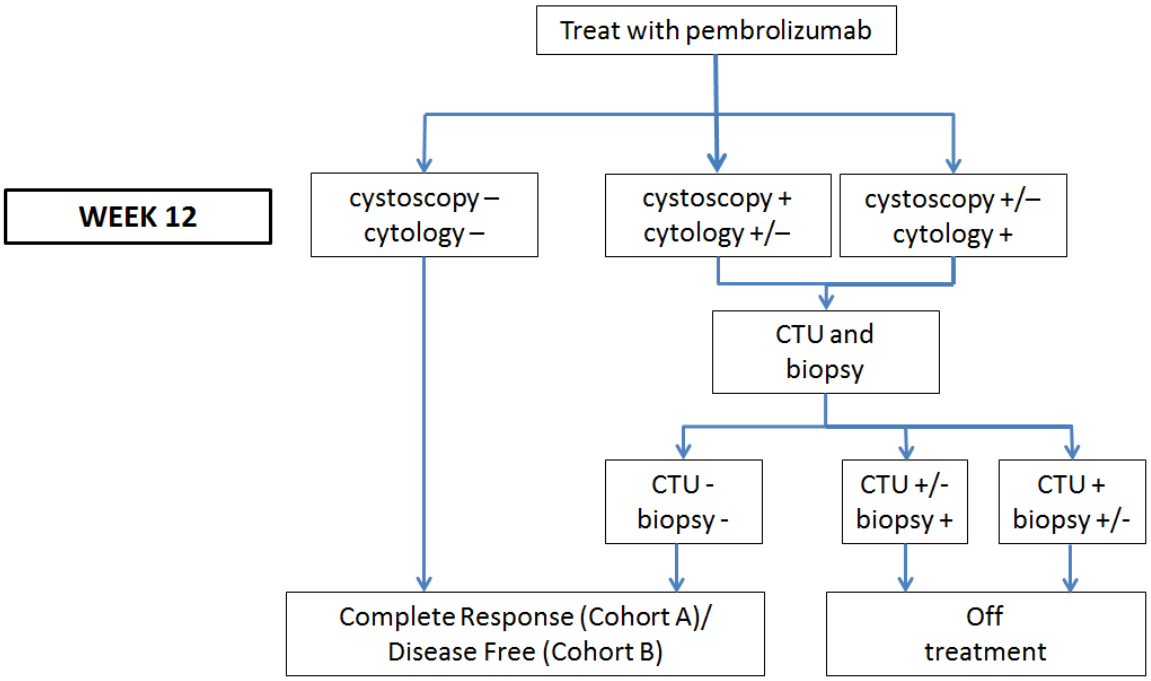
Subjects in the Follow-up Phase will be assessed using the schedule above until the start of new anticancer treatment or documented disease progression/high-risk recurrence by central pathology and radiology review. At that time, subjects will enter Survival Follow-up and should be contacted every 12 weeks (± 2 weeks) to assess for survival and bladder status (for a total duration of approximately 5 years).

7.1.2.10 Assessment of Disease

Disease will be assessed based on the integrated evaluation of cystoscopy, urine cytology, TURBT/biopsy (when applicable), and radiologic (CTU) studies when applicable as described in Section 5.2.3 - Treatment After Disease Recurrence. All urine cytology and TURBT/biopsy specimens will be evaluated by central pathology review, whereas all radiologic studies will be evaluated by a combination of local radiology review and independent central radiology review.

Cohort A subjects will be considered to have a CR and Cohort B subjects will be considered to be disease-free of **any disease** at 12-week efficacy review, as shown in Figure 4. In Cohort C, subjects will be considered to have a CR at Month 3 using the 12-week efficacy review, subjects will be considered to have a CR at Month 6 using the 24-week efficacy review, and subjects will be considered to have a CR at Month 12 using the 48-week efficacy review as shown in Figure 5. Subjects who have central pathology-confirmed persistent or recurrent CIS or high grade Ta at the 24-week efficacy review or thereafter, or T1 or disease progression to T2 or worse at any time will be discontinued from the study treatment.

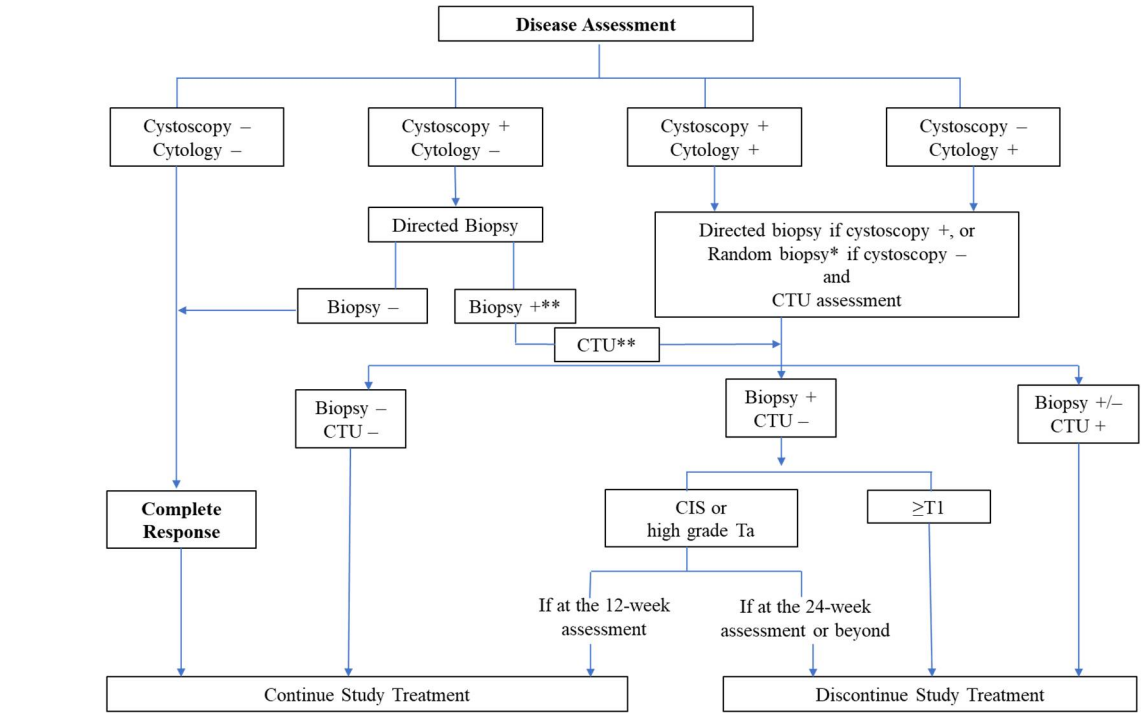
Figure 4 Week 12 Efficacy Review Flowchart – Cohorts A and B



CIS = carcinoma-in-situ; CTU = computed tomography urography.

Note: Positive cystoscopy is defined as suspicious for malignancy (eCRF interpretation = "Abnormal" and "Suspicious for malignancy"). Negative cystoscopy is defined as no evidence of high-risk NMIBC (eCRF interpretation = "Normal"). Positive cytology is defined as positive for malignant cells (central vendor interpretation = "Suspicious for High Grade Urothelial Carcinoma or "High Grade Urothelial Carcinoma"). Negative cytology is defined as no evidence of high-risk NMIBC (central vendor interpretation = "Negative for High Grade Urothelial Carcinoma," "Atypical Urothelial Cells Present," or "Low Grade Urothelial Neoplasm").

Figure 5 Efficacy Review Flowchart – Cohort C



*Random biopsy is required at the Week 48 (Month 12) time point
**If study treatment discontinued prior to CTU evaluation, then obtain CTU at the end of treatment visit if CTU not obtained in the past 4 weeks

CIS = carcinoma-in-situ; CTU = computed tomography urography.

Note: Positive cystoscopy is defined as suspicious for malignancy (eCRF interpretation = "Abnormal" and "Suspicious for malignancy"). Negative cystoscopy is defined as no evidence of high-risk NMIBC (eCRF interpretation = "Normal"). Positive cytology is defined as positive for malignant cells (central vendor interpretation = "Suspicious for High Grade Urothelial Carcinoma or "High Grade Urothelial Carcinoma"). Negative cytology is defined as no evidence of high-risk NMIBC (central vendor interpretation = "Negative for High Grade Urothelial Carcinoma," "Atypical Urothelial Cells Present," or "Low Grade Urothelial Neoplasm"). Positive biopsy is defined as presence of high-risk NMIBC defined as high grade Ta, any CIS, or any T1 disease of the bladder, urethra, ureter, or renal pelvis; or presence of muscle invasive bladder cancer (≥T2). Negative biopsy is defined as absence of high-risk NMIBC (ie, no urothelial carcinoma or low grade Ta diagnosis).

All subjects will be considered disease-free of **any disease** after Week 12 efficacy review if the Figure 4 (for Cohorts A and B) and Figure 5 (for Cohort C) criteria are met hereafter (Weeks 24, 36, 48, 60, 72, 84, and 96).

All subjects who have centrally confirmed pathology of **low grade Ta** at Week 12 or any efficacy review thereafter (Weeks 24, 36, 48, 60, 72, 84, or 96) will be considered to be disease-free or absent of **high-risk NMIBC** or **progression**.

Cohorts A and C subjects will be considered to have persistent disease (**high-risk NMIBC** recurrence) at Week 12 if urothelial CIS is assessed by central pathology review in the absence of any malignant findings by CTU. In this case, subjects in Cohort C will continue to receive the study treatment until 24 weeks. Any CIS or high-risk NMIBC recurrence at

efficacy reviews after subjects have demonstrated a CR at Week 12 will be considered progression.

Cohort B subjects are considered to have progressive disease at Week 12 or any efficacy review thereafter (Weeks 24, 36, 48, 60, 72, 84, or 96) if subject has recurrent high-risk NMIBC or any malignant findings by CTU.

Progressive disease by pathology is to be defined according to the IBCG definition of increasing grade (ie, low grade → high grade) or depth of invasion (ie, Ta → T1, CIS → T1, T1 → T2 or greater) or death.

Tumor grade and stage is to be assessed according to WHO 2016 pathologic classification by central pathology.

7.1.2.11 Tumor Tissue Collection and Correlative Blood Sampling

An archival FFPE tumor sample or any newly obtained excisional biopsies (fine needle aspirate is not adequate) must be submitted to the central lab for high-risk NMIBC confirmation at screening for characterization of PD-L1 expression. The tumor tissue must be received by the central lab for evaluation prior to subject enrollment.

Blood for correlative biomarker studies should be collected prior to dosing on Cycle 1 Day 1, Cycle 2 Day 1, and Cycle 3 Day 1, and at study treatment discontinuation (see Section 6.0 – Trial Flow Chart and Procedures Manual for additional details) in Cohorts A and B only.

All tumor tissues obtained during the study must be sent to the central lab for evaluation. Detailed instructions for tissue collection, processing, and shipment are provided in the Procedures Manual.

7.1.2.12 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 subjects as specified in the Trial Flow Chart (Section 6.1):

- Blood for ctDNA analysis (Cohort C only)
- Urine for utDNA analysis (Cohort C only)
- Tumor tissue
- Blood for Genetic analysis

Sample collection, storage, and shipment instructions for the exploratory biomarker specimens will be in the operations/laboratory manual.

7.1.2.13 Patient-reported Outcomes (For Cohorts A and B Only)

Subjects are to complete the EQ-5D, FACT-Bl, and CLSS questionnaires on their own at the site using an electronic data capture tool at the appropriate study visit (see Section 6.0 – Trial

Flow Chart). It is strongly recommended that ePROs are administered prior to drug administration, adverse event evaluation and disease status notification; an exception to this recommendation may occur at the treatment discontinuation visit where patients may have already been notified of their disease status or an AE evaluation is known prior to them arriving to the clinic.

Questionnaires are to be completed in the following order: EQ-5D first, then FACT-Bl followed by CLSS.

7.1.3 Laboratory Procedures/Assessments

Details regarding specific laboratory procedures/assessments to be performed in this trial are provided below. The total amount of blood/tissue to be drawn/collected over the course of the trial (from pre-trial to post-trial visits), including approximate blood/tissue volumes drawn/collected by visit and by sample type per subject can be found in the Procedures Manual.

7.1.3.1 Laboratory Safety Evaluations (Hematology, Chemistry and Urinalysis)

Laboratory tests for hematology, chemistry and urinalysis are specified in Table 6. Refer Appendix 12.8.3 for country-specific requirements.

Table 6 Laboratory Tests

Hematology	Chemistry	Urinalysis	Other
Hematocrit	Albumin	Blood	Serum human chorionic gonadotropin (hCG)[a]
Hemoglobin	Alkaline phosphatase	Glucose	PT (INR)
Platelet count	Alanine aminotransferase (ALT)	Protein	aPTT
WBC (total and differential)	Aspartate aminotransferase (AST)	Specific gravity	Total triiodothyronine (T3) (or Free T3)[b]
Red Blood Cell Count	Bicarbonate[b]	Microscopic examination if abnormal results are noted	Free thyroxine (T4)
Absolute Neutrophil Count	Calcium	Urine pregnancy test[a]	Thyroid-stimulating hormone (TSH)
Absolute Lymphocyte Count	Chloride		Cardiac enzyme Troponin (TnT)[e]
	Creatinine[c]		
	Glucose		
	Phosphorus		
	Potassium		
	Sodium		
	Total Bilirubin		
	Direct Bilirubin if total bilirubin is elevated above the upper limit of normal		
	Total protein		
	Blood urea nitrogen[d]		
	Carbon dioxide (CO_2 or bicarbonate)[b]		
	Uric acid		

[a] Perform on women of childbearing potential only. If urine pregnancy results cannot be confirmed as negative, a serum pregnancy test will be required. See Appendix 12.8 for country-specific requirements.

[b] If considered standard of care in your region.

[c.] For subjects with a baseline calculated creatinine clearance below the normal institutional laboratory range, a baseline-measured creatinine clearance should be performed.

[d.] Urea may be tested if blood urea nitrogen is unavailable.

[e] Measurement of cardiac enzyme Troponin (TnT) is a country-specific requirement (see Appendix 12.8).

Laboratory tests for screening should be performed within 28 days prior to the first dose of trial treatment. After Cycle 1, predose laboratory procedures can be conducted up to 72 hours prior to dosing. Results must be reviewed by the investigator or qualified designee and found to be acceptable prior to each dose of trial treatment.

7.1.3.1.1 Pregnancy Testing

Pregnancy testing requirements for study inclusion are described in Section 5.1.2 – Subject Inclusion Criteria.

Pregnancy testing (urine or serum as required by local regulations) should be conducted at every protocol treatment cycle per Section 6.0 – Trial Flow Chart.

Pregnancy testing (urine or serum as required by local regulations) should be conducted 120 days after the last dose of pembrolizumab, MK-7684A, or MK-4280A or 30 days following cessation of treatment if the subject initiates new anticancer therapy, whichever is earlier.

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 subject's participation in the study.

7.1.3.2 Pharmacokinetic and Anti-drug Antibody Evaluations

The accumulation of robust PK and ADA data has allowed for the adequate characterization of the clinical pharmacology of pembrolizumab across indications. Therefore, upon approval of Amendment 04 each site is to stop the collection of PK and ADA samples for all subjects. Blood samples for PK and ADA collected prior to Amendment 04 may be stored. Analysis will be performed only if required.

7.1.3.3 Future Biomedical Research

The following specimens are to be obtained as part of Future Biomedical Research:

- Leftover DNA for future use
- Leftover tumor
- Leftover DNA, RNA, plasma, and serum from correlative studies for future use

7.1.4 Other Procedures

7.1.4.1 Withdrawal/Discontinuation

When a subject discontinues/withdraws from participation in the trial, all applicable activities scheduled for the final trial visit should be performed at the time of discontinuation. Any adverse events which are present at the time of discontinuation/withdrawal should be followed in accordance with the safety requirements outlined in Section 7.2 - Assessing and Recording Adverse Events. Subjects who discontinue from trial treatment for any of the reasons listed in Section 5.8 should return to the site for a Safety Follow-up Visit (described in Section 7.1.5.3.1 – Safety Follow-up Visit) and then proceed to the Follow-up Phase of the study (described in Section 7.1.5.3.2 – Follow-up Phase). These subjects should remain on study and should continue study-related disease assessments including cystoscopy, urine cytology, and imaging on schedule until (1) the start of new anticancer treatment, (2) disease progression as assessed by central pathology and radiology review, (3) death, (4) withdrawal of consent, or (5) the end of the study, for a total of up to 5 years (Week 264), whichever occurs first.

7.1.4.1.1 Withdrawal from Future Biomedical Research

Subjects may withdraw their consent for Future Biomedical Research and have their specimens and all derivatives destroyed. Subjects may withdraw consent at any time by contacting the principal investigator for the main trial. If medical records for the main trial are still available, the investigator will contact the Sponsor using the designated mailbox (clinical.specimen.management@MSD.com), and a form will be provided by the Sponsor to obtain appropriate information to complete specimen withdrawal. Subsequently, the subject's specimens will be removed from the biorepository and be destroyed. A letter will be sent from the Sponsor to the investigator confirming the destruction. It is the responsibility of the investigator to inform the subject of completion of destruction. Any analyses in progress at the time of request for destruction or already performed prior to the request being received by the Sponsor will continue to be used as part of the overall research trial data and results. No new analyses would be generated after the request is received.

In the event that the medical records for the main trial are no longer available (e.g., if the investigator is no longer required by regulatory authorities to retain the main trial records) or the specimens have been completely anonymized, there will no longer be a link between the subject's personal information and their specimens. In this situation, the request for specimen destruction cannot be processed.

7.1.4.2 Blinding/Unblinding

This is an open-label trial; there is no blinding for this trial.

7.1.4.3 Calibration of Critical Equipment

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

Critical Equipment for this trial includes:

- Laboratory equipment – as required for inclusion labs and trial assessments
- Imaging equipment – as required for trial objectives
- Infusion Equipment – as required for administering drug product.

See protocol-specified guidance in the Administrative Binder, Procedures Manual, Pharmacy Manual and Site Imaging Manual.

7.1.5 Visit Requirements

Visit requirements are outlined in Section 6.0 - Trial Flow Chart. Specific procedure-related details are provided above in Section 7.1 - Trial Procedures.

7.1.5.1 Screening

Approximately 28 days (for Cohorts A and B) and 42 days (for Cohort C) prior to randomization, potential subjects will be evaluated to determine that they fulfill the entry requirements as set forth in Section 5.1 – Entry Criteria. Screening procedures may be repeated after consultation with the Sponsor.

