Protocol Title: A Phase 3, Multinational, Randomized, Open-Label, Three Parallel-Arm Study of PF-06801591, an Anti-PD-1 antibody, in Combination With Bacillus Calmette-Guerin (BCG Induction With or Without BCG Maintenance) Versus BCG (Induction and Maintenance) in Participants With High-Risk, BCG-Naïve Non-Muscle Invasive Bladder Cancer or PF-06801591 as a Single Agent in Participants With BCG-Unresponsive NMIBC

Protocol Number: B8011006

Amendment Number: 5

Compound Number: PF-06801591

Study Intervention Name: sasanlimab

Study Phase: Phase 3

Short Title: CREST - Phase 3 Study of Sasanlimab (PF-06801591) in Combination With Bacillus Calmette-Guerin (BCG) or as a Single Agent in Participants With High-Risk Non-Muscle Invasive Bladder Cancer

Acronym: CREST: Combination of sasanlimab and alternative BCG Regimens to Evaluate outcomes with Subcutaneous anti-PD-1 Treatment

Sponsor Name: Pfizer, Inc

Legal Registered Address: 66 Hudson Boulevard East, New York, NY 10001, USA

Regulatory Agency Identifier Number(s)

Registry	ID
IND	125,681
EU CT	2023-509089-39-00

Approval Date: 17 June 2024

Document History

Document	Version Date
Amendment 5	17 June 2024
Amendment 4	10 November 2022
Amendment 3	12 January 2022
Amendment 2	21 September 2021
Amendment 1	26 June 2020
Original protocol	15 October 2019

This amendment incorporates all revisions to date, including amendments made at the request of country health authorities and IRBs/ECs and any protocol administrative change letter(s).

Protocol Amendment Summary of Changes Table

Amendment 5: 17 June 2024

Overall Rationale for the Amendment: Sponsor has revised the Cohort A study analysis plan for primary and key secondary study objectives. The rationale for this change is based on the observation that EFS events are accumulating at a much slower rate than originally projected, together with an increasing rate of participants dropping out from EFS observation. The IA2 will be removed, and the FA for EFS based on a calendar-based data cut-off date will be conducted.

Description of Change	Brief Rationale	Section # and Name
Substantial Modifications		
Update was made to the plan for the timing of the statistical analysis, including removal of EFS interim analysis 2, timing of EFS final analysis, and primary completion date.	Update was made to support change to planned analysis of primary and key secondary objective.	Synopsis 9.2.1 Sample Size Determination Cohort A
Non Substantial Modifications		
Updates made to analysis plan for EFS interim analyses to reflect that only interim analysis 1 was conducted as	Update was made to support change to statistical analysis for the study overall.	9.5. Interim Analyses (Cohort A only)

Description of Change	Brief Rationale	Section # and Name
originally planned, and interim analysis 2 will not take place as originally planned.		
Changed the multiplicity control testing strategy	Testing strategy updated to support the change to analysis plan for primary and key secondary study objectives	9.2.1 Sample Size Determination Cohort A Figure 5
Updated statistical analysis methods for primary and key secondary objectives and clarified that these analyses are based on investigator assessments	Statistical analysis methods updated to support overall change in analysis plan for primary and key secondary objectives and to clarify which data will be used for primary analyses.	9.4.1.1 Efficacy Analysis Cohort A
Primary estimand language was updated to align with updates to primary and secondary objectives.	Update was made to support change to planned analysis of primary and key secondary objective.	Synopsis 3.1. BCG-Naïve Cohort (Cohort A) 9.1.1.1. Estimands - Cohort A 9.4.1.1. efficacy analyses-Cohort A
Language regarding types of medical device deficiencies to be reported, definition of device deficiency, and process for reporting device deficiencies was updated.	Following update to protocol template. Text was implemented via PACL dated 04 December 2023.	8.3.9.1 Time Period for Detecting Medical Device Deficiencies 8.3.9.2. Follow-Up of Medical Device Deficiencies 8.3.9.4. Regulatory Reporting Requirements for Device Deficiencies 10.7.2 Definition of SAE, SADE, and Unanticipated Serious Adverse Device Effect

Description of Change	Brief Rationale	Section # and Name
		10.7.3 Definition of Device Deficiency 10.7.4 Recording/Reporting and Follow-Up of AEs and/or SAEs and Device Deficiencies
Editorial updates made to clarify that SRSD should be reviewed and approved by sponsor and submitted to IRB/EC, requirement for health authority approval of protocols and amendments, and update to EU Medical Device Regulation references.	Following update to protocol template.	10.1.1. Regulatory and Ethical Considerations
Process for facilitating access to a medically qualified professional from Pfizer has been updated.	Following update to protocol template. Text was implemented via PACL dated 01 February 2024.	10.1.12. Sponsor's Qualified Medical Personnel
Editorial updates and clarifications were made.	Following update to protocol template.	10.1.3. Informed Consent Process 10.1.4 Data Protection 10.1.6. Dissemination of Clinical Study Data 10.1.7 10.1.7. Data Quality Assurance 10.1.9. Use of Medical Records

Description of Change	Brief Rationale	Section # and Name
		10.1.10. Study and Site Closure
Protocol amendment 4 summary of changes moved from this Protocol Amendment Summary of Changes Table to Appendix 17 and replaced in this table with the current summary of changes for protocol amendment 5.	Summary of Changes Table updated with changes for current amendment and changes for previous amendment moved to Appendix 17.	Protocol Amendment Summary of Changes Table 10.17. Appendix 17: Protocol Amendment History
Typos, punctuation, and grammar were corrected as applicable.	Editorial updates	All

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1. PROTOCOL SUMMARY

1.1. Synopsis

Protocol Title: A Phase 3, Multinational, Randomized, Open-Label, Three Parallel-Arm Study of PF-06801591, an Anti-PD-1 antibody, in Combination With Bacillus Calmette-Guerin (BCG Induction With or Without BCG Maintenance) Versus BCG (Induction and Maintenance) in Participants With High-Risk, BCG-Naïve Non-Muscle Invasive Bladder Cancer or PF-06801591 as a Single Agent in Participants With BCG-Unresponsive NMIBC

Short Title: CREST - Phase 3 Study of Sasanlimab (PF-06801591) in Combination With Bacillus Calmette-Guerin (BCG) or as a Single Agent in Participants With High-Risk Non-Muscle Invasive Bladder Cancer

Rationale:
Overall, incidence and mortality for bladder cancer (BC) has changed very little over the past 20 years.[1] Vaccination using BCG was the first Food and Drug Administration (FDA) approved immunotherapy indication in the 1980s and for patients with high-risk non-muscle invasive bladder cancer (NMIBC) after transurethral resection of the bladder tumor (TURBT), induction with BCG followed by maintenance still represents the standard of care (SOC).[7] While treatment with BCG has been shown to reduce the risk of tumor recurrence, approximately 40% of patients with NMIBC will eventually have disease recurrence or progression despite BCG therapy;[32] thus, alternative treatments are urgently required to improve the outcome.[33]

Increased programmed death – ligand (PD-L) 1 expression was observed in bladder cancer cells in response to BCG treatment both in vitro and in vivo preclinical models and the combination of BCG and anti-PD-L1 agent induced an antitumor immune response.[2] In addition, the combination showed higher tumor growth inhibition and prolonged survival as compared to either agent alone.

Sasanlimab (PF-06801591) is a humanized, monoclonal antibody (mAb) specific for human programmed death – 1 (PD-1) that blocks the interaction between PD-1 and PD-L1/PD-L2. PF-06801591 administered at 300 mg subcutaneous (SC) every 4 weeks has been evaluated in the Phase 1 Study B8011001 in participants with advanced solid tumors. The clinical safety data available to date suggest an acceptable safety profile, aligned with other anti-PD-1/PD-L1 agents, and also preliminary evidence of clinical efficacy aligned with other anti-PD-1/PD-L1 agents in patients with advanced urothelial cancer (UC).

The role of PD-L1 expression level as a predictive factor of response to BCG therapy in patients with high-risk NMIBC was recently suggested in a retrospective evaluation suggesting that higher PD-L1 expression level is associated with failure of BCG treatment.[3] Supportive of this hypothesis, pembrolizumab showed promising activity in Keynote-057, a Phase 2 study in participants with high-risk NMIBC unresponsive to BCG. In an analysis of 101 participants with carcinoma in situ (CIS), a complete response (CR) rate of 41% (95% confidence interval [CI]: 30.7, 51.1) was reported with a median duration of CR of 16.2 months (95% CI: 6.7, 36.2). The most common (>5%) treatment-

related adverse events (AEs) included diarrhea (11%), fatigue (11%), pruritis (11%), hypothyroidism (7.0%), maculopapular rash (6%), rash, hyperthyroidism, and nausea (each 5%), which was consistent with the known adverse event (AE) profile of pembrolizumab in the advanced disease setting.[4]

Rationale for Cohort A

A Phase 1 study of pembrolizumab in combination with BCG in participants with high-grade NMIBC persisting or recurring following at least 2 courses of intravesical therapy or 1 course of BCG (induction and maintenance), showed that the combination regimen of pembrolizumab (at 100 mg and 200 mg fixed doses) and BCG was well tolerated.[6] Fatigue, dysuria, spasm, urgency, sensitivity and frequency were the most frequently reported AEs, with all AEs reported as Grade 1 or 2.[6] Of the first 9 participants enrolled, 7 participants (78%) had no evidence of disease in the bladder at 19 weeks. These data suggest an improved clinical activity over each of the agents alone, considering BCG alone is expected to have minimal or no clinical activity in the treatment setting and pembrolizumab showed a CR rate 41% in a similar population.[4]

To treat patients with NMIBC appropriately, treatment considerations include the European Organisation for Research and Treatment of Cancer (EORTC) risk table scores of recurrence and progression.[7] For patients with high-risk NMIBC, the current standard of care is TURBT followed by intravesical BCG.[7] The standard schedule for BCG is induction (once weekly for 6 weeks) followed by maintenance for a minimum of 1 year. Full-dose BCG maintenance, administered once per week for 3 weeks, starting at 3 months after the first BCG dose of induction course (ie, 6 weeks after completion of induction BCG), and at 6 months, and then every 6 months, as used in the Southwest Oncology Group (SWOG) 8507 and European Organization for Research and Treatment of Cancer (EORTC) 30911 and 30962 trials,[8,11] is the most appropriate maintenance schedule. Indeed, addition of maintenance to induction treatment with BCG according to the administration schedule described in the study is currently recommended in the European Association of Urology (EAU) and National Comprehensive Cancer Network (NCCN) guidelines[7,9] because it has proven to reduce both progression and recurrence of the disease.[10]

The optimal duration of BCG maintenance therapy has been investigated in the European Organization for Research and Treatment of Cancer Genito-Urinary (EORTC-GU) Study 30962.[11] In this study, full dose BCG maintenance for 3 years was associated with a reduction in recurrence (hazard ratio [HR] = 1.61, 95% CI: 1.13-2.30, p = 0.009) in high-risk participants as compared with 1 year of BCG maintenance; however, there were no differences in progression or survival.[11] For this reason, the benefit of the 2 additional years of maintenance should be weighed against its additional costs, inconveniences, and tolerability. Therefore, the study design for Cohort A of B8011006 includes a BCG maintenance duration of up to 2 years (Arm A: BCG plus PF-06801591, Arm C: BCG alone). Considering the expected improved clinical activity of the PF-06801591 plus BCG combination regimen, investigation of PF-06801591 plus BCG induction only, is justified (Arm B).

Based on preclinical and clinical data, an intervention in BCG-naïve participants with high-risk NMIBC, with PF-06801591 in combination with BCG induction therapy (with or without maintenance therapy) may provide a greater benefit with longer event-free survival and reduction in the rate of subsequent cystectomy as compared to SOC BCG treatment. In addition, PF-06801591 is administered subcutaneously (SC) every 4 weeks which is expected to reduce burden for the participants and for the healthcare system.

Rationale for Cohorts B1 and B2

BCG treatment fails in approximately 40% of patients with high-risk NMIBC[32] and limited therapeutic options are available for those with BCG-unresponsive disease after adequate BCG therapy (defined as a minimum of 5 out of 6 doses of an induction course followed by either 2 out of 6 doses of a re-induction course, or 2 of 3 doses of a maintenance course). [12] Patients with BCG-unresponsive disease are unlikely to respond to further BCG therapy, which is associated with an increased risk of progression, and radical cystectomy is therefore the standard and preferred option according to the treatment guidelines.[13,14] Radical cystectomy is considered curative for some patients, but it is associated with significant morbidity and mortality.[15] The overall 90-day complication rates are up to 28-64% [16,17] and the majority of early complications following radical cystectomy include gastrointestinal (29%), infection (25%), intestinal obstruction (23%), wound-related complications (15%) and deep vein thrombosis (4.7%); late complications include gastrointestinal bowel obstruction, urinary tract infection, deterioration in renal function, calculi formation, voiding dysfunction and metabolic complications.[15, 17]

Non-surgical treatment options for patients with BCG-unresponsive NMIBC are currently limited. Valrubicin is approved by the US but response rates are low (18-21%) and not durable.[18, 19] A recent meta-analysis reported data from 42 studies in 2254 patients with NMIBC treated after BCG failure with 24 different treatments, including approved and investigational agents. The median CR rates in the treatment of CIS-containing tumors were 26%, 17%, and 8% at 6, 12, and 24 months, respectively.[20] In the studies that enrolled patients with papillary disease without CIS the median recurrence-free rates were 67%, 44%, and 10% at 6, 12, and 24 months, respectively.[20] Similar results were reported from another meta-analysis that included 4 randomized-controlled studies and 24 single-arm studies that evaluated different bladder-sparing treatment options: the pooled 12-month response rates were 24% (95% CI: 16-32%) for trials with two or more prior BCG courses and 36% (95% CI: 25-47%) for those with one or more prior BCG courses.[21] Even considering the heterogeneity of the patient population, the different definitions of BCG failure, and the different study designs, these results define the high unmet need for new treatment options treatments to improve clinical outcomes in patients with NMIBC that recurs after initial BCG treatment.

Based on the results of the Keynote-057 study[4], pembrolizumab has been recently approved by the FDA for the treatment of patients with BCG-unresponsive CIS who are ineligible for or decline to undergo radical cystectomy.[22] In this study after a median duration of follow-up of 36.4 months (IQR 32.0 - 40.7), the CR rate was 41% (95% CI, 30.7-51.1) with a median duration of CR of 16.2 months (95% CI, 6.7 – 36.2).[4] In addition, atezolizumab has shown

signs of clinical efficacy in patients with BCG-unresponsive CIS [CR rate at 3 months was 41.1% (95% CI, 29.7-53.2)][53] and in patients with BCG-unresponsive papillary disease [EFS rate at 18 months was 45% (95% CI, 34-57)].[54]

PF-06801591 300 mg SC Q4W showed a safety and efficacy profile aligned to the other anti-PD-1/PD-L1 agents in patients with advanced UC and NSCLC[23] and PF-06801591 600 mg SC every 6 weeks (Q6W) showed a safety profile consistent with the B8011001 study and with the safety profiles of other PD-1 agents (data summarized in IB). Both dosing regimens offer the convenience of subcutaneous administration. Indeed, real world evidence of oncology biologics show that subcutaneous administration reduces healthcare resource utilization and associated costs by saving time in drug preparation and administration compared to intravenous (IV) therapy. SC administration also reduces time spent in the infusion chair and in caregiver assistance, while patients report better quality of life and preference for SC therapy over IV therapy.[24] In addition, the Q6W dosing frequency of PF-06801591, which will be evaluated in Cohort B2, explores an extended dosing interval for PF-06801591 to further reduce the burden for the participants, their caregivers and the healthcare system.

In summary, an unmet need exists for new innovative bladder-sparing treatment options for patients with BCG-unresponsive NMIBC that delay disease recurrence, progression, and radical cystectomy. PF-06801591 may provide greater clinical benefit with higher CR rate, durable responses and longer event-free survival relative to currently approved intravesical chemotherapies (valrubicin). Furthermore, the subcutaneous administration route and the lower frequency of dosing associated with the longer dosing interval are expected to reduce burden for the participants and for the healthcare system while maintaining a safety and efficacy profile aligned to other anti-PD-1/PD-L1 agents administered intravenously (pembrolizumab).

Cohorts B1 and B2 of B8011006 will include patients with BCG-unresponsive NMIBC. Cohort B1 will include participants with CIS (with or without Ta/T1 papillary disease) and Cohort B2 will include participants with high-grade Ta/T1 papillary disease only.

As of 31 August 2022, enrollment in Cohorts B1 and B2 was closed by the sponsor for business strategy reasons. This decision was not made due to any safety concerns, new emerging data, or regulatory interaction. Participants that have already been enrolled into Cohorts B1 and B2 may continue treatment and study procedures and assessments per the Cohorts B1 and B2 SoA.

Due to the decision to close enrollment in Cohorts B1 and B2, the Cohort B1 and B2 study objectives are no longer required.

Objectives, Estimands and Endpoints

Cohort A	
Primary Objectives	**Primary Endpoints**
• To demonstrate that PF-06801591 + BCG (induction and maintenance) is superior to BCG (induction and maintenance) in prolonging event-free survival (EFS) in participants with high-risk NMIBC.	• EFS as assessed by the investigator
Key Secondary Objectives	**Key Secondary Endpoints**
• To demonstrate that PF-06801591 + BCG (induction) is superior to BCG (induction and maintenance) in prolonging EFS in participants with high-risk NMIBC	• EFS as assessed by the investigator
• To demonstrate that PF-06801591 + BCG (induction and maintenance) is superior to BCG (induction and maintenance) in prolonging overall survival (OS) in participants with high-risk NMIBC.	• OS
• To demonstrate that PF06801591 + BCG (induction) is superior to BCG (induction and maintenance) in prolonging OS in participants with high-risk NMIBC.	• OS
Secondary Objectives	**Secondary Endpoints**
• To estimate the complete response (CR) rate of PF-06801591 + BCG (induction and maintenance or induction) and BCG (induction and maintenance) in participants with CIS at randomization.	• CR as assessed by the investigator (in participants with CIS at randomization)
• To evaluate the duration of CR of PF06801591 + BCG (induction and maintenance or induction) and BCG (induction and maintenance) in participants with CIS at randomization.	• Duration of CR for participants with CR as assessed by the investigator (in participants with CIS at randomization)
• To evaluate the time to recurrence of low grade disease of PF-06801591 + BCG (induction and maintenance or induction) and BCG (induction and maintenance) in participants with high-risk NMIBC.	• Time to recurrence of low-grade disease as assessed by the investigator

Cohort A	
• To evaluate the time to cystectomy of PF06801591 + BCG (induction and maintenance or induction) and BCG (induction and maintenance) in participants with high-risk NMIBC.	• Time to cystectomy
• To evaluate the disease-specific survival (DSS) of PF-06801591 + BCG (induction and maintenance or induction) and BCG (induction and maintenance) in participants with high-risk NMIBC.	• DSS as assessed by the investigator
• To evaluate the overall safety profile of PF06801591+BCG (induction and maintenance or induction) and BCG (induction and maintenance) in participants with high-risk NMIBC.	• AEs as characterized by type, severity (as graded by National Cancer Institute Common Terminology Criteria for Adverse Events [NCI CTCAE] v5.0), timing, seriousness, and relationship to study therapy. Laboratory abnormalities as characterized by type, severity (as graded by NCI CTCAE v5.0), and timing
• To assess the effects of PF06801591 + BCG (induction and maintenance or induction) and BCG (induction and maintenance) on patient-reported health-related quality of life in participants with high-risk NMIBC.	• Health-related quality of life as measured by: 1) EORTC QLQ-C30 (European Organization for Treatment of Cancer Quality of Life Questionnaire), 2) EORTC QLQ-NMIBC24, 3) PTAB (Patient Treatment Administration Burden Questionnaire)
• To characterize the PK of PF06801591 + BCG (induction and maintenance or induction).	• C_{trough} of PF-06801591 when in combination with BCG (induction and maintenance or induction). Arms A and B only.
• To evaluate the immunogenicity of PF06801591 + BCG (induction and maintenance or induction).	• ADAs; NAbs of PF-06801591 when in combination with BCG (induction and maintenance or induction). Arms A and B only.
• To evaluate PD-L1 expression in pre-treatment tumor tissue that may aid in the identification of a participant subpopulation most likely to benefit from treatment with	• Tumor sample biomarker status based on PD-L1 expression (high or low)

Cohort A	
PF06801591 + BCG (induction and maintenance or induction).	

Cohorts B1 and B2	
Primary Objectives	**Primary Endpoints**
• To estimate the CR rate of PF-06801591 in participants with BCG-unresponsive CIS (Cohort B1 only)	• CR as assessed by the BICR
• To evaluate the EFS of PF-06801591 in participants with BCG-unresponsive NMIBC (Cohort B2 only)	• EFS as assessed by the investigator
Secondary Objectives	**Secondary Endpoints**
• To evaluate the duration of CR of PF-06801591 in participants with BCG-unresponsive CIS (Cohort B1 only).	• Duration of CR for participants with CR as assessed by the BICR
• To estimate the CR rate of PF-06801591 at 12 months in participants with BCG-unresponsive CIS (Cohort B1 only)	• CR at 12 months as assessed by the BICR
• To evaluate the EFS of PF-06801591 in participants with BCG-unresponsive CIS (Cohort B1 only)	• EFS as assessed by the investigator
• To evaluate the time to cystectomy of PF-06801591 in participants with BCG-unresponsive NMIBC (Cohorts B1 and B2).	• Time to cystectomy
• To evaluate OS in participants with BCG-unresponsive NMIBC treated with PF-06801591 (Cohorts B1 and B2).	• OS
• To evaluate the overall safety of PF-06801591 in participants with BCG-unresponsive NMIBC (Cohorts B1 and B2).	• AEs as characterized by type, severity (as graded by National Cancer Institute Common Terminology Criteria for Adverse Events [NCI CTCAE] v5.0), timing, seriousness, and relationship to study therapy. Laboratory abnormalities as characterized by type, severity (as graded by NCI CTCAE v5.0), and timing
• To assess the effects of PF-06801591 on patient-reported health-related quality of life	• Health-related quality of life as measured by: 1) EORTC QLQ-C30 (European

Cohorts B1 and B2	
in participants with BCG-unresponsive NMIBC (Cohorts B1 and B2).	Organization for Treatment of Cancer Quality of Life Questionnaire), 2) EORTC QLQ-NMIBC24, 3) PTAB (Patient Treatment Administration Burden Questionnaire)
• To evaluate PD-L1 expression in pretreatment tumor tissue that may aid in the identification of a subpopulation of participants with BCG unresponsive NMIBC most likely to benefit from PF-06801591 (Cohorts B1 and B2).	• PD-L1 expression
• To characterize the PK and immunogenicity of PF06801591 single agent in participants with BCG-unresponsive NMIBC (Cohorts B1 and B2).	• C_{trough}, C_{max} (Cohort B2 only), ADAs and NAbs following PF-06801591 single agent.

Estimands are defined below for the primary and key secondary endpoints of the study.

Table 2 (Section 9.1.1) defines the possible clinical outcomes for the EFS evaluation. The clinical definitions of recurrence of high-grade disease, progressive disease, persistence of CIS, recurrence of low-grade disease and CR are included in Section 10.9. For Cohort A, in participants with CIS at randomization "persistence of CIS" is defined as persistence of CIS after induction or, if re-induction is administered, after re-induction. Persistence of CIS after induction with CR after re-induction is not considered persistence of CIS. For Cohort B1, persistence of CIS is defined as persistence of CIS at the 12 week disease assessment. The censoring and event date options to be considered for the EFS analyses are presented in Table 3 (Section 9.1.1).

Cohort A

Primary Estimand (event-free survival [EFS] for Arm A vs Arm C) and Key Secondary Estimand (EFS for Arm B vs Arm C): treatment effect, estimated based on data from all randomized participants, of each experimental arm (Arm A and Arm B) on EFS compared to Arm C from randomization to the earliest of recurrence of high-grade disease, progression of disease, persistence of CIS, or death regardless of tolerability, duration of study treatment, or initiation of subsequent anti-cancer therapy. The date of the event (event as defined in Table 2) is the date of disease assessment documenting recurrence of high-grade disease, progression of disease, persistence of CIS (applicable only to participants with CIS at randomization), or death, whichever occurs earlier. The date of persistence of CIS is the earliest date when persistence of CIS is observed, if CR is not observed after re-induction.

- Variable: EFS defined as the time from randomization until recurrence of high-grade disease, progression of disease, persistence of CIS, or death due to any cause, whichever occurs first.

- Censoring: See Table 3.

- Population-level summary measure: hazard ratio for EFS including all randomized participants.

Supportive Estimand 1 (EFS): treatment effect, estimated based on data from all randomized participants, of each experimental arm (Arm A and Arm B) on EFS compared to Arm C from randomization to the earliest of recurrence of high-grade disease, progression of disease, persistence of CIS, or death, regardless of tolerability, duration of study treatment, initiation of subsequent anti-cancer therapy. The date of the event (event as defined in Table 2) is the date of disease assessment documenting recurrence of high-grade disease, progression of disease, date of randomization for participants with persistent CIS (applicable only to participants with CIS at randomization), or death, whichever occurs earlier.

- Variable: EFS defined as the time from randomization until recurrence of high-grade disease, progression of disease, persistence of CIS, or death due to any cause, whichever occurs first.

- Censoring: See Table 3.

- Population-level summary measure: hazard ratio for EFS including all randomized participants.

Supportive Estimand 2 (EFS): treatment effect of each experimental arm (Arm A and Arm B) on EFS compared to Arm C from randomization to the earliest of recurrence of high-grade disease, progression of disease, persistence of CIS, or death regardless of tolerability, duration of study treatment, or initiation of subsequent anti-cancer therapy. Data from randomized participants who do not meet per-protocol criteria as defined below are excluded. The date of the event (event as defined in Table 2) is the date of disease assessment documenting recurrence of high-grade disease, progression of disease, persistence of CIS (applicable only to participants with CIS at randomization), or death, whichever occurs earlier. The date of persistence of CIS is the earliest date when persistence of CIS is observed, if CR is not observed after re-induction.

- Variable: EFS defined as the time from randomization until recurrence of high-grade disease, progression of disease, persistence of CIS, or death due to any cause, whichever occurs first.

- Censoring: See Table 3.

- Population-level summary measure: hazard ratio for EFS excluding randomized participants who did not receive at least 1 dose of study drug, did not meet inclusion criteria 2 or 3, or met exclusion criteria 1 or 2.

Key Secondary Estimand (overall survival [OS]): Treatment effect, estimated based on data from all randomized participants, of each experimental arm (Arm A and Arm B) on OS compared to Arm C regardless of tolerability, duration of study treatment, initiation of subsequent anti-cancer therapy or participant's request to discontinue study procedures.

- Variable: OS

- Censoring: data for participants not known to have died are censored at the time of last contact.

- Population-level summary measure: hazard ratio for OS, including all randomized participants.

Overall Design:
This is a Phase 3, multicenter, multinational, randomized, open label, parallel, 3-arm study to evaluate PF-06801591 in combination with BCG vs BCG in participants with high-risk, BCG-naïve non-muscle invasive bladder cancer (Cohort A). The study will also evaluate PF-06801591 as a single agent in participants with BCG unresponsive, NMIBC in 2 separate non-randomized cohorts (Cohorts B1 and B2).

Randomization (1:1:1) in Cohort A will occur via interactive response technology (IRT) within approximately 28 days of start of screening. Randomization will be stratified by the presence of CIS (yes vs no) and geography (United States [US] vs Western Europe and Canada vs rest of world [ROW]). Registration into Cohorts B1 and B2 will occur via interactive response technology (IRT) within approximately 28 days of start of screening. For Cohort B1, diagnosis of CIS alone or with concomitant recurrent Ta/T1 disease and absence of muscle-invasive bladder cancer and extravesical disease must be confirmed by the BICR prior to registration.

In order to conduct a preliminary assessment of the safety profile of PF-06801591 plus BCG regimen, a review of safety data will be performed by an external data monitoring committee (EDMC) approximately 6 weeks after 20 participants have been randomized in each of the 3 arms and have received at least one dose of study treatment. The enrollment will continue during EDMC review. The EDMC will convene to monitor safety in the study (Cohort A only) approximately every 6 months thereafter. The EDMC will also review cumulative safety data during the study conduct as well as review the futility interim analysis (IA) data for EFS from Cohort A.

Based on protocol amendment 5, the IA2 will be removed, and the FA for EFS based on a calendar-based data cut-off date will be conducted. Randomization to Cohort A was completed on 16 November 2021 and the EFS FA data cut-off date will be set to allow for approximately 3 years of follow-up after last randomized participant.

Based on the blinded observed EFS event accrual rate, approximately 261 EFS events are expected to have occurred across the three study arms by the EFS FA data cut-off date.

Disclosure Statement:
Cohort A is a Parallel Treatment study with 3 arms that have No masking.

Number of Participants:

Cohort A: Approximately 999 participants (including a minimum of 250 participants with CIS) will be randomized to one of 3 treatment arms (A, B, and C) in this Cohort, each arm will have approximately 333 randomized participants. As of 16 November 2021, enrollment to Cohort A has completed with 1056 participants randomized.

Intervention Groups and Duration:
Cohort A

- Arm A: PF-06801591 + BCG (induction and maintenance period)
- Arm B: PF-06801591 + BCG (induction period only)
- Arm C: BCG only (induction and maintenance period)

BCG Dosing (intravesical instillation):

- Induction period: one dose every week (QW) for 6 consecutive weeks (QWx6)
- Re-Induction period: Following first induction period, participants with CIS at randomization who have persistent disease and participants with recurrence of high grade Ta disease may receive re-induction (QWx6)
- Maintenance period: (Arm A and Arm C): Doses on D1, D8, D15 during Cycles C4, C7, C13, C19 and C25. For participants that have a re-induction period, the maintenance period will begin at C7D1.

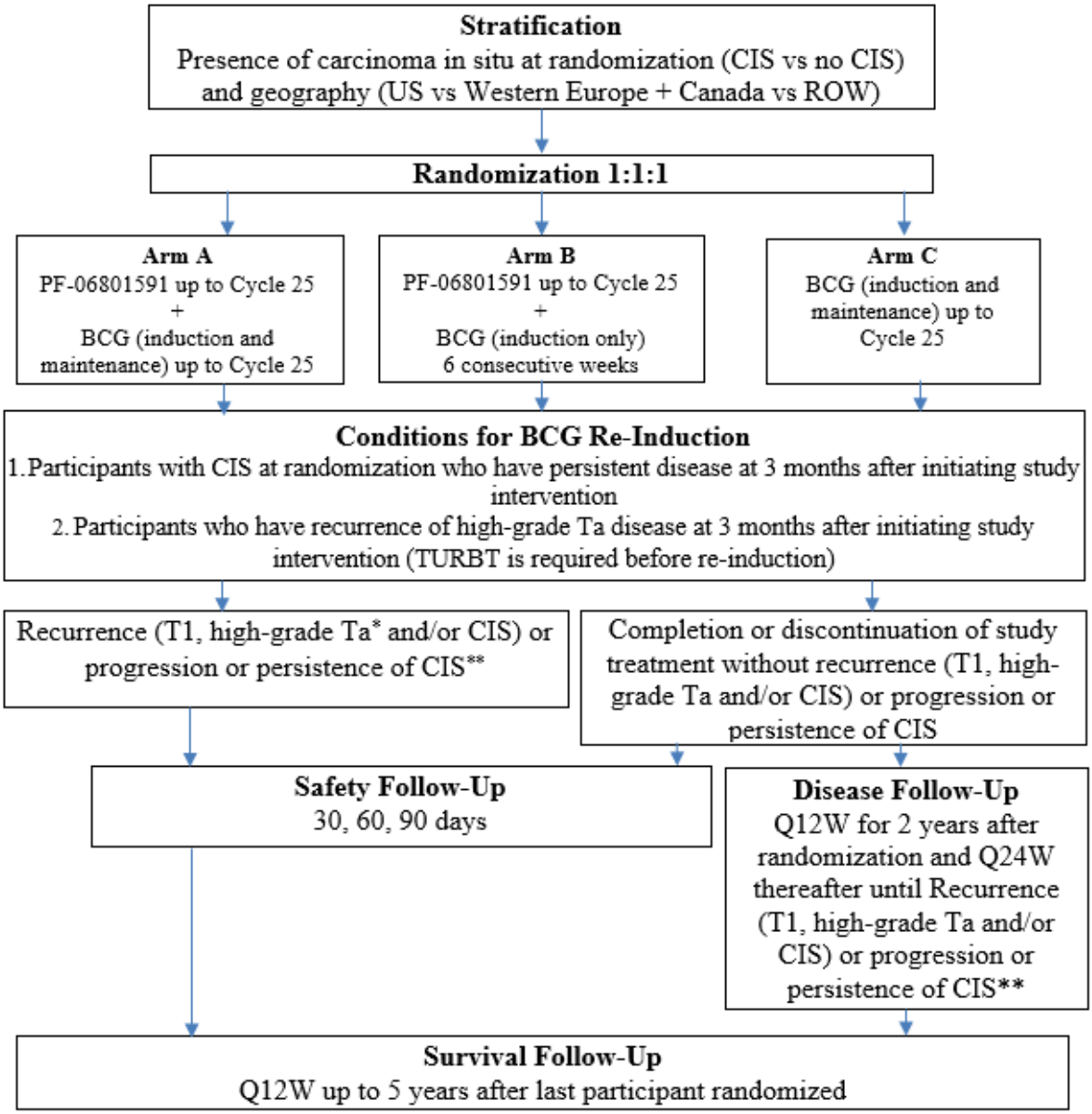
PF-06801591 Dosing (subcutaneous injection):
Once every 4 weeks 300 mg up to Cycle 25 (cycle = 4 weeks).

All participants will enter the safety follow-up period at end of treatment (EOT). Concurrent to the safety follow-up, participants with no recurrence of high-grade disease, progression of disease, or persistence of CIS before EOT, will continue disease assessment through the disease follow-up period (assessments every 12 weeks for 2 years after randomization and every 24 weeks thereafter until recurrence of high grade disease or progression of disease, withdrawal of consent for further participation in the study, lost to follow-up, or death). After recurrence of high-grade disease, persistence of CIS, or progression of disease participants will be followed for survival via telephone calls every 12 weeks until the earliest of withdrawal of consent, lost to follow-up, death, study termination by the sponsor, or end of study (5 years from last participant randomized).

Data Monitoring Committee: Yes

1.2. Schema

Figure 1. B8011006: Study Schematic – Cohort A



*See Section 4.1 for additional details

** For participants with CIS at randomization

CIS: carcinoma in situ, BCG: Bacillus Calmette-Guerin; ROW: rest of world; US: United States

Cohorts B1 and B2:

- PF-06801591 as a single agent

PF-06801591 Dosing (subcutaneous injection):
Cohort B1: Once every 4 weeks 300 mg up to Cycle 25 (cycle = 4 weeks).

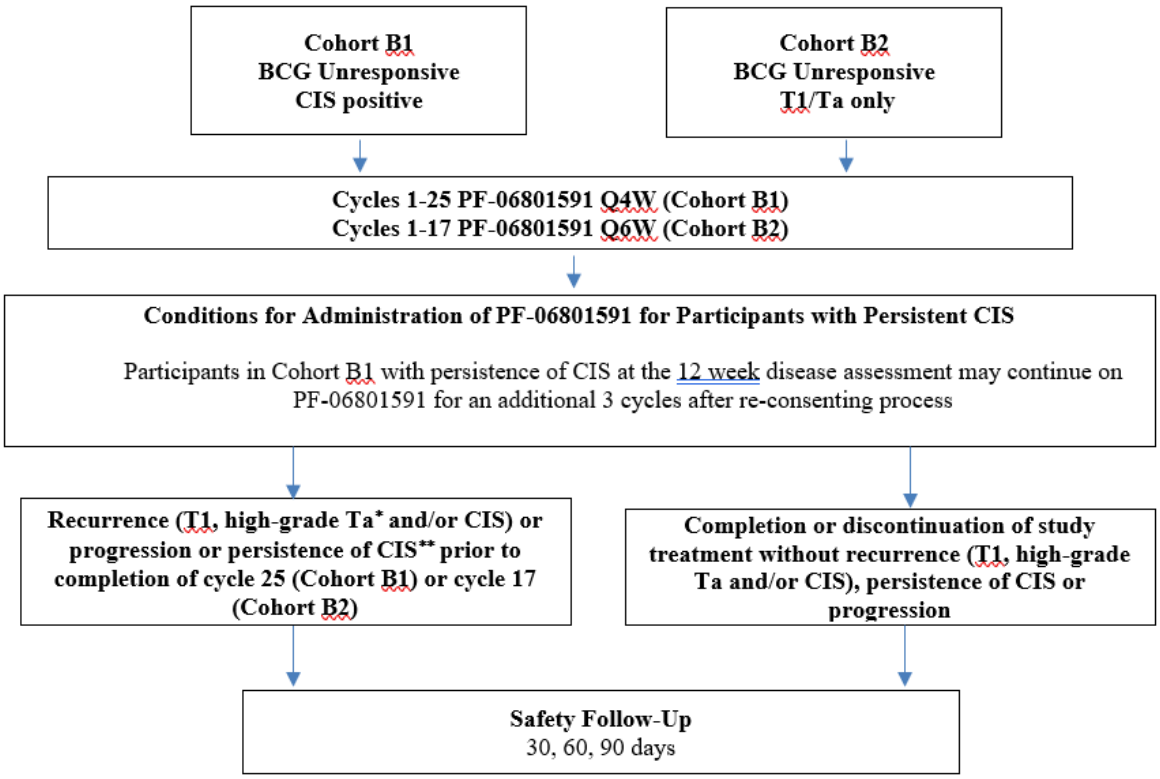
Cohort B2: Once every 6 weeks 600 mg up to Cycle 17 (cycle = 6 weeks).

As noted in Figure 2, participants in Cohort B1 with persistence of CIS at the 12 week disease assessment may continue on PF-06801591 for an additional 3 cycles (until the 24 week disease assessment). This may only occur after the investigator and participant discuss the option of cystectomy, and the participant re-consents to 3 additional cycles of PF-06801591 instead of cystectomy. Participants with persistence of CIS at or after the 24 week disease assessment will enter the post-treatment follow-up period for safety visits.

All participants will enter the safety follow-up period at end of treatment (EOT).

Data Monitoring Committee: No

Figure 2. B8011006 Study Schematic - Cohorts B1 and B2



*See Section 4.1 for additional details
** For participants in Cohort B1 with CIS at registration

CIS: carcinoma in situ

1.3. Schedule of Activities (SoA)

Screening and Induction Period – Cohort A

	Screening	Induction Period							Notes
		Cycle 1				Cycle 2		Cycle 3	Cycle = 4 weeks
	D -28 to D -1	D1	D8	D15	D22	D1	D8	D1	
Visit Window (Days)		±0	±3	±3	±3	±3	±3	±3	
Informed Consent	X								Informed consent may be obtained more than 28 days prior to randomization. All screening procedures must be completed within 28 days of randomization. The Consent for future research will be signed as applicable. Participants must sign consent prior to any trial-specific procedure. See Section 10.1.3.
Tumor and Medical History	X								See Section 8 for details.
Physical Examination	X	X				X		X	Physical examinations should be performed according to clinical practice. Any abnormalities should be recorded as AEs. See Section 8.2.1.
Weight	X	X				X		X	
Vital Signs	X	X				X		X	BP and pulse rate will be performed. Any clinically significant abnormalities should be recorded as AEs. See Section 8.2.2.
ECOG PS	X	X				X		X	Refer to Section 8.2.3. and Section 10.10.
12-Lead ECG	X	X				X	As clinically indicated		Single 12-lead ECG will be collected prior to dosing of PF-06801591. See Section 8.2.4 for details.
Adverse Events	X								See Section 8.3 and Section 10.3.
Concomitant Therapy	X								See Section 6.5.
Contraception Check		X				X		X	Must be performed D1 of each cycle. See Section 10.4 for details.
Chest X-Ray/ Laboratory Assessment/ Skin Test to Exclude Tuberculosis	X	As clinically indicated							Active tuberculosis is to be excluded per local guidelines or the applicable BCG product label prior to randomization. If tuberculosis is excluded by chest x-ray, the chest x-ray is not required to be repeated at screening if performed within 90 days prior to randomization. Methods of ruling out tuberculosis other than those specified in the protocol are permitted, if they are local standard practice.
Laboratory									
Hematology	X	X				X		X	See Section 10.2 for the list of the tests.
Blood Chemistry	X	X				X		X	

	Screening	Induction Period							Notes
		Cycle 1				Cycle 2		Cycle 3	Cycle = 4 weeks
Visit Window (Days)	**D -28 to D -1**	**D1 ±0**	**D8 ±3**	**D15 ±3**	**D22 ±3**	**D1 ±3**	**D8 ±3**	**D1 ±3**	
Coagulation	X							X	Not necessary to repeat on C1D1 if performed within 7 days prior to C1D1 as part of Screening. Laboratory tests may be performed up to 3 days prior to the scheduled clinic visit, so that results will be available for review before study treatment administration, including C1D1. See Section 8.2.7 for requirements on minimum labs to be reviewed prior to dosing.
Urinalysis	X	X				X		X	Collect sample before BCG administration. Not necessary to repeat on C1D1 if performed within 7 days prior to C1D1 as part of Screening. See Section 10.2 for the list of the tests.
Pregnancy Test	X	X				X		X	A negative highly sensitive test is required prior to study treatment dosing on Day 1 of all cycles. Results must be available for review prior to dosing. See Section 8.2.8 and Section 10.4. Pregnancy testing after C1D1 per local guidelines.
FSH	X								For female postmenopausal participants under the age of 60 and not using hormonal contraception or HRT, a serum FSH test is required at screening only, to confirm postmenopausal status. FSH is not required for participants not meeting these criteria. See Section 10.2 and Section 10.4.
Hepatitis B and C	X								HBV surface antigen and anti-HCV antibody tests. If HBV surface antigen or anti-HCV antibody test is positive, reflex testing must be carried out, as detailed in Table 5
ACTH & Thyroid Function Test	X	X				X		X	Not necessary to repeat on C1D1 if performed within 7 days prior to C1D1 as part of Screening.
Randomization		**X**							Participants will receive assigned treatment within 3 days after randomization.
BCG Administration **(All Arms)**		X	X	X	X	X	X		Follow calendar days for dosing, not the schedule cycles. See Section 6.1.2 for details. On days when BCG and PF-06801591 are both administered, BCG is administered first.
PF-06801591 Administration (Arms A & B)		X				X		X	Administer subcutaneously. See Section 6.1.2.
Disease Assessments									
CT or MRI	X					As clinically indicated			CT/MRI/Urogram of the abdomen and pelvis/urinary tract. Imaging performed with contrast agents unless contraindicated for medical reasons. As clinically indicated to confirm and/or rule out distant metastasis. See Section 8.1.1.3 for additional details.
Cystoscopy, with or without Biopsy	X								Cystoscopy is required during screening. Same equipment and methods by the same study staff should be used for the duration of the study whenever possible. See Section 8.1.1.1.

	Screening	Induction Period							Notes
		Cycle 1				Cycle 2		Cycle 3	Cycle = 4 weeks
	D -28 to D -1	D1	D8	D15	D22	D1	D8	D1	
Visit Window (Days)		±0	±3	±3	±3	±3	±3	±3	
Cytology	X								Urine cytology; ±7 days allowed for on-treatment assessment. Same equipment and methods by the same study staff should be used for the duration of the study whenever possible. See Section 8.1.1.2.
Patient Reported Outcomes (PROs)									
EORTC-QLQ-C30, EORTC NMIBC24	X	X				X		X	All PROs will be completed prior to clinical assessments and procedures and/treatment administration, with the exception of the PTAB, which will be completed immediately after treatment administration. Laboratory assessments may be done prior to PROs if laboratory assessments are done on a date prior to the rest of the study visit. PROs will be administered in following order: EORTC QLQ-C30, EORTC NMIBC24, EQ-5D-5L, PGIS, PGIC, TSQ, PTAB. See Section 8.1.2.
EQ-5D-5L		X				X		X	
PGIS	X	X				X		X	
PGIC						X		X	
TSQ						X			
PTAB		X				X			
Immunogenicity, Pharmacokinetic, Pharmacodynamic, Biomarker Analyses									
Immunogenicity		X				X			Collected pre-dose at each time point for Anti-PF-06801591 Antibody (ADA/NAb) measurement. See Section 8.8.3. Arms A and B only.
Pharmacokinetics		X				X			Collected pre-dose at each time point for PK analysis of PF-06801591. All efforts should be made to obtain PK samples within 2 hours prior to PF-06801591 dosing. See Section 8.5. Arms A and B only.
Tumor Tissue Sample from Most Recent TURBT	X								See Section 8.8.1.
Whole Blood Biomarkers	X	X				X			See Section 8.8.
Plasma and Serum Biomarker Sample	X	X				X			See Section 8.8.
Banked Biospecimen		X							See Section 8.7.2.

