Janssen Research & Development *

Clinical Protocol

A Randomized Phase 2 Study of Erdafitinib Versus Investigator Choice of Intravesical Chemotherapy in Subjects Who Received Bacillus Calmette-Guérin (BCG) and Recurred With High Risk Non-Muscle-Invasive Bladder Cancer (NMIBC) and FGFR Mutations or Fusions

Protocol 42756493BLC2003; Phase 2

Amendment 6

JNJ-42756493 (erdafitinib)

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United States (US) sites of this study will be conducted under US Food & Drug Administration Investigational New Drug (IND) regulations (21 CFR Part 312).

Regulatory Agency Identifier Number(s):

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GCP Compliance: This study will be conducted in compliance with Good Clinical Practice, and applicable regulatory requirements.

PROTOCOL AMENDMENT SUMMARY OF CHANGES TABLE

DOCUMENT HISTORY	
Document	**Date**
Amendment 6	13 July 2023
Amendment 5	24-Sep-2021
Amendment 4	08-Feb-2021
Amendment 3	26-Oct-2020
Amendment 2	26-Mar-2020
Amendment 1	06-Nov-2019
Original Protocol	24-Sep-2019

A Protocol Amendment Summary of Changes Table for the current amendment is provided below. Protocol Amendment Summary of Changes Tables for previous amendments are provided in Section 10.15 (Appendix 15).

Amendment 6 (13 July 2023)

Overall Rationale for the Amendment: to add the Long-term Extension (LTE) Phase, which requires modification of the Study Completion, End of Study, and Subject Completion definitions. The LTE Phase will allow continued access to study drug for subjects who continue to derive benefit from treatment, as determined by their investigator. As an alternative to entering the LTE Phase, subjects receiving erdafitinib may exit the study and continue to receive treatment on any other post-trial access program, when permitted by local regulations. Other key changes made with this amendment include:

- to update statistical language within the protocol to reflect early enrollment termination and change in study's regulatory intent from registrational to non-registrational;
- to state that no additional subjects will be allowed to crossover from Investigator's Choice to erdafitinib;
- to clarify visit windows for the End-of-Treatment (EOT) visit and for Disease Assessment Follow-up visits in the Follow-up Phase;
- to remove requirement for urine collection for assay development at the time of high-risk disease recurrence; and
- to state that it is no longer required to send redacted images of Optical Coherence Tomography (OCT) scans, photographs, and fluorescein angiograms to the sponsor-selected central vendor.

Section Number and Name	Description of Change	Brief Rationale
1.1, Synopsis (Objectives and Endpoints, Overall Design, Statistical Methods); 1.2, Schema; 1.3, Schedule of Activities; 2.3, Benefit-Risk Assessment; 3, Objectives and	Statistical language has been updated throughout the protocol. Changes include: • Secondary endpoints for Cohort 1 limited to time to progression (TTP), overall survival (OS), and recurrence-free survival (RFS) rate at 6 months and 12 months • Exploratory efficacy endpoints for Cohort 2 modified to complete response (CR) rate at 8 weeks, CR rate at 32 weeks, and duration of response (DOR)	To reflect early enrollment termination and change in study's regulatory intent from registrational to non-registrational.

Section Number and Name	Description of Change	Brief Rationale
Endpoints; 4.1, Overall Design; 4.2, Scientific Rationale for Study Design; 8, Study Assessments and Procedures; 8.1.1.3, Full-study Screening Phase; 8.2.2, Patient-Reported Outcomes; 8.3, Safety Assessments; 8.10, Medical Resource Utilization and Health Economics; 9.1, Statistical Hypothesis; 9.2, Sample Size Determination; 9.3, Populations for Analyses; 9.4.1, General Considerations; 9.4.2, Primary Endpoint (Cohort 1); 9.4.3, Secondary Efficacy Endpoints (Cohort 1); 9.4.4, Tertiary/Exploratory Endpoints; 9.4.5, Safety Analyses; 9.4.6.1, Pharmacokinetic Analyses; 9.4.6.3, Medical Resource Utilization Analyses (removed); 9.5, Interim Analysis; 9.6, Independent Data Monitoring Committee; 10.2, Appendix 2: Regulatory, Ethical, and Study Oversight Considerations (Committees Structure)	• Exploratory efficacy endpoints for Cohort 3 modified to CR rate, best overall response (BOR), and DOR • Evaluation of health-related quality of life (HRQoL) removed as secondary objective for all cohorts, therefore, patient-reported outcome (PRO) assessment/data collection is no longer required for all subjects in all phases. • Stated that due to early enrollment termination and change in study's regulatory intent for Cohort 1 from registrational to non-registrational, no formal hypothesis testing will be performed for any of the cohorts. • Actual numbers of subjects enrolled to each cohort are shown along with planned sample sizes • Removed all analyses other than descriptive reporting • Revised to show that interim analyses are no longer planned • Streamlined planned summaries for clinical laboratory tests and electrocardiograms • Streamlined planned pharmacokinetic (PK) analyses • Removed planned medical resource utilization (MRU) analyses, therefore, MRU data collection is no longer required for all subjects in all phases. • Cessation of Independent Data Monitoring Committee (IDMC) oversight	

Section Number and Name	Description of Change	Brief Rationale
1.1, Synopsis (Overall Design, Treatment Groups and Duration); 4.1, Overall Design; 6.1.2, Investigator's Choice of Treatment – Cohort 1 Only; 6.1.3, Continuation of Treatment After Disease Recurrence; 6.1.4, Erdafitinib Crossover; 10.10, Appendix 10: Erdafitinib Crossover	The following text has been added to the listed sections of the protocol: 'Note: no additional crossover from Investigator's Choice to erdafitinib will be permitted.'	Due to early termination of study enrollment, the risk-benefit of erdafitinib has not been established for this indication, therefore new cross-overs to erdafitinib will not be permitted.
1.1, Synopsis (Overall Design); 1.2, Schema; 1.3, Schedule of Activities; 4.1, Overall Design; 4.4, Study Completion, End of Study, and Subject Completion Definitions; 6.7, Access to Study Drug in the Long-term Extension Phase; 8, Study Assessments and Procedures; 8.1.2, Treatment Phase; 8.1.3.2, Long-term Follow-up; 8.1.3.2.1, Disease Assessment Follow-up; 8.1.3.2.2, Survival Follow-up; 8.1.5, Long-term Extension Phase (new section); 8.3, Safety Assessments; 8.4, Adverse Events and Serious Adverse Events; 10.14, Appendix 14: Long-term Extension Phase (new appendix)	The LTE Phase was added to the protocol with Section 10.14, Appendix 14, which includes a Schedule of Activities. The LTE Phase is also reflected as appropriate in the synopsis and body of the protocol. As an alternative to entering the LTE Phase, subjects receiving erdafitinib may exit the study and continue to receive treatment on any other post-trial access program, when permitted by local regulations. Within Section 4.4, to align with incorporation of the LTE Phase, definitions for Study Completion, End of Study, and Subject Completion have been modified.	The LTE Phase will allow continued access to study drug for subjects who continue to derive benefit from treatment, as determined by their investigator.

Section Number and Name	Description of Change	Brief Rationale
1.3, Schedule of Activities	Window for the EOT visit has been modified as follows (deleted text in strikethrough, new text in bold): +7 days after ~~last dose~~ **permanent treatment discontinuation**	For consistency with existing language in Section 8.1.2, Treatment Phase.
1.3, Schedule of Activities	Within the Follow-up Phase, the visit window for Disease Assessment Follow-up visits now reads as follows (text in bold has been added): 'Every 24 **weeks (**±2 weeks**) from the last disease assessment visit in the Treatment Phase**'	Clarification.
1.3, Schedule of Activities (Cystoscopy row)	The following text has been added (in bold): Cohort 1 and Cohort 2: C3D1 then every 12 weeks (±1 week) until C26D1, end of treatment, or until disease recurrence or progression**, whichever occurs first**. Cohort 3 only: C2D1, C3D1, C4D1 (±1 week) or until CR (if earlier). After CR, every 12 weeks (±1 week) until C26D1, end of treatment, or until disease recurrence or progression**, whichever occurs first**. If PR, see Section 8.2.1.5.	Clarification.
1.3, Schedule of Activities; 4.1, Overall Design; 8.9, Biomarkers	The pre-transurethral resection of bladder tumor (TURBT) voided urine sample that was to be collected for assay development at the time of high-risk disease recurrence has been marked as 'no longer required' in the Schedule of Activities. Corresponding changes have been made in the protocol body.	This sample is not needed due to early enrollment termination.
5.4, Screen Failures	The following text has been added: 'This study will use IWRS. The investigator will generate screening and enrollment logs directly from IWRS.'	To align with protocol template.
7.1, Discontinuation of Study Drug	The following criterion has been added to the list of reasons for which a subject's study drug must be discontinued: • Subject reaches the maximum treatment duration as defined in Section 6.1.	Internal consistency.
8.1.2, Treatment Phase	The following text has been added (in bold): **With the exception of hyperphosphatemia (see Table 3),** adverse event information will be graded using the National Cancer Institute Common Terminology Criteria for Adverse Events (NCI-CTCAE), Version 5.0.	Clarification.
8.3.5, Ophthalmologic Examination	Added text stating that it is no longer required to send redacted images of OCT scans, photographs, and fluorescein angiograms to the sponsor-selected central vendor.	This review is not needed due to change in study's regulatory intent from registrational to non-registrational.
8.4.1, Time Period and Frequency for Collecting Adverse	Text in strikethrough has been removed, and text in bold has been added to this sentence:	To align with protocol template.

Section Number and Name	Description of Change	Brief Rationale
Event and Serious Adverse Event Information	'All serious adverse events occurring during the study must be reported to the appropriate sponsor contact person by study-site personnel ~~within~~ **immediately but no later than** 24 hours of their knowledge of the event.'	
10.2, Appendix 2: Regulatory, Ethical, and Study Oversight Considerations (Informed Consent Process)	The screening period now reflects 35 days (previously 30 days). Also, added that subjects undergoing molecular screening do not need to re-sign a new Molecular Eligibility ICF to submit historical samples to the central laboratory.	Aligned screening period with body of protocol and added clarification regarding molecular eligibility consent.
Throughout the protocol	Minor grammatical, formatting, or spelling changes were made. Country revised to country/territory throughout.	To correct minor errors and to align with current protocol template.

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1. PROTOCOL SUMMARY

1.1. Synopsis

A Randomized Phase 2 Study of Erdafitinib Versus Investigator Choice of Intravesical Chemotherapy in Subjects Who Received Bacillus Calmette-Guérin (BCG) and Recurred With High Risk Non-Muscle-Invasive Bladder Cancer (NMIBC) and FGFR Mutations or Fusions

Erdafitinib (JNJ-42756493) is an oral pan-fibroblast growth factor receptor (FGFR) 1-4 inhibitor with demonstrated clinical activity in subjects with solid tumors, including urothelial carcinoma, with alterations in the FGFR pathway.

OBJECTIVES AND ENDPOINTS

Cohort 1 (papillary disease only)

Primary Objective: To evaluate recurrence-free survival (RFS) in subjects treated with erdafitinib vs Investigator's Choice, for subjects with high-risk NMIBC who harbor FGFR mutations or fusions, and who recurred after BCG therapy.

Secondary Objective and Endpoints: To evaluate other measures of efficacy. Endpoints include time to progression, overall survival (OS), and RFS rate at 6 months and 12 months.

Cohort 2 (carcinoma in situ [CIS] with or without papillary disease)

Exploratory Objective: To evaluate the efficacy of erdafitinib in terms of the complete response (CR) rate at 8 weeks, CR rate at 32 weeks, and duration of response (DOR) in subjects with high-risk, BCG-unresponsive NMIBC and FGFR mutations or fusions.

Cohort 3 (intermediate-risk marker lesion) at select study sites

Exploratory Objective: To evaluate the efficacy of erdafitinib in terms of the CR rate, best overall response (BOR), and DOR in subjects with intermediate-risk NMIBC and FGFR mutations or fusions.

Other secondary objectives for all cohorts

Secondary objectives for all cohorts include the following:

- To evaluate erdafitinib pharmacokinetics
- To evaluate safety and tolerability of erdafitinib

Hypothesis

For Cohort 1, erdafitinib treatment will delay the onset of tumor recurrence for subjects with papillary disease only, who recurred after BCG therapy, with FGFR mutations or fusions, and with all lesions removed.

For Cohort 2, erdafitinib treatment will lead to CR for subjects with CIS with or without papillary disease and FGFR mutations or fusions.

For Cohort 3, erdafitinib treatment will lead to CR in the marker lesion for subjects with a papillary marker lesion and FGFR mutations or fusions.

Due to early enrollment termination and change in study's regulatory intent for Cohort 1 from registrational to non-registrational, no formal hypothesis testing will be performed for any of the cohorts.

OVERALL DESIGN

This is an open-label, global, multicenter, randomized, Phase 2 study of the safety and efficacy of erdafitinib in subjects with NMIBC and FGFR mutations or fusions (see Section 5.1).

Cohort 1 (n=240 planned) will include subjects with high-risk NMIBC presenting as papillary tumor only, with disease recurrence after BCG therapy, and who either refuse or are not eligible for cystectomy. The reason for not being eligible for cystectomy or for refusing cystectomy will be entered into the electronic case report form (eCRF). Subjects will be assigned randomly 2:1 to treatment with erdafitinib or the investigator's choice of either intravesical gemcitabine or intravesical mitomycin C (MMC)/hyperthermic MMC, respectively. Randomization will be stratified by tumor stage (Ta vs T1) and type of prior BCG therapy (BCG-unresponsive vs BCG-experienced). BCG strain administered will also be documented in the eCRF. Subjects in the BCG-experienced strata will be capped at approximately 50% of the total study population (See Section 6.3). Investigators must choose between intravesical gemcitabine or intravesical MMC/hyperthermic MMC for each subject at screening, and the choice of the agent must take prior exposure into consideration. Subjects in Cohort 1 with locally confirmed high-risk recurrence on Investigator's Choice may cross over to treatment with erdafitinib. Note: no additional crossover from Investigator's Choice to erdafitinib will be permitted. Molecular screening must start within 12 weeks after the last transurethral resection of bladder tumor (TURBT) done for high risk recurrence if molecular testing is being done on post-BCG specimen. Peri-operative intravesical chemotherapy prior to study entry per local standard of care and prior immunotherapy (eg, PD1 inhibitor etc) are allowed.

Cohort 2 and Cohort 3 are exploratory.

Cohort 2 (n=20 planned) will include subjects with high-risk, BCG-unresponsive NMIBC presenting as CIS with or without concurrent papillary tumor, and who either refuse or are not eligible for cystectomy. The reason for not being eligible for cystectomy or for refusing cystectomy will be entered into the eCRF. All subjects enrolled in Cohort 2 will receive treatment with erdafitinib. Peri-operative intravesical chemotherapy prior to study entry per local standard of care and prior immunotherapy (eg, PD1 inhibitor etc) are allowed. Additionally, subjects in this cohort may receive chemotherapy as bridging therapy after adequate BCG therapy while being considered for trial.

Cohort 3 (n=20 planned) will be enrolled at select study sites and will include subjects with intermediate-risk NMIBC presenting as papillary disease only. All previous tumors for these subjects must be low grade (G1-G2), Ta, or T1, with no previous CIS. Furthermore, subjects must have a risk of progression less than 5% for 2 years, and the risk of recurrence must be greater than 50% as calculated using the European Organisation for Research and Treatment of Cancer (EORTC) risk calculator.[19] There are no predefined BCG or intravesical chemotherapy requirements for subjects enrolled in Cohort 3. All tumors must be removed except for a single, untouched 5 to 10 mm lesion. All subjects enrolled in Cohort 3 will receive treatment with erdafitinib.

Molecular eligibility will be determined before screening for remaining eligibility criteria. The Treatment Phase will begin on Day 1 for subjects meeting all eligibility criteria. The Follow-up Phase includes a 30-day Safety Follow-up Visit, disease assessment follow-up, and survival follow-up. An Independent Data Monitoring Committee (IDMC) will be commissioned for the study. Due to the company decision to terminate study enrollment and considering the recent IDMC review (6 July 2022) found the safety of erdafitinib in this study to be consistent with the known safety profile of erdafitinib, no further monitoring by the IDMC will be conducted.

The Long-term Extension (LTE) Phase will allow continued access to study drug for subjects who continue to derive benefit from treatment, as determined by their investigator. Subjects may enter the LTE Phase following implementation of Amendment 6, provided they meet the criteria for entry specified in the protocol. No data will be collected in the eCRF during the LTE Phase, and only serious adverse events (SAEs) will be reported to the company safety repository. As an alternative to entering the LTE Phase,

subjects receiving erdafitinib may exit the study and continue to receive treatment on any other post-trial access program, when permitted by local regulations.

TREATMENT GROUPS AND DURATION

Subjects receiving erdafitinib will take erdafitinib tablets orally, at a starting dose of 6 mg, once daily for 28 days in a 28-day cycle. After review of safety and tolerability data from approximately 5 to 10 additional subjects dosed with the 6-mg daily regimen (without up-titration), the IDMC may recommend a modification of the dosing regimen to include up-titration to 8 mg daily. The details of the IDMC recommendation will be communicated in writing to the investigative sites and, per local regulation, to health authorities. With the exceptions noted below for Cohort 2 and Cohort 3, treatment may continue for a maximum of 2 years or until the subject has disease recurrence or progression, intolerable toxicity, withdraws consent, there is a decision by the investigator to discontinue treatment, or the study is closed, whichever occurs first.

- For Cohort 2, erdafitinib must be discontinued if CR is not observed within 3 months.
- For Cohort 3, after 3 months of study treatment: 1) Subjects with stable disease or progression of the marker lesion must discontinue erdafitinib and a TURBT of the marker lesion must be performed. 2) Subjects with CR may continue erdafitinib. 3) Subjects with partial response (PR) may, at the investigator's discretion, either continue treatment with erdafitinib or discontinue erdafitinib and undergo TURBT of the marker lesion.

Subjects in Cohort 1 assigned to Investigator's Choice will receive intravesical gemcitabine or intravesical MMC/hyperthermic MMC as described in Section 6.1.2. All dose modifications or omissions will be managed by the treating physician per local standard of care after discussion with the sponsor. Investigator's Choice treatment will be given once weekly for at least 4 doses of induction followed by monthly maintenance for at least 6 months. Additional doses of induction or maintenance are allowed per local standard of care. This treatment may continue until it is completed, disease recurrence, intolerable toxicity, withdrawal of consent, a decision by the investigator to discontinue treatment, or the study is closed, whichever occurs first.

Subjects in Cohort 1 with locally confirmed high-risk recurrence on Investigator's Choice may cross over to treatment with erdafitinib (Section 10.10). Note: no additional crossover from Investigator's Choice to erdafitinib will be permitted.