Results of a test performed prior to the subject providing documented informed consent as part of routine clinical management are acceptable in lieu of a screening test if performed within the specified time frame. Screening procedures (including laboratory tests and evaluation of ECOG status) are to be completed within 28 days prior to the first dose trial treatment except for the following:

a. For women of reproductive potential, a urine pregnancy test will be performed within 72 hours prior to the first dose of trial treatment. If urine pregnancy results are positive or cannot be confirmed as negative, a serum pregnancy test will be required (performed by the local study site laboratory).

b. Initial CTU tumor imaging must be performed and eligibility confirmation from central imaging vendor must be received within 28 days (for Cohorts A and B) and 42 days (for Cohort C). Eligibility confirmation from central vendor must be received before subject randomization.

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

7.1.5.2 Treatment Period

Visit requirements are outlined in Section 6.0 – Trial Flow Chart. Specific procedure-related details are provided above in Section 7.1 – Trial Procedures.

7.1.5.3 Posttreatment Visits

7.1.5.3.1 Safety Follow-up Visit

The mandatory Safety Follow-up Visit should be conducted in all subjects approximately 30 days after the last dose of trial treatment. Procedures and assessments performed at the Safety Follow-up Visit and thereafter should follow the guidelines described in Section 6.0 – Trial Flow Chart. Beyond 90 days, only SAEs that are considered related to trial treatment should be reported.

In subjects who start another anticancer therapy before 30 days after discontinuation of trial treatment, the Safety Follow-up Visit should occur prior to the subject receiving another anticancer therapy.

7.1.5.3.2 Follow-up Phase

Subjects who discontinue trial treatment for a reason other than persistence or recurrence of high-risk NMIBC or disease progression will move into the Follow-up Phase and should be assessed to monitor disease status. Please refer to Section 7.1.2.9 for timing of disease assessments. Every effort should be made to collect information regarding disease status until the start of new anticancer therapy, disease progression, withdrawal of consent, death, or end of trial. Information regarding post-trial anticancer treatment will be collected if new treatment is initiated.

7.1.5.3.3 Survival Follow-up

Subjects who experience confirmed disease progression or persistence or recurrence of high-risk NMIBC or start a new anticancer therapy will move into the Survival Follow-up Phase and should be contacted approximately every 12 weeks to assess for survival and bladder status until death, withdrawal of consent, or the end of the trial (for a total duration of approximately 5 years), whichever occurs first.

Details of the new anticancer therapy should be recorded in the trial database. This would include, but not be limited to, surgical procedures such as TURBT/biopsy and cystectomy, and oncologics and biologics such as additional BCG and systemic or intravesical chemotherapies.

7.1.5.4 Survival Status

To ensure current and complete survival and bladder data are available at the time of database locks, updated survival and bladder disease status (eg, whether the bladder remains intact or removed by a surgical procedure, including cystectomy and T-stage by pathology and disease status ie, CR, stable, persistent/recurrent, locally advanced or metastatic) may be requested during the course of the study by the Sponsor. For example, updated survival and bladder disease status may be requested prior to, but not limited to, an external Data Monitoring Committee review, interim and/or final analysis. Upon Sponsor notification, all subjects who do not/will not have a scheduled study visit or study contact during the Sponsor-defined time period will be contacted for their survival and bladder status (excluding subjects that have a previously recorded death event in the collection tool).

7.2 Assessing and Recording Adverse Events

An adverse event is defined as any untoward medical occurrence in a patient or clinical investigation subject administered a pharmaceutical product and which does not necessarily have to have a causal relationship with this treatment. An adverse event can therefore be any unfavorable and unintended sign (including an abnormal laboratory finding, for example), symptom, or disease temporally associated with the use of a medicinal product or protocol-

specified procedure, whether or not considered related to the medicinal product or protocol-specified procedure. Any worsening (ie, any clinically significant adverse change in frequency and/or intensity) of a pre-existing condition that is temporally associated with the use of the Sponsor's product, is also an adverse event.

Changes resulting from normal growth and development that do not vary significantly in frequency or severity from expected levels are not to be considered adverse events. Examples of this may include, but are not limited to, teething, typical crying in infants and children and onset of menses or menopause occurring at a physiologically appropriate time.

Sponsor's product includes any pharmaceutical product, biological product, device, diagnostic agent or protocol-specified procedure, whether investigational (including placebo or active comparator medication) or marketed, manufactured by, licensed by, provided by or distributed by the Sponsor for human use.

Adverse events may occur during clinical trials, or as prescribed in clinical practice, from overdose (whether accidental or intentional), from abuse and from withdrawal.

Progression of the cancer under study is not considered an adverse event.

All adverse events that occur after the subject provides documented informed consent, but before randomization, must be reported by the investigator if they cause the subject to be excluded from the trial, or are the result of a protocol-specified intervention, including, but not limited to, washout or discontinuation of usual therapy, diet, placebo treatment or a procedure. From the time of randomization through 30 days following cessation of treatment, all adverse events must be reported by the investigator. Such events will be recorded at each examination on the adverse event case report forms/worksheets. The reporting timeframe for adverse events meeting any serious criteria is described in Section 7.2.3. The investigator will make every attempt to follow all subjects with non-serious adverse events for outcome.

Electronic reporting procedures can be found in the Electronic Data Capture (EDC) data entry guidelines. Paper reporting procedures can be found in the Investigator Trial File Binder (or equivalent).

Adverse events will not be collected for subjects during the pre-screening period (for determination of archival tissue status) as long as that subject has not undergone any protocol-specified procedure or intervention. If the subject requires a blood draw, fresh tumor biopsy etc., the subject is first required to provide consent to the main study and AEs will be captured according to guidelines for standard AE reporting.

7.2.1 Definitions of Medication Error, Misuse, and Abuse

Investigators need to document if an AE and/or SAE is associated with a medication error, misuse, or 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 subject.

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 non-therapeutic effect.

7.2.2 Definition of an Overdose for This Protocol and Reporting of Overdose to the Sponsor

Pembrolizumab:

For purposes of this trial, an overdose of pembrolizumab will be defined as any dose of 1,000 mg or greater (≥5x the indicated dose). No specific information is available on the treatment of overdose of pembrolizumab. In the event of overdose, the subject should be observed closely for signs of toxicity. Appropriate supportive treatment should be provided if clinically indicated.

MK-7684A:

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

MK-4280A:

For this study, an overdose of MK-4280A will be defined as any dose exceeding 2 times or 200% the prescribed dose. No specific information is available on the treatment of overdose of MK-4280A. In the event of overdose, the subject should be observed closely for signs of toxicity. Appropriate supportive intervention should be provided if clinically indicated.

If an adverse event(s) is associated with ("results from") the overdose of Sponsor's product or vaccine, the adverse event(s) is reported as a serious adverse event, even if no other seriousness criteria are met.

If a dose of Sponsor's product or vaccine meeting the protocol definition of overdose is taken without any associated clinical symptoms or abnormal laboratory results, the overdose is

reported as a non-serious Event of Clinical Interest (ECI), using the terminology "accidental or intentional overdose without adverse effect."

All reports of overdose with and without an adverse event must be reported by the investigator within 24 hours to the Sponsor either by electronic media or paper. Electronic reporting procedures can be found in the EDC data entry guidelines. Paper reporting procedures can be found in the Investigator Trial File Binder (or equivalent).

7.2.3 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 causes 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, SAEs, and other reportable safety events from the time of 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.

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.

All pregnancies and exposure during breastfeeding, from the time of randomization through the time required to eliminate systemic exposure after cessation of study intervention as described in Sections 5.1 and 7.2.3.2, or 30 days after cessation of study intervention if the participant initiates new anticancer therapy must be reported by the investigator.

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 AE Collection Period	**Reporting Period:** After the Protocol-specified AE Collection 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
Potential DILI/DILI (requiring regulatory reporting)	Report if: – due to intervention – causes exclusion	Report - potential DILI/DILI - to be reported as a SAE with OME criteria in the absence of other serious criteria	Previously reported – Follow to completion/ termination; report outcome	Within 24 hours of learning of event

Type of Event	**Reporting Period:** Consent to Randomization/ Allocation	**Reporting Period:** Randomization/ Allocation Through Protocol-specified AE Collection Period	**Reporting Period:** After the Protocol-specified AE Collection Period	Time Frame to Report Event and Follow-up Information to Sponsor
ECI (requiring regulatory reporting)	Report if: – due to intervention – causes exclusion	Report – requiring regulatory reporting	Previously reported – Follow to completion/ termination; report outcome	Within 24 hours of learning of event
ECI (does not require regulatory reporting)	Report if: – due to intervention – causes exclusion	Report – those not requiring regulatory reporting	Not required	Within 5 calendar days of learning of event (unless an SAE)
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 an SAE)
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 an SAE)

DILI=drug-induced liver injury; ECI=event of clinical interest; NSAE=nonserious adverse event; OME=other important medical event; SAE=serious adverse event.

7.2.3.1 Serious Adverse Events

A serious adverse event is any adverse event occurring at any dose or during any use of Sponsor's product that:

- Results in death;
- Is life threatening;
- Results in persistent or significant disability/incapacity;
- Results in or prolongs an existing inpatient hospitalization;
- Is a congenital anomaly/birth defect;
- Is an other important medical event.

Note: In addition to the above criteria, adverse events meeting either of the below criteria, although not serious per ICH definition, are reportable to the Sponsor in the same timeframe as SAEs to meet certain local requirements. Therefore, these events are considered serious by the Sponsor for collection purposes.

- Is a new cancer (that is not a condition of the study);
- Is associated with an overdose;
- All events of potential DILI/DILI will be reported as a SAE with OME criteria in the absence of other serious criteria.

Refer to Table 8 for additional details regarding each of the above criteria.

All subjects with serious adverse events must be followed up for outcome.

7.2.3.2 Reporting of Pregnancy and Lactation to the Sponsor

Although pregnancy and lactation are not considered adverse events, it is the responsibility of investigators or their designees to report any pregnancy or lactation in a subject (spontaneously reported to them) that occurs during the trial.

Pregnancies and lactations that occur after the subject provides documented informed consent but before randomization must be reported by the investigator if they cause the subject to be excluded from the trial, or are the result of a protocol-specified intervention, including but not limited to washout or discontinuation of usual therapy, diet, placebo treatment or a procedure. Pregnancies and lactations that occur from the time of randomization through 120 days following cessation of Sponsor's product or 30 days following cessation of treatment if the subject initiates new anticancer therapy, whichever is earlier, must be reported by the investigator. All reported pregnancies must be followed to the completion/termination of the pregnancy. Pregnancy outcomes of 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.

Such events must be reported within 24 hours to the Sponsor either by electronic media or paper. Electronic reporting procedures can be found in the EDC data entry guidelines. Paper reporting procedures can be found in the Investigator Trial File Binder (or equivalent).

7.2.3.3 Events of Clinical Interest

Selected non-serious and serious adverse events are also known as ECI and must be reported to the Sponsor.

For the time period beginning when the subject provides documented informed consent until randomization, any ECI, or follow-up to an ECI, that occurs to any subject must be reported within 24 hours of learning of event to the Sponsor if it causes the subject to be excluded from the trial, or is the result of a protocol-specified intervention, including but not limited to washout or discontinuation of usual therapy, diet, placebo treatment or a procedure.

For the time period beginning at randomization through 30 days following cessation of treatment, any ECI, or follow-up to an ECI, whether or not related to the Sponsor's product, must be reported within 24 hours of learning of event to the Sponsor, either by electronic

media or paper. Electronic reporting procedures can be found in the EDC data entry guidelines. Paper reporting procedures can be found in the Investigator Trial File Binder (or equivalent).

Events of clinical interest for this trial include:

1. an overdose of Sponsor's product, as defined in Section 7.2.2 - Definition of an Overdose for This Protocol and Reporting of Overdose to the Sponsor that is not associated with clinical symptoms or abnormal laboratory results.

2. DILI, defined as:

   - an elevated AST or ALT lab value that is greater than or equal to 3X the upper limit of normal and

   - an elevated total bilirubin lab value that is greater than or equal to 2X the upper limit of normal and,

   - at the same time, an alkaline phosphatase lab value that is less than 2X the upper limit of normal, as determined by way of protocol-specified laboratory testing or unscheduled laboratory testing.*

   *Note: These criteria are based upon 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 trial site guidance for assessment and follow-up of these criteria can be found in the Investigator Trial File Binder (or equivalent).

All potential DILI/DILI will be reported to the Sponsor as a SAE, within 24 hours, with OME criteria in the absence of other SAE criteria.

7.2.3.4 Protocol-Specific Exceptions to Serious Adverse Event Reporting

Efficacy endpoints as outlined in this section will not be reported to the Sponsor as described in Sections 7.2.3.1 through 7.2.3.3.

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

The Sponsor will monitor unblinded aggregated efficacy endpoint events and safety data to ensure the safety of the subjects in the trial. Any suspected endpoint which upon review is not progression of the cancer under study will be forwarded to global safety as a SAE within 24 hours of determination that the event is not progression of the cancer under study.

7.2.4 Evaluating Adverse Events

An investigator who is a qualified physician will evaluate all adverse events according to the NCI Common Terminology for Adverse Events (CTCAE), version 4.0. Any adverse event which changes CTCAE grade over the course of a given episode will have each change of grade recorded on the adverse event case report forms/worksheets.

All adverse events regardless of CTCAE grade must also be evaluated for seriousness.

Table 8 Evaluating Adverse Events

An investigator who is a qualified physician, will evaluate all adverse events as to:

V4.0 CTCAE Grading	**Grade 1**	**Mild; asymptomatic or mid 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 or hospitalization indicated; disabling; limiting self-care ADL.**
	Grade 4	**Life threatening consequences; urgent intervention indicated.**
	Grade 5	**Death related to AE**
Seriousness	A serious adverse event is any adverse event occurring at any dose or during any use of Sponsor's product that:	
	†**Results in death**; or	
	†**Is life threatening; or** places the subject, in the view of the investigator, at immediate risk of death from the event as it occurred (Note: This does not include an adverse event that, had it occurred in a more severe form, might have caused death.); or	
	†**Results in a persistent or significant disability/incapacity** (substantial disruption of one's ability to conduct normal life functions); or	
	†**Results in or prolongs an existing inpatient 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 pre-existing condition that has not worsened is not a serious adverse event. A pre-existing condition is a clinical condition that is diagnosed prior to the use of an MSD product and is documented in the patient's medical history.); or	
	†**Is a congenital anomaly/birth defect** (in offspring of subject taking the product regardless of time to diagnosis);or	
	Is a new **cancer** (that is not a condition of the study) **(**although not serious per ICH definition, is reportable to the Sponsor within 24 hours to meet certain local requirements); **or**	
	Is an overdose (whether accidental or intentional). Any adverse event associated with an overdose is considered a serious adverse event for collection purposes. An overdose that is not associated with an adverse event is considered a non-serious event of clinical interest and must be reported within 24 hours.	
	Other important medical events that may not result in death, not be life threatening, or not require hospitalization may be considered a serious adverse event when, based upon appropriate medical judgment, the event may jeopardize the subject and may require medical or surgical intervention to prevent one of the outcomes listed previously (designated above by a †).	
Duration	Record the start and stop dates of the adverse event. If less than 1 day, indicate the appropriate length of time and units	
Action taken	Did the adverse event cause the Sponsor's product to be discontinued?	
Relationship to test drug	Did the Sponsor's product cause the adverse event? The determination of the likelihood that the Sponsor's product caused the adverse event 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 drug and the adverse event 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 subject 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 trials with investigational medicinal product)?
	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

Relationship to Sponsor's Product (continued)	**The following components are to be used to assess the relationship between the test drug and the AE: (continued)**	
	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; or (3) the trial is a single-dose drug trial); or (4) Sponsor's product(s) is/are only used one time.)
	Rechallenge	Was the subject 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 trial is a single-dose drug trial); or (3) Sponsor's product(s) is/are used only one time). NOTE: IF A RECHALLENGE IS PLANNED FOR AN ADVERSE EVENT WHICH WAS SERIOUS AND WHICH MAY HAVE BEEN CAUSED BY THE SPONSOR'S PRODUCT, OR IF REEXPOSURE TO THE SPONSOR'S PRODUCT POSES ADDITIONAL POTENTIAL SIGNIFICANT RISK TO THE SUBJECT, THEN THE RECHALLENGE MUST BE APPROVED IN ADVANCE BY THE SPONSOR CLINICAL DIRECTOR AS PER DOSE MODIFICATION GUIDELINES IN THE PROTOCOL.
	Consistency with Trial Treatment 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 his/her best clinical judgment, including consideration of the above elements.		
Record one of the following		**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		Subject 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 subject with overdose without an associated AE.)

7.2.5 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. All AEs, SAEs, and other reportable safety events, including potential DILI/DILI, 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 5.8). In addition, the investigator will also make every attempt to follow all nonserious AEs that occur in randomized participants for outcome. Further information on follow-up procedures is given in Section 7.2.

7.2.6 Sponsor Responsibility for Reporting Adverse Events

All Adverse Events will be reported to regulatory authorities, IRB/IECs and investigators in accordance with all applicable global laws and regulations, ie, per ICH Topic E6 (R1) Guidelines for Good Clinical Practice.

Refer to Section 12.8 for country-specific requirements.

7.3 TRIAL GOVERNANCE AND OVERSIGHT

7.3.1 Scientific Advisory Committee

This trial was developed in collaboration with a Scientific Advisory Committee (SAC). The SAC comprises both Sponsor and non-Sponsor scientific experts who provide input with respect to trial design, interpretation of trial results and subsequent peer-reviewed scientific publications.

7.3.2 Data Monitoring Committee

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

The DMC will make recommendations to the Sponsor regarding steps to ensure both subject safety and the continued ethical integrity of the trial. Also, the DMC will review interim trial results, consider the overall risk and benefit to trial subjects (see Section 8.7 - Interim Analyses) and recommend to the Sponsor if the trial 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; meeting facilitation; the trial governance structure; and requirements for decision-making, inclusive of Complete Response (CR) and Duration of Response (DOR) for this protocol, and proper documentation of DMC reports, minutes, and recommendations will be described in a separate charter that is

reviewed and approved by the DMC. The DMC will monitor the trial at an appropriate frequency, as described in the detailed DMC charter. The DMC will also make recommendations to the Sponsor regarding steps to ensure both subject safety and the continued ethical integrity of the trial.

8.0 STATISTICAL ANALYSIS PLAN

Changes that apply as of Amendment 12 are listed in Section 1.0 and supersede any protocol content/instructions from previous amendments. Existing protocol content in this section is retained for historical reference.