AE: adverse event, ACTH: adrenocorticotropic hormone, ADA: anti-drug antibodies; BCG: Bacillus Calmette Guérin, BP: blood pressure; CT: computed tomography, ECG: electrocardiogram, ECOG PS: Eastern Cooperative Oncology Group Performance Status, EORTC-QLQ-C30: European Organisation for Research and Treatment of Cancer Quality of Life Questionnaire–30 (items), FSH: follicle-stimulating hormone, HRT: hormone replacement therapy, MRI: magnetic resonance imaging, NAb: neutralizing antibodies; NMIBC: non-muscle invasive bladder cancer, PGIC: Patient Global Impression of Change; PGIS: Patient Global Impression of Severity; PK: pharmacokinetics, PTAB: Patient Treatment Administration Burden; TSQ: Treatment Satisfaction Questionnaire; TURBT: transurethral resection of bladder tumor

Maintenance Period – Cohort A

Maintenance Period: Cycles 4 to 25 (Cycle = 4 Weeks) for participants without re-induction BCG Re-induction Period for Participants Who Receive BCG Re-induction: Cycles 4-6 ; Maintenance Period: Cycles 7 to 25													
	C4D1	**C5D1**	**C6D1**	**C7D1**	**C8D1**	**C9D1**	**C10D1**	**C11D1**	**C12D1**	**C13D1**	**C14D1**	**C15D1 thru C25D1**	**Notes**
Visit Window (Days)	**±7**	**±7**	**±7**	**±7**	**±7**	**±7**	**±7**	**±7**	**±7**	**±7**	**±7**	**±7**	
Physical Examination	X	X	X	X	X	X	X	X	X	X	X	X	Physical examinations should be performed according to clinical practice. Any clinically significant abnormalities should be recorded as AEs. See Section 8.2.1.
Weight	X	X	X	X	X	X	X	X	X	X	X	X	
Vital Signs	X	X	X	X	X	X	X	X	X	X	X	X	BP and pulse rate will be performed. Any clinically significant abnormalities should be recorded as AEs. See Section 8.2.2.
Contraception Check	X	X	X	X	X	X	X	X	X	X	X	X	Must be performed D1 of each cycle. See Section 10.4 for details.
ECOG PS	X	X	X	X	X	X	X	X	X	X	X	X	See Section 8.2.3 and Section 10.10.
Concomitant Therapy	X												See Section 6.5.
Adverse Events	X												See Section 8.3 and Section 10.3.
12-Lead ECG	X	X	X	As clinically indicated									Prior to dosing. See Section 8.2.4. Completed on Day 1 of Cycles 4, 5, and 6 only. For all other cycles in maintenance, ECG will be completed as clinically indicated.
Chest X-Ray	As clinically indicated												
Laboratory													
Hematology	X	X	X	X	X	X	X	X	X	X	X	X	See Section 10.2 for the list of the tests. Laboratory tests may be performed up to 3 days prior to the scheduled clinic visit, so that results will be available for review before study treatment administration. See Section 8.2.7 for requirements on minimum labs to be reviewed prior to dosing.
Blood Chemistry	X	X	X	X	X	X	X	X	X	X	X	X	
Coagulation			X			X			X			X*	*Completed on Day 1 of Cycles 15, 18, 21, 24.

Maintenance Period: Cycles 4 to 25 (Cycle = 4 Weeks) for participants without re-induction BCG Re-induction Period for Participants Who Receive BCG Re-induction: Cycles 4-6 ; Maintenance Period: Cycles 7 to 25													
	C4D1	**C5D1**	**C6D1**	**C7D1**	**C8D1**	**C9D1**	**C10D1**	**C11D1**	**C12D1**	**C13D1**	**C14D1**	**C15D1 thru C25D1**	**Notes**
Visit Window (Days)	**±7**	**±7**	**±7**	**±7**	**±7**	**±7**	**±7**	**±7**	**±7**	**±7**	**±7**	**±7**	
Urinalysis	X	X*		X						X		X**	Collect sample prior to each BCG administration as indicated, including: *during the re-induction, as applicable (Cycles 4 and 5) **during Cycles 19 and 25. As clinically indicated during other cycles. See Section 10.2 for the list of the tests.
Pregnancy Test	X	X	X	X	X	X	X	X	X	X	X	X	A negative highly sensitive test is required prior to study intervention dosing on Day 1 of all cycles. Results must be available for review prior to dosing. See Section 8.2.8 and Section 10.4. Pregnancy testing per local guidelines.
ACTH & Thyroid Function Test			X			X			X			X*	*Completed on Day 1 of Cycles 15, 18, 21, 24, 25.
BCG Administration **(Arms A & C)**	X*#	X*		X#						X#		X#	Follow calendar cycle for dosing, not the schedule. See Section 6.1.2 for details. On days when BCG and PF-06801591 are both administered, BCG is administered first. *Re-induction period: See Section 4.1 for participants who may meet criteria for re-induction. Suggested instillations on C4D1, C4D8, C4D15, C4D22, C5D1, and C5D8. Maintenance will then begin on C7D1. If TURBT is performed, BCG re-induction schedule should be modified according to the product label. #Maintenance BCG schedule: D1, D8, D15 of Cycles 4, 7, 13, 19, and 25.
PF-06801591 Administration **(Arms A & B)**	X	X	X	X	X	X	X	X	X	X	X	X	Administer subcutaneously Q4W up to Cycle 25. See Section 6.1.2.

Maintenance Period: Cycles 4 to 25 (Cycle = 4 Weeks) for participants without re-induction BCG Re-induction Period for Participants Who Receive BCG Re-induction: Cycles 4-6 ; Maintenance Period: Cycles 7 to 25													
	C4D1	**C5D1**	**C6D1**	**C7D1**	**C8D1**	**C9D1**	**C10D1**	**C11D1**	**C12D1**	**C13D1**	**C14D1**	**C15D1 thru C25D1**	**Notes**
Visit Window (Days)	**±7**	**±7**	**±7**	**±7**	**±7**	**±7**	**±7**	**±7**	**±7**	**±7**	**±7**	**±7**	
Disease Assessments													
CT or MRI	As clinically indicated												CT/MRI/Urogram of the abdomen and pelvis/urinary tract. Imaging performed with contrast agents unless contraindicated for medical reasons. As clinically indicated to confirm and/or rule out distant metastasis. See Section 8.1.1.3.
Cystoscopy with or without Biopsy	X			X			X			X		X*	Participants with CIS at randomization who do not achieve a CR within 6 months of initiating study intervention will discontinue study treatment and enter the post-treatment follow-up period. Cystoscopy with or without tumor biopsy; ±7 days allowed for on-treatment assessment. Same equipment and methods by the same study staff should be used for the duration of the study whenever possible. See Section 8.1.1.1. * Completed every 12 weeks.
Cytology	X			X			X			X		X*	Urine cytology; ±7 days allowed for on-treatment assessment. Same equipment and methods by the same study staff should be used for the duration of the study whenever possible. See Section 8.1.1.2. *Completed every 12 weeks.
Patient Reported Outcomes (PROs)													
EORTC-QLQ-C30, EORTC NMIBC24,	X	X	X	X			X			X		X*	All PROs will be completed prior to clinical assessments and procedures and treatment administration, with the exception of the PTAB, which will be completed immediately after treatment administration. Laboratory assessments may be done prior to PROs if laboratory assessments are done on a date prior to the rest of the study visit. See
EQ-5D-5L	X	X	X	X			X			X		X*	
PGIS	X	X	X	X			X			X		X*	
PGIC	X	X	X	X			X			X		X*	
TSQ	X			X						X		X*	

Maintenance Period: Cycles 4 to 25 (Cycle = 4 Weeks) for participants without re-induction BCG Re-induction Period for Participants Who Receive BCG Re-induction: Cycles 4-6 ; Maintenance Period: Cycles 7 to 25													
	C4D1	**C5D1**	**C6D1**	**C7D1**	**C8D1**	**C9D1**	**C10D1**	**C11D1**	**C12D1**	**C13D1**	**C14D1**	**C15D1 thru C25D1**	**Notes**
Visit Window (Days)	±7	±7	±7	±7	±7	±7	±7	±7	±7	±7	±7	±7	
PTAB	X			X						X		X*	Section 8.1.2. PROs will be administered in the following order: EORTC QLQ-C30, EORTC NMIBC24, EQ-5D-5L, PGIS, PGIC, TSQ, PTAB. *Completed on Day 1 of Cycles 19 and 25.
Immunogenicity, Pharmacokinetic, and Pharmacodynamic Biospecimen													
Immunogenicity	X		X		X		X			X			Collected pre-dose at each time point for Anti-PF-06801591 Antibody (ADA/NAb) measurement. See Section 8.8.3. Arms A and B only.
Pharmacokinetics	X		X		X		X			X			Collected pre-dose at each time point for PK analysis of PF-06801591. All efforts should be made to obtain PK samples within 2 hours prior to PF-06801591 dosing. See Section 8.5. Arms A and B only.
Whole blood biomarkers	X		X		X		X			X			See Section 8.8.
Plasma and Serum Biomarker Sample	X		X		X		X			X			See Section 8.8.

AE: adverse event, ACTH: adrenocorticotropic hormone, ADA: anti-drug antibodies; BCG: Bacillus Calmette Guérin, BP: blood pressure; CIS: carcinoma in situ; CT: computed tomography, ECG: electrocardiogram, ECOG PS: Eastern Cooperative Oncology Group Performance Status, EORTC-QLQ-C30: European Organisation for Research and Treatment of Cancer Quality of Life Questionnaire–30 (items); EOT: end of treatment; MRI: magnetic resonance imaging, NAb: neutralizing antibodies; NMIBC: non-muscle invasive bladder cancer, PGIC: Patient Global Impression of Change; PGIS: Patient Global Impression of Severity; PK: pharmacokinetics, PTAB: Patient Treatment Administration Burden; Q4W: every 4 weeks; TSQ: Treatment Satisfaction Questionnaire

End of Treatment Visit and Follow-Up Period – Cohort A

	EOT*	Post-Treatment Period			*EOT: End of Treatment visit will take place within 7 days of the last dose of PF-06801591 or BCG (whichever is later) or decision to discontinue both drugs. This includes participants that complete the full 25 cycles of treatment as well as participants that discontinue treatment early. **Safety Follow-Up: All participants enter safety follow-up period at EOT. Visits at 30, 60, and 90 days post-EOT. ***Disease Follow-Up: Participants with no recurrence of high-grade disease, disease progression, or persistence of CIS before EOT will be assessed Q12W for 2 years after randomization and Q24W thereafter until recurrence of high-grade disease or disease progression, consent withdrawal, lost to follow-up, or death. Timing of disease assessment is fixed according to the calendar, starting with randomization and should not be adjusted. ****Survival Follow-Up: Q12W until consent withdrawal, lost to follow-up, death, or end of study (5 yrs from last participant randomized). Sponsor may request that sites complete additional survival follow-up to facilitate planned analyses as needed.
		Safety Follow-Up**	**Disease Follow-Up*****	**Survival Follow-Up******	
Visit Window (Days)	+7	±7	±7	±7	
Physical Examination	X	X			Physical examinations should be performed according to clinical practice. Any abnormalities should be recorded as adverse events. See Section 8.2.1.
Weight	X	X			
Vital Signs	X	X			BP and pulse rate will be performed. Any abnormalities should be recorded as AEs. See Section 8.2.2.
Contraception check	X	X			
ECOG PS	X				
AEs	X	X			Treatment-related SAEs will be reported during the disease follow-up and survival follow-up. See Section 8.3 and Section 10.3.
Concomitant Therapy	X	X			See Section 6.5.
Laboratory					
Hematology	X	X			See Section 10.2 for the list of the tests. Laboratory tests may be performed up to 3 days prior to the scheduled clinic visit, so that results will be available for review before study treatment administration. See Section 8.2.7 for requirements on minimum labs to be reviewed prior to dosing.
Blood Chemistry	X	X			
Coagulation	X				
Urinalysis	X				

	EOT*	Post-Treatment Period			*EOT: End of Treatment visit will take place within 7 days of the last dose of PF-06801591 or BCG (whichever is later) or decision to discontinue both drugs. This includes participants that complete the full 25 cycles of treatment as well as participants that discontinue treatment early. **Safety Follow-Up: All participants enter safety follow-up period at EOT. Visits at 30, 60, and 90 days post-EOT. ***Disease Follow-Up: Participants with no recurrence of high-grade disease, disease progression, or persistence of CIS before EOT will be assessed Q12W for 2 years after randomization and Q24W thereafter until recurrence of high-grade disease or disease progression, consent withdrawal, lost to follow-up, or death. Timing of disease assessment is fixed according to the calendar, starting with randomization and should not be adjusted. ****Survival Follow-Up: Q12W until consent withdrawal, lost to follow-up, death, or end of study (5 yrs from last participant randomized). Sponsor may request that sites complete additional survival follow-up to facilitate planned analyses as needed.
		Safety Follow-Up**	**Disease Follow-Up*****	**Survival Follow-Up******	
Visit Window (Days)	+7	±7	±7	±7	
Pregnancy Test	X	X			Required 30 days (±7 days) after last dose. At Day 90 and Day 180 after EOT, pregnancy status should be discussed (may be done by telephone, unless the participant is visiting the site for other reasons) and pregnancy test can be conducted as necessary. See Section 8.2.8, Section 10.2, and Section 10.4.
Disease Assessments					
CT or MRI	As clinically indicated				CT/MRI/Urogram of the abdomen and pelvis/urinary tract. Imaging performed with contrast agents unless contraindicated for medical reasons. As clinically indicated to confirm and/or rule out distant metastasis. See Section 8.1.1.3 for additional details.
Cystoscopy with or without Biopsy and Cytology		X			Q12W for 2 years after randomization and Q24W thereafter until recurrence of high-grade disease or disease progression, consent withdrawal, lost to follow-up, or death. Same equipment and methods by the same study staff should be used for the duration of the study whenever possible. Disease assessment will include urine cytology and cystoscopy with or without tumor biopsy according to the modalities described in Section 8.1.1.1 and Section 8.1.1.2.
Patient Reported Outcomes (PROs)					
EORTC-QLQ-C30, EORTC NMIBC24,	X	X	X		All PROs will be completed prior to assessments with the exception of the PTAB, which will be completed immediately after treatment administration. Laboratory assessments may be done prior to PROs if laboratory assessments are done on a date prior to the rest of the study visit. If the EOT and last treatment visits are not on the same day, the PTAB assessment does not need to be completed.
EQ-5D-5L	X	X			
PGIS	X	X			
PGIC	X	X			
TSQ	X				

	EOT*	Post-Treatment Period			*EOT: End of Treatment visit will take place within 7 days of the last dose of PF-06801591 or BCG (whichever is later) or decision to discontinue both drugs. This includes participants that complete the full 25 cycles of treatment as well as participants that discontinue treatment early. **Safety Follow-Up: All participants enter safety follow-up period at EOT. Visits at 30, 60, and 90 days post-EOT. ***Disease Follow-Up: Participants with no recurrence of high-grade disease, disease progression, or persistence of CIS before EOT will be assessed Q12W for 2 years after randomization and Q24W thereafter until recurrence of high-grade disease or disease progression, consent withdrawal, lost to follow-up, or death. Timing of disease assessment is fixed according to the calendar, starting with randomization and should not be adjusted. ****Survival Follow-Up: Q12W until consent withdrawal, lost to follow-up, death, or end of study (5 yrs from last participant randomized). Sponsor may request that sites complete additional survival follow-up to facilitate planned analyses as needed.
		Safety Follow-Up**	**Disease Follow-Up*****	**Survival Follow-Up******	
Visit Window (Days)	+7	±7	±7	±7	
PTAB	X				PROs will be administered in following order: EORTC QLQ-C30, EORTC NMIBC24, EQ-5D-5L, PGIS, PGIC, TSQ, PTAB. See Section 8.1.2.
Survival					
Subsequent Anti-cancer Therapy	X	X	X	X	Start date and other details of anti-cancer therapy (including cystectomy) subsequent to the study treatment will be recorded.
Survival Follow-up				X	Visit is a phone call Q12W. See Section 8.2.6.
Immunogenicity and Pharmacodynamic Biospecimen					
Pharmacokinetics	X				Collect the last PK sample at EOT. If EOT is done on the same date as the last dose of PF-06801591, all efforts should be made to obtain PK samples within 2 hours prior to PF-06801591 dosing. Arms A and B only. See Section 8.5.
Immunogenicity	X				Collect the last immunogenicity sample at EOT. See Section 8.8.3. Arms A and B only.

AE: adverse event, ADA: anti-drug antibodies; BP: blood pressure; CT: computed tomography, ECG: electrocardiogram, EORTC-QLQ-C30: European Organisation for Research and Treatment of Cancer Quality of Life Questionnaire–30 (items); EOT: end of treatment; MRI: magnetic resonance imaging, NAb: neutralizing antibodies; NMIBC: non-muscle invasive bladder cancer, PGIC: Patient Global Impression of Change; PGIS: Patient Global Impression of Severity; PK: pharmacokinetics, PTAB: Patient Treatment Administration Burden; SAE: serious adverse event; TSQ: Treatment Satisfaction Questionnaire

Screening and Treatment Period – Cohorts B1 and B2

	Screening	Treatment Period	Notes
		Cycles 1-25 (Cohort B1) **Cycles 1-17 (Cohort B2)**	**Cohort B1: Cycle = 4 weeks** **Cohort B2: Cycle = 6 weeks**
	D -28 to D -1	**D1**	
Visit Window (Days)		**±0 (C1)** **±7** **C2-25 [Cohort B1]** **C2-C17 [Cohort B2]**	
Informed Consent	X	X	Informed consent may be obtained more than 28 days prior to start of study treatment. All screening procedures must be completed within 28 days of registration. The Consent for continuation of treatment at 12 weeks for those participants in Cohort B1 with persistent CIS and Consent for future research will be signed as applicable. Participants must sign consent prior to any trial-specific procedure. See Section 10.1.3.
Tumor and Medical History	X		Detailed information about prior BCG usage, response to prior BCG, and details regarding disease persistence or recurrence will be collected in the CRF. Reasons for subject ineligibility or refusal of radical cystectomy will also be collected. See Section 8 for details.
Physical Examination	X	X	Physical examinations should be performed according to clinical practice. Any abnormalities should be recorded as AEs. See Section 8.2.1.
Weight	X	X	
Vital Signs	X	X	BP and pulse rate will be performed. Any clinically significant abnormalities should be recorded in the eCRF as AEs. See Section 8.2.2.
ECOG PS	X	X	See Section 8.2.3. and Section 10.10.
12-Lead ECG	X	X	Single 12-lead ECG will be collected prior to dosing of PF-06801591 on day 1 of cycles 1, 2, 4, 5, 6. After cycle 6, ECGs will only be required as clinically indicated. See Section 8.2.4 for details.
AEs	X		See Section 8.3 and Section 10.3.
Concomitant Therapy	X		See Section 6.5.
Contraception Check		X	Must be performed on D1 of each cycle. See Section 10.4 for details.
Laboratory			
Hematology	X	X	See Section 10.2. Not necessary to repeat on C1D1 if performed within 7 days prior to C1D1 as part of Screening. Laboratory tests may be performed up to 3 days prior to the scheduled clinic visit, so that results will be available for review before study intervention administration, including C1D1. See Section 8.2.7 for requirements on minimum labs to be reviewed prior to dosing. Coagulation testing should be done on day 1 of cycles 3, 6, 9, 12, 15, 18, 21, and 24 (up to cycle 17 for Cohort B2)

	Screening	Treatment Period	Notes
		Cycles 1-25 (Cohort B1) **Cycles 1-17 (Cohort B2)**	**Cohort B1: Cycle = 4 weeks** **Cohort B2: Cycle = 6 weeks**
	D -28 to D -1	**D1**	
Visit Window (Days)		**±0 (C1)** **±7** **C2-25 [Cohort B1]** **C2-C17 [Cohort B2]**	
Blood Chemistry	X	X	
Coagulation	X	X	
Urinalysis	X	X	Not necessary to repeat on C1D1 if performed within 7 days prior to C1D1 as part of Screening. Urinalysis should be collected on day 1 of cycles 1, 2, 3, 4, 5, 7, and 13 (Cohorts B1 and B2), and 19 and 25 (Cohort B1), and as clinically indicated. See Section 10.2.
Pregnancy Test	X	X	A negative highly sensitive test is required prior to study intervention dosing on Day 1 of all cycles. Results must be available for review prior to dosing. See Section 8.2.8 and Section 10.4. Pregnancy testing after C1D1 per local guidelines.
FSH	X		For female postmenopausal participants under the age of 60 and not using hormonal contraception or HRT, a serum FSH test is required at screening only, to confirm postmenopausal status. FSH is not required for participants not meeting these criteria. See Section 10.2 and Section 10.4.
Hepatitis B and C	X		HBS Ag and HCV Ab tests. If HBS Ag or HCV Ab test is positive, reflex testing must be carried out, as detailed in Section 10.2 Table 5.
ACTH & Thyroid Function Test	X	X	Not necessary to repeat on C1D1 if performed within 7 days prior to C1D1 as part of Screening. ACTH and Thyroid Function Test should be done at cycles 1, 2, 3, 6, 9, 12, 15, 18, 21, 24, 25 (up to cycle 17 for Cohort B2) and as clinically indicated. See Section 10.2 Table 5.
PF-06801591 Administration		X	Administer subcutaneously. See Section 6.1.2.
Disease Assessments			
CT or MRI	X	X	CT/MRI/Urogram of the abdomen and pelvis/urinary tract. Imaging performed with contrast agents unless contraindicated for medical reasons. For Cohort B1, screening imaging must be reviewed by the BICR prior to registration. The same method should be used for the duration of the study. For Cohort B1, imaging should be performed every 24 weeks for 2 years after initiation of study intervention until persistence of CIS, recurrence of high-grade disease or disease progression, consent withdrawal, lost to follow-up, EOT, or death. Additional imaging may be performed as clinically indicated to confirm and/or rule out distant metastasis. For Cohort B2, imaging is done as clinically indicated. See Section 8.1.1.3 and Appendix 9 for additional details.
Cystoscopy, With or Without Biopsy	X	X	Cystoscopy should be performed for disease assessment on day 1 of cycles 4, 7, 10, **14**, 16, 19, 22, 25 for Cohort B1 and day 1 of cycles 3, 5, 7, 9, 11, 13, 15 and 17 for Cohort B2. At most disease assessments, biopsy may or may not be required, depending on outcome of cystoscopy and cytology. Same equipment and methods by the same study staff should be used for the duration of the study whenever possible. See Section 8.1.1.1 and Appendix 9.

	Screening	Treatment Period	Notes
		Cycles 1-25 (Cohort B1) **Cycles 1-17 (Cohort B2)**	**Cohort B1: Cycle = 4 weeks** **Cohort B2: Cycle = 6 weeks**
	D -28 to D -1	**D1**	
Visit Window (Days)		**±0 (C1)** **±7** **C2-25 [Cohort B1]** **C2-C17 [Cohort B2]**	
Cytology	X	X	For Cohort B1, screening cytology must be reviewed by the BICR prior to registration. Urine cytology should be performed for disease assessment on day 1 of cycles 4, 7, 10, **14,** 16, 19, 22, 25 for Cohort B1 and day 1 of cycles 3, 5, 7, 9, 11, 13, 15 and 17 for Cohort B2. Same equipment and methods by the same study staff should be used for the duration of the study whenever possible. See Section 8.1.1.2.
Tumor Tissue			
Tumor Tissue Sample from Most Recent TURBT	X		See Section 8.8.1. For Cohort B1 tumor tissue sample must be reviewed by the BICR prior to registration.

AE: adverse event, ACTH: adrenocorticotropic hormone, BP: blood pressure; CT: computed tomography, ECG: electrocardiogram, ECOG PS: Eastern Cooperative Oncology Group Performance Status, FSH: follicle-stimulating hormone, HRT: hormone replacement therapy, MRI: magnetic resonance imaging, NMIBC: non-muscle invasive bladder cancer, TURBT: transurethral resection of bladder tumor

End of Treatment Visit and Follow-Up Period – Cohorts B1 and B2

	EOT*	Post-Treatment Period	***EOT:** End of Treatment visit will take place within 7 days of the last dose of PF-06801591 or decision to discontinue PF-06801591. This includes participants that complete the full 25 cycles (Cohort B1) or 17 cycles (Cohort B2) of treatment as well as participants that discontinue treatment early. ****Safety Follow-Up:** All participants enter safety follow-up period at EOT. Visits at 30, 60, and 90 days post-EOT.
		Safety Follow-Up**	
Visit Window (Days)	+7	±7	
Physical Examination	X	X	Physical examinations should be performed according to clinical practice. Any abnormalities should be recorded in the eCRF as adverse events. See Section 8.2.1.
Weight	X	X	
Vital Signs	X	X	BP and pulse rate will be performed. Any abnormalities should be recorded in the eCRF as AEs. See Section 8.2.2.
Contraception Check	X	X	See Section 10.4.
ECOG PS	X		See Section 10.10.
AEs	X	X	Treatment-related SAEs will be reported during the disease follow-up and survival follow-up. See Section 8.3 and Section 10.3.
Concomitant Therapy	X	X	See Section 6.5.
Hematology	X	X	See Section 10.2. Laboratory tests may be performed up to 3 days prior to the scheduled clinic visit, so that results will be available for review before study intervention administration. See Section 8.2.7 for requirements on minimum labs to be reviewed prior to dosing.
Blood Chemistry	X	X	
Coagulation	X		
Urinalysis	X		
Pregnancy Test	X	X	Required 30 days (±7 days) after last dose. At Day 90 and Day 180 after EOT, pregnancy status should be discussed (may be done by telephone, unless the participant is visiting the site for other reasons) and pregnancy test can be conducted as necessary. See Section 8.2.8, Section 10.2, and Section 10.4.

AE: adverse event, BP: blood pressure; CT: computed tomography, ECG: electrocardiogram, EOT: end of treatment; MRI: magnetic resonance imaging, NMIBC: non-muscle invasive bladder cancer, SAE: serious adverse event

2. INTRODUCTION

PF-06801591 is a humanized, hinge region stabilized immunoglobulin G4 (IgG) monoclonal antibody (mAb) specific for human PD-1 that can selectively bind to human PD-1 and block the interaction between PD-1 and PD-L1/PD-L2. Extensive preclinical and clinical research have demonstrated that anti-PD-1/PD-L1 agents are efficacious in several tumor types and these agents have been utilized in clinical practice since 2014, when anti-PD-1 agent pembrolizumab was approved by the US FDA for treatment of advanced melanoma. Anti-PD-1/PD-L1 agents have also demonstrated clinical activity in the treatment of advanced UC with 5 drugs (nivolumab, atezolizumab, pembrolizumab, durvalumab, and avelumab) currently approved for this indication.[25,26,27,28,29]

UC includes tumors originating from the urothelial cells lining the bladder, renal pelvis, ureter, and urethra.[9] Of these, BC accounts for more than 90% of UC,[9] and is the tenth most prevalent cancer worldwide, with approximately 500,000 new cases diagnosed and 200,000 deaths attributed to this disease each year.[30] Approximately 75% of cases of BC are non-muscle invasive bladder cancer (NMIBC) and the current standard of care (SOC) for patients with high-risk NMIBC is transurethral resection of the bladder tumor (TURBT) followed by intravesical instillation of Bacillus Calmette-Guerin (BCG).[7] Whilst treatment with BCG has been shown to reduce the risk of tumor recurrence, BCG therapy will eventually fail in approximately 40% of patients with NMIBC resulting in recurrence or progression to more advanced disease; thus, alternative treatments are urgently required to improve the outcome.[7,32,33]

2.1. Study Rationale

Overall, incidence and mortality for bladder cancer (BC) has changed very little over the past 20 years.[1] Vaccination using BCG was the first Food and Drug Administration (FDA) approved immunotherapy indication in the 1980s and for patients with high-risk non-muscle invasive bladder cancer (NMIBC) after transurethral resection of the bladder tumor (TURBT), induction with BCG followed by maintenance still represents the standard of care (SOC).[7] While treatment with BCG has been shown to reduce the risk of tumor recurrence, approximately 40% of patients with NMIBC will eventually have disease recurrence or progression despite BCG therapy;[32] thus, alternative treatments are urgently required to improve the outcome.[33]

Increased programmed death – ligand (PD-L) 1 expression was observed in bladder cancer cells in response to BCG treatment both in vitro and in vivo preclinical models and the combination of BCG and anti-PD-L1 agent induced an antitumor immune response.[2] In addition, the combination showed higher tumor growth inhibition and prolonged survival as compared to either agent alone.

Sasanlimab (PF-06801591) is a humanized, monoclonal antibody (mAb) specific for human programmed death – 1 (PD-1) that blocks the interaction between PD-1 and PD-L1/PD-L2. PF-06801591 administered at 300 mg subcutaneous (SC) every 4 weeks has been evaluated in the Phase 1 Study B8011001 in participants with advanced solid tumors and at 600 mg SC every 6 weeks in patients with advanced malignancies in study B8011007. The clinical safety

data available to date suggest an acceptable safety profile, aligned with other anti-PD-1/PD-L1 agents, and also preliminary evidence of clinical efficacy aligned with other anti-PD-1/PD-L1 agents in patients with advanced urothelial cancer (UC).

The role of PD-L1 expression level as a predictive factor of response to BCG therapy in patients with high-risk NMIBC was recently suggested in a retrospective evaluation suggesting that higher PD-L1 expression level is associated with failure of BCG treatment.[3] Supportive of this hypothesis, pembrolizumab showed promising activity in Keynote-057, a Phase 2 study in participants with high-risk NMIBC unresponsive to BCG. In an analysis of 101 participants with carcinoma in situ (CIS), a complete response (CR) rate of 41% (95% confidence interval [CI]: 30.7, 51.1) was reported with a median duration of CR of 16.2 months (95% CI: 6.7, 36.2). The most common (>5%) treatment-related adverse events (AEs) included diarrhea (11%), fatigue (11%), pruritis (11%), hypothyroidism (7.0%), maculopapular rash (6%), rash, hyperthyroidism, and nausea (each 5%), which was consistent with the known adverse event (AE) profile of pembrolizumab in the advanced disease setting.[4]

2.1.1. Study Rationale for the BCG-Naive Cohort (Cohort A)

A Phase 1 study of pembrolizumab in combination with BCG in participants with high-grade NMIBC persisting or recurring following at least 2 courses of intravesical therapy or 1 course of BCG (induction and maintenance), showed that the combination regimen of pembrolizumab (at 100 mg and 200 mg fixed doses) and BCG was well tolerated.[6] Fatigue, dysuria, spasm, urgency, sensitivity and frequency were the most frequently reported AEs, with all AEs reported as Grade 1 or 2.[6] Of the first 9 participants enrolled, 7 participants (78%) had no evidence of disease in the bladder at 19 weeks. These data suggest an improved clinical activity over each of the agents alone, considering BCG alone is expected to have minimal or no clinical activity in the treatment setting and pembrolizumab showed a CR rate 41% in a similar population.[4]

To treat patients with NMIBC appropriately, treatment considerations include the European Organisation for Research and Treatment of Cancer (EORTC) risk table scores of recurrence and progression.[7] For patients with high-risk NMIBC, the current standard of care is TURBT followed by intravesical BCG.[7] The standard schedule for BCG is induction (once weekly for 6 weeks) followed by maintenance for a minimum of 1 year. Full-dose BCG maintenance, administered once per week for 3 weeks, starting at 3 months after the first BCG dose of induction course (ie, 6 weeks after completion of induction BCG), and at 6 months, and then every 6 months, as used in the Southwest Oncology Group (SWOG) 8507 and European Organization for Research and Treatment of Cancer (EORTC) 30911 and 30962 trials,[8,11] is the most appropriate maintenance schedule. Indeed, addition of maintenance to induction treatment with BCG according to the administration schedule described in the study is currently recommended in the European Association of Urology (EAU) and National Comprehensive Cancer Network (NCCN) guidelines[7,9] because it has proven to reduce both progression and recurrence of the disease.[10]

The optimal duration of BCG maintenance therapy has been investigated in the European Organization for Research and Treatment of Cancer Genito-Urinary (EORTC-GU) Study

30962.[11] In this study, full dose BCG maintenance for 3 years was associated with a reduction in recurrence (hazard ratio [HR] = 1.61, 95% CI: 1.13-2.30, p = 0.009) in high-risk participants as compared with 1 year of BCG maintenance; however, there were no differences in progression or survival.[11] For this reason, the benefit of the 2 additional years of maintenance should be weighed against its additional costs, inconveniences, and tolerability. Therefore, the study design for Cohort A of B8011006 includes a BCG maintenance duration of up to 2 years (Arm A: BCG plus PF-06801591, Arm C: BCG alone). Considering the expected improved clinical activity of the PF-06801591 plus BCG combination regimen, investigation of PF-06801591 plus BCG induction only, is justified (Arm B).

Based on preclinical and clinical data, an intervention in BCG-naïve participants with high-risk NMIBC, with PF-06801591 in combination with BCG induction therapy (with or without maintenance therapy) may provide a greater benefit with longer event-free survival and reduction in the rate of subsequent cystectomy as compared to SOC BCG treatment. In addition, PF-06801591 is administered subcutaneously (SC) every 4 weeks which is expected to reduce burden for the participants and for the healthcare system.

2.1.2. Study Rationale for the BCG-Unresponsive Cohort (Cohorts B1 and B2)

BCG treatment fails in approximately 40% of patients with high-risk NMIBC [32] and limited therapeutic options are available for those with BCG-unresponsive disease after adequate BCG therapy defined as a minimum of 5 out of 6 doses of an induction course followed by either 2 out of 6 doses of a re-induction course, or 2 of 3 doses of a maintenance course.[12] Currently, a shortage of BCG supply is ongoing globally, and recommendations aimed to optimize the administration of BCG and prioritize its use in patients with high-risk NMIBC have been issued by several organizations such as the AUA and have been included in the most recent version of the NCCN guidelines.[9] Some of the proposed BCG schedule modifications consist of a reduction in the dose of BCG intravesical instillations. Specifically, the AUA and the NCCN guidelines recommend prioritizing use of full dose BCG for induction and either do not administer maintenance therapy or split the BCG dose to 1/3 or 1/2.[9,13] The EORTC 30962 study assessed the impact of a reduced dose of BCG (1/3 vs full dose in both induction and maintenance) on treatment outcomes in patients with high-risk NMIBC. No difference in progression or survival rate between 1/3 and full dose BCG was reported even if 1/3 BCG dose was associated with a 5-year disease-free rate of 58.5% as compared to 61.7% for BCG full dose (HR = 1.15; 95% CI: 0.98–1.35; p = 0.045).[11] Considering these results, the persisting shortage of BCG supplies, and based on the NCCN and AUA treatment recommendations, administration of a reduced dose (1/3 or 1/2) during the prior maintenance course is considered as adequate prior BCG therapy. Administration of full dose BCG during the prior induction BCG course will be required.

Patients with BCG-unresponsive disease are unlikely to respond to further BCG therapy, which is associated with an increased risk of progression, and radical cystectomy is therefore the standard and preferred option according to the treatment guidelines.[13,14] Radical cystectomy is considered curative for some patients, but it is associated with significant morbidity and mortality.[15] The overall 90-day complication rates are up to 28%-64% [16,17] and the majority of early complications following radical cystectomy include gastrointestinal

(29%), infection (25%), intestinal obstruction (23%), wound-related complications (15%), and deep vein thrombosis (4.7%); late complications include gastrointestinal bowel obstruction, urinary tract infection, deterioration in renal function, calculi formation, voiding dysfunction, and metabolic complications.[15, 17]

Non-surgical treatment options for patients with BCG-unresponsive NMIBC are currently limited. Valrubicin is approved by the US but response rates are low (18%-21%) and not durable.[18, 19] A recent meta-analysis reported data from 42 studies in 2254 patients with NMIBC treated after BCG failure with 24 different treatments, including approved and investigational agents. The median CR rates in the treatment of CIS-containing tumors were 26%, 17%, and 8% at 6, 12, and 24 months, respectively.[20] In the studies that enrolled patients with papillary disease without CIS the median recurrence-free rates were 67%, 44%, and 10% at 6, 12, and 24 months, respectively.[20] Similar results were reported from another meta-analysis that included 4 randomized-controlled studies and 24 single-arm studies that evaluated different bladder-sparing treatment options: the pooled 12-month response rates were 24% (95% CI: 16-32%) for trials with 2 or more prior BCG courses and 36% (95% CI: 25-47%) for those with 1 or more prior BCG courses.[21] Even considering the heterogeneity of the patients population, the different definitions of BCG failure, and the different study designs, these results define the high unmet need for new treatment options treatments to improve clinical outcomes in patients with NMIBC that recurs after initial BCG treatment.

Based on the results of the Keynote-057 study[4], pembrolizumab has been recently approved by the FDA for the treatment of patients with BCG-unresponsive CIS who are ineligible for or decline to undergo radical cystectomy.[22] In the Keynote-057 study, after a median duration of follow-up of 36.4 months (IQR 32.0 – 40.7), the CR rate was 41% (95% CI, 30.7-51.1) with a median duration of CR of 16.2 months (95% CI, 6.7 – 36.2).[4] In addition, atezolizumab has shown signs on clinical efficacy in patients with BCG-unresponsive CIS [CR rate at 3 months was 41.1% (95% CI, 29.7-53.2)][53] and in patients with BCG-unresponsive papillary disease [EFS rate at 18 months was 45% (95% CI, 34-57)].[54]

PF-06801591 300 mg SC Q4W showed a safety and efficacy profile aligned to the other anti-PD-1/PD-L1 agents in patients with advanced UC and NSCLC[23] and PF-06801591 600 mg SC Q6W showed a safety profile consistent with the B8011001 study and with the safety profiles of other PD-1 agents (data summarized in IB). Both dosing regimens offer the convenience of subcutaneous administration. Indeed, real world evidence of oncology biologics show that subcutaneous administration reduces healthcare resource utilization and associated costs by saving time in drug preparation and administration compared to intravenous (IV) therapy. SC administration also reduces time spent in the infusion chair and in caregiver assistance, while patients report better quality of life and preference for SC therapy over IV therapy.[24] In addition, the Q6W dosing frequency of PF-06801591, which will be evaluated in Cohort B2, explores an extended dosing interval for PF-06801591 to further reduce the burden for the participants, their caregivers and the healthcare system.

In summary, an unmet need exists for new innovative bladder-sparing treatment options for patients with BCG-unresponsive NMIBC that delay disease recurrence, progression and radical cystectomy. PF-06801591 may provide greater clinical benefit with higher CR rate,

durable responses and longer event-free survival relative to currently approved intravesical chemotherapies (valrubicin) and subcutaneous administration is expected to reduce burden for the participants and for the healthcare system while maintaining a safety and efficacy profile aligned to other anti-PD-1/PD-L1 agents administered intravenously (pembrolizumab).

Cohorts B1 and B2 of B8011006 will include participants with BCG-unresponsive NMIBC. Cohort B1 will include participants with CIS (with or without Ta/T1 papillary disease) and Cohort B2 will include participants with high-grade Ta/T1 papillary disease only.

As of 31 August 2022, enrollment in Cohorts B1 and B2 was closed by the sponsor for business strategy reasons. Participants that have already been enrolled into Cohorts B1 and B2 may continue treatment and study procedures and assessments per the Schedule of Activities per the Cohorts B1 and B2 SoA.

2.2. Background

2.2.1. Clinical Background

Study B8011001

Early data on pharmacokinetics (PK), safety, and efficacy of PF-06801591 are available from B8011001, an ongoing Phase 1, open-label, dose escalation and expansion study in participants with locally advanced or metastatic melanoma, squamous cell carcinoma of the head and neck (SCCHN), ovarian cancer, sarcoma, non-small cell lung cancer (NSCLC), urothelial carcinoma (UC) or other solid tumors. The study was divided into a dose escalation phase, and a dose expansion phase. The dose escalation phase evaluated 4 pre-specified intravenous (IV) dose levels (0.5, 1, 3, and 10 milligram/kilogram (mg/kg) administered every 3 weeks [Q3W]), and 1 SC dose level (300 mg administered every 4 weeks [Q4W]). In the dose expansion phase of the study, 1 SC dose level (300 mg Q4W) was explored. No dose limiting toxicities (DLTs) were observed and no maximum tolerated dose (MTD) was identified during the dose escalation phase of the study.

During the dose expansion phase 106 participants (68 participants with NSCLC and 38 participants with UC) were evaluated, who were anti-PD-1/anti-PD-L1 treatment-naïve and who had progressive disease (PD) on or were intolerant to systemic therapy or for whom SOC systemic therapy was refused or unavailable. Participants with UC could have received up to 2 lines of prior systemic therapies for locally advanced or metastatic disease. The eligible participants had adequate renal, bone marrow, liver, and cardiac function, with Eastern Cooperative Oncology Group (ECOG) performance status 0 or 1. All participants received 300 mg of PF-06801591 SC every 4 weeks.

Safety during the dose expansion phase: Of 106 participants exposed to 1 or more 300 mg SC injections of study drug, 103 participants (97.2%) experienced at least one treatment-emergent AE (TEAE) while on the study. The most common AEs (experienced by ≥10% of participants) were anemia (n = 24, 22.6%) followed by disease progression (n = 20, 18.9%), dyspnea (n = 14, 13.2%), decreased appetite (n = 13, 12.3%), asthenia, fatigue, and amylase increased (n = 12 each , 11.3%), and aspartate aminotransferase increased, hyperthyroidism,

and pruritis (n = 11 each, 10.4%). A total of 60 participants (56.6%) had a least one treatment-related AE (TRAE) while on study. The most common TRAEs (experienced by >5% of participants) were hyperthyroidism (n = 11, 10.4%), lipase increased and pruritis (n = 7 each, 6.6%), and amylase increased, hypothyroidism, and anemia (n = 6 each, 5.7%). Ten participants had maximum Grade 3 TRAEs and 2 had maximum Grade 4 TRAE. Grade 3 TRAEs were lipase increased, amylase increased (n = 2 each, 1.9%), blood alkaline phosphatase increased, decreased appetite, hypermagnesemia, pneumonitis, ageusia, anosmia, and jaundice (n = 1 each, 0.9%). There were 3 Grade 4 TRAEs of lipase increased, white blood cell count decreased, and neutrophil count decreased (n = 1 each, 0.9%). One Grade 5 treatment-related arrhythmia was reported (n = 1, 0.9%).

Serious Adverse Events (SAEs): Across both phases of the B8011001 study, there were 122 SAEs reported in 78 participants and 7 treatment-related SAEs reported: pneumonitis (n = 3), death (n = 2), arrythmia and cognitive disorder (n = 1 each). In the dose expansion phase, a fatal AE of arrhythmia occurred in a PPD-year old PPD subject approximately 47 days after starting treatment with SC PF-06801591 for UC. Medical history included PPD The subject was hospitalized at an institution outside the study site due to third degree heart block. Details of the hospital admission were only verbally reported due to refusal of the treating institution to release further information. Elevated levels of troponin, transaminases and creatinine were reported by the treating hospital although serious electrolyte abnormalities, infection, or ischemic heart disease were reportedly excluded. The subject received a pacemaker implant on Day 13 of the hospitalization, and unspecified complications were reported. One day later, the subject died. The reason for death was unclear, and no autopsy was performed. The Investigator considered the event was possibly related to PF-06801591. The Sponsor considered the event unrelated to PF-06801591 as there is insufficient information regarding the clinical course of events to support a causal relationship and that complications successive to pacemaker placement may provide an alternative explanation for the event.

Efficacy during the dose expansion phase: The objective response rate (ORR) in the UC cohort was 21.1% (n=8 confirmed partial response [PR], 95% CI: 9.6, 37.3%), consistent with historical data reported for other anti-PD-1 treatments in similar therapeutic setting. In the NSCLC cohort the ORR was 19.1% (n=13 confirmed PR, 95% CI: 10.6, 30.5%). This efficacy profile also is aligned with the one reported for other anti-PD-1 treatments in similar therapeutic setting.[34,35,36]

Summary of Clinical Pharmacology: PF-06801591 demonstrated PK characteristics typical of IgG4 monoclonal antibodies. Over the Q3W IV dose range of 0.5 -10 mg/kg evaluated in Study B8011001, increases in PF-06801591 exposures (C_{max}, C_{trough} and AUC) were linear and dose proportional. Following 300 mg Q4W SC dosing, median T_{max} was approximately 8 days, $t_{1/2}$ was approximately 13 days, and steady-state was reached by Cycle 4 (week 12) with approximately 2-fold accumulation. Steady-state concentrations following 300 mg SC Q4W fell within the concentration range observed following the 1 mg/kg and 3 mg/kg Q3W IV doses. Population PK-derived clearance was 0.158 L/day with no evidence of variance over time. Incidence of anti-PF-06801591 antibody formation was low (<10%) across both IV and SC dosing regimens.