EVALUATIONS

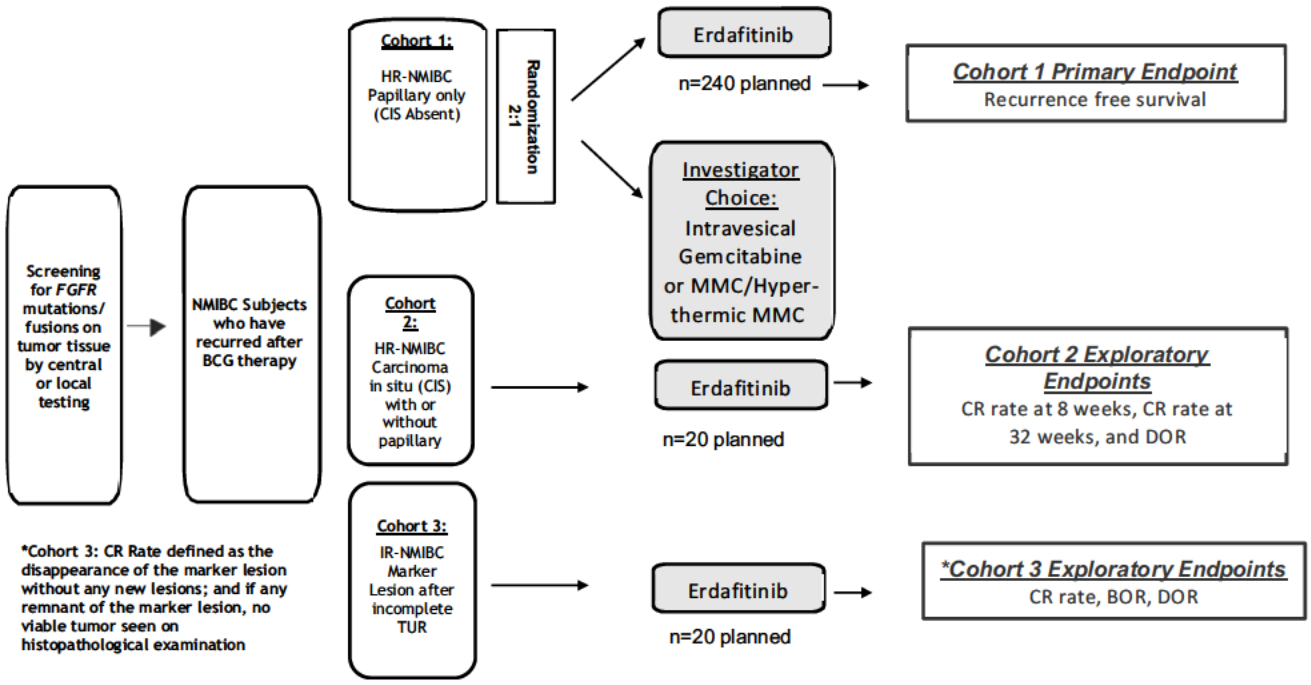
The timing of all study evaluations is provided in the Schedule of Activities (Section 1.3). Disease assessments include regularly scheduled cystoscopy, bladder mapping, local assessment of urine cytology, and contrast-enhanced computed tomography (CT) or magnetic resonance imaging (MRI) urograms. Central histopathologic review of biopsied tumor tissue will be performed for Cohort 1. Biomarker assessments include molecular screening to determine eligibility for the study and exploratory DNA, RNA, and protein analyses using archival or fresh biopsy tissue, urine, and blood. Erdafitinib concentration will be measured in blood and biopsied tissue for pharmacokinetic analysis. Safety assessments will include adverse event reports, physical examinations, 12-lead electrocardiograms (ECGs), clinical laboratory tests, vital sign measurements, β-human chorionic gonadotropin (β-hCG) pregnancy tests, and ophthalmologic examinations.

STATISTICAL METHODS

The cohorts will be analyzed separately. Descriptive statistics and subject listings will be used to summarize the data. For continuous variables, number of observations, means, standard deviations, medians, interquartiles (IQs), and ranges will be used. For discrete variables, frequency will be summarized. The comparisons between the 2 treatment groups in Cohort 1 will be performed using descriptive statistics.

1.2. Schema

Figure 1: Schematic Overview of the Study



Note: the Long-Term Extension Phase is not included in the schema (see Section 10.14, Appendix 14).
BCG=bacillus Calmette-Guérin; BOR=best overall response; CIS=carcinoma in situ; CR=complete response; DOR=duration of response; FGFR=fibroblast growth factor receptor; HR=high risk; IR=intermediate risk; MMC=mitomycin C; NMIBC=non-muscle-invasive bladder cancer; TUR=transurethral resection

1.3. Schedule of Activities

For the Long-term Extension Phase Schedule of Activities, please refer to Section 10.14, Appendix 14.

	NOTES	Urine Sample for Assay Development	Molecular Eligibility Phase	Screening Phase		Treatment Phase[a] (28 days Cycle)				Follow-up Phase[a]		
						Cycles 1, 2, 3		Cycle 4+				
						Day 1	Day 14	Day1	EoT Visit	30-day Safety Follow-up Visit	Disease Assessment Follow-up	Survival Follow-up
Visit window		After disease recurrence and before TURBT	N/A	- 35 days	- 14 days	C1:0 days C2, C3: ±2 days	±2 days	±2 days	+7 days after permanent treatment discontinuation	30 (+7) days after last dose	Every 24 weeks (±2 weeks) from the last disease assessment visit in the Treatment Phase	Every 12 ±2 weeks
Screening/Administrative: Minimum criteria for the availability of documentation supporting the eligibility criteria are described in Section 10.2 (Appendix 2). Check clinical status again before first dose of study drug. Molecular screening must start within 12 weeks after the last TURBT done for high risk recurrence if molecular testing is being done on post-BCG specimen.												
Urine Sample for Assay Development ICF	Only for subjects who provide a voided urine sample after disease recurrence and before TURBT. (Subjects being considered for study after TURBT will not provide this urine sample or sign this ICF).	X										
Molecular Eligibility ICF	Only required before assessing archived tumor tissue tor FGFR status. See Section 8.1.1.1 and Section 8.1.1.2. Consent for molecular eligibility screening (but not full-study screening) may be performed remotely including consent by telephone or video consultation, unless not permitted according to local guidance.		X									
Main-study ICF	Required before collection of fresh biopsy for FGFR assessment and for subjects meeting molecular eligibility before any other study-related activity. See Section 8.1.1.1, Section 8.1.1.2 and Section 8.1.1.3. Procedures conducted, before signing the Main-study ICF, as part of the subject's routine clinical management (eg, blood count, disease assessment) may be used			X								

	NOTES	Urine Sample for Assay Development	Molecular Eligibility Phase	Screening Phase		Treatment Phase[a] (28 days Cycle)				Follow-up Phase[a]		
						Cycles 1, 2, 3		Cycle 4+	EoT Visit	30-day Safety Follow-up Visit	Disease Assessment Follow-up	Survival Follow-up
						Day 1	Day 14	Day1				
Visit window		**After disease recurrence and before TURBT**	**N/A**	**- 35 days**	**- 14 days**	**C1:0 days C2, C3: ±2 days**	**±2 days**	**±2 days**	**+7 days after permanent treatment discontinuation**	**30 (+7) days after last dose**	**Every 24 weeks (±2 weeks) from the last disease assessment visit in the Treatment Phase**	**Every 12 ±2 weeks**
	for screening or baseline purposes provided the procedure meets the protocol-defined criteria and has been performed within 35 days prior to dosing.											
Inclusion/exclusion criteria	See Section 5.1 and Section 5.2. Confirm inclusion/exclusion criteria C1D1			X		X C1D1 predose						
Medical history including smoking history	Record histological documentation of specific tumor type, prior anticancer therapy, demographic information.			X								
Tumor tissue for molecular eligibility, histopathology staging, and biomarker testing	During the Molecular Eligibility Phase, send biopsy sample to the central laboratory for FGFR testing (all cohorts). After a FGFR status is confirmed, send central histopathologic sample for a blinded independent central review (BICR) (Cohort 1 only). Biomarker evaluation (all cohorts) will be analyzed from the tissue sent for FGFR analysis.[b] See Section 8.6.1 and the Laboratory Manual for instruction on sample handling. Also see Section 5.1 (Inclusion Criterion no. 3), Section 8.1.1.1, Section 8.1.1.2, Section 8.2.1 and Section 8.9 (tissue biomarkers).		X								

	NOTES	Urine Sample for Assay Development	Molecular Eligibility Phase	Screening Phase		Treatment Phase[a] (28 days Cycle)				Follow-up Phase[a]		
						Cycles 1, 2, 3		Cycle 4+				
						Day 1	Day 14	Day1	EoT Visit	30-day Safety Follow-up Visit	Disease Assessment Follow-up	Survival Follow-up
Visit window		**After disease recurrence and before TURBT**	**N/A**	**- 35 days**	**- 14 days**	**C1:0 days C2, C3: ±2 days**	**±2 days**	**±2 days**	**+7 days after permanent treatment discontinuation**	**30 (+7) days after last dose**	**Every 24 weeks (±2 weeks) from the last disease assessment visit in the Treatment Phase**	**Every 12 ±2 weeks**
ECOG performance status				X								
Ophthalmologic examination	All subjects: To be performed by an ophthalmologist; see Section 8.3.5. *During screening and then every 4 months while on study treatment up to 2 years. Repeat OCT scan in case of quality issue. *Ophthalmologic examinations will be performed at EOT if the last ophthalmologic examination was done ≥4 months prior to the EOT visit.			X				C5D1 C9D1 C13D1 C17D1 C21D1 C25D1 (±2 weeks)	X *See note			
Randomization Cohort 1	All screening results must be available (except parathyroid hormone and 1,25-dihydroxyvitamin D) and all inclusion/ exclusion criteria confirmed before randomization. Subjects may be randomized up to 1 day before C1D1 but no later than C1D1 predose.					X C1D1 predose						
Enrollment Cohort 2, Cohort 3						X						
Study Drug Administration (Main Study)												
Erdafitinib	The dosing regimen will be 6 mg daily (After review of safety and tolerability data					Once daily until 2 years of treatment have been						

	NOTES	Urine Sample for Assay Development	Molecular Eligibility Phase	Screening Phase		Treatment Phase[a] (28 days Cycle)				Follow-up Phase[a]		
						Cycles 1, 2, 3		Cycle 4+	EoT Visit	30-day Safety Follow-up Visit	Disease Assessment Follow-up	Survival Follow-up
						Day 1	Day 14	Day1				
Visit window		**After disease recurrence and before TURBT**	**N/A**	**- 35 days**	**- 14 days**	**C1:0 days C2, C3: ±2 days**	**±2 days**	**±2 days**	**+7 days after permanent treatment discontinuation**	**30 (+7) days after last dose**	**Every 24 weeks (±2 weeks) from the last disease assessment visit in the Treatment Phase**	**Every 12 ±2 weeks**
	from approximately 5 to 10 additional subjects dosed with the 6-mg daily regimen, the IDMC may recommend a modification of the dosing regimen to allow up-titration to the 8-mg daily regimen based on phosphate levels measured on Cycle 2 Day 1. See Section 10.12, Appendix 12.) (see Section 4.3.1 and guidelines in Section 6.6.1). See Section 6.1.1 for guidelines on treatment discontinuation for subjects in Cohort 2 and Cohort 3 with limited response after 3 months of treatment.					completed, disease recurrence or progression (Cohort 1, Cohort 2, and Cohort 3), intolerable toxicity, withdrawal of consent, a decision by the investigator to discontinue treatment, or study termination, whichever occurs first						
Investigator's Choice	Cohort 1 only. Intravesical gemcitabine or intravesical MMC/hyperthermic MMC as Investigator's Choice. See Section 6.1.2 for additional information. Other assessments required for Day 14 in the Schedule of Activities will be performed on Day 15 for Investigator's Choice subjects. On C1D8 and C1D22, AEs and any new concomitant therapies will be recorded in the eCRF.					Investigator's Choice treatment will be given once weekly for at least 4 doses of induction on C1D1, C1D8, C1D15, C1D22 (±2 days) followed by monthly maintenance on C2D1, C3D1, C4D1, C5D1, C6D1, C7D1 (±2 days). Additional doses of induction or maintenance are allowed per local standard of care. If >4 induction doses are given and the start of the monthly maintenance dose falls either on Day 8,						

	NOTES	Urine Sample for Assay Development	Molecular Eligibility Phase	Screening Phase		Treatment Phase[a] (28 days Cycle)				Follow-up Phase[a]		
						Cycles 1, 2, 3		Cycle 4+	EoT Visit	30-day Safety Follow-up Visit	Disease Assessment Follow-up	Survival Follow-up
						Day 1	Day 14	Day1				
Visit window		**After disease recurrence and before TURBT**	**N/A**	**- 35 days**	**- 14 days**	**C1:0 days C2, C3: ±2 days**	**±2 days**	**±2 days**	**+7 days after permanent treatment discontinuation**	**30 (+7) days after last dose**	**Every 24 weeks (±2 weeks) from the last disease assessment visit in the Treatment Phase**	**Every 12 ±2 weeks**
						Day 15, or Day 22 of subsequent cycles, all corresponding pre-dose assessment should be done on the same day (±2 days) as the maintenance dose is administered (See Section 8.9 for further detail.) Treatment may continue until it is completed, disease recurrence, intolerable toxicity, withdrawal of consent, a decision by the investigator to discontinue treatment, or study termination, whichever occurs first.						
Safety Assessments: The 30-day Safety Follow-up Visit should occur before the start of any subsequent anticancer therapy, if such therapy starts within 30 days after last dose of study drug.												
Physical examination	Perform a complete physical examination at screening. Repeat at C1D1 before the first dose of study drug if the screening assessment was >14 days prior. Targeted physical examination beginning at C2D1. Height and weight measurement only required at screening. See Section 8.3.1.			X		X		X C4D1, C5D1, C6D1, then every 3 cycles	X	X		
Vital Signs	See Section 8.3.2.			X		X	X	X	X	X		

	NOTES	Urine Sample for Assay Development	Molecular Eligibility Phase	Screening Phase		Treatment Phase[a] (28 days Cycle)				Follow-up Phase[a]		
						Cycles 1, 2, 3		Cycle 4+	EoT Visit	30-day Safety Follow-up Visit	Disease Assessment Follow-up	Survival Follow-up
						Day 1	Day 14	Day1				
Visit window		**After disease recurrence and before TURBT**	**N/A**	**- 35 days**	**- 14 days**	**C1:0 days C2, C3: ±2 days**	**±2 days**	**±2 days**	**+7 days after permanent treatment discontinuation**	**30 (+7) days after last dose**	**Every 24 weeks (±2 weeks) from the last disease assessment visit in the Treatment Phase**	**Every 12 ±2 weeks**
12-lead ECG	ECGs should be performed at approximately the same time of day when possible. See Section 8.3.3.			X		X C2D1 only (predose)		X C4D1 only (pre-dose)				
Review adverse events	Collected from the day the Main-study ICF is signed until 30 days after last dose of study drug (see Section 8.4).			X						X		
Concomitant medications	See Section 6.5.			X						X		
Urine or serum β-hCG pregnancy test	Women of childbearing potential only. Screening test within 7 days before randomization (Cohort 1) or the first dose of study drug (Cohort 2, Cohort 3). See Section 8.3.6.				-7 days	X predose C1		X	X	X		
Amsler Grid Test	All subjects: To be performed by treating study physician or nurse (as directed by specific site instructions). See Section 8.3.5.			X		X		X		X		
Clinical Safety Laboratory Assessments: Clinical laboratory test results (except parathyroid hormone and 1,25-dihydroxyvitamin D) must be available before the start of treatment at C1D1. Results of previous testing should be available for comparison as clinically necessary. Clinical laboratory testing will be performed at a local laboratory. The 30-day Safety Follow-up Visit should occur before the start of any subsequent anticancer therapy, if such therapy starts within 30 days after last dose of study drug.												
Hematology	All subjects. If screening sample is drawn within 3 days before C1D1, C1D1 measurement does not have to be repeated. For exact assessment see Section 8.3.4. After Cycle 6 Visit, perform every 3 cycles until end of treatment, eg, Cycle 6, Cycle 9, Cycle 12.				X	X		X	X			

	NOTES	Urine Sample for Assay Development	Molecular Eligibility Phase	Screening Phase		Treatment Phase[a] (28 days Cycle)				Follow-up Phase[a]		
						Cycles 1, 2, 3		Cycle 4+	EoT Visit	30-day Safety Follow-up Visit	Disease Assessment Follow-up	Survival Follow-up
						Day 1	Day 14	Day1				
Visit window		**After disease recurrence and before TURBT**	**N/A**	**- 35 days**	**- 14 days**	**C1:0 days C2, C3: ±2 days**	**±2 days**	**±2 days**	**+7 days after permanent treatment discontinuation**	**30 (+7) days after last dose**	**Every 24 weeks (±2 weeks) from the last disease assessment visit in the Treatment Phase**	**Every 12 ±2 weeks**
Comprehensive metabolic panel	All Subjects. If screening sample is drawn within 3 days before C1D1, C1D1 measurement does not have to be repeated. For exact assessment see Section 8.3.4. After Cycle 6 Visit, perform every 3 cycles until end of treatment, eg, Cycle 6, Cycle 9, Cycle 12.				X	X	X	X	X	X		
Phosphate	All subjects during screening. Before dosing on C1D1. Only erdafitinib-treated subjects from C1D1. See Section 8.3.4				X	X	X	X				
1,25-dihydroxyvitamin D	All subjects				X	X All subjects: C13D1 (±1 week)			X			
Parathyroid hormone	All subjects during screening. Only erdafitinib-treated subjects from C1D1. After Cycle 6 Visit, perform every 3 cycles until end of treatment, eg, Cycle 6, Cycle 9, Cycle 12 (see Section 8.3.4).				X	X C2, C3 only	X C1 only	X				