This section outlines the statistical analysis strategy and procedures for the study. If, after the study has begun, but prior to finale database lock, changes 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 non-confirmatory analyses made after the protocol has been finalized, but prior to finale database lock, will be documented in a supplemental statistical analysis plan (sSAP) and referenced in the CSR for the study. Post hoc exploratory analyses will be clearly identified in the CSR.

8.1 Statistical Analysis Plan Summary

Key elements of the statistical analysis plan are summarized below; the comprehensive plan is provided in Sections 8.2-8.12.

Study Design Overview	A Phase II Clinical Trial to Study the Efficacy and Safety of Pembrolizumab (MK-3475) and Pembrolizumab in Combination with Other Investigational Agents in Subjects with High-risk Non-muscle Invasive Bladder Cancer (NMIBC) Unresponsive to Bacillus Calmette-Guerin (BCG) Therapy
Treatment Assignment	Open-label, 3 cohorts (Cohorts A and B are single-arm; subjects in Cohort C are randomly assigned to 1 of the 2 treatment arms)
Analysis Populations	Efficacy: Full Analysis Set (FAS) Safety: All Patients as Treated (APaT)
Primary Endpoint(s)	Cohort A: CR rate of high-risk NMIBC in the overall population Cohort B: 12-month DFS rate of high-risk NMIBC in the overall population Cohort C: 12-month CR rate of high-risk NMIBC in the overall population
Key Secondary Endpoints	Cohort A: CR rate of any disease in the overall population; DOR of high-risk NMIBC and any disease Cohort B: 12-month DFS rate of any disease in the overall population

Statistical Methods for Key Efficacy Analyses	Cohort A: The primary and key secondary hypotheses will be evaluated by assessing the CR rate of high-risk NMIBC and any disease, respectively, using the binomial exact method and comparing the lower bounds of the 95% confidence intervals (CI) with the historical control rate of 20%. DOR for responders will be estimated by Kaplan-Meier (KM) method. Cohort B: The primary and key secondary hypotheses will be evaluated by assessing the 12-month DFS rate of high-risk NMIBC and any disease, respectively, using the KM method and comparing the lower bounds of the 95% CI with the historical control rate of 20%. Cohort C: There is no formal hypothesis testing for Cohort C. The primary objective will be evaluated by assessing the point estimate of 12-month CR rate of high-risk NMIBC and its 95% confident interval using the binomial exact method.
Statistical Methods for Key Safety Analyses	Summary statistics and 95% CIs for AEs of clinical interest.
Interim Analyses	A POC Efficacy IA will be conducted in Cohort A of this study (see Section 8.7). Final analysis will be conducted at full enrollment plus a minimum of 12 months duration of response follow-up for Cohort A, full enrollment plus 12 months DFS follow-up for Cohort B, and full enrollment plus 12-month CR follow-up for Cohort C.
Multiplicity	There is only one primary hypothesis per cohort for Cohorts A and B and each primary hypothesis will be tested at 5% (2-sided) alpha level within each cohort. There is no formal hypothesis testing for Cohort C. Hence, no multiplicity adjustment is required for Cohort C.

Sample Size and Power	The planned sample size is 320 subjects total, with 130 subjects in Cohorts A and B, and additional 60 subjects in the signal-finding Cohort C, where 30 subjects will be enrolled into each arm. Cohort A: For the primary endpoint of the CR rate of high-risk NMIBC in this cohort, a sample size of 130 can have approximately 97% power to reject the null hypothesis of the overall population with the lower bound of the 2-sided 95% CI by the binomial exact method excluding 20%. Cohort B: For the primary endpoint of the 12-month DFS rate of high-risk NMIBC in this cohort, a sample size of 130 can have approximately 97% power to reject the null hypothesis of the overall population with the lower bound of the 2-sided 95% CI by the KM method excluding 20%. Cohort C: With 30 subjects per arm, assuming 12-month CR rate of CCI [redacted] in each arm by the binomial exact method.

8.2 Responsibility for Analyses/In-House Blinding

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

This trial is being conducted as an open-label study, ie, subjects, investigators, and Sponsor personnel will be aware of subject treatment assignments after each subject is enrolled and treatment is assigned. Clinical outcome and subject-level PD-L1 biomarker results will not be masked in the database to the study team at the Sponsor.

The Clinical Biostatistics department will generate the allocation schedule(s) for study treatment assignment. Allocation will be implemented in an IVRS.

Planned interim analyses are described in Section 8.7 – Interim Analyses. Study enrollment is likely to be ongoing at the time of any interim analyses.

8.3 Hypotheses/Estimation

Objectives and hypotheses of the study are stated in Section 3.0 – Objective(s) & Hypothesis(es).

8.4 Analysis Endpoints

Efficacy and safety endpoints that will be evaluated for within-treatment differences are listed below, followed by the descriptions of the derivations of selected endpoints.

8.4.1 Efficacy Endpoints

In Cohort A, the primary efficacy endpoint is the CR rate of **high-risk NMIBC**. The key secondary endpoints in this cohort are the CR rate of any disease, DOR of high-risk NMIBC, and DOR of any disease. In Cohort B, the primary and key secondary efficacy endpoints are the 12-month DFS rates of **high-risk NMIBC** and **any disease**, respectively. In Cohort C, the primary endpoint is 12-month CR rate of high-risk NMIBC.

The CR rate of high-risk NMIBC in Cohort A is defined as the proportion of subjects in the analysis population whose tumors are in response to treatment and who are then free of the disease of high-risk NMIBC or worse per central pathology and radiology review. Similarly, the CR rate of any disease is defined by the proportion of subjects who respond and are then free of any disease. The DOR of high-risk NMIBC is defined as the time from the first documented evidence of CR until the recurrence high-risk NMIBC or worse per central pathology and radiology review; similarly, the DOR of any disease is defined as the time from CR to recurrence of any disease. Complete response (Cohort A) at each analysis time point is defined in Section 7.1.2.10 – Assessment of Disease.

The DFS of high-risk NMIBC in Cohort B is the time from the first dose to the first occurrence of high-risk NMIBC or worse per central pathology and radiology review. The 12-month DFS rate of high-risk NMIBC is defined as the probability of subjects in this analysis population remaining free of high-risk NMIBC or worse for at least 12 months. Similarly, the DFS rate of any disease is defined as the time from the first dose to the first occurrence of any disease, and the 12-month DFS rate of any disease is defined as the probability of subjects in this analysis population remaining disease-free for at least 12 months. Of note, subjects who develop high grade urothelial carcinoma involving the upper urinary tract will be considered to have developed recurrent high-risk NMIBC and will be taken off study. Table 12 shows the detailed definitions of failure events and censoring rules for DFS of high-risk NMIBC in Cohort B.

The 12-month CR rate of high-risk NMIBC in Cohort C, assessing CR rate at a specific time point (ie, 12 months), is defined as the proportion of subjects in the analysis population whose tumors are in response to treatment and who are then free of the disease of high-risk NMIBC or worse per central pathology and radiology review at Month 12 using their 48-week efficacy review. The DOR of high-risk NMIBC is defined as the time from the first documented evidence of CR until the recurrence high-risk NMIBC or worse per central pathology and radiology review. CR (Cohort C) at each analysis time point is defined in Section 7.1.2.10 – Assessment of Disease.

Other efficacy endpoints:

- In Cohort A and Cohort C only, the DOR rate is defined as the probability of maintaining a DOR at specific time points (eg, at 6 months, 12 months, etc.).

- In Cohort C only, the 3-month CR rate of high-risk NMIBC is defined as the proportion of subjects in the analysis population whose tumors are in response to treatment and who are then free of the disease of high-risk NMIBC or worse per central pathology and radiology review at Month 3 using the 12-week efficacy review.

- In Cohort C only, the 6-month CR rate of high-risk NMIBC is defined as the proportion of subjects in the analysis population whose tumors are in response to treatment and who are then free of the disease of high-risk NMIBC or worse per central pathology and radiology review at Month 6 using the 24-week efficacy review.

- In Cohort C only, the overall CR rate of high-risk NMIBC is defined as the proportion of subjects in the analysis population whose tumors are in response to treatment and who are then free of the disease of high-risk NMIBC or worse per central pathology and radiology review at either Month 3 using the 12-week efficacy review or Month 6 using the 24-week efficacy review.

- The PFS to worsening of grade or stage or death is defined as time from the first dose to progression to worse grade or stage or death per central urology, pathology and radiology review.

- The PFS to muscle invasive or metastatic disease or death is defined as the time from the first dose to the first documented muscle invasive or metastatic disease or death per central urology, pathology and radiology review.

- The OS is defined as the time from the first dose to death due to any cause.

8.4.2 Safety Endpoints

A description of safety measures is provided in Section 4.2.3.2 – Safety Endpoints.

In each of the 3 cohorts, the primary safety endpoints are AEs graded using CTCAE (Version 4.0) criteria. Safety will be assessed by quantifying the toxicities and grades experienced by subjects who have received pembrolizumab, MK-7684A, or MK-4280A, including SAEs and ECIs. Other safety endpoints include laboratory safety assessments, ECOG performance status, vital signs and physical examinations.

8.5 Analysis Population

8.5.1 Efficacy Analysis Population

The FAS population will serve as the primary population for the analysis of efficacy data in this study. The FAS population for the final analysis consists of all enrolled subjects who receive at least one dose of trial treatment and have a baseline evaluation consisting of pre-enrollment cystoscopy, TURBT/biopsy, urine cytology, and baseline CTU imaging. For

all efficacy analyses prior to the final efficacy analysis, only those subjects in Cohorts A and B with at least one post-baseline disease assessment will be included in the efficacy analysis.

Details on the approach to handling missing data are provided in Section 8.6 – Statistical Methods.

8.5.2 Safety Analysis Populations

The APaT population will be used for the analysis of safety data in this study. The APaT population consists of all randomized subjects who received at least one dose of study treatment.

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

8.6 Statistical Methods

Statistical testing and inference for efficacy analyses are described in Section 8.6.1 - Statistical Methods for Efficacy Analyses. Statistical testing and inference for safety analyses are described in Section 8.6.2 - Statistical Methods for Safety Analyses. Summaries of baseline characteristics, demographics, and other analyses are described in Section 8.6.3 - Summaries of Baseline Characteristics, Demographics, and Other Analyses. Efficacy results that will be deemed to be statistically significant after consideration of the Type I error control strategy are described in Section 8.8. 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.

8.6.1 Statistical Methods for Efficacy Analyses

This section describes the statistical methods that address the primary and secondary objectives. Methods related to exploratory objectives will be described in the sSAP.

For the primary and key secondary endpoints of the CR rates in Cohort A, the point estimates and 95% CI of the rates will be provided using the binomial exact method and compared with the historical control of 20%. In Cohort B, the primary and key secondary endpoints of the 12-month DFS rates will be evaluated using the KM method. The point estimates and 95% CIs will be provided and compared with the historical control of 20%. The secondary endpoints of DFS rates at other specific time points will be evaluated similarly as the above. In Cohort C, there is no formal hypothesis testing. For the primary endpoint of the 12-month CR rate, the point estimate and 95% CI in each arm will be provided using the binomial exact method.

For other time-to-event secondary efficacy endpoints on overall DFS, PFS, or OS, KM curves, and median estimates from the KM curves will be provided as appropriate. Subjects without efficacy evaluation data or without survival data will be censored at Day 1. Table 9 and Table 10 summarize the key efficacy analyses of Cohort A and Cohort B, respectively.

Table 11 summarizes the key efficacy analyses of Cohort C. Additional sensitivity analyses regarding the key efficacy endpoints in Cohort C will be documented in the sSAP. The definition of failure events and censoring rules for the primary efficacy and key secondary endpoints in Cohort B are summarized in Table 12.

Table 9 Analysis Strategy for Key Efficacy Variables in Overall Population and PD-L1 Positive Population of **Cohort A**

Endpoint/Variable (Description, Time Point)	Statistical Method	Analysis Population	Missing Data Approach
Primary Analysis:			
CR rate of high-risk NMIBC	Exact test of binomial parameter	FAS	Subjects with missing data are considered as non-responders for final analysis. Subjects who were missing the required assessments† at Week 12 will be deemed non-evaluable at the interim analyses.
Key Secondary Analysis:			
Duration of Response for high-risk NMIBC and any disease	Summary statistics using Kaplan-Meier method	All responders	Censored at last assessment
CR rate of any disease	Exact test of binomial parameter	FAS	Subjects with missing data are considered as non-responders for final analysis. Subjects who were missing the required assessments† at Week 12 will be deemed non-evaluable format the interim analyses.
Other Secondary Analyses:			
DOR rate at a specific time point (eg, at 6 months, 12 months, etc.) of both high-risk NMIBC and any disease	Kaplan-Meier method	All responders	Censored at last assessment
Progression free survival (PFS) to worsening of grade or stage or death	Summary statistics using Kaplan-Meier method	FAS	Censored at last assessment
PFS to muscle invasive or metastatic disease or death	Summary statistics using Kaplan-Meier method	FAS	Censored at last assessment
Overall Survival (OS)	Summary statistics using Kaplan-Meier method	FAS	censored at last contact date
† The required assessments at Week 12 are urine cytology and cystoscopy.			

CR = complete response; DOR = duration of response; FAS = full analysis set; NMIBC = non-muscle invasive bladder cancer.

Table 10 Analysis Strategy for Key Efficacy Variables in Overall Population and PD-L1 Positive Population of **Cohort B**

Endpoint/Variable (Description, Time Point)	Statistical Method	Analysis Population	Missing Data Approach
Primary Analysis:			
12-month DFS rate of high-risk NMIBC	Kaplan-Meier method	FAS	See censoring rules in Table 12.
Key Secondary Analysis:			
12-month DFS rate of any disease	Kaplan-Meier method	FAS	See censoring rules in Table 12.
Other Secondary Analyses:			
Overall DFS and 3-month/6-month DFS rates of both high-risk NMIBC and any disease	Kaplan-Meier method	FAS	See censoring rules in Table 12.
Progression free survival (PFS) to worsening of grade or stage or death	Summary statistics using Kaplan-Meier method	FAS	Censored at last assessment
PFS to muscle invasive or metastatic disease or death	Summary statistics using Kaplan-Meier method	FAS	Censored at last assessment
Overall Survival (OS)	Summary statistics using Kaplan-Meier method	FAS	Censored at last contact date

DFS = disease-free survival; DOR = duration of response; FAS = full analysis set; NMIBC = non-muscle invasive bladder cancer.

Table 11 Analysis Strategy for Key Efficacy Variables in Overall Population of **Cohort C**

Endpoint/Variable (Description, Time Point)	Statistical Method	Analysis Population	Missing Data Approach
Primary Analysis:			
12-month CR rate of high-risk NMIBC	Point estimate and CI using the binomial exact method	FAS	Subjects who are missing the required assessments† at Week 48 will be deemed non-evaluable and are considered as non-responders for final analysis.
Secondary Analysis:			
Duration of Response for high-risk NMIBC	Summary statistics using Kaplan-Meier method	All responders	Censored at last assessment
CR rate of high-risk NMIBC at 3 months CR rate of high-risk NMIBC at 6 months	Point estimate and CI using the binomial exact method	FAS	Subjects who are missing the required assessments† at Week 12 are considered as non-responders for final analysis. Subjects who are missing the required assessments† at Week 24 are considered as non-responders for final analysis.
Overall CR rate of high-risk NMIBC	Point estimate and CI using the binomial exact method	FAS	Subjects who are missing the required assessments† at both 3 months and 6 months are considered as non-responders for final analysis.
DOR rate at a specific time point (eg, at 6 months, 12 months, etc.) of high-risk NMIBC	Kaplan-Meier method	All responders based on overall CR	Censored at last assessment
Progression free survival (PFS) to worsening of grade or stage or death	Summary statistics using Kaplan-Meier method	FAS	Censored at last assessment
PFS to muscle invasive or metastatic disease or death	Summary statistics using Kaplan-Meier method	FAS	Censored at last assessment
Overall Survival (OS)	Summary statistics using Kaplan-Meier method	FAS	censored at last contact date
† The required assessments at the specified timepoint are urine cytology and cystoscopy.			

CI = confidence interval; CR = complete response; DOR = duration of response; FAS = full analysis set; NMIBC = non-muscle invasive bladder cancer.

Table 12 Failure Events and Censoring Rules in **Cohort B** for DFS (of High-risk NMIBC and any Disease, Respectively)

Situation	Censoring Rule
For DFS of high-risk NMIBC only: any high-risk NMIBC (high grade Ta, low/high grade T1 or Tis or high grade urothelial carcinoma involving the upper urinary tract), any disease with worse stage, or death after allocation	Failure event of the DFS of high-risk NMIBC at the time of first documented high-risk NMIBC, disease with worse stage, or death after the first dose
For DFS of any disease only: any disease or death after the first dose	Failure event of the DFS of any disease at the time of the first documented any disease or death after the first dose
Discontinue study follow-up due to toxicity without any other failure events	Failure event at the time of discontinuation
Discontinue study follow-up without toxicity and any other failure event	Censored at the time of last disease assessment before discontinuation
No failure event; new anticancer treatment is not initiated	Censored at last disease assessment
No failure event; new anticancer treatment is initiated	Censored at last disease assessment at or before new anticancer treatment
Failure event documented after ≥1 missed disease assessments	Failure event at the time of the documented failure event

DFS = disease-free survival; NMIBC = non-muscle invasive bladder cancer.

8.6.2 Statistical Methods for Safety Analyses

In each of the 3 cohorts, safety and tolerability will be assessed by clinical review of all relevant parameters, including AEs, laboratory tests, and vital signs. Summary statistics (counts, percentage, mean, standard deviation, etc.) will be provided for the safety endpoints as appropriate. The 95% CI for the incidence rate of Grade 2 or higher adverse events with an immune etiology and the incidence rate of Grade 4/5 AEs will be provided as appropriate.

8.6.3 Summaries of Baseline Characteristics, Demographics, and Other Analyses

In each of the 3 cohorts, baseline characteristics will be assessed by the use of tables and/or graphs for each cohort. No statistical hypothesis tests will be performed on these characteristics. The number and percentage of subjects screened, randomized, and the primary reasons for screening failure and discontinuation will be displayed. Demographic variables (eg, age, gender), baseline characteristics, primary and secondary diagnoses, and prior and concomitant therapies will be summarized by treatment either by descriptive statistics or categorical tables.

8.7 Interim Analyses

No early stop for strong efficacy is planned for Cohorts A and B. No IA is planned for Cohort C.