Study B8011007

The feasibility of increasing time between PF-06801591 SC administration from Q4W to Q6W to further improve dosing convenience for patients, their caregivers, and the healthcare system, is being investigated in Study B8011007. This study consists of 2 parts: Phase 1b (dose escalation and dose expansion) for participants with advanced malignancies, and a Phase 2 in participants with NSCLC. PF-06801591 monotherapy is administered in both phases as either 300 mg SC Q4W or 600 mg SC Q6W. As of 01 July 2021, 144 participants have been treated: 57 with 300 mg SC Q4W (n = 16 in the Phase 1b and n = 41 in the Phase 2) and 87 with 600 mg SC Q6W (n = 7 in the Phase 1b and n = 80 in the Phase 2). In Phase 1 of the study, dose escalation has been completed and currently dose expansion is ongoing. No DLT has been reported so far and both treatment regimens were well tolerated. The Phase 2 completed enrollment, and safety and efficacy evaluations are ongoing. As of the data cut-off date (01 July 2021), in Phase 2 300 mg SC Q4W cohort (n = 41), 35 (85.4%) of the 41 participants reported TEAEs. The most commonly reported TEAEs in ≥10% participants were: dyspnea, decreased appetite, and anemia in 7 (17.1%) participants, asthenia in 6 (14.6%) participants, and chest pain in 5 (12.2%) participants. In Phase 2 600 mg SC Q6W cohort (n = 80), 59 (73.8%) participants reported TEAEs. The most commonly reported TEAE in ≥10% participants was dyspnea in 9 (11.3%) participants. No increase in frequency of TEAEs was observed in the 600 mg SC Q6W cohorts relative to the 300 mg Q4W cohorts. Further detailed information is summarized in the IB. Based on preliminary analyses, the overall safety profiles across the two treatment regimens were similar and the safety profile in this B8011007 study (both treatment regimens) is consistent with that observed in Study B8011001, and with the safety profiles of other PD-1 agents. No new safety signals have been identified. Although efficacy data was immature at data cut off, currently no clinically meaningful differences have been observed between the two dosing regimens and there is no expectation that the 600 mg SC Q6W regimen will result in unexpected safety concerns or a compromise in efficacy.

2.2.2. Preclinical Safety and Efficacy

Detailed information about the preclinical data for PF-06801591 may be found in the Investigator's Brochure.[37]

2.3. Benefit/Risk Assessment

The benefit risk relationship has been carefully considered in the planning of this study.

PF-06801591 administered at 300 mg SC every 4 weeks has been evaluated in the Phase 1 study B8011001 in participants with advanced solid tumors and 600 mg SC every 6 weeks in the Phase 1/2 study B8011007 in patients with advanced malignancies as described in Section 2.2.1. The clinical safety data available to date with single agent PF-06801591 suggest an acceptable safety profile with most of the observed AEs in line with those expected in participants with advanced solid tumors or with similar class effects of mAbs blocking the PD-1/PD-L1 axis. Immune-related AEs (irAEs) have been identified as important risks for PF-06801591 and risk mitigation measures have been implemented in all ongoing clinical studies, including this study. These measures include guidelines for

treatment interruption and discontinuation in case of toxicities, and guidelines for steroid treatment implementation. In the same study PF-06801591 has shown preliminary evidence of clinical activity aligned to other anti-PD-1/PD-L1 single agents in participants with advanced UC.

Additionally, a Phase 1 study of pembrolizumab in combination with BCG in participants with high-grade NMIBC persisting or recurring following at least 2 courses of intravesical therapy or one course of BCG (induction and maintenance) showed that the combination was well tolerated and preliminary evidences of clinical activity were observed (Section 2.1).

Intravesical BCG administration is currently SOC for the patient population eligible for this study. Bladder irritability symptoms are commonly expected. Most of the adverse reactions from BCG instillation, such as urinary frequency, burning, mild malaise, and low-grade fever, are a result of the immune stimulation by BCG that is required to effectively eradicate cancer cells.[38] The rarely occurring systemic BCG infections are almost invariably associated with systemic absorption of BCG. By excluding patients with active tuberculosis, withholding BCG when participants have cystitis, previous high fever, or most importantly, traumatic catheterization, systemic absorption of BCG can be avoided, and systemic reactions can be nearly eliminated.[39]

The safety profile of BCG is distinct from that of PF-06801591 with limited overlapping toxicities so exacerbation of the toxicities related to both agents is not expected when administered in combination. In order to conduct a preliminary assessment of the safety profile of PF-06801591 plus BCG regimen, a review of safety data will be performed by an external data monitoring committee (EDMC) approximately 6 weeks after 20 participants in each of the 3 treatment arms have been randomized and received at least one dose of study treatment (Section 4.1). The enrollment will continue during EDMC review. The EDMC will convene to monitor safety in the study (Cohort A only) approximately every 6 months thereafter. The EDMC will also review cumulative safety data during the study conduct as well as review the futility interim analysis data from Cohort A for EFS (see Section 9.5.1).

Based on the manageable safety profiles of PF-06801591 and BCG and the anticipated enhanced anti-tumor activity described in Section 2.1, the benefit-risk assessment of PF-06801591 given in combination with BCG (induction and maintenance or induction only) is expected to be favorable and it is considered appropriate to proceed with the proposed clinical investigation in participants with high-risk NMIBC.

More detailed information about the known and expected benefits and risks and reasonably expected adverse events of PF-06801591 may be found in the SRSD, which is the Investigator's Brochure (IB) for PF-06801591.[37] For additional information about BCG refer to the current local product label. TICE USPI[40] will serve as SRSD for additional safety reporting that is required by the health authority in Japan.

3. OBJECTIVES, ESTIMANDS AND ENDPOINTS

3.1. BCG-Naïve Cohort (Cohort A)

Objectives	Endpoints
Primary	
• To demonstrate that PF-06801591 + BCG (induction and maintenance) is superior to BCG (induction and maintenance) in prolonging event-free survival (EFS) in participants with high-risk NMIBC.	• EFS as assessed by the investigator
Key Secondary	
• To demonstrate that PF-06801591 + BCG (induction) is superior to BCG (induction and maintenance) in prolonging EFS in participants with high-risk NMIBC.	• EFS as assessed by the investigator
• To demonstrate that PF-06801591 + BCG (induction and maintenance) is superior to BCG (induction and maintenance) in prolonging overall survival (OS) in participants with high-risk NMIBC.	• OS
• To demonstrate that PF-06801591 + BCG (induction) is superior to BCG (induction and maintenance) in prolonging OS in participants with high-risk NMIBC.	• OS
Secondary	
• To estimate the complete response (CR) rate of PF-06801591 + BCG (induction and maintenance or induction) and BCG (induction and maintenance) in participants with CIS at randomization.	• CR as assessed by the investigator (in participants with CIS at randomization)
• To evaluate the duration of CR of PF-06801591 + BCG (induction and maintenance or induction) and BCG (induction and maintenance) in participants with CIS at randomization	• Duration of CR for participants with CR as assessed by the investigator (in participants with CIS at randomization)

Objectives	Endpoints
• To evaluate the time to recurrence of low-grade disease of PF-06801591 + BCG (induction and maintenance or induction) and BCG (induction and maintenance) in participants with high-risk NMIBC.	• Time to recurrence of low-grade disease as assessed by the investigator
• To evaluate the time to cystectomy of PF-06801591 + BCG (induction and maintenance or induction) and BCG (induction and maintenance) in participants with high-risk NMIBC.	• Time to cystectomy
• To evaluate the disease-specific survival (DSS) of PF-06801591 + BCG (induction and maintenance or induction) and BCG (induction and maintenance) in participants with high-risk NMIBC.	• DSS as assessed by the investigator
• To evaluate the overall safety profile of PF-06801591+BCG (induction and maintenance or induction) and BCG (induction and maintenance) in participants with high-risk NMIBC.	• AEs as characterized by type, severity (as graded by National Cancer Institute Common Terminology Criteria for Adverse Events [NCI CTCAE] v5.0), timing, seriousness, and relationship to study therapy. Laboratory abnormalities as characterized by type, severity (as graded by NCI CTCAE v5.0), and timing
• To assess the effects of PF-06801591+BCG (induction and maintenance or induction) and BCG (induction and maintenance) on patient-reported health-related quality of life in participants with high-risk NMIBC.	• Health-related quality of life as measured by: 1) EORTC QLQ-C30 (European Organization for Treatment of Cancer Quality of Life Questionnaire), 2) EORTC QLQ-NMIBC24, 3) PTAB (Patient Treatment Administration Burden Questionnaire)
• To characterize the PK of PF-06801591+BCG (induction and maintenance or induction).	• C_{trough} of PF-06801591 when in combination with BCG (induction and maintenance or induction); Arms A and B only.
• To evaluate the immunogenicity of PF-06801591+BCG (induction and maintenance or induction).	• ADAs; NAbs of PF-06801591 when in combination with BCG (induction and maintenance or induction); Arms A and B only.

Objectives	Endpoints
• To evaluate PD-L1 expression in pre-treatment tumor tissue that may aid in the identification of a participant subpopulation most likely to benefit from treatment with PF-06801591 + BCG (induction and maintenance or induction).	• Tumor sample biomarker status based on PD-L1 expression (high or low)
Tertiary/Exploratory	
• To assess the effects of PF-06801591+BCG (induction and maintenance or induction) and BCG (induction and maintenance) on patient reported outcomes (PROs) in participants with high-risk NMIBC.	• Health state utilities as measured by the Euro Qol 5 Dimension (EQ5D-5L) & VAS • Overall assessment of disease severity as measured by the Patient Global Impression of Severity (PGIS) • Overall assessment of change as measured by the Patient Global Impression of Change (PGIC) • Patient satisfaction as measured by the Treatment Satisfaction Questionnaire (TSQ)
• To explore the predictive and pharmacodynamic characteristics of peripheral blood and additional tumor tissue biomarkers that may be relevant to the mechanism of action of, or resistance to, treatment with PF-06801591 + BCG (induction and maintenance or induction), including but not limited to biomarkers related to antitumor immune response or target modulation.	• Peripheral blood and additional tumor tissue biomarkers consisting of the levels of cells, deoxyribonucleic acid (DNA), ribonucleic acid (RNA), or proteins that may be related to antitumor immune response or disease progression.

Estimands

This section defines the estimands associated with the primary and key secondary endpoints of Cohort A of the study.

Table 2 (Section 9.1.1) defines the possible clinical outcomes for the EFS evaluation. The clinical definitions of recurrence of high-grade disease, progressive disease, persistence of CIS, recurrence of low-grade disease and CR are included in Section 10.9. In participants with CIS at randomization "persistence of CIS" is defined as persistence of CIS after induction or, if re-induction is administered, after re-induction. Persistence of CIS after induction with CR after re-induction is not considered persistence of CIS. The censoring and

event date options to be considered for the EFS analyses are presented in Table 3 (Section 9.1.1).

Primary Estimand (EFS for Arm A vs Arm C) and Key Secondary Estimand (EFS for Arm B vs Arm C): treatment effect, estimated based on data from all randomized participants, of each experimental arm (Arm A and Arm B) on EFS compared to Arm C from randomization to the earliest of recurrence of high-grade disease, progression of disease, persistence of CIS, or death regardless of tolerability, duration of study treatment, or initiation of subsequent anti-cancer therapy. The date of the event (event as defined in Table 2) is the date of disease assessment documenting recurrence of high-grade disease, progression of disease, persistence of CIS (applicable only to participants with CIS at randomization), or death, whichever occurs earlier. The date of persistence of CIS is the earliest date when persistence of CIS is observed, if CR is not observed after re-induction.

- Variable: EFS defined as the time from randomization until recurrence of high-grade disease, progression of disease, persistence of CIS or death due to any cause, whichever occurs first.
- Censoring: see Table 3.
- Population-level summary measure: hazard ratio for EFS including all randomized participants.

Supportive Estimand 1 (EFS): treatment effect, estimated based on data from all randomized participants, of each experimental arm (Arm A and Arm B) on EFS compared to Arm C from randomization to the earliest of recurrence of high-grade disease, progression of disease, persistence of CIS, or death, regardless of tolerability, duration of study treatment or initiation of subsequent anti-cancer therapy. The date of the event (event as defined in Table 2) is the date of disease assessment documenting recurrence of high-grade disease, progression of disease, date of randomization for participants with persistent CIS (applicable only to participants with CIS at randomization), or death, whichever occurs earlier.

- Variable: EFS defined as the time from randomization until recurrence of high-grade disease, progression of disease, persistence of CIS, or death due to any cause, whichever occurs first.
- Censoring: see Table 3
- Population-level summary measure: hazard ratio for EFS including all randomized participants.

Supportive Estimand 2 (EFS): treatment effect of each experimental arm (Arm A and Arm B) on EFS compared to Arm C from randomization to the earliest of recurrence of high-grade disease, progression of disease, persistence of CIS, or death regardless of tolerability, duration of study treatment, or initiation of subsequent anti-cancer therapy. Data from randomized participants who do not meet per-protocol criteria as defined below are excluded.

The date of the event (event as defined in Table 2) is the date of disease assessment documenting recurrence of high-grade disease, progression of disease, persistence of CIS (applicable only to participants with CIS at randomization), or death, whichever occurs earlier. The date of persistence of CIS is the earliest date when persistence of CIS is observed, if CR is not observed after re-induction.

- Variable: EFS defined as the time from randomization until recurrence of high-grade disease, progression of disease, persistence of CIS, or death due to any cause, whichever occurs first.
- Censoring: see Table 3
- Population-level summary measure: hazard ratio for EFS excluding randomized participants who did not receive at least 1 dose of study drug, did not meet inclusion criteria 2 or 3, or met exclusion criteria 1 or 2.

Key Secondary Estimand (OS): treatment effect, estimated based on data from all randomized participants, of each experimental arm (Arm A and Arm B) on OS compared to Arm C regardless of tolerability, duration of study treatment, initiation of subsequent anti-cancer therapy or participant's request to discontinue study procedures.

- Variable: OS
- Censoring: data for participants not known to have died are censored at the time of last contact.
- Population-level summary measure: hazard ratio for OS, including all randomized participants.

3.2. BCG-Unresponsive Cohorts (Cohorts B1 and B2)

Due to the decision to close enrollment in Cohorts B1 and B2, the Cohort B1 and B2 study objectives are no longer required.

Primary Objectives	Primary Endpoints
• To estimate the CR rate of PF-06801591 in participants with BCG-unresponsive CIS (Cohort B1 only)	• CR as assessed by the BICR
• To evaluate the EFS of PF-06801591 in participants with BCG-unresponsive NMIBC (Cohort B2 only)	• EFS as assessed by the investigator
Secondary Objectives	**Secondary Endpoints**
• To evaluate the duration of CR of PF-06801591 in participants with BCG-unresponsive CIS (Cohort B1 only).	• Duration of CR for participants with CR as assessed by the BICR

• To estimate the CR rate of PF-06801591 at 12 months in participants with BCG-unresponsive CIS (Cohort B1 only)	• CR at 12 months as assessed by the BICR
• To evaluate the EFS of PF-06801591 in participants with BCG unresponsive CIS (Cohort B1 only)	• EFS as assessed by the investigator
• To evaluate the time to cystectomy of PF-06801591 in participants with BCG-unresponsive NMIBC (Cohorts B1 and B2).	• Time to cystectomy
• To evaluate OS of PF-06801591 in participants with BCG-unresponsive NMIBC treated with PF-06801591 (Cohorts B1 and B2).	• OS
• To evaluate the overall safety of PF-06801591 in participants with BCG-unresponsive NMIBC (Cohorts B1 and B2).	• AEs as characterized by type, severity (as graded by NCI CTCAE v5.0, timing, seriousness, and relationship to study therapy. Laboratory abnormalities as characterized by type, severity (as graded by NCI CTCAE v5.0), and timing
• To assess the effects of PF-06801591 on patient-reported health-related quality of life in participants with BCG-unresponsive NMIBC (Cohorts B1 and B2).	• Health-related quality of life as measured by: 1) EORTC QLQ-C30 , 2) EORTC QLQ-NMIBC24, 3) PTAB
• To evaluate PD-L1 expression in pretreatment tumor tissue that may aid in the identification of a subpopulation of participants with BCG unresponsive NMIBC most likely to benefit from PF-06801591 (Cohorts B1 and B2).	• PD-L1 expression
• To characterize the PK and immunogenicity of PF06801591 single agent in participants with BCG-unresponsive NMIBC (Cohorts B1 and B2).	• C_{trough}, C_{max} (Cohort B2 only), ADAs and NAbs following PF-06801591 single agent.
Tertiary/Exploratory	
• To assess the effects of PF-06801591 on patient reported outcomes (PROs) in participants with BCG unresponsive NMIBC (Cohorts B1 and B2).	• Health state utilities as measured by the EQ5D-5L & VAS • Overall assessment of disease severity as measured by the PGIS • Overall assessment of change as measured by the PGIC

	• Patient satisfaction as measured by the TSQ
• To explore the predictive and pharmacodynamic characteristics of peripheral blood and additional tumor tissue biomarkers that may be relevant to the mechanism of action of, or resistance to, treatment with PF-06801591, including but not limited to biomarkers related to antitumor immune response or target modulation (Cohorts B1 and B2).	• Peripheral blood and additional tumor tissue biomarkers consisting of the levels of cells, deoxyribonucleic acid (DNA), ribonucleic acid (RNA), or proteins that may be related to antitumor immune response or disease progression.

Table 2 (Section 9.1.1) defines the possible clinical outcomes for the EFS evaluation. The clinical definitions of recurrence of high-grade disease, progressive disease, persistence of CIS, recurrence of low-grade disease and CR are included in Section 10.9. The censoring and event date options to be considered for the EFS analyses are presented in Table 3 (replacing date of randomization with the date of first dose) (Section 9.1.1).

4. STUDY DESIGN

4.1. Overall Design

This is a Phase 3, multicenter, multinational, randomized, open-label, parallel, 3-arm study to evaluate PF-06801591 in combination with BCG vs BCG in participants with high-risk, BCG-naïve NMIBC (Cohort A). The study will also evaluate PF-06801591 as a single agent in participants with BCG-unresponsive, non-muscle invasive bladder cancer in 2 separate non-randomized cohorts (Cohorts B1 and B2). Cohort B1 will enroll participants with BCG-unresponsive CIS alone or with concomitant recurrent Ta/T1 disease. Cohort B2 will enroll participants with BCG-unresponsive recurrent high-grade Ta/T1 disease. The study will be conducted in conformance with Good Clinical Practices (GCPs).

4.1.1. BCG-Naïve Cohort (Cohort A)

A total of approximately 999 participants with BCG naïve, high-risk, NMIBC (including a minimum of 250 participants with CIS) will be randomized in a 1:1:1 ratio to one of 3 treatment arms below. As of 16 November 2021, enrollment to Cohort A has completed with 1056 participants randomized.

- Arm A: PF-06801591 + BCG (induction and maintenance period)
- Arm B: PF-06801591 + BCG (induction period only)
- Arm C: BCG only (induction and maintenance period)

BCG Dosing:

- Induction period: one dose every week via intravesical instillation for 6 consecutive weeks (QWx6: Cycle [C]1Day [D]1, C1D8, C1D15, C1D22, C2D1, C2D8)
- Re-Induction period: Following first induction period, participants with CIS at randomization who have persistent disease and participants with recurrence of high- grade Ta disease may receive re-induction with one dose every week via intravesical instillation for up to 6 consecutive weeks. Suggested schedule is C4D1, C4D8, C4D15, C4D22, C5D1, C5D8. Maintenance will then begin on C7D1. If TURBT is performed, schedule for BCG re-induction should be modified according to the product label.
- Maintenance period: (Arm A and Arm C): Doses on D1, D8, D15 during Cycles C4, C7, C13, C19 and C25. For participants that have a re-induction period, the maintenance period will begin at C7D1.

PF-06801591 Dosing
Once every 4 weeks (Q4W) 300 mg SC up to Cycle 25.

Randomization will be stratified by the presence of CIS (yes vs no) and geography (US vs Western Europe and Canada vs ROW).

The study was initially designed with two primary objectives: 1) to demonstrate that PF-06801591 given in combination with BCG (induction and maintenance) is superior to BCG alone (induction and maintenance) in prolonging EFS in participants with high-risk NMIBC and 2) to demonstrate that PF-06801591 given in combination with BCG (induction only) is superior to BCG alone (induction and maintenance) in prolonging EFS in participants with high-risk NMIBC.

The study was initially designed with two key secondary objectives: 1) to demonstrate that PF-06801591 + BCG (induction and maintenance) is superior to BCG (induction and maintenance) in prolonging OS in participants with high-risk NMIBC and 2) to demonstrate that PF-06801591 + BCG (induction) is superior to BCG (induction and maintenance) in prolonging OS in participants with high-risk NMIBC.

As of Amendment 5, the study will have one primary objective (to demonstrate that PF-06801591 given in combination with BCG [induction and maintenance] is superior to BCG alone [induction and maintenance] in prolonging EFS in participants with high-risk NMIBC. The objective to demonstrate that PF-06801591 given in combination with BCG (induction only) is superior to BCG alone (induction and maintenance) in prolonging EFS in participants with high-risk NMIBC will be considered a key secondary objective.

In order to conduct a preliminary assessment that the safety profile of PF-06801591 plus BCG regimen remains aligned with that expected from each agent separately, a review of safety data will be performed by an external data monitoring committee (EDMC) approximately 6 weeks after 20 participants in each of the 3 arms have been randomized and received at least one dose of study treatment. The EDMC will convene to monitor safety in the study (Cohort A only) approximately every 6 months thereafter. The EDMC will also

review cumulative safety data during the study conduct as well as review the futility interim analysis (IA) data for EFS (see Section 9.5.1).

Participants who meet the following criteria will enter the post-treatment follow-up period for safety visits.

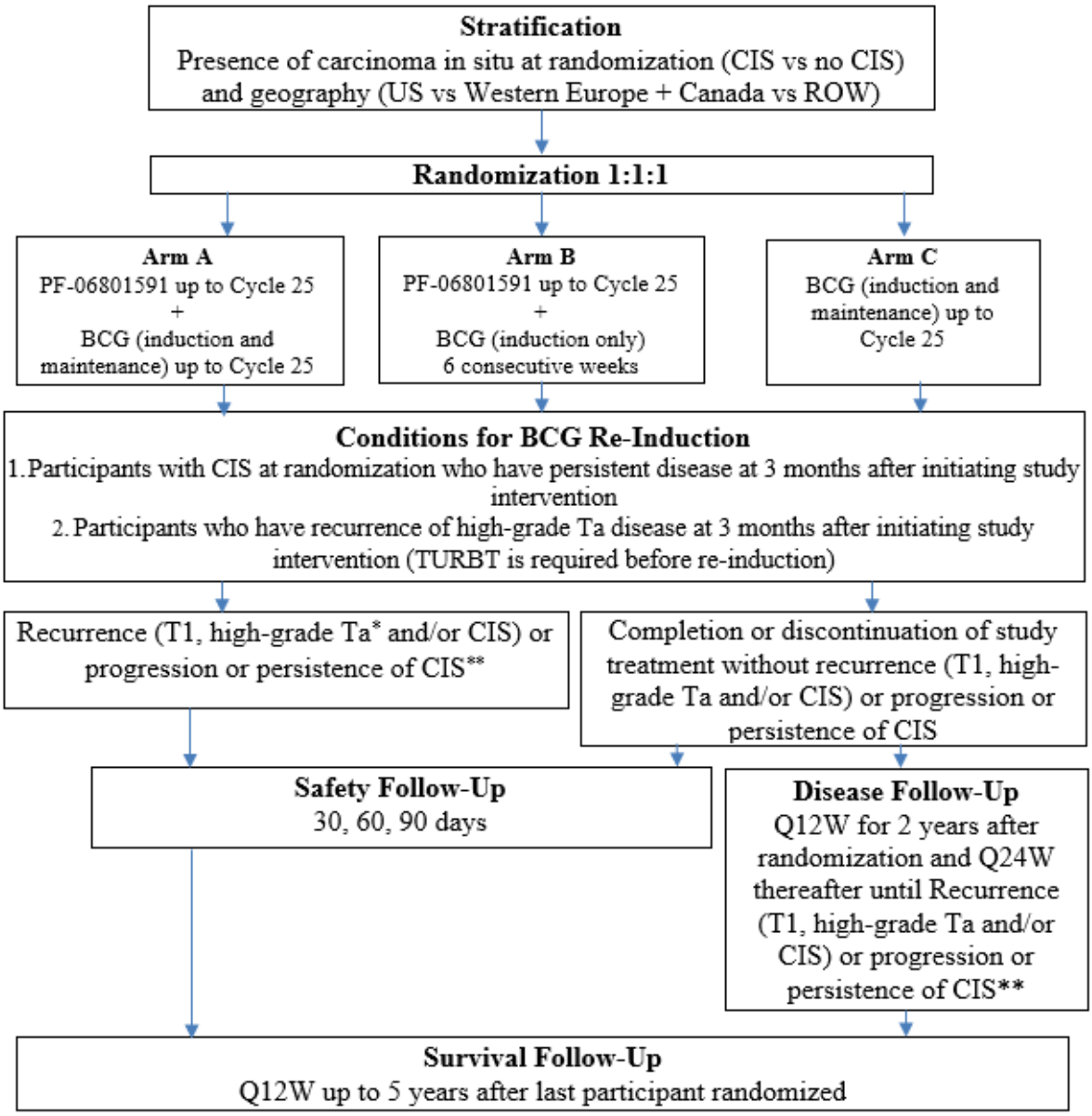
- Progression of NMIBC
- Recurrence (T1 [stage of cancer in which the cancer cells are only growing in the most superficial layer of tissues and have not grown into deeper tissues. In bladder cancer, T1 is defined as an invasion into the lamina propria without invasion into the muscularis propria], high-grade Ta [non-invasive papillary carcinoma], and/or CIS). Participants with high-grade Ta recurrence at 3 months after initiating study intervention following first induction period may receive re-induction. Following re-induction if recurrence of high-grade Ta disease occurs at 6 months of initiating study intervention, participants will discontinue study treatment and enter the post-treatment follow-up period.
- Participants with CIS at randomization that is not responding within 6 months of initiating study intervention, following induction or re-induction (persistence of CIS).
- Participants who complete or those who permanently discontinue study intervention early.

All participants will enter the safety follow-up period at EOT. Visits will occur 30 days, 60 days, and 90 days after EOT. Concurrent to the safety follow-up, participants with no recurrence of high-grade disease, progression of disease, or persistence of CIS before EOT, will also continue disease assessment after EOT through the disease follow-up period and will be assessed every 12 weeks for 2 years after randomization and every 24 weeks thereafter until recurrence of high-grade disease or progression of disease, withdrawal of consent for further participation in the study, lost to follow-up, or death.

All participants after recurrence of high-grade disease, persistence of CIS, or progression of disease will be followed via telephone visits every 12 weeks for survival until the earliest of withdrawal of consent for further participation in the study, lost to follow-up, death, study termination by the sponsor, or end of study (5 years from last participant randomized).

The study design for Cohort A is illustrated in Figure 3

Figure 3. B8011006: Study Schematic Cohort A



*See Section 4.1 for additional details
** For participants with CIS at randomization
CIS: carcinoma in situ, BCG: Bacillus Calmette-Guerin; ROW: rest of world; US: United States

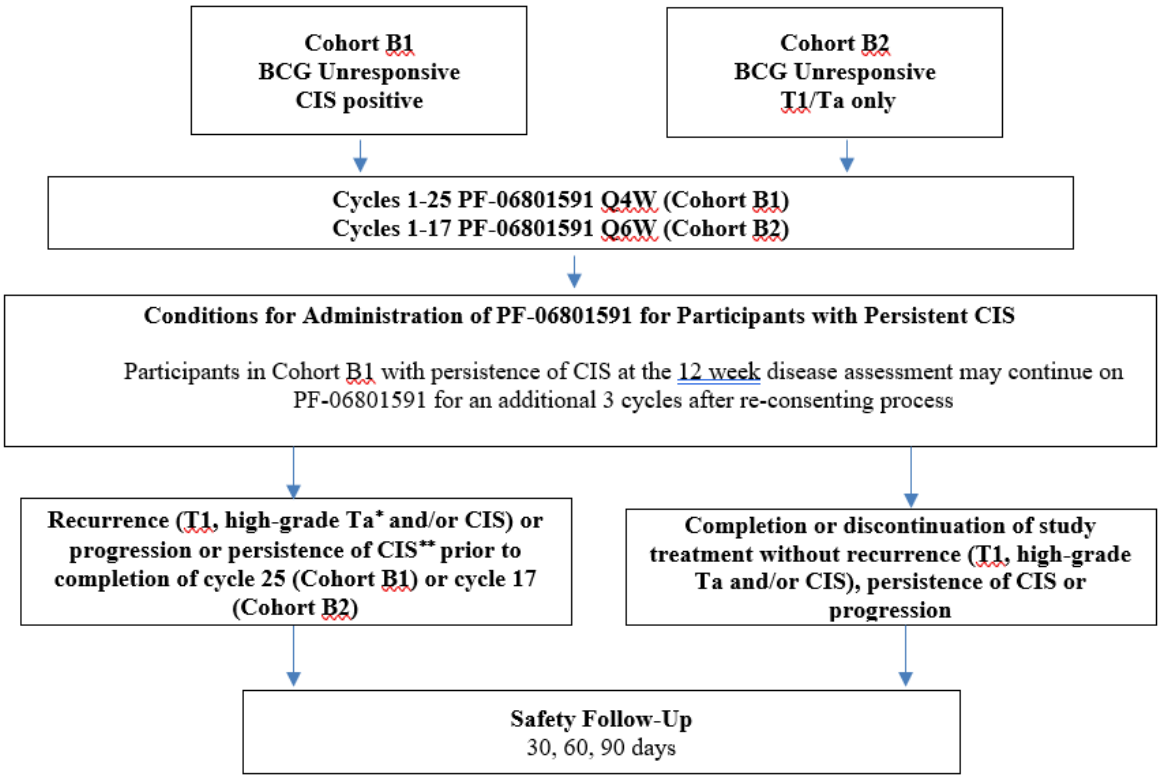
4.1.2. Cohorts B1 and B2

Approximately 160 participants with BCG-unresponsive high-risk NMIBC (including a minimum of 110 participants with CIS) will be enrolled to receive PF-06801591 as a single agent. For Cohort B1, diagnosis of CIS alone or with concomitant recurrent Ta/T1 disease and absence of muscle-invasive bladder cancer and extravesical disease must be confirmed

by the BICR prior to registration. Participants discontinuing from Arm C of Cohort A will not be eligible to enroll into Cohorts B1 or B2.

As of 31 August 2022, enrollment in Cohorts B1 and B2 was closed by the sponsor for business strategy reasons. Participants that have already been enrolled into Cohorts B1 and B2 may continue treatment and study procedures and assessments per the Cohorts B1 and B2 SoA.

Figure 4. B8011006 Study Schematic Cohorts B1 and B2



*See Section 4.1 for additional details
** For participants in Cohort B1 with CIS at registration

CIS: carcinoma in situ

PF-06801591 Dosing

Cohort B1: Once every 4 weeks (Q4W) 300 mg SC up to Cycle 25.

Cohort B2: Once every 6 weeks (Q6W) 600 mg SC up to Cycle 17.

Due to the decision to close enrollment in Cohorts B1 and B2, the Cohort B1 and B2 study objectives are no longer required.

As noted in Figure 4, participants in Cohort B1 with persistence of CIS at the 12 week disease assessment may continue on PF-06801591 for an additional 3 cycles (until the 24 week disease assessment). This may only occur after the investigator and participant discuss the option of cystectomy, and the participant re-consents to 3 additional cycles of PF-06801591 instead of cystectomy. Participants with persistence of CIS at the 24 week disease assessment will enter the post-treatment follow-up period for safety visits. Participants with recurrence of high-grade Ta, T1 or CIS disease at or after the 12 week disease assessment will enter the post-treatment follow-up period for safety visits. Continuation of treatment for 1 additional cycle while waiting for confirmation of recurrence of high-grade Ta, T1 or CIS disease by the BICR will be allowed at the discretion of the investigator. If the 12 week disease assessment is "Not Evaluable" per the BICR, the assessment with a non-evaluable result should be repeated as soon as possible.

For Cohort B2, participants with recurrence of high-grade Ta, T1 or CIS disease at or after the 12 week disease assessment will enter the post-treatment follow-up period for safety visits.

Participants who meet the following criteria will enter the post-treatment follow-up period for safety visits.

- Progression of NMIBC.
- Recurrence (T1, high-grade Ta, and/or CIS).
- Persistence of CIS (for those participants in Cohort B1): Participants with CIS that are not responding at or after the 12 or 24 week disease assessment.
- Participants who complete or those who permanently discontinue study intervention early.

All participants will enter the safety follow-up period at EOT. Visits will occur 30 days, 60 days, and 90 days after EOT.

The study design for Cohorts B1 and B2 is illustrated in Figure 4.

4.2. Scientific Rationale for Study Design

Refer to Section 2.1 for the Study Rationale.

The efficacy endpoints selected for this study (EFS, OS, CR [for participant with CIS at randomization], time to cystectomy, and disease-specific survival [DSS]) are accepted by the regulatory agencies for validation of clinical efficacy in oncology clinical trials in similar therapeutic setting. Similarly, safety evaluations for oncology intervention(s) are typically characterized using National Cancer Institute Common Terminology Criteria for Adverse Events (NCI CTCAE) criteria.

Patients with NMIBC have a 5-year survival rate of approximately 80%;[11] therefore, health-related quality of life (HRQoL) and management of symptoms and the associated treatment burden are important considerations. The PRO instruments were selected for this trial in order to study the impact of treatment on patient health-related quality of life (EORTC QLQ-C30 and EORTC QLQ-NMIBC24 [24 items]), health state utilities (Euro Qol 5 Dimension [EQ-5D-5L]), burden of treatment administration (Patient Treatment Administration Burden [PTAB]), overall change in disease (Patient Global Impression of Change, [PGIC]), overall disease severity (Patient Global Impression of Severity [PGIS]), and satisfaction with the treatment (Treatment Satisfaction Questionnaire [TSQ]).

Banked Biospecimens will be collected for exploratory pharmacogenomic/genomic/biomarker analyses and retained in the Biospecimen Banking System (BBS), which makes it possible to better understand the study intervention's mechanism of action and to seek explanations for differences in, for example, exposure, tolerability, safety, and/or efficacy not anticipated prior to the beginning of the study.

4.3. Justification for Dose

4.3.1. PF-06801591

During the dose escalation phase of the Phase 1 study B8011001, an MTD was not determined and DLTs were not observed. The proposed dose of 300 mg SC Q4W was selected with considerations of the nonclinical safety of PF-06801591, the clinical safety and tolerability data from the IV and SC administration cohorts in study B8011001, together with the feasibility, in terms of the injection volume with the current formulation.[37] The safety, efficacy, PK, and immunogenicity data from study B8011001 are described in Section 2.2.1.

PF-06801591 600 mg will be also investigated SC Q6W in Cohort B2. The 600 mg Q6W dosing regimen is currently being investigated in Study B8011007 and was chosen to 1) maintain a similar minimum exposure ($C_{trough\ ss}$) to the 300 mg Q4W dosing regimen and 2) to accommodate the SC presentation (as pre-filled syringe) that is currently formulated for 300 mg injection increments. Data from Study B8011001 were combined with preliminary PK data from Study B8011007 to model expected exposures following PF-06801591 dosing regimens with longer, Q6W, dosing interval. PF-06801591 600 mg Q6W SC was chosen to be investigated in Cohort B2 of this B8011006 study, based on similar model-predicted steady-state C_{trough} (approximately 3% higher relative to 300 mg Q4W SC). While the predicted steady-state average concentrations over the dosing interval ($C_{ave,\ ss} = AUC_{\tau\ ss}/\tau$) and $C_{max\ ss}$ are expected to be respectively 36% and 59% higher following the 600 mg Q6W SC relative to 300 mg Q4W SC dosing regimens, those higher exposures are still well below those observed following the highest, 10 mg/kg Q3W dose level tested in humans in Study B8011001, where no DLTs were observed. Additionally, dose-exposure data from Study B8011001 suggest relatively flat exposure-response relationships for safety of PF-06801591.

Based on the last PK/ADA data cut-off in study B8011007 (31 May 2021) there was no apparent difference in ADA incidence between the 300 mg Q4W (7.7%, n = 39) and 600 mg Q6W (1.3%, n = 77) dose groups.

Therefore, there is no expectation that the 600 mg Q6W regimen will result in unexpected safety concerns.

4.3.2. BCG

The intravesical instillation dose for BCG is 1 therapeutic dose per the product label for the strain given (this is often 1 vial, but please refer to the applicable BCG strain product label). Please see locally approved label for dose justification.[40] Justification for BCG regimen is provided in Section 2.1.

4.4. End of Study Definition

A participant is considered to have completed the study if he/she has completed all phases of the study including the last visit or the last scheduled procedure shown in the SoA.

The end of the study is defined as 5-years after randomization of the last participant into Cohort A.

5. STUDY POPULATION

Prospective approval of protocol deviations to recruitment and enrollment criteria, also known as protocol waivers or exemptions, is not permitted. The Sponsor must review and approve certain eligibility criteria prior to registration/randomization into the study.

5.1. Inclusion Criteria

Participants are eligible to be included in the study only if all the following criteria apply. The following criteria apply to all Cohorts ie, A, B1, and B2 unless otherwise noted:

Age

1. Participant must be ≥18 years of age, at the time of signing the informed consent (except in Japan, where participants must be ≥20 years).

Type of Participant and Disease Characteristics

2. Histological confirmed diagnosis of high-risk, non-muscle invasive transitional cell carcinoma (TCC) of the urothelium of the urinary bladder (tumors of mixed transitional/non-transitional cell histology are allowed, but TCC must be the predominant histology) defined as any of the following per World Health Organization grading system.[41, 42, 43]
    a. T1 tumor;
    b. High-grade Ta tumor;
    c. Carcinoma in situ (CIS);
3. Complete resection of all Ta/T1 papillary disease (including participants with concurrent CIS), with most recent positive TURBT occurring within 12 weeks prior to randomization for participants in Cohort A, or within 12 weeks prior to initiation of study intervention for participants in Cohorts B1 and B2 . A second TURBT must have been performed if indicated according to the current locally applicable guidelines, ie, American Urological Association, European Association of Urology.

4. Availability of the tumor tissue from the most recent TURBT for the assessment of the PD-L1 expression. If a second TURBT was performed, as indicated according to the current locally applicable guidelines, the tumor tissue from the TURBT procedure that supports the primary diagnosis for study eligibility should be the tumor tissue used for the PD-L1 expression testing.
5. ECOG Performance Status (PS) ≤ 2.
6. Adequate Bone Marrow Function (without hematopoietic growth factor or transfusion support within 14 days prior to study randomization for participants in Cohort A, or within 14 days prior to initiation of study intervention for participants in Cohorts B1 and B2), including:
    a. Absolute neutrophil count (ANC) ≥1,500/mm^3 or ≥1.5 x 10^9/L;
    b. Platelets ≥100,000/mm^3 or 100 x 10^9/L;
    c. Hemoglobin ≥9 g/dL (≥5.6 mmol/L).
7. Adequate renal function defined by an estimated creatinine clearance ≥30 mL/min according to the Cockcroft Gault formula or by 24-hour urine collection for creatinine clearance, or according to local institutional standard method.
8. Adequate liver function, including:
    a. Total serum bilirubin ≤1.5 × the upper limit of normal range (ULN). Participants with Gilbert syndrome who should have total serum bilirubin <3 x ULN;
    b. Aspartate and alanine aminotransferase (AST and ALT) ≤ 2.5 × ULN.
9. Willing and able to comply with scheduled visits, treatment plan, laboratory tests, and other procedures.

Sex

10. Male or Female

Contraceptive use by men or women should be consistent with local regulations regarding the methods of contraception for those participating in clinical studies

Male Participants:

Male participants are eligible to participate if they agree to the following during the intervention period and for at least 6 months after the last dose of study treatment:

- Refrain from donating sperm

PLUS either:

- Be abstinent from heterosexual or homosexual intercourse as their preferred and usual lifestyle (abstinent on a long term and persistent basis) and agree to remain abstinent

OR

- Must agree to use contraception/barrier as detailed below

Agree to use a male condom and should also be advised of the benefit for a female partner to use a highly effective method of contraception as a condom may break or leak when having sexual intercourse with a woman of childbearing potential who is not currently pregnant.

Female Participants:

A female participant is eligible to participate if she is not pregnant or breast-feeding, and at least one of the following conditions applies:

- Is not a woman of childbearing potential; (WOCBP) refer to Section 10.4 for definition.

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, as described in Section 10.4 during the intervention period and for at least 6 months after the last dose of study treatment. The investigator should evaluate the effectiveness of the contraceptive method in relationship to the first dose of study treatment.

- A WOCBP must have a negative highly sensitive (at least 25 IU/Ml) pregnancy test (urine or serum as required by local regulations) within 24 hours before the first dose of study treatment.

- If a urine test cannot be confirmed as negative (eg, an ambiguous result), a serum pregnancy test is required. In such cases, the participant must be excluded from participation if the serum pregnancy result is positive.

- Additional requirements for pregnancy testing during and after study treatment are located in Section 10.2.

- 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.

Informed Consent

11. Capable of giving signed informed consent as described in Section 10.1.3 which includes compliance with the requirements and restrictions listed in the informed consent document (ICD) and in this protocol

Type of Participant and Disease Characteristics (BCG-Unresponsive Cohorts B1 and B2 only)

12. Histological confirmed diagnosis of BCG-unresponsive high-risk, non-muscle invasive TCC of the urothelium of the urinary bladder defined as any of the following:
    a) Cohort B1: persistent or recurrent CIS alone or with concomitant recurrent Ta/T1 disease within 12 months of completion of adequate BCG therapy. Stage and grade must be confirmed by the BICR prior to registration;
    b) Cohort B2: recurrent high-grade Ta/T1 disease within 6 months of completion of adequate BCG therapy;
    c) Cohort B2: T1 high-grade disease at the first evaluation following an adequate (at least 5 of 6 doses) induction BCG course. It is not required that the participant receive BCG maintenance or a second induction course of BCG per inclusion criterion 13.

13. Have received adequate BCG therapy defined as at least one of the following:
    a) At least 5 of 6 doses of an initial induction course plus at least 2 of 3 doses of maintenance therapy;
    b) At least 5 of 6 doses of an initial induction course plus at least 2 of 6 doses of a second induction course.

    Note: The 2 courses described in "a" and "b" should have been administered within a 12 months period (ie the second course started within 12 months from the start of the first course).

    Note: Additional doses or courses of BCG above the minimum 5 + 2 described in "a" and "b" are allowed, and these do not have to be within the 12 month period.

    Note: The BCG dose administered in maintenance courses may be 1/2 or 1/3 dose in the event of a BCG shortage, according to NCCN and AUA treatment guidelines.

    Note: Prior BCG courses must have been comprised ONLY of one or more of the following strains: TICE, RIVM, TOKYO172, IMURON-VAC or Verity BCG (BCG-1), D2PB302, Danish (SSI).

14. Have refused or are ineligible for radical cystectomy.

5.2. Exclusion Criteria

Participants are excluded from the study if any of the following criteria apply. The following criteria apply to Cohorts A, B1, and B2 unless otherwise noted:

Medical Conditions

1. Evidence of muscle-invasive, locally advanced or metastatic urothelial cancer or concurrent extravesical, non-muscle invasive TCC of the urothelium. For Cohort B1, absence of muscle-invasive and extravesical disease must be confirmed by the BICR prior to registration.
2. Active or prior autoimmune disease that might deteriorate when receiving an immunostimulatory agent. Participants with diabetes type I, vitiligo, psoriasis, or hypo or hyperthyroid disease not requiring immunosuppressive treatment are eligible.
3. Severe active infections including pulmonary tuberculosis requiring systemic therapeutic oral or IV antibiotics within 2 weeks prior to randomization for participants in Cohort A, or within 2 weeks prior to initiation of study intervention for participants in Cohorts B1 and B2. Patients receiving prophylactic antibiotics (e.g., for prevention of a urinary tract infection) are eligible.
4. Other malignancy within 5 years prior to randomization for participants in Cohort A, or within 5 years prior to initiation of study intervention for participants in Cohorts B1 and B2, except for adequately treated basal cell or squamous cell skin cancer, or carcinoma in situ of the breast or of the cervix, or low-grade (Gleason 6 or below) prostate cancer on surveillance without any plans for treatment intervention (eg, surgery, radiation, or castration) or other concurrent malignancy the investigator feels has a very low likelihood to become metastatic after discussion with the sponsor.
5. Clinically significant multiple or severe drug allergies, intolerance to topical corticosteroids, or severe post-treatment hypersensitivity reactions (including, but not limited to, erythema multiforme major, linear immunoglobulin A (IgA) dermatosis, toxic epidermal necrolysis, and exfoliative dermatitis.
6. Current unstable liver or biliary disease per investigator assessment defined by the presence of ascites, encephalopathy, coagulopathy, hypoalbuminaemia, oesophageal or gastric varices, persistent jaundice, or cirrhosis. NOTE: Stable chronic liver disease (including Gilbert's syndrome, asymptomatic gallstones, and chronic stable hepatitis B or C -eg, presence of hepatitis B surface antigen (HBsAg) or positive hepatitis C antibody test result at screening or within 3 months prior to randomization for participants in Cohort A, or within 3 months prior to initiation of study intervention for participants in Cohorts B1 and B2) is acceptable if the participant otherwise meets entry criteria.