	NOTES	Urine Sample for Assay Development	Molecular Eligibility Phase	Screening Phase		Treatment Phase[a] (28 days Cycle)				Follow-up Phase[a]		
						Cycles 1, 2, 3		Cycle 4+				
						Day 1	Day 14	Day1	EoT Visit	30-day Safety Follow-up Visit	Disease Assessment Follow-up	Survival Follow-up
Visit window		**After disease recurrence and before TURBT**	**N/A**	**- 35 days**	**- 14 days**	**C1:0 days C2, C3: ±2 days**	**±2 days**	**±2 days**	**+7 days after permanent treatment discontinuation**	**30 (+7) days after last dose**	**Every 24 weeks (±2 weeks) from the last disease assessment visit in the Treatment Phase**	**Every 12 ±2 weeks**
Efficacy and other assessments: The 30-day Safety Follow-up Visit should occur before the start of any subsequent anticancer therapy, if such therapy starts within 30 days after last dose of study drug.												
Cystoscopy (with biopsy of visible lesions if present) Urine sample during cystoscopy Voided urine bladder washing	At screening, if TURBT was done within 6 weeks before randomization, then the findings of the complete resection from TURBT can be used instead of screening cystoscopy. Cohort 1 and Cohort 2 only: During the Treatment Phase, subjects who demonstrate a positive urine cytology with a negative cystoscopy will remain on study drug until the next disease assessment. If both the urine cytology and cystoscopy are positive for high-risk recurrence or progression at the next disease assessment, the subject will discontinue study drug. All cohorts: Tissue from any positive biopsy (any grade of recurrence) should be sent for exploratory biomarker analysis to central laboratory. Cohort 1 only: Send tissue slides/blocks from subjects with locally confirmed recurrence or progression for central histopathologic review (see Section 8.2.1.5).			X		Cohort 1 and Cohort 2: C3D1 then every 12 weeks (±1 week) until C26D1, end of treatment, or until disease recurrence or progression, whichever occurs first. Cohort 3 only: C2D1, C3D1, C4D1 (±1 week) or until CR (if earlier). After CR, every 12 weeks (±1 week) until C26D1, end of treatment, or until disease recurrence or progression, whichever occurs first. If PR, see Section 8.2.1.5.			X		X For 2 years or until disease recurrence/ progression (see Section 8.1.3.2.1)	
TURBT	See Section 4.1; Section 8.1.1.2; and Section 8.2.1.		X When clinically indicated									

	NOTES	Urine Sample for Assay Development	Molecular Eligibility Phase	Screening Phase		Treatment Phase[a] (28 days Cycle)				Follow-up Phase[a]		
						Cycles 1, 2, 3		Cycle 4+	EoT Visit	30-day Safety Follow-up Visit	Disease Assessment Follow-up	Survival Follow-up
						Day 1	Day 14	Day1				
Visit window		**After disease recurrence and before TURBT**	**N/A**	**- 35 days**	**- 14 days**	**C1:0 days C2, C3: ±2 days**	**±2 days**	**±2 days**	**+7 days after permanent treatment discontinuation**	**30 (+7) days after last dose**	**Every 24 weeks (±2 weeks) from the last disease assessment visit in the Treatment Phase**	**Every 12 ±2 weeks**
Bladder mapping	Cohort 1: For subjects in Cohort 1, bladder mapping at screening will be only done if there is prior history of CIS. During treatment or follow-up phase will only be done if urine cytology is positive for malignant cells and cystoscopy is negative. Cohort 2: All subjects in Cohort 2 will have bladder mapping at screening and at Cycle 12. Cohort 3: No bladder mapping will be done for subjects in Cohort 3. See Section 8.2.1.5 Cohorts 1 and 2: In addition, tissue from any positive biopsy (any grade of recurrence) from bladder mapping should be sent for exploratory biomarker analysis to central laboratory.			X				Cohort 2 only C12D1 (±1 week)				
Urine cytology	Cohort 1 and Cohort 2 only: Urine sample may be collected either from bladder washing during cystoscopy or from a voided urine specimen (bladder wash specimen is preferred). Analysis will be done locally (see Section 8.2.1). Cohort 3: will perform a urine cytology during bladder washing at time of CR only.			X		Cohort 1 and Cohort 2: C3D1 then every 12 weeks (±1 week) until C26D1, end of treatment, or until disease recurrence or progression. Cohort 3 will perform a urine cytology during bladder washing at time of CR only.			X		X For 2 years or until disease recurrence/ progression (see Section 8.1.3.2.1)	

	NOTES	Urine Sample for Assay Development	Molecular Eligibility Phase	Screening Phase		Treatment Phase[a] (28 days Cycle)				Follow-up Phase[a]		
						Cycles 1, 2, 3		Cycle 4+				
						Day 1	Day 14	Day1	EoT Visit	30-day Safety Follow-up Visit	Disease Assessment Follow-up	Survival Follow-up
Visit window		**After disease recurrence and before TURBT**	**N/A**	**- 35 days**	**- 14 days**	**C1:0 days C2, C3: ±2 days**	**±2 days**	**±2 days**	**+7 days after permanent treatment discontinuation**	**30 (+7) days after last dose**	**Every 24 weeks (±2 weeks) from the last disease assessment visit in the Treatment Phase**	**Every 12 ±2 weeks**
MRU Data Collection	Cohort 1 and Cohort 2 only. See Section 8.10. Note: MRU data collection is no longer required for all subjects in all phases.			X		Cohort 1 and Cohort 2 only: C3D1 then every 12 weeks (±1 week) until C26D1, end of treatment, or until disease recurrence or progression.			X		X For 2 years or until disease recurrence/ progression (see Section 8.1.3.2.1)	
CT/MRI Urogram	If a subject cannot tolerate intravenous contrast, a retrograde pyelogram is acceptable (see Section 8.2.1).			X				Starting from Cycle 6, every 24 weeks (±2 weeks) until recurrence/progression.				
PGIC	PRO measures to be completed before any other study procedures. See Section 8.2.2. Note: PRO assessment/data collection is no longer required for all subjects in all phases.					X C2D1 only			X			
PGIS EORTC QLQ-C30 EORTC QLQ-NMIBC24 EQ-5D-5L	PRO assessments will be completed before any other study procedures at the corresponding visit. See Section 8.2.2 for additional detail. Note: PRO assessment/ data collection is no longer required for all subjects in all phases.			X		X Day 1 of each cycle while on treatment				X		
Voided urine sample for assay development	A voided urine sample will be collected after disease recurrence and before TURBT (except for patients being considered for study after TURBT). Samples for subjects who are found to have low or intermediate risk disease	X							X (pre TURBT) No longer required			

	NOTES	Urine Sample for Assay Development	Molecular Eligibility Phase	Screening Phase		Treatment Phase[a] (28 days Cycle)				Follow-up Phase[a]		
						Cycles 1, 2, 3		Cycle 4+				
						Day 1	Day 14	Day1	EoT Visit	30-day Safety Follow-up Visit	Disease Assessment Follow-up	Survival Follow-up
Visit window		**After disease recurrence and before TURBT**	**N/A**	**- 35 days**	**- 14 days**	**C1:0 days C2, C3: ±2 days**	**±2 days**	**±2 days**	**+7 days after permanent treatment discontinuation**	**30 (+7) days after last dose**	**Every 24 weeks (±2 weeks) from the last disease assessment visit in the Treatment Phase**	**Every 12 ±2 weeks**
	recurrence must be discarded (except for eligible Cohort 3 subjects).											
Urine for [redacted] (ie, for biomarker research)	Samples for urine biomarker research will not interfere with urine cytology and will be taken from excess bladder washing sample/ urine/cells remaining after urine cytology sample amount is aliquoted for testing or from independent sampling, as appropriate.			X		All Cohorts: C3D1 then every 12 weeks (±1 week) until C26D1, end of treatment, or until disease recurrence or progression.			X		X For 2 years or until disease recurrence/ progression (see Section 8.1.3.2.1)	
Blood (plasma) for ctDNA	See Section 8.9.					All Cohorts: C1D1 (predose), C3D1, then every 12 weeks (±1 week) until C26D1, end of treatment, or until disease recurrence or progression.			X		X For 2 years or until disease recurrence/ progression (see Section 8.1.3.2.1)	
PK: blood sample for erdafitinib	Subjects receiving erdafitinib only. Record dosing and PK collection times. If indicated by the emerging safety findings or if the scheduled PK samples are not collected due to treatment interruption, C2D1 blood samples may be collected at a later site visit (C2D14, C3D1, or C3D14). See Section 8.6.1.					X C1D14: predose X C2D1: predose and 3h (±1 h) postdose						

	NOTES	Urine Sample for Assay Development	Molecular Eligibility Phase	Screening Phase		Treatment Phase[a] (28 days Cycle)				Follow-up Phase[a]		
						Cycles 1, 2, 3		Cycle 4+		30-day Safety Follow-up Visit	Disease Assessment Follow-up	Survival Follow-up
						Day 1	Day 14	Day1	EoT Visit			
Visit window		**After disease recurrence and before TURBT**	**N/A**	**- 35 days**	**- 14 days**	**C1:0 days C2, C3: ±2 days**	**±2 days**	**±2 days**	**+7 days after permanent treatment discontinuation**	**30 (+7) days after last dose**	**Every 24 weeks (±2 weeks) from the last disease assessment visit in the Treatment Phase**	**Every 12 ±2 weeks**
PK: blood sample for erdafitinib at time of tissue specimen collection	Subjects receiving erdafitinib only. See Section 8.6.1					Plasma PK sample collected at the same time as the tissue specimen collection during the Treatment Phase						
PK: tissue specimen for erdafitinib	Subjects receiving erdafitinib only. See Section 8.6.1 and Laboratory Manual for instruction on tissue sample handling					Tissue specimens from any biopsy during the Treatment Phase including bladder mapping biopsies (Cohort 1 and Cohort 2)						
Protein binding blood sample	Subjects receiving erdafitinib only. See Section 8.6.1 and the Laboratory Manual for description of the assessment and sample processing.					X C2D1 3h (±1 h) postdose						
Blood sample for CYP2C9 genotyping	Subjects receiving erdafitinib only. See Section 8.8.					X C1D14 anytime (or later time point)						
24-hour PK urine sample	First approximately 20 subjects receiving erdafitinib (from any cohort): 24-hour urine collection: subjects will need to return the 24-hour urine collection on C1D15.						X C1					
Survival status and subsequent anticancer therapy	May be assessed via telephone call, email, or visit to the study site. Survival status, start of alternate anticancer therapy, and results of standard-of-care cystoscopy will be monitored at least every 12 weeks (±2 weeks) until death, withdrawal of consent,											X

						Treatment Phase[a] (28 days Cycle)				Follow-up Phase[a]		
						Cycles 1, 2, 3		Cycle 4+				
		Urine Sample for Assay Development	Molecular Eligibility Phase	Screening Phase		Day 1	Day 14	Day1	EoT Visit	30-day Safety Follow-up Visit	Disease Assessment Follow-up	Survival Follow-up
Visit window	NOTES	After disease recurrence and before TURBT	N/A	- 35 days	- 14 days	C1:0 days C2, C3: ±2 days	±2 days	±2 days	+7 days after permanent treatment discontinuation	30 (+7) days after last dose	Every 24 weeks (±2 weeks) from the last disease assessment visit in the Treatment Phase	Every 12 ±2 weeks
	or end of study, whichever occurs first. See Section 8.1.3.2.2.											

β-hCG= beta-human chorionic gonadotropin; BCG= bacillus Calmette-Guérin; C=cycle; CR=complete response; CIS=carcinoma in situ; CT=computed tomography; ctDNA=circulating tumor DNA; CXDX=Cycle X Day X; D=day; ECG=electrocardiogram; ECOG=Eastern Cooperative Oncology Group; EORTC QLQ-C30=European Organisation for Research and Treatment of Cancer Quality-of-life Questionnaire Core 30; ePRO=electronic patient-reported outcome; EQ-5D-5L=European Quality of Life – 5 Dimensions-5 Levels; EoT=End of Treatment; FGFR=fibroblast growth factor receptor; ICF=informed consent form; IDMC=Independent Data Monitoring Committee; MMC=mitomycin C; MRI=magnetic resonance imaging; MRU=medical resource utilization; NMIBC=non-muscle-invasive bladder cancer; PGIC=Patient's Global Impression of Change (of cancer); PGIS=Patient's Global Impression of Severity (of cancer); PK=pharmacokinetic; PR=partial response; SoA=Schedule of Activities; TURBT=transurethral resection of bladder tumor

[a] Guidance for study conduct for ongoing subjects in the event of a national disaster is provided in Section 10.13 (Appendix 13).

[b] Subjects enrolling in the study based on Molecular eligibility from pre-BCG tissue specimen and post-BCG local NGS/PCR testing must also submit the post-BCG tissue specimen tissue for central confirmation of Molecular eligibility status.

2. INTRODUCTION

Erdafitinib (JNJ-42756493) is an oral pan-FGFR 1-4 inhibitor with demonstrated clinical activity in subjects with solid tumors, including urothelial carcinoma, identified to have alterations in the FGFR pathway. In the United States, erdafitinib (BALVERSA™) was approved on 12 April 2019 for the treatment of adult patients with locally advanced or metastatic urothelial carcinoma that has susceptible FGFR3 or FGFR2 genetic alterations and has progressed during or following at least 1 line of prior platinum-containing chemotherapy, including within 12 months of neoadjuvant or adjuvant platinum-containing chemotherapy. This Phase 2 study will evaluate the safety and efficacy of erdafitinib in subjects with high-risk NMIBC and FGFR mutations or fusions, who received BCG therapy and recurred.

For the most comprehensive nonclinical and clinical information regarding erdafitinib, refer to the latest version of the Investigator's Brochure (IB) and Addenda for erdafitinib.

The term "sponsor" used throughout this document refers to the entities listed in the Contact Information page(s), which will be provided as a separate document.

2.1. Study Rationale

Bladder cancer is the tenth most common malignancy worldwide, with an estimated 549,000 new cases and 200,000 deaths reported in 2018.[7] Seventy percent of these patients are diagnosed with an early stage NMIBC.[26] Approximately 25% of NMIBC patients with poorly differentiated, low-stage tumors are considered to have 'high risk non-muscle-invasive bladder cancer' (high-risk NMIBC; including high-grade pTa, pTis, and pT1).[24] The natural history of high-risk NMIBC is unpredictable; rates of recurrence vary from 15 to 78%, and rates of progression to muscle invasion and metastasis vary from <1 to 45%,[42] and long-term outcomes suggest that around 20 to 25% of these patients die from bladder cancer.[43]

The mainstay of treatment for high-risk NMIBC is TURBT (biopsy only for patients with CIS) followed by intravesical treatment with BCG. Primary radical cystectomy is an option for some patients. Approximately 30 to 40% of patients will experience recurrence after BCG therapy.[6] Valrubicin is the only US Food and Drug Administration (FDA)-approved intravesical treatment for BCG-refractory CIS in patients who are unfit or unwilling to undergo cystectomy. Valrubicin is not approved for treatment of papillary disease. The CR rate after valrubicin treatment is 18%, and 4% of patients are disease-free 2 years following therapy.[15] Once the disease progresses to muscle-invasive bladder cancer, prognosis is poor, even with combined-modality therapy, with a 10-year OS of 36%. Hence, radical cystectomy is considered the standard of care for any patient with BCG-unresponsive high-grade NMIBC.[5,29]

Radical cystectomy entails high morbidity (up to 60%) and negatively affects HRQoL. These comorbidities occur even in high-volume centers of excellence and regardless of open versus robotic approaches.[34] The procedure itself has a mortality rate of 3%.[40] Hence, some patients refuse surgery. Additionally, some patients are medically unfit for surgery due to such factors as age, functional status, American Society of Anesthesiologists class, comorbidities, body mass

index, etc. Therefore, there is a need for new therapies to prevent invasive bladder cancer in the intact bladder.

Fibroblast growth factor receptors FGFR1 to FGFR4 are tyrosine kinases that are present in many types of endothelial and tumor cells and are shown to play an important role in tumor cell growth, survival, and migration as well as in maintaining tumor angiogenesis.[25] There are varied mechanisms for FGFR-related oncogenesis, including gene amplification, mutations, and fusions.[13] FGFR3 genetic alterations are found in 60 to 70% of early stage NMIBC.[28] The observed frequency of FGFR alterations in bladder cancer changes with tumor stage and grade. For example, in one study, TaG1 (158/257) and TaG2 (139/239) tumors displayed similar mutation frequencies of 61.5% and 58.1%, respectively. The mutation frequency was lower among TaG3 (30/88; 34.1%), T1G2 (7/26; 26.9%), and T1G3 tumors (20/119; 17%).[23] Hernandez et al, in a prospective cohort of 772 patients with NMIBC, showed that FGFR3 mutations are prevalent in low-grade Ta and that these mutations are independent predictors of recurrence in patients with low-grade Ta tumors.[23,26]

Erdafitinib is a pan-FGFR tyrosine kinase inhibitor. In Study 42756493BLC2001 (NCT02365597), erdafitinib demonstrated clinical activity in subjects with metastatic urothelial cancer and prespecified FGFR mutations and fusions.[36] The presence of CCI [redacted] in NMIBC and the CCI [redacted] provide a CCI [redacted] in patients with NMIBC who recurred following BCG treatment. Erdafitinib differs in 3 aspects from existing therapies: 1) the treatment is a targeted therapy for a subset of patients with an activating FGFR genetic aberration in the tumor; 2) selected patients may benefit by avoiding or delaying cystectomy; and 3) erdafitinib is systemic therapy with proven efficacy in advanced disease and, therefore, may safeguard against risk of developing invasive/metastatic disease.

2.2. Background

2.2.1. Fibroblast Growth Factor Receptors

Fibroblast growth factor receptors FGFR1 to FGFR4 are tyrosine kinases that are present in many types of normal and tumor cells and are shown to play an important role in tumor cell growth, survival, and migration as well as in maintaining tumor angiogenesis.[25] Upon binding to their natural ligand, FGF family members, FGFRs dimerize and autophosphorylate the tyrosine residue in the kinase domain activation loop to become fully activated. Activated FGFR further phosphorylate multiple signaling proteins bound to their intracellular portion, resulting in activation of Ras/mitogen-activated protein kinase (MAPK) and PI3-kinase/Akt signaling pathways. Other downstream signaling components of FGFRs include Src and Rsk. The result is FGFR stimulation of cell growth, survival, migration, and differentiation, depending on the cell type.

Overexpression of FGFRs, or aberrant regulation of their activity, has been implicated in many forms of human malignancies including urothelial carcinoma. There are varied mechanisms for FGFR-related oncogenesis including gene amplification, mutations, and fusions. Therefore, targeting FGFRs with a small molecule kinase inhibitor is an attractive strategy for the development of a novel cancer treatment.

FGFR Alterations in High-risk NMIBC

FGFR3 genetic alterations are found in 60 to 70% of early stage NMIBC.[28] The timing and sequence of FGFR3 (and other mutations) may correlate with bladder cancer stage and grade. The observed frequency of FGFR alterations in bladder cancer changes with tumor stage and grade. For example, in one study, TaG1 (158/ 257) and TaG2 (139/239) tumors displayed similar mutation frequencies of 61.5% and 58.1%, respectively. The mutation frequency is lower among TaG3 (30/88; 34.1%), T1G2 (7/26; 26.9%), and T1G3 tumors (20/119; 17%).[23] Hernandez et al, in a prospective cohort of 772 patients with NMIBC, showed that FGFR3 mutations are prevalent in low-grade Ta and that these mutations are independent predictors of recurrence in patients with low-grade Ta tumors.[23,26] In a more recent study with pooled dataset of matched clinical and genomic data for 263 patients with stage pT1 showed that FGFR alterations were frequent in high-risk pts (39% mutations, 6% fusions, not mutually exclusive). Additionally, this study distinct from previous reports, showed that prognosis for patients with FGFR alterations was not different from those without FGFR alterations.[8]

2.2.2. Erdafitinib

Nonclinical Studies

Erdafitinib has been shown to have high affinity and low nanomolar inhibitory activity for all FGFR family members, FGFR 1, 2, 3 and 4. It has demonstrated activity in FGFR pathway-activated cancer cell lines including squamous non-small cell lung cancer, gastric, breast, hepatocellular cancer, endometrial, bladder, multiple myeloma, and acute myeloid leukemia. Target inhibition and pathway modulation have been demonstrated in cellular models at active cellular concentrations. Brief exposure to erdafitinib has been demonstrated to result in long-term target inhibition. Erdafitinib has been shown to have in vivo antitumor activity in mouse xenograft models of FGFR-driven gastric, bladder, and squamous non-small-cell lung carcinoma (NSCLC) tumor models, and in patient-derived xenografts from squamous NSCLC, gastric, breast, and hepatocellular tumors.