The first efficacy IA1 will be conducted by the study team at the Sponsor to assess the POC of pembrolizumab on the endpoint of CR rate of high-risk NMIBC in Cohort A when at least

20 subjects complete the Week 12 (Month 3) evaluation. The prevalence of available PD-L1 biomarker data will be summarized and documented by the study team prior to the efficacy IA1. For all FAS subjects enrolled in Cohort A at the time of efficacy IA1, only those with at least one post-baseline disease assessment can be included in this efficacy IA.

The POC is considered achieved if the upper bound of the 2-sided 95% CI for the CR of high-risk NMIBC is CCI or greater as assessed by the binomial exact method, which is equivalent to observing 3 or more CR with a sample size of CCI If the POC is achieved, then the study will continue enrolling all subjects in both cohorts and the second efficacy IA (IA2) will be conducted when 50 subjects complete Month 6 evaluation. The CR rate of high-risk disease and DOR from this efficacy IA will be summarized and reviewed by the DMC. The DMC charter will include guidelines will be provided to the DMC for interpretation of these results.

If the POC is not achieved at efficacy IA1, the study will stop enrolling the PD-L1 negative subjects in both cohorts. Another POC efficacy IA for the PD-L1 positive subjects in Cohort A will be conducted when CC such subjects complete the CCI evaluation. The criteria for the POC will be the same as efficacy IA1. After the POC is achieved in this analysis population, efficacy IA2 will be conducted for the PD-L1 positive subjects when 50 such subjects complete the Month 6 evaluation. The CR rate of high-risk disease and the DOR from this efficacy IA will be summarized and reviewed by the DMC.

The flowchart of this POC efficacy IA process can be found in Figure 6. Operating characteristics of the POC efficacy IA rule are summarized in Table 13. For all FAS subjects enrolled in Cohort A and Cohort B at the time of efficacy IA2 (and any subsequent efficacy IAs), only those with at least one post-baseline disease assessment can be included in this efficacy IA.

Safety interim analyses will be conducted at periodic intervals as specified in the DMC charter.



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8.8 Multiplicity

In Cohorts A and B, there is only one primary hypothesis per cohort and each primary hypothesis will be tested at 5% (2-sided) alpha level within each cohort. The type I error rate between the primary and key secondary hypothesis is strongly controlled within each of the 2 cohorts at 5% (2-sided) alpha level with a step-down procedure. Only after the primary hypothesis of the overall population is successful, a type I error rate of 5% can be rolled over to the key secondary hypothesis in the overall population (Figure 7).



8.9 Sample Size and Power Calculation

A total of 130 subjects with underlying CIS at baseline will be enrolled into Cohort A. If the enrollment of the PD-L1 negative subjects is stopped based on the POC IA, a total of 130 PD-L1 positive subjects will be enrolled for the final analysis conditional on the POC being achieved in the PD-L1 positive subjects. With 130 subjects, there is approximately 97% power to reject the null hypothesis with the lower bound of the 2-sided 95% CI by the binomial exact method excluding 20%. The power calculation assumes an alternative CR rate of 35%.

Similarly, a total of 130 subjects without underlying CIS at baseline, either from overall population or PD-L1 positive only population as determined by the outcome of POC IA in Cohort A, will be enrolled into Cohort B. Assuming no censoring, with 130 subjects the study has approximately 97% power to reject the null hypothesis 20% with the lower bound of the 2-sided 95% CI. Again, the power calculation is based on an assumed alternative of 35%.

Table 14 and Table 15 list the power of excluding the historical control rate in the null hypothesis under different assumptions of the true rates. When there is no censoring, the KM method has the same power as the binomial exact method.

Table 14 Power for Primary Analysis in **Cohort A** under Different Assumptions of the True Rate and Assuming use of the Binomial Exact Method

True CR Rate	Power of Excluding 20% with the Lower Bound of the 2-sided 95%[§] CI in Overall Population; N=130[$]
35%	97%
20%	2.2%

CI = confidence interval; CR = complete response

§ The 95% CI is corresponding to a 5% alpha (2-sided) assigned for the primary hypothesis of the overall population.

CCI [redacted]

The sample size and power calculation for this cohort were performed in the software R with simulations based on exponential distribution and Kaplan-Meier method.

A total of 60 subjects, 30 subjects in each arm, with underlying CIS at baseline will be enrolled into Cohort C.

There is no formal hypothesis testing for Cohort C. Table 16 CCI [redacted] for different observed response rates based on the binomial exact method of Clopper and Pearson (1934) [98].

Table 16 CCI

CCI

The timing of the final analysis is defined as full enrollment plus a minimum of 12 months duration of response follow-up for Cohort A, full enrollment plus 12 months DFS follow-up for Cohort B, and full enrollment plus 12-month CR follow-up for Cohort C.

8.10 Subgroup Analyses and Effect of Baseline Factors

To determine whether the treatment effect is consistent across various subgroups in Cohort A, the estimate of the within-cohort treatment effect (with a nominal 95% CI) for the primary endpoint (CR) will be estimated and plotted within each category of each subgroup for Cohorts A and B based on the following subgroups:

1. Age category (<65 vs. ≥65 years)
2. Sex (female vs. male)
3. Race (white vs. non-white)
4. ECOG PS (0 vs. 1/2)
5. PD-L1 subgroup (positive vs. negative)
6. Tumor stage (Ta, T1 or Tis/CIS) at baseline (Cohort A only)
7. Tumor stage (Ta or T1) at baseline (Cohort B only)
8. Pattern of BCG failure (persistent versus progressive versus recurrent high-risk NMIBC) (Cohort A only)
9. Pattern of BCG failure (progressive versus recurrent high-risk NMIBC) (Cohort B only)

For Cohort C, the details of subgroup analyses, if any, will be documented in the sSAP.

8.11 Compliance (Medication Adherence)

Drug accountability data for trial treatment will be collected during the study. Compliance with trial treatment administration will be measured by subjects: (1) receiving unscheduled study agent infusions/injections; (2) missing an infusion/injection. Numbers and percentages of subjects and infusion/injection visits with any deviation in these measures will be reported for the FAS population.

8.12 Extent of Exposure

The extent of exposure will be summarized as duration of treatment in cycles. Dose intensity will also be summarized as appropriate.

9.0 LABELING, PACKAGING, STORAGE AND RETURN OF CLINICAL SUPPLIES

Changes that apply as of Amendment 12 are listed in Section 1.0 and supersede any protocol content/instructions from previous amendments. Existing protocol content in this section is retained for historical reference.

9.1 Investigational Product

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 investigational product in accordance with the protocol and any applicable laws and regulations.

Clinical Supplies will be provided by the Sponsor as summarized in Section 5.2 – Trial Treatment.

Product Name & Potency	Dosage Form
Pembrolizumab (MK-3475) 25 mg/mL	Solution for infusion
MK-7684A (MK-7684 200 mg + pembrolizumab 200 mg/ 20 mL vial)	Solution for infusion
MK-4280A (MK-4280 20 mg/mL + pembrolizumab 5 mg/mL)	Solution for infusion

9.2 Packaging and Labeling Information

Clinical supplies will be affixed with a clinical label in accordance with regulatory requirements.

Subjects will receive open-label pembrolizumab (MK-3475) vials.

9.3 Clinical Supplies Disclosure

This trial is open-label; therefore, the subject, the trial site personnel, the Sponsor and/or designee are not blinded. Treatment (name, strength or potency) is included in the label text; random code/disclosure envelopes or lists are not provided.

9.4 Storage and Handling Requirements

Clinical supplies must be stored in a secure, limited access location under the storage conditions specified on the label.

Receipt and dispensing of trial medication must be recorded by an authorized person at the trial site.

Clinical supplies may not be used for any purpose other than that stated in the protocol.

9.5 Discard/Destruction/Returns and Reconciliation

The investigator is responsible for keeping accurate records of the clinical supplies received from the Sponsor or designee, the amount dispensed to and returned by the subjects and the amount remaining at the conclusion of the trial. For all trial 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.

9.6 Standard Policies

Trial site personnel will have access to a central electronic randomization system (IVRS/IWRS system) to allocate subjects, to assign treatment to subjects and to manage the distribution of clinical supplies. Each person accessing the IVRS system must be assigned an individual unique PIN. They must use only their assigned PIN to access the system, and they must not share their assigned PIN with anyone.

10.0 ADMINISTRATIVE AND REGULATORY DETAILS

Changes that apply as of Amendment 12 are listed in Section 1.0 and supersede any protocol content/instructions from previous amendments. Existing protocol content in this section is retained for historical reference.

10.1 Confidentiality

10.1.1 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 institutional review board, ethics review committee (IRB/ERC) 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 trial 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.

10.1.2 Confidentiality of Subject Records

By signing this protocol, the investigator agrees that the Sponsor (or Sponsor representative), IRB/ERC, or regulatory authority representatives may consult and/or copy trial documents in order to verify worksheet/case report form data. By providing documented informed consent, the subject agrees to this process. If trial documents will be photocopied during the process of verifying worksheet/case report form information, the subject will be identified by unique code only; full names/initials will be masked prior to transmission to the Sponsor.

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

10.1.3 Confidentiality of Investigator Information

By signing this protocol, the investigator recognizes that certain personal identifying information with respect to the investigator, and all subinvestigators and trial site personnel, may be used and disclosed for trial management purposes, as part of a regulatory submissions, and as required by law. This information may include:

1. Name, address, telephone number and email address;

2. Hospital or clinic address and telephone number;

3. Curriculum vitae or other summary of qualifications and credentials; and

4. Other professional documentation.

Consistent with the purposes described above, this information may be transmitted to the Sponsor, and subsidiaries, affiliates and agents of the Sponsor, in your country and other countries, including countries that do not have laws protecting such information. Additionally, the investigator's name and business contact information may be included when reporting certain serious adverse events to regulatory authorities or to other investigators. By signing this protocol, the investigator expressly consents to these uses and disclosures.

If this is a multicenter trial, in order to facilitate contact between investigators, the Sponsor may share an investigator's name and contact information with other participating investigators upon request.

10.1.4 Confidentiality of IRB/IEC Information

The Sponsor is required to record the name and address of each IRB/IEC member that reviews and approves this trial. 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.

10.2 Compliance with Financial Disclosure Requirements

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 his/her 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, commonly known as a financial disclosure form, provided by the Sponsor or through a secure password-protected electronic portal 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.

10.3 Compliance with Law, Audit and Debarment

By signing this protocol, the investigator agrees to conduct the trial in an efficient and diligent manner and in conformance with this protocol; generally accepted standards of Good Clinical Practice (e.g., International Conference on Harmonization of Technical Requirements for Registration of Pharmaceuticals for Human Use Good Clinical Practice: Consolidated Guideline and other generally accepted standards of Good Clinical Practice); and all applicable federal, state and local laws, rules and regulations relating to the conduct of the clinical trial.

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 Appendix 12.1 - Code of Conduct for Clinical Trials.

The investigator also agrees to allow monitoring, audits, IRB/ERC review and regulatory authority inspection of trial-related documents and procedures and provide for direct access to all trial-related source data and documents.

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

The investigator shall prepare and maintain complete and accurate trial documentation in compliance with Good Clinical Practice standards and applicable federal, state and local laws, rules and regulations; and, for each subject participating in the trial, provide all data, and, upon completion or termination of the clinical trial, submit any other reports to the Sponsor as required by this protocol or as otherwise required pursuant to any agreement with the Sponsor.

Trial documentation will be promptly and fully disclosed to the Sponsor by the investigator upon request and also shall be made available at the trial 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 as a result of an audit to cure deficiencies in the trial documentation and worksheets/case report forms.

The investigator must maintain copies of all documentation and records relating to the conduct of the trial in compliance with all applicable legal and regulatory requirements. This documentation includes, but is not limited to, the protocol, worksheets/case report forms, advertising for subject participation, adverse event reports, subject source data, correspondence with regulatory authorities and IRBs/ERCs, consent forms, investigator's curricula vitae, monitor visit logs, laboratory reference ranges, laboratory certification or quality control procedures and laboratory director curriculum vitae. By signing this protocol, the investigator agrees that documentation shall be retained until at least 2 years after the last approval of a marketing application in an ICH region or until there are no pending or contemplated marketing applications in an ICH region or until at least 2 years have elapsed since the formal discontinuation of clinical development of the investigational product. Because the clinical development and marketing application process is variable, it is anticipated that the retention period can be up to 15 years or longer after protocol database lock. The Sponsor will determine the minimum retention period and notify the investigator when documents may be destroyed. The Sponsor will determine the minimum retention period and upon request, will provide guidance to the investigator when documents no longer need to be retained. The Sponsor also recognizes that documents may need to be retained for a longer period if required by local regulatory requirements (eg, Regulation [EU] 536/2014; 25 years after the end of the clinical study). All trial documents shall be made available if required by relevant regulatory authorities. The investigator must consult with and obtain written approval by the Sponsor prior to destroying trial and/or subject files.

ICH Good Clinical Practice guidelines recommend that the investigator inform the subject's primary physician about the subject's participation in the trial if the subject has a primary physician and if the subject agrees to the primary physician being informed.

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

Persons debarred from conducting or working on clinical trials by any court or regulatory authority will not be allowed to conduct or work on this Sponsor's trials. The investigator will immediately disclose in writing to the Sponsor if any person who is involved in

conducting the trial is debarred or if any proceeding for debarment is pending or, to the best of the investigator's knowledge, threatened.

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

According to European legislation, a Sponsor must designate an overall coordinating investigator for a multicenter trial (including multinational). When more than one trial site is open in an EU country, MSD, as the Sponsor, will designate, per country, a national principal coordinator (Protocol CI), responsible for coordinating the work of the principal investigators at the different trial sites in that Member State, according to national regulations. For a single-center trial, the Protocol CI is the principal investigator. In addition, the Sponsor must designate a principal or coordinating investigator to review the trial report that summarizes the trial results and confirm that, to the best of his/her knowledge, the report accurately describes the conduct and results of the trial (Clinical Study Report [CSR] CI). The Sponsor may consider one or more factors in the selection of the individual to serve as the Protocol CI and or CSR CI (e.g., availability of the CI during the anticipated review process, thorough understanding of clinical trial methods, appropriate enrollment of subject cohort, timely achievement of trial milestones). The Protocol CI must be a participating trial investigator.

10.4 Compliance with Trial Registration and Results Posting Requirements

Under the terms of the Food and Drug Administration Modernization Act (FDAMA) and the Food and Drug Administration Amendments Act (FDAAA), the Sponsor of the trial is solely responsible for determining whether the trial and its results are subject to the requirements for submission to the Clinical Trials Data Bank, http://www.clinicaltrials.gov. MSD, as Sponsor of this trial, will review this protocol and submit the information necessary to fulfill these requirements. MSD entries are not limited to FDAMA/FDAAA mandated trials. Information posted will allow subjects to identify potentially appropriate trials for their disease conditions and pursue participation by calling a central contact number for further information on appropriate trial locations and trial site contact information.

By signing this protocol, the investigator acknowledges that the statutory obligations under FDAMA/FDAAA are that of the Sponsor and agrees not to submit any information about this trial or its results to the Clinical Trials Data Bank.

10.5 Quality Management System

By signing this protocol, the Sponsor agrees to be responsible for implementing and maintaining a quality management system with written development procedures and functional area standard operating procedures (SOPs) to ensure that trials are conducted and data are generated, documented, and reported in compliance with the protocol, accepted standards of Good Clinical Practice, and all applicable federal, state, and local laws, rules and regulations relating to the conduct of the clinical trial.

10.6 Data Management

The investigator or qualified designee is responsible for recording and verifying the accuracy of subject data. By signing this protocol, the investigator acknowledges that his/her electronic signature is the legally binding equivalent of a written signature. By entering his/her electronic signature, the investigator confirms that all recorded data have been verified as accurate.

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

10.7 Publications

This trial is intended for publication, even if terminated prematurely. Publication may include any or all of the following: posting of a synopsis online, abstract and/or presentation at a scientific conference, or publication of a full manuscript. The Sponsor will work with the authors to submit a manuscript describing trial results within 12 months after the last data become available, which may take up to several months after the last subject visit in some cases such as vaccine trials. However, manuscript submission timelines may be extended on OTC trials. For trials intended for pediatric-related regulatory filings, the investigator agrees to delay publication of the trial results until the Sponsor notifies the investigator that all relevant regulatory authority decisions on the trial drug have been made with regard to pediatric-related regulatory filings. MSD will post a synopsis of trial results for approved products on www.clinicaltrials.gov by 12 months after the last subject's last visit for the primary outcome, 12 months after the decision to discontinue development, or product marketing (dispensed, administered, delivered or promoted), whichever is later.

These timelines may be extended for products that are not yet marketed, if additional time is needed for analysis, to protect intellectual property, or to comply with confidentiality agreements with other parties. Authors of the primary results manuscript will be provided the complete results from the Clinical Study Report, subject to the confidentiality agreement. When a manuscript is submitted to a biomedical journal, the Sponsor's policy is to also include the protocol and statistical analysis plan to facilitate the peer and editorial review of the manuscript. If the manuscript is subsequently accepted for publication, the Sponsor will allow the journal, if it so desires, to post on its website the key sections of the protocol that are relevant to evaluating the trial, specifically those sections describing the trial objectives and hypotheses, the subject inclusion and exclusion criteria, the trial design and procedures, the efficacy and safety measures, the statistical analysis plan, and any amendments relating to those sections. The Sponsor reserves the right to redact proprietary information.

For multicenter trials, subsequent to the multicenter publication (or after public disclosure of the results online at www.clinicaltrials.gov if a multicenter manuscript is not planned), an investigator and his/her colleagues may publish their data independently. In most cases, publication of individual trial site data does not add value to complete multicenter results, due to statistical concerns. In rare cases, publication of single trial site data prior to the main paper may be of value. Limitations of single trial site observations in a multicenter trial should always be described in such a manuscript.

Authorship credit should be based on 1) substantial contributions to conception and design, or acquisition of data, or analysis and interpretation of data; 2) drafting the article or revising it critically for important intellectual content; and 3) final approval of the version to be published. Authors must meet conditions 1, 2 and 3. Significant contributions to trial execution may also be taken into account to determine authorship, provided that contributions have also been made to all 3 of the preceding authorship criteria. Although publication planning may begin before conducting the trial, final decisions on authorship and the order of authors' names will be made based on participation and actual contributions to the trial and writing, as discussed above. The first author is responsible for defending the integrity of the data, method(s) of data analysis and the scientific content of the manuscript.