Prior/Concomitant Therapy

7. Cohort A: Intravesical BCG therapy within 2 years prior to randomization. Cohorts B1 and B2: Any systemic or intravesical chemotherapy or immunotherapy from the time of most recent positive TURBT to initiation of study intervention (single-dose intravesical chemotherapy as part of the most recent positive TURBT according to the current locally applicable guidelines is allowed). Prior intravesical chemotherapy for NMIBC is allowed in all Cohorts.

8. Prior immunotherapy with anti PD-1, anti PD-L1, anti PD-L2, or anti cytotoxic T-lymphocyte-associated antigen-4 (CTLA-4) antibody.
9. Prior treatment with immunostimulatory agents including interleukin (IL)-2, IL-15, interferon (INF)-γ.
10. Prior radiation therapy to the bladder.
11. Treatment with systemic anti-cancer therapy including investigational agents within 4 weeks prior to randomization for participants in Cohort A, or within 4 weeks prior to initiation of study intervention for participants in Cohorts B1 and B2.
12. Vaccination with live attenuated vaccines within 4 weeks prior to randomization for participants in Cohort A, or within 4 weeks prior to initiation of study intervention for participants in Cohorts B1 and B2 is prohibited; however, inactivated vaccines are permitted.
13. Patients with a condition requiring systemic treatment with either corticosteroids (>10 mg daily prednisone equivalents) or other immunosuppressive medications within 14 days of study drug administration. Inhaled or topical steroids, and adrenal replacement doses >10 mg daily prednisone equivalents are permitted in the absence of active autoimmune disease.

Prior/Concurrent Clinical Study Experience

14. Participation in other studies involving investigational drug(s) within 4 weeks prior to randomization for participants in Cohort A, or within 4 weeks prior to initiation of study intervention for participants in Cohorts B1 and B2.

Diagnostic assessments

15. Cohort A: Known or documented absolute and/or relative contraindication of adjuvant intravesical BCG treatment:
    a. Prior BCG sepsis or systemic infection (including current urinary tract infection)
    b. Total bladder incontinence defined as use more than 6 pads in 24 hours
    c. Adverse experience to previous BCG instillation that resulted in treatment discontinuation or precludes re-treatment.
16. Clinically significant (ie, active) cardiovascular disease including the following: cerebral vascular accident/stroke (<6 months prior to randomization for participants in Cohort A, or <6 months prior to initiation of study intervention for participants in Cohorts B1 and B2); myocardial infarction (<6 months prior to randomization for participants in Cohort A, or <6 months prior to initiation of study intervention for participants in Cohorts B1 and B2); unstable angina; congestive heart failure (≥New York Heart Association Classification Class II); or serious cardiac arrhythmia (uncontrolled, clinically significant) requiring medication.
17. Q-T interval corrected for heart rate (QTc) >450 msec for male participants or QTc >470 msec for female participants or QTc >480 msec in participants with right bundle branch block

Other Exclusions

18. Major surgery within 2 weeks prior to randomization for participants in Cohort A, or within 2 weeks prior to initiation of study intervention for participants in Cohorts B1 and B2.
19. Prior organ transplantation or allogenic stem cell transplantation.
20. Known history of: immune-mediated colitis, inflammatory bowel disease, pneumonitis, or pulmonary fibrosis.
21. Patient has AE(s) due to cancer therapeutics administered >4 weeks earlier, which have not recovered to CTCAE Grade ≤1 (except alopecia, and except for AEs not constituting a safety risk by investigator judgment).
22. Patients with intolerance to or who have had a severe (Grade ≥3) allergic or anaphylactic reaction to antibodies or infused therapeutic proteins.
23. Pregnant female patients; breastfeeding female patients; male patients able to father children and female patients of childbearing potential who are unwilling or unable to use a highly effective method(s) of contraception as outlined in this protocol for the duration of the study treatment and for at least 6 months after the last dose of PF-06801591 (Arm A and Arm B only).
24. Severe acute or chronic medical or psychiatric condition, including recent (within the past year) or active suicidal ideation or behavior, or laboratory abnormality that may increase the risk associated with study participation or study intervention administration or may interfere with the interpretation of study results and, in the judgment of the investigator, would make the patient inappropriate for entry into this study.
25. Investigator site staff members directly involved in the conduct of the study and their family members, site staff members otherwise supervised by the investigator, or patients who are Pfizer employees, including their family members, directly involved in the conduct of the study.
26. Cohorts B1 and B2: Prior participation in Cohort A.

5.3. Lifestyle Considerations

The investigator or his or her designee, in consultation with the participant, will confirm that the participant has selected an appropriate method of contraception for the individual participant and his or her partners from the permitted list of contraception methods (see Section 10.4, Section 10.4.4) and will confirm that the participant has been instructed in its consistent and correct use. At time points indicated in the SoA (Section 1.3), the investigator or designee will inform the participant of the need to use highly effective contraception consistently and correctly and document the conversation and the participant's affirmation in the participant's chart (participants need to affirm their consistent and correct use of at least 1 of the selected methods of contraception; as for female participants using a highly effective method that is user dependent, this contraception method must be used together with a second effective method of contraception, as described in Section 10.4. In addition, the

investigator or designee will instruct the participant to call immediately if the selected contraception method is discontinued or if pregnancy is known or suspected in the participant or partner.

5.4. Screen Failures

Screen failures are defined as participants who consent to participate in the clinical study but are not subsequently randomly assigned to study treatment. A minimal set of screen failure information is required to ensure transparent reporting of screen failure participants to meet the Consolidated Standards of Reporting Trials (CONSORT) publishing requirements and to respond to queries from regulatory authorities. Minimal information includes demography, screen failure details, eligibility criteria, and any serious adverse event (SAE).

Individuals who do not meet the criteria for participation in Cohorts A, B1 or B2 of this study (screen failure) may be rescreened. Rescreened participants should be assigned a new participant number as for the initial screening.

6. STUDY INTERVENTION

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

In this study, PF-06801591 is an investigational medicinal product (IMP). The IMP will be provided in prefilled syringe (PFS) for SC injection. The PFS is a medical device.

If BCG is sourced locally by the study site, the site should ensure that sufficient quantities of BCG are available to support the participant for the study treatment duration, prior to randomization. It is recommended that a participant receive the same strain of BCG for the duration of study treatment. Please contact the study team prior to changing the strain of BCG that a participant is receiving. In the event that there is a shortage of the BCG strain that a site typically uses (TICE, RIVM, TOKYO172, IMURON-VAC, D2PB302), the Investigator may be allowed to use a different BCG strain during re-induction or maintenance only, provided that it is permissible for use in these circumstances under the auspices of the relevant local authority. This option should only be used when necessary and must be discussed with and approved by the Sponsor prior to implementation.

6.1. Study Intervention(s) Administered

ARM Name – Cohort A	A	B	C
Intervention Name	PF-06801591 + BCG (induction and maintenance)	PF-06801591 + BCG (induction only)	BCG only (induction and maintenance)
Type	Biological product	Biological product	Biological product
Dosage Form	PF-06801591: Solution for injection	PF-06801591: Solution for injection	BCG: intravesical instillation

ARM Name – Cohort A	A	B	C
	BCG: intravesical instillation	BCG: intravesical instillation	
Dose Strength	PF-06801591: 150 mg/mL, 2 mL (300 mg total) prefilled syringe BCG: full dose as per the label (TICE, RIVM, TOKYO172, IMURON-VAC (BCG-1), BCG China Strain (D2PB302))	PF-06801591: 150 mg/mL, 2 mL (300 mg total) prefilled syringe BCG: full dose as per the label (TICE, RIVM, TOKYO172, IMURON-VAC (BCG-1), BCG China Strain (D2PB302))	BCG: full dose as per the label (TICE, RIVM, TOKYO172, IMURON-VAC (BCG-1), BCG China Strain (D2PB302))
Dosage	PF-06801591: 300 mg Q4W BCG: Induction period: 1 dose for 6 consecutive weeks* Maintenance: D1, D8, D15 during Cycles 4, 7, 13, 19, 25	PF-06801591: 300 mg Q4W BCG: Induction period: 1 dose for 6 consecutive weeks*	BCG: Induction period: 1 dose, for 6 consecutive weeks* Maintenance: D1, D8, D15 during Cycles 4, 7, 13, 19, 25
Route of Administration	PF-06801591: SC injection BCG: intravesical instillation	PF-06801591: SC injection BCG: intravesical instillation	BCG: intravesical instillation
IMP and NIMP	PF-06801591= IMP BCG = NIMP	PF-06801591= IMP BCG = NIMP	BCG = NIMP
Sourcing	PF-06801591: Provided centrally by the Sponsor (manufactured by Pfizer) BCG: Sourced centrally/locally by the Sponsor or sourced locally by the site.**	PF-06801591: Provided centrally by the Sponsor (manufactured by Pfizer) BCG: Sourced centrally/locally by the Sponsor or sourced locally by the site.**	BCG: Sourced centrally/locally by the Sponsor or sourced locally by the site.**
Packaging and Labeling	PF 06801591: PFS for 300 mg dose. Each PFS will be labeled as required per country requirement. BCG: Commercial package and label	PF 06801591: PFS for 300 mg dose. Each PFS will be labeled as required per country requirement. BCG: Commercial package and label	BCG: Commercial package and label available in local market

ARM Name – Cohort A	A	B	C

* Following induction period, participants with CIS at randomization who have persistent disease and participants with recurrence of high-grade Ta disease may receive re-induction with up to 6 additional weekly doses of BCG.
**If BCG is sourced locally, the investigational sites should ensure that sufficient quantities of BCG are available to support the participant for the study treatment duration, prior to randomization.

Group Name	Cohort B1	Cohort B2
Intervention Name	PF-06801591	PF-06801591
Type	Biological product	Biological product
Dosage Form	Solution for injection	Solution for injection
Dose Strength	150 mg/mL, 2 mL (300 mg total) prefilled syringe	Two 150 mg/mL, 2 mL prefilled syringes (300 mg dose per syringe), 600 mg total dose)
Dosage	300 mg Q4W	600 mg Q6W
Route of Administration	SC injection	SC injection
IMP and NIMP	PF-06801591= IMP	PF-06801591= IMP
Sourcing	Provided centrally by the Sponsor (manufactured by Pfizer)	Provided centrally by the Sponsor (manufactured by Pfizer)
Packaging and Labeling	PFS for 300 mg dose. Each PFS will be labeled as required per country requirement.	PFS for 300 mg dose. Each PFS will be labeled as required per country requirement.

6.1.1. Medical Devices

1. The medical device used to deliver PF-06801591 is a PFS.
2. Instructions for medical device use are provided in the Investigational Product (IP) Manual.
3. All medical device deficiencies (including malfunction, use error, and inadequate labeling) shall be documented and reported by the investigator throughout the clinical investigation (see Section 8.3.9) and appropriately managed by the sponsor.

6.1.2. Administration of the Study Intervention

BCG: Qualified and trained investigator site personnel will administer a full dose of BCG per labeling guidelines. In Cohort A, BCG administration will take place as follows:

- Induction period: C1D1, C1D8, C1D15, C1D22, C2D1, and C2D8.
- Re-induction period, up to 6 consecutive weeks (following induction period, for participants with CIS at randomization who have persistent disease and participants with recurrence of high-grade Ta disease): Suggested schedule is C4D1, C4D8, C4D15, C4D22, C5D1, and C5D8. Maintenance will then begin on C7D1. If TURBT is performed, schedule for BCG re-induction should be modified according to the product label.
- Maintenance period (Arm A and Arm C): Doses on D1, D8, D15 during Cycles C4, C7, C13, C19 and C25. For participants that have a re-induction period, the maintenance period will begin at C7D1.

PF-06801591: Qualified and trained investigator site personnel will administer PF-06801591 at a fixed dose by one SC injection to the abdomen of participants in Cohorts A, and B1. One PFS must be administered SC Q4W (last dose at Cycle 25) for a dose of 300 mg PF-06801591.

In Cohort B2, qualified and trained investigator site personnel will administer PF-06801591 as a fixed dose by two SC injections to the abdomen. Two PFS must be administered SC Q6W (last dose at Cycle 17) for a dose of 600 mg PF-06801591. For the 600 mg SC dose, PF-06801591 should be administered to 2 different quadrants of the abdomen.

See Section 8.2.5 for local site injection tolerability assessment.

Injections to the abdomen are preferred. If SC injections in the abdominal location are not possible, SC injections can be administered in a distributed manner in the thighs. SC injections in the upper extremities (eg, deltoid, upper and lower arm) are not permitted.

On cycles when PF-06801591 and BCG are both administered for Arms A and B of Cohort A, BCG will be administered first. It is strongly preferred that participants randomized to Arm A or Arm B receive the first administration of PF-06801591 and BCG at the C1D1 visit as long as this can be done while maintaining participant safety. Participants enrolled with CIS who have persistent disease and participants with recurrence of high-grade Ta disease following first induction are eligible for a re-induction period of up to 6 additional weekly treatments.

In Cohort A, participants randomized with CIS who do not respond within 6 months of initiating study intervention and participants with recurrence of high-grade Ta disease at or after 6 months of initiating study intervention will enter the post-treatment follow-up period for safety visits.

In Cohort B1, participants with persistence of CIS at the 12 week disease assessment may continue on PF-06801591 for an additional 3 cycles (until the 24 week disease assessment).

This may only occur after the investigator and participant discuss the option of cystectomy, and the participant re-consents to 3 additional cycles of PF-06801591 instead of cystectomy.

Participants with persistence of CIS at the 24 week disease assessment will enter the post-treatment follow-up period for safety visits. Participants with recurrence of high-grade Ta, T1 or CIS disease at or after the 12 week disease assessment will enter the post-treatment follow-up period for safety visits. Continuation of treatment for 1 additional cycle while waiting for confirmation of recurrence of high-grade Ta, T1 or CIS disease by the BICR will be allowed at the discretion of the investigator. If the 12 week disease assessment is "Not Evaluable" per the BICR, the assessment with a non-evaluable result should be repeated as soon as possible.

In Cohort B2, participants with recurrence of high-grade Ta, T1 or CIS disease at or after the 12 week disease assessment will enter the post-treatment follow-up period for safety visits.

Study staff should refer to the IP Manual for specific instructions on the handling and administration of both study interventions.

For participants in Cohorts A, B1, and B2, a cycle is defined as the time from Day 1 dose to the next Day 1 dose. Participants will receive a single dose of PF-06801591 on Day 1 of each cycle. In Cohort A, a cycle will be 28 days (±3 days prior to Cycle 4, ±7 days for Cycle 4 through EOT), in Cohort B1, a cycle will be 28 days (±3 days prior to Cycle 2, ±7 days for Cycle 2 through EOT), and in Cohort B2, a cycle will be 42 days (±3 days prior to Cycle 2, ±7 days for Cycle 2 through EOT) for SC administration. Each participant may receive PF-06801591 until the earliest of the following events: completion of study treatment (Cycle 25 for Cohorts A and B1 and Cycle 17 for Cohort B2) recurrence of high-grade disease or progression of disease, unacceptable toxicity, withdrawal of consent, participant no longer willing to participate in trial, or study termination.

6.2. Preparation/Handling/Storage/Accountability

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

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

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

4. Further guidance and information for the final disposition of unused study treatments are provided in the Study Reference Manual.

6.3. Measures to Minimize Bias: Randomization and Blinding

Open-label using central randomization via interactive response technology (IRT) (IVRS/IWRS) Applies to Cohorts A, B1, and B2	This is an open-label study; however, the specific intervention to be taken by a participant will be assigned using an IVRS/IWRS. Potential bias will be reduced by the central randomization. Before the study is initiated, the telephone number and call-in directions for the IVRS and/or the log in information & directions for the IWRS will be provided to each site. The site will contact the IVRS/IWRS prior to the start of study treatment administration for each participant. Randomization (Cohort A) or registration (Cohorts B1 and B2) will occur via IRT within approximately 28 days of start of screening. Randomized or registered participants will be dosed within 3 days after randomization or registration. The site will record the randomized intervention assignment on the applicable case report form, if required. Once a randomization number has been assigned it must not be re-assigned.

As this is an open label study, the sponsor may conduct unblinded reviews of the data during the course of the study for the purpose of data cleaning at the patient level.

6.4. Study Intervention Compliance

Compliance with the protocol required regimen will be assessed by drug accountability form/record. Deviation(s) from the prescribed dosage regimen should be recorded in the electronic case report form (eCRF).

6.5. Concomitant Therapy

Concomitant treatment considered necessary for the participant's wellbeing may be given at discretion of the treating physician.

All concomitant treatments, blood products, and saline infusions, as well as non-drug interventions (eg, analgesic use for paracentesis) received by participants from screening until the end of safety follow-up period will be recorded on the eCRF including the name of the procedure or medication, route and duration of treatment, and reason (eg, AE).

6.5.1. Other Anti-tumor/Anti-cancer or Experimental Drugs

Additional anticancer treatment including chemotherapy, hormonal therapy, radiotherapy, and experimental anticancer medications are not permitted while participants are receiving study treatment. Additionally, the concurrent use of herbal supplements for an anti-cancer treatment is not permitted. Prior intravesical chemotherapy for NMIBC is allowed.

6.5.2. Supportive Care

Palliative and supportive care for disease related symptoms may be administered at the investigator's discretion and according to any available American Society of Clinical Oncology (ASCO) guidelines.

6.5.3. Hematopoietic Growth Factors

Granulocyte-colony stimulating factors may be used to treat treatment emergent neutropenia as indicated by the current ASCO guidelines.[44]

Erythropoietin may be used at the investigator's discretion for the supportive treatment of anemia. Erythropoietin is not approved in some countries for anemia caused by cancer treatment. For those countries where the indication and dosage of G-CSF (granulocyte colony-stimulating factor) compounds may differ from ASCO guidelines, refer to local product label or follow usual clinical practice in those countries.

6.5.4. Anti-Diarrhea, Anti Emetic Therapy

Primary prophylaxis of diarrhea, nausea, and vomiting is permitted in the first cycle. Primary prophylaxis in subsequent cycles is at the investigator's discretion. The choice of the prophylactic drug is up to the investigator with sponsor approval, assuming there is no known or expected drug-drug interaction.

6.5.5. Anti-inflammatory and Narcotic Therapy

Anti-inflammatory or narcotic analgesic may be offered as needed assuming there is no known or expected drug-drug interaction. Narcotic analgesic may hide colonic perforation in case of colitis and should be used with caution. Anti-tumor necrosis factor (TNF) drugs are contraindicated in case of perforation, sepsis, or liver insufficiency.

6.5.6. Corticosteroids

Chronic, systemic corticosteroid use (prednisone >10 mg/day or equivalents) for palliative or supportive purpose is not permitted. Acute emergency and short-term administration, topical applications, inhaled sprays, eye drops, or local injections of corticosteroids are allowed. If immune-related AEs occur, immune suppressive treatment should be administered according to local standards or practice (Section 10.13).

6.5.7. Surgery

Caution is advised on theoretical grounds for any surgical procedures during the study. The appropriate interval of time between surgery and PF-06801591 required to minimize the risk of impaired wound healing and bleeding has not been determined. Stopping PF-06801591 is recommended at least 7 days prior to surgery. Postoperatively, the decision to reinitiate PF-06801591 treatment should be based on a clinical assessment of satisfactory wound healing and recovery from surgery. TURBT is allowed during the study conduct in case of positive cystoscopy (presence of malignant or suspicious lesions) and it will be performed as indicated by local guidance. BCG administration should be modified according to the product label after TURBT. See also 10.9 for disease assessment guidance.

6.5.8. Radiation Therapy

Radiation therapy is not allowed.

6.5.9. Vaccines

Live attenuated vaccines within 4 weeks prior to the first dose of PF-06801591 and through 30 days following the last dose of PF-06801591 are not allowed. Examples of live attenuated vaccines include, but are not limited to, the following: measles, mumps, rubella, chickenpox, yellow fever, rabies, and oral typhoid vaccine. Seasonal influenza vaccines for injection are inactivated virus vaccines and are allowed; however intranasal influenza vaccines (eg, FluMist®) are live attenuated vaccines, and are not allowed.

Drug Interaction with BCG

Immunosuppressants, bone-marrow suppressants and radiation all have the potential to interfere with the development of immune response and should not be used concurrently with BCG. Anti-tuberculosis drugs (e.g. isoniazid) should not be used to prevent or treat local irritations associated with BCG. Intravesical instillations of BCG should be postponed during treatment with antibiotics.

6.6. Dose Modification

Every effort should be made to administer the study treatment on the planned dose and schedule. In the event of significant toxicity, dosing may be skipped (PF-06801591 or BCG) or delayed (BCG). In the event of multiple toxicities, treatment modifications should be based on the worst toxicity observed. Participants are to be instructed to notify investigators at the first occurrence of any adverse symptom. Treatment modifications may occur independently for each study treatment in the combination based on the observed toxicity and the general guidance, as follows:

- PF-06801591: No dose reductions are permitted, but the next dosing of PF-06801591 may be skipped for the cycle based on persisting toxicity
- BCG: Dosing can be skipped or delayed according to the product label.

All dose modifications must be clearly documented in the participant's medical chart and in the eCRF.

Appropriate follow-up assessments should be done until adequate recovery occurs as assessed by the investigator.

In addition to the recommended dose modifications, investigators are encouraged to employ best supportive care according to local institutional clinical practices.

In the event of a treatment interruption for reasons other than treatment-related toxicity (eg, elective surgery) for >7 consecutive days, treatment resumption will be decided in consultation with the sponsor.

6.6.1. Dose Modifications for PF-06801591

Table 1. PF-06801591 Recommended Treatment Modifications for Drug-Related Toxicity (Excluding Immune-Related AEs)

Hematologic toxicities	
Grade 1 and Grade 2	• Continue as per schedule.
• **Anemia Grade ≥3** (hemoglobin <8 g/dL)	• Hold PF-06801591 and monitor weekly until resolution to Grade ≤1 or baseline. • Resume PF-06801591 at the next scheduled dose after recovery to Grade ≤1 or baseline. • Permanently discontinue PF-06801591 if anemia does not resolve to Grade ≤1 or baseline within 12 weeks or if the same Grade 3 toxicity recurs.
• **Neutropenia Grade ≥3** (ANC <1000/µL)	• Hold PF-06801591 and monitor weekly until resolution to Grade ≤1 or baseline. • Resume PF-06801591 at the next scheduled dose after recovery to Grade ≤1 or baseline. • Permanently discontinue PF-06801591 if neutropenia does not resolve to Grade ≤1 or baseline within 12 weeks or if the same Grade 3 toxicity recurs.
• **Thrombocytopenia Grade ≥3** (platelets <50,000/µL)	• Hold PF-06801591 and monitor weekly until resolution to Grade ≤1 or baseline. • Resume PF-06801591 at the next scheduled dose after recovery to Grade ≤1 or baseline. • Permanently discontinue PF-06801591 if thrombocytopenia does not resolve to Grade ≤1 or baseline within 12 weeks or if the same Grade 3 toxicity recurs.
Non-hematologic toxicities	
Grade 1 and Grade 2	• Continue as per schedule.
Grade 3	• Hold PF-06801591. • Resume PF-06801591 at the next scheduled dose after recovery to Grade ≤1 or baseline. • Permanently discontinue if toxicity does not resolve to Grade ≤1 or baseline within 12 weeks or if the same Grade 3 toxicity recurs. • **Exceptions are:** laboratory values that do not have any clinical correlate. • For suspected immune-related toxicity follow guidance in Section 6.6.1.2.
Grade 4	• Permanently discontinue PF-06801591. • **Exceptions are**: laboratory values that do not have any clinical correlate. • For suspected immune-related toxicity follow guidance in Section 6.6.1.2.

6.6.1.1. Hypersensitivity Types 1 and 3

Type 1 hypersensitivity or allergic (eg, shortness of breath, urticaria, anaphylaxis, angioedema) reactions are theoretically possible in response to any injected protein. Immune

complex mediated Type 3 hypersensitivity reactions are similar to the AEs of Type 1 reactions but are likely to be delayed from the time of administration and may include symptoms such as rash, urticaria, polyarthritis, myalgias, polysynovitis, fever, and, if severe, glomerulonephritis.

All participants should be closely observed while receiving the study intervention and monitoring for clinical signs of a systemic reaction will continue thereafter for clinical signs of allergic reactions/hypersensitivity.

Clinical management of these events is discussed in Section 10.12.

6.6.1.2. Immune-Related Adverse Events

While theoretically any immune checkpoint–blockade toxicity can occur at any time, certain toxicities have been reported earlier in the treatment course, while others develop as later complications. Commonly encountered irAEs include rash/dermatitis, diarrhea/colitis, hepatitis, and endocrinopathies. Algorithms for the clinical management of these events are provided in Section 10.13.

Prior to administration of the next dose of PF-06801591, the investigator should perform a comprehensive review of systems with specific focus on common and serious toxicities, such as skin changes, diarrhea and abdominal pain, headache, fever, shortness of breath, cough, and neurologic changes. Routine laboratory testing, including hematologic profile, comprehensive metabolic panel, and thyroid stimulating hormone (TSH) level, should be reviewed. Any new symptoms or abnormalities in examination or laboratory test results should be evaluated prior to administration of the next dose of PF-06801591.

Clinical management of these events are provided in Section 10.13.

6.6.2. Precautions for Administration of BCG

BCG is an infectious agent, and study personnel who use this product should be aware of certain toxicities and precautions when planning administration. Prior to administration of BCG, study personnel should ensure absence of febrile illness, urinary tract infection that represents a contraindication to BCG treatment, and gross hematuria. Seven to 14 days should elapse before BCG is administered following biopsy, TURBT, or traumatic catheterization. Algorithms for clinical management of BCG related toxicity based on the product label for TICE BCG, can be found in Section 10.14. When managing BCG associated toxicity for other strains of BCG, please refer to the appropriate product label for the BCG strain given to a participant.

6.7. Intervention after the End of the Study

There are no interventions planned after the end of this study.

7. DISCONTINUATION OF STUDY INTERVENTION AND PARTICIPANT DISCONTINUATION/WITHDRAWAL

7.1. Discontinuation of Study Intervention

For participants in Cohort A, it may be necessary for a participant to permanently discontinue one of the two study interventions. In that case, please note that the participant will still continue with the other study intervention. If it is necessary for the participant to permanently discontinue both PF-06801591 and BCG, the participant will remain in the study and move into the post-treatment follow-up period to allow for an adequate evaluation of the study objectives based on the prespecified estimands.

Note that permanent discontinuation of study treatment does not represent withdrawal from the study.

Participants may withdraw from study treatment at any time at their own request, or they may be withdrawn at the discretion of the investigator or sponsor for safety or behavioral reasons, or the inability of the participant to comply with the protocol-required schedule of study visits or procedures at a given study site.

Reasons for withdrawal of study treatment in Cohorts A, B1, and B2 may include:

- Completion of study treatment (25 cycles for Cohort A, Arms A, B and C, and Cohort B1, and 17 cycles for Cohort B2)
- Participants with CIS at baseline who do not achieve a CR within 6 months of initiating study intervention will be withdrawn from study treatment
- Recurrence of high-grade disease (Section 10.9) or progression of disease
- Global deterioration of health status requiring discontinuation of study treatment
- Unacceptable toxicity
- Pregnancy
- Significant protocol violation
- Lost to follow-up
- Participant refused further treatment
- Study terminated by sponsor
- Death

Discontinuation of study treatment for abnormal liver function should be considered by the investigator when a participant meets one of the conditions outlined or if the investigator believes that it is in best interest of the participant. See Section 10.6 for details.

If a clinically significant finding is identified (including, but not limited to changes from baseline in QT interval corrected using Fridericia's formula [QTcF] after enrollment), the investigator or qualified designee will determine if the participant can continue in the study and if any change in participant management is needed. This review of the electrocardiogram (ECG) printed at the time of collection must be documented. Any new clinically relevant finding should be reported as an AE. Refer to Section 8.2.4 for detailed information on criteria for holding or discontinuing study treatment in the case of change in QT interval.

See the SoA for data to be collected at the time of intervention discontinuation and follow-up and for any further evaluations that need to be completed.

7.2. Participant Discontinuation/Withdrawal from the Study

A participant may withdraw from the study at any time at his/her own request. Reasons for discontinuation from the study include the following:

- Refused further follow-up
- Lost to follow-up
- Death
- Study terminated by sponsor

If a participant withdraws from the study, he/she may request destruction of any remaining samples taken and not tested, and the investigator must document any such requests in the site study records and notify the sponsor accordingly.

If the participant withdraws from the study and also withdraws consent (see Section 7.2.1) for disclosure of future information, no further evaluations should be performed, and no additional data should be collected. The sponsor may retain and continue to use any data collected before such withdrawal of consent.

Lack of completion of all or any of the withdrawal/early termination procedures will not be viewed as protocol deviations so long as the participant's safety was preserved.

7.2.1. Withdrawal of Consent

Participants who request to discontinue receipt of study intervention will remain in the study and must continue to be followed for protocol specified follow-up procedures. The only exception to this is when a participant specifically withdraws consent for any further contact with him or her or persons previously authorized by the participant to provide this information. Participants should notify the investigator in writing of the decision to withdraw consent from future follow-up, whenever possible. The withdrawal of consent

should be explained in detail in the medical records by the investigator, as to whether the withdrawal is only from further receipt of study intervention or also from study procedures and/or posttreatment study follow-up and entered on the appropriate eCRF page. In the event that vital status (whether the participant is alive or dead) is being measured, publicly available information should be used to determine vital status only as appropriately directed in accordance with local law.

7.3. Lost to Follow-up

A participant will be considered lost to follow-up if he or she repeatedly fails to return for scheduled visits and is unable to be contacted by the study site.

The following actions must be taken if a participant fails to return to the clinic for a required study visit:

- The site must attempt to contact the participant and reschedule the missed visit as soon as possible and counsel the participant on the importance of maintaining the assigned visit schedule and ascertain whether or not the participant wishes to and/or should continue in the study.

- Before a participant is deemed lost to follow-up, the investigator or designee must make every effort to regain contact with the participant (where possible, 3 telephone calls and, if necessary, a certified letter to the participant's last known mailing address or local equivalent methods). These contact attempts should be documented in the participant's medical record.

- Should the participant continue to be unreachable, he/she will be considered to have withdrawn from the study.

All attempts to contact the participant and information received during contact attempts must be documented in the participant's medical record. In any circumstance, every effort should be made to document participant outcome, if possible. The investigator should enquire about the reason for withdrawal, request the participant to return for a final visit, if applicable, and follow up with the participant regarding any unresolved AEs.

If it is determined that the participant has died, the site will use permissible local methods to obtain the date and cause of death. If, after all attempts, the participant remains lost to follow-up, then the last-known-alive date as determined by the investigator should be reported and documented in the participant's medical records.

8. STUDY ASSESSMENTS AND PROCEDURES

- Study procedures and their timing are summarized in the SoA. Protocol waivers or exemptions are not allowed.

- Immediate safety concerns should be discussed with the sponsor immediately upon occurrence or awareness to determine if the participant should continue or discontinue study treatment.

- Adherence to the study design requirements, including those specified in the SoA, is essential and required for study conduct.

- All screening evaluations must be completed and reviewed to confirm that potential participants meet all eligibility criteria. The investigator will maintain a screening log to record details of all participants screened and to confirm eligibility or record reasons for screening failure, as applicable. For patients in screening for Cohort B1, the BICR must review screening biopsy, cytology, and imaging prior to registration to confirm diagnosis of CIS alone or with concomitant recurrent Ta/T1 disease and absence of muscle-invasive bladder cancer and extravesical disease.

- Procedures conducted as part of the participant's routine clinical management (eg, blood count) and obtained before signing of the ICD may be utilized for screening or baseline purposes provided the procedures met the protocol-specified criteria and were performed within the time frame defined in the SoA.

Medical history of the participants will be collected per the SoA as follows:

- Tumor history: Includes history of NMIBC including details of primary diagnosis and treatment history.
    - For Cohorts B1 and B2, detailed information about prior BCG usage (number of doses administered, date of dosing, dose levels, and strain used), disease persistence or recurrence after BCG treatment (including grade and stage) and the date of disease persistence or recurrence.
    - For Cohorts B1 and B2, reasons for subject ineligibility or refusal of radical cystectomy.
- Medical History: Includes history of disease process (eg, staging) other than the cancer under study (active or resolved) and concurrent illness. Includes prior treatments and any current medical treatments for any condition.

8.1. Efficacy Assessments

8.1.1. Clinical Assessments

Cytology and cystoscopy results will be read locally by qualified and experienced study personnel. Data obtained from cystoscopy, cytology, biopsy and imaging (computed tomography [CT] / magnetic resonance imaging [MRI]) will be evaluated locally during the course of the study according to the disease assessment decision algorithm in Section 10.9 and will be used for primary analyses in Cohort A and Cohort B2.

Independent reviewers will provide retrospective central assessment of imaging and tumor tissue samples taken during the study for Cohort A. This includes the tumor tissue sample(s) taken from the TURBT supporting the primary diagnosis for the study during the screening period, biopsies or TURBT samples collected at the time of recurrence of high-grade disease,

disease progression, persistence of CIS (applicable only to participants with CIS at randomization), or complete response (applicable only to participants with CIS at randomization), and done after a positive cystoscopy or cytology.

For Cohort B1, independent reviewers will provide central assessment of tumor tissue samples (from the TURBT or biopsies supporting the primary diagnosis for the study), cytology, and imaging during screening for the purposes of eligibility evaluation prior to registration. During treatment, independent reviewers will provide retrospective central assessment of biopsies or TURBT samples collected, as well as cytology, cystoscopy, and imaging results and the BICR assessments will be sent to the sites on a regular basis.

See the Study Manual for process details on sending the tissue sample for blinded independent central review (BICR).

8.1.1.1. Cystoscopy

Cystoscopy should be performed and assessed using the same method and equipment by the same study staff (whenever possible), for the duration of the study, in order to reduce subjectivity across multiple assessments. White light, blue light or narrow-band imaging are allowed in this study and blue light is preferred. Number, size and location of the tumors should be documented.

Disease status will be assessed through cystoscopy conducted at screening, every 12 weeks for 2 years following randomization, and every 24 weeks during the rest of follow-up, and as clinically indicated. Timing of disease assessment is to be fixed according to the calendar (±7 days) starting with randomization for Cohort A and initiation of study intervention for Cohorts B1 and B2, and should not be adjusted for study intervention dose modifications. Please refer to the Schedule of Activities for disease assessment time points for each Cohort.

Cystoscopy with biopsy is required at the time of recurrence of high-grade disease, disease progression, persistence of CIS (applicable only to participants with CIS at randomization), or complete response (applicable only to participants with CIS at randomization) as described in Section 10.9.

In Cohort A, biopsy for confirmation of complete response for participants with CIS should be performed at the 24 week disease assessment, unless collection at the 12 week disease assessment is routinely performed at the given institution. Please consider that if the bladder biopsy collection at the Week 12 disease assessment fails to confirm CR, the biopsy collection must be repeated at the Week 24 disease assessment. If it is not possible to perform the bladder biopsy collection by the Week 24 disease assessment, biopsies should be collected as soon as possible at the next scheduled disease assessment.

Timing of disease assessment is to be fixed according to the calendar (±7 days), starting with randomization for Cohort A, and initiation of study intervention for Cohorts B1 and B2, and should not be adjusted for study treatment dose modifications.

For cystoscopy without biopsy, either flexible or rigid cystoscopy may be conducted as per the Investigator's clinical judgement or institutional guidance/preference. Further specifications for the procedure are provided in the Study Manual.

For cystoscopy with biopsy, a full thickness tissue specimen is required to be obtained and Sponsor recommends a rigid cystoscopy.

Cystoscopy results from Cohorts A and B1 provided by the investigator will also be included in the BICR assessment.

Independent pathology reviewers will provide central assessment prior to registration for Cohort B1, and retrospective central assessment of all biopsies for Cohorts A and B1. Refer to the manual for process details on sending the slides for the BICR assessment.

8.1.1.2. Cytology

Urine cytology should be performed using the same methods and equipment for the duration of the study, with results being assessed and adjudicated by the same study staff. This is to reduce subjectivity across multiple assessments.

Disease status will be assessed through urine cytology conducted at screening, every 12 weeks during the first 2 years from randomization, every 24 weeks during the rest of follow-up, and as clinically indicated. Timing of disease assessment should be fixed according to the calendar (±7 days), starting with randomization for Cohort A, and initiation of study intervention for Cohorts B1 and B2, and should not be adjusted for study treatment dose modifications. Please refer to the Schedule of Activities for disease assessment time points for each Cohort.

Cytology results provided by the investigator will also be included in the BICR assessment for Cohort A. For Cohort B1, urine cytology specimens will be included in the BICR assessment.

Cytology results are defined as the following:

1. Positive - if indicative or suggestive of malignant cells:
- High-grade urothelial carcinoma
- Suspicious for high-grade urothelial carcinoma

2. Negative if NOT indicative or suggestive of malignant cells:
- Negative for high-grade urothelial carcinoma cells
- Presence of low-grade urothelial carcinoma cells
- Atypical urothelial cell not abnormal enough to be considered as cancerous

3. Indeterminate: unsatisfactory sample.

8.1.1.3. Imaging

CT or MRI or urogram of the abdomen and pelvis/urinary tract are the recommended imaging modalities. Other areas may be scanned as clinically indicated. Imaging should be performed with contrast agents unless contraindicated for medical reasons. The same imaging technique used at screening will be employed in the tumor assessments conducted on study.

For Cohort B1, disease status will be assessed through imaging at screening, every 24 weeks for 2 years after initiation of study intervention. Imaging will be performed until persistence of CIS, recurrence of high-grade disease or disease progression, consent withdrawal, lost to follow-up, EOT, or death. Additional imaging may be performed as clinically indicated. For Cohort A and Cohort B2, imaging is done as clinically indicated.

Guidance for integration of imaging in the disease assessment are provided in the disease assessment decision algorithm in Section 10.9.

Independent reviewers will provide central assessment prior to registration for Cohort B1, and retrospective central assessment of all imaging for Cohorts A and B1. Refer to the manual for process details on sending the scans for the BICR assessment.

8.1.2. Patient Reported Outcomes (PROs)

All PRO questionnaires will be administered electronically and will be completed during the visit prior to any other clinical assessments and study procedures, with the exception of the PTAB which will be completed immediately after the study intervention. If laboratory assessments are done on a date prior to the main visit date, PROs may be completed as the first assessment at the main visit. PROs will be administered in following order: EORTC QLQ-C30, EORTC NMIBC24, EQ5D5L, PGIS, PGIC, TSQ, and PTAB.

As of 12 September 2022, PROs will not be required for Cohort B1 and B2 participants.

8.1.2.1. EORTC QLQ-C30

The EORTC QLQ-C30 is a well-known, validated and self-administered PRO.[45,46] The EORTC QLQ-C30 is a 30-question survey, which can be grouped into 5 functional domain subscales, including a physical functioning subscale, a role functioning subscale, an emotional functioning subscale, a cognitive functioning subscale and a social functioning subscale. Higher scores on the functional domains are indicative of higher levels of functioning. Oncology related symptoms assessed by the EORTC QLQ-C30 include fatigue (3 items), pain (2 items), nausea and vomiting (2 items), and dyspnea, insomnia, appetite loss, constipation, diarrhea, and financial impact (1 item each). Higher scores are reflective of a greater presence of symptoms.

8.1.2.2. EORTC QLQ-NMIBC24

The EORTC QLQ NMIBC24 is a PRO developed and tested by the EORTC group specifically for patients with non-muscle invasive bladder cancer.[47] The NMIBC24 has 24 items which can be grouped into 6 subscales: urinary symptoms (7 items), malaise (2 items),

future worries (4 items), bloating/flatulence (2 items), sexual functioning (2 items), and male sexual issues (2 items). The NMIBC24 also assesses intravesical treatment, female sexual issues, sexual intimacy, risk of contaminating a partner, and sexual enjoyment (1 item each). Higher scores indicate greater impairment, with the exception of the sexual function and sexual enjoyment items, where higher scores indicate better function.

8.1.2.3. EuroQol 5 Dimensions, 5-Level (EQ-5D-5L) and Visual Analog Scale (VAS)

The EQ-5D-5L is a 6-item patient-completed questionnaire designed to assess health status in terms of a single index value or utility score.[48] There are 2 components, a Health State Profile which has individuals rate their level of problems (none, slight, moderate, severe, extreme/unable) in 5 areas (mobility, self-care, usual activities, pain/discomfort, and anxiety/depression), and a VAS in which participants rate their overall health status from 0 (worst imaginable) to 100 (best imaginable). Published weights are available that allow for the creation of a single summary score. Overall scores range from 0 to 1, with lower scores representing a higher level of dysfunction.

8.1.2.4. Patient Global Impression of Severity (PGIS)

The PGIS is a single-item PRO designed to facilitate an anchor-based methodology for establishing meaningful within person change (MWPC) of other PRO-based endpoints such as the EORTC QLQ-C30 and QLQ-NMIBC24. There are 4 response options, ranging from “none” to “severe”. The instrument is available in Section 10.16.1.

8.1.2.5. Patient Global Impression of Change (PGIC)

The PGIC is a single-item PRO designed to assess the participants overall impression of the degree of change they have experienced since the start of study treatment. There are 5 response options, ranging from “much worse” to “much better”. The instrument is available in Section 10.16.2.

8.1.2.6. Patient Treatment Administration Burden (PTAB)

The PTAB questionnaire is a 2-item PRO designed to assess, from the participant perspective, any pain associated with the treatment administration and the burden of the amount of time required to complete the treatment administration procedures (1 item each). The PTAB is available in Section 10.16.3.

8.1.2.7. Treatment Satisfaction Questionnaire (TSQ)

The TSQ is a 3-item PRO designed to assess participant satisfaction with the study treatments. The TSQ assesses overall satisfaction with the study treatment, number of treatment administrations, and the form of treatment administration (injection into stomach and catheter into bladder) (1 item each). The instrument is available in Section 10.16.4.

8.2. Safety Assessments

Planned time points for all safety assessments are provided in the SoA. Unscheduled clinical laboratory measurements may be obtained at any time during the study to assess any perceived safety issues.

8.2.1. Physical Examinations

Physical examinations should be performed according to clinical practice, but will not be recorded in the eCRF. Rather, any abnormalities should be recorded in the eCRF as AEs.

8.2.2. Vital Signs

- Vital signs will be measured as indicated in the SoA. Any abnormalities will be recorded in the eCRF as AEs.
- BP and pulse rate will be assessed in a supine position with a completely automated device. Manual techniques will be used only if an automated device is not available.
- BP and pulse rate should be preceded by at least 5 minutes of rest for the participant in a quiet setting without distractions (eg, television, cell phones).

8.2.3. ECOG Performance Status

Refer to Section 10.10 for ECOG Performance Status Criteria. ECOG will be performed per SoA.

8.2.4. Electrocardiograms

Electrocardiogram (12-Lead)

- A single 12-lead ECG tracing (with a 10 second rhythm strip) will be obtained at the time points described in the SoA.
- Generally, baseline and all corresponding time point ECGs should not be collected within 3 hours after food or beverage consumption and should be performed after the participant has rested quietly for at least 10 minutes in a supine position. All 12-lead ECGs should be confirmed by a qualified person at the institution.
- ECGs will be collected prior to dosing of study intervention as indicated in the SoA. When the timing of these measurements coincides with a blood collection, the ECG should be obtained prior to the nominal time of the blood collection, BP, and pulse rate.
- For the purposes of eligibility assessment and general safety monitoring, sites must enter the QTcF value provided by their ECG machine or calculated manually.
- If the QTcF is prolonged (≥60 msec from the pre-dose baseline or is >500 msec), then the ECGs should be reevaluated by a qualified person at the site for confirmation as soon as the finding is made, including verification that the machine reading is accurate. If

manual reading verifies a QTcF of ≥60 msec from the pre-dose baseline or is >500 msec, immediate correction for reversible causes (including electrolyte abnormalities, hypoxia and concomitant medications for drugs with the potential to prolong the QTcF interval) should be performed. In addition, repeat ECGs should be immediately performed hourly for at least 3 hours until the QTcF interval falls below ≥60 msec from the pre-dose baseline or is ≤500 msec depending on the type of change originally observed. If QTcF interval reverts to less than 60 msec from the pre-dose baseline or is ≤500 msec, and in the judgment of the investigator(s) and sponsor is determined to be due to cause(s) other than the study intervention, treatment may be continued with regular ECG monitoring. If in that timeframe the QTcF intervals rise above ≥60 msec from the pre-dose baseline or is >500 msec the study intervention will be held until the QTcF interval decreases to ≤60 msec from the pre-dose baseline or is ≤500 msec, depending on the type of change originally observed.