An in vitro metabolism study in human liver microsomes and hepatocytes showed major involvement of cytochrome 450 (CYP) enzymes CYP2C9 and CYP3A4. Long terminal phase half-life of erdafitinib (>50 hours) in plasma was observed resulting in approximately 3-fold accumulation of C_{max} and area under the curve (AUC) following multiple daily dosing.

Clinical Studies

In humans, erdafitinib exhibited dose-related increase in the maximum concentration (C_{max}) and AUC and time-independent PK within the dose range of 0.5 mg to 12 mg, both after single and multiple daily dosing. Median time to maximum concentration (t_{max}) observed ranged from 2 to 4 hours (erdafitinib as capsule). Relative bioavailability was comparable under fed and fasted conditions. Erdafitinib is highly bound to plasma proteins such as α1-acid glycoprotein (α1-AGP). Free fractions of erdafitinib in human plasma were small (average ~0.36%). Erdafitinib is a P-glycoprotein (P-gp) substrate.

In a Phase 1 study (Study 42756493EDI1001, n=187), the antitumor effect of erdafitinib was observed in subjects with urothelial cancer with selected FGFR aberrations, as well as other solid tumors. For all subjects with relapsed/refractory urothelial cancer, the overall response rate (ORR) across dose levels was 40.0% (12/30 subjects). At the 9 mg dose level, ORR was 70.0% (7/10 subjects) for response-evaluable subjects with urothelial cancer who harbored selected FGFR aberrations. The most frequently reported adverse events were hyperphosphatemia (65%), dry mouth (46%), asthenia (45%), stomatitis (39%), constipation (37%), and decreased appetite (34%).

In the global Phase 2 study (Study 42756493BLC2001, n=210), the antitumor effect of erdafitinib was further demonstrated in subjects with relapsed/refractory advanced urothelial cancer with defined FGFR mutations and gene fusions. In this study, multiple dosing regimens were evaluated including the 6-mg and 8 mg-daily regimens with up-titration. Subjects enrolled in the erdafitinib 6-mg daily regimen (78 subjects) received the 6-mg daily starting dose with up-titration to 8 mg daily or remained at the 6-mg daily dose based on the phosphate level measured at Cycle 2 Day 1. Subjects enrolled in 8-mg daily regimen (99 subjects) received the 8-mg daily starting dose with up-titration to 9 mg daily or remained at the 8-mg daily dose based on the phosphate level measured on Cycle 1 Day 14. Selected efficacy and safety data from the BLC2001[a] study for the 6-mg and 8-mg daily regimens are shown below:

BLC2001 Efficacy	**6-mg Daily Dosing Regimen**	**8-mg Daily Dosing Regimen**
Overall Response Rate (ORR) and Confidence interval	34.6% (24.1%, 45.2%)	40.4% (30.7%, 50.1%)
Disease Control Rate (DCR) and Confidence interval	73.1% (63.2%, 82.9%)	79.8% (71.9%, 87.7%)
BLC2001 Drug-related Treatment-emergent Adverse Events (TEAEs)		
Drug-related TEAEs	88.5%	97.0%
Drug-related Grade 3-4 TEAEs	28.2%	45.5%
Drug-related TEAEs leading to dose interruption	46.2%	61.6%
Drug-related TEAEs leading to treatment discontinuations	7.7%	12.1%

[a] The analysis is based on the BLC2001 Primary Analysis.

Selected efficacy and safety data from an analysis of the BLC2001[a] 6-mg daily dosing regimens (with and without up-titration) are shown below:

BLC2001 Efficacy	6-mg Daily Dosing Regimen (Not Up-titrated)	6-mg Daily Dosing Regimen (Up-titrated)
Overall Response Rate (ORR) and Confidence interval	34.0% (20.5%, 47.6%)	35.5% (18.6%, 52.3%)
Disease Control Rate (DCR) and Confidence interval	68.1% (54.8%, 81.4%)	80.6% (66.7%, 94.6%)
BLC2001 Drug-related Treatment-emergent Adverse Events (TEAEs)		
Drug-related TEAEs	83.0%	96.8%
Drug-related Grade 3-4 TEAEs	29.8%	25.8%
Drug-related TEAEs leading to dose interruption	48.9%	41.9%
Drug-related TEAEs leading to treatment discontinuations	10.6%	3.2%

Furthermore, subjects received a starting dose of erdafitinib 8 mg once daily with a dose increase to 9 mg once daily for subjects whose serum phosphate levels were below the target of 5.5 mg/dL between days 14 and 17; a dose increase occurred in 41% of subjects. The ORR (CR + PR) was 32.2% as assessed by a blinded independent review committee, and duration of response (DoR) was 5.4 months. The most frequently reported adverse events were hyperphosphatemia (76%), stomatitis (56%), diarrhea (47%), and dry mouth (45%).

For the most comprehensive nonclinical and clinical information regarding erdafitinib, refer to the latest version of the Investigator's Brochure.

2.2.3. Comparator Drugs

Subjects in Cohort 1 who are assigned to receive treatment with Investigator's Choice will receive either intravesical gemcitabine or intravesical MMC/hyperthermic MMC. The subject's treating physician will determine during screening based on clinical judgment, which comparator, gemcitabine or MMC/hyperthermic MMC, is appropriate for the individual subject.

2.2.3.1. Gemcitabine

Gemcitabine is a pyrimidine antimetabolite that inhibits DNA synthesis by inhibition of DNA polymerase and ribonucleotide reductase. It is cell cycle-specific for the S-phase of the cycle. Gemcitabine has been extensively studied as a salvage intravesical chemotherapeutic option with many different regimens. Intravesicular gemcitabine may have similar efficacy and lower incidence of dysuria and hematuria compared with BCG.[45] For patients with high-risk NMIBC who are unresponsive to BCG and who are unsuitable for radical cystectomy, bladder sparing strategies are warranted, indicating that the use of intravesical use of gemcitabine and MMC should be considered.[18] In a multicenter Phase 2 study of 58 patients who had undergone 2 or more prior BCG courses, gemcitabine demonstrated a 12-month disease-free rate of 28%.[38] Although a

[a] The analysis is based on the BLC2001 Primary Analysis.

second induction of BCG may be an option for patients who recur or persist after a single course of induction intravesical BCG, a Phase 2 randomized trial demonstrated that intravesical gemcitabine was associated with a superior 2-year RFS compared to BCG (19% versus 3%; p<0.008) among patients with high-risk non-muscle-invasive recurrence after a single course of BCG, albeit with no significant difference in progression.[14]

An intravesical regimen of 2 g gemcitabine weekly for 6 weeks and then monthly to 12 months was used in the SWOG S0353 study.[38] Intravesical administration of gemcitabine can lead to local irritation of bladder, which can lead to a sense of urination, burning during urination, infection, abdominal pain, fever, and rarely ulcers in bladder. Refer to current product labeling for additional information.

2.2.3.2. Mitomycin C

Mitomycin C is the only approved chemotherapeutic among the class of mitomycin therapies and is often referred to as mitomycin. Mitomycin alkylates DNA to produce DNA cross-linking (primarily with guanine and cytosine pairs) and inhibits DNA and RNA synthesis. Mitomycin is not cell cycle-specific but has its maximum effect against cells in late G and early S phases. Multiple studies have evaluated MMC for the treatment of bladder cancer. Intravesicular MMC has also been evaluated extensively and widely used in patients who are unresponsive to BCG and who are unsuitable for radical cystectomy. Mitomycin C was evaluated by Addeo et al. in 120 previously treated patients. After a median follow-up of 36 months, MMC demonstrated a recurrence-free rate of 61%, and therapy was generally well tolerated.[1] Di Stasi et al used a regimen of 6 weekly treatments, a further 6 weekly treatments for nonresponders, and 10 monthly follow-up treatments for responders.[16] Intravesical administration of MMC can lead to local irritation of bladder, which can lead to a sense of urination, burning during urination, infection, abdominal pain, fever, and rarely ulcers in bladder. Refer to current product labeling for additional information.

2.3. Benefit-Risk Assessment

Patients with high-risk NMIBC who recurred after BCG treatment are at high risk for adverse outcomes with an 11.4% probability of progression at 1 year and a disease-specific death rate of 4.8% at 1 year.[9] Hence, both the American Urological Association (AUA) and European Association of Urology (EAU) guidelines recommend radical cystectomy as the only standard therapy for these patients. There is an ongoing shortage of BCG necessitating development of strategies to prioritize use of intravesical BCG (alternate schedule and reduced dose approaches) and identify alternate treatment approaches, such as use of intravesical chemotherapies. Consequently, many patients are either not receiving the full prescribed dose of BCG, or not receiving BCG treatment at all, and are being treated with intravesical chemotherapeutic agents. Additionally, a proportion of patients do not tolerate the full dose or course of BCG treatment. Data presented by Richards et al of US Surveillance, Epidemiology and End Results (SEER)-Medicare database evaluating 39,532 NMIBC patients demonstrated that only 30% of intermediate-risk and 29% of high-risk patients received adequate BCG.[33]

The superiority of BCG compared with intravesical chemotherapy to prevent recurrence of high-risk NMIBC is proven. However, the optimal number of induction instillations and the optimal frequency and duration of maintenance instillations is not fully known. A full dose of BCG must comprise 1 full vial with a minimum of 1 x 10^8 colony forming units (CFU). The largest individual study of 1,355 patients (EORTC 30962) compared different BCG strengths (full dose vs 1/3 dose) and different BCG maintenance schedules (1 year vs 3 years) and found no difference in RFS between 1/3 dose and full dose administered for either 1 year or 3 years.[31] Although a subset of high-risk patients treated with a 3-year full dose schedule had an improved RFS with no difference in progression or survival, the study was not formally powered to test this hypothesis.

Many patients are medically unfit to undergo surgery and some refuse due to the high morbidity (up to 60%) the procedure entails and negative effects on quality of life. These comorbidities occur even in high-volume centers of excellence and regardless of open versus robotic approaches.[34] The procedure itself has a mortality rate of 3%.[40] Hence, some patients refuse surgery. Additionally, some patients are medically unfit for surgery due to such factors as age, functional status, American Society of Anesthesiologists class, comorbidities, body mass index, etc. Valrubicin is the only FDA-approved intravesical treatment for BCG-refractory CIS in patients who are unfit or unwilling to undergo cystectomy. The CR rate after valrubicin treatment is 18%; 4% of patients are disease-free at 2 years following therapy.[15] Other salvage therapies such as intravesical gemcitabine have shown activity.[12]

The FGFR pathway has a central role in the pathogenesis of NMIBC. Thirty percent of patients progressing to high-risk NMIBC harbor FGFR3 mutations. Furthermore, the molecular luminal subtype of bladder cancer, which is enriched with the FGFR3 mutation, has an immunoquiescent immune signature suggesting that they may not benefit from immunotherapy.[11] In clinical studies in the advanced bladder cancer disease setting, erdafitinib treatment resulted in durable antitumor response. Corresponding DoR, progression-free survival (PFS), and OS endpoints suggest clinical benefit for patients with locally advanced or metastatic urothelial cancer who have FGFR alterations and have relapsed after platinum-based chemotherapy. FGFR mutation is an early molecular event in bladder cancer and appears to be one of the main drivers of bladder carcinogenesis. Study BLC2001 demonstrated clinically meaningful efficacy in heavily pretreated metastatic bladder cancer patients. Metastatic bladder cancer is well known to have clonal evolution and higher genomic instability compared with earlier stages of disease, such as NMIBC. Therefore, it was hypothesized that testing erdafitinib in early-stage bladder cancer might offer clinically meaningful benefit for patients with FGFR mutations.

The potential risks of erdafitinib to adults, include central serous retinopathy and hyperphosphatemia. The benefit-risk of erdafitinib was acceptable in the urothelial cancer population; the profile was characterized by mostly mild to moderate eye, skin, and nail disorders. The events in the urothelial population were manageable with available medical measures, temporary treatment interruption, or eventual dose reduction.

Taking into account the measures utilized to minimize risk to subjects in this study (guidance for specific erdafitinib toxicities in Section 6.6.2, prohibited medications in Section 6.5.2, precautions for concomitant medications in Section 6.5.3, and monitoring of results of safety assessments in

Section 8.3), the potential risks identified in association with erdafitinib are justified by the anticipated benefits that may be afforded to patients with high-risk NMIBC and FGFR gene alterations, CCI [redacted] More detailed information about the known and expected benefits and risks of erdafitinib may be found in the Investigator's Brochure.

3. OBJECTIVES AND ENDPOINTS

Cohort 1 Efficacy Objectives	Cohort 1 Efficacy Endpoints
Primary	
To evaluate RFS in subjects treated with erdafitinib vs Investigator's Choice, for subjects with high-risk NMIBC who harbor FGFR mutations or fusions, and who recurred after BCG therapy	• Recurrence-free survival (RFS)
Secondary	
To evaluate other measures of efficacy	• Time to progression • OS • RFS rate at 6 months and 12 months
Cohort 2 Efficacy Objective	**Cohort 2 Exploratory Efficacy Endpoints**
Exploratory	
To evaluate the efficacy of erdafitinib in subjects with high-risk, BCG-unresponsive NMIBC and FGFR mutations or fusions	• CR rate at 8 weeks • CR rate at 32 weeks • Duration of response (DOR)
Cohort 3 Efficacy Objective	**Cohort 3 Exploratory Efficacy Endpoints**
Exploratory	
To evaluate the efficacy of erdafitinib in subjects with intermediate-risk NMIBC and FGFR mutations or fusions	• CR rate • Best overall response (BOR) • DOR
Other Secondary Objectives – All Cohorts	**Other Secondary Endpoints – All Cohorts**
To evaluate erdafitinib PK	• PK concentration and PK parameters derived using the existing population PK model
To evaluate safety and tolerability of erdafitinib	• Incidence and severity of adverse events

Refer to Section 8, Study Assessments and Procedures, for evaluations related to endpoints.

HYPOTHESIS

For Cohort 1, erdafitinib treatment will delay the onset of tumor recurrence for subjects with papillary disease only, who recurred after BCG treatment, with FGFR mutations or fusions, and with all lesions removed.

For Cohort 2, erdafitinib treatment will lead to CR for subjects with CIS with or without papillary disease and FGFR mutations or fusions.

For Cohort 3, erdafitinib treatment will lead to CR in the marker lesion for subjects with a papillary marker lesion and FGFR mutations or fusions.

Due to early enrollment termination and change in study's regulatory intent for Cohort 1 from registrational to non-registrational, no formal hypothesis testing will be performed for any of the cohorts.

4. STUDY DESIGN

4.1. Overall Design

This is an open-label, global, multicenter, randomized, Phase 2 study of the safety and efficacy of erdafitinib in subjects with NMIBC and FGFR mutations or fusions (see Section 5.1).

Cohort 1 (n=240 planned) will include subjects with high-risk NMIBC presenting as papillary tumor only, with disease recurrence after BCG therapy, and who either refuse or are not eligible for cystectomy. It is essential that the subject's refusal to receive or medical ineligibility for cystectomy be documented clearly in source documents at screening (see Section 10.2, Source Documents). The reason for not being eligible for cystectomy or for refusing cystectomy will be entered into the eCRF. These subjects will be assigned randomly 2:1 to treatment with either erdafitinib or the investigator's choice of either intravesical gemcitabine or intravesical MMC/hyperthermic MMC (Investigator's Choice), respectively. Randomization will be stratified by tumor stage (Ta vs T1) and type of prior BCG therapy (BCG-unresponsive vs BCG-experienced). BCG strain administered will also be documented in the eCRF. Investigators must choose between intravesical gemcitabine or intravesical MMC/hyperthermic MMC for each subject at screening, and the choice of agent must take prior exposure into consideration. Peri-operative intravesical chemotherapy prior to study entry per local standard of care and prior immunotherapy (eg, PD1 inhibitor etc) are allowed.

Cohort 2 and Cohort 3 are exploratory.

Cohort 2 (n=20 planned) will include subjects with high-risk, BCG-unresponsive NMIBC presenting as CIS with or without concurrent papillary tumor, who either refuse or are not eligible for cystectomy. The reason for not being eligible for cystectomy or for refusing cystectomy will be entered into the eCRF. All subjects enrolled into Cohort 2 will receive treatment with erdafitinib. Peri-operative intravesical chemotherapy prior to study entry per local standard of care and prior immunotherapy (eg, PD1 inhibitor etc) are allowed. Additionally, subjects in this cohort may receive chemotherapy as bridging therapy after adequate BCG therapy while being considered for trial.

Cohort 3 (n=20 planned) will be enrolled at select study sites and will include subjects with intermediate-risk NMIBC presenting as papillary disease only. All previous tumors for these subjects must be low grade (G1-G2), Ta or T1, with no previous CIS. Furthermore, subjects must have a risk of progression less than 5% for 2 years, and the risk of recurrence must be greater than 50% as calculated using the EORTC risk calculator.[19] There are no predefined BCG or intravesical chemotherapy requirements for subjects enrolled in Cohort 3. All tumors must be removed except

for a single, untouched 5 to 10 mm lesion. All subjects enrolled in Cohort 3 will receive treatment with erdafitinib.

The first approximately 20 subjects participating who receive erdafitinib (from any cohort) will provide a 24-hour urine collection for assessment of erdafitinib pharmacokinetics.

The primary endpoint for Cohort 1 is RFS. Exploratory endpoints for Cohort 2 are CR rate at 8 weeks, CR rate at 32 weeks, and DOR. Exploratory endpoints for Cohort 3 are CR rate, best overall response (BOR), and DOR. A diagram of the study design is provided in Section 1.2, Schema.

The study comprises molecular eligibility, screening, treatment, follow-up, and LTE phases. For Cohort 1 and Cohort 2, molecular eligibility will be established for each potential subject before screening for other eligibility criteria. This assessment may be performed by either the central laboratory or by sponsor review of existing local laboratory reports generated by a Clinical Laboratory Improvement Amendments (CLIA)-certified[10] or equivalent laboratory. Molecular-eligible subjects may then be screened for remaining eligibility criteria. For Cohort 3, see Section 8.1.1.2 for guidelines to establish molecular eligibility. Subjects being considered for the study before the TURBT, will provide a voided urine sample after disease recurrence and before TURBT. These subjects must sign the Informed Consent Form (ICF) for Urine Sample for Assay Development. Subjects being considered for study after TURBT will not provide this urine sample.