The Sponsor must have the opportunity to review all proposed abstracts, manuscripts or presentations regarding this trial 45 days prior to submission for publication/presentation. Any information identified by the Sponsor as confidential must be deleted prior to submission; this confidentiality does not include efficacy and safety results. Sponsor review can be expedited to meet publication timelines.

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12.0 APPENDICES

Changes that apply as of Amendment 12 are listed in Section 1.0 and supersede any protocol content/instructions from previous amendments. Existing protocol content in this section is retained for historical reference.

12.1 Code of Conduct for Clinical Trials

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

Code of Conduct for Interventional Clinical Trials

I. Introduction

A. Purpose

MSD, through its subsidiaries, conducts clinical trials worldwide to evaluate the safety and effectiveness of our products. As such, we are committed to designing, implementing, conducting, analyzing, and reporting these trials in compliance with the highest ethical and scientific standards. Protection of subjects 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 local and/or national regulations (including Regulation [EU] 536/2014 and all applicable data protection laws and regulations), and International Council for Harmonisation Good Clinical Practice (ICH-GCP), and also 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 (ie, subject population, duration, statistical power) must be adequate to address the specific purpose of the trial and shall respect the data protection rights of all subjects, trial site staff and, where applicable, third parties. All trial protocols are and will be assessed for the need and capability to enroll underrepresented groups. subjects 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 subjects, 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.

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. Subject 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. Changes to the protocol that are required urgently to eliminate an immediate hazard and to protect subject safety may be enacted in anticipation of ethics committee approval. MSD will inform regulatory authorities of such new measures to protect subject safety, in compliance with local and/or national regulations.

B.Safety

The guiding principle in decision-making in clinical trials is that subject welfare is of primary importance. Potential subjects 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. subjects enter the trial only after informed consent is obtained. subjects 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.

C.Confidentiality

MSD is committed to safeguarding subject 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 subject by name.

D.Genomic Research

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

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 subjects 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 subject referrals. However, MSD may compensate referring physicians for time spent on chart review and medical evaluation to identify potentially eligible subjects.

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.

12.2 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 collected in this trial as outlined in Section 7.1.3.3 – Future Biomedical Research will be used to study various causes for how subjects may respond to a drug/vaccine. Future biomedical research specimen(s) will be stored to provide a resource for future trials conducted by MSD focused on the study of biomarkers responsible for how a drug/vaccine enters and is removed by the body, how a drug/vaccine works, other pathways a drug/vaccine may interact with, or other aspects 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 MSD or designees and research will be monitored and reviewed by a committee of our scientists and clinicians.

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

a. Subjects for Enrollment

All subjects enrolled in the clinical trial 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 subjects or legal guardians, at a trial visit by the investigator or his or her designate. Informed consent for Future

Biomedical Research should be presented to the subjects on Visit 1. If delayed, present consent at next possible Subject Visit. Informed consent must be obtained prior to collection of all Future Biomedical Research specimens. Documentation of informed consent provided by the subject will be kept at the clinical trial site under secure storage for regulatory reasons. Information contained on the consent form alone cannot be traced to any specimens, test results, or medical information once the specimens have been rendered deidentified.

A template of each trial site's approved informed consent will be stored in the Sponsor's clinical document repository. Each consent will be assessed for appropriate specimen permissions.

Each informed consent approved by an ethics committee is assigned a unique tracking number. The tracking number on this document will be used to assign specimen permissions for each specimen into the Entrusted Keyholder's Specimen Database.

c. eCRF Documentation for Future Biomedical Research Specimens

Documentation of both consent and acquisition of Future Biomedical Research specimens will be captured in the electronic Case Report Forms (eCRFs). Reconciliation of both forms will be performed to assure that only appropriately consented specimens are used for Future Biomedical Research purposes. Any specimens for which such an informed consent cannot be verified will be destroyed.

d. Future Biomedical Research Specimen Collections

Blood specimens for DNA or RNA isolation will usually be obtained at a time when the subject is having blood drawn for other trial purposes. Specimens like tissue and bone marrow will usually be obtained at a time when the subject is having such a procedure for clinical purposes.

Specimens will be collected and sent to the laboratory designated for the trial where they will be processed (e.g., DNA or RNA extraction, etc) following the MSD approved policies and procedures for specimen handling and preparation.

If specimens are collected for a specific genotype or expression analysis as an objective to the main trial, this analysis is detailed in the main body of this protocol (**Section 8.0 – Statistical Analysis Plan**). These specimens will be processed, analyzed, and the remainder of the specimen will be destroyed. The results of these analyses will be reported along with the other trial results. A separate specimen will be obtained from properly-consented subjects in this protocol for storage in the biorepository for Future Biomedical Research.

4. Confidential Subject 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 subject' clinical information with future test results. In fact little or no research can be conducted without connecting the clinical trial data to the specimen. The clinical data allow specific analyses to be conducted. Knowing subject characteristics like gender, age, medical history and treatment outcomes are critical to understanding clinical context of analytical results.

To maintain privacy of information collected from specimens obtained for Future Biomedical Research, MSD has developed secure policies and procedures. All specimens will be deidentified as described below.

At the clinical trial site, unique codes will be placed on the Future Biomedical Research specimens for transfer to the storage facility. This first code is a random number which does not contain any personally identifying information embedded within it. The link (or key) between subject identifiers and this first unique code will be held at the trial site. No personal identifiers will appear on the specimen tube.

This first code will be replaced with a second code at a MSD designated storage/lab facility. The second code is linked to the first code via a second key. The specimen is now double coded. Specimens with the second code are sometimes referred to as deidentified specimens. The use of the second code provides additional confidentiality and privacy protection for subjects over the use of a single code. Access to both keys would be needed to link any data or specimens back to the subject's identification.

The second code is stored separately from the first code and all associated personal specimen identifiers. A secure link, the second key, will be utilized to match the second code to the first code to allow clinical information collected during the course of the trial to be associated with the specimen. This second key will be transferred under secure procedures by the MSD designated facility to an Entrusted Keyholder at MSD. The second code will be logged into the primary biorepository database at MSD and, in this database, this identifier will not have identifying demographic data or identifying clinical information (ie, race, sex, age, diagnosis, lab values) associated with it. The specimen will be stored in a designated biorepository site with secure policies and procedures for specimen storage and usage.

The second key can be utilized to reconstruct the link between the results of future biomedical research and the clinical information, at the time of analysis. This linkage would not be possible for the scientist conducting the analysis, but can only be done by the MSD Entrusted Keyholder under strict security policies and procedures. The MSD Entrusted Keyholder will link the information and then issue a deidentified data set for analysis. The only other circumstance by which future biomedical research data would be directly linked to the full clinical data set would be those situations mandated by regulatory authorities (e.g., EMEA, FDA), whereby this information would be directly transferred to the regulatory authority.

5. Biorepository Specimen Usage[3, 4]

Specimens obtained for the MSD Biorepository will be used for analyses using good scientific practices. However, exploratory analyses will not be conducted under the highly validated conditions usually associated with regulatory approval of diagnostics. The scope of research performed on these specimens is limited to the investigation of the variability in biomarkers that may correlate with a clinical phenotype in subjects.

Analyses utilizing the Future Biomedical Research specimens may be performed by MSD, or an additional third party (e.g., a university investigator) designated by MSD. The investigator conducting the analysis will be provided with double coded specimens. Re-association of analysis results with corresponding clinical data will only be conducted by the MSD Entrusted Keyholder. 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 the specific analysis is performed will be returned to the Sponsor or destroyed and documentation of destruction will be reported to MSD.

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

Subjects may withdraw their consent for Future Biomedical Research and have their specimens and all derivatives destroyed. Subjects may withdraw consent at any time by contacting the principal investigator for the main trial. If medical records for the main trial are still available, the investigator will contact MSD using the designated mailbox (clinical.specimen.management@MSD.com) and a form will be provided by MSD to obtain appropriate information to complete specimen withdrawal. Subsequently, the subject's specimens will be removed from the biorepository and be destroyed. A letter will be sent from MSD to the investigator confirming the destruction. It is the responsibility of the investigator to inform the subject of completion of destruction. Any analyses in progress at the time of request for destruction or already performed prior to the request being received by the Sponsor will continue to be used as part of the overall research trial data and results. No new analyses would be generated after the request is received.

In the event that the medical records for the main trial are no longer available (e.g., if the investigator is no longer required by regulatory authorities to retain the main trial records) or the specimens have been completely anonymized, there will no longer be a link between the subject's personal information and their specimens. In this situation, the request for specimen 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 acquisition. 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 trial site will be shipped to a central laboratory and then shipped to the MSD 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 MSD policies and procedures and this destruction will be documented in the biorepository database.

8. Data Security[3, 4]

Separate databases for specimen information and for results from Future Biomedical Research will be maintained by MSD. This is done to separate the future exploratory test results (which include genetic data) from the clinical trial database thereby maintaining a separation of subject number and these results. The separate databases are accessible only to the authorized Sponsor and the designated trial administrator research personnel and/or collaborators. Database user authentication is highly secure, and is accomplished using network security policies and practices based in international standards (e.g., ISO17799) to protect against unauthorized access. The MSD Entrusted Keyholder maintains control over access to all specimen data. These data are collected for future biomedical research purposes only as specified in this section and will not be used for any other purpose.

9. Reporting of Future Biomedical Research Data to Subjects[3, 4]

There is no definitive requirement in either authoritative ethical guidelines or in relevant laws/regulations globally that research results have to be, in all circumstances, returned to the trial subject. Some guidelines advocate a proactive return of data in certain instances. No information obtained from exploratory laboratory studies will be reported to the subject or family, and this information will not be entered into the clinical database maintained by MSD on subjects. Principle reasons not to inform or return results to the subject include: lack of relevance to subject health, limitations of predictive capability, concerns of misinterpretation and absence of Good Clinical Practice standards in exploratory research typically used for diagnostic testing.

If any exploratory results are definitively associated with clinical significance for subjects while the clinical trial is ongoing, investigators will be contacted with information as to how to offer clinical diagnostic testing (paid for by MSD) to subjects enrolled and will be advised that counseling should be made available for all who choose to participate in this diagnostic testing.

If any exploratory results are definitively associated with clinical significance after completion of a clinical trial, MSD will publish the results without revealing specific subject information, inform all trial sites who participated in the MSD clinical trial and post anonymized results on our website or other accredited website(s) that allow for public access (e.g., disease societies who have primary interest in the results) in order that physicians and patients may pursue clinical diagnostic testing if they wish to do so.

10. Gender, Ethnicity and Minorities[3, 4]

Although many diagnoses differ in terms of frequency by ethnic population and gender, every effort will be made to recruit all subjects diagnosed and treated on MSD clinical trials for future biomedical research. When trials with specimens are conducted and subjects identified to serve as controls, every effort will be made to group specimens from subjects and controls to represent the ethnic and gender population representative of the disease under current investigation.

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

For future biomedical research, risks to the subject have been minimized. Risks include those associated with venipuncture to obtain the whole blood specimen. This specimen will be obtained at the time of routine blood specimens drawn in the main trial.

MSD has developed strict security, policies and procedures to address subject 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.

It is necessary for subject-related data (ie, ethnicity, diagnosis, drug therapy and dosage, age, toxicities, etc.) to be re-associated to double coded specimens at the time of data analysis. These subject data will be kept in a separate, secure MSD database, and all specimens will be stripped of subject identifiers. No information concerning results obtained from future biomedical research will be entered into clinical records, nor will it be released to outside persons or agencies, in any way that could be tied to an individual subject.

12. Questions

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

13. References

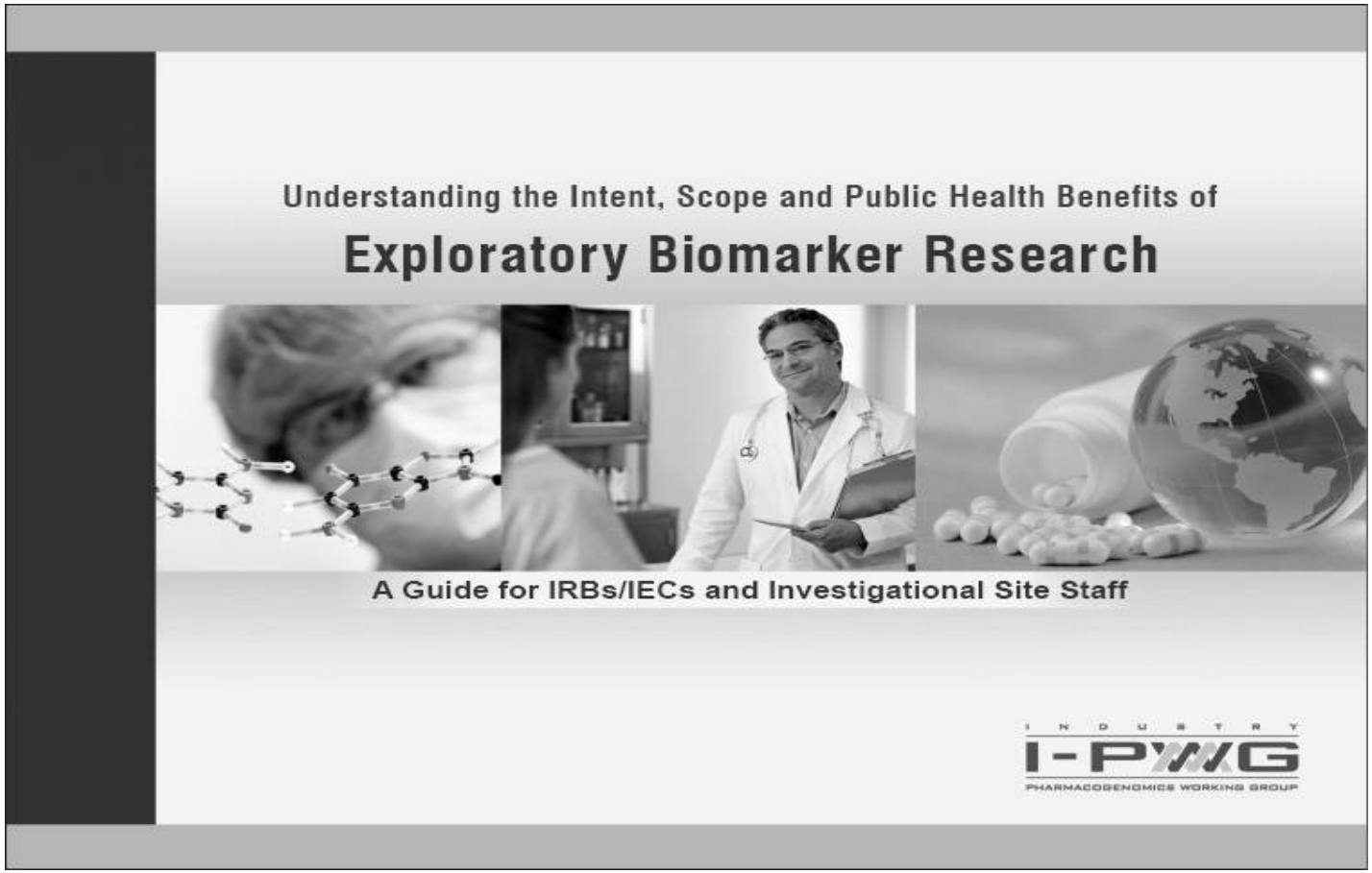
1. National Cancer Institute: http://www.cancer.gov/dictionary/?searchTxt=biomarker

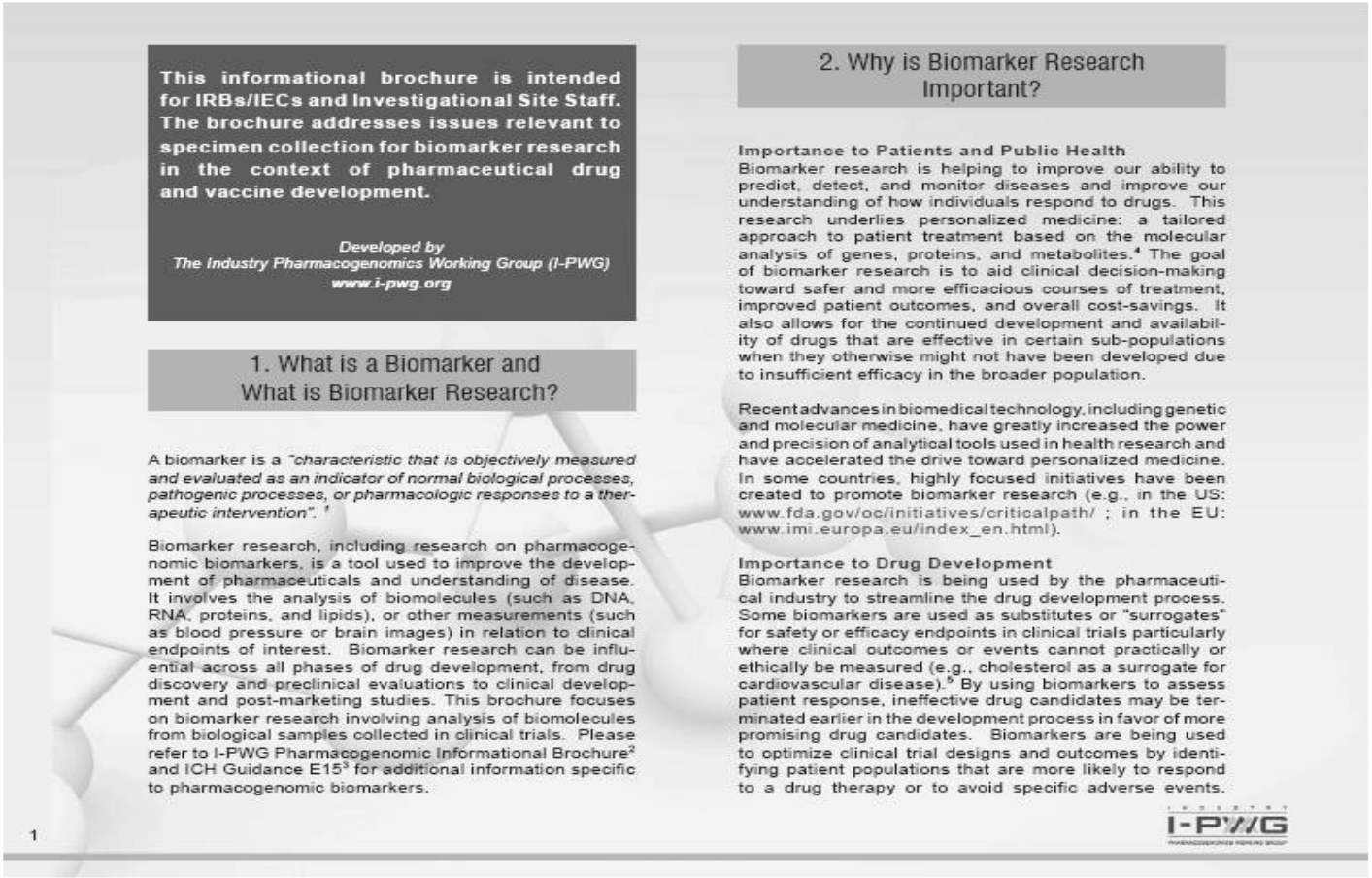
2. International Conference on Harmonization: DEFINITIONS FOR GENOMIC BIOMARKERS, PHARMACOGENOMICS, PHARMACOGENETICS, GENOMIC DATA AND SAMPLE CODING CATEGORIES - E15; http://www.ich.org/LOB/media/MEDIA3383.pdf

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/

12.3 Understanding the Intent, Scope and Public Health Benefits of Exploratory Biomarker Research: A Guide for IRBs/IECs and Investigational Site Staff





This informational brochure is intended for IRBs/IECs and Investigational Site Staff. The brochure addresses issues relevant to specimen collection for biomarker research in the context of pharmaceutical drug and vaccine development.