- Note: If QTc values remain >500 msec (or ≥60 msec from the pre-dose baseline) for greater than 4 hours (or earlier at the discretion of the investigator); or QTc intervals get progressively longer, the participant should undergo continuous ECG monitoring. A cardiologist should be consulted if QTc intervals do not return to less than 500 msec (or to <60 msec above the pre-dose baseline) after 8 hours of monitoring (or earlier at the discretion of the investigator).

- Once the QTcF interval decreases to ≤60 msec from the pre-dose baseline or ≤500 msec, depending on the type of change originally observed, participants may restart the study intervention. If the QTcF interval has still not decreased to ≤60 msec from the pre-dose baseline or ≤500 msec after 2 weeks (depending on the type of change originally observed), or if at any time a participant has a QTcF interval >515 msec or becomes symptomatic, the participant will be removed from the study. Additional triplicate ECGs may be performed as clinically indicated.

- Prior to concluding that an episode of QTcF interval prolongation is due to the study intervention, thorough consideration should be given to potential precipitating factors (eg, change in participant clinical condition, effect of concurrent medication, electrolyte disturbance) and possible evaluation by specialist.

- If participant experiences a cardiac or neurologic AE (specifically syncope, dizziness, seizures, or stroke), triplicate ECGs should be obtained at the time of the event.

- In some cases, it may be appropriate to repeat abnormal ECGs to rule out improper lead placement as contributing to the ECG abnormality. It is important that leads are placed in the same positions each time in order to achieve precise ECG recordings. If a machine read QTc value is prolonged, as defined above, repeat measurements may not be necessary if a qualified physician's interpretation determines that the QTc values are in the acceptable range.

8.2.5. Local Site Injection Tolerability Assessment (PF-06801591 only)

Any injection site reactions will be recorded as adverse events.

8.2.6. Survival Follow-up

To collect OS data for Cohort A participants only, once participants enter the survival follow-up period, they will be contacted by telephone every 12 weeks (±7 days) until consent withdrawal, lost to follow-up, death, or end of the study (5 years after last participant randomized to Cohort A). If the participant is seen in the clinic during the window of time that a scheduled telephone call is to be made to collect survival data, then the clinic visit may replace the survival telephone call. For Cohort A participants only, any subsequent anti-cancer therapy (including cystectomy), if administered, will be documented and recorded for participants who discontinue the study intervention and continue in post-treatment safety follow-up until recurrence of high-grade disease or progression of disease. The sponsor may request that sites complete additional survival follow-up to facilitate planned analyses as needed.

8.2.7. Clinical Safety Laboratory Assessments

- See Section 10.2 for the list of clinical laboratory tests to be performed and to the SoA for the timing and frequency. Specimen for laboratory assessments may also be drawn when clinically indicated.

- Repeat samples do not have to be drawn on C1D1 if the samples were drawn in the prior 7 days. Laboratory tests may be performed up to 3 days prior to the scheduled clinic visit including the C1D1 visit, so that results will be available for review before study treatment administration.

    - Assessments and physician's evaluation of the following labs, at a minimum, must be performed prior to dosing at visits per Section 1.3, Schedule of Activities:

        - Pregnancy test (as applicable)
        - Hematology (per Section 6.6.1)
        - Liver function: AST, ALT, and bilirubin (per Section 10.13)
        - Renal function: Creatinine (per Section 10.13)
        - Any other per protocol lab test(s) that correlate to clinical signs or symptoms
- Results from pregnancy tests, if taken, must be available for review prior to dosing.

- Laboratory assessments will be collected per SoA.

- Laboratory assessments must be performed, and results reviewed by the treating physician as soon as they are available.

- The investigator must review the laboratory report, document this review, and record any clinically relevant changes occurring during the study in the AE section of the eCRF. The laboratory reports must be filed with the source documents. Clinically significant abnormal laboratory findings are those which are not associated with the underlying disease, unless judged by the investigator to be more severe than expected for the participant's condition.

- All laboratory tests with values considered clinically significantly abnormal during participation in the study or within AE/SAE reporting criteria after the last dose of study treatment should be repeated until the values return to normal or baseline or are no longer considered clinically significant by the investigator or medical monitor.
    - If such values do not return to normal/baseline within a period of time judged reasonable by the investigator, the etiology should be identified, and the sponsor notified.
    - All protocol-required laboratory assessments, as defined in Section 10.2, must be conducted in accordance with the SoA.
    - If laboratory values from non-protocol specified laboratory assessments performed at the institution's local laboratory require a change in participant management or are considered clinically significant by the investigator (eg, SAE or AE or dose modification), then the results must be recorded in the eCRF.

8.2.8. Pregnancy Testing

Pregnancy tests may be urine or serum tests but must have a sensitivity of at least 25mIU/mL.

Pregnancy tests will be performed in WOCBP at the times listed in the SoA. Following a negative pregnancy test result at screening, appropriate contraception must be commenced and a second negative pregnancy test result will be required at the baseline visit prior to the participant's receiving the study intervention. Pregnancy tests will also be done whenever 1 menstrual cycle is missed during the active treatment period (or when potential pregnancy is otherwise suspected) and at the end of the study. Pregnancy tests may also be repeated if requested by IRBs/ ECs or if required by local regulations. If a urine test cannot be confirmed as negative (eg, an ambiguous result), a serum pregnancy test is required. In such cases, the participant must be excluded if the serum pregnancy result is positive.

8.3. Adverse Events and Serious Adverse Events

The definitions of an AE and an SAE can be found in Section 10.3.

The definitions of device-related safety events (ADEs and SADEs) can be found in Section 10.7. Device deficiencies are covered in Section 8.3.9.

AEs will be reported by the participant (or, when appropriate, by a caregiver, surrogate, or the participant's legally authorized representative).

The investigator and any qualified designees are responsible for detecting, documenting, and recording events that meet the definition of an AE or SAE and remain responsible to pursue and obtain adequate information both to determine the outcome and to assess whether it meets the criteria for classification as an SAE, or that caused the participant to discontinue the study intervention (see Section 7.1).

Each participant will be questioned about the occurrence of AEs in a nonleading manner.

In addition, the investigator may be requested by Pfizer Safety to obtain specific follow-up information in an expedited fashion.

8.3.1. Time Period and Frequency for Collecting AE and SAE Information

The time period for actively eliciting and collecting AEs and SAEs ("active collection period") for each participant begins from the time the participant provides informed consent, which is obtained before the participant's participation in the study (ie, before undergoing any study-related procedure and/or receiving study intervention), through and including a minimum of 90 calendar days after the last administration of the study intervention.

For participants who are screen failures, the active collection period ends when screen failure status is determined.

Follow-up by the investigator continues throughout and after the active collection period and until the AE or SAE or its sequelae resolve or stabilize at a level acceptable to the investigator and Pfizer concurs with that assessment.

For participants who are screen failures, the active collection period ends when screen failure status is determined.

If the participant withdraws from the study and also withdraws consent for the collection of future information, the active collection period ends when consent is withdrawn.

If a participant definitively discontinues or temporarily discontinues study intervention because of an AE or SAE, the AE or SAE must be recorded on the eCRF and the SAE reported using the CT SAE Report Form.

Investigators are not obligated to actively seek AEs or SAEs after the participant has concluded study participation. However, if the investigator learns of any SAE, including a death, at any time after a participant has completed the study, and he/she considers the event to be reasonably related to the study intervention, the investigator must promptly report the SAE to Pfizer using the CT SAE Report Form.

8.3.1.1. Reporting SAEs to Pfizer Safety

All SAEs occurring in a participant during the active collection period as described in Section 8.3.1 are reported to Pfizer Safety on the CT SAE Report Form immediately upon awareness and under no circumstance should this exceed 24 hours, as indicated in Section 10.3. The investigator will submit any updated SAE data to the sponsor within 24 hours of it being available.

If a participant begins a new anticancer therapy, SAEs occurring during the above-indicated active collection period must still be reported to Pfizer Safety irrespective of any intervening treatment. Note that a switch to a commercially available version of the study intervention is considered as a new anticancer therapy for the purposes of SAE reporting.

8.3.1.2. Recording Nonserious AEs and SAEs on the eCRF

All nonserious AEs and SAEs occurring in a participant during the active collection period, which begins after obtaining informed consent as described in Section 8.3.1, will be recorded on the AE section of the eCRF.

The investigator is to record on the eCRF all directly observed and all spontaneously reported AEs and SAEs reported by the participant.

If a participant begins a new anticancer therapy, the recording period for nonserious AEs ends at the time the new treatment is started; however, SAEs must continue to be recorded on the eCRF during the above-indicated active collection period. Note that a switch to a commercially available version of the study intervention is considered as a new anticancer therapy for the purposes of SAE reporting.

8.3.2. Method of Detecting AEs and SAEs

The method of recording, evaluating, and assessing causality of AE and SAE and the procedures for completing and transmitting SAE reports are provided in Section 10.3.

Care will be taken not to introduce bias when detecting AEs and/or SAEs. Open-ended and non-leading verbal questioning of the participant is the preferred method to inquire about AE occurrences.

8.3.3. Follow-up of AEs and SAEs

After the initial AE/SAE report, the investigator is required to proactively follow each participant at subsequent visits/contacts. For each event, the investigator must pursue and obtain adequate information until resolution, stabilization, the event is otherwise explained, or the participant is lost to follow-up (as defined in Section 7.3).

In general, follow-up information will include a description of the event in sufficient detail to allow for a complete medical assessment of the case and independent determination of possible causality. Any information relevant to the event, such as concomitant medications and illnesses, must be provided. In the case of a participant death, a summary of available autopsy findings must be submitted as soon as possible to Pfizer Safety.

Further information on follow-up procedures is given in Section 10.3.

8.3.4. Regulatory Reporting Requirements for SAEs

- Prompt notification by the investigator to the sponsor of a SAE is essential so that legal obligations and ethical responsibilities towards the safety of participants and the safety of a study intervention under clinical investigation are met.

- The sponsor has a legal responsibility to notify both the local regulatory authority and other regulatory agencies about the safety of a study treatment under clinical investigation. The sponsor will comply with country-specific regulatory requirements relating to safety reporting to the regulatory authority, IRBs/EC), and investigators.

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

- An investigator who receives SUSARs or other specific safety information (eg, summary or listing of SAEs) from the sponsor will review and then file it along with the SRSD(s) for the study and will notify the IRB/EC, if appropriate according to local requirements.

8.3.5. Exposure During Pregnancy or Breastfeeding, and Occupational Exposure

Exposure to the intervention under study during pregnancy or breastfeeding and occupational exposure are reportable to Pfizer Safety within 24 hours of investigator awareness.

8.3.5.1. Exposure During Pregnancy

An EDP occurs if:

- A female participant is found to be pregnant while receiving or after discontinuing study intervention.

- A male participant who is receiving or has discontinued study intervention exposes a female partner prior to or around the time of conception.

- A female is found to be pregnant while being exposed or having been exposed to study intervention due to environmental exposure. Below are examples of environmental exposure during pregnancy:

  - A female family member or healthcare provider reports that she is pregnant after having been exposed to the study intervention by any routes of exposure (eg, injection, ingestion, inhalation, or skin contact).

  - A male family member or healthcare provider who has been exposed to the study intervention by any routes of exposure (eg, injection, ingestion, inhalation, or skin contact) then exposes his female partner prior to or around the time of conception.

The investigator must report EDP to Pfizer Safety within 24 hours of the investigator's awareness, irrespective of whether an SAE has occurred. The initial information submitted should include the anticipated date of delivery (see below for information related to termination of pregnancy).

- If EDP occurs in a participant or a participant's partner, the investigator must report this information to Pfizer Safety on the CT SAE Report Form and an EDP Supplemental Form, regardless of whether an SAE has occurred. Details of the pregnancy will be collected after the start of study intervention and until at least 180 days after the last dose.

- If EDP occurs in the setting of environmental exposure, the investigator must report information to Pfizer Safety using the CT SAE Report Form and EDP Supplemental

Form. Since the exposure information does not pertain to the participant enrolled in the study, the information is not recorded on an eCRF; however, a copy of the completed CT SAE Report Form is maintained in the investigator site file.

Follow-up is conducted to obtain general information on the pregnancy and its outcome for all EDP reports with an unknown outcome. The investigator will follow the pregnancy until completion (or until pregnancy termination) and notify Pfizer Safety of the outcome as a follow-up to the initial EDP Supplemental Form. In the case of a live birth, the structural integrity of the neonate can be assessed at the time of birth. In the event of a termination, the reason(s) for termination should be specified and, if clinically possible, the structural integrity of the terminated fetus should be assessed by gross visual inspection (unless preprocedure test findings are conclusive for a congenital anomaly and the findings are reported).

Abnormal pregnancy outcomes are considered SAEs. If the outcome of the pregnancy meets the criteria for an SAE (ie, ectopic pregnancy, spontaneous abortion, intrauterine fetal demise, neonatal death, or congenital anomaly in a live-born baby, a terminated fetus, an intrauterine fetal demise, or a neonatal death), the investigator should follow the procedures for reporting SAEs. Additional information about pregnancy outcomes that are reported to Pfizer Safety as SAEs follows:

- Spontaneous abortion including miscarriage and missed abortion;
- Neonatal deaths that occur within 1 month of birth should be reported, without regard to causality, as SAEs. In addition, infant deaths after 1 month should be reported as SAEs when the investigator assesses the infant death as related or possibly related to exposure to the study intervention.

Additional information regarding the EDP may be requested by the sponsor. Further follow-up of birth outcomes will be handled on a case-by-case basis (eg, follow-up on preterm infants to identify developmental delays). In the case of paternal exposure, the investigator will provide the participant with the Pregnant Partner Release of Information Form to deliver to his partner. The investigator must document in the source documents that the participant was given the Pregnant Partner Release of Information Form to provide to his partner.

8.3.5.2. Exposure During Breastfeeding

An exposure during breastfeeding occurs if:

- A female participant is found to be breastfeeding while receiving or after discontinuing study intervention.
- A female is found to be breastfeeding while being exposed or having been exposed to study intervention (ie, environmental exposure). An example of environmental exposure during breastfeeding is a female family member or healthcare provider who

reports that she is breastfeeding after having been exposed to the study intervention by inhalation or skin contact.

The investigator must report exposure during breastfeeding to Pfizer Safety within 24 hours of the investigator's awareness, irrespective of whether an SAE has occurred. The information must be reported using the CT SAE Report Form. When exposure during breastfeeding occurs in the setting of environmental exposure, the exposure information does not pertain to the participant enrolled in the study**,** so the information is not recorded on an eCRF. However, a copy of the completed CT SAE Report Form is maintained in the investigator site file.

An exposure during breastfeeding report is not created when a Pfizer drug specifically approved for use in breastfeeding women (eg, vitamins) is administered in accord with authorized use. However, if the infant experiences an SAE associated with such a drug, the SAE is reported together with the exposure during breastfeeding.

8.3.5.3. Occupational Exposure

An occupational exposure occurs when a person receives unplanned direct contact with the study intervention, which may or may not lead to the occurrence of an AE. Such persons may include health care providers, family members, and other roles that are involved in the trial participant's care.

The investigator must report occupational exposure to Pfizer Safety within 24 hours of the investigator's awareness, regardless of whether there is an associated SAE. The information must be reported using the CT SAE Report Form. Since the information does not pertain to a participant enrolled in the study, the information is not recorded on an eCRF; however, a copy of the completed CT SAE Report Form is maintained in the investigator site file.

8.3.6. Cardiovascular and Death Events

Not applicable.

8.3.7. Disease-Related Events and/or Disease-Related Outcomes Not Qualifying as AEs or SAEs

Not applicable.

8.3.8. Adverse Events of Special Interest

Any AE that is suspected to be a potential irAE is considered an AE of special interest (AESI). Specific guidance for the management of irAEs is provided in Section 10.13. All AESIs must be reported as an AE or SAE following the procedures described in Sections 8.3.1 through 8.3.4. An AESI is to be recorded as an AE or SAE on the eCRF. In addition, an AESI that is also an SAE must be reported using the CT SAE Report Form.

8.3.8.1. Lack of Efficacy

Lack of efficacy (see Section 10.3.1) is reportable to Pfizer Safety only if associated with an SAE.

8.3.9. Medical Device Deficiencies

Medical devices being provided for use in this study as the study intervention are supplied as a PFS for SC injection. In order to fulfill regulatory reporting obligations worldwide, the investigator is responsible for the detection and documentation of events meeting the definitions of device deficiency that occur during the study with such devices.

The definition of a medical device deficiency can be found in Section 10.7.

NOTE: Deficiencies fulfilling the definition of an AE/SAE will also follow the processes outlined in Section 8.3.1 through 8.3.4 and Section 10.3 of the protocol.

8.3.9.1. Time Period for Detecting Medical Device Deficiencies

- Medical device deficiencies that result in an incident will be detected, documented, and reported during all periods of the study in which the medical device is used. Importantly, reportable device deficiencies are not limited to problems with the device itself but also include incorrect or improper use of the device and even intentional misuse, etc.

- If the investigator learns of any device deficiency at any time after a participant has been discharged from the study, and such incident is considered reasonably related to a medical device provided for the study, the investigator will promptly notify the sponsor.

The method of documenting medical device deficiencies is provided in Section 10.7 and the IP Manual.

8.3.9.2. Follow-Up of Medical Device Deficiencies

AEs and/or SAEs that are associated with the medical device deficiency will follow the same processes as other AEs or SAEs, as outlined in Section 8.3.1. (Time Period and Frequency for Collecting AE and SAE Information) and Section 8.3.4 Regulatory Reporting Requirements for SAEs and Appendix 3: Adverse Events: Definitions and Procedures for Recording, Evaluating, Follow-Up, and Reporting.

8.3.9.3. Prompt Reporting of Device Deficiencies to Sponsor

Device deficiencies will be reported to the sponsor, within one day after the investigator determines that the event meets the protocol definition of a medical device deficiency. Information will be provided to the sponsor as described in the IP Manual.

Any device deficiency that is associated with an SAE must be reported to Pfizer Safety within 24 hours upon the investigator's awareness as outlined in Section 8.3.1.1 and 8.3.1.2.

The sponsor will be the contact for the receipt of device deficiency information.

8.3.9.4. Regulatory Reporting Requirements for Device Deficiencies

- The investigator will promptly report all device deficiencies occurring with any medical device provided for use in the study in order for the sponsor to fulfill the legal responsibility to notify appropriate regulatory authorities and other entities about certain safety information relating to medical devices being used in clinical studies.

- The investigator, or responsible person according to local requirements (eg, the head of the medical institution), will comply with the applicable local regulatory requirements relating to the reporting of device deficiencies to the IRB/EC.

- Note: There are additional reporting obligations for medical device deficiencies that are potentially related to SAEs (ie, an SADE) that must fulfill the legal responsibility to notify appropriate regulatory authorities and other entities about certain safety information relating to medical devices being used in clinical studies.

  - Any device deficiency that is associated with an SAE must be reported to the sponsor within 24 hours after the investigator determines that the event meets the definition of a device deficiency.

  - The sponsor shall review all device deficiencies and determine and document in writing whether they could have led to an SAE. These shall be reported to the regulatory authorities and IRBs/ECs as required by national regulations.

8.3.10. Medication Errors

Medication errors may result from the administration or consumption of the study intervention by the wrong participant, or at the wrong time, or at the wrong dosage strength, or from inadvertent exposure.

Exposures to the intervention under study may occur in clinical trial settings, such as medication errors.

Safety Event	Recorded on the eCRF	Reported on the CT SAE Report Form to Pfizer Safety Within 24 Hours of Awareness
Medication errors	All (regardless of whether associated with an AE)	Only if associated with an SAE

Medication errors include:

- Medication errors involving participant exposure to the study intervention
- Potential medication errors or uses outside of what is foreseen in the protocol that do or do not involve the participant
- Incorrect study treatment taken by participant
- Overdose

Such medication errors occurring to a study participant are to be captured on the medication error page of the eCRF, which is a specific version of the AE page.

In the event of a medication dosing error, the sponsor should be notified within 24 hours.

Whether or not the medication error is accompanied by an AE, as determined by the investigator, the medication error is recorded on the medication error page of the eCRF and, if applicable, any associated AE(s), serious and nonserious, are recorded on an AE page of the eCRF.

Medication errors should be reported to Pfizer Safety within 24 hours on a CT SAE Report Form **only when associated with an SAE**.

8.4. Treatment of Overdose

Injection of any dose of PF-06801591 greater than one complete PFS for Cohorts A and B1 and greater than two complete PFS for Cohort B2 at any scheduled administration visit will be considered an overdose.

Pfizer does not recommend specific treatment for an overdose.

In the event of an overdose, the investigator/treating physician should:

1. Contact the medical monitor within 24 hours.
2. Closely monitor the participant for any AEs/SAEs and laboratory abnormalities for at least 6 months after the overdose of PF-06801591.
3. Document the quantity of the excess dose as well as the duration of the overdose in the eCRF.
4. Overdose is reportable to Safety **only when associated with an SAE.**

Decisions regarding dose interruptions or modifications will be made by the investigator in consultation with the medical monitor based on the clinical evaluation of the participant.

8.5. Pharmacokinetics

Blood samples to provide serum for the analysis of PF-06801591 pre-dose/C_{trough} concentrations will be collected as outlined in the SoA for Arms A and B only in Cohort A. As of 12 September 2022, no PK samples will be collected from participants in Cohorts B1 and B2. The PK sampling schedule may be modified based on emerging PK data.

All efforts will be made to obtain pre-dose PK samples within 2 hours prior to PF-06801591 dosing. However, samples obtained outside that time window will not be captured as a protocol deviation, as long as they are collected on the day of, and prior to, PF-06801591 administration, and the exact time (24-hour clock time) of the sample collection is noted on the source document and data collection tool (eg, eCRF). If a scheduled blood sample

collection cannot be completed for any reason, the missed sample time may be rescheduled with agreement of the clinical investigator, participant, and sponsor.

Sample for PK analysis will be assayed for PF-06801591 using a validated analytical method in compliance with Pfizer standard operating procedures. To increase the understanding of the PK of PF-06801591, samples may be used for the evaluation of the bioanalytical method as well as other internal exploratory purposes unless prohibited by local regulations or ethics committee decision. These data will not be included in the clinical study report. Details regarding the collection, processing, storage, and shipping of the blood samples will be provided in the laboratory manual.

- The PK samples must be processed and shipped as indicated in the instructions provided to the investigator site to maintain sample integrity. Any deviations from the PK sample handling procedure (eg, sample collection and processing steps, interim storage or shipping conditions), including any actions taken, must be documented and reported to the sponsor. On a case-by-case basis, the sponsor may make a determination as to whether sample integrity has been compromised.

8.6. Pharmacodynamics

The biospecimens for pharmacodynamic (PD) assessments will be collected per the SoA and are also listed in Section 8.8.

Pre-dose blood samples will be collected to enable measurements which may include but are not limited to: immune repertoire, proteomic profiles, circulating free deoxyribonucleic acid (cfDNA) or epigenetics at the timepoints specified in the SoA.

As part of understanding the PD of the study intervention, samples may be used for evaluation of the bioanalytical method, as well as for other internal exploratory purposes unless prohibited by local regulations or ethics committee decision. These data will not be included in the clinical study report (CSR).

Some samples may be analyzed using a validated analytical method in compliance with applicable SOPs while others will be analyzed using a non-characterized assay (non-validated).

The PD samples must be processed and shipped as indicated in the instructions provided to the investigator site to maintain sample integrity. Any deviations from the PD sample handling procedure (eg, sample collection and processing steps, interim storage or shipping conditions), including any actions taken, must be documented and reported to the sponsor. On a case-by-case basis, the sponsor may make a determination as to whether sample integrity has been compromised.

As of 12 September 2022, no PD samples will be collected from participants enrolled in Cohorts B1 and B2.

8.7. Genetics

8.7.1. Specified Genetics

No specific samples will be collected for genetic analyses.

8.7.2. Banked Biospecimens for Genetics

Approximately 4 mL blood sample optimized for DNA isolation (Prep D1) will be collected as local regulations and IRBs/IECs allow.

Banked Biospecimens may be used for research related to drug response and NMIBC. Genes and other analytes (eg, proteins, RNA non-drug metabolites) may be studied using the banked samples.

Unless prohibited by local regulations (eg, China and other countries as applicable) or IRB/EC decision, participants will be asked to indicate on the consent form whether they will allow their Banked Biospecimens to also be used to design and conduct research in order to gain a further understanding of other diseases and to advance science, including development of other medicines for patients. This component of the sample banking is optional for participants; they may still participate in the study even if they do not agree to the additional research on their Banked Biospecimens. The optional additional research does not require the collection of any further samples.

See Section 10.5 for Information regarding genetic research. Details on processes for collection and shipment and destruction of these samples can be found in the laboratory manual.

8.8. Biomarkers

Unless prohibited by local regulations or IRB/EC decision, the following samples for biomarker research are required and will be collected from all participants in this study as specified in the SoA:

- Pre-treatment tumor tissue samples to enable assessment of PD-L1 status and cluster of differentiation 8 (CD8) + TIL, whole exome sequencing and gene expression analyses
- 4 mL whole blood samples at baseline and on treatment to enable immune repertoire analyses, epigenetic profiling and filtering of somatic mutation data
- Two 10 mL blood samples at baseline and on treatment to be processed to plasma to enable assessment of cfDNA
- Approximately one 10 mL blood sample at baseline and on treatment to be processed to serum to facilitate proteomic profiling

The objectives of biomarker analyses applied to pre-treatment (TURBT), on-treatment and end-of-treatment tumor biospecimen are to evaluate candidate predictive biomarkers that may be proven useful in identifying participants who may preferentially benefit from the

study treatments and to evaluate mechanisms of action and/or resistance for each of the combinations being assessed.

As of 12 September 2022, no biomarker samples will be collected from participants enrolled in Cohorts B1 and B2.

8.8.1. Tumor Tissue Assessments

Tumor biospecimens representing tissue samples from tumor resection or biopsy will be used to analyze candidate DNA, RNA, or protein markers, or relevant signature of markers for their ability to identify those participants who are most likely to benefit from treatment with the study drugs.

Participants must provide formalin-fixed paraffin-embedded (FFPE) tissue from the TURBT supporting the primary diagnosis for the study and taken within 12 weeks prior to randomization. An FFPE tumor tissue block is requested for all subjects, however, if an FFPE tissue block cannot be provided to due to local, regional or institutional policies, 15 unstained slides (10 minimum) containing recently cut, 5µm sections on positively charged slides will be acceptable. This sample will also be used to reconfirm the diagnosis.

Independent pathology reviewers will provide central assessment of biopsies supporting the primary diagnosis for the study prior to registration in Cohort B1, and retrospective central assessment of all biopsies for participants in Cohorts A and B1. Refer to the laboratory manual for process details on sending the slides for the BICR assessment.

Samples collected during biopsy procedures performed throughout the study (as clinically indicated) should adhere to the same requirements/procedures as the archival samples.

8.8.2. Other Biomarker Assessments

8.8.2.1. Cluster of Differentiation 8 Immunohistochemistry (CD8 IHC)

Immunohistochemistry for CD8 will be performed to quantify the number/proportion of CD8+ T lymphocytes infiltrating each participant's tumor sample.

8.8.2.2. Circulating Free DNA (cfDNA)

cfDNA in double spun plasma samples previously noted in Section 8.6 may be used to quantify/examine cfDNA in pre and post-treatment blood samples.

8.8.3. Immunogenicity Assessments: Analysis of Anti-PF-06801591 Antibodies (ADA) and Neutralizing Anti-PF-06801591 Antibodies (NAb)

Blood samples to provide serum for detection of ADA and NAb against PF-06801591 will be collected into appropriately labeled tubes at times specified in the SoA for Arms A and B only in Cohort A. As of 12 September 2022, no immunogenicity samples will be collected for ADA and NAb analyses from participants enrolled in Cohorts B1 and B2. Additional instructions for sample collection, processing, storage, and shipping will be provided in the lab manual. On PF-06801591 dosing days when immunogenicity is assessed, the blood

samples for ADA analysis should be taken prior to PF-06801591 administration, preferably at the same time as the companion blood sample for the determination of PF-06801591 concentration, which will be collected in conjunction with the ADA/NAb sample collection to facilitate immunogenicity assessment. The actual date and time (24-hour clock time) of each sample will be recorded.

The ADA/NAb samples will be analyzed using a validated assay in compliance with Pfizer standard operating procedures. The sample analysis will follow a tiered approach of screening, confirmation, and titer determination for ADA. Samples tested positive for ADA will be further analyzed for NAb using a validated assay in compliance with Pfizer standard operating procedures.

As part of understanding the immunogenicity of the study drug, samples may be used for additional characterization of an observed immunogenicity response and/or evaluation of the bioanalytical method. These data will be used for internal exploratory purposes and will not be included in the clinical report. Genetic analyses will not be performed on these blood samples. Participant confidentiality will be maintained. Samples collected for this purpose will be retained in accordance with local regulations and, if not used within this timeframe, will be destroyed.

8.8.4. Specified Gene Expression (RNA) Research

An FFPE tissue sample for RNA isolation will be collected as noted previously in Section 8.8.1. The samples will be analyzed by RNA seq. transcriptome profiling to identify signatures associated with response, resistance and adverse events in response to treatment.

Although it is anticipated that most samples will be consumed by planned analyses during the course of the study, any unused samples may be stored at a facility selected by the sponsor indefinitely or for a maximum of 10 years (or according to local regulations) following the last participant's last visit for the study.

8.8.5. Specified Protein Research

Approximately 5 mL serum sample for protein analyses will be collected. The sample(s) may be analyzed for proteomic signatures associated with response or resistance to therapy in pre-treatment and on-treatment samples.

Details on processes for collection and shipment of these sample(s) can be found in the laboratory manual.

Although it is anticipated that most samples will be consumed by planned analyses during the course of the study, any unused samples may be stored at a facility selected by the sponsor indefinitely or for a maximum of 10 years (or according to local regulations) following the last participant's last visit for the study.

8.9. Health Economics

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

9. STATISTICAL CONSIDERATIONS

9.1. Estimands and Statistical Hypotheses

9.1.1. Estimands

Estimands are defined below for the primary and key secondary endpoints.

Table 2 defines the possible clinical outcomes for the EFS evaluation. The clinical definitions of recurrence of high-grade disease, progressive disease, persistence of CIS, recurrence of low-grade disease and CR are included in Section 10.9. For Cohort A, in participants with CIS at randomization "persistence of CIS" is defined as persistence of CIS after induction or, if re-induction is administered, after re-induction. Persistence of CIS after induction with CR after re-induction is not considered persistence of CIS. For Cohort B1 persistence of CIS is defined as persistence of CIS at the 12 week or 24 week disease assessment. Persistence of CIS at the 12 week disease assessment followed by CR at the 24 week disease assessment is not considered persistence of CIS. The censoring and event date options to be considered for the EFS analyses are presented in Table 3.

9.1.1.1. Cohort A

Primary Estimand (EFS for Arm A vs Arm C) and Key Secondary Estimand (EFS for Arm B vs Arm C): treatment effect, estimated based on data from all randomized participants, of each experimental arm (Arm A and Arm B) on EFS compared to Arm C from randomization to the earliest of recurrence of high-grade disease, progression of disease, persistence of CIS, or death, regardless of tolerability, duration of study treatment or initiation of subsequent anti-cancer therapy. The date of the event (event as defined in Table 2) is the date of disease assessment documenting recurrence of high-grade disease, progression of disease, persistence of CIS (applicable only to participants with CIS at randomization), or death, whichever occurs earlier. The date of persistence of CIS is the earliest date when persistence of CIS is observed, if CR is not observed after re-induction.

- Variable: EFS defined as the time from randomization until recurrence of high-grade disease, progression of disease, persistence of CIS, or death due to any cause, whichever occurs first.
- Censoring: See Table 3
- Population-level summary measure: hazard ratio for EFS including all randomized participants.

Supportive Estimand 1 (EFS): treatment effect, estimated based on data from all randomized participants, of each experimental arm (Arm A and Arm B) on EFS compared to Arm C from

randomization to the earliest of recurrence of high-grade disease, progression of disease, persistence of CIS, or death, regardless of tolerability, duration of study treatment or initiation of subsequent anti-cancer therapy. The date of the event (event as defined in Table 2) is the date of disease assessment documenting recurrence of high-grade disease, progression of disease, date of randomization for participants with persistent CIS (applicable only to participants with CIS at randomization), or death, whichever occurs earlier.

- Variable: EFS defined as the time from randomization until recurrence of high-grade disease, progression of disease, persistence of CIS, or death due to any cause, whichever occurs first.

- Censoring: see Table 3

- Population-level summary measure: hazard ratio for EFS including all randomized participants.

Supportive Estimand 2 (EFS): treatment effect of each experimental arm (Arm A and Arm B) on EFS compared to Arm C from randomization to the earliest of recurrence of high-grade disease, progression of disease, persistence of CIS, or death, regardless of tolerability, duration of study treatment, or initiation of subsequent anti-cancer therapy; data from randomized participants who do not meet per-protocol criteria as defined below are excluded. The date of the event (event as defined in Table 2) is the date of disease assessment documenting recurrence of high-grade disease, progression of disease, persistence of CIS (applicable only to participants with CIS at randomization), or death, whichever occurs earlier. The date of persistence of CIS is the earliest date when persistence of CIS is observed, if CR is not observed after re-induction.

- Variable: EFS defined as the time from randomization until recurrence of high-grade disease, progression of disease, persistence of CIS, or death due to any cause, whichever occurs first.

- Censoring: see Table 3

- Population-level summary measure: hazard ratio for EFS excluding randomized participants who did not receive at least one dose of study drug, did not meet inclusion criteria 2 or 3, or met exclusion criteria 1 or 2.

Table 2. Possible Clinical Outcomes for Participants with or without CIS at Randomization and EFS Evaluation

Population	Disease Assessment	EFS Event Y/N
Participants with CIS at randomization	Progressive disease [a] before achieving a CR for participants with CIS only at randomization	Y
	Progressive disease after achieving a CR	Y
	Recurrence of high-grade disease before achieving a CR for participants with CIS and concurrent papillary disease at randomization.	Y
	Recurrence of high-grade disease after achieving a CR	Y
	Persistence of CIS (non-CR) [b]	Y
	Recurrence of low-grade disease	N
Participants without CIS at randomization	Progressive disease	Y
	Recurrence of high-grade disease	Y
	Recurrence of low-grade disease	N

[a] Including appearance of new high-grade Ta or T1 disease for participants with CIS only at randomization.
[b] Persistence of CIS after induction, with CR after re-induction is not considered an event.

Table 3. Outcome and Event Dates for EFS

Scenario	Date of event/censoring	Outcome
No adequate baseline assessment	Date of randomization [a]	Censored [a]
Event - After at most one missing or inadequate post-baseline disease assessment, OR - ≤ 24 weeks after the date of randomization	Date of event	Event
Event - After 2 or more missing or inadequate post-baseline disease assessments	Date of last adequate disease assessment [b] documenting no event	Censored
No event	Date of last adequate disease assessment [b] documenting no event	Censored

[a] However, if the participant dies ≤24 weeks after the date of randomization the death is an event with date on death date

[b] An adequate post-baseline disease assessment is defined as an assessment with progression of disease (all participants), recurrence of high-grade disease (all participants), recurrence of low-grade disease (all participants), CR (participants with CIS at randomization), persistence of CIS disease (participants with CIS at randomization), or no evidence of disease (participants with papillary disease and no CIS at randomization).

Key Secondary Estimand (OS): treatment effect, estimated based on data from all randomized participants, of each experimental arm (Arm A and Arm B) on OS compared to Arm C regardless of tolerability, duration of study treatment, initiation of subsequent anti-cancer therapy or participant's request to discontinue study procedures.

- Variable: OS.

- Censoring: data for participants not known to have died are censored at the time of last contact.

- Population-level summary measure: hazard ratio for OS, including all randomized participants.

9.1.1.2. Cohorts B1 and B2

Due to the decision to close enrollment in Cohorts B1 and B2, the Cohort B1 and B2 estimands are no longer required.

9.2. Sample Size Determination

9.2.1. Cohort A

Approximately 999 participants (including a minimum of 250 participants with CIS) will be randomized in a 1:1:1 ratio to 1 of the 3 treatment arms (A, B, or C) with approximately 333 participants randomized to each treatment arm. Participants were stratified by the presence of CIS (yes vs no) and geography (US vs Western Europe and Canada vs ROW).

The primary objective is to demonstrate that PF-06801591 given in combination with BCG (maintenance and induction) is superior to BCG alone (induction and maintenance) in prolonging EFS in participants with high-risk NMIBC.

The key secondary objectives are:

1) To demonstrate that PF-06801591 given in combination with BCG (induction only) is superior to BCG alone (induction and maintenance) in prolonging EFS in participants with high-risk NMIBC.

2) To demonstrate that PF-06801591 + BCG (induction and maintenance) is superior to BCG (induction and maintenance) in prolonging OS in participants with high-risk NMIBC, and

3) To demonstrate that PF-06801591 + BCG (induction) is superior to BCG (induction and maintenance) in prolonging OS in participants with high-risk NMIBC.

The primary objective will be tested at a significance level of 0.025 (1-sided) associated with hypothesis H_{01} described below:

$$H_{01}: HR_{EFS(AvsC)} \geq 1 \text{ vs. } H_{11}: HR_{EFS(AvsC)} < 1$$

where $HR_{EFS(AvsC)}$ is the hazard ratio for EFS for Arm A vs Arm C.

In addition, the following statistical hypotheses will be tested to address the key secondary objectives:

H_{02}: $HR_{EFS(BvsC)} \geq 1$ vs. H_{12}: $HR_{EFS(BvsC)} < 1$
H_{03}: $HR_{OS(AvsC)} \geqslant 1$ vs. H_{13}: $HR_{OS(AvsC)} < 1$
H_{04}: $HR_{OS(BvsC)} \geqslant 1$ vs. H_{14}: $HR_{OS(BvsC)} < 1$

where $HR_{EFS(BvsC)}$ is the hazard ratio for EFS for Arm B vs Arm C, $HR_{OS(AvsC)}$ is the hazard ratio for OS for Arm A vs Arm C, and $HR_{OS(BvsC)}$ is the hazard ratio for OS for Arm B vs Arm C.

A graphical approach with group sequential testing outlined in Bretz et al. (2009) [31] will be used to strongly control the family-wise type I error rate at a 1-sided 0.025 level as shown in Figure 5 The initial 1-sided alpha allocated to H_{01} is 0.025. If H_{01} is statistically significant, H_{02} and H_{03} will be formally tested at initial 1-sided alpha of 0.023 and 0.002, respectively. If H_{02} is statistically significant, alpha recycling will be applied to evaluate H_{03} at 1-sided 0.025 level. If H_{03} is statistically significant, all the alpha will be recycled to formally test H_{04}.

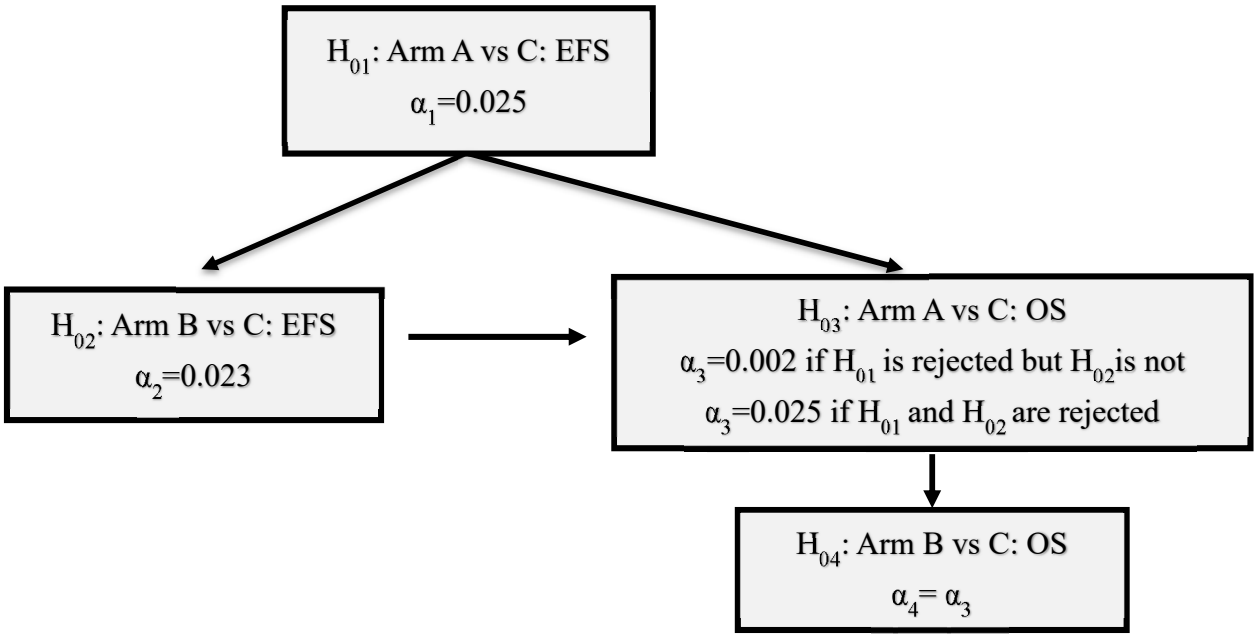
Based on protocol amendment 5, the IA2 will be removed, and the FA for EFS based on a calendar-based data cut-off date will be conducted. Randomization to Cohort A was completed on 16 November 2021 and the EFS FA data cut-off date will be set to allow for approximately 3 years of follow-up after last randomized participant. The treatment period was completed on 16 November 2023. Based on the blinded observed EFS events accrual rate and assuming equal event rate across three arms, approximately 261 EFS events are expected to have occurred across all three arms by (approximately 174 events for each two-arm comparison) by the EFS FA data cut-off date.

For the primary endpoint, if the true HR is 0.69, 174 EFS events in Arm A and Arm C combined will provide 68.7% power to detect a difference using a 1-sided log-rank test at a significance level of 0.025.

One interim and one final efficacy analyses are planned for OS endpoints. A 2-look group sequential design with Haybittle-Peto α spending function will be used to determine the efficacy boundary. The IA for OS will be performed at the time of the final analysis for EFS. The FA for OS will be performed at the end of the study, which is approximately 5 years after the last participant has been randomized in Cohort A.

Cohort A will be considered positive if the primary objective is met.

Figure 5. Testing Strategy



9.2.2. Cohorts B1 and B2

Approximately 110 participants with BCG-unresponsive CIS will be enrolled in Cohort B1; this takes into account 10% of participants not meeting eligibility criteria. This sample size will allow for a 95% CI width for the CR rate to not exceed 0.21. The CR rate will be estimated in BCG-unresponsive CIS participants treated with PF-06801591.

Table 4 provides exact 95% CIs for CR rate based on different possible observed responses in the BCG unresponsive CIS Cohort (Cohort B1).

Table 4. Sample Size and Exact 95% CIs for CR Rate – BCG Unresponsive CIS Cohort B1

Number of participants	Number of observed CRs	Observed CR rate	95% CI for True CR Rate
100	20	20%	(12.67%, 29.18%)
	25	25%	(16.88%, 34.66%)
	30	30%	(21.24%, 39.98%)
	35	35%	(25.73%, 45.18%)
	40	40%	(30.33%, 50.28%)
	45	45%	(35.03%, 55.27%)

Table 4. Sample Size and Exact 95% CIs for CR Rate – BCG Unresponsive CIS Cohort B1

Number of participants	Number of observed CRs	Observed CR rate	95% CI for True CR Rate
	50	50%	(39.83%, 60.17%)
	55	55%	(44.73%, 64.97%)
	60	60%	(49.72%, 69.67%)

In addition, approximately 50 participants with BCG-unresponsive recurrent high-grade Ta/T1 disease will be enrolled in Cohort B2 to further assess safety and efficacy of PF-06801591. The sample size is based on logistic feasibility and not driven by statistical considerations.