Subjects with T1 disease will undergo TURBT of the base of the lesion (the biopsy should contain muscle fibers) before study entry to ensure the absence of muscle-invasive disease. If there are no muscle fibers in the biopsy, the subject must undergo re-TURBT before randomization or enrollment and must have evidence of uninvolved muscularis propria in the pathologic specimen from either the first or the second TURBT.

The Treatment Phase will begin on Day 1 for subjects meeting all eligibility criteria, at which time subjects will receive their study drug. Subjects receiving erdafitinib will take erdafitinib tablets orally, 6 mg once daily for 28 days in a 28-day cycle. After review of safety and tolerability data from approximately 5 to 10 additional subjects dosed with the 6-mg daily regimen (without up-titration), the Independent Data Monitoring Committee (IDMC) may recommend a modification of the dosing regimen to allow up-titration to the 8-mg daily regimen. The details of the IDMC recommendation will be communicated in writing to the investigative sites and, per local regulation, to health authorities. With the exceptions noted below for Cohort 2 and Cohort 3, treatment may continue until the subject has high risk disease recurrence or progression, intolerable toxicity, withdraws consent, there is a decision by the investigator to discontinue treatment, or the study is closed, whichever occurs first. Treatment with erdafitinib may continue for a maximum of 2 years.

- For Cohort 2, erdafitinib must be discontinued if CR is not observed within 3 months.
- For Cohort 3, after 3 months of study treatment: 1) Subjects with stable disease or progression of the marker lesion must discontinue erdafitinib and a TURBT of the marker lesion must be performed. 2) Subjects with CR may continue erdafitinib. 3) Subjects with PR may, at the

investigator's discretion, either continue treatment with erdafitinib or discontinue erdafitinib and undergo TURBT of the marker lesion.

For subjects in Cohort 1 who have locally confirmed high-risk recurrence on Investigator's Choice, the subject may cross over to erdafitinib (Section 10.10). Note: no additional crossover from Investigator's Choice to erdafitinib will be permitted.

The Follow-up Phase includes a 30-day Safety Follow-up Visit, disease assessment follow-up, and survival follow-up.

The LTE Phase will allow continued access to study drug for subjects who continue to derive benefit from treatment, as determined by their investigator. Subjects may enter the LTE Phase following implementation of Amendment 6, provided they meet the criteria for entry specified in LTE Figure 1. Limits for continuation of study drug in this phase are described in Section 6.7. No data will be collected in the eCRF during the LTE Phase, and only SAEs will be reported to the company safety repository. As an alternative to entering the LTE Phase, subjects receiving erdafitinib may exit the study and continue to receive treatment on any other post-trial access program, when permitted by local regulations. Detail regarding the LTE Phase (including a Schedule of Activities) is provided in Section 10.14, Appendix 14.

Subjects will be assessed for disease response by cystoscopy and bladder mapping for detection of new lesions, local assessment of urine cytology, and CT/MRI urograms. Tissue slides/blocks from subjects in Cohort 1 with any locally confirmed recurrence or progression will be sent for central histopathologic review. Health-related quality-of-life assessments will use the following PRO measures: PGIS, PGIC, EORTC QLQ-C30, EORTC QLQ-NMIBC24, and EQ-5D-5L. Note: PRO assessment/data collection is no longer required for all subjects in all phases. Refer to Section 8.2, Efficacy Assessments, for additional information. Safety assessments will include medical review of adverse events, ophthalmologic assessment, targeted physical examinations, vital sign measurements, 12-lead ECG assessments, clinical laboratory tests, and pregnancy testing (see Section 8.3, Safety Assessments).

An IDMC will be commissioned to review safety and efficacy data during the study, primarily for Cohort 1 (refer to Committees Structure in Section 10.2, Regulatory, Ethical, and Study Oversight Considerations for details). Due to the company decision to terminate study enrollment and considering the recent IDMC review (6 July 2022) found the safety of erdafitinib in this study to be consistent with the known safety profile of erdafitinib, no further monitoring by the IDMC will be conducted. The originally planned interim analyses will not be conducted.

Subjects who receive erdafitinib during the main study will have plasma erdafitinib concentration measurements during the Treatment Phase for pharmacokinetic assessment.

Biomarker assessments will be performed for all subjects. Biomarker assessments include molecular screening to determine eligibility for the study and exploratory DNA, RNA, and protein analyses using archival or fresh biopsy tissue and blood (ctDNA), as well as urine samples, for exploratory biomarker research (see Section 8.9). An additional urine sample will be collected for assay development (see Section 8.9).

4.2. Scientific Rationale for Study Design

Choice of Comparator for Cohort 1

While the primary treatment for high-risk NMIBC is transurethral resection (biopsy only for patients with CIS) followed by intravesical treatment with BCG, approximately 30 to 40% of patients will experience recurrence after BCG therapy. For patients with , papillary NMIBC who have high-risk NMIBC, the only recommended treatment option following progression or recurrence after BCG therapy is radical cystectomy. However, many patients either are medically unfit to undergo surgery or refuse it. In this setting, there are few effective treatment options available.

There are very limited treatment options to treat BCG-unresponsive, high-risk papillary NMIBC. In a multicenter Phase 2 study of 58 patients who had undergone 2 or more prior BCG courses, gemcitabine demonstrated a 12-month disease-free rate of 28%.[38] Furthermore, National Comprehensive Cancer Care guidelines acknowledge gemcitabine as an option for treatment of these patients.[30] While a second induction of BCG may be an option for patients who recur or persist after a single course of induction intravesical BCG, a Phase 2 randomized trial demonstrated that intravesical gemcitabine was associated with a superior 2-year RFS compared to BCG (19% versus 3%; $p<0.008$) among patients with high-risk non-muscle-invasive recurrence after a single course of BCG, albeit with no significant difference in progression.[14] Mitomycin C has also been evaluated and widely used in this setting, and in one study where BCG-refractory NMIBC patients were followed up over a 15-month-period, 31% remained recurrence-free.[39] Valrubicin is approved in the United States only for treatment of CIS; however, subjects in Cohort 1 are limited to those with papillary disease only, and efficacy in the approved indication is limited (see Section 2.1).

Thus, the choice of gemcitabine and MMC/hyperthermic MMC as comparators to erdafitinib is supported by current treatment practice and clinical data.[2]

Three-cohort Design

Urothelial bladder cancer is a heterogenous disease with 2 distinct pathways leading to bladder carcinogenesis.[28] The two-pathway' model proposes that papillary NMIBC develops via epithelial hyperplasia and recruitment of a branching vasculature; whereas, CIS is proposed to develop via flat dysplasia. These 2 subtypes pose distinct challenges for clinical management and appear to be directed by 2 separate molecular drivers.

Papillary bladder cancers, which constitute 80% of bladder cancer at diagnosis, have a more insidious course compared with CIS. Despite its high recurrence rate (40-80%), papillary NMIBC generally shows a favorable prognosis. However, progression to muscle-invasive and/or metastatic disease occurs in approximately 15% of patients, and once patients develop progression, their prognoses are generally unfavorable.[20] Papillary cancers are characterized by very high frequencies of activating mutations in FGFR3 (>70% in early stages). Conversely, CIS patients make up ~20% of bladder cancer patients at diagnosis but have a high risk for progression to muscle-invasive and metastatic disease. Patients with CIS commonly test positive for classical

tumor suppressor genes, most notably TP53 and RB1.[28] Pietzak showed FGFR mutations in 5/22 (23%) of NMIBC samples with concurrent papillary and CIS. FGFR positivity in a pure CIS population has not been reported.[32] Hence, Cohort 2 was originally planned to be a 20-subject exploratory cohort.

Papillary disease and CIS are distinct entities at a molecular level and have different clinical outcomes. However, aside from the option to resect papillary disease (but not CIS), they are currently treated uniformly with intravesical BCG, which is a tuberculosis-like mycobacterium that produces a local immune response that mediates tumor regression. Even though most patients initially respond to BCG, approximately 30 to 40% of patients will become unresponsive and experience recurrence after BCG. These tumors are at high risk for progression, with a 1-year rate for TiG3 of 11.4%, and patients are faced with the option of removal of the bladder.[9] For patients who are either unfit or refuse cystectomy there are very few treatment options available. Treatment has not advanced for several decades, and new approaches to systemic therapy are needed.

It is prudent to differentiate across 2 separate cohorts, because papillary NMIBC and CIS are different molecularly and prognostically. In Cohort 1 (papillary disease) without active disease at study entry, a randomized controlled study design using a time-to-event endpoint such as RFS is acceptable. In Cohort 2 (CIS), in absence of pharmacologic intervention or cystectomy, disease will progress; and, therefore, a single-arm study with CR rate as the primary endpoint is appropriate (FDA BCG-unresponsive NMIBC: Developing Drugs and Biologics for Treatment; Guidance for Industry).

All current available treatments are applied as adjuvant therapy in patients with papillary NMIBC. This precludes on-target efficacy assessment, as studies are done without measurable disease. Hence, it is logical to test newer therapies on measurable cancer, such as a marker lesion, which offers the prospect of avoiding treatment of patients with ineffective agents. A review of 23 well documented marker lesion studies involving more than 1,200 patients suggest that marker lesion studies are safe to perform without risk of progression in patients who have multiple recurrent, non-muscle-invasive bladder tumors with all previous tumors being low grade (G1-G2) Ta or T1, no previous CIS, and negative urinary cytology. Subjects must have a risk of progression less than 5% for 2 years, and the risk of recurrence must be greater than 50% as calculated using EORTC risk calculator.[19,22] Hence, it is prudent to evaluate the marker lesion study as a separate cohort (Cohort 3), given that it will enroll a different risk group (intermediate risk) compared with Cohort 1 and Cohort 2 (high risk).

Blinding, Control, Study Phase/Periods, Treatment Groups

An active control will be used in Cohort 1 to determine the sensitivity of the clinical endpoints in this study. Randomization stratified by tumor stage (Ta vs T1) and type of prior BCG therapy (BCG-unresponsive vs BCG-experienced) will be used to minimize bias in the assignment of subjects to treatment groups, to increase the likelihood that known and unknown subject attributes (eg, demographic and baseline characteristics) are evenly balanced across treatment groups, and to enhance the validity of statistical comparisons across treatment groups. Neither the sponsor, investigators, nor subjects will be blinded to treatment assignment in Cohort 1. Using a placebo

control is not practical and would place an enormous burden on subjects, as erdafitinib is an oral regimen and the comparators require intravesical administration.

Biomarker Collection

The goal of the biomarker analyses is to further understand the CCI [redacted]. Biomarker samples may be used to help address emerging issues and to enable the development of safer, more effective, and ultimately CCI [redacted].

Patient-reported Outcomes Research

Patient-reported outcome data complement data collected by other methods to support the clinical data and cost-effectiveness modeling as well as contributing to enhanced communication of value to patients, clinicians, regulators, and payers. The PRO endpoints of interest include domain scales from the EORTC QLQ-C30, EORTC NMIBC24, and EQ-5D-5L. These PRO measures will be administered to test the hypothesis that treatment with erdafitinib maintains HRQoL as measured by time to symptom and functional deterioration by a prespecified meaningful change threshold. PRO data will be collected as outlined in the Schedule of Activities (Section 1.3) to understand how the endpoints change over time, with treatment and with the clinical state of the subject. Note: PRO assessment/data collection is no longer required for all subjects in all phases.

Medical Resource Utilization Data Collection

Treatment of NMIBC with erdafitinib versus Investigator's Choice may result in lower utilization of healthcare resources.

4.2.1. Study-Specific Ethical Design Considerations

Potential subjects will be fully informed of the risks and requirements of the study and, during the study, subjects will be given any new information that may affect their decision to continue participation. They will be told that their consent to participate in the study is voluntary and may be withdrawn at any time with no reason given and without penalty or loss of benefits to which they would otherwise be entitled. Only subjects who are fully able to understand the risks, benefits, and potential adverse events of the study, and provide their consent voluntarily will be enrolled.

The intermediate-risk population selected for the marker lesion cohort (Cohort 3) has a low risk of disease progression (less than 5% for 2 years). Furthermore, the subjects are a molecularly selected subgroup being treated with a targeted therapy given systemically that has shown clinical efficiency in metastatic bladder cancer. This may further reduce any risk of progression. The safety of subjects in this cohort will be closely monitored, as outlined in the Schedule of Activities. Guidance has been provided in the protocol to limit the possibility that an ineligible subject is enrolled into Cohort 3 (see Section 8.1.1.2). This is expected to minimize the risk that subjects with non-qualifying marker lesions will need to undergo additional cystoscopy and resection.

The total blood volume (approximately 682 mL) that will be collected is considered within the normal range allowed for this subject population over this time frame. An additional 682 mL may be collected from subjects who participate in the Erdafitinib Crossover (see Section 10.10). For

adult subjects, the amount of blood collected is less than the American Red Cross standard blood donation of 500 mL over 60 days[3] and is aligned with World Health Organization blood donation guidelines.[44]

4.2.2. Participant Input Into Design

The results of the study may be made available to all participants through a plain language summary; a technical summary of results on registries such as clinicaltrials.gov, clinicaltrialsregister.eu or other national registries at the conclusion of the study according to local standards/restrictions.

4.3. Justification for Dose

4.3.1. Erdafitinib Dose Selection

The starting dose of erdafitinib will be 6 mg daily. Erdafitinib will be provided as tablets for oral administration. Subjects will be instructed to take a 6-mg daily dose on a continuous dosing schedule. A cycle is defined as 28 days.

Clinical efficacy and safety data considered for dose selection are summarized in Section 2.2.2. The erdafitinib dosing regimen of 6 mg daily (with and without up-titration) has demonstrated clinical activity with lower rates of Grades 3 to 4 drug-related TEAEs, drug-related TEAEs leading to dose interruption, and drug-related TEAEs leading to discontinuation relative to the 8-mg daily regimen (with up-titration) in subjects with advanced or metastatic urothelial carcinoma.

The BLC2003 IDMC reviewed safety data for the first 4 subjects treated with erdafitinib and recommended the change in dosing to 6 mg daily. The lower dose of 6 mg daily (without up-titration)CCI [redacted] this regimen with a lower dose of 6 mg daily may be better suited, with respect to the overall risk-benefit profile, for the NMIBC patient population without advanced, imminently life-threatening disease.

4.3.2. Gemcitabine Dose Selection

The dose of intravesical gemcitabine is 2,000 mg. Gemcitabine will be provided by the sponsor. It will be administered at the site once weekly for at least 4 weeks of induction and then monthly for at least 6 months. Additional doses of induction or maintenance are allowed per local standard of care. Please refer to the gemcitabine Investigational Product Preparation Instructions (IPPI) for additional information on the preparation, handling, and administration of gemcitabine.

It is the expert opinion in the AUA and EAU Guidelines that indicate if a high-risk NMIBC patient is unwilling or unfit for cystectomy following BCG, a clinical trial or intravesical chemotherapy is appropriate.[4,17,18] Therefore, receiving intravesical gemcitabine in a clinical trial is a reasonable option for patients who refuse or are unfit for cystectomy.

4.3.3. Mitomycin C Dose Selection

The dose of intravesical mitomycin C is 40 mg. Mitomycin C will be provided by the sponsor. It will be administered at the site once weekly for at least 4 weeks of induction and then monthly for at least 6 months. Additional doses of induction or maintenance are allowed per local standard of care. Mitomycin C may also be given as hyperthermic MMC.[2] Please refer to the MMC IPPI for additional information on the preparation, handling, and administration of MMC.

Mitomycin C is indicated for intravesical infusion at the dose of 40 mg/40mL and the European Urological Association Guidelines recommend 20 to 40 mg as the standard dose of MMC for patients for whom BCG has failed in NMIBC.[18,41]

4.4. Study Completion, End of Study, and Subject Completion Definitions

Study Completion Definition

The study is considered completed when the last subject on the study transitions to the LTE Phase or discontinues from the study. At the time of study completion, there will be no further data collection in the study database.

End of Study Definition

The end of study is defined as when the last subject receives the last dose of study drug on the study, including administration in the LTE Phase (see Section 10.14, Appendix 14).

Subject Completion Definitions

A subject will be considered as having completed treatment if he or she has completed 2 years of erdafitinib or has completed a maximum duration of Investigator's Choice therapy per local standard of care (including any treatment received in the LTE Phase).

A subject's participation in the main study (not including the LTE Phase) will be considered completed when one of the following criteria is met, whichever occurs first:

- 18 months have elapsed since the first dose of study treatment (ie, Cycle 1 Day 1)
- Subject experiences confirmed high-risk disease recurrence/progression at any point during the study.
- Subject death.

5. STUDY POPULATION

This study will enroll subjects with NMIBC and FGFR mutations or fusions. Potential subjects intended for enrollment in Cohort 1 or Cohort 2 who meet molecular eligibility criteria (see Inclusion Criterion no. 3) may be screened for the additional inclusion and exclusion criteria described in the following sections during the 35-day period before the first dose of study drug. Subjects intended for enrollment in Cohort 3 will have molecular eligibility and screening for other eligibility criteria performed as described in Section 8.1.1.2. Screening procedures (Section 8.1.1.3) should be completed according to the timing provided in the Schedule of

Activities (Section 1.3). Refer to Section 5.4, Screen Failures, for conditions under which the repeat of any screening procedure is allowed.

The inclusion and exclusion criteria for enrolling subjects in this study are described below. If there is a question about these criteria, the investigator must consult with the appropriate sponsor representative and resolve any issues before enrolling a subject in the study. Waivers are not allowed.

For a discussion of the statistical considerations of subject selection, refer to Section 9.2, Sample Size Determination.

5.1. Inclusion Criteria

Each potential subject must satisfy all of the following criteria to be enrolled in the study:

1. ≥18 years of age (or the legal age of consent in the jurisdiction in which the study is taking place).

2. Histologically confirmed, recurrent, non-muscle-invasive urothelial carcinoma of the bladder.

    a. Histopathology: any urothelial cell carcinoma (UCC) variant (ie, UCC with squamous and/or glandular differentiation, micropapillary, nested, plasmacytoid, neuroendocrine, sarcomatoid) are allowed. Presence of any lymphovascular invasion (LVI) will be considered as evidence of high risk.
    b. Papillary disease (Cohort 1) must be high-risk disease, defined as high-grade Ta/T1 lesion. Additionally, subjects must have all visible tumor resected completely prior to randomization and documented at baseline cystoscopy. Negative cytology for high-grade urothelial carcinoma is required before randomization.
    c. CIS (Cohort 2) is not expected to be completely excised, but concurrent papillary disease must be completely excised before enrollment and documented at baseline cystoscopy. Urine cytology is not expected to be negative for malignant cells.
    d. Marker Lesion (Cohort 3) must have recurrent intermediate-risk disease with all previous tumors being low grade (G1-G2), Ta or T1, and no previous CIS. Additionally, subjects must have a risk of progression less than 5% in the next 2 years and a risk of recurrence greater than 50%, calculated using the EORTC risk calculator.[19] All tumors must be removed except for a single untouched 5 to 10 mm lesion (Marker Lesion).