Developed by
The Industry Pharmacogenomics Working Group (I-PWG)
www.i-pwg.org

1. What is a Biomarker and What is Biomarker Research?

A biomarker is a *"characteristic that is objectively measured and evaluated as an indicator of normal biological processes, pathogenic processes, or pharmacologic responses to a therapeutic intervention".* [1]

Biomarker research, including research on pharmacogenomic biomarkers, is a tool used to improve the development of pharmaceuticals and understanding of disease. It involves the analysis of biomolecules (such as DNA, RNA, proteins, and lipids), or other measurements (such as blood pressure or brain images) in relation to clinical endpoints of interest. Biomarker research can be influential across all phases of drug development, from drug discovery and preclinical evaluations to clinical development and post-marketing studies. This brochure focuses on biomarker research involving analysis of biomolecules from biological samples collected in clinical trials. Please refer to I-PWG Pharmacogenomic Informational Brochure[2] and ICH Guidance E15[3] for additional information specific to pharmacogenomic biomarkers.

2. Why is Biomarker Research Important?

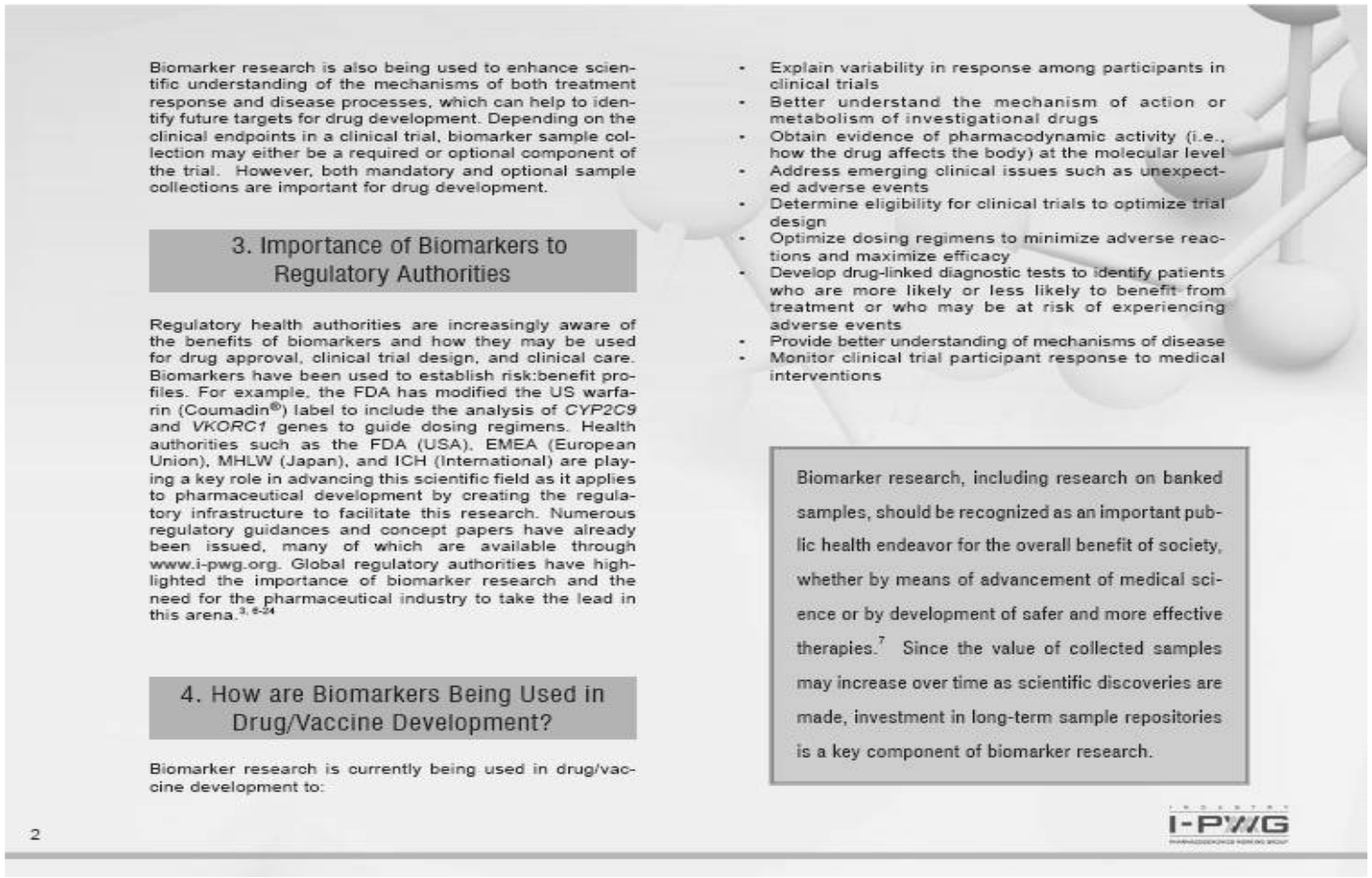
Importance to Patients and Public Health
Biomarker research is helping to improve our ability to predict, detect, and monitor diseases and improve our understanding of how individuals respond to drugs. This research underlies personalized medicine: a tailored approach to patient treatment based on the molecular analysis of genes, proteins, and metabolites.[4] The goal of biomarker research is to aid clinical decision-making toward safer and more efficacious courses of treatment, improved patient outcomes, and overall cost-savings. It also allows for the continued development and availability of drugs that are effective in certain sub-populations when they otherwise might not have been developed due to insufficient efficacy in the broader population.

Recent advances in biomedical technology, including genetic and molecular medicine, have greatly increased the power and precision of analytical tools used in health research and have accelerated the drive toward personalized medicine. In some countries, highly focused initiatives have been created to promote biomarker research (e.g., in the US: www.fda.gov/oc/initiatives/criticalpath/ ; in the EU: www.imi.europa.eu/index_en.html).

Importance to Drug Development
Biomarker research is being used by the pharmaceutical industry to streamline the drug development process. Some biomarkers are used as substitutes or "surrogates" for safety or efficacy endpoints in clinical trials particularly where clinical outcomes or events cannot practically or ethically be measured (e.g., cholesterol as a surrogate for cardiovascular disease).[5] By using biomarkers to assess patient response, ineffective drug candidates may be terminated earlier in the development process in favor of more promising drug candidates. Biomarkers are being used to optimize clinical trial designs and outcomes by identifying patient populations that are more likely to respond to a drug therapy or to avoid specific adverse events.

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Biomarker research is also being used to enhance scientific understanding of the mechanisms of both treatment response and disease processes, which can help to identify future targets for drug development. Depending on the clinical endpoints in a clinical trial, biomarker sample collection may either be a required or optional component of the trial. However, both mandatory and optional sample collections are important for drug development.

3. Importance of Biomarkers to Regulatory Authorities

Regulatory health authorities are increasingly aware of the benefits of biomarkers and how they may be used for drug approval, clinical trial design, and clinical care. Biomarkers have been used to establish risk:benefit profiles. For example, the FDA has modified the US warfarin (Coumadin®) label to include the analysis of *CYP2C9* and *VKORC1* genes to guide dosing regimens. Health authorities such as the FDA (USA), EMEA (European Union), MHLW (Japan), and ICH (International) are playing a key role in advancing this scientific field as it applies to pharmaceutical development by creating the regulatory infrastructure to facilitate this research. Numerous regulatory guidances and concept papers have already been issued, many of which are available through www.i-pwg.org. Global regulatory authorities have highlighted the importance of biomarker research and the need for the pharmaceutical industry to take the lead in this arena.[3, 6-24]

4. How are Biomarkers Being Used in Drug/Vaccine Development?

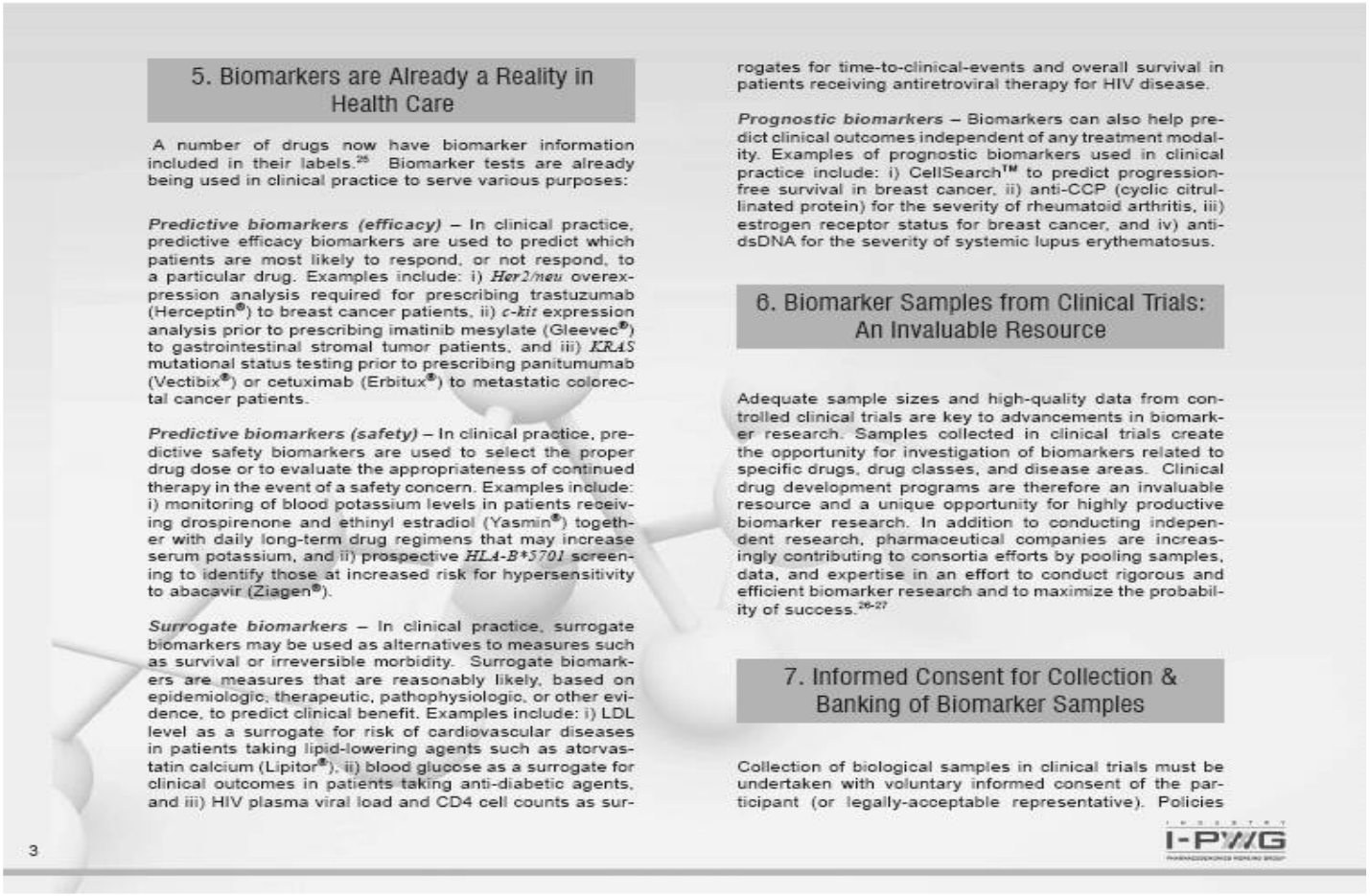
Biomarker research is currently being used in drug/vaccine development to:

- Explain variability in response among participants in clinical trials
- Better understand the mechanism of action or metabolism of investigational drugs
- Obtain evidence of pharmacodynamic activity (i.e., how the drug affects the body) at the molecular level
- Address emerging clinical issues such as unexpected adverse events
- Determine eligibility for clinical trials to optimize trial design
- Optimize dosing regimens to minimize adverse reactions and maximize efficacy
- Develop drug-linked diagnostic tests to identify patients who are more likely or less likely to benefit from treatment or who may be at risk of experiencing adverse events
- Provide better understanding of mechanisms of disease
- Monitor clinical trial participant response to medical interventions

Biomarker research, including research on banked samples, should be recognized as an important public health endeavor for the overall benefit of society, whether by means of advancement of medical science or by development of safer and more effective therapies.[7] Since the value of collected samples may increase over time as scientific discoveries are made, investment in long-term sample repositories is a key component of biomarker research.

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5. Biomarkers are Already a Reality in Health Care

A number of drugs now have biomarker information included in their labels.[25] Biomarker tests are already being used in clinical practice to serve various purposes:

Predictive biomarkers (efficacy) – In clinical practice, predictive efficacy biomarkers are used to predict which patients are most likely to respond, or not respond, to a particular drug. Examples include: i) *Her2/neu* overexpression analysis required for prescribing trastuzumab (Herceptin®) to breast cancer patients, ii) *c-kit* expression analysis prior to prescribing imatinib mesylate (Gleevec®) to gastrointestinal stromal tumor patients, and iii) *KRAS* mutational status testing prior to prescribing panitumumab (Vectibix®) or cetuximab (Erbitux®) to metastatic colorectal cancer patients.

Predictive biomarkers (safety) – In clinical practice, predictive safety biomarkers are used to select the proper drug dose or to evaluate the appropriateness of continued therapy in the event of a safety concern. Examples include: i) monitoring of blood potassium levels in patients receiving drospirenone and ethinyl estradiol (Yasmin®) together with daily long-term drug regimens that may increase serum potassium, and ii) prospective *HLA-B*5701* screening to identify those at increased risk for hypersensitivity to abacavir (Ziagen®).

Surrogate biomarkers – In clinical practice, surrogate biomarkers may be used as alternatives to measures such as survival or irreversible morbidity. Surrogate biomarkers are measures that are reasonably likely, based on epidemiologic, therapeutic, pathophysiologic, or other evidence, to predict clinical benefit. Examples include: i) LDL level as a surrogate for risk of cardiovascular diseases in patients taking lipid-lowering agents such as atorvastatin calcium (Lipitor®), ii) blood glucose as a surrogate for clinical outcomes in patients taking anti-diabetic agents, and iii) HIV plasma viral load and CD4 cell counts as surrogates for time-to-clinical-events and overall survival in patients receiving antiretroviral therapy for HIV disease.

Prognostic biomarkers – Biomarkers can also help predict clinical outcomes independent of any treatment modality. Examples of prognostic biomarkers used in clinical practice include: i) CellSearch™ to predict progression-free survival in breast cancer, ii) anti-CCP (cyclic citrullinated protein) for the severity of rheumatoid arthritis, iii) estrogen receptor status for breast cancer, and iv) anti-dsDNA for the severity of systemic lupus erythematosus.