As of 31 August 2022, enrollment in Cohorts B1 and B2 was closed by the sponsor for business strategy reasons so the planned sample sizes will not be reached in these Cohorts.

9.3. Populations for Analyses

For purposes of analysis, the following populations are defined:

Population	Description
Enrolled	All participants who sign the ICD
Full Analysis Set (Cohort A) - Randomly Assigned to Study treatment	All participants who are randomized. Participants will be classified according to the study treatment assigned at randomization.
Full Analysis Set (Cohort B1)	All participants who receive at least 1 dose of study drug and are BCG unresponsive with CIS.
Full Analysis Set (Cohort B2)	All participants who receive at least 1 dose of study drug and are BCG unresponsive with papillary disease only.
Per Protocol	Participants randomized excluding those who did not receive at least 1 dose of study drug, did not meet inclusion criteria 2 or 3, or met exclusion criteria 1 or 2.
Safety	All participants who receive at least 1 dose of study drug. For Cohort A, participants will be classified according to the study treatment assigned at randomization unless the incorrect treatment(s) was/were received throughout the dosing period in which case participants will be classified according to the first study treatment received.
Biomarker	The biomarker populations are a subset of the safety population and will include participants with at least 1 of the PD or biomarkers evaluated at pre and/or post dose.
Immunogenicity	Immunogenicity population is a subset of the safety population and will include participants who have at least 1 ADA/NAb sample collected for PF-06801591.

Population	Description
PK	The PK concentration analysis population is a subset of the safety population and will include participants who have at least 1 post-1st dose concentration measurement above the lower limit of quantitation (LLQ) for PF-06801591. The PK parameter population is the same as the PK concentration analysis population.

9.4. Statistical Analyses

The SAP will be developed and finalized before database lock and will describe the participant populations to be included in the analyses, and procedures for accounting for missing, unused, and spurious data. This section is a summary of the planned statistical analyses of the primary and secondary endpoints.

9.4.1. Efficacy Analyses

9.4.1.1. Cohort A

Endpoint	Statistical Analysis Methods
Primary endpoint of EFS for Arm A vs Arm C and key secondary endpoint of EFS for Arm B vs Arm C: defined as time from randomization to the time of recurrence of high-grade disease, progression of disease in high risk NMIBC, or death due to any cause as assessed by the investigator.	For the primary analysis of EFS, all data from randomized participants will be included. The treatment effect will be estimated using a Cox's Proportional Hazard model stratified by randomization strata to calculate the hazard ratio along with 95% CI for EFS between each experimental arm and Arm C *. For the supportive analysis 2 of EFS, data from randomized participants who did not meet the per-protocol population criteria will be excluded. The treatment effect will be estimated using a Cox's Proportional Hazard model stratified by randomization strata to calculate the hazard ratio along with 95% CI for EFS between each experimental arm and Arm C *. For the primary analysis of EFS and supportive analysis 2 of EFS, the date of the event (event as defined in Table 2) is the date of disease assessment documenting recurrence of high-grade disease, progression of disease, persistence of CIS (applicable only to participants with CIS at randomization) or death, whichever occurs earlier. For the supportive analysis 1 of EFS, the date of the event (event as defined in Table 2) is the date of disease assessment documenting recurrence of high-grade disease, progression of disease, date of randomization for participants with persistence of CIS (applicable only to participants with CIS at randomization), or death, whichever occurs earlier. EFS data will be censored as outlined in Table 3. A stratified log-rank test (one-sided) stratified by randomization stratification factors will be used at the significance level associated with the testing strategy outlined in Section 9.2. Kaplan-Meier estimates (product-limit estimates) will be presented by treatment arm together with a summary of associated statistics including the median EFS time with 2-sided 95% CIs. EFS rates at different time points will be estimated with corresponding 2-sided 95% CIs. The CIs for the median will be calculated according to Brookmeyer and Crowley (1982) and the CIs for the survival function estimates at the time points will be derived using the log-log transformation according to

Endpoint	Statistical Analysis Methods
	Kalbfleisch and Prentice (2002) (with back transformation to a CI on the untransformed scale).[50,51] The estimate of the standard error will be computed using Greenwood's formula. An additional analysis for EFS, using the same methodology as the primary estimand and key secondary estimand, will be performed based on BICR results.
Key Secondary: OS	The treatment effect for OS will be estimated using a Cox's Proportional Hazard model stratified by randomization strata to calculate the hazard ratio for OS between each experimental arm and Arm C, including all randomized participants. Data for participants not known to have died are censored at the time of last contact. A stratified log-rank test (one-sided) stratified by randomization stratification factors will be used at the interim and/or final analyses at the significance level associated with the testing strategy outlined in Section 9.2. OS will be analyzed using Kaplan-Meier methods. In order to account for the group sequential design in Cohort A, the repeated CI (RCI) method (Jennison and Turnbull, 2000),[49] will be used to construct the 2-sided RCIs for the hazard ratio at the interim and the final analyses of OS. In addition, the unadjusted 95% CIs for the hazard ratio will also be reported at the interim and the final analyses for OS. Kaplan-Meier estimates (product-limit estimates) will be presented by treatment arm together with a summary of associated statistics including the median OS time with 2-sided 95% CIs. OS rates at different time points will be estimated with corresponding 2-sided 95% CIs. The CIs for the median will be calculated according to Brookmeyer and Crowley (1982) and the CIs for the survival function estimates at the time points will be derived using the log-log transformation according to Kalbfleisch and Prentice (2002) (with back transformation to a CI on the untransformed scale).[50,51] The estimate of the standard error will be computed using Greenwood's formula.
Secondary: DSS, defined as the time from randomization to death resulting from bladder cancer, as assessed by the investigator.	The treatment effect will be estimated using a Cox's Proportional Hazard model stratified by randomization strata to calculate the hazard ratio for DSS between each experimental arm and Arm C. Kaplan-Meier estimates (product-limit estimates) will be presented by treatment arm together with a summary of associated statistics including the median DSS time with 2-sided 95% CIs. DSS rates at various time points will be estimated with corresponding 2-sided 95% CIs. The CIs for the median will be calculated according to Brookmeyer and Crowley (1982) and the CIs for the survival function estimates at the time points will be derived using the log-log transformation according to Kalbfleisch and Prentice (2002) (with back transformation to a CI on the untransformed scale). [50,51] The estimate of the standard error will be computed using Greenwood's formula.
Secondary: CR as assessed by investigator, defined as histologic	Complete response rate for participants with CIS at randomization will be calculated along with the 2-sided 95% CI using the Clopper-Pearson method for each treatment arm. Participants with inadequate data for disease assessment (eg, no follow-up

Endpoint	Statistical Analysis Methods
disappearance of malignancy on bladder biopsy with negative cytology and cystoscopy or negative cytology and positive cystoscopy with biopsy-proven low-grade Ta lesion or non-malignant tissue for participants with CIS at randomization	assessments) will be considered as non-responders in the assessment of complete response. The difference in CR rates between each experimental arm (Arm A and Arm B) and the control arm (Arm C) will be tested with a 2-sided p-value using a stratified analysis stratified by the randomization stratum of geographic region. An additional analysis for CR rate, using the same methodology as above, will be performed based on BICR results.
Secondary: Duration of CR as assessed by investigator, defined as the time from the first documentation of complete response to the date of an EFS event for participants with CR and with CIS at randomization.	Duration of CR will be summarized by treatment arm using Kaplan-Meier methods and displayed graphically, where appropriate. The median duration of CR and 95% CI for the median will be provided for each treatment arm, as well as duration of CR rates at different time points. The CIs for the median will be calculated according to Brookmeyer and Crowley (1982) and the CIs for the survival function estimates at the time points will be derived using the log-log transformation according to Kalbfleisch and Prentice (2002) with back transformation to a CI on the untransformed scale. [50,51] The estimate of the standard error will be computed using Greenwood's formula. Duration of CR will be censored as defined for the primary analysis of EFS except for censoring due to no baseline assessment which is not applicable for participants with CR. An additional analysis of duration of CR, using the same methodology as above, will be performed based on BICR results.
Secondary: Time to recurrence of low-grade disease as assessed by investigator, defined as the time from randomization to the date of first documentation of recurrence of low-grade disease or death due to any cause.	The treatment effect will be estimated using a Cox's Proportional Hazard model stratified by randomization strata to calculate the hazard ratio for time to recurrence of low-grade disease between each experimental arm and Arm C. Time to recurrence of low-grade disease will be analyzed using Kaplan-Meier methods. Kaplan-Meier estimates (product-limit estimates) will be presented by treatment arm together with a summary of associated statistics including the median time to recurrence of low-grade disease with 2-sided 95% CIs. Time to recurrence of low-grade disease rates at various time points will be estimated with corresponding 2-sided 95% CIs. The CIs for the median will be calculated according to Brookmeyer and Crowley (1982) and the CIs for the survival function estimates at the time points will be derived using the log-log transformation according to Kalbfleisch and Prentice (2002) (with back transformation to a CI on the untransformed scale). [50,51] The estimate of the standard error will be computed using Greenwood's formula. Time to recurrence of low-grade disease will be censored as defined in Table 3 for the primary analysis of EFS but with event being recurrence of low-grade disease or death due to any cause.

Endpoint	Statistical Analysis Methods
Secondary: Time to cystectomy, defined as time from randomization to cystectomy.	The treatment effect will be estimated using a Cox's Proportional Hazard model stratified by randomization strata to calculate the hazard ratio for time to cystectomy between each experimental arm and Arm C. Time to cystectomy will be analyzed using Kaplan-Meier methods. Kaplan-Meier estimates (product-limit estimates) and corresponding 2-sided 95% CIs will be presented. Participants without cystectomy will be censored at date last known not to have a cystectomy.

* If there are large deviations from the proportional hazards assumption, the clinical meaning of the hazard ratio becomes difficult, if not impossible, to interpret. In such situations the Restricted Mean Survival Time (RMST) methodology [Royston and Parmar, 2011; Uno, Wei, et al., 2014; Zhang, 2013] can be more meaningfully used than the Cox proportional hazards model to derive an estimate of relative treatment effect.

9.4.1.2. Cohorts B1 and B2

Due to the decision to close enrollment in Cohorts B1 and B2, the Cohort B1 and B2 study objectives are no longer required.

9.4.2. Safety Analyses

All safety analyses will be performed on the Safety Population.

Endpoint	Statistical Analysis Methods
Secondary	Simple summary statistics (descriptive) will be presented for participants with SAEs, AEs of special interest, laboratory test abnormalities and other secondary safety endpoints during the on-treatment period (defined as the time from the first dose of study treatment through minimum (30 days + last dose of study treatment, start day of new anti-cancer drug therapy – 1 day) unless otherwise described in the Statistical Analysis plan (SAP).

9.4.3. Other Analyses

Descriptive statistics will be used to summarize all participant characteristics, treatment administration/compliance, safety parameters, and biomarkers. Data will also be displayed graphically, where appropriate. PK, pharmacodynamic (PD), immunogenicity, PRO, and biomarker exploratory analyses will be described in the statistical analysis plan finalized before database lock.

9.4.3.1. Patient Reported Outcomes

The EORTC QLQ-C30 & NMIBC24, and EQ-5D-5L will be scored according to their respective user guides.

For the EORTC QLQ-C30 & NMIBC24 and EQ-5D-5L, missing items will be handled per the respective scoring manuals of each questionnaire. For the PGIS, PGIC, PTAB, and TSQ, there will be no adjustments for missing data.

Summary statistics [mean (and SD), median, range and 95% CI] of absolute scores will be reported for all of the subscales of the EORTC QLQ-C30 & NMIBC24, PTAB, and the EQ-5D-5L. The mean change of absolute scores from baseline (and 95% CI) will also be assessed. Longitudinal mixed effect-model analyses will be used to assess change from baseline in the EORTC QLQ-C30 & NMIBC24 domains and EQ-5D-5L between the 3 treatment arms in Cohort A. Additional exploratory analyses may be performed, such as analyses of time to deterioration or improvement, if warranted.

9.4.3.2. Pharmacokinetics

The pre-dose (C_{trough}) concentration-time data of PF-06801591 will be summarized by descriptive statistics (n, mean and standard deviation, coefficient of variation, median, minimum, maximum, and geometric mean) for each arm of Cohort A and pooled across both arms of Cohort A. The summary will be presented by cycle and study day.

9.4.3.3. Immunogenicity

ADA/ NAb data for PF-06801591 will be summarized for each arm of Cohort A and pooled across Cohort A.

9.4.3.4. Population Pharmacokinetic Analysis or Pharmacokinetic (PK)/ Pharmacodynamic Modeling

Pharmacokinetic and pharmacodynamic data from this study may be analyzed using modeling approaches and may also be pooled with data from other studies to investigate any association between PF-06801591 exposure and biomarkers or significant safety endpoints. The results of these analyses, if performed, may be reported separately.

9.4.3.5. Biomarkers

In Cohort A, biomarker data will be assessed separately for tumor tissue and peripheral blood. Summary statistics for levels of PD-L1 expression, and number and percentage of participants with tumors categorized with baseline PD-L1 expression level (high vs low) will be presented by arm for Cohort A and overall. For exploratory biomarkers, summary statistics for pre-treatment biomarkers will be presented and summary statistics for on-treatment biomarkers will additionally include the ratio to baseline for continuous biomarkers, and a contingency table for non-continuous biomarkers, as appropriate.

9.5. Interim Analyses (Cohort A only)

Prior to protocol amendment 5, an interim futility analysis of EFS was conducted after 620 participants were randomized to Cohort A, with a total of 25 EFS events for all 3 arms combined. The goal of this futility analysis was to assess if enrollment in an experimental arm should be stopped for futility.

Any safety evaluation performed at the time of the IA for EFS was based on the safety analysis set.

Access to the IA results for the futility analysis of EFS was limited to the EDMC (Section 9.5.1) and independent reporting team.

The Statistical Analysis Plan will describe the planned interim analyses in greater detail.

9.5.1. External Data Monitoring Committee (EDMC)

This study will use an external data monitoring committee (EDMC) to review cumulative safety data during the study conduct, as well as review the IA results for the futility analysis of EFS. In order to confirm that the safety profile of PF-06801591 plus BCG regimen remains aligned with that expected from each agent separately, a review of safety data will be performed by the EDMC approximately 6 weeks after 20 participants in each of the 3 arms have been randomized and received at least 1 dose of study treatments. The EDMC will convene to monitor safety in the study (Cohort A only) approximately every 6 months thereafter until the final analysis of EFS is conducted. The EDMC charter describes the role of the EDMC and data reviews in more detail.

10. SUPPORTING DOCUMENTATION AND OPERATIONAL CONSIDERATIONS

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

10.1.1. Regulatory and Ethical Considerations

- This study will be conducted in accordance with the protocol and with the following:
  - Consensus ethical principles derived from international guidelines including the Declaration of Helsinki and Council for International Organizations of Medical Sciences (CIOMS) International Ethical Guidelines
  - Applicable International Council for Harmonisation (ICH) Good Clinical Practice (GCP) Guidelines
  - Applicable laws and regulations, including applicable privacy laws.

- The protocol, protocol amendments, ICD, SRSD(s), and other relevant documents (eg, advertisements) must be reviewed and approved by the sponsor and submitted to an IRB/IEC by the investigator and reviewed and approved by the IRB/IEC before the study is initiated.

- Any amendments to the protocol will require IRB/IEC approval before implementation of changes made to the study design, except for changes necessary to eliminate an immediate hazard to study participants.

- Protocols and any substantial amendments to the protocol will require health authority approval prior to initiation except for changes necessary to eliminate an immediate hazard to study participants.

- The investigator will be responsible for the following:
  - Providing written summaries of the status of the study to the IRB/IEC annually or more frequently in accordance with the requirements, policies, and procedures established by the IRB/IEC
  - Notifying the IRB/IEC of SAEs or other significant safety findings as required by IRB/IEC procedures
  - Providing oversight of the conduct of the study at the site and adherence to requirements of Code of Federal Regulations, Title 21 (21CFR), ICH GCP guidelines, the IRB/IEC, European regulation 536/2014 for clinical studies (if applicable), European Medical Device Regulation 2017/745 for clinical device research, and all other applicable local regulations

10.1.1.1. Reporting of Safety Issues and Serious Breaches of the Protocol or ICH GCP

- In the event of any prohibition or restriction imposed (ie, clinical hold) by an applicable regulatory authority in any area of the world, or if the investigator is aware

of any new information that might influence the evaluation of the benefits and risks of the study intervention, Pfizer should be informed immediately.

- In addition, the investigator will inform Pfizer immediately of any urgent safety measures taken by the investigator to protect the study participants against any immediate hazard, and of any serious breaches of this protocol or of ICH GCP that the investigator becomes aware of.

10.1.2. Financial Disclosure

Investigators and subinvestigators will provide the sponsor with sufficient, accurate financial information as requested to allow the sponsor to submit complete and accurate financial certification or disclosure statements to the appropriate regulatory authorities. Investigators are responsible for providing information on financial interests during the course of the study and for 1 year after completion of the study.

10.1.3. Informed Consent Process

- The investigator or his/her representative will explain the nature of the study, including the risks and benefits, to the participant or his/her legally authorized representative and answer all questions regarding the study. The participant or their legally authorized representative should be given sufficient time and opportunity to ask questions and to decide whether or not to participate in the trial.

- Participants must be informed that their participation is voluntary. Participants or their legally authorized representative will be required to sign a statement of informed consent that meets the requirements of 21 CFR 50, local regulations, ICH GCP guidelines, Health Insurance Portability and Accountability Act (HIPAA) requirements, where applicable, and the IRB/IEC or study center.

- The investigator must ensure that each study participant or his or her legally authorized representative is fully informed about the nature and objectives of the study, the sharing of data related to the study and possible risks associated with participation, including the risks associated with the processing of the participant's personal data. The participant must be informed that his/her personal study-related data will be used by the sponsor in accordance with local data protection law. The level of disclosure must also be explained to the participant.

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

- The investigator further must ensure that each study participant or his or her legally authorized representative is fully informed about his or her right to access and correct his or her personal data and to withdraw consent for the processing of his or her personal data.

- The medical record must include a statement that written informed consent was obtained before the participant was enrolled in the study and the date the written consent was obtained. The authorized person obtaining the informed consent must also sign the ICD.

- Participants must be re-consented to the most current version of the IRB/EC-approved ICD(s) during their participation in the study as required per local regulations.

- A copy of the ICD(s) must be provided to the participant or the participant's legally authorized representative.

Participants who are rescreened are required to sign a new ICD.

The ICD will contain a separate section that addresses the use of remaining mandatory samples for optional exploratory research. The investigator or authorized designee will explain to each participant the objectives of the exploratory research. Participants will be told that they are free to refuse to participate and may withdraw their consent at any time and for any reason during the storage period. A separate signature will be required to document a participant's agreement to allow any remaining specimens to be used for exploratory research. Participants who decline to participate in this optional research will not provide this separate signature.

10.1.4. Data Protection

- All parties will comply with all applicable laws, including laws regarding the implementation of organizational and technical measures to ensure protection of participant data.

- Participants' personal data will be stored at the study site in encrypted electronic form and will be password protected to ensure that only authorized study staff have access. The study site will implement appropriate technical and organizational measures to ensure that the personal data can be recovered in the event of disaster. In the event of a potential personal data breach, the study site shall be responsible for determining whether a personal data breach has in fact occurred and, if so, providing breach notifications as required by law.

- To protect the rights and freedoms of natural persons with regard to the processing of personal data, participants will be assigned a single, participant-specific numerical code. Any participant records or datasets that are transferred to the sponsor will contain the numerical code; participant names will not be transferred. All other identifiable data transferred to the sponsor will be identified by this single, participant-specific code. The study site will maintain a confidential list of participants who participated in the study, linking each participant's numerical code to his or her actual identity. In case of data transfer, the sponsor will protect the confidentiality of participants' personal data consistent with the Clinical Study Agreement and applicable privacy laws.

- Information technology systems used to collect, process, and store study-related data are secured by technical and organizational security measures designed to protect such data against accidental or unlawful loss, alteration, or unauthorized disclosure or access.

- The sponsor maintains SOPs on how to respond in the event of unauthorized access, use, or disclosure of sponsor information or systems.

10.1.5. Committees Structure

This study will use an EDMC and a Steering Committee.

The EDMC will be responsible for ongoing monitoring of the safety of participants in the study according to the charter. The recommendations made by the EDMC to alter the conduct of the study will be forwarded to Pfizer for final decision. Pfizer will forward such decisions, which may include summaries of aggregate analyses of endpoint events and of safety data that are not endpoints, to regulatory authorities, as appropriate.

The Steering Committee will include leading experts in the field of oncology. The committee is a general resource for the latest developments in the use of immunotherapies for patients with bladder cancer and will provide advice on several aspects of the protocol including, but not limited to, medical questions, responses to regulatory feedback, and protocol amendment design, as needed.

10.1.6. Dissemination of Clinical Study Data

Pfizer fulfills its commitment to publicly disclose clinical study results through posting the results of studies on www.clinicaltrials.gov (ClinicalTrials.gov), the EudraCT/CTIS, and/or www.pfizer.com, and other public registries in accordance with applicable local laws/regulations. In addition, Pfizer reports study results outside of the requirements of local laws/regulations pursuant to its standard operating procedures (SOPs).

In all cases, study results are reported by Pfizer in an objective, accurate, balanced, and complete manner and are reported regardless of the outcome of the study or the country in which the study was conducted.

www.clinicaltrials.gov

Pfizer posts clinical trial US Basic Results on www.clinicaltrials.gov for Pfizer-sponsored interventional studies (conducted in patients) that evaluate the safety and/or efficacy of a product, regardless of the geographical location in which the study is conducted. These results are submitted for posting in accordance with the format and timelines set forth by US law.

EudraCT/CTIS

Pfizer posts European Union (EU) Basic Results on EudraCT/CTIS for all Pfizer-sponsored interventional studies that are in scope of EU requirements.

www.pfizer.com

Pfizer posts CSR synopses and plain-language study results summaries on www.pfizer.com for Pfizer-sponsored interventional studies at the same time the corresponding study results are posted to www.clinicaltrials.gov. CSR synopses will have personally identifiable information anonymized.

Documents within marketing applications

Pfizer complies with applicable local laws/regulations to publish clinical documents included in marketing applications. Clinical documents include summary documents and CSRs including the protocol and protocol amendments, sample CRFs, and SAPs. Clinical documents will have personally identifiable information anonymized.

Data Sharing

Pfizer provides researchers secure access to participant-level data or full CSRs for the purposes of "bona-fide scientific research" that contribute to the scientific understanding of the disease, target, or compound class. Pfizer will make data from these trials available 18 months after study completion. Participant-level data will be anonymized in accordance with applicable privacy laws and regulations. CSRs will have personally identifiable information redacted.

Data requests are considered from qualified researchers with the appropriate competencies to perform the proposed analyses. Research teams must include a biostatistician. Data will not be provided to applicants with significant conflicts of interest, including individuals requesting access for commercial/competitive or legal purposes.

10.1.7. Data Quality Assurance

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

- Guidance on completion of CRFs will be provided in the CRF Completion Requirements document.

- The investigator must ensure that the eCRFs are securely stored at the study site in encrypted electronic form and are password protected to prevent access by unauthorized third parties.

- The investigator must permit study-related monitoring, audits, IRB/IEC review, and regulatory agency inspections and provide direct access to source data documents. This verification may also occur after study completion. It is important that the investigator(s) and their relevant personnel are available during the monitoring visits and possible audits or inspections and that sufficient time is devoted to the process.

- Monitoring details describing strategy , including definition of study-critical data items and processes (eg, risk-based initiatives in operations and quality such as risk management and mitigation strategies and analytical risk-based monitoring), methods, responsibilities, and requirements, including handling of noncompliance issues and monitoring techniques (central, virtual, or on-site monitoring), are provided in the data management plan maintained and utilized by the sponsor or designee.

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

- Records and documents, including signed ICDs, pertaining to the conduct of this study must be retained by the investigator for 15 years after study completion unless local regulations or institutional policies require a longer retention period. No records may be destroyed during the retention period without the written approval of the sponsor. No records may be transferred to another location or party without written notification to the sponsor. The investigator must ensure that the records continue to be stored securely for so long as they are maintained.

- When participant data are to be deleted, the investigator will ensure that all copies of such data are promptly and irrevocably deleted from all systems.

- The investigator(s) will notify sponsor or its agents immediately of any regulatory inspection notification in relation to the study. Furthermore, the investigator will cooperate with sponsor or its agents to prepare the investigator site for the inspection and will allow sponsor or its agent, whenever feasible, to be present during the inspection. The investigator site and investigator will promptly resolve any discrepancies that are identified between the study data and the participant's medical records. The investigator will promptly provide copies of the inspection findings to sponsor or its agent. Before response submission to the regulatory authorities, the investigator will provide sponsor or its agents with an opportunity to review and comment on responses to any such findings.

10.1.8. Source Documents

- Source documents provide evidence for the existence of the participant and substantiate the integrity of the data collected. Source documents are filed at the investigator's site.
- Data reported on the CRF or entered in the eCRF that are transcribed from source documents must be consistent with the source documents or the discrepancies must be explained. The investigator may need to request previous medical records or transfer records, depending on the study. Also, current medical records must be available.
- Definition of what constitutes source data can be found in the study monitoring plan.

10.1.9. Use of Medical Records

There may be instances when copies of medical records for certain cases are requested by Pfizer Safety, where ethically and scientifically justified and permitted by local regulations, to ensure participant safety.

Due to the potential for a participant to be re-identified from their medical records, the following actions must be taken when medical records are sent to the sponsor or sponsor designee:

- The investigator or site staff must redact personal information from the medical record. The personal information includes, but is not limited to, the following: participant names or initials, participant dates (eg, birth date, date of hospital admission/discharge, date of death), participant identification numbers (eg, Social Security number, health insurance number, medical record number, hospital/institution identifier), participant location information (eg, street address, city, country, postal code, IP address), participant contact information (eg, telephone/fax number, email address).

- Each medical record must be transmitted to the sponsor or sponsor designee using systems with technical and organizational security measures to ensure the protection of personal data (eg, Florence is the preferred system if available).

- There may be unplanned situations where the sponsor may request medical records (eg, sharing medical records so that the sponsor can provide study-related advice to the investigator). The medical records should be submitted according to the procedure described above.

10.1.10. Study and Site Closure

The study start date is the date of the first participant's first visit.

The sponsor designee reserves the right to close the study site or terminate the study at any time for any reason at the sole discretion of the sponsor. Study sites will be closed upon study completion. A study site is considered closed when all required documents and study supplies have been collected and a study-site closure visit has been performed.

The investigator may initiate study-site closure at any time upon notification to the contract research organization (CRO) if requested to do so by the responsible IRB/IEC or if such termination is required to protect the health of Study Participants.

Reasons for the early closure of a study site by the sponsor may include but are not limited to:

- Failure of the investigator to comply with the protocol, the requirements of the IRB/IEC or local health authorities, the sponsor's procedures, or GCP guidelines

- Inadequate recruitment of participants by the investigator

- Discontinuation of further study treatment development

If the study is prematurely terminated or suspended, the sponsor shall promptly inform the investigators, the ECs/IRBs, the regulatory authorities, and any CRO(s) used in the study of the reason for termination or suspension, as specified by the applicable regulatory requirements. The investigator shall promptly inform the participant and should assure appropriate participant therapy and/or follow-up.

If the sponsor decides to terminate the study for a reason unrelated to the safety of PF-06801591 or BCG, participants may continue to receive that study intervention(s) per the investigator's judgment and protocol-specified safety assessments will continue to be performed for these participants until the end of the study as defined in Section 4.4.

Nonsafety related study procedures and assessments may be stopped upon written notification from the sponsor will be detailed upon notification of decision to terminate the study.

Study termination is also provided for in the clinical study agreement. If there is any conflict between the contract and this protocol the contract will control as to termination rights.

10.1.11. Publication Policy

- The results of this study may be published or presented at scientific meetings by the Investigator after publication of the overall study results or one year after end of the study (or study termination), whichever comes first.

- The investigator agrees to refer to the primary publication in any subsequent publications such as secondary manuscripts, and to submit all manuscripts or abstracts to the sponsor 30 days before submission. This allows the sponsor to protect proprietary information and to provide comments and the Investigator will, on request, remove any previously undisclosed confidential information before disclosure, except for any study- or Pfizer intervention-related information necessary to the appropriate scientific presentation or understanding of the study results.

- For all publications relating to the study, the Investigator will comply with recognized ethical standards concerning publications and authorship, including those established by the International Committee of Medical Journal Editors.

- The sponsor will comply with the requirements for publication of the overall study results covering all Investigator sites. In accordance with standard editorial and ethical practice, the sponsor will support publication of multicenter studies only in their entirety and not as individual site data. In this case, a coordinating investigator will be designated by mutual agreement.

- Authorship of publications for the overall study results will be determined by mutual agreement and in line with International Committee of Medical Journal Editors authorship requirements.

- If publication is addressed in the clinical study agreement, the publication policy set out in this section will not apply.

10.1.12. Sponsor's Qualified Medical Personnel

The sponsor will designate a medically qualified individual (MQI, also known as the medical monitor) to advise the investigator on study-related medical questions. The contact information for the study medical monitor is documented in the Study Team Contact List located in the Investigator Site File.

Participants are provided with a Pfizer study information card at the time of informed consent which includes contact information for their investigator in case of study-related medical questions. The study information card contains, at a minimum, (a) study number, (b) participant's study identification number, and (c) principal investigator contact information.

10.2. Appendix 2: Clinical Laboratory Tests

Hematology and blood chemistry will be drawn at the time points described in the SoA.

- The tests detailed in Table 5 will be performed by the local laboratory.
- Protocol-specific requirements for inclusion or exclusion of participants are detailed in Section 5 of the protocol.
- Additional tests may be performed at any time during the study as determined necessary by the investigator or required by local regulations.
- Pregnancy Testing
    - Refer to Section 5.1 Inclusion Criteria for screening pregnancy criteria.
    - Pregnancy testing (urine or serum as required by local regulations) should be conducted at monthly intervals (eg, Day 1 of each cycle) during intervention as per SoA. Following a negative pregnancy test result at screening, appropriate contraception must be commenced, and a second negative pregnancy test result will then be required at the baseline visit on C1D1 before the participant may receive the study treatment. Pregnancy tests will also be done whenever 1 menstrual cycle is missed during the active treatment period (or when potential pregnancy is otherwise suspected) and at the end of the study. If a urine test cannot be confirmed as negative (eg, an ambiguous result), a serum pregnancy test is required. In such cases, the participant must be excluded from participation if the serum pregnancy result is positive.
        - Pregnancy testing (urine or serum as required by local regulations) should be conducted at the end of relevant systemic exposure plus an additional 30 days.
        - At Day 90 and Day 180 after EOT, pregnancy status should be discussed (may be done by telephone, unless the participant is visiting the site for other reasons) and pregnancy test can be conducted as necessary.
        - 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.

Table 5. Protocol Specified Laboratory Tests

Hematology	Chemistry	Coagulation	Serology	Urinalysis[a]	Pregnancy Test or Postmenopausal Status
Hematocrit	ALT	INR	HBsAg,	Urine dipstick for urine protein: If positive, collect a spot urine to calculate UPCR or collect 24-hr and microscopic (Reflex Testing).	For female participants of childbearing potential, serum or urine test (sensitivity ≥25 mIU/mL); For female postmenopausal participants under the age of 60 and not using hormonal contraception or HRT a serum FSH test is required at screening only, to confirm postmenopausal status.
Hemoglobin	AST	PTT or aPTT[c]	HCV Ab[d]		
	LDH				
Platelets	Alkaline Phosphatase				
WBC	Sodium				
Absolute Neutrophils	Potassium				
Lymphocytes	Magnesium			Urine dipstick for urine blood: If positive twice or as clinically indicated perform microscopic analysis (Reflex Testing).	
Monocytes	Chloride				
Eosinophils	Total Calcium				
Basophils	Total Bilirubin[b]				
	BUN or Urea				
	Creatinine				
	Uric Acid				
	Glucose (non-fasted)				
	Albumin				
	Phosphorous or Phosphate				
	Lipase				
	Amylase				
	Thyroid function test + reflex free T4 and free T3				
	ACTH				
	Cohorts B1 and B2 only: CK (If total CK ≥ 3 x ULN, then measure isoenzymes CK-MB and CK-MM)				

ALT = alanine aminotransferase; AST = aspartate aminotransferase; BUN = blood urea nitrogen; CK = creatine kinase; CK-MB = creatine kinase-muscle type, myocardial band; CK-MM = creatine kinase-skeletal muscle; FSH = follicle stimulating hormone; HBsAg = hepatitis B antigen; HCV = hepatitis C virus; INR = international normalized ratio; LDH = lactate dehydrogenase; PTT = partial thromboplastin time; aPTT = activated partial thromboplastin time; T3 = triiodothyronine; T4 = thyroxine; UPCR = urine protein to creatinine ratio

a. Dipstick is acceptable to perform urinalysis. Microscopic analyses if clinically indicated (eg, only after the second positive dipstick result for heme). If ≥2+ protein on urine dipstick, then collect spot urine sample to calculate UPCR or collect 24hr urine.

b. For potential Hy's Law cases, in addition to repeating AST and ALT, laboratory tests should include albumin, creatine kinase, total bilirubin, direct and indirect bilirubin, gamma glutamyl transferase, prothrombin time (PT) or INR, alkaline phosphatase, total bile acids, and acetaminophen drug and/or protein adduct levels.

c. Use either PTT or aPPT consistently at all time points for each participant throughout the course of the study.

d. In the case of apparent ongoing HBV or HCV infection, reflex serum viral load testing will be performed.

Investigators must document their review of each laboratory safety report.

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

10.3.1. Definition of AE

AE Definition
• An AE is any untoward medical occurrence in a participant or clinical study participant, temporally associated with the use of study treatment, whether or not considered related to the study treatment. • NOTE: An AE can therefore be any unfavorable and unintended sign (including an abnormal laboratory finding), symptom, or disease (new or exacerbated) temporally associated with the use of study treatment.

Events Meeting the AE Definition

• Any abnormal laboratory test results (hematology, clinical chemistry, or urinalysis) or other safety assessments (eg, ECG, radiological scans, vital signs measurements), including those that worsen from baseline, considered clinically significant in the medical and scientific judgment of the investigator. Any abnormal laboratory test results that meet any of the conditions below must be recorded as an AE:
  • Is associated with accompanying symptoms.
  • Requires additional diagnostic testing or medical/surgical intervention.
  • Leads to a change in study dosing (outside of any protocol-specified dose adjustments) or discontinuation from the study, significant additional concomitant drug treatment, or other therapy.
• Exacerbation of a chronic or intermittent preexisting condition including either an increase in frequency and/or intensity of the condition.
• New conditions detected or diagnosed after study intervention administration even though it may have been present before the start of the study.
• Signs, symptoms, or the clinical sequelae of a suspected drug-drug interaction.
• Signs, symptoms, or the clinical sequelae of a suspected overdose of either study intervention or a concomitant medication. Overdose per se will not be reported as an AE/SAE unless it is an intentional overdose taken with possible suicidal/self-harming intent. Such overdoses should be reported regardless of sequelae.
• The signs, symptoms, and/or clinical sequelae resulting from lack of efficacy will be reported as an AE or SAE if they fulfill the definition of an AE or SAE and meet the requirements as per Section 8.3.8.1. Also, “lack of efficacy” or “failure of expected pharmacological action” does not constitute an AE or SAE.

Events NOT Meeting the AE Definition
• Any clinically significant abnormal laboratory findings or other abnormal safety assessments which are associated with the underlying disease, unless judged by the investigator to be more severe than expected for the participant's condition. • The disease/disorder being studied or expected progression, signs, or symptoms of the disease/disorder being studied, unless more severe than expected for the participant's condition. • Medical or surgical procedure (eg, endoscopy, appendectomy): the condition that leads to the procedure is the AE. • Situations in which an untoward medical occurrence did not occur (social and/or convenience admission to a hospital). • Anticipated day-to-day fluctuations of preexisting disease(s) or condition(s) present or detected at the start of the study that do not worsen. • Worsening of signs and symptoms of the malignancy under study should be recorded as AEs in the appropriate section of the eCRF. Disease progression assessed by measurement of malignant lesions on radiographs or other methods should not be reported as AEs.

10.3.2. Definition of SAE

If an event is not an AE per definition above, then it cannot be an SAE even if serious conditions are met (eg, hospitalization for signs/symptoms of the disease under study, death due to progression of disease).

An SAE is defined as any untoward medical occurrence that, at any dose:
a. Results in death
b. Is life-threatening The term "life-threatening" in the definition of "serious" refers to an event in which the participant was at risk of death at the time of the event. It does not refer to an event, that hypothetically might have caused death, if it were more severe.
c. Requires inpatient hospitalization or prolongation of existing hospitalization In general, hospitalization signifies that the participant has been detained (usually involving at least an overnight stay) at the hospital or emergency ward for observation and/or treatment that would not have been appropriate in the physician's office or outpatient setting. Complications that occur during hospitalization are AEs. If a complication prolongs hospitalization or fulfills any other serious criteria, the event is serious. When in doubt as to whether "hospitalization" occurred or was necessary, the AE should be considered serious. Hospitalization for elective treatment of a preexisting condition that did not worsen from baseline is not considered an AE.

d. Results in persistent disability/incapacity

- The term disability means a substantial disruption of a person's ability to conduct normal life functions.
- This definition is not intended to include experiences of relatively minor medical significance such as uncomplicated headache, nausea, vomiting, diarrhea, influenza, and accidental trauma (eg, sprained ankle) which may interfere with or prevent everyday life functions but do not constitute a substantial disruption.

e. Is a congenital anomaly/birth defect

f. Other situations:

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

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

- Progression of the malignancy under study (including signs and symptoms of progression) should not be reported as an SAE unless the outcome is fatal within the active collection period. Hospitalization due to signs and symptoms of disease progression should not be reported as an SAE. If the malignancy has a fatal outcome during the study or within the active collection period, then the event leading to death must be recorded as an AE on the eCRF, and as an SAE with CTCAE Grade 5 (see the Assessment of Intensity section).
- Suspected transmission via a Pfizer product of an infectious agent, pathogenic or non-pathogenic, is considered serious. The event may be suspected from clinical symptoms or laboratory findings indicating an infection in a participant exposed to a Pfizer product. The terms "suspected transmission" and "transmission" are considered synonymous. These cases are considered unexpected and handled as serious expedited cases by pharmacovigilance personnel. Such cases are also considered for reporting as product defects, if appropriate.

10.3.3. Recording and Follow-Up of AE and/or SAE

AE and SAE Recording/Reporting

The table below summarizes the requirements for recording adverse events on the eCRF and for reporting serious adverse events on the CT SAE Report Form to Pfizer Safety. These requirements are delineated for 3 types of events: (1) SAEs; (2) nonserious adverse events (AEs); and (3) exposure to the intervention under study during pregnancy or breastfeeding, and occupational exposure.

It should be noted that the CT SAE Report Form for reporting of SAE information is not the same as the AE page of the eCRF. When the same data are collected, the forms must be completed in a consistent manner. AEs should be recorded using concise medical terminology and the same AE term should be used on both the eCRF and the CT SAE Report Form for reporting of SAE information

Safety Event	**Recorded on the eCRF**	**Reported on the CT SAE Report Form to Pfizer Safety Within 24 Hours of Awareness**
SAE	All	All
Nonserious AE	All	None
Exposure to the intervention under study during pregnancy or breastfeeding, and occupational exposure	All AEs/SAEs associated with exposure during pregnancy or breastfeeding Occupational exposure is not recorded.	All (And EDP supplemental form for EDP) Note: Include all SAEs associated with exposure during pregnancy or breastfeeding. Include all AEs/SAEs associated with occupational exposure.

- When an AE/SAE occurs, it is the responsibility of the investigator to review all documentation (eg, hospital progress notes, laboratory reports, and diagnostics reports) related to the event.
- The investigator will then record all relevant AE/SAE information in the eCRF.
- It is **not** acceptable for the investigator to send photocopies of the participant's medical records to Pfizer Safety in lieu of completion of the CT SAE Report Form/AE/SAE eCRF page.
- There may be instances when copies of medical records for certain cases are requested by Pfizer Safety. In this case, all participant identifiers, with the exception of the participant number, will be redacted on the copies of the medical records before submission to Pfizer Safety.

- The investigator will attempt to establish a diagnosis of the event based on signs, symptoms, and/or other clinical information. Whenever possible, the diagnosis (not the individual signs/symptoms) will be documented as the AE/SAE.

Assessment of Intensity

The investigator will make an assessment of intensity for each AE and SAE reported during the study and assign it to 1 of the following categories:

GRADE	Clinical Description of Severity
1	MILD adverse event
2	MODERATE adverse event
3	SEVERE adverse event
4	LIFE-THREATENING consequences; urgent intervention indicated
5	DEATH RELATED TO adverse event

An event is defined as "serious" when it meets at least 1 of the predefined outcomes as described in the definition of an SAE, NOT when it is rated as severe.

Assessment of Causality

- The investigator is obligated to assess the relationship between study intervention and each occurrence of each AE/SAE.
- A "reasonable possibility" of a relationship conveys that there are facts, evidence, and/or arguments to suggest a causal relationship, rather than a relationship cannot be ruled out.
- The investigator will use clinical judgment to determine the relationship.
- Alternative causes, such as underlying disease(s), concomitant therapy, and other risk factors, as well as the temporal relationship of the event to study intervention administration will be considered and investigated.
- The investigator will also consult the IB and/or Product Information, for marketed products, in his/her assessment.
- For each AE/SAE, the investigator **must** document in the medical notes that he/she has reviewed the AE/SAE and has provided an assessment of causality.

- There may be situations in which an SAE has occurred, and the investigator has minimal information to include in the initial report to the sponsor. However, **it is very important that the investigator always make an assessment of causality for every event before the initial transmission of the SAE data to Pfizer Safety.**
  - The investigator may change his/her opinion of causality in light of follow-up information and send a SAE follow-up report with the updated causality assessment.

- The causality assessment is one of the criteria used when determining regulatory reporting requirements.
- If the investigator does not know whether or not the study intervention caused the event, then the event will be handled as "related to study intervention" for reporting purposes, as defined by the sponsor. In addition, if the investigator determines that an SAE is associated with study procedures, the investigator must record this causal relationship in the source documents and eCRF, and report such an assessment in the dedicated section of the CT SAE Report Form and in accordance with the SAE reporting requirements.

Follow-Up of AEs and SAEs

- The investigator is obligated to perform or arrange for the conduct of supplemental measurements and/or evaluations as medically indicated or as requested by the sponsor to elucidate the nature and/or causality of the AE or SAE as fully as possible. This may include additional laboratory tests or investigations, histopathological examinations, or consultation with other health care providers.
- If a participant dies during participation in the study or during a recognized follow-up period, the investigator will provide Pfizer Safety with a copy of any post-mortem findings including histopathology.
- New or updated information will be recorded in the originally completed eCRF.
- The investigator will submit any updated SAE data to the Sponsor within 24 hours of receipt of the information.

10.3.4. Reporting of SAEs

SAE Reporting to Pfizer Safety via CT SAE Report Form

- Facsimile transmission of the CT SAE Report Form is the preferred method to transmit this information to Pfizer Safety.
- In rare circumstances when the facsimile is not working, notification by telephone is acceptable with a copy of the CT SAE Report Form sent by overnight mail or courier service.
- Initial notification via telephone does not replace the need for the investigator to complete and sign the SAE CRF Report Form pages within the designated reporting time frames.

10.4. Appendix 4: Contraceptive Guidance

10.4.1. Male Participant Reproductive Inclusion Criteria

Male participants are eligible to participate if they agree to the following during the intervention period and for at least 6 months after the last dose of study intervention, which corresponds to the time needed to eliminate reproductive and BCG transmission risks of the study intervention(s).

- Refrain from donating sperm

PLUS either:

Be abstinent from heterosexual or homosexual intercourse as their preferred and usual lifestyle (abstinent on a long term and persistent basis) and agree to remain abstinent

OR

Must agree to use contraception/barrier as detailed below

- Agree to use a male condom and should also be advised of the benefit for a female partner to use a highly effective method of contraception as a condom may break or leak when having sexual intercourse with a woman of childbearing potential who is not currently pregnant.

10.4.2. Female Participant Reproductive Inclusion Criteria

A female participant is eligible to participate if she is not pregnant or breastfeeding, including participants who intend to interrupt breastfeeding, and at least one of the following conditions applies:

Is not a woman of childbearing potential (WOCBP)

OR

Is a WOCBP and using a contraceptive method that is highly effective (with a failure rate of <1% per year) preferably with low user dependency, as described in the table below during the intervention period and for at least 6 months after the last dose of study intervention which corresponds to the time needed to eliminate any reproductive safety risk of the study intervention; and agrees not to donate eggs (ova, oocytes) for the purpose of reproduction during this period. As for participants using a highly effective methods that is user dependent, this contraception method must be used together with a second effective method of contraception, as described below. The investigator should evaluate the effectiveness of the contraceptive method in relationship to the first dose of study intervention.