3. Criterion modified per Amendment 2

    3.1 Criterion modified per Amendment 3

    3.2 At least 1 of the following tumor FGFR mutations or fusions as determined by local* or central testing:

FGFR3 Mutations	FGFR2 and FGFR3 Gene Fusions
• R248C	• FGFR2-BICC1
• S249C	• FGFR2-CASP7
• G370C	• FGFR3-TACC3
• Y373C	• FGFR3-BAIAP2L1

*Local tissue-based results (if already existing) from next-generation sequencing (NGS) or polymerase chain reaction (PCR) tests performed in CLIA-certified or equivalent laboratories, or results from commercially available NGS tests. Subjects enrolling based on local testing must submit tissue for central confirmation of FGFR status. Subjects enrolling as referrals from ANNAR study do not need to submit tissue for central FGFR confirmation. If archival tissue is not available, contact the sponsor for further guidance.

4. Criterion modified per Amendment 1.
4.1.
4a. BCG-unresponsive.
BCG-unresponsive subjects must meet at least one of the following:

i. Persistent or recurrent CIS alone or with recurrent Ta/T1 (noninvasive papillary disease/tumor invades the subepithelial connective tissue) disease within 12 months of completion of **adequate BCG therapy** (Cohort 2 only).
ii. Recurrent high-grade Ta/T1 disease within 6 months of completion of **adequate BCG therapy**.
iii. T1 high-grade at the first disease assessment following an induction BCG course.

Adequate BCG (Minimum Treatment Requirements)

1) At least 5 of 6 full doses of an initial induction course plus at least 1 maintenance (2 of 3 full weekly full doses) in a 6-month period. (See Section 2.3 for a description of "full dose".)
OR
2) At least 5 of 6 full doses of an initial induction course plus at least 2 of 6 full doses of a second induction course.

4b BCG Experienced.
BCG experienced subjects must meet the following:

i. Recurrent high-grade Ta/T1 disease within 12 months of completion of BCG therapy (as defined below).

Prior BCG (Minimum Treatment Requirements)

1) At least 5 of 6 full doses of an initial induction course.
OR
2) At least 5 of 6 full doses of an initial induction course plus at least 1 maintenance (2 of 3 weekly doses) in a 6-month period. One-half dose or one-third dose is allowed during maintenance.

*Note: Cohort 1: may be BCG-unresponsive as defined in 4a or BCG experienced as defined in 4b.

Cohort 2: must be BCG-unresponsive as defined in 4a.
Cohort 3: has no predefined prior BCG or intravesical chemotherapy requirement.

5. Refuses or is not eligible for cystectomy (Cohort 1 and Cohort 2 only)

6. Eastern Cooperative Oncology Group (ECOG) performance status Grade 0 or 1 (Section 10.5)

7. Criterion modified per Amendment 2

7.1 Criterion modified per Amendment 4

7.2 Adequate bone marrow, liver, and renal function:

a. Bone marrow function (without the support of cytokines or erythropoiesis-stimulating agent in preceding 2 weeks):

i. Absolute neutrophil count (ANC) ≥1,000/mm^3

ii. Platelet count ≥75,000/mm^3

iii. Hemoglobin ≥8.0 g/dL

b. Liver function:

i. Total bilirubin ≤1.5 x institutional ULN OR direct bilirubin ≤ULN for subjects with total bilirubin levels >1.5xULN

ii. Alanine aminotransferase (ALT) and aspartate aminotransferase (AST) ≤2.5x institutional ULN

c. Renal function:

Creatinine clearance >30 mL/min calculated using the Cockcroft-Gault formula (Section 10.6).

d. Phosphate:

<ULN within 14 days before the first dose of study drug on Cycle 1 Day 1 (medical management allowed)

8. Must sign an informed consent form (ICF) (or their legally acceptable representative must sign) indicating that he or she understands the purpose of, and procedures required for, the study and is willing to participate in the study.

9. A woman of childbearing potential must have a negative pregnancy test (β-hCG) (urine or serum) within 7 days before randomization (Cohort 1) or the first dose of study drug (Cohort 2 and Cohort 3).

10. Criterion modified per Amendment 2

10.1 Contraceptive use by men or women should be consistent with local regulations regarding the use of contraceptive methods for subjects participating in clinical studies.

a. For women of childbearing potential (defined as: fertile, following menarche and until becoming postmenopausal unless permanently sterile):

- Highly effective method of contraception (failure rate of <1% per year when used consistently and correctly).
- Permanent sterilization methods (for the purposes of this study) include hysterectomy, bilateral salpingectomy, and bilateral oophorectomy.
- Examples of highly effective contraceptives include:
  - user-independent methods: implantable progestogen-only hormone contraception associated with inhibition of ovulation; intrauterine device; intrauterine hormone-releasing system; vasectomized partner; sexual abstinence: true abstinence when this is in line with the preferred and usual lifestyle of the subject (Note: periodic abstinence [eg, calendar, ovulation, symptothermal, post-ovulation methods], declaration of abstinence for the duration of exposure to study drug, and withdrawal are not acceptable methods of contraception.)
  - user-dependent methods: combined (estrogen- and progestogen-containing) hormonal contraception associated with inhibition of ovulation: oral, intravaginal, and transdermal; progestogen-only hormone contraception associated with inhibition of ovulation: oral and injectable
- agrees to remain on a highly effective method of contraception during the study and for at least 6 months after the last dose of study drug
- agrees to not donate eggs (ova, oocytes) for the purposes of assisted reproduction during the study and for at least 6 months after the last dose of study drug
- not breastfeeding and not planning to become pregnant during the study and for at least 6 months after the last dose of study drug

b. For men who are sexually active with women of childbearing potential:

- agrees to use a condom with spermicidal foam/gel/film/cream/suppository
- agrees to not donate sperm during the study and for at least 6 months after the last dose of study drug
- not planning to father a child during the study or within 6 months after the last dose of study drug

5.2. Exclusion Criteria

Any potential subject who meets any of the following criteria will be excluded from participating in the study:

1. Histologically confirmed, muscle-invasive (T2 or higher stage) urothelial carcinoma of the bladder

2. Histopathology demonstrating any small cell component, pure adenocarcinoma, pure squamous cell carcinoma, or pure squamous CIS of the bladder

3. Prior treatment with an FGFR inhibitor

4. Active malignancies (ie, progressing or requiring treatment change in the last 24 months) other than the disease being treated under study. The only allowed exceptions are:

    a. skin cancer treated within the last 24 months that is considered completely cured

    b. adequately treated lobular carcinoma in situ (LCIS) and ductal CIS

    c. history of localized breast cancer and receiving antihormonal agents, or history of localized prostate cancer (N0M0) and receiving androgen deprivation therapy

5. Current central serous retinopathy or retinal pigment epithelial detachment of any grade

6. History of uncontrolled cardiovascular disease including:

    a. any of the following in the preceding 3 months: unstable angina, myocardial infarction, ventricular fibrillation, Torsades de Pointes, cardiac arrest, or known congestive New York Heart Association Class III-IV heart failure (Section 10.7), cerebrovascular accident, or transient ischemic attack.

    b. QTc prolongation as confirmed by ECG assessment at screening (Fridericia; QTc >480 milliseconds).

    c. Pulmonary embolism or other venous thromboembolism within the preceding 2 months.

7. Criterion modified per Amendment 1.

    7.1. Known human immunodeficiency virus (HIV) infection, unless the subject has been on a stable anti-retroviral therapy regimen for the last 6 months or more and has had no opportunistic infections and a CD4 count >350 in the last 6 months.

8. Criterion modified per Amendment 1.

8.1. Evidence of active hepatitis B or C infection (for example, subjects with history of hepatitis C infection but normal hepatitis C virus polymerase chain reaction test and subjects with hepatitis B with positive HBsAg antibody are allowed).

9. Not recovered from toxicity of prior anticancer therapy (except toxicities which are not clinically significant such as alopecia, skin discoloration, neuropathy, hearing loss)

10. Impaired wound healing capacity defined as skin/decubitus ulcers, chronic leg ulcers, known gastric ulcers, or unhealed incisions

11. Major surgery within 4 weeks before Cycle 1 Day 1 (TURBT is not considered major surgery)

12. Criterion modified per Amendment 2

12.1 Severe hypocalcemia (corrected serum calcium of <7 mg/dl), acute and unhealed bone fractures, known underlying bone disease, or at an increased risk of bone fracture. In addition, any condition for which, in the opinion of the investigator, participation would not be in the best interest of the subjects (eg, compromise the well-being) or that could prevent, limit, or confound the protocol-specified assessments. Examples include ongoing active infection requiring systemic therapy and uncontrolled ongoing medical conditions.

13. Criterion deleted per Amendment 3

14. Criterion added per Amendment 2

As determined by the investigator, contraindications to the use of gemcitabine or MMC/hyperthermic MMC (Cohort 1) per local prescribing information

15. Criterion added per Amendment 3

Treatment with any other investigational agent within 30 days prior to randomization.

NOTE: Investigators should ensure that all study enrollment criteria have been met at screening. If a subject's clinical status changes (including any available laboratory results or receipt of additional medical records) after screening but before the first dose of study treatment, such that he or she no longer meets all eligibility criteria, then the subject should be excluded from participation in the study. Section 5.4, Screen Failures, describes options for retesting. The required source documentation to support meeting the enrollment criteria are noted in Section 10.2, Regulatory, Ethical, and Study Oversight Considerations.

5.3. Lifestyle Considerations

Potential subjects must be willing and able to adhere to the following lifestyle restrictions during the study to be eligible for participation:

1. Refer to Section 6.5, Concomitant Therapy, for details regarding prohibited and restricted therapy during the study.

2. Subjects should avoid consuming grapefruit or Seville oranges (or products containing grapefruit or Seville oranges) due to CYP 3A4/5 inhibition.

3. Agree to follow all requirements that must be met during the study as noted in the Inclusion and Exclusion Criteria (eg, contraceptive requirements; see Section 10.4)

4. Male and female subjects should be advised on sperm banking and egg preservation, respectively, prior to entering the study, if appropriate.

Subjects should check with the study sites before taking over-the-counter medication known to increase serum levels of phosphate, such as potassium phosphate supplements (oral or IV), vitamin D supplements, antacids, and phosphate-containing enemas and laxatives (oral/rectal) thought to increase serum phosphate level (Section 6.5.3).

5.4. Screen Failures

Subject Identification, Enrollment, and Screening Logs

The investigator agrees to complete a subject identification and enrollment log to permit easy identification of each subject during and after the study. This document will be reviewed by the sponsor study-site contact for completeness. This study will use IWRS. The investigator will generate screening and enrollment logs directly from IWRS.

The subject identification and enrollment log will be treated as confidential and will be filed by the investigator in the study file. To ensure subject confidentiality, no copy will be made. All reports and communications relating to the study will identify subjects by subject identification and age at initial informed consent. In cases where the subject is not randomized (Cohort 1) or enrolled (Cohort 2 and Cohort 3) into the study, the date seen and age at initial informed consent will be used.

If insufficient tissue is available at the first molecular eligibility assessment, another tissue sample may be submitted (this is not considered rescreening). Subjects will be allowed to be rescreened once for main study eligibility after consultation with the sponsor's medical monitor, if the investigator has a valid reason to rescreen (eg, resolution of conditions previously meeting the exclusion criteria).

6. STUDY DRUG

For this study, study drug refers to erdafitinib (administered during the main study or Erdafitinib Crossover; Section 10.10) and Investigator's Choice provided by the sponsor. Study drugs used as part of the main study are described in the following sections.

6.1. Study Drug Administered

6.1.1. Erdafitinib

Erdafitinib will be provided as tablets for oral administration. Subjects will be instructed to take a 6-mg daily dose (without up-titration) beginning on Cycle 1 Day 1, with continuous dosing on a 28 day schedule. With the exceptions noted below for Cohort 2 and Cohort 3, treatment with erdafitinib may continue for a maximum of 2 years or until the subject has high risk disease recurrence or progression, intolerable toxicity, withdraws consent, there is a decision by the investigator to discontinue treatment, or the study is closed, whichever occurs first.

- For Cohort 2, erdafitinib must be discontinued if CR is not observed within 3 months.
- For Cohort 3, after 3 months of study treatment: 1) Subjects with stable disease or progression of the marker lesion must discontinue erdafitinib and a TURBT of the marker lesion must be performed. 2) Subjects with CR may continue erdafitinib. 3) Subjects with PR may, at the investigator's discretion, either continue treatment with erdafitinib or discontinue erdafitinib and undergo TURBT of the marker lesion.

The erdafitinib dose may be modified with guidance to up-titrate to the 8-mg daily regimen, after IDMC review of safety and tolerability data from approximately 5 to 10 additional subjects who received the 6-mg daily regimen. Details of any such recommendation will be communicated separately. Should the dosing regimen be modified to include up-titration, please follow the instruction in Section 10.12 Appendix 12.

Each dose should be taken at approximately the same time each day, with or without food. Erdafitinib is to be taken with approximately 240 mL (8 ounces) of water. The tablets should be swallowed intact. Subjects should avoid consuming food or drinks containing grapefruit or Seville oranges due to CYP 3A4/5 inhibition. Refer to the pharmacy manual/study site investigational product manual for additional guidance on study drug preparation, handling, and storage.

If a dose of erdafitinib is missed, subjects should take the missed dose as soon as possible up to 6 hours after the normal schedule of that day. If it has been more than 6 hours since the missed dose, then that dose should be skipped, and resume the regular daily dose schedule for erdafitinib the next day. Extra tablets should not be taken to make up for the missed dose. If vomiting occurred with drug administration, no replacement dose will be taken. If the subject vomits up to 4 hours after the study drug administration, document the study drug as administered on the dose form in the eCRF, with a comment noting that the subject vomited and at how many hours after the study drug administration.

On days when pharmacokinetic sampling is performed, erdafitinib dosing and predose pharmacokinetic sample collection must be coordinated so that at least 4 hours have elapsed between the last dose of erdafitinib and collection of the predose pharmacokinetic sample. This may require that subjects receive their daily dose of erdafitinib at the study site after collection of the predose pharmacokinetic samples.

Erdafitinib will be dispensed at the first visit of each cycle. All study drug doses dispensed must be captured in the source documents. Unused study drug in the issued bottles and empty bottles must be returned to the site at each study visit. Study drug must be returned to the site when a subject discontinues study treatment. Returned tablets may not be reissued in this study or outside the study (follow study drug accountability guidelines in the study Investigational Product Procedures Manual [IPPM]). Erdafitinib administration must be captured in the source documents and the eCRF.

Erdafitinib will be manufactured and provided under the responsibility of the sponsor. Refer to the IB for a list of excipients.

The exposure of erdafitinib is predicted to increase by 50% in subjects with the CYP2C9 *3/*3 genotype, estimated to be 0.4% to 3% of the population among various ethnic groups. Therefore, monitor for increased adverse reactions in subjects who are known or suspected to have CYP2C9*3/*3 genotype. Dose titration is guided by serum phosphate levels in all subjects irrespective of genotype; therefore, the implications of higher exposures of erdafitinib including safety may be addressed.

6.1.2. Investigator's Choice of Treatment – Cohort 1 Only

Subjects in Cohort 1 assigned to receive Investigator's Choice will receive either intravesical gemcitabine or intravesical MMC/hyperthermic MMC. Investigator's choice treatment will be given once weekly for at least 4 doses of induction followed by monthly maintenance for at least 6 months. Additional doses of induction or maintenance are allowed per local standard of care.

If more than 4 induction doses are given and the start of the monthly maintenance dose falls on Day 8, Day 15, or Day 22 of subsequent cycles, all corresponding pre-dose assessments should be done on the same day (±2 days) as the maintenance dose is administered as highlighted in the example below:

- If subject starts monthly maintenance at C2D8, the following visits will occur at C3D8; C4D8; C5D8; C6D8; C7D8; C8D8.
- If subject starts monthly maintenance at C2D15, following visits will occur at C3D15; C4D15; C5D15; C6D15; C7D15; C8D15.
- If subject starts monthly maintenance at C2D22, following visits will occur at C3D22; C4D22; C5D22; C6D22; C7D22; and C8D22.

Treatment may continue until treatment is completed, high risk disease recurrence, intolerable toxicity, withdrawal of consent, a decision by the investigator to discontinue treatment, or the study is closed, whichever occurs first. As all subjects in Cohort 1 would have recurred within 12 months of last dose of BCG, they are considered not to be candidates for re-treatment with BCG.[21]

Dose modifications or omissions will be managed by the treating physician per local standard of care after discussion with the sponsor. Investigators must indicate their Investigator's Choice selection for each subject in the interactive web response system (IWRS) at screening, and the

choice of the agent must take prior exposure into consideration. Subjects may not be switched to the alternate Investigator's Choice agent after randomization has occurred.

For subjects in Cohort 1 who have locally confirmed high-risk recurrence on Investigator's Choice, the subject may cross over to erdafitinib (see Section 10.10). Note: no additional crossover from Investigator's Choice to erdafitinib will be permitted.

6.1.2.1. Gemcitabine Administration

Gemcitabine will be administered as an intravesical instillation with 2,000 mg dose once weekly for at least 4 induction doses followed by monthly maintenance for at least 6 months. Additional doses of induction or maintenance are allowed per local standard of care.

Gemcitabine instillation must be captured in the source documents and the eCRF.

Refer to the IPPI provided separately for additional information on the preparation, handling, and administration of gemcitabine.

6.1.2.2. Mitomycin C Administration

Mitomycin C or hyperthermic MMC will be administered as an intravesical instillation with 40 mg dose once weekly for at least 4 induction doses followed by monthly maintenance for at least 6 months. Additional doses of maintenance are allowed per local standard of care.

Mitomycin C or hyperthermic MMC instillation must be captured in the source documents and the eCRF.

Refer to the IPPI provided separately for additional information on the preparation, handling, and administration of MMC/hyperthermic MMC.

6.1.3. Continuation of Treatment After Disease Recurrence

Subjects will not continue erdafitinib treatment after high risk disease recurrence or progression.

For subjects in Cohort 1 who have locally confirmed high-risk recurrence on Investigator's Choice, the subject may cross over to erdafitinib, if by the assessment of investigator, this is best treatment option for subject (Section 10.10). Subjects will have an End-of-Treatment (EoT) Visit for the comparator and begin the crossover with erdafitinib beginning at C1D1. Note: no additional crossover from Investigator's Choice to erdafitinib will be permitted.

In Cohort 2 or Cohort 3, erdafitinib must be discontinued at the time of progression or recurrence as described in Section 6.1.1.