6. Biomarker Samples from Clinical Trials: An Invaluable Resource

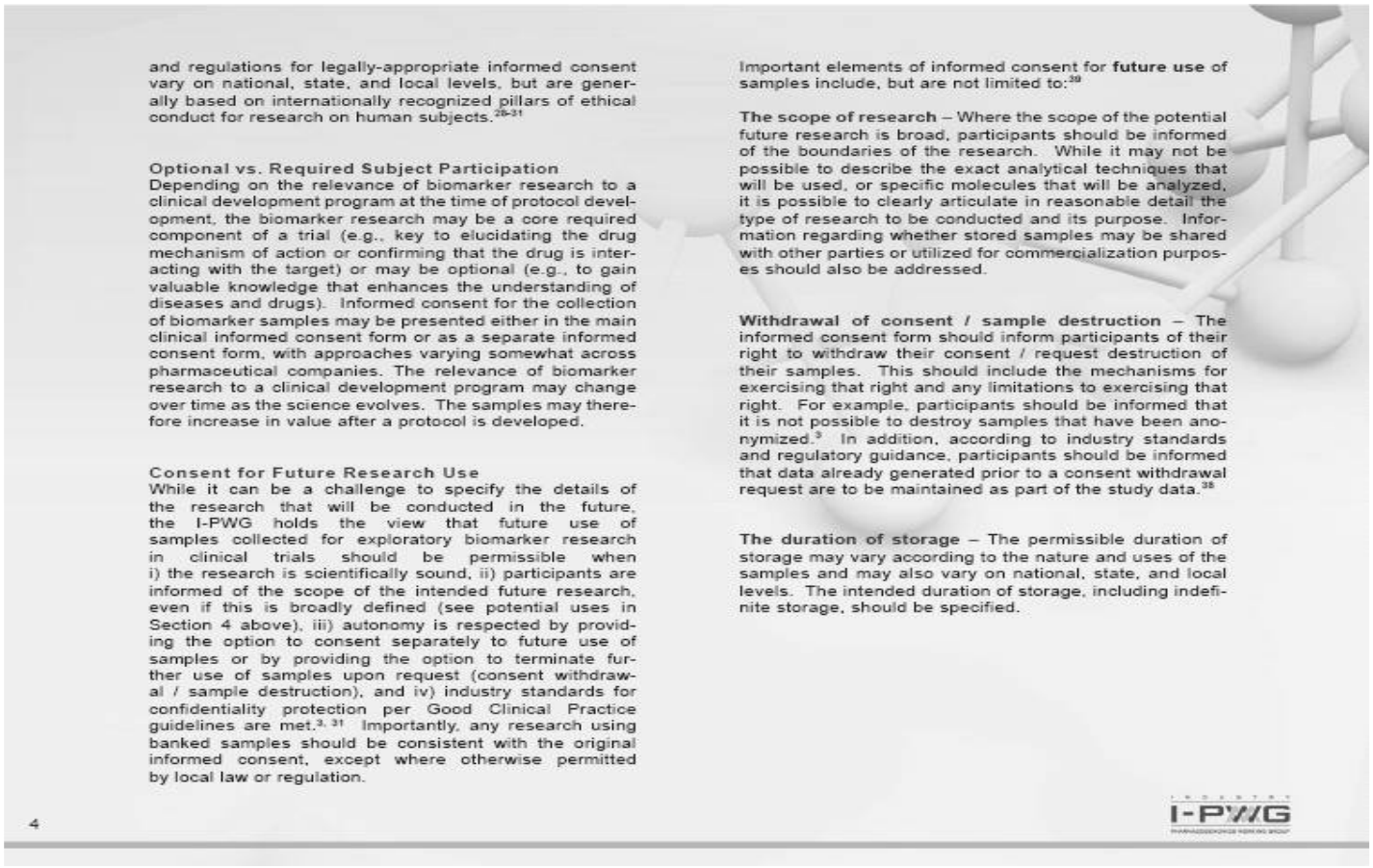
Adequate sample sizes and high-quality data from controlled clinical trials are key to advancements in biomarker research. Samples collected in clinical trials create the opportunity for investigation of biomarkers related to specific drugs, drug classes, and disease areas. Clinical drug development programs are therefore an invaluable resource and a unique opportunity for highly productive biomarker research. In addition to conducting independent research, pharmaceutical companies are increasingly contributing to consortia efforts by pooling samples, data, and expertise in an effort to conduct rigorous and efficient biomarker research and to maximize the probability of success.[26-27]

7. Informed Consent for Collection & Banking of Biomarker Samples

Collection of biological samples in clinical trials must be undertaken with voluntary informed consent of the participant (or legally-acceptable representative). Policies

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and regulations for legally-appropriate informed consent vary on national, state, and local levels, but are generally based on internationally recognized pillars of ethical conduct for research on human subjects.[28-31]

Optional vs. Required Subject Participation
Depending on the relevance of biomarker research to a clinical development program at the time of protocol development, the biomarker research may be a core required component of a trial (e.g., key to elucidating the drug mechanism of action or confirming that the drug is interacting with the target) or may be optional (e.g., to gain valuable knowledge that enhances the understanding of diseases and drugs). Informed consent for the collection of biomarker samples may be presented either in the main clinical informed consent form or as a separate informed consent form, with approaches varying somewhat across pharmaceutical companies. The relevance of biomarker research to a clinical development program may change over time as the science evolves. The samples may therefore increase in value after a protocol is developed.

Consent for Future Research Use
While it can be a challenge to specify the details of the research that will be conducted in the future, the I-PWG holds the view that future use of samples collected for exploratory biomarker research in clinical trials should be permissible when i) the research is scientifically sound, ii) participants are informed of the scope of the intended future research, even if this is broadly defined (see potential uses in Section 4 above), iii) autonomy is respected by providing the option to consent separately to future use of samples or by providing the option to terminate further use of samples upon request (consent withdrawal / sample destruction), and iv) industry standards for confidentiality protection per Good Clinical Practice guidelines are met.[3, 31] Importantly, any research using banked samples should be consistent with the original informed consent, except where otherwise permitted by local law or regulation.

Important elements of informed consent for **future use** of samples include, but are not limited to:[39]

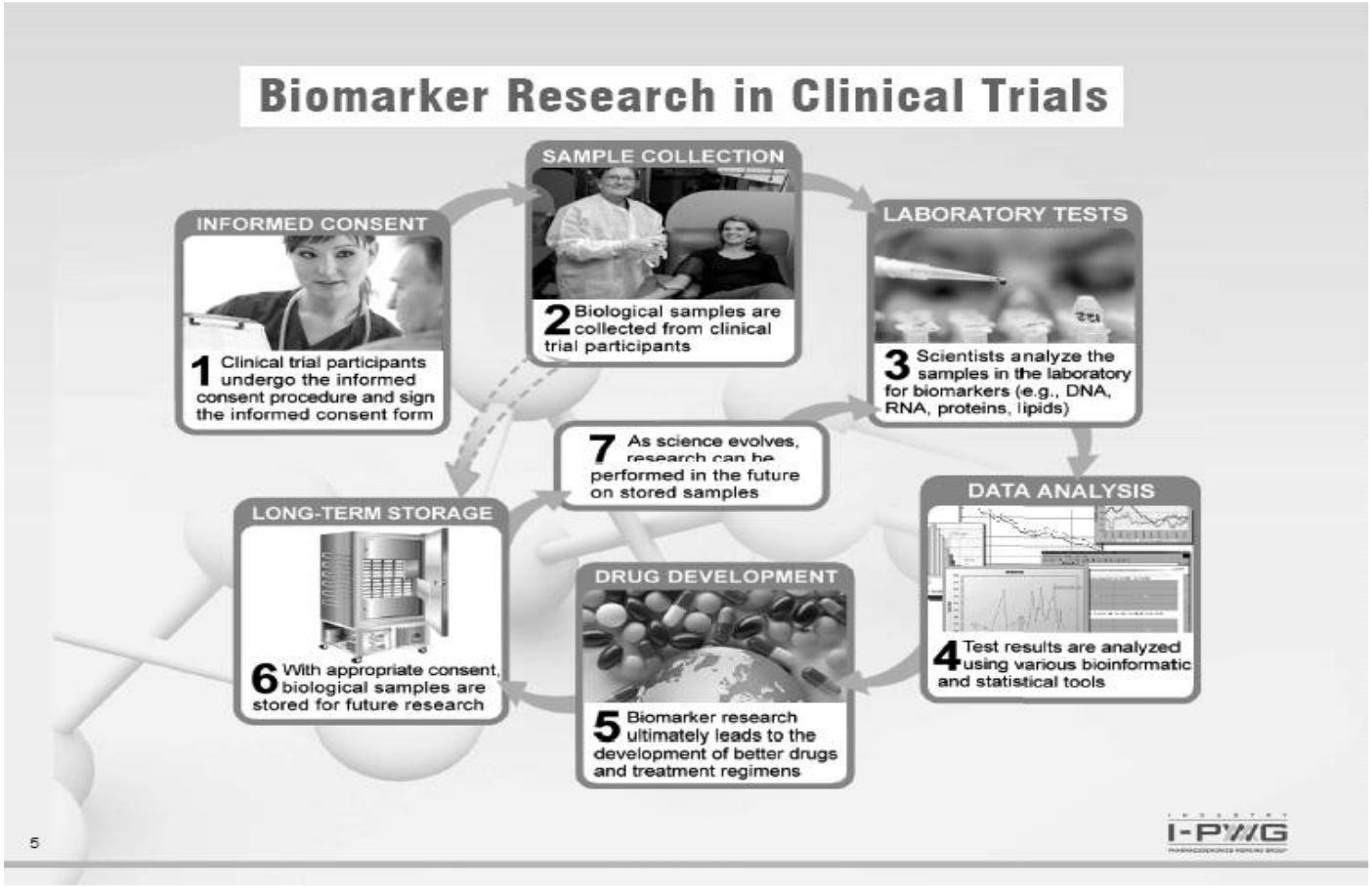
The scope of research – Where the scope of the potential future research is broad, participants should be informed of the boundaries of the research. While it may not be possible to describe the exact analytical techniques that will be used, or specific molecules that will be analyzed, it is possible to clearly articulate in reasonable detail the type of research to be conducted and its purpose. Information regarding whether stored samples may be shared with other parties or utilized for commercialization purposes should also be addressed.

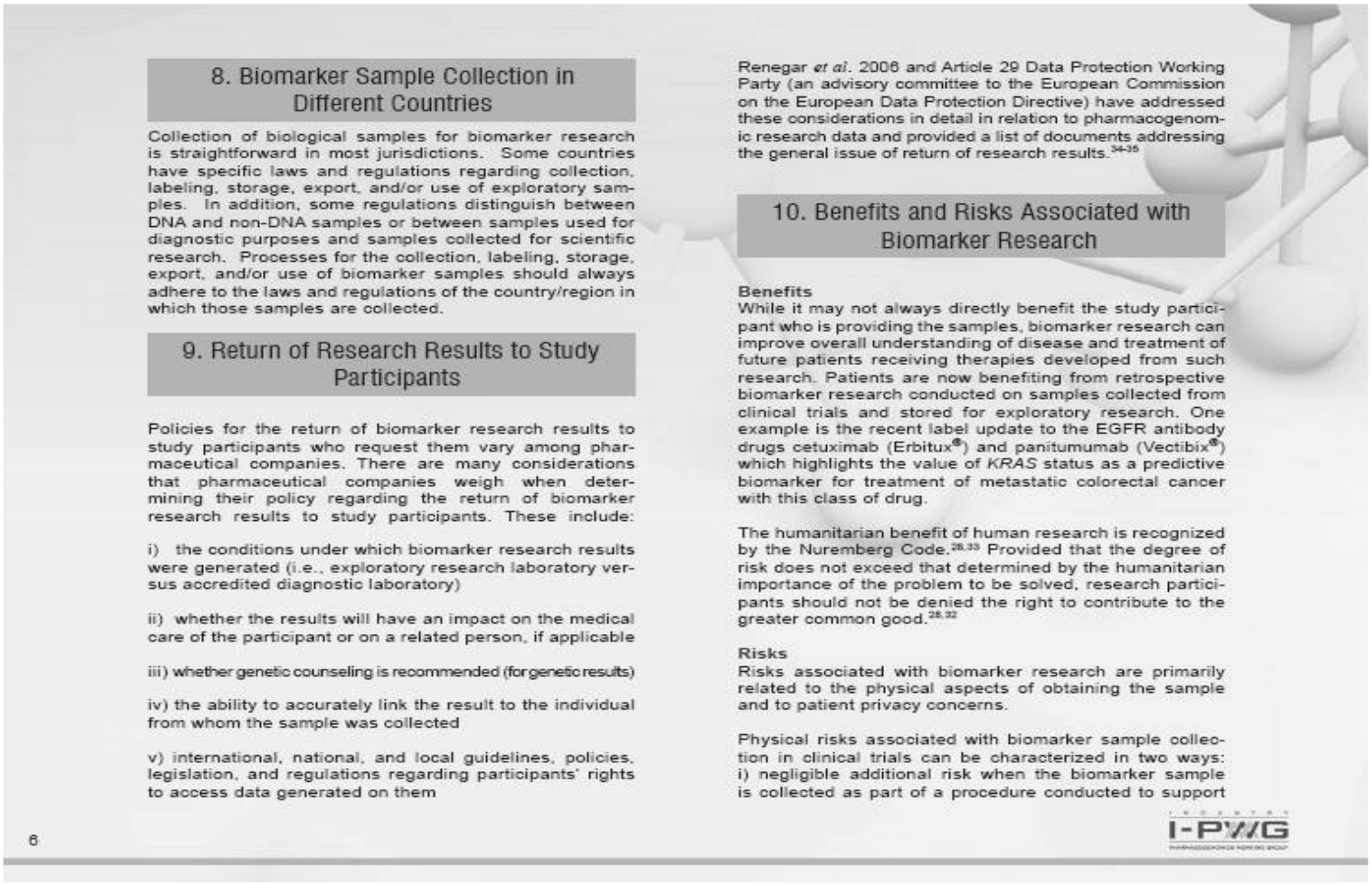
Withdrawal of consent / sample destruction – The informed consent form should inform participants of their right to withdraw their consent / request destruction of their samples. This should include the mechanisms for exercising that right and any limitations to exercising that right. For example, participants should be informed that it is not possible to destroy samples that have been anonymized.[3] In addition, according to industry standards and regulatory guidance, participants should be informed that data already generated prior to a consent withdrawal request are to be maintained as part of the study data.[38]

The duration of storage – The permissible duration of storage may vary according to the nature and uses of the samples and may also vary on national, state, and local levels. The intended duration of storage, including indefinite storage, should be specified.

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Biomarker Research in Clinical Trials
SAMPLE COLLECTION
2 Biological samples are collected from clinical trial participants
LABORATORY TESTS
3 Scientists analyze the samples in the laboratory for biomarkers (e.g., DNA, RNA, proteins, lipids)
INFORMED CONSENT
1 Clinical trial participants undergo the informed consent procedure and sign the informed consent form
7 As science evolves, research can be performed in the future on stored samples
DATA ANALYSIS
4 Test results are analyzed using various bioinformatic and statistical tools
LONG-TERM STORAGE
6 With appropriate consent, biological samples are stored for future research
DRUG DEVELOPMENT
5 Biomarker research ultimately leads to the development of better drugs and treatment regimens
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8. Biomarker Sample Collection in Different Countries

Collection of biological samples for biomarker research is straightforward in most jurisdictions. Some countries have specific laws and regulations regarding collection, labeling, storage, export, and/or use of exploratory samples. In addition, some regulations distinguish between DNA and non-DNA samples or between samples used for diagnostic purposes and samples collected for scientific research. Processes for the collection, labeling, storage, export, and/or use of biomarker samples should always adhere to the laws and regulations of the country/region in which those samples are collected.

9. Return of Research Results to Study Participants

Policies for the return of biomarker research results to study participants who request them vary among pharmaceutical companies. There are many considerations that pharmaceutical companies weigh when determining their policy regarding the return of biomarker research results to study participants. These include:

i) the conditions under which biomarker research results were generated (i.e., exploratory research laboratory versus accredited diagnostic laboratory)

ii) whether the results will have an impact on the medical care of the participant or on a related person, if applicable

iii) whether genetic counseling is recommended (for genetic results)

iv) the ability to accurately link the result to the individual from whom the sample was collected

v) international, national, and local guidelines, policies, legislation, and regulations regarding participants' rights to access data generated on them

Renegar *et al*. 2006 and Article 29 Data Protection Working Party (an advisory committee to the European Commission on the European Data Protection Directive) have addressed these considerations in detail in relation to pharmacogenomic research data and provided a list of documents addressing the general issue of return of research results.[34-35]

10. Benefits and Risks Associated with Biomarker Research

Benefits
While it may not always directly benefit the study participant who is providing the samples, biomarker research can improve overall understanding of disease and treatment of future patients receiving therapies developed from such research. Patients are now benefiting from retrospective biomarker research conducted on samples collected from clinical trials and stored for exploratory research. One example is the recent label update to the EGFR antibody drugs cetuximab (Erbitux®) and panitumumab (Vectibix®) which highlights the value of *KRAS* status as a predictive biomarker for treatment of metastatic colorectal cancer with this class of drug.

The humanitarian benefit of human research is recognized by the Nuremberg Code.[28,33] Provided that the degree of risk does not exceed that determined by the humanitarian importance of the problem to be solved, research participants should not be denied the right to contribute to the greater common good.[28,32]

Risks
Risks associated with biomarker research are primarily related to the physical aspects of obtaining the sample and to patient privacy concerns.

Physical risks associated with biomarker sample collection in clinical trials can be characterized in two ways: i) negligible additional risk when the biomarker sample is collected as part of a procedure conducted to support

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other core trial objectives, and ii) some added risk where the sampling procedure would otherwise have not been performed as a core component of a trial. Risks are also determined by the invasiveness of the sample collection procedure.

Privacy risks are generally those associated with the inappropriate disclosure and misuse of data. Pharmaceutical companies have policies and procedures for confidentiality protection to minimize this risk for all data collected and generated in clinical trials. These may vary across companies, but are based on industry standards of confidentiality and privacy protection highlighted in the following section. Importantly, privacy risks inherent to biomarker data are no greater than other data collected in a clinical trial.

11. Privacy, Confidentiality, and Patient Rights

Maintaining the privacy of study participants and the confidentiality of information relating to them is of paramount concern to industry researchers, regulators, and patients. Good Clinical Practice (GCP), the standard adhered to in pharmaceutical clinical research, is a standard that

"...provides assurance that the data and reported results are credible and accurate, and that the rights, integrity, and confidentiality of trial subjects are protected",

where confidentiality is defined as, *"The prevention of disclosure, to other than authorized individuals, of a sponsor's proprietary information or of a subject's identity."*

This standard dictates that *"the confidentiality of records that could identify subjects should be protected, respecting the privacy and confidentiality rules in accordance with applicable regulatory requirements."* [31]

Exploratory biomarker research in pharmaceutical development is commonly conducted in research laboratories that are not accredited to perform diagnostic tests used for healthcare decision-making. Therefore, results from exploratory biomarker research usually are not appropriate for use in making decisions about a trial participant's health. In addition, exploratory research data should not be included as part of a participant's medical record accessible for use by insurance companies. Legislation and policies to protect individuals against discrimination based on genetic information continually evolve based on social, ethical, and legal considerations. Examples of such legislation include the Human Tissue Act 2004 (UK) and the Genetic Information Nondiscrimination Act (GINA) 2008 (USA).[36-37]

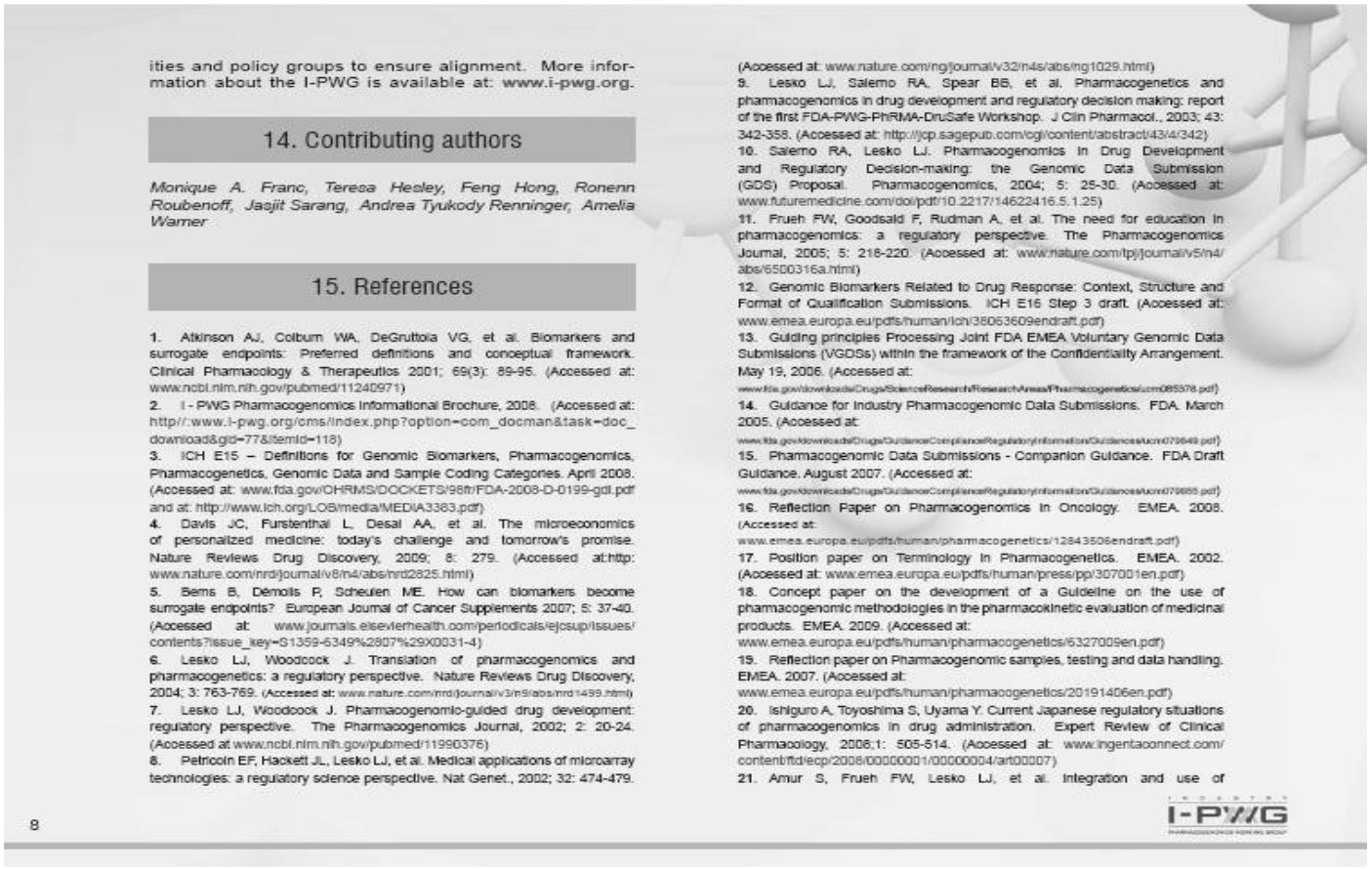
12.Where to Get More Information?