- 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.

10.4.3. Woman of Childbearing Potential

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 treatment, additional evaluation should be considered.

Women in the following categories are not considered WOCBP

1. 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 for any of the above conditions can come from the site personnel's review of the participant's medical records, medical examination, or medical history interview. The method of documentation should be recorded in the participant's medical record for the study.

2. Postmenopausal female

    - A postmenopausal state is defined as no menses for 12 months without an alternative medical cause. In addition, a
        - high FSH level in the postmenopausal range must be used to confirm a postmenopausal state in women under 60 years of age and not using hormonal contraception or HRT.
    - Females on HRT and whose menopausal status is in doubt will be required to use one of the non-estrogen hormonal highly effective contraception methods if they wish to continue their HRT during the study. Otherwise, they must discontinue HRT to allow confirmation of postmenopausal status before study enrollment.

10.4.4. Contraception Methods

Contraceptive use by men or women should be consistent with local availability/regulations regarding the use of contraceptive methods for those participating in clinical trials.

CONTRACEPTIVES ALLOWED DURING THE STUDY INCLUDE:
Highly Effective Methods That Have Low User Dependency
• Implantable progestogen-only hormone contraception associated with inhibition of ovulation
• Intrauterine device (IUD)
• Intrauterine hormone-releasing system (IUS)
• Bilateral tubal occlusion
• Vasectomized partner o Vasectomized partner is a highly effective contraceptive method provided that the partner is the sole sexual partner of the woman of childbearing potential and the absence of sperm has been confirmed. If not, an additional highly effective method of contraception should be used. Spermatogenesis cycle is approximately 90 days.
Highly Effective Methods That Are User Dependent
• Combined (estrogen and progesterone containing) hormonal contraception associated with inhibition of ovulation o oral o intravaginal o transdermal
• Progestogen-only hormone contraception associated with inhibition of ovulation o oral o injectable
• Sexual Abstinence o Sexual abstinence is considered a highly effective method only if defined as refraining from heterosexual intercourse during the entire period of risk associated with the study intervention. The reliability of sexual abstinence needs to be evaluated in relation to the duration of the study and the preferred and usual lifestyle of the participant.
• One of the following effective barrier methods must be used in addition to the highly effective methods listed above that are user dependent: o Male or female condom with or without spermicide o Cervical cap, diaphragm, or sponge with spermicide o A combination of male condom with either cervical cap, diaphragm, or sponge with spermicide (double-barrier methods)

10.5. Appendix 5: Genetics

Use/Analysis of DNA

- Genetic variation may impact a participant's response to study intervention, susceptibility to, and severity and progression of disease. Therefore, where local regulations and IRB/IEC allow, a blood sample will be collected for DNA analysis.

- Genetic research may consist of the analysis of one or more candidate genes or the analysis of genetic markers throughout the genome or analysis of the entire genome (as appropriate).

- The samples may be analyzed as part of a multi-study assessment of genetic factors involved in the response to study intervention or study interventions of this class, treatments for the disease(s) under study or the disease(s) themselves.

- The results of genetic analyses may be reported in the CSR or in a separate study summary or may be used for internal decision-making without being included in a study report.

- The sponsor will store the DNA samples in a secure storage space with adequate measures to protect confidentiality.

- The samples will be retained as indicated:

  - Samples for specified genetic analysis (see Section 8.7) will be stored for up to 15 years or other period as per local requirements or will not be stored beyond the completion of this study (eg, Clinical Study Report finalization).

  - Samples for banking (see Section 8.7.2) will be stored indefinitely or other period as per local requirements.

- Participants may withdraw their consent for the storage and/or use of their Banked Biospecimens at any time by making a request to the investigator; in this case, any remaining material will be destroyed. Data already generated from the samples will be retained to protect the integrity of existing analyses.

- Banked Biospecimens will be labeled with a code. The key between the code and the participant's personally identifying information (eg, name, address) will be held at the study site and will not be provided to the sample bank.

10.6. Appendix 6: Liver Safety: Suggested Actions and Follow-up Assessments

Humans exposed to a drug who show no sign of liver injury (as determined by elevations in transaminases) are termed “tolerators,” while those who show transient liver injury, but adapt are termed “adaptors.” In some participants, transaminase elevations are a harbinger of a more serious potential outcome. These participants fail to adapt and therefore are "susceptible" to progressive and serious liver injury, commonly referred to as drug-induced liver injury (DILI). Participants who experience a transaminase elevation above 3 times the upper limit of normal (× ULN) should be monitored more frequently to determine if they are an “adaptor” or are “susceptible.”

In the majority of DILI cases, elevations in aspartate aminotransferase (AST) and/or alanine aminotransferase (ALT) precede total bilirubin (TBili) elevations (>2 × ULN) by several days or weeks. The increase in TBili typically occurs while AST/ALT is/are still elevated above 3 × ULN (ie, AST/ALT and TBili values will be elevated within the same lab sample). In rare instances, by the time TBili elevations are detected, AST/ALT values might have decreased. This occurrence is still regarded as a potential DILI. Therefore, abnormal elevations in either AST OR ALT in addition to TBili that meet the criteria outlined below are considered potential DILI (assessed per Hy’s law criteria) cases and should always be considered important medical events, even before all other possible causes of liver injury have been excluded.

The threshold of laboratory abnormalities for a potential DILI case depends on the participant’s individual baseline values and underlying conditions. Participants who present with the following laboratory abnormalities should be evaluated further as potential DILI (Hy’s law) cases to definitively determine the etiology of the abnormal laboratory values:

- Participants with AST/ALT and TBili baseline values within the normal range who subsequently present with AST OR ALT values >3 × ULN AND a TBili value >2 × ULN with no evidence of hemolysis and an alkaline phosphatase value <2 × ULN or not available;

- For participants with baseline AST OR ALT OR TBili values above the ULN, the following threshold values are used in the definition mentioned above, as needed, depending on which values are above the ULN at baseline:

    - Preexisting AST or ALT baseline values above the normal range: AST or ALT values >2 times the baseline values AND >3 × ULN; or >8 × ULN (whichever is smaller).

    - Preexisting values of TBili above the normal range: TBili level increased from baseline value by an amount of at least 1 × ULN or if the value reaches >3 × ULN (whichever is smaller).

Rises in AST/ALT and TBili separated by more than a few weeks should be assessed individually based on clinical judgment; any case where uncertainty remains as to whether it represents a potential Hy’s law case should be reviewed with the sponsor. The participant

should return to the investigator site and be evaluated as soon as possible, preferably within 48 hours from awareness of the abnormal results. This evaluation should include laboratory tests, detailed history, and physical assessment. The possibility of hepatic neoplasia (primary or secondary) should be considered.

In addition to repeating measurements of AST and ALT and TBili for suspected cases of Hy's Law, additional laboratory tests should include albumin, creatine kinase (CK), direct and indirect bilirubin, gamma-glutamyl transferase (GGT), prothrombin time (PT) or international normalized ratio (INR), total bile acids, and alkaline phosphatase. Consideration should also be given to drawing a separate tube of clotted blood and an anticoagulated tube of blood for further testing, as needed, for further contemporaneous analyses at the time of the recognized initial abnormalities to determine etiology. A detailed history, including relevant information, such as review of ethanol, acetaminophen (either by itself or as a coformulated product in prescription or over-the-counter medications), recreational drug, supplement (herbal) use and consumption, family history, sexual history, travel history, history of contact with a jaundiced person, surgery, blood transfusion, history of liver or allergic disease, and potential occupational exposure to chemicals, should be collected. Further testing for acute hepatitis A, B, C, D, and E infection and liver imaging (eg, biliary tract) and collection of serum sample for acetaminophen drug and/or protein adduct levels may be warranted.

All cases demonstrated on repeat testing as meeting the laboratory criteria of AST/ALT and TBili elevation defined above should be considered potential DILI (Hy's law) cases if no other reason for the LFT abnormalities has yet been found. **Such potential DILI (Hy's law) cases are to be reported as SAEs, irrespective of availability of all the results of the investigations performed to determine etiology of the LFT abnormalities.**

A potential DILI (Hy's law) case becomes a confirmed case only after all results of reasonable investigations have been received and have excluded an alternative etiology.

10.7. Appendix 7: AEs, ADEs, SAEs, USADEs and Device Deficiencies: Definition and Procedures for Recording, Evaluating, Follow-Up, and Reporting in Medical Device Studies

Definitions of a Medical Device Deficiency

The definitions and procedures detailed in this Section are in accordance with ISO 14155 and the European MDR 2017/745 for clinical device research (if applicable).

Both the investigator and the sponsor will comply with all local reporting requirements for medical devices.

The detection and documentation procedures described in this protocol apply to all sponsor medical devices provided for use in the study (see Section 6.1.1) for the list of sponsor medical devices).

10.7.1. Definition of AE and ADE

AE and ADE Definition
• An AE is defined in Appendix 3: Adverse Events: Definitions and Procedures for Recording, Evaluating, Follow-Up, and Reporting • An ADE is defined as an adverse event related to the use of an investigational medical device. This definition includes any adverse events resulting from insufficient or inadequate instructions for use, deployment, implantation, installation, or operation, or any malfunction of the investigational medical device as well as any event resulting from use error or from intentional misuse of the investigational medical device.

10.7.2. Definition of SAE, SADE, and Unanticipated Serious Adverse Device Effect

An SAE is defined in Appendix 3: Adverse Events: Definitions and Procedures for Recording, Evaluating, Follow-Up, and Reporting.

SAE definition:
An SAE is defined in Appendix 10.3.
SADE Definition
• An SADE is defined as an ADE that has resulted in any of the consequences characteristic of an SAE. • Any device deficiency that might have led to an SAE if appropriate action had not been taken, intervention had not occurred, or circumstances had been less fortunate.
USADE Definition
• A USADE (also identified as UADE in US Regulation 21 CFR 813.3) is an SADE which by its nature, incidence, severity, or outcome has not been identified in the current version of the risk analysis management file.

10.7.3. Definition of Device Deficiency

Device Deficiency Definition
• A device deficiency is an inadequacy of a medical device with respect to its identity, quality, durability, reliability, safety, or performance. Device deficiencies include malfunctions, use errors, and inadequate information supplied by the manufacturer.

10.7.4. Recording/Reporting and Follow-Up of Device Deficiencies

Device Deficiency Recording
• When a device deficiency occurs, it is the responsibility of the investigator to review all documentation (eg, hospital progress notes, laboratory reports, and diagnostic reports) related to the event. • The investigator will then record all relevant device deficiency information in the participant's medical records, in accordance with the investigator's normal clinical practice. • If an AE (either serious or nonserious) associated with the device deficiency occurs, then the AE must be entered into the AE section of the CRF. • It is **not** acceptable for the investigator to send photocopies of the participant's medical records to Pfizer Safety.

- There may be instances when copies of medical records for certain cases are requested by Pfizer Safety. In this case, all participant identifiers, with the exception of the participant number, will be redacted on the copies of the medical records before submission to Pfizer Safety. Refer to Section 10.1.9 Use of Medical Records for actions that must be taken when medical records are sent to the sponsor or sponsor designee.
- For device deficiencies, it is very important that the investigator describes any corrective or remedial actions taken to prevent recurrence of the incident.
  - A remedial action is any action other than routine maintenance or servicing of a medical device where such action is necessary to prevent recurrence of a device deficiency. This includes any amendment to the device design to prevent recurrence.
- The PI will notify the sponsor study team by contact method (eg, telephone, email) within 1 business day of determining that the incident meets the protocol definition of a medical device deficiency.
- The Pfizer study team will also capture the required information on the Medical Device Complaint Form along with any associated AE (either serious or nonserious) when applicable and send to the appropriate product quality complaint group.
- If the PI determines that the medical device deficiency may have injured the participant (ie, the medical device deficiency is associated with an AE or SAE), then the PI will attempt to establish a diagnosis of the event based on signs, symptoms, and/or other clinical information. Whenever possible, the diagnosis will be documented in the participant's medical record and recorded as the AE or SAE rather than the individual signs/symptoms. All relevant details related to the role of the device in regard to the SAE must be included in the narrative section of the CT SAE Report Form as outlined in protocol Section 8.3.1.1 Reporting SAEs to Pfizer Safety and Section 8.3.1.2 Recording Non-serious AEs and SAEs on the CRF.

Assessment of Causality Occurring in Conjunction With a Medical Device Deficiency

- If an AE or SAE has occurred in conjunction with a medical device deficiency, the investigator must assess the relationship between each occurrence of the AE or SAE and the medical device deficiency. The investigator will use clinical judgment to determine the relationship.
- A "reasonable possibility" of a relationship conveys that there are facts, evidence, and/or arguments to suggest a causal relationship, rather than a relationship cannot be ruled out.

- Alternative causes, such as underlying disease(s), concomitant therapy, and other risk factors, as well as the temporal relationship of the event to study intervention administration will be considered and investigated.
- The investigator will also consult the IB in thier assessment.
- For each device deficiency, the investigator **must** document in the medical notes that he/she has reviewed the AE/SAE/device deficiency and has provided an assessment of causality.
- There may be situations in which an SAE has occurred and the investigator has minimal information to include in the initial report to the sponsor. However, it is very important that the investigator always make an assessment of causality for every event before the initial transmission of the SAE data to the sponsor.
- The investigator may change their opinion of causality in light of follow-up information and send an SAE follow-up report with the updated causality assessment.
- The causality assessment is one of the criteria used when determining regulatory reporting requirements.

Follow-Up of \ Medical Device Deficiency

- The investigator is obligated to perform or arrange for the conduct of supplemental measurements and/or evaluations as medically indicated or as requested by the sponsor to elucidate the nature and/or causality of the AE or SAE/device deficiency as fully as possible. This may include additional laboratory tests or investigations, histopathological examinations, or consultation with other healthcare providers.
- Follow-up applies to all participants, including those who discontinue study intervention.
- New or updated information regarding the nature of the device deficiency will be recorded in the originally completed Medical Device Complaint form by the Pfizer study team.
- New or updated information regarding any SAE that was potentially associated with the medical device deficiency will be submitted to Pfizer Safety on the CT SAE Report Form/Medical Device Constituent Supplemental Form within 24 hours of receipt of the information according to the requirements provided in Appendix 10.3.

10.8. Appendix 8: Country-specific Requirements

10.8.1. France Contrat Unique

This country specific appendix captures operational items not included in the mandatory contract format for France (i.e. French "Contrat Unique"), which Pfizer includes in standard contract language for other countries.

1. GCP Training

Before enrolling any participants, the investigator and any subinvestigators will complete the Pfizer-provided Good Clinical Practice training course ("Pfizer GCP Training") or training deemed equivalent by Pfizer. Any investigators who later join the study will do the same before performing study-related duties. For studies of applicable duration, the investigator and subinvestigators will complete Pfizer GCP Training or equivalent every 3 years during the term of the study, or more often if there are significant changes to the ICH GCP guidelines or course materials.

2. Study Intervention

No participants or third-party payers will be charged for study intervention.

3. Record Retention

If the investigator becomes unable for any reason to continue to retain study records for the required period (e.g., retirement, relocation), Pfizer should be prospectively notified. The study records must be transferred to a designee acceptable to Pfizer, such as another investigator, another institution, or to an independent third party arranged by Pfizer. Investigator records must be kept for a minimum of 15 years after completion or discontinuation of the study or for longer if required by applicable local regulations. The investigator must obtain Pfizer's written permission before disposing of any records, even if the retention requirements have been met.

4. SUSARs

Pursuant to a sponsor's safety reporting obligations under 21 CFR 312.32(c)(1), Pfizer will report to the investigator all Serious Unexpected Suspected Adverse Reactions ("SUSARs"). Investigator will receive and review SUSAR reports and report SUSARs to the responsible IRB/IEC according to institution's guidelines. Institution will retain SUSAR reports consistent with Section 10.1.7 of the Protocol.

5. Collection of Ethnic Origin Information

Information regarding ethnic origin will be collected in this study in compliance with the French Data Protection Authority (CNIL): Deliberation no. 2016-262 of 21 July 2016 amending the reference methodology for the processing of the personal data conducted in connection with biomedical research (MR-001), § 2.2.3 Nature of the data.

Individuals participating in this study will consent that this information can be collected in the study before they enter the study.

The electronic Case Report Form (eCRF) will be used as the source file for ethnic origin in France. This information will not be recorded in the participant's medical records.

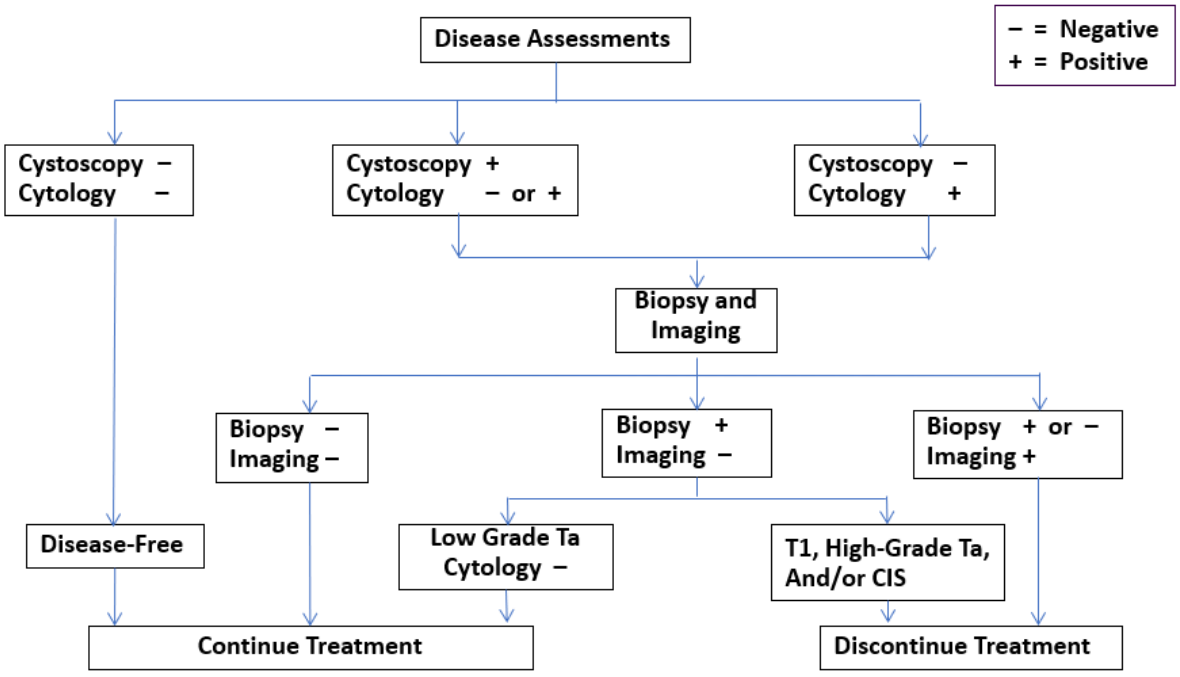
10.8.2. Japan-specific Regulatory Requirements

10.8.2.1. Definitions of Serious Adverse Event, Serious Adverse Event Caused by Medical Device, and Unanticipated Serious Adverse Event Caused by Medical Device

Definition of serious adverse event caused by medical device

A serious adverse event caused by medical device is defined as an adverse event caused by a medical device which led to an outcome characteristic to serious adverse events, or a device-related incident whose recurrence might lead to death or serious deterioration in health.

10.9. Appendix 9: Decision Algorithm for Disease Assessment



Abbreviations: CIS = carcinoma in situ

The above diagram illustrates how cystoscopy, urine cytology, biopsy and imaging should be integrated to assess achievement of CR for participants with CIS at baseline, recurrence of high-grade disease, persistence of CIS or progression of disease. Participants enrolled in Cohort A with CIS with persistent disease and participants with recurrence of high-grade Ta disease following first induction period are eligible for a re-induction period of up to 6 additional weekly doses of BCG treatments (see study Schema for Cohort A). Below, definitions are provided for no evidence of disease, CR, recurrence of high-grade disease, persistence of CIS, and progression of disease.

Cytology results are defined as the following:

1. Positive - if indicative or suggestive of malignant cells:

- High-grade urothelial carcinoma
- Suspicious for high-grade urothelial carcinoma

2. Negative if NOT indicative or suggestive of malignant cells:

- Negative for high-grade urothelial carcinoma cells
- Presence of low-grade urothelial carcinoma cells
- Atypical urothelial cell not abnormal enough to be considered as cancerous

3. Indeterminate: unsatisfactory sample.

In Cohort B1, when cystoscopy is negative and cytology is positive at a given disease assessment timepoint, biopsies must be collected from the bladder dome, trigone, right lateral wall, left lateral wall, anterior and posterior wall, and prostatic urethra for male participants.

For participants in Cohort B1, decision to continue treatment following disease assessment will be made by the investigator as described in the diagram above with BICR review of disease assessment (including tumor tissue samples, cytology, cystoscopy and imaging) occurring in an expedited manner. For participants in Cohort B1 continuation of treatment for 1 additional cycle while waiting for confirmation of recurrence of high-grade Ta, T1 or CIS disease by the BICR will be allowed at the discretion of the investigator. If the 12 week disease assessment is "Not Evaluable" per the BICR, the assessment with a non-evaluable result should be repeated as soon as possible.

In case of discordant results at a given disease assessment timepoint with negative cytology as assessed by the investigator and positive cytology as assessed by the BICR, the following assessments should be performed as soon as possible:

- Cystoscopy with collection of random biopsies from bladder (dome, trigone, right and left lateral wall, and anterior and posterior wall) and prostatic urethra in male participants OR collection of suspicious lesions, if present;
- Cytology;
- Imaging

No Evidence of Disease only applies to participants without CIS at baseline (Cohort A and Cohort B2) and is defined as disease that was completely resected prior to randomization (Cohort A)/initiation of study intervention (Cohort B2) and does not meet the criteria of progression of disease, recurrence of high-grade disease, or recurrence of low-grade disease while on study. The date of imaging, biopsy, cystoscopy, or cytology (whichever result of the available assessments is earliest) that supports no evidence of disease will be used as the date of no evidence of disease.

Complete Response, in participants with CIS at baseline, is defined as histologic disappearance of malignancy on bladder biopsy with negative cytology and cystoscopy or negative cytology and positive cystoscopy with biopsy-proven low-grade Ta lesion or non-malignant tissue. The date of biopsy, cystoscopy, or cytology (whichever is earliest) will be used as the date of Complete Response. See section 8.1.1.1 for guidance regarding timing of these biopsies.

Persistence of CIS, in participants with CIS at baseline in Cohort A, is defined as persistence of CIS after induction or re-induction (if re-induction is administered). For participants in Cohort B1, persistence of CIS is defined as persistence of CIS at the 12 week or 24 week disease assessment. This will require a cystoscopy or cytology positive result with biopsy positive for CIS. The date of positive biopsy, cystoscopy, or cytology (whichever positive result is earliest) will be used as the date of persistence of CIS.

Recurrence of high-grade disease is defined as re-appearance of high-grade disease (high-grade Ta, T1 or CIS) after randomization/initiation of study intervention or re-appearance of high-grade disease after CR for participants with CIS at baseline or re-appearance of high-grade disease before CR for participants with CIS and concurrent papillary disease at baseline in Cohort A or B1. This will require a cystoscopy or cytology positive result, with biopsy positive for T1, high-grade Ta and/or CIS. The date of positive biopsy, cystoscopy, or cytology (whichever positive result is earliest) will be used as the date of recurrence of high-grade disease. In Cohort B1, if the investigator determines that high-grade disease is present, the participant may continue on study for 1 additional cycle, until BICR review confirms diagnosis of high-grade disease. At that time, if high-grade disease recurrence is confirmed by the BICR, the participant must discontinue study treatment.

Recurrence of low-grade disease is defined as re-appearance of low-grade disease (low-grade Ta) after randomization (Cohort A)/initiation of study intervention (Cohort B). This will require a cystoscopy or cytology positive result, with biopsy positive for low-grade Ta. The date of positive biopsy, cystoscopy or cytology (whichever positive result is earliest) will be used as the date of recurrence of low-grade disease.

Progression of disease is defined as any of the following:

- Lamina propria invasion (eg, increase from Ta to T1 or CIS to T1)
- Muscle invasive disease (stage ≥ T2)
- Lymph node positive disease (N+)
- Metastatic disease (M1)
- Appearance of high-grade Ta or T1 in participants with CIS only at baseline (Cohort A and Cohort B1) before achieving a CR.

This will require a cystoscopy or cytology positive result with imaging positive and/or biopsy positive for disease progression as described above. The date of positive biopsy, imaging for new lesion, positive cystoscopy, or positive cytology (whichever positive result is earliest) will be used as the date of progression.

10.10. Appendix 10: ECOG PS

Grade	ECOG Performance Status
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, eg, light house work, 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

Source: Oken M et al. 1982.[52]

10.11. Appendix 11: ECG Findings of Potential Clinical Concern

ECG Findings That <u>May</u> Qualify as Adverse Events (AEs)
• Marked sinus bradycardia (rate <40 bpm) lasting minutes. • New PR interval prolongation >280 msec. • New prolongation of QTcF to >480 msec (absolute) or by ≥60 msec from baseline. • New-onset atrial flutter or fibrillation, with controlled ventricular response rate: ie, rate <120 beats per minute (bpm). • New-onset type I second-degree (Wenckebach) atrioventricular (AV) block of >30 seconds' duration. • Frequent premature ventricular complexes (PVCs), triplets, or short intervals (<30 seconds) of consecutive ventricular complexes.
ECG Findings That <u>May</u> Qualify as Serious Adverse Events (SAEs)

• QTcF prolongation >500 msec.
• New ST-T changes suggestive of myocardial ischemia.
• New-onset left bundle branch block (QRS >120 msec).
• New-onset right bundle branch block (QRS >120 msec).
• Symptomatic bradycardia.
• Asystole:
  • In awake, symptom-free participants in sinus rhythm, with documented periods of asystole ≥3.0 seconds or any escape rate <40 bpm, or with an escape rhythm that is below the AV node.
  • In awake, symptom-free participants with atrial fibrillation and bradycardia with 1 or more pauses of at least 5 seconds or longer.
  • Atrial flutter or fibrillation, with rapid ventricular response rate: rapid = rate >120 bpm.
• Sustained supraventricular tachycardia (rate >120 bpm) ("sustained" = short duration with relevant symptoms or lasting >1 minute).
• Ventricular rhythms >30 seconds' duration, including idioventricular rhythm (rate <40 bpm), accelerated idioventricular rhythm (40< x <100), and

monomorphic/polymorphic ventricular tachycardia >100 bpm (such as torsades de pointes).

- Type II second-degree (Mobitz II) AV block.
- Complete (third-degree) heart block.

ECG Findings That Qualify as Serious Adverse Events

- Change in pattern suggestive of new myocardial infarction.
- Sustained ventricular tachyarrhythmias (>30 seconds' duration).
- Second- or third-degree AV block requiring pacemaker placement.
- Asystolic pauses requiring pacemaker placement.
- Atrial flutter or fibrillation with rapid ventricular response requiring cardioversion.
- Ventricular fibrillation/flutter.
- At the discretion of the investigator, any arrhythmia classified as an adverse experience.

The enumerated list of major events of potential clinical concern are recommended as "alerts" or notifications from the core ECG laboratory to the investigator and Pfizer study team, and not to be considered as all inclusive of what to be reported as AEs/SAEs.

10.12. Appendix 12: Recommendations for Management of Allergic/Hypersensitivity Reactions, Cytokine Release Syndrome or Anaphylaxis

Following the first administration of some monoclonal antibody therapeutics, some patients experience fever, headache, nausea, vomiting or hypotension. These AEs are generally ascribed to lysis of cellular targets, cytokine release, or complement activation.

Type 1 hypersensitivity or allergic (eg, shortness of breath, urticaria, anaphylaxis, angioedema) reactions are theoretically possible in response to any injected protein. Immune complex mediated Type 3 hypersensitivity reactions are similar to the AEs of Type 1 reactions but are likely to be delayed from the time of administration and may include symptoms such as rash, urticaria, polyarthritis, myalgias, polysynovitis, fever, and, if severe, glomerulonephritis.

All participants should be closely observed while receiving PF-06801591. Monitoring for clinical signs of a systemic reaction should continue thereafter for clinical signs of allergic reactions/hypersensitivity.

In the case of a hypersensitivity reaction, the participant will be treated symptomatically, with supportive care and further monitoring until the end of the study.

In cases of suspected cytokine release syndrome, a serum sample should be provided for cytokine release assay analysis by the central lab so as long as the sampling does not interfere with the medical treatment of the participant.

Detailed guidance on treatment, dose interruptions and potential retreatment is provided in Section 6.6.1.

10.13. Appendix 13: Management of Immune-related Adverse Events (irAEs)

Gastrointestinal irAEs		
Severity of Diarrhea/Colitis (NCI-CTCAE v5.0)	**Initial Management**	**Follow-up Management**
Grade 1 Diarrhea: < 4 stools/day over Baseline Colitis: asymptomatic	-Continue study treatment -Symptomatic treatment (eg loperamide)	-Close monitoring for worsening symptoms. -Educate participant to report worsening immediately. -If worsens: Treat as Grade 2, 3 or 4.
Grade 2 Diarrhea: 4 to 6 stools per day over Baseline; IV fluids indicated < 24 hours; not interfering with ADL Colitis: abdominal pain; blood in stool	-Withhold study treatment - Symptomatic treatment	-If improves to Grade ≤ 1: Resume study treatment. -If persists > 5-7 days or recurs: Treat as Grade 3 or 4.
Grade 3 to 4 Diarrhea (Grade 3): ≥ 7 stools per day over Baseline; incontinence; IV fluids ≥ 24 hours; interfering with ADL Colitis (Grade 3): severe abdominal pain, medical intervention indicated, peritoneal signs Grade 4: life-threatening, perforation	-Withhold for Grade 3 -Permanently discontinue study treatment for Grade 4 or recurrent Grade 3 -1.0 to 2.0 mg/kg/day prednisone IV or equivalent -Add prophylactic antibiotics for opportunistic infections -Consider lower endoscopy	-If improves: -Continue steroids until Grade ≤ 1, then taper over at least 1 month; resume study treatment following steroids taper (for initial Grade 3). -If worsens, persists >3 to 5 days, or recurs after improvement. -Add infliximab 5 mg/kg (if no contraindication). -Note: infliximab should not be used in cases of perforation or sepsis.

Dermatological irAEs		
Grade of Rash (NCI-CTCAE v5.0)	**Initial Management**	**Follow-up Management**
Grade 1 to 2 Covering ≤ 30% body surface area	-Continue study treatment -Symptomatic therapy (for example, antihistamines, topical steroids)	-If persists > 1 to 2 weeks or recurs: -Withhold study treatment -Consider skin biopsy -Consider 0.5-1.0 mg/kg/day prednisone or equivalent. Once improving, taper steroids over at least 1 month, consider prophylactic antibiotics for opportunistic infections, and resume study treatment following steroids taper. -If worsens: Treat as Grade 3 to 4.
Grade 3 to 4 Grade 3: Covering > 30% body surface area; Grade 4: Life threatening consequences	-Withhold study treatment for Grade 3 -Permanently discontinue for Grade 4 or recurrent Grade 3 -Consider skin biopsy -Dermatology consult -1.0 to 2.0 mg/kg/day prednisone or equivalent -Add prophylactic antibiotics for opportunistic infections	-If improves to Grade ≤ 1: -Taper steroids over at least 1 month; resume study treatment following steroids taper (for initial Grade 3).

Pulmonary irAEs		
Grade of Pneumonitis (NCI-CTCAE v5.0)	**Initial Management**	**Follow-up Management**
Grade 1 Radiographic changes only	-Consider withholding study treatment -Monitor for symptoms every 2 to 3 days -Consider Pulmonary and Infectious Disease consults	-Re-assess at least every 3 weeks. -If worsens: Treat as Grade 2 or Grade 3 to 4.
Grade 2 Mild to moderate new symptoms	-Withhold study treatment -Pulmonary and Infectious Disease consults -Monitor symptoms daily; consider hospitalization -1.0 to 2.0 mg/kg/day prednisone or equivalent -Add prophylactic antibiotics for opportunistic infections -Consider bronchoscopy, lung biopsy	-Re-assess every 1 to 3 days If improves: -When symptoms return to Grade ≤ 1, taper steroids over at least 1 month, and then resume study treatment following steroids taper. -If not improving after 2 weeks or worsening: Treat as Grade 3 to 4.
Grade 3 to 4 Grade 3: Severe new symptoms; New/worsening hypoxia; Grade 4: Life-threatening	-Permanently discontinue study treatment. -Hospitalize -Pulmonary and Infectious Disease consults -1.0 to 2.0 mg/kg/day prednisone or equivalent -Add prophylactic antibiotics for opportunistic infections -Consider bronchoscopy, lung biopsy	-If improves to Grade ≤ 1: -Taper steroids over at least 1 month. -If not improving after 48 hours or worsening: Add additional immunosuppression (for example, infliximab, cyclophosphamide, IV immunoglobulin, or mycophenolate mofetil).

Hepatic irAEs		
Grade of Liver Test Elevation (NCI-CTCAE v5.0)	**Initial Management**	**Follow-up Management**
Grade 1 Grade 1 AST or ALT > ULN to 3.0 x ULN and/or Total bilirubin > ULN to 1.5 x ULN	-Continue study treatment	-Continue liver function monitoring -If worsens: Treat as Grade 2 or 3 – 4.
Grade 2 AST or ALT > 3.0 to ≤ 5 x ULN and/or total bilirubin > 1.5 to ≤ 3 x ULN	-Withhold study treatment -Increase frequency of monitoring to every 3 days	-If returns to Grade ≤ 1: -Resume routine monitoring; resume study treatment. -If elevation persists > 5 to 7 days or worsens: -Treat as Grade 3 to 4.
Grade 3 to 4 AST or ALT > 5 x ULN and/or total bilirubin > 3 x ULN	-Permanently discontinue study treatment -Increase frequency of monitoring to every 1 to 2 days -1.0 to 2.0 mg/kg/day prednisone or equivalent -Add prophylactic antibiotics for opportunistic infections -Consult gastroenterologist/ hepatologist -Consider obtaining MRI/CT scan of liver and liver biopsy if clinically warranted	-If returns to Grade ≤ 1: -Taper steroids over at least 1 month. -If does not improve in > 3 to 5 days, worsens or rebounds: -Add mycophenolate mofetil 1 gram (g) twice daily. -If no response within an additional 3 to 5 days, consider other immunosuppressants per local guidelines.

Renal irAEs		
Grade of Creatinine Increased (NCI-CTCAE v5.0)	**Initial Management**	**Follow-up Management**
Grade 1 Creatinine increased > ULN to 1.5 x ULN	-Continue study treatment	-Continue renal function monitoring. -If worsens: Treat as Grade 2 to 3 or 4.
Grade 2 to 3 Creatinine increased > 1.5 and ≤ 6 x ULN	-Withhold study treatment -Increase frequency of monitoring to every 3 days -1.0 to 2.0 mg/kg/day prednisone or equivalent. -Add prophylactic antibiotics for opportunistic infections -Consider renal biopsy	-If returns to Grade ≤1: -Taper steroids over at least 1 month, and resume study treatment following steroids taper. -If worsens: -Treat as Grade 4.
Grade 4 Creatinine increased > 6 x ULN	-Permanently discontinue study treatment -Monitor creatinine daily -1.0 to 2.0 mg/kg/day prednisone or equivalent. -Add prophylactic antibiotics for opportunistic infections Consider renal biopsy -Nephrology consult	-If returns to Grade ≤1: Taper steroids over at least 1 month.

Cardiac irAEs		
Myocarditis	**Initial Management**	**Follow-up Management**
New onset of cardiac signs or symptoms and / or new laboratory cardiac biomarker elevations (e.g. troponin I, CK-MB, BNP) or cardiac imaging abnormalities suggestive of myocarditis	-Withhold study treatment -Hospitalize -In the presence of life threatening cardiac decompensation, consider transfer to a facility experienced in advanced heart failure and arrhythmia management -Consult cardiologist to establish etiology and rule-out immune-mediated myocarditis -Guideline based supportive treatment as per cardiology consult* -Consider myocardial biopsy if recommended per cardiology consult	-If symptoms improve and immune-mediated etiology is ruled out, re-start study treatment. -If symptoms do not improve/worsen, viral myocarditis is excluded, and immune-mediated etiology is suspected or confirmed following cardiology consult, manage as immune-mediated myocarditis.
Immune-mediated myocarditis	-Permanently discontinue study treatment -Guideline based supportive treatment as appropriate as per cardiology consult.* 1.0 to 2.0 mg/kg/day prednisone or equivalent -Add prophylactic antibiotics for opportunistic infections	-Once improving, taper steroids over at least 1 month. If no improvement or worsening, consider additional immunosuppressants (e.g. azathioprine, cyclosporine A, abatacept).

*Local guidelines, or eg. ESC or AHA guidelines

Endocrine irAEs		
Endocrine Disorder	**Initial Management**	**Follow-up Management**
Grade 1 or Grade 2 endocrinopathies (hypothyroidism, hyperthyroidism, adrenal insufficiency, type I diabetes mellitus)	-Continue study treatment -Endocrinology consult if needed -Start thyroid hormone replacement therapy (for hypothyroidism), anti-thyroid treatment (for hyperthyroidism), corticosteroids (for adrenal insufficiency) or insulin (for Type I diabetes mellitus) as appropriate -Rule-out secondary endocrinopathies (ie, hypopituitarism / hypophysitis)	-Continue hormone replacement/suppression and monitoring of endocrine function as appropriate.*
Grade 3 or Grade 4 endocrinopathies (hypothyroidism, hyperthyroidism, adrenal insufficiency, type I diabetes mellitus)	-Withhold study treatment -Consider hospitalization - Endocrinology consult -Start thyroid hormone replacement therapy (for hypothyroidism), anti-thyroid treatment (for hyperthyroidism), corticosteroids (for adrenal insufficiency) or insulin (for type I diabetes mellitus) as appropriate -Rule-out secondary endocrinopathies (ie, hypopituitarism / hypophysitis)	-Resume study treatment once symptoms and/or laboratory tests improve to Grade ≤ 1 (with or without hormone replacement/suppression). -Continue hormone replacement/suppression and monitoring of endocrine function as appropriate.*
Hypopituitarism/ Hypophysitis (secondary endocrinopathies)	-If secondary thyroid and/or adrenal insufficiency is confirmed (ie, subnormal serum FT4 with inappropriately low TSH and/or low serum cortisol with inappropriately low ACTH): -Refer to endocrinologist for dynamic testing as indicated and measurement of other hormones (FSH, LH, GH/IGF-1, PRL, testosterone in men, estrogens in women) -Hormone replacement/suppressive therapy as appropriate -Perform pituitary MRI and visual field examination as indicated **-If hypophysitis is confirmed:** -Continue study treatment if mild symptoms with normal MRI. Repeat the MRI in 1 month	-Resume study treatment once symptoms and hormone tests improve to Grade ≤ 1 (with or without hormone replacement). -In addition, for hypophysitis with abnormal MRI, resume study treatment only once shrinkage of the pituitary gland on MRI/CT scan is documented. -Continue hormone replacement/suppression therapy as appropriate.

Endocrine irAEs		
Endocrine Disorder	**Initial Management**	**Follow-up Management**
	-Withhold study treatment if moderate, severe or life-threatening symptoms of hypophysitis and/or abnormal MRI. Consider hospitalization. Initiate corticosteroids (1 to 2 mg/kg/day prednisone or equivalent) followed by corticosteroids taper during at least 1 month -Add prophylactic antibiotics for opportunistic infections	

* If a study participant experiences immune-related grade 3 or 4 endocrinopathies (hypothyroidism, hyperthyroidism, adrenal insufficiency, type I diabetes mellitus) management guidelines should be followed, including withholding of study drug, as indicated. Treatment may be resumed once symptoms and/or laboratory tests improve, and the participant's condition becomes stable and well controlled with or without supportive treatment.

Other irAEs (not described above)		
Grade of other irAEs (NCI-CTCAE v5.0)	**Initial Management**	**Follow-up Management**
Grade 2 or Grade 3 clinical signs or symptoms suggestive of a potential irAE	-Withhold study treatment pending clinical investigation	-If irAE is ruled out, manage as appropriate according to the diagnosis and consider re-starting study treatment -If irAE is confirmed, treat as Grade 2 or 3 irAE.
Grade 2 irAE or first occurrence of Grade 3 irAE	-Withhold study treatment -1.0 to 2.0 mg/kg/day prednisone or equivalent -Add prophylactic antibiotics for opportunistic infections -Specialty consult as appropriate	-If improves to Grade ≤ 1: -Taper steroids over at least 1 month and resume study treatment following steroids taper.
Recurrence of same Grade 3 irAEs	-Permanently discontinue study treatment -1.0 to 2.0 mg/kg/day prednisone or equivalent -Add prophylactic antibiotics for opportunistic infections -Specialty consult as appropriate	-If improves to Grade ≤ 1: Taper steroids over at least 1 month.
Grade 4	-Permanently discontinue study treatment -1.0 to 2.0 mg/kg/day prednisone or equivalent and/or other immunosuppressant as needed -Add prophylactic antibiotics for opportunistic infections -Specialty consult	-If improves to Grade ≤ 1: Taper steroids over at least 1 month.
Requirement for 10 mg per day or greater prednisone or equivalent for more than 12 weeks for reasons other than hormonal replacement for adrenal insufficiency **Persistent Grade 2 or 3 irAE lasting 12 weeks or longer**	- Permanently discontinue study treatment -Specialty consult	

Abbreviations: ACTH=adrenocorticotropic hormone; ADL=activities of daily living; ALT=alanine aminotransferase; AST=aspartate aminotransferase; BNP=B-type natriuretic peptide; CK-MB=creatine kinase MB; CT= computed tomography; FSH=follicle-stimulating hormone; GH=growth hormone; IGF-1=insulin-like growth factor 1; irAE=immune-related adverse event; IV=intravenous; LH=luteinizing hormone; MRI=magnetic resonance imaging; NCI-CTCAE=National Cancer Institute-Common Terminology Criteria for Adverse Events; PRL=prolactin; T4=thyroxine; TSH=thyroid-stimulating hormone; ULN=upper limit of normal.

10.14. Appendix 14 Management of BCG Associated Toxicity

Systemic BCG Reaction

The language in this section is based on the TICE USPI and provides an example of management of BCG associated toxicity. The product label for the strain of BCG administered should be used for reference if other than TICE.

Deaths have been reported as a result of systemic BCG infection and sepsis. Participants should be monitored for the presence of symptoms and signs of toxicity after each intravesical treatment. Febrile episodes with flu-like symptoms lasting more than 72 hours, fever ≥103°F, systemic manifestations increasing in intensity with repeated instillations, or persistent abnormalities of liver function tests suggest systemic BCG infection and may require antituberculous therapy. Local symptoms (prostatitis, epididymitis, orchitis) lasting more than 2 to 3 days may also suggest active infection.

Acute, localized irritative toxicities of TICE® BCG may be accompanied by systemic manifestations, consistent with a "flu-like" syndrome. Systemic adverse effects of 1 to 2 days' duration such as malaise, fever, and chills often reflect hypersensitivity reactions. However, **symptoms such as fever of ≥38.5°C (101.3°F), or acute localized inflammation such as epididymitis, prostatitis, or orchitis persisting longer than 2 to 3 days suggest active infection, and evaluation for serious infectious complication should be considered.**

In participants who develop persistent fever or experience an acute febrile illness consistent with BCG infection, 2 or more antimycobacterial agents should be administered while diagnostic evaluation, including cultures, is conducted. **BCG treatment should be discontinued.**

Negative cultures do not necessarily rule out infection. Physicians using this product should be familiar with the literature on prevention, diagnosis, and treatment of BCG-related complications and, when appropriate, should consult an infectious disease specialist or other physician with experience in the diagnosis and treatment of mycobacterial infections.

TICE BCG is sensitive to the most commonly used antituberculous agents (isoniazid, rifampin, and ethambutol). **TICE BCG is not sensitive to pyrazinamide.**

Intravesical instillations of BCG should be postponed during treatment with antibiotics, since antimicrobial therapy may interfere with the effectiveness of TICE BCG (see **PRECAUTIONS**). TICE BCG should not be used in individuals with concurrent infections.

Source: TICE USPI[40]

10.15. Appendix 15 Alternative Measures During Public Emergencies

The alternative study measures described in this section are to be followed during public emergencies, including the COVID-19 pandemic. This Section applies for the duration of the COVID-19 pandemic globally and will become effective for other public emergencies only upon written notification from Pfizer.