6.1.4. Erdafitinib Crossover

Subjects who are randomized to gemcitabine or MMC/hyperthermic MMC in Cohort 1 and demonstrate locally confirmed high-risk recurrence while receiving study drug will have the opportunity to cross over to treatment with erdafitinib. There must be an agreement to do so by the investigator, subject, and the sponsor's medical monitor. Documentation of high-risk disease

recurrence will be reviewed by the sponsor's medical monitor before crossover occurs and must be entered onto the eCRF. Please refer to Section 10.10 for the schedule of assessments. Note: no additional crossover from Investigator's Choice to erdafitinib will be permitted.

6.2. Preparation/Handling/Storage/Accountability

Preparation/Handling/Storage

Refer to the study pharmacy manual (Investigational Product Binder) /study IPPI and IPPM for additional guidance on study drug preparation, handling, and storage.

Accountability

The investigator is responsible for ensuring that all study drug received at the site is inventoried and accounted for throughout the study. The dispensing of study drug to the subject, and the return of study drug from the subject (if applicable), must be documented on the drug accountability form. Subjects, or their legally acceptable representatives where applicable, must be instructed to return all original containers, whether empty or containing study drug. All study drug will be stored and disposed of according to the sponsor's instructions. Study-site personnel must not combine contents of the study drug containers.

Study drug must be handled in strict accordance with the protocol and the container label and must be stored at the study site in a limited-access area or in a locked cabinet under appropriate environmental conditions. Unused study drug, and study drug returned by the subject, must be available for verification by the sponsor's study site monitor during on-site monitoring visits. The return to the sponsor of unused study drug, or used returned study drug for destruction, will be documented on the drug return form. When the study site is an authorized destruction unit and study drug supplies are destroyed on-site, this must also be documented on the drug return form.

Study drug should be dispensed under the supervision of the investigator or a qualified member of the study-site personnel, or by a hospital/clinic pharmacist. Study drug will be supplied only to subjects participating in the study. Returned study drug must not be dispensed again, even to the same subject. Whenever a subject brings his or her study drug to the study site for pill count, this is not seen as a return of supplies. Study drug may not be relabeled or reassigned for use by other subjects. The investigator agrees neither to dispense the study drug from, nor store it at, any site other than the study sites agreed upon with the sponsor. Further guidance and information for the final disposition of unused study drugs are provided in the study IPPI and IPPM.

6.3. Measures to Minimize Bias: Randomization and Blinding

This is an open-label study; neither the sponsor, investigators, nor subjects will be blinded to assigned treatment. Central randomization will be implemented in this study. In Cohort 1, subjects will be randomly assigned to 1 of 2 treatment groups in a 2:1 randomization ratio (erdafitinib: Investigator's Choice) based on a computer-generated randomization schedule prepared before the study by or under the supervision of the sponsor. The randomization will be balanced by using randomly permuted blocks and will be stratified by the type of resected papillary disease (Ta vs T1) and type of prior BCG therapy (BCG-unresponsive vs BCG experienced). Subjects in the

BCG-experienced strata will be capped at approximately 50% of the total study population. The IWRS will assign a unique code, which will dictate the study drug assignment and matching study drug kit for the subject. The requestor must use his or her own user identification and personal identification number when contacting the IWRS and will then give the relevant subject details to uniquely identify the subject. Investigators must indicate their Investigator's Choice selection for each subject during screening. All tissue samples with a local investigator assessment of any recurrence will be sent to central lab for an independent pathologic assessment regardless of risk category in order to decrease bias.

All subjects in Cohort 2 and Cohort 3 will be assigned to treatment with erdafitinib.

6.4. Study Drug Compliance

The investigator or designated study personnel will maintain a log of the amount of study drug dispensed and returned, if applicable. Drug supplies will be inventoried and accounted for throughout the study.

Subjects will receive instructions on erdafitinib compliance at their Cycle 1 Day 1 visit. The time of erdafitinib intake will be recorded on days when PK sampling occurs. On days when the subject visits the study site for dose administration or PK sampling, the investigator or designee will supervise administration of the study drug and the exact time of administration will be recorded in the eCRF. During the study, the investigator or designated study research staff will be responsible for providing additional instruction to reeducate any subject who is not compliant with the study drug schedule.

6.5. Concomitant Therapy

Concomitant therapies must be recorded at the time of study screening (concomitant therapy within the 35 days before Cycle 1 Day 1), during the Treatment Phase, and up to 30 days after the last dose of study drug (30-day Safety Follow-up Visit). All therapies (prescription or over-the-counter medications) continued at the start of the study or started during the study and different from the study drug must be recorded in the eCRF.

The sponsor must be notified in advance (or as soon as possible thereafter) of any instances in which prohibited therapies are administered.

In addition to concomitant therapy, all prior anticancer therapy will be recorded in the eCRF.

6.5.1. Permitted Medications

Permitted medications are to be recorded at the time of screening (within 35 days prior to the first dose of study drug), throughout the study, and up to 30 days after the last dose of study drug in the appropriate section of the eCRF.

- Symptomatic treatment: Supportive care, such as antibiotics, analgesics, transfusions, etc., and concomitant medications for the symptomatic treatment of related toxicities (Grade 1 to 4) may be administered according to the standard of care at the site, and the treating physician's discretion, as clinically indicated.

- Prophylactic medication: Appropriate prophylactic antiemetic regimens may be provided if required, in accordance with local institutional guidelines or practice guidelines.
- Chronic supportive therapies are permitted as medically necessary.
- COVID-19 vaccination: Note: Administration of non-live vaccines approved or authorized for emergency use (eg, COVID-19) by local health authorities are allowed before or during this study.

6.5.2. Prohibited Medications

The following concomitant medications are prohibited during the study. The sponsor must be notified in advance, or as soon as possible thereafter, of any instances in which prohibited therapies were administered.

- Concurrent investigational agents during the Treatment Phase
- Concurrent antineoplastic agents or hormonal anticancer therapy during the Treatment Phase, except as allowed by Exclusion Criterion no. 4 (see Section 5.2)

6.5.3. Precautions for Concomitant Medications

The following precautions are advised:

- Based on in vitro data, erdafitinib is metabolized by cytochrome CYP2C9 and CYP3A4. A clinical DDI study showed that on average, erdafitinib exposure (C_{max} and AUC) was increased by 5% to 34%, respectively, when co-administered with itraconazole (a strong inhibitor of CYP3A4) and 21% to 48%, respectively, when co-administered with fluconazole (a moderate inhibitor of CYP2C9). For this reason, strong CYP3A4 and moderate CYP2C9 inhibitors should be used with caution (See Section 10.9). Consider alternative therapies with no or minimal CYP2C9 or CYP3A4 inhibition potential during treatment with erdafitinib. If co-administration of a moderate inhibitor of CYP2C9 or strong inhibitor of CYP3A4 is unavoidable, monitor the subject closely for adverse reactions and consider dose modifications accordingly. If the strong inhibitor is discontinued, the erdafitinib dose may be increased in the absence of drug-related toxicity.
- The impact of moderate CYP2C9 inducers and strong CYP3A inducers (such as rifampin) on erdafitinib was not clinically studied. Co-administration of erdafitinib with these agents may significantly decrease erdafitinib exposure. Therefore, the concomitant use of these agents with erdafitinib should be avoided (see Section 10.9). Co-administration of erdafitinib with moderate CYP3A inducers may decrease erdafitinib exposure. Caution should be exercised for concomitant administration of erdafitinib and moderate inducers of CYP3A4 (see Section 10.9).
- Until further data become available, concomitant use of erdafitinib with CYP3A4 substrates with narrow therapeutic indices should be avoided.
- Erdafitinib was shown to inhibit, via in vitro experiments, human P-gp at concentrations achieved at therapeutic doses in humans. If the compound is administered with drugs that are substrates of P-gp, there is the potential for observing increased concentrations of the substrate drug. Caution should be exercised for co-administered drugs that are P-gp substrates; separate

erdafitinib administration by at least 6 hours before or after administration of P-gp substrates with narrow therapeutic index.

- Erdafitinib was shown to be an OCT2 inhibitor in vitro. PBPK simulations with metformin, an OCT2 substrate, predicted a lack of clinically relevant interaction with erdafitinib. However, until further data are available, consider reducing the dose of OCT2 substrates or consider alternative agents based on tolerability.
- For subjects taking erdafitinib, medications known or thought to increase serum levels of phosphate including potassium phosphate supplements (oral or IV), vitamin D supplements, antacids, and phosphate-containing enemas and laxatives (oral/rectal) should be used with caution in case of strong medical need and when the benefit outweighs the risk. Check phosphate levels more regularly during treatment.

6.6. Dose Modification

Any dose/dosage adjustment should be overseen by medically-qualified study-site personnel (principal or subinvestigator unless an immediate safety risk appears to be present).

6.6.1. Erdafitinib Up-titration Guidelines

The erdaftinib dose is modified to the 6-mg daily regimen (without up-titration). After review of safety and tolerability data from approximately 5 to 10 additional subjects who received the 6-mg daily regimen, the IDMC may recommend that the erdafitinib dose be modified to allow up-titration to the 8-mg daily regimen. Details of any such recommendation will be communicated separately. Should the dosing regimen be modified to include up-titration, please follow the instruction in Section 10.12, Appendix 12.

6.6.2. Erdafitinib Dose Interruptions

Treatment with erdafitinib should be discontinued or modified based on toxicities as described in Table 1. For eye, skin/nail, dry mouth/mucositis, and phosphate toxicity, specific recommendations in the management guidelines are provided in Section 6.6.2.1.

Table 1: Erdafitinib Dose Modification Rules Based on Toxicity Severity

Toxicity Grade	Action	Dose modification after resolution of adverse event[a]
1	None	Continue same dose.
2	None, or consider interruption if the toxicity is considered clinically significant	If interrupted, restart at same dose if toxicity is completely resolved to baseline or consider restarting at 1 dose lower[b] if not completely resolved to baseline (but resolved to Grade 1).
3	Interrupt drug	Restart at 1 dose lower[b] if recovered to baseline (to ≤Grade 1 or back to baseline for non-hematologic toxicity) within 28 days; restart at 2 doses lower[b] if not completely resolved to baseline (but resolved to Grade 1) within 28 days. Discontinue drug if unresolved for >28 days.
4	Interrupt drug	Discontinue.

[a] For eye, skin/nail, dry mouth/mucositis, and phosphate toxicity please follow specific recommendations in the management guidelines (Section 6.6.2.1).
[b] Please refer to Table 2.

- Subjects with any grade of toxicity (Grade 1 to 4) should be provided symptomatic treatment where applicable.
- If erdafitinib is interrupted consecutively for 1 week or longer due to drug-related toxicity, the study drug may be reintroduced at either the same dose level or the first reduced dose level following recovery from the toxicity (see dose reduction levels in Table 2). A second dose reduction may be implemented following a second occurrence of drug-related toxicity.
- If erdafitinib must be withheld for more than 28 days for a drug-related adverse event that fails to resolve to an acceptable level (eg, ≤Grade 1 non-hematologic toxicity or back to baseline), treatment with erdafitinib should be discontinued except when the subject has been deriving benefit from treatment, and the investigator believes, based on his or her clinical judgment, that continued treatment with erdafitinib is in the best interest of the subject. Erdafitinib may be restarted at the same or a lower dose (Table 2) if the sponsor's medical monitor concurs with the assessment.
- If the erdafitinib dose was reduced and the adverse event that was the reason for this dose reduction has completely resolved, the dose may be re-escalated to the next higher dose if the subject was deriving benefit from treatment, and the investigator believes, based on his or her clinical judgment, that dose re-escalation of erdafitinib is in the best interest of the subject and the sponsor's medical monitor concurs with the assessment.
- In all cases of clinically significant impaired wound healing or imminent surgery or potential bleeding complications, it is recommended that dose administration be interrupted, appropriate clinical laboratory data (eg, coagulation parameters) be carefully monitored, and supportive therapy administered, where applicable. Dose administration may be restarted when it is considered safe and at an appropriate dose, according to the investigator's assessment.

Table 2: Erdafitinib Dose Reduction Levels

Category	Dose
Starting dose	6 mg
1st dose reduction	5 mg
2nd dose reduction	4 mg
3rd dose reduction	**STOP**

Note that the erdafitinib dose reduction levels table for the 6-mg daily regimen with up-titration to the 8-mg daily regimen is provided in Section 10.12, Appendix 12.

6.6.2.1. Guidance for Specific Erdafitinib Toxicities

6.6.2.1.1. Guidelines for the Management of Elevated Phosphate Levels

Hyperphosphatemia will be graded as outlined in Table 3. Guidelines for the clinical management of elevated serum phosphate levels are presented in

Table 4.

Table 3: Grading of Hyperphosphatemia Adverse Events

Adverse Event	Grade 0	Grade 1	Grade 2	Grade 3	Grade 4
Hyperphosphatemia	<5.50 mg/dL <1.75 mmol/L	5.50-6.99 mg/dL	7.00-8.99 mg/dL	9.00-10.00 mg/dL (2.91-3.20 mmol/L), or	>10.00 mg/dL (>3.20 mmol/L), or symptomatic

		1.75-2.24 mmol/L	2.25-2.90 mmol/L	asymptomatic soft-tissue calcification with any phosphate level	soft-tissue calcification with any phosphate level

Table 4: Guidelines for Management of Serum Phosphate Elevation

Serum Phosphate Level	Study Drug Management	Symptom Management
<5.50 mg/dL (<1.75 mmol/L) (Grade 0)	Continue erdafitinib treatment.	None.
5.50-6.99 mg/dL (1.75-2.24 mmol/L) (Grade 1)	Continue erdafitinib treatment.	Restriction of phosphate intake to 600 – 800 mg/day.
7.00-8.99 mg/dL (2.25-2.90 mmol/L) (Grade 2)	Continue erdafitinib treatment. A dose reduction will be implemented for persistent[a] hyperphosphatemia (defined as serum phosphate ≥7 mg/dL for a period of 2 months) or if clinically necessary (eg, in the presence of additional adverse events linked to hyperphosphatemia or electrolyte disturbances)	Restriction of phosphate intake to 600 – 800 mg/day. Start sevelamer 800 to 1,600 mg TID with food until phosphate level is <7.0 mg/dL.
9.00-10.00 mg/dL (>2.91-3.20 mmol/L) (Grade 3)	Withhold[b] erdafitinib treatment until serum phosphate level returns to <7.0 mg/dL (weekly testing recommended). Restart treatment at the same dose level. A dose reduction will be implemented for persistent [a] hyperphosphatemia (defined as serum phosphate ≥9 mg/dL for a period of 1 month) or if clinically necessary (eg, in the presence of additional adverse events linked to hyperphosphatemia or electrolyte disturbances)	Restriction of phosphate intake to 600 – 800 mg/day. Sevelamer up to 1,600 mg TID with food until serum phosphate level is <7.0 mg/dL.
>10.00 mg/dL (>3.20 mmol/L) (Grade 4)	Withhold[b] erdafitinib treatment until serum phosphate level returns to <7.0 mg/dL (weekly testing recommended). Restart treatment at the first reduced dose level. If persistent[a] hyperphosphatemia (≥10.00 mg/dL) for >2 weeks, erdafitinib must be discontinued permanently.	Medical management as clinically appropriate.
Significant alteration in baseline renal function or Grade 3 hypocalcemia	Erdafitinib must be discontinued permanently. (In situations where the subject is having clinical benefit and the investigator and the sponsor's medical monitor agree that continuation of treatment is in the best interest of the subject, the drug may be restarted at 2 dose levels lower if appropriate. Follow other recommendations described above, Section 6.6.2.)	Medical management as clinically appropriate.

Note: These are general guidelines that are based on emerging data and consensus experience of participating investigators or the experts in the field. The treating physicians must use clinical judgment and local standard of care to decide the best way to manage phosphate elevation. If sevelamer hydrochloride (Renagel®) is not available, use of other phosphate binders (non-calcium containing) based on the local standard is recommended, including sevelamer carbonate (Renvela) or lanthanum carbonate (Fosrenol®). These guidelines will be updated based on emerging data. Additional information on phosphorous in foods by class of food can also be found at www.permanente.net/homepage/kaiser/pdf/42025.pdf. Additional information for

phosphate management and diet can be found at the National Kidney Foundation website (http://www.kidney.org/atoz/content/phosphorus.cfm)

a. Persistent hyperphosphatemia is considered to be more than 1 sequential phosphate value above the cut-off.
b. Study drug interruptions for hyperphosphatemia suggested to be 7 days in duration.

6.6.2.1.2. Guidelines for the Management of Dry Mouth and Mucositis

Guidelines for the clinical management of dry mouth (xerostomia) and mucositis are provided in Table 5 and Table 6, respectively.

- General Prophylaxis for dry mouth and oral mucositis:
  - Good oral hygiene
  - Use a soft toothbrush
  - Avoidance of spicy, acidic, hard, and hot food and beverages
  - Use of mild-flavored toothpastes
  - Use of salt and baking soda mouthwashes 3 or 4 times per day
  - Water soluble lubrication agents like artificial saliva (for xerostomia or dry mouth)

Table 5: Guidelines for Management of Dry Mouth (Xerostomia)

Grade and Definition	Study Drug (Erdafitinib) Management	Symptom Management
Grade 1: symptomatic (eg, dry or thick saliva) without significant dietary alteration; unstimulated saliva flow >0.2 mL/min	Continue erdafitinib at current dose.	Sorbitol lozenges as needed
Grade 2: moderate symptoms; oral intake alterations (eg, copious water, other lubricants, diet limited to purees or soft, moist foods); unstimulated saliva 0.1 to 0.2 mL/min	Continue erdafitinib at current dose.	Sorbitol lozenges as needed and Cevimeline 30 mg TID or Pilocarpine 5 mg TID, orally
Grade 3: inability to adequately aliment orally; tube feeding or TPN indicated; unstimulated saliva less than 0.1 mL/min	Hold erdafitinib (for up to 28 days), with weekly reassessments of clinical condition. When resolved to ≤Grade 1 or baseline, restart at 1 dose level below in consultation with the medical monitor.	Sorbitol lozenges as needed and Cevimeline 30 mg TID or Pilocarpine 5 mg TID, orally
Grade 4: life-threatening consequences, urgent intervention indicated	Discontinue erdafitinib.	Evaluation and therapy as clinically indicated

Table 6: Guidelines for the Management of Oral Mucositis

Grade	Study Drug (Erdafitinib) Management	Symptom Management
Grade 1	Continue erdafitinib at current dose.	• Continue general prophylaxis recommendations. • Dexamethasone solution (0.5 mg/5 mL solution) swish and spit QID or similar solution that is available in your country/territory and lidocaine 2-5% jelly or solution. • Consider clotrimazole/nystatin if subjects are at risk of developing oral candidiasis.
Grade 2	• Consider holding erdafitinib if the subject has other study drug-related concomitant Grade 2 AEs. • Hold erdafitinib if the subject was already on symptom management (dexamethasone solution swish and spit and lidocaine 2%-5% jelly or solution) for more than a week. • If the erdafitinib is withheld, reassess in 1-2 weeks. • If this is the first occurrence of toxicity and resolves to ≤ Grade 1 or baseline within 2 weeks, restart at same dose. • If recurrent event or takes > 2 weeks to resolve to ≤ Grade 1 or baseline, then restart at 1 dose level below.	• Dexamethasone solution (0.5 mg/5 mL solution) swish and spit QID or similar solution that is available in your country/territory and lidocaine 2-5% jelly or solution. • Consider concomitant etiologies such as oral candidiasis, oral herpes and recommend appropriate anti-fungal or anti-viral agents.
Grade 3	Hold erdafitinib, with reassessments of clinical condition in 1-2 weeks. When resolves to ≤Grade 1 or baseline, restart at 1 dose level below in consultation with the medical monitor.	Dexamethasone solution (0.5 mg/5 mL solution) swish and spit QID or similar solution that is available in your country/territory and lidocaine 2%-5% jelly or solution. Consider pain management strategies. Consider IV hydration.
Grade 4	Discontinue erdafitinib.	Evaluation and therapy as clinically indicated.