Educational resources related to biomarker and pharmacogenomic research that caters to health care professionals, IRBs/IECs, scientists, and patients are continually being created and are publicly available. Links to many of these resources are available through the I-PWG website: www.i-pwg.org.

13. What is I-PWG?

The Industry Pharmacogenomics Working Group (I-PWG) (formerly the Pharmacogenetics Working Group) is a voluntary association of pharmaceutical companies engaged in pharmacogenomic research. The Group's activities focus on non-competitive educational, informational, ethical, legal, and regulatory topics. The Group provides information and expert opinions on these topics and sponsors educational/informational programs to promote better understanding of pharmacogenomic and other biomarker research for key stakeholders. The I-PWG interacts with regulatory author-

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ities and policy groups to ensure alignment. More information about the I-PWG is available at: www.i-pwg.org.

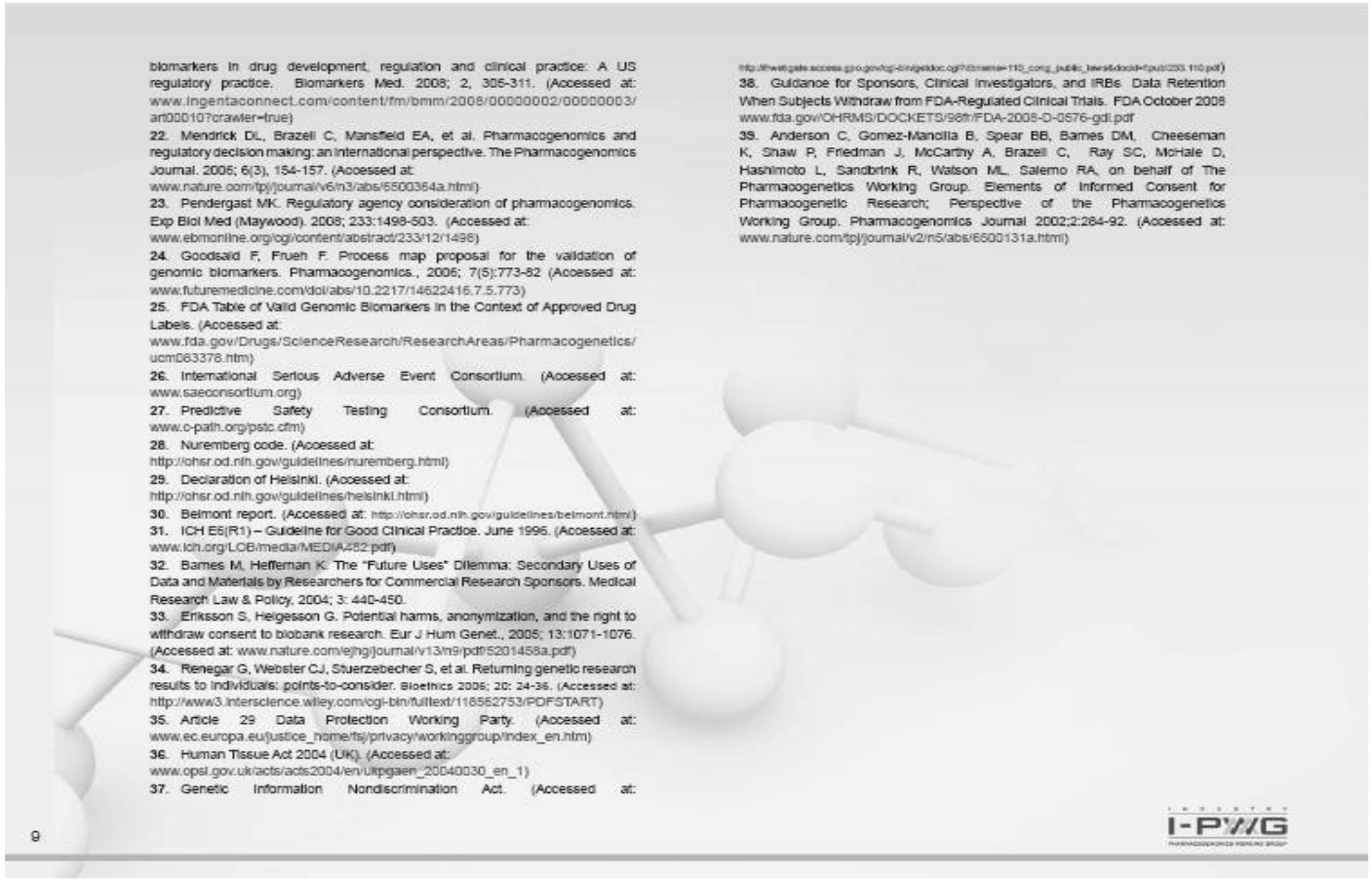
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Monique A. Franc, Teresa Hesley, Feng Hong, Ronenn Roubenoff, Jasjit Sarang, Andrea Tyukody Renninger, Amelia Warner

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12.4 Abbreviations

Abbreviation/Term	Definition
AE	Adverse Event
ADA	Anti-Drug Antibodies
ALT	Alanine Aminotransferase
APaT	All Patients as Treated Population
ART	Antiretroviral therapy
AST	Aspartate Aminotransferase
AUA	American Urological Association
BCG	Bacillus Calmette-Guérin
BICR	Blinded Independent Central Review
BNP	B type natriuretic peptide
hCG	Human Chorionic Gonadotropin
CBC	Complete Blood Count
CI	Confidence Interval
CIS	Carcinoma-in-situ
COVID-19	coronavirus disease caused by severe acute respiratory syndrome coronavirus 2
CR	Complete Response
CRC	Colorectal Cancer
CrCl	Creatinine Clearance
CRF	Case Report Form
CSR	Clinical Study Report
CTCAE	Common Toxicity Criteria for Adverse Events
CTFG	Clinical Trials Facilitation Group
CTLA-4	Cytotoxic T-Lymphocyte-Associated Antigen-4
CTU	Computed Tomography Urography
DILI	Drug Induced Liver Injury
DFS	Disease-free Survival
DLT	Dose-Limiting Toxicity
DNA	Deoxyribonucleic acid
DOCR	Duration of Complete Response
ECI	Event of Clinical Interest
ECG	Electrocardiogram
ECOG	Eastern Cooperative Oncology Group
EDC	Electronic Data Capture
EEA	European Economic Area
EORTC	European Organisation for Research and Treatment of Cancer
EOT	End of Trial
ePRO	Electronic Patient-reported Outcomes
ERC	Ethics Review Committee
FAS	Full Analyses Set
FBR	Future Biomedical Research
FDA	Food and Drug Administration
FDAAA	Food and Drug Administration Amendments Act
FDAMA	Food and Drug Administration Modernization Act
FFPE	Formalin-fixed Paraffin Embedded
FSH	Follicle-Stimulating Hormone
GCP	Good Clinical Practice
GFR	Glomerular Filtration Rate
GI	Gastrointestinal
HbA1C	hemoglobin A1c
HBsAg	Hepatitis B surface antigen

Abbreviation/Term	Definition
HBV	Hepatitis B virus
HCV	Hepatitis C virus
HIV	Human Immunodeficiency Virus
HRT	Hormone replacement therapy
IA	Interim Analysis
IB	Investigator's Brochure
IBCG	International Bladder Cancer Group
ICF	Informed Consent Form
ICH	International Conference for Harmonization
ICSR	Individual Case Safety Report
IEC	Independent Ethics Committee
IHC	Immunohistochemistry
IMP	Investigational Medicinal Product
INR	International Normalized Ratio
IO	Immuno-oncology
irAEs	Immune-related Adverse Events
IRB	Institutional Review Board
ITIM	Immunoreceptor Tyrosine-based Switch Motif
ITSM	Immunoreceptor Tyrosine-based Switch Motif
ITT	Intent-to-Treat
IV	Intravenous
IVRS/IWRS	Interactive Voice Response System/Interactive Web Response System
KM	Kaplan-Meier
LAG-3	Lymphocyte Activation Gene 3
LLOQ	Lower limit of quantification
LUTS	Lower Urinary Tract Symptoms
mAb	Monoclonal Antibody
mcL	Millimeters
MEL	Melanoma
mg	Milligram
mg/kg	Milligram per Kilogram
MHC	Major Histocompatability Complex
mL	milliliter
MRI	Magnetic Resonance Imaging
mRNA	messenger RNA
MRU	Magnetic Resonance Urography
MSD	Merck Sharp & Dohme
MSI	Microsatellite Instability
MTD	Maximum Tolerated Dose
NA or N/A	Not Applicable
NCI	National Cancer Institute
NP	Natriuretic peptide
NK	Natural Killer cells
NKT	Natural Killer T-cells
NMIBC	Non-Muscle Invasive Bladder Cancer
NSAE	Non-Serious Adverse Event
NSAID	Non-steroidal Anti-inflammatory Drug
NSCLC	Non–small Cell Lung Cancer
NT pro-BNP	N terminal pro-B type natriuretic peptide
OME	Other Medical Event
ORR	Overall Response Rate
OS	Overall Survival

Abbreviation/Term	Definition
OTC	Over the Counter
PCL	Protocol Clarification Letter
PD-1	Programmed Cell Death 1
PD-L1	Programmed Cell Death Ligand 1
PD-L2	Programmed Cell Death Ligand 2
PFS	Progression Free Survival
PGt	Pharmacogenetic
PIN	Personal Identification Number
PK	Pharmacokinetic
PK/PD	Pharmacokinetic/Pharmacodynamic
PO	Oral Administration
POC	Proof-of-Concept
PR	Partial Response
PSA	Prostate Specific Antigen
PTT	Prothrombin Time
RECIST	Response Evaluation Criteria in Solid Tumors
RNA	Ribonucleic Acid
QALY	Quality-adjusted Life Years
Q2W	Every 2 Weeks
Q3W	Every 3 Weeks
sLAG-3	Soluble Form of Lymphocyte Activation Gene 3
SAC	Scientific Advisory Committee
SAE	Serious Adverse Events
SAP	Statistical Analysis Plan
SGOT	Serum Glutamic Oxaloacetic Transaminase
SGPT	Serum Glutamic Pyruvic Transaminase
SOC	Standard of Care
sSAP	Supplemental Statistical Analysis Plan
SUSAR	Suspected Unexpected Serious Adverse Reaction
TCC	Transitional Cell Carcinoma
TIL	Tumor-Infiltrating Lymphocytes
TIGIT	T-cell Immunoglobulin and Immunoreceptor Tyrosine-based Inhibitory Motif
TNBC	Triple-Negative Breast Cancer
TnT	Cardiac Enzyme Measurement Troponin
TSH	Thyroid-stimulating Hormone
TURBT	Transurethral Resection of the Bladder Tumor
UC	Urothelial Carcinoma
ULN	Upper Limit of Normal
US	United States
UTI	Urinary Tract Infection
Vc	Central Volume of Distribution
WHO	World Health Organization

12.5 ECOG Performance Status

Grade	Description
0	Fully active, able to carry on all pre-disease performance without restriction
1	Restricted in physically strenuous activity, but ambulatory and able to carry out work of a light or sedentary nature, e.g., light housework, office work
2	Ambulatory and capable of all self-care, but unable to carry out any work activities; up and about more than 50% of waking hours
3	Capable of only limited self-care; confined to bed or chair more than 50% of waking hours
4	Completely disabled; cannot carry on any self-care; totally confined to bed or chair
5	Dead
Oken M, Creech R, Tormey D, et al. Toxicity and response criteria of the Eastern Cooperative Oncology Group. *Am J Clin Oncol.* 1982;5:649-655 http://ecog-acrin.org/resources/ecog-performance-status	

12.6 Common Terminology Criteria for Adverse Events V4.0 (CTCAE)

The descriptions and grading scales found in the revised NCI Common Terminology Criteria for Adverse Events (CTCAE) Version 4.0 will be utilized for adverse event reporting. (http://ctep.cancer.gov/reporting/ctc.html).

12.7 Response Evaluation Criteria in Solid Tumors (RECIST) 1.1 Criteria For Evaluating Response in Solid Tumors

RECIST version 1.1* will be used in this study for assessment of tumor progression if systemic disease is noted on CT scans.

* As published in the European Journal of Cancer:

E.A. Eisenhauer, P. Therasse, J. Bogaerts, L.H. Schwartz, D. Sargent, R. Ford, J. Dancey, S. Arbuck, S. Gwyther, M. Mooney, L. Rubinstein, L. Shankar, L. Dodd, R. Kaplan, D. Lacombe, J. Verweij. New response evaluation criteria in solid tumors: Revised RECIST guideline (version 1.1). Eur J Cancer. 2009 Jan;45(2):228-47.

12.8 Country-specific Requirements

12.8.1 United Kingdom

5.5.2 Prohibited Concomitant Medications

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

> Live vaccines should not be used for 120 days after the last dose of study treatment administration. Refer to Section 5.5 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.

6 Trial Flow Chart

6.1 Treatment and Follow-up Phase

Monthly pregnancy testing is required for United Kingdom subjects, as stipulated by the CTFG guidance.

7.1.3.1 Laboratory Safety Evaluations (Hematology, Chemistry and Urinalysis)

Monthly pregnancy (serum and/or urine) testing should be conducted in the United Kingdom per local requirements and as stipulated in CTFG guidance.

12.8.2 Italy

6.1 Treatment and Follow-up Phase

Pregnancy testing by urine or serum beta-human chorionic gonadotropin (β-HCG) for women of childbearing potential (WOCBP) is required at least monthly during study treatment, at the time of study intervention discontinuation, and for 120 days after study treatment discontinuation (for Cohort C only).

12.8.3 Finland

6.1 Treatment and Follow-up Phase

The cardiac enzyme measurement Troponin (TnT), for all Finland subjects is required at screening (ie, at least 72 hours prior to first dose of study treatment) and may be repeated as clinically indicated (for Cohort C only).

12.8.4 EEA-specific Requirements

As recruitment is typically managed locally, the Sponsor is unable to specify all methods used globally or local requirements within the protocol. Sites may attempt to identify and recruit candidates who may be eligible for the study using recruitment procedures and participant-facing recruitment materials that have received IRB/IEC approval per ICH GCP.

6.0 Trial Flow Chart

For all EEA countries, HbA1C, lipid profile, and NP markers (BNP and NT pro-BNP) are required at Screening and then every 12 months until the End of Treatment Visit. Additional assessments can be performed as clinically indicated or as per institutional guidelines and standards.

7.2.6 Sponsor Responsibility for Reporting Adverse Events

The Sponsor will report suspected unexpected serious adverse reactions (SUSARs) to the Eudravigilance database via E2B(R3) electronic Individual Case Safety Report (ICSR) form in compliance with Regulation (EU) 536/2014.

12.9 Contraceptive Guidance

12.9.1 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 subject'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 nonhormonal 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.

12.9.2 Contraception 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,d] IUS[c] 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 subject can come from the site personnel's review of the subject'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,d] - Oral - Intravaginal - Transdermal - Injectable
Progestogen-only hormonal contraception[c,d] - 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 subject.
[a] Contraceptive use by men or women should be consistent with local regulations regarding the use of contraceptive methods for subjects 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).

13.0 SIGNATURES

13.1 Sponsor's Representative

TYPED NAME	
TITLE	
SIGNATURE	
DATE SIGNED	

13.2 Investigator

I agree to conduct this clinical trial in accordance with the design outlined in this protocol and to abide by all provisions of this protocol (including other manuals and documents referenced from this protocol). I agree to conduct the trial in accordance with generally accepted standards of Good Clinical Practice. I also agree to report all information or data in accordance with the protocol and, in particular, I agree to report any serious adverse events as defined in Section 7.2 – Assessing and Recording Adverse Events. I also agree to handle all clinical supplies provided by the Sponsor and collect and handle all clinical specimens in accordance with the protocol. I understand that information that identifies me will be used and disclosed as described in the protocol, and that such information may be transferred to countries that do not have laws protecting such information. Since the information in this protocol and the referenced Investigator's Brochure is confidential, I understand that its disclosure to any third parties, other than those involved in approval, supervision, or conduct of the trial is prohibited. I will ensure that the necessary precautions are taken to protect such information from loss, inadvertent disclosure or access by third parties.

TYPED NAME	
TITLE	
SIGNATURE	
DATE SIGNED	