Use of these alternative study measures are expected to cease upon the return of business as usual circumstances (including the lifting of any quarantines and travel bans/advisories).

10.15.1. Telehealth Visits

In the event that in-clinic study visits cannot be conducted, every effort should be made to follow up on the safety of study participants at scheduled visits per the Schedule of Activities or unscheduled visits. Telehealth visits may be used to continue to assess participant safety and collect data points. Telehealth includes the exchange of healthcare information and services via telecommunication technologies (e.g., audio, video, video-conferencing software) remotely, allowing the participant and the investigator to communicate on aspects of clinical care, including medical advice, reminders, education, and safety monitoring. The following assessments must be performed during a telehealth visit:

- Review and record any AEs and SAEs since the last contact. Refer to Section 8.3.
- Review and record any new concomitant treatments or changes in concomitant treatments since the last contact.
- Review and record contraceptive method and results of pregnancy testing if applicable for the participant. Confirm that the participant is adhering to the contraception method(s) required in the protocol. Refer to Section 10.4 and Section 10.15.2.1 of this Section regarding pregnancy tests.
- Assess ECOG performance status

The following assessments are strongly recommended to be performed if applicable for the visit:

PROs (EORTC-QLQ-C30, EORTC NMIBC24, EQ-5D-5L, PGIS, PGIC)

Study participants must be reminded to promptly notify site staff about any change in their health status.

10.15.2. Alternative Facilities for Safety Assessments

Alternative facilities to the study site may be used as described in this section.

10.15.2.1. Laboratory Testing

If a study participant is unable to visit the site for protocol-specified safety laboratory evaluations, testing may be conducted at a local laboratory if permitted by local regulations. Note that per protocol, participants may have safety labs completed at a local

laboratory even in the absence of a public emergency; however, this section is included to highlight the option to use local labs if needed to facilitate collection of safety laboratory assessments during a public emergency. The local laboratory may be a standalone institution or within a hospital. The following safety laboratory evaluations may be performed at a local laboratory:

- Hematology panel
- Chemistry panel (including ACTH & Thyroid Function Tests for applicable visits)
- Coagulation panel
- Urinalysis
- Pregnancy test (if applicable for the participant)

If a local laboratory is used, qualified study site personnel must order, receive, and review results. Site staff must collect the local laboratory reference ranges and certifications/ accreditations for filing at the site. Laboratory test results are to be provided to the site staff as soon as possible. The local laboratory reports should be filed in the participant's source documents/medical records. Relevant data from the local laboratory report should be recorded on the eCRF.

If a participant requiring pregnancy testing cannot visit a local laboratory for pregnancy testing, a home urine pregnancy testing kit with a sensitivity of at least 25 IU/mL may be used by the participant to perform the test at home, if compliant with local regulatory requirements. The pregnancy test outcome should be documented in the participant's source documents/medical records and relevant data recorded on the eCRF. Confirm that the participant is adhering to the contraception method(s) required in the protocol.

10.15.2.2. Electrocardiograms

If the participant is unable to visit the study site for ECGs, the participant may visit an alternative facility to have the ECGs performed. Qualified study site personnel must order, receive, and review results. Note that per protocol, participants may have ECGs completed at an alternative facility to the site even in the absence of a public emergency; however, this section is included to highlight the option to use an alternative facility if needed to allow completion of ECGs during a public emergency.

10.15.3. Study Intervention

If the safety of a trial participant is at risk because they cannot complete required evaluations or adhere to critical mitigation steps, then discontinuing that participant from study intervention must be considered.

This guidance below is intended to support decision making, but it is not meant to supersede clinical assessment of any individual study participant case.

Regarding the **continued administration of PF-06801591 and BCG** for ongoing participants who have active confirmed (positive by regulatory authority-approved test) or presumed (test pending/clinical suspicion) SARS-CoV2 infection, the following is recommend:

- For symptomatic participants with active SARS-CoV2 infection, study drug treatment should be delayed for at least 14 days from the start of symptoms. This delay is intended to allow the resolution of symptoms of SARS-CoV2 infection.
- Prior to restarting treatment, the participant should be afebrile for 72 hours, and SARS-CoV2-related symptoms should have recovered to ≤ Grade 1 for a minimum of 72 hours. It is requested that the site inform the study team when treatment is restarted.
- PF-06801591 treatment may be delayed within the allowed treatment window in order to meet these criteria; however, PF-06801591 will not be given out of the allowed treatment window and may be skipped as needed in order to meet these re-treatment criteria.
- Continue to consider potential drug-drug interactions for any concomitant medication administered for treatment of SARS-CoV2 infection.

10.15.4. Home Health Visits

A home health care service may be utilized to facilitate scheduled visits per the Schedule of Activities if feasible and locally permitted. Home health visits include a healthcare provider conducting an in-person study visit at the participant's location, rather than an in-person study visit at the site. All assessments must be performed by someone meeting local requirements for performing the assessments. The following may be performed during a home health visit:

- Physical Examination
- Weight
- Vital Signs
- ECG
- PROs
- Review and record any AEs and SAEs since the last contact. Refer to Section 8.3.
- Review and record any new concomitant treatments or changes in concomitant treatments since the last contact.
- Review and record contraceptive method if applicable for the participant. Confirm that the participant is adhering to the contraception method(s) required in the protocol.
- Assess ECOG performance status
- Laboratory sample collection
    - Hematology panel
    - Chemistry panel (including ACTH & Thyroid Function Tests for applicable visits)
    - Coagulation panel
    - Urinalysis

- Pregnancy test (if applicable for the participant)

10.15.5. Adverse Events and Serious Adverse Events

If a participant has COVID-19 during the study, this should be reported as an adverse event (AE) or serious adverse events (SAE) and appropriate medical intervention provided.

It is recommended that the investigator discuss temporary or permanent discontinuation of study intervention with the study sponsor.

10.15.6. Efficacy Assessments

If the participant is unable to visit the study site for CT/MRI, the participant may visit an alternative facility to have the CT/MRI performed. Qualified study site personnel must order, receive, and review results. Note that per protocol, participants may have imaging completed at an alternative facility to the site even in the absence of a public emergency; however, this section is included to highlight the option to use an alternative facility if needed to allow completion of imaging during a public emergency.

10.15.7. Independent Oversight Committees

The EDMC and Steering Committee will be notified in a timely manner of any risk mitigation strategies adopted for the study based on a risk/benefit assessment. The committees may also make recommendations for risk mitigation strategies for the study as needed.

Timing of planned EDMC and Steering Committee meetings may be adjusted as needed in response to a public emergency. In the event that a planned meeting of the EDMC or Steering Committee must be postponed, the study team may consider issuing an update as applicable. Ad hoc EDMC or Steering Committee meetings may be held to discuss any issues within the committee remit. Any proposed changes to the planned meeting schedule will be communicated to committee members.

If any changes to the SAP or to the committee charter for the EDMC or the Steering Committee are needed as a result of a public emergency, they will be communicated to the committee members.

10.16. Appendix 16: Patient Reported Outcomes

10.16.1. Patient Global Impression of Severity

Please choose the response below that best describes the severity of your bladder cancer over the past 7 days. (select only ONE response):

None	☐
Mild	☐
Moderate	☐
Severe	☐

10.16.2. Patient Global Impression of Change

Please choose the response below that best describes the overall change in your bladder cancer since you started taking the study medication (Select only ONE response):

Much better	☐
A little better	☐
No change	☐
A little worse	☐
Much worse	☐

10.16.3. Patient Treatment Administration Burden Questionnaire

(Administer Post Procedure)

Please consider the [ARMS RECEIVING PF-06801591 & BCG insert: two-part] treatment administration procedure [ARMS RECEIVING PF-06801591 & BCG insert: (catheter to your bladder followed by injection into your stomach); ARMS RECEIVING BCG ONLY: (catheter to your bladder); ARM RECEIVING PF-06801591 ONLY: (injection into your stomach)] that you just received for your bladder cancer.

1. How would you characterize any **pain** you may have experienced **during the administration** of treatment?

   □0 No pain
   □1 Mild pain
   □2 Moderate Pain
   □3 Severe pain
   □4 Extremely severe pain

2. How would you characterize the **amount of time needed to complete** the [ARMS RECEIVING PF-06801591 & BCG INSERT: two-part] treatment administration procedure?

   □0 Not at all burdensome
   □1 Slightly burdensome
   □2 Somewhat burdensome
   □3 Very burdensome
   □4 Extremely burdensome

10.16.4. Treatment Satisfaction Questionnaire (TSQ)

Please consider the treatment that you received in the past 4 weeks for your bladder cancer [ARMS RECEIVING PF-06801591 ONLY INSERT: (injection into your stomach); ARMS RECEIVING BCG ONLY INSERT: (catheter to your bladder); ARMS RECEIVING PF-06801591 & BCG INSERT: (catheter to your bladder followed by injection into your stomach)].

1. Over the **past 4 weeks**, how satisfied were you with the **form** of treatment administration that you received?

   □0 Very Dissatisfied
   □1 Dissatisfied
   □2 Neither satisfied nor dissatisfied
   □3 Satisfied
   □4 Very Satisfied

2. Over the **past 4 weeks**, how satisfied were the **number** of treatment administrations that you received?

   □0 Very Dissatisfied
   □1 Dissatisfied
   □2 Neither satisfied nor dissatisfied
   □3 Satisfied
   □4 Very Satisfied

3. Over the **past 4 weeks**, how satisfied were you **overall** with the treatment that you received?

   □0 Very Dissatisfied
   □1 Dissatisfied
   □2 Neither satisfied nor dissatisfied
   □3 Satisfied
   □4 Very Satisfied

10.17. Appendix 17: Protocol Amendment History

The Protocol Amendment Summary of Changes Table for the current amendment is located directly before the table of contents (TOC). The protocol amendment summary of changes tables for past amendment(s) can be found below:

Amendment 4: 22 November 2022

Overall Rationale for the Amendment: Sponsor has closed enrollment to Cohorts B1 and B2 due to a business strategy decision.

Description of Change	Brief Rationale	Section # and Name
Substantial Modifications		
A statement explaining that enrollment to Cohorts B1 and B2 has been closed and that previously enrolled Cohort B1 and B2 participants may continue study treatment was added.	Enrollment to Cohorts B1 and B2 has been closed for business strategy reasons, but previously enrolled participants in these Cohorts will be permitted to continue treatment.	1.1 Synopsis 2.1.2 Study Rationale for the BCG-Unresponsive Cohort (Cohorts B1 and B2) 4.1.2 Cohorts B1 and B2 9.2.2 Cohorts B1 and B2
A statement that Cohort B1 and B2 study objectives are no longer required was added. Cohort B1 and B2 estimands were removed from Sections 1.1, 3.2, and 9.1.1.2. Efficacy endpoint statistical analysis methods were deleted from Section 9.4.1.2, and Section 9.4.1.3 Cohort B2, was deleted.	Given the small numbers of participants enrolled in Cohorts B1 and B2, it will no longer be feasible to complete the Cohort B1 and B2 analyses as previously planned.	1.1 Synopsis 3.2 BCG-Unresponsive Cohorts (Cohorts B1 and B2) 9.1.1.2 Cohorts B1 and B2 9.4.1.3 Cohort B2
The following updates were made to the Schedule of Activities (SoA) – Cohorts B1 and B2 and to the corresponding protocol text: clarification that cohort B1 imaging is only applicable until end of treatment which per protocol does not exceed 2 years, the Cycle 14 biopsy confirming CR for Cohort B1 participants was removed,	Study procedures only intended to facilitate Cohort B1 and B2 study objectives and endpoints that are not needed to properly monitor participants enrolled in Cohort B1 and B2 are no longer needed and have been removed.	1.3 Schedule of Activities (SoA) Screening and Treatment Period – Cohorts B1 and B2 1.3 Schedule of Activities End of Treatment Visit and Follow-Up Period – Cohorts B1 and B2 8.1.1.1. Cystoscopy

PROs for Cohorts B1 and B2 were removed, collection of immunogenicity, PK, PD, and biomarker samples for Cohorts B1 and B2 were removed, disease follow-up after EOT and survival follow-up were removed, and abbreviations that are no longer applicable were removed.		8.1.1.3. Imaging 8.1.2. Patient Reported Outcomes (PROs) 8.5. Pharmacokinetics 8.6. Pharmacodynamics 8.8 Biomarkers 8.8.3. Immunogenicity Assessments: Analysis of Anti-PF-06801591 Antibodies (ADA) and Neutralizing Anti PF-06801591 Antibodies (NAb)
Clarifications that disease assessment and survival follow-up after EOT will now only be applicable to Cohort A were added, language regarding disease follow-up and survival follow-up for Cohorts B1 and B2 was deleted, and Figures 2 and 4 were updated to remove disease follow-up and survival follow-up for Cohorts B1 and B2.	Given the small numbers of participants enrolled in Cohorts B1 and B2, efficacy objectives are no longer applicable and/or feasible and therefore it is no longer necessary to collect disease follow-up and survival follow-up after EOT for Cohort B1 and B2 participants.	1.2 Schema 1.2 Schema Figure 2 B8011006 Study Schematic - Cohorts B1 and B2 4.1.2 Figure 4 Cohorts B1 and B2 8.1.1. Clinical Assessments 8.2.6. Survival Follow-up
The requirement for random bladder biopsies in the event of discordant cytology results between investigator and BICR was removed.	Study procedures only intended to facilitate Cohort B1 and B2 study objectives and endpoints that are not needed to properly monitor participants in Cohort B1 and B2 are no longer needed and have been removed.	8.1.1.2 Cytology
Cohorts B1 and B2 were removed from the PK,	Given the small numbers of participants enrolled in Cohorts B1 and B2, it	9.4.3.2. Pharmacokinetics 9.4.3.3. Immunogenicity

immunogenicity, and biomarker analyses.	will no longer be feasible to analyze Cohort B1 and B2 PK, immunogenicity, and biomarker data as originally planned.	9.4.3.5. Biomarkers
Non Substantial Modifications		
The EDMC will no longer review data from Cohorts B1 and B2.	External data monitoring is no longer needed for Cohorts B1 and B2 that have been closed to enrollment.	1.1 Synopsis 1.2 Schema, Cohorts B1 and B2 2.3. Benefit/Risk Assessment 4.1.1. BCG-Naïve Cohort (Cohort A) 9.5.1. External Data Monitoring Committee (EDMC)
A clarification that the sponsor may request that sites complete additional survival follow-up for Cohort A to facilitate planned analyses as needed was added.	This will enable availability of the most current survival data to support Cohort A objectives at the time of planned analyses.	1.3 Schedule of Activities (SoA) End of Treatment Visit and Follow-Up Period – Cohort A 8.2.6. Survival Follow-up
It was clarified that participants meeting Inclusion 12c are not required to receive BCG maintenance or a second induction course of BCG per inclusion criterion 13.	This clarification was made per the Protocol Amendment Changes and Clarification letter dated 12 May 2022 and adds clarity to the originally intended Inclusion criteria.	5.1 Inclusion Criteria
It was clarified that if CK ≥ 3 x ULN, the isoenzymes CK-MB and CK-MM are to be measured.	This clarification was made per the Protocol Amendment Changes and Clarification letter dated 12 May 2022 and adds more specificity to the type of isoenzymes to be	10.2 Appendix 2: Clinical Laboratory Tests Table 6 Protocol Specified Laboratory Tests

	measures if CK ≥ 3 x ULN.	
Protocol amendment 3 summary of changes moved from this Protocol Amendment Summary of Changes Table to Appendix 17 and replaced in this table with the current summary of changes for protocol amendment 4.	Summary of Changes Table updated with changes for current amendment and changes for previous amendment moved to Appendix 17.	Protocol Amendment Summary of Changes Table 10.17. Appendix 17: Protocol Amendment History
Typos, punctuation, and grammar were corrected as applicable.	Editorial updates	All

Amendment 3: 12 January 2022

Overall Rationale for the Amendment: Modification of dose level and schedule of PF-06801591 for participants in Cohort B2 in order to explore possibility of reducing dosing frequency burden for participants, their caregivers and the healthcare system.

1.1 Synopsis 1.2 Study Schema 1.3 Schedule of Activities 2.1 Study Rationale 2.1.2 Study Rationale for the BCG-Unresponsive Cohort (Cohorts B1 and B2) 2.2.1 Clinical Background 2.3 Benefit/Risk Assessment 3.2 Objectives, Estimands and Endpoints for Cohorts B1 and B2 4.1.2 Overall Design Cohorts B1 and B2	Language was added to support the dosing modification to Cohort B2. Updated language provides rationale for the updated design, and updates to objectives, endpoints, and study procedures for Cohort B2.	Update was included to support updated Cohort B2 dosing regimen.

4.3.1 Justification for Dose of PF-06801591 6.1 Study Intervention Administered 7.1 Discontinuation of Study Intervention 8.4 Treatment of Overdose		
1.3 Schedule of Activities	Frequency of urinalysis was updated for Cohorts B1 and B2.	Updated to more clinically appropriate time points.
5. Study Population	Sentence was added to describe Sponsor eligibility approval process.	Process update added for clarification to sites.
5.1 Inclusion Criteria	Allowance for prior treatment with Verity strain of BCG was added.	Verity strain is the same strain as the Imuron-vac strain, but with a different brand name. Allowance added for clarity.
8.5 Pharmacokinetics 9.4.3.2 Pharmacokinetics	Post-dose PK samples were added for participants in Cohort B2.	Sampling time point was added to support PK analysis of Cohort B2 dosing regimen.
10.2 Clinical Laboratory Tests Table 6	Creatine kinase testing was added to the chemistry panel for Cohorts B1 and B2.	Test added to support collection of additional safety data for Sasanlimab.
10.9 Decision Algorithm for Disease Assessment	Definition of "No Evidence of Disease" was added, as this previously appeared only in the CRF completion guidelines but not in the protocol.	Clarification to sites.
1.1 Synopsis 3.2 Objectives, Estimands and Endpoints for Cohorts B1 and B2	Clarification of censoring strategy and primary estimand text for Cohorts B1 and B2.	Editorial update.

9.1.1.2 Estimands Cohorts B1 and B2 9.4.1.2 Efficacy Analyses Cohort B1		
7.1 Discontinuation of Study Intervention 9.1.1.1 Cohort A Table 2	Description of EFS events and discontinuation criteria for participants with CIS at baseline was clarified.	Clarification for sites.
9.4.3.1 Patient Reported Outcomes Analyses 9.4.3.2 Pharmacokinetics 9.4.3.3 Immunogenicity 9.4.3.5 Biomarker Analyses	Editorial updates were made to match the Statistical Analysis Plan.	Editorial update for document consistency.
2.1 Study Rationale for Cohort A	Repetitive text was removed.	Editorial update.
10.17 Protocol Amendment History	Section was updated to summarize changes included in Amendment 2.	Amendment 2 changes were moved to appendix.
10.18 Abbreviations	List of abbreviations was updated with missing items.	Editorial update.
All	The word ‘patient’ was replaced with ‘participant’ where necessary.	Editorial update.
All	Typos and inconsistencies were corrected, minor clarifications were added, sections were harmonized, language that is not applicable has been removed.	Editorial update.

Amendment 2 (21 September 2021)

Overall Rationale for the Amendment: Addition of two non-randomized Cohorts to enroll participants with BCG unresponsive NMIBC (Cohorts B1 and B2) and evaluate single-agent PF-06801591 in this population. Data from Cohort B1 and Cohort B2 will be analyzed separately from the data of the randomized Cohort A in BCG-naïve high-risk NMIBC. The study design of Cohort A is not modified.

Section # and Name	Description of Change	Brief Rationale
Title and short title	Title was updated.	Update was to include patient population being studied in Cohorts B1 and B2.
1 Protocol Summary 2 Introduction 3 Objectives, Estimands and Endpoints 4 Study Design 5 Study Population 6 Study Intervention 7 Discontinuation of Study Intervention and Participant Discontinuation/Withdrawal 8 Study Assessments and Procedures 9 Statistical Considerations 10 Supporting Documentation	Addition of language regarding background, rationale, study design, objectives and endpoints, eligibility, procedures, statistical considerations and supporting documentations for newly added Cohorts B1 and B2. The original arms of the study (Arms A, B and C) are now labeled as cohort A and language applying to cohort A has been labeled and differentiated from cohorts B1 and 2 throughout the protocol.	Language supports addition of two non-randomized Cohorts (B1 and B2) to evaluate single-agent PF-06801591 in participants with BCG unresponsive NMIBC.
1.1 Synopsis	Cohort A CR objective was changed from "evaluate" to "estimate".	Updated to appropriate terminology.
1.3 SoA for Cohort A	Edited with a reminder that all screening procedures must be completed within 28 days of randomization.	Clarification for sites.
1.3 SoA for Cohort A	Added "pulse rate" to be performed.	Added to match text in section 8.2.2. Also clarified that pulse rate will be 'performed' and not 'collected' since this data is not collected on the CRF.
1.3 SoA for Cohort A	Edited to clarify that methods of testing for tuberculosis during	Clarification for sites regarding acceptable tuberculosis testing methods.

Section # and Name	Description of Change	Brief Rationale
	screening may be per local practices.	
1.3 SoA for Cohort A and Table 6 (Formerly Table 5)	Updated to remove HCV RNA/HBcAB test.	This test is not necessary for screening or on study as it cannot test for active infection.
1.3 SoA for Cohort A	Edited to clarify need for reflex testing for positive HBV surface antigen. This is already in Table 6.	Reminder to sites that this reflex testing must be done, per language already in Table 6.
1.3 SoA for Cohort A	Edited to clarify screening cystoscopy to state that it is required and not "as clinically indicated".	Clarification for sites to prevent errors in screening procedures.
1.3 SoA for Cohort A	Edited to remove notes regarding immunogenicity testing for cycles 1 and 2.	Editorial change.
1.3 SoA for Cohort A	Edited to clarify timing of disease assessments as being fixed according to the calendar based on randomization.	Clarification regarding study procedure timing.
1.3 SoA for Cohort A and 8.2.6 Survival Follow-up	Updated to add a reminder that cystectomy must be recorded as follow-up cancer treatment post treatment discontinuation.	Clarification for sites.
1.3 SoA for Cohort A	Updated to remove biomarker sampling at End of Treatment.	This sample is not needed at EoT to support biomarker objectives.

Section # and Name	Description of Change	Brief Rationale
2.1 Study Rationale	Updated with most recent data from the Keynote-057 study.	Update with current data supporting study rationale.
3.1 Objectives and Estimands	CR objective was changed from “evaluate” to “estimate”.	Updated to appropriate terminology.
5.1 Inclusion Criteria	Edited to clarify inclusion #3 and that the TURBT within 12 weeks of randomization must be positive (i.e. show tumor tissue that is HG Ta, T1 or CIS).	Eligibility clarification for sites.
5.2 Exclusion Criteria	Exclusion #4 was updated to clarify that sites should contact sponsor to discuss prior malignancies before patients join the study.	Eligibility clarification for sites.
6 Study Intervention	Updated to clarify that sites may use BCG strain that is not listed in the protocol, only in the case of serious BCG shortage and when permitted by local health authorities and after review with the sponsor.	Clarification on actions to be taken when BCG shortage affects strains being used in the study.
6.1 Study intervention	Updated to clarify the dosage form and dosage for PF-06801591.	Updated to use correct terminology.
6.6 Dose Modifications	Updated to clarify that BCG dose can be skipped.	Dose modification clarification for BCG, per BCG label.
6.6.2 Precautions for Administration of BCG	Updated to clarify requirements for BCG dosing when a UTI is present.	Dose modification clarification for BCG, per BCG label.

Section # and Name	Description of Change	Brief Rationale
7.2 Participant Discontinuation / Withdrawal from Study	Clarification that destruction of samples can be requested by the participant for remaining samples only.	Clarification on policy.
8.1.1.1 Cystoscopy	Updated to clarify timing of disease assessment (every 12 weeks from randomization for Cohort A).	Clarification for sites.
8.1.1.1 Cystoscopy	Updated to clarify timing around biopsy to confirm complete response for those participants with CIS at randomization.	Clarification for sites on timing of biopsy.
8.1.1.1 Cystoscopy	Updated to clarify that biopsy samples will be reviewed by the BICR.	Clarification to sites regarding which samples will be reviewed by BICR.
8.1.1.2 Cytology	Updated to clarify timing of disease assessment.	Clarification for sites.
8.2 Safety Assessments	Clarification added regarding timing of unscheduled safety labs.	Per Pfizer standard protocol template update.
8.2.4 Electrocardiograms	Updated to clarify that ECG method of QTc calculation during screening must only be QTcF.	Clarification for sites regarding QTc calculation method.
8.2.8 Pregnancy Testing	Clarification around timing of pregnancy testing added.	Per Pfizer standard protocol template update.
Table 3 Outcome and Event Dates for EFS	Updated to clarify EFS scenarios in the case of no adequate baseline disease assessment.	Statistical analysis clarifications in case of missing or inadequate data.

Section # and Name	Description of Change	Brief Rationale
9.4.1.1 Efficacy Analyses - Cohort A	Updated to remove "defined above" which was referring to time points. "Specific time points" was changed to "the time points" for consistency.	Editorial changes.
9.4.1.1 Efficacy Analyses – Cohort A	Updated to remove text "no baseline disease assessments" as an example of participants with inadequate data for disease assessment, as it is not applicable for patients with CIS who are being evaluated for CR.	Clarification of language to match update in SAP as only participants with CIS are being assessed for CR.
9.4.3 Other Analyses	Updated to clarify language regarding PK, PD and immunogenicity analysis.	Editorial update.
10.4.1 Male Participant Reproductive Inclusion Criteria	Text was updated to clarify rationale for contraception.	Clarification for sites.
10.4.4 Contraception Methods	Allowance for injectable birth control was removed.	Per Pfizer standard protocol template update.
10.9 Decision Algorithm for Disease Assessment	Updated to clarify definition of dates for response, recurrence and persistence of disease.	Clarification for sites on entry of overall assessment data.
10.9 Decision Algorithm for Disease Assessment	Cytology result definitions added.	Clarification for sites.
10.13 Management of irAEs	Updated to include clarifying footnote in the Endocrine irAE table.	Clarification for sites regarding monitoring of endocrine irAEs.

Section # and Name	Description of Change	Brief Rationale
10.13 Management of irAEs	Website links for management of cardiac irAEs were removed.	Site should follow instructions in the table, and consult with cardiologist, who may choose to use most recent available references.
10.15.3 Study Intervention	Updated to include clarification on timing of PF-06801591 dosing in the event that a participant is diagnosed with SARS-CoV2.	Clarification on timing of PF-06801591 dosing when doses are delayed due to SARS-CoV2 infection.
10.16 Patient Reported Outcomes	Updated to remove examples of the EORTC-QLQ-C30, EORTC NMIBC24 and EQ-5D-5L.	These questionnaires are copyrighted and must be removed for public disclosure compliance.
10.17 Protocol Amendment History	Section was added to summarize changes included in previous protocol amendments.	Update to the standard Pfizer protocol template.
10.18 Abbreviations	List of abbreviations was updated with missing or unused terms.	Editorial update.
All	Typos and inconsistencies were corrected, minor clarifications were added, language that is not applicable has been removed, and formatting of graphics was updated for readability as needed.	Editorial update.

Amendment 1 (26-June-2020)

Overall Rationale for the Amendment:

• The following PROs will now be completed during Safety Follow-Up in addition to the timepoints specified in the original protocol: EORTC QLQ-C30, EORTC QLQ-NMIBC24, EQ-5D-5L, PGIS, PGIC. This is reflected in Section 1.3, Schedule of Activities. The addition of these PROs during Safety Follow-Up was requested by the European regulatory authority and will allow for collection of the PROs after an EFS event for participants that have had an EFS event so that a potential difference due to drug effects can be evaluated.

Section # and Name	Description of Change	Brief Rationale
1.1 Synopsis 2 Introduction	Sasanlimab, the generic name for PF-06801591 was added to the header, title page and Introduction	
Title Page 1.1 Synopsis	The protocol acronym CREST was added to the protocol title page and the short protocol title	
1.1 Synopsis 1.2 Schema 4.1 Overall Design 9.2 Sample size	Western EU was updated to Western Europe	Clarification made to account for Brexit
1.3 SoA	Updated to indicate that participants must sign consent prior to any trial-specific procedure.	Clarification for sites
1.3 SoA	Updated to indicate that active tuberculosis may be excluded by laboratory test or skin test per the applicable local guidelines or BCG product label. Chest x-ray may continue to be used as well.	Clarification to sites regarding acceptable methods of tuberculosis testing
1.3 SoA 8.2.7 Clinical safety labs	Updated to indicate that laboratory tests may be performed up to 3 days prior to the scheduled clinic visit, so that results will be available for review before study treatment administration, including C1D1.	Clarification for sites regarding timing of lab tests
1.3 SoA 8.2.7 clinical safety lab tests	Updated to clarify the minimum labs to be reviewed prior to dosing.	Updated to clarify for site required labs to be

Section # and Name	Description of Change	Brief Rationale
		reviewed prior to dosing for safety purposes
1.3 SOA 10.2 Clinical lab tests 10.4 Contraceptive Guidance	For female postmenopausal participants under the age of 60 and not using hormonal contraception or HRT, a serum FSH test is required at screening only, to confirm postmenopausal status. FSH is not required for participants not meeting these criteria.	Clarification on requirement for confirming postmenopausal status for WOCBP
1.3 SoA	BCG will be administered first on days when a participant receives both BCG and PF-06801591.	Clarification for sites around timing of two study interventions
1.3 SoA 8.1.2 Patient Reported Outcomes	If labs are done on a date prior to the main visit date, PROs may be completed as the first assessment at the main visit.	Clarification around timing of PROs when labs are done a day earlier
1.3 SoA 8.5 Pharmacokinetics	PK samples should be taken within 2 hours prior to dosing including at the EOT visit if the EOT visit is on the same date as the last dose of study drug.	Clarification around timing of PK samples in relation to study drug dosing
1.3 SoA	The footnote symbols in Section 1.3, Schedule of Activities, for BCG administration were updated to correctly indicate that the suggested BCG re-induction schedule is during Cycles 4 and 5 and that maintenance BCG may be given during Cycles 4, 7, 13, 19, and 25.	Editorial update of footnote symbols
1.3 SoA 7.2 Participant Discontinuation/Withdrawal from study	The window for the EOT visit was defined as being within 7 days after the last dose of PF-06801591 or BCG (whichever is later) or decision to permanently discontinue both drugs and references to an early discontinuation visit were removed because participants that discontinue early will have an EOT visit. References to	Clarification on timing of EOT visit

Section # and Name	Description of Change	Brief Rationale
	early discontinuation were also removed in Section 7.2.	
1.3 SoA	AEs will be collected during Safety Follow-Up, but not during Disease Follow-Up extending beyond Safety Follow-Up with the exception of treatment-related SAEs.	Clarification on collection of AEs during post treatment study periods
1.3 SoA 10.2 Clinical Laboratory Tests	Pregnancy status will be checked at 90 and 180 days after EOT for applicable participants.	Clarification on timing of pregnancy testing in the post treatment study period
2.2.1 Clinical background	Safety and efficacy data was updated in line with the October 2019 PF-06801591 IB.	Update of available safety and efficacy data to align with most recent IB.
2.3 Benefit/Risk Assessment	Source for additional information on BCG was clarified to be the local product label and the SRSD for BCG was clarified to be the TICE USPI.	Clarification on source of SRSD for BCG
4.1 Overall Design 6.1.2 Administration of Study Intervention	Clarification that the maintenance period begins at C7D1 for participants that receive re-induction.	Clarification for sites on start of maintenance period
4.3.2 BCG	BCG dosing is 1 therapeutic dose. This may be 1 or more vials depending on the strain and the applicable BCG product label should be consulted.	Clarification on dose of BCG for sites using different strains of BCG
5.1 Inclusion criteria	Inclusion criterion 2 was updated to include a reference to the WHO grading system for bladder cancer.	Grading system used for the study was clarified
5.1 Inclusion Criteria 8.1.1 Clinical Assessments 8.8.1 Tumor Tissue Assessments	Inclusion criterion 4 was updated to clarify that if a participant has had multiple TURBTs within 12 weeks prior to randomization, tumor tissue should be provided from the TURBT supporting the primary diagnosis for the study.	Clarification on which tumor tissue to be sent for analysis

Section # and Name	Description of Change	Brief Rationale
5.2 Exclusion criteria 6.5.9 Vaccines	Information about vaccines was updated in exclusion criterion 12 was added to state that live attenuated vaccines are not allowed as concomitant medications and to provide examples.	Clarification on permitted vaccines while on study
5.3 Lifestyle considerations 6.1.1 Medical Devices 8.3 Adverse events and SAEs 8.3.6 Cardiovascular and Death Events 10.3 Adverse Events 10.4 Contraceptive Guidance	Updated due to Pfizer protocol template updates.	Sponsor protocol template updates
6.0 Study Intervention	It is recommended that participants receive the same strain of BCG throughout the duration of study treatment.	Reminder to sites regarding BCG strain
6.1 Study Intervention	The name of the CHENGDU Danish strain was corrected to BCG China strain.	Strain terminology corrected
6.1 Study Intervention	Updated to indicate that BCG is a NIMP in all countries.	Categorization of BCG as non -IMP
6.1.2 Administration of Study Intervention	It is strongly preferred that participants start PF-06801591 and BCG on the same date if possible.	Clarification on timing of study drugs
6.1.2 Administration of Study Intervention	Clarification that the visit window is ±3 days for visits prior to Cycle 4 and ±7 days for Cycle 4 through EOT.	Visit window clarification
6.5.3 Hematopoietic Growth Factors	Updated to clarify that erythropoietin may not be approved for anemia in some countries and local guidelines should be followed in that case.	Clarification on acceptable treatment for anemia
6.6.2 Precautions for administration of BCG 10.14 Management of irAEs	Updated to clarify that the TICE USPI language is provided in the protocol as an example for BCG-related AE management, but the product label for the strain of BCG administered	Source of AE management information clarified

Section # and Name	Description of Change	Brief Rationale
	should be used for reference if other than TICE.	
7.1 Discontinuation of Study Intervention	Reference to Section 8.2.4 for participants with a change in QT interval was added.	Cross reference added
8.1.1 Efficacy Assessments 8.1.1.1 Cystoscopy 8.1.1.2 Cytology 8.1.1.3 Imaging	Updated to clarify that biopsies, tumor tissue, cytology results, and imaging will be submitted for BICR assessment. Additional details are now given on the scope of biopsy and tumor tissue to be provided for BICR.	Clarification on what BICR will review
8.2.7 Clinical Safety Labs	Clarified to state that laboratory assessments must be reviewed prior to dosing at each visit.	Reminder to sites to review labs prior to dosing
8.3.10 Medication errors	Medication error examples were updated	Clarification to sites
8.4 Overdose	Definition of overdose and instructions for overdose were updated	Clarification and update to definitions
8.6 Pharmacodynamics 8.8 Biomarkers	Clarification that PK, PD, and biomarker samples will not be collected if prohibited by local regulations and/or IRBs/ECs.	Clarification on sample collection
8.5 Pharmacokinetics	Clarifications about PK samples and analysis of PK samples.	Clarifications to site
8.8.3 Immunogenicity	Updated to clarify the timing and type of immunogenicity assessments.	Clarifications on sample test timing
9.2 Sample size determination	Hypothesis numbering for the secondary objectives were corrected.	Editorial correction
9.3 Population for analysis	Clarification that the PK parameter population is the same as the PK concentration analysis population.	PK population clarification
9.4.3.2 Pharmacokinetics 9.4.3.3 Immunogenicity	Updated to remove specific details of the ADA and NAb analyses, as these will be outlined in the SAP.	Editorial update
9.5 Interim Analysis Table 4	Updated to include minus signs for the efficacy z-value boundaries for IA 1 (for both	Editorial update

Section # and Name	Description of Change	Brief Rationale
	Arm A vs Arm C and Arm B vs Arm C) that had been inadvertently omitted in the original protocol.	
10.1.5 Committees Structure	Updated to provide information about the Steering Committee.	Clarification
10.2	Updated to remove the requirement for a pre-dose C1D1 serum sample for cytokine measurement that did not appear in the SoA.	Editorial update
10.2 Clinical Laboratory Tests Table 5	Updated to indicate that either PTT or aPTT may be reported for the coagulation panel.	Testing clarification
10.8 Country specific amendments	Updated to include country specific requirements in France (Contrat Unique) and Japan (regulatory language for medical device studies).	Regional requirement added
10.12 Recommendations for management of Allergic/Hypersensitivity Reactions	Corrected to refer to Section 6.6.1 of the protocol for guidance on treatment, dose interruptions, and potential retreatment.	Editorial update
10.13 Management of irAEs	The cardiac irAE section of Section 10.13 was updated to give troponin I, as opposed to troponin, as an example of a cardiac biomarker that may be elevated and to include abatacept as an example of an immunosuppressant to treat cardiac irAEs.	Clinical update and clarification
10.15 Alternative Measures during Public Emergencies	Added in response to the COVID-19 pandemic and any potential future public emergencies.	Addition post COVID-19 pandemic
All	Typos and inconsistencies were corrected, minor clarifications were added, language that is not applicable has been removed, formatting of graphics was	Editorial update

Section # and Name	Description of Change	Brief Rationale
	updated for readability as needed, and the abbreviation list was updated.	

10.18. Appendix 18: Abbreviations

Abbreviation	Term
Ab	antibody
ACTH	adrenocorticotropic hormone
ADA	anti-drug antibodies
ADE	adverse device effect
ADL	activities of daily living
AE	adverse event
AESI	adverse events of special interest
Ag	antigen
AHA	American Heart Association
ALT	alanine aminotransferase
ANC	absolute neutrophil count
ANOVA	analysis of variance
aPTT	activated partial thromboplastin time
ASCO	American Society of Clinical Oncology
AST	aspartate aminotransferase
AUA	American Urological Association
AUC	Area Under the Curve
AV	atrioventricular
BBS	Biospecimen Banking System
BC	bladder cancer
BCG	Bacille Calmette Guérin
BICR	blinded independent central review
BNP	B-type natriuretic peptide
BP	blood pressure
bpm	beats per minute
BUN	blood urea nitrogen
CD8	cluster of differentiation-8
cfDNA	circulating free DNA
CFR	Code of Federal Regulations
CI	confidence interval
CIOMS	Council for International Organizations of Medical Sciences
CIS	carcinoma in situ
CK	creatine kinase
CK-MB	creatine kinase-muscle type, myocardial band
CK-MM	creatine kinase-skeletal muscle
C_{max}	maximum observed concentration
CNIL	French data protection authority
CONSORT	Consolidated Standards of Reporting Trials
COVID-19	coronavirus disease 2019
CR	complete response

Abbreviation	Term
CREST	Combination of sasanlimab and alternative BCG Regimens to Evaluate outcomes with Subcutaneous anti-PD-1 Treatment
CRF	case report form
CRO	contract research organization
CSR	clinical study report
CT	computed tomography / clinical trial
CTCAE	Common Terminology Criteria for Adverse Events
CTLA-4	cytotoxic T lymphocyte-associated antigen 4
C_{trough}	concentration at trough
CxDx	cycle x day x
DILI	drug-induced liver injury
DLT	dose-limiting toxicity
DNA	deoxyribonucleic acid
DSS	disease-specific survival
EAU	European Association of Urology
EC	Ethics committee
ECG	electrocardiogram
ECOG	Eastern Cooperative Oncology Group
eCRF	electronic case report form
EDMC	external data monitoring committee
EDP	exposure during pregnancy
EFS	event free survival
EMA	European Medicines Agency
EORTC	European Organisation for Research and Treatment of Cancer
EORTC-GU	EORTC-Genito-Urinary
EORTC-QLQ NMIBC24	EORTC-Quality of Life Questionnaire Non-Muscle Invasive Bladder Cancer 24 (items)
EOT	end of treatment
ESC	European Society of Cardiology
EQ-5D-5L	EuroQol 5 Dimensions, 5-Level
EU	European Union
EudraCT	European Clinical Trials Database
FA	final analyses
FDA	Food and Drug Administration
FFPE	formalin-fixed paraffin-embedded
FSH	follicle-stimulating hormone
FT4	free thyroxine
GCP	Good Clinical Practice
G-CSF	granulocyte colony-stimulating factor
GGT	gamma-glutamyl transferase
GH	growth hormone
HBcAb	hepatitis B core antibody

Abbreviation	Term
HBsAg	hepatitis B surface antigen
HBV	hepatitis B virus
HCV	hepatitis C virus
HG	High-grade
HIPPA	Health Insurance Portability and Accountability Act
HR	hazard ratio
HRQoL	health-related quality of life
HRT	hormone replacement therapy
IA	interim analysis
IB	Investigator's Brochure
ICD	informed consent document
ICH	International Council for Harmonisation of Technical Requirements for Pharmaceuticals for Human Use
IEC	Independent Ethics Committee
IgA	immunoglobulin A
IGF-1	insulin-like growth factor 1
IgG	immunoglobulin G
IHC	immunohistochemistry
IL	interleukin
IMP	investigational medicinal product
IND	Investigational new drug
INF-y	interferon-y
INR	international normalized ratio
IP	investigational product
irAE	immune-related adverse events
IRB	Institutional Review Board
IRT	interactive response technology
ISO	International Organization for Standardization
IUD	Intrauterine Device
IUS	Intrauterine hormone-releasing system
IV	Intravenous
IVRS	interactive voice response system
IWRS	Interactive Web Response System
LDH	lactate dehydrogenase
LFT	liver function test
LH	luteinizing hormone
LLQ	lower limit of quantitation
mAbs	monoclonal antibodies
MQI	Medically qualified individual
MRI	magnetic resonance imaging
MTD	maximum tolerated dose
MWPC	meaningful within person change
N+	lymph node positive disease

Abbreviation	Term
N/A	not applicable
NAb	neutralizing antibodies
NCCN	National Comprehensive Cancer Network
NCI	National Cancer Institute
NCI CTCAE	National Cancer Institute Common Terminology Criteria for Adverse Events
NIMP	non-investigational medicinal product
NMIBC	non-muscle invasive bladder cancer
NSCLC	non-small cell lung cancer
ORR	objective response rate
OS	overall survival
PCD	primary completion date
PD	pharmacodynamics; progressive disease
PD-1	programmed death - 1
PD-L	programmed death - ligand
PFS	pre-filled syringe
PGIC	Patient Global Impression of Change
PGIS	Patient Global Impression of Severity
PK	pharmacokinetics
PR	partial response
PRL	prolactin
PRO	patient reported outcome
PS	performance status
PT	prothrombin time
PTAB	Patient Treatment Administration Burden
PTT	partial thromboplastin time
PVC	premature ventricular complexes
Q3W	every 3 weeks
Q4W	every 4 weeks
Q6W	Every 6 weeks
QLQ-C30	Quality of Life Questionnaire–30 (items)
QT	time from the beginning of the QRS complex to the end of the T wave
QTc	QT interval corrected for heart rate
QTcF	QTc corrected using Fridericia's formula
QW	once weekly
QxW	every X weeks
RCI	repeated confidence interval
RMST	restricted mean survival time
RNA	ribonucleic acid
ROW	rest of world
SADE	serious adverse device effect
SAE	serious adverse event
SAP	Statistical Analysis Plan

Abbreviation	Term
SARS-CoV2	severe acute respiratory syndrome coronavirus
SC	subcutaneous
SCCHN	squamous cell carcinoma of the head and neck
SD	standard deviation
SE	standard error
SoA	schedule of activities
SOC	standard of care
SOP	standard operating procedure
SRSD	single reference safety document
SUSAR	Suspected Unexpected Serious Adverse Reaction
SWOG	Southwest Oncology Group
T1	stage of cancer in which the cancer cells are only growing in the most superficial layer of tissues and have not grown into deeper tissues; in bladder cancer, T1 is defined as an invasion into the lamina propria without invasion into the muscularis propria
$t_{1/2}$	terminal phase half-life
T3	triiodothyronine
T4	thyroxine
Ta	stage of bladder cancer defined as a non-invasive papillary carcinoma
TBili	total bilirubin
TCC	transitional cell carcinoma
TEAE	treatment-emergent adverse event
TIL	tumor infiltrating lymphocytes
T_{max}	time to first occurrence of C_{max}
TNF	tumor necrosis factor
TRAE	Treatment-related adverse event
TSH	thyroid stimulating hormone
TSQ	Treatment Satisfaction Questionnaire
TURBT	transurethral resection of the bladder tumor
UC	urothelial cancer
ULN	upper limit of normal
UPCR	urine protein:creatinine ratio
US	United States
USA	United States of America
USADE	unexpected serious adverse device effect
USPI	United States Prescribing Information
UTI	Urinary tract infection
VAS	visual analog scale
WBC	white blood cells
WHO	World Health Organization
WOCBP	woman/women of childbearing potential

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