6.6.2.1.3. Guidelines for the Management of Dry Skin and Skin Toxicity

Guidelines for the management of dry skin are provided in
Table 7.

- General prophylaxis for dry skin and skin toxicity**:**
  - Avoid unnecessary exposure to sunlight and excessive use of soap.

- Avoid bathing in excess; use tepid rather than hot water.
- Use moisturizers regularly; apply thick, alcohol-free and oil-in-water based emollient cream on exposed and dry areas of the body.
- Avoid perfumed products, bubble bath, perfumed soaps, and take breaks from shaving.
- Use broad spectrum sunscreen with a skin protection factor (SPF) ≥15.
- Wear cotton clothes next to skin rather than wool, synthetic fibers, or rough clothing.
- Use occlusive alcohol-free emollient creams (jar or tub) for treatment of mild/moderate xerosis.
- For scaly areas, use exfoliants (ammonium lactate 12% or lactic acid cream 12%).

Table 7: Guidelines for Management of Dry Skin

Grade and Definition	Study Drug (Erdafitinib) Management	Symptom Management
Grade 1: Dry skin covering less than 10% body surface area (BSA) and no associated erythema or pruritus	Continue erdafitinib at current dose.	Use fragrance free moisturizing cream or ointment BID over entire body. Use ammonium lactate 12% cream or salicylic acid 6% cream BID over dry/scaly/hyperkeratotic areas such as palms and soles.
Grade 2: Dry skin covering 10% to 30% BSA and associated with erythema or pruritis with limited instrumental activities of daily living (IADL)	Continue erdafitinib at current dose.	Use fragrance free moisturizing cream or ointment BID over entire body. Use ammonium lactate 12% cream or salicylic acid 6% cream BID over dry/scaly/hyperkeratotic areas such as palms and soles. Use zinc oxide 13%-40% at night for areas with fissures.
Grade 3: Dry skin covering >30% BSA and associated with pruritis; limiting self-care activities of daily living (ADL)	Hold erdafitinib (for up to 28 days), with weekly reassessments of clinical condition. When resolves to ≤Grade 1 or baseline, restart at 1 dose level below in consultation with the medical monitor.	Use topical corticosteroid ointment or cream* BID and zinc oxide 13% -40% at night for areas with fissures.
Grade 4: Dry skin with life-threatening consequences, urgent intervention indicated	Discontinue erdafitinib.	Evaluation and therapy as clinically indicated

*Topical Corticosteroid Ointments: Clobetasol 0.05%, Betamethasone 0.05%, Fluocinonide 0.05%
BID=twice a day

6.6.2.1.4. Guidelines for Management of Nail Toxicity (Onycholysis, Onychodystrophy, and Paronychia)

Adverse events related to nails will be graded as outlined in Table 8. Guidelines for the management of nail discoloration/loss/ridging (onycholysis/onychodystrophy) are provided in Table 9. Guidelines for the management of paronychia are provided in Table 10.

Table 8: Grading of Nails Adverse Events

Adverse Event	Grade 1	Grade 2	Grade 3	Grade 4
Nail Changes (onychodystrophy)	Nail discoloration, asymptomatic separation of the nail bed from the nail plate or nail loss	Nail/finger tips pain, symptomatic separation of the nail bed from the nail plate or nail loss; limiting instrumental ADL	Severe nail finger tips pain, symptomatic separation of the nail bed from the nail plate or nail loss; significantly limiting instrumental ADL	Life-threatening consequences, urgent intervention indicated

ADL= activities of daily living

- General Prophylaxis for nail toxicity:
  - Good hygienic practices; keep fingers and toes clean
  - Keep nails trimmed but avoid aggressive manicuring
  - Use gloves for housecleaning and gardening to minimize damage and prevent infection
  - Nail polish and imitation fingernails should not be worn until the nails have grown out and returned to normal
  - Wear comfortable shoes (wide sized shoes with room for the toes)

Table 9: Guidelines for Management of Nail Toxicity (Onycholysis/Onychodystrophy)

Grade	Study Drug (Erdafitinib) Management	Symptom Management
Grade 1	Continue erdafitinib at current dose.	• Continue general prophylaxis recommendations. • Over-the-counter nail strengthener OR poly-urea urethane nail lacquer (Nuvail™) OR diethylene glycol monoethylether nail lacquer daily (Genadur) daily. • Use non-alcohol- containing moisturizing creams.
Grade 2	Consider holding erdafitinib with reassessment in 1-2 weeks. If first occurrence and it resolves to ≤Grade 1 or baseline within 2 weeks, restart at same dose. If recurrent event or takes >2 weeks to resolve to ≤Grade 1 or baseline, then restart at 1 dose level below in consultation with the medical monitor.	• Manage as per Grade 1. • For signs of infection (periungual edema/erythema/ tenderness or discharge), obtain bacterial cultures, and then start the following: ○ treatment with oral antibiotic for 2 weeks (cefadroxil 500 mg BID, ciprofloxacin 500 mg BID, or sulfamethoxazole/ trimethoprim BID) AND ○ topical antifungal lacquer daily for 6+ weeks (ciclopirox olamine 8% OR efinaconazole 10% OR amorolfine 5% weekly OR bifonazole/urea ointment daily) • Silver nitrate application weekly AND topical antibiotics AND vinegar soaks[a].
Grade 3	Hold erdafitinib, with reassessment in 1-2 weeks. When resolves to ≤Grade 1 or baseline, restart at 1 dose level below in consultation with the medical monitor.	Silver nitrate application weekly AND topical antibiotics AND vinegar soaks.[a] For signs of infection (periungal edema/erythema/ tenderness or discharge), obtain bacterial cultures, and then start the following: treatment with oral antibiotic for 2 weeks (cefadroxil 500 mg BID, ciprofloxacin 500 mg BID, or sulfamethoxazole/trimethoprim BID). For cases of severe/refractory infection consider intravenous antibiotics. Consider dermatological or surgical evaluation.
Grade 4	Discontinue erdafitinib	Evaluation and therapy as clinically indicated

[a] Vinegar soaks consist of soaking fingers or toes in a solution of white vinegar in water 1:1 for 15 minutes every day. Examples of topical antibiotic ointments: Mupirocin 2%, gentamycin, bacitracin zinc/polymixin B

BID= bis in die (two times each day)

Table 10: Guidelines for Management of Paronychia

Grade	Study Drug (Erdafitinib) Management	Symptom Management
Grade 1	Continue erdafitinib at current dose.	Topical antibiotics AND vinegar soaks[a]
Grade 2	Continue erdafitinib at current dose. Consider erdafitinib holding if no improvement in 1 to 2 weeks. When resolves to ≤Grade 1 or baseline, restart at same or 1 dose level below in consultation with the medical monitor	Topical antibiotics AND vinegar soaks[a] AND topical antifungal lacquer daily for 6+ weeks (ciclopirox olamine 8% OR efinaconazole 10% OR amorolfine 5% weekly OR bifonazole/urea ointment daily) For signs of infection (periungal edema/erythema/tenderness or discharge), obtain bacterial cultures, and then start the following: treatment with oral antibiotic for 2 weeks (cefadroxil 500 mg BID, ciprofloxacin 500 mg BID, or sulfamethoxazole/ trimethoprim [Bactrim™] DS BID).
Grade 3	Hold erdafitinib (for up to 28 days), with weekly reassessments of clinical condition. When resolves to ≤Grade 1 or base line, restart at one dose level below in consultation with the medical monitor.	Vinegar soaks[a] AND consider nail avulsion For signs of infection (periungal edema/erythema/tenderness or discharge), obtain bacterial cultures, and then start the following: treatment with oral antibiotic for 2 weeks (cefadroxil 500 mg BID, ciprofloxacin 500 mg BID, or sulfamethoxazole/ trimethoprim [Bactrim] DS BID). For cases of severe/refractory infection consider intravenous antibiotics. Consider dermatological or surgical evaluation.

[a] Vinegar soaks consist of soaking fingers or toes in a solution of white vinegar in water 1:1 for 15 minutes every day. Examples of topical antibiotic ointments: Mupirocin 2%, gentamycin, bacitracin zinc/polymixin B

6.6.2.1.5. Guidelines for the Management of Eye Toxicity Associated With Vision Changes

Any new or worsening visual symptoms, for example, blurred vision, partial or complete loss of vision, double vision, floaters or color spots or halos around light, change in color or night vision, photophobia, ocular pain or stinging sensation, or foreign body sensation should be further evaluated and managed per the guidelines in Table 11.

Amsler grid (illustrated in Section 10.8): For any positive Amsler grid test, the subject should be referred for a full ophthalmologic examination within 7 days. However, if the subject has an abnormal Amsler grid test and otherwise normal ophthalmologic examination at baseline (during screening), a repeat ophthalmologic examination would be recommended only if, in the opinion of the investigator, there is a likelihood of significant change from the subject's baseline Amsler grid test at screening, or the subject has developed new clinical symptoms.

Table 11: Guidelines for Management of Eye Toxicity

Grade and Definition	Study Drug (Erdafitinib) Management	Symptom Management
Grade 1: Asymptomatic or mild symptoms; clinical or diagnostic observations only Or abnormal Amsler grid test	Refer for an ophthalmologic examination. If an ophthalmologic examination cannot be performed within 7 days, withhold treatment with erdafitinib until an examination can be performed. If there is no evidence of eye toxicity on ophthalmologic examination, continue erdafitinib at the same dose level. If diagnosis from ophthalmologic examination is keratitis or retinal abnormality such as central serous retinopathy (CSR)/ retinal pigment epithelial detachments (RPED), withhold erdafitinib until signs and symptoms have resolved. If toxicity is reversible (complete resolution or stabilization and asymptomatic) in 4 weeks according to ophthalmologic examination, resume erdafitinib at the next lower dose level after consultation with the sponsor's medical monitor. Retinal pigment epithelial detachment, if observed, should be monitored at approximately 2-3-week intervals until resolution. Monitor for recurrence every 1 to 2 weeks for a month and as clinically appropriate thereafter. If there is no recurrence, then re-escalation can be considered in consultation with the medical monitor.	Refer the subject for an ophthalmologic examination. For retinal pathology perform OCT as appropriate and consider referral to a retinal specialist for further evaluation. Follow specific treatment per the ophthalmologist's recommendation.
Grade 2: Moderate; minimal, local or noninvasive intervention indicated; limiting age appropriate instrumental ADL	Immediately withhold erdafitinib. If there is no evidence of drug-related corneal or retinal pathology on ophthalmologic examination, withhold erdafitinib until signs and symptoms have resolved. Resume erdafitinib therapy at the next lower dose level. If diagnosis from ophthalmologic examination is keratitis or retinal abnormality such as CSR/RPED, withhold erdafitinib until signs and symptoms have resolved, stabilized, or subject is lost to follow-up or withdraws consent (which ever happens first). If toxicity is reversible (complete resolution or stabilization and asymptomatic) within 4 weeks according to ophthalmologic examination, resume erdafitinib at the next lower dose level after consultation with the sponsor's medical monitor. Retinal pigment epithelial detachment, if observed, should be monitored at approximately 2-3-week intervals until resolution. Monitor for recurrence every 1 to 2 weeks for a month and as clinically appropriate thereafter. If there is no recurrence, then re-escalation can be considered in consultation with the medical monitor.	Refer subject to an ophthalmologist for evaluation with an ophthalmologic examination. For retinal pathology, perform OCT as appropriate and consider referral to a retinal specialist for further evaluation. Follow specific treatment per the ophthalmologist's recommendation.
Grade 3: Severe or medically significant but not immediate sight-threatening; hospitalization or prolongation of existing hospitalization indicated; disabling; limiting self-care ADL	If the toxicity is Grade 3, report as a serious adverse event and withhold erdafitinib. If the toxicity is Grade 3 and reversible (complete resolution or stabilization and asymptomatic) within 4 weeks and the subject is having clinical benefit, and the investigator and the sponsor's medical monitor agree that continuation of treatment is in the best interest of the subject, then erdafitinib may be resumed at 2 dose levels lower if appropriate. Retinal pigment epithelial detachment, if observed, should be monitored at approximately 2-3-week intervals until resolution. Monitor for recurrence using appropriate investigations every	Refer subject to an ophthalmologist for evaluation with an ophthalmologic examination. For retinal pathology, perform OCT as appropriate and consider referral to a retinal specialist for further evaluation. Follow specific treatment per the ophthalmologist's recommendation.

Table 11: Guidelines for Management of Eye Toxicity

Grade and Definition	Study Drug (Erdafitinib) Management	Symptom Management
	1 to 2 weeks for a month and as clinically appropriate thereafter. For cases of recurrence, consider permanent discontinuation.	
Grade 4: Sight-threatening consequences; urgent intervention indicated; blindness (20/200 or worse) in the affected eye	Permanently discontinue treatment with erdafitinib. Report as a serious adverse event and monitor resolution of the event until complete resolution, stabilization or the subject is lost to follow-up or withdraws consent (which ever happens first).	Promptly refer subject to an ophthalmologist for evaluation with an ophthalmologic examination. Follow specific treatment per the ophthalmologist's recommendation.

ADL=Activities of Daily Living, OCT= Optical Coherence Tomography

6.6.2.1.6. Guidelines for the Management of Dry Eye

- **General considerations:** Avoid unnecessary exposure to sunlight, use sunglasses in bright light.
- **Prophylactic management:** Frequent use of artificial tear substitutes and ocular demulcents is strongly recommended, ie, every 2 hours during time awake.
- **Reactive management**:
  - Withhold erdafitinib for Grade 3 toxicity
  - Artificial tear substitutes if not started, every 2 hours during time awake
  - Ocular demulcents
  - Severe treatment-related dry eye should be evaluated by an ophthalmologist

6.6.3. Investigator's Choice Dose Modification

Changes to intravesical gemcitabine or intravesical MMC/hyperthermic MMC dose or regimen for subjects in Cohort 1 assigned to receive Investigator's Choice (ie, additional doses of induction or maintenance) will be directed by local standard of care at the study site (see Section 6.1.2).

6.7. Access to Study Drug in the Long-term Extension Phase

The LTE Phase will allow continued access to study drug for subjects who continue to derive benefit from treatment, as determined by their investigator. Subjects may enter the LTE Phase following implementation of Amendment 6, provided they meet the criteria for entry specified in LTE Figure 1.

The continuation of study drug in the LTE Phase is limited as follows:

- Erdafitinib (Cohort 1, Cohort 2, Cohort 3): Provision of erdafitinib may continue for a maximum of 2 years in total (inclusive of administration in the Treatment Phase, Erdafitinib Crossover, and the LTE Phase, as applicable) or until the investigator decides it is in the best interest of the subject that erdafitinib be discontinued, whichever comes first.
- Investigator's choice of either intravesical gemcitabine or intravesical MMC/hyperthermic MMC (Cohort 1): provision of intravesical gemcitabine or intravesical MMC/hyperthermic MMC may continue per local standard of care.

No data will be collected in the eCRF during the LTE Phase, and only SAEs will be reported to the company safety repository. As an alternative to entering the LTE Phase, subjects receiving erdafitinib may exit the study and continue to receive treatment on any other post-trial access program, when permitted by local regulations. Detail regarding the LTE Phase (including a Schedule of Activities) is provided in Section 10.14, Appendix 14.

7. DISCONTINUATION OF STUDY DRUG/SUBJECT DISCONTINUATION/WITHDRAWAL/STUDY CLOSURE

7.1. Discontinuation of Study Drug

A subject's study drug must be discontinued if:

- The subject withdraws consent to receive study drug.
- The investigator believes that for safety reasons or tolerability reasons (eg, adverse event) it is in the best interest of the subject to discontinue study drug.
- The subject becomes pregnant; discontinuation of study drug in this instance should be discussed with the sponsor's medical monitor.
- High-risk recurrence (Cohort 1) or progression of disease (Cohort 1, Cohort 2 and Cohort 3) is assessed, except as described in Section 6.1.3.
- Subject reaches the maximum treatment duration as defined in Section 6.1.
- The sponsor closes the study.
  - The sponsor reserves the right to close the study or close the study site at any time for any reason at the sole discretion of the sponsor, e.g. in case of unacceptable risk, intolerable toxicity, or change in the risk/benefit profile; this might include recurrence of adverse events of which character, severity, or frequency is new in comparison to the existing risk profile. Also, data derived from other clinical trials or toxicology studies which negatively influence the risk/benefit assessment might cause discontinuation or termination of the study.

If a subject discontinues study drug for any reason before the end of the Treatment Phase, an EoT Visit should be performed. The primary reason for drug discontinuation will be clearly documented in the subject's medical record and recorded in the eCRF. Study drug assigned to the subject who discontinued study drug may not be assigned to another subject.

7.2. Subject Discontinuation/Withdrawal From the Study

A subject will be withdrawn from the study for any of the following reasons:

- Lost to follow-up
- Withdrawal of consent
- Death

When a subject withdraws before study completion, the reason for withdrawal is to be documented in the eCRF and in the source document. If the reason for withdrawal from the study is withdrawal of consent, then no additional assessments are allowed.

Withdrawal of Consent

A subject declining to return for scheduled visits does not necessarily constitute withdrawal of consent. Alternate follow-up mechanisms that the subject agreed to when signing the consent form apply as local regulations permit.

7.2.1. Withdrawal From the Future Use of Research Samples

The subject may withdraw consent for use of samples for future research. In such a case, samples will be destroyed after they are no longer needed for the clinical study. Details of the sample retention for research are presented in the ICF.

7.3. Lost to Follow-up

A subject 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. A subject cannot be deemed lost to follow-up until all reasonable efforts made by the study-site personnel to contact the subject are deemed futile. The following actions must be taken if a subject fails to return to the study site for a required study visit:

- The study-site personnel must attempt to contact the subject to reschedule the missed visit as soon as possible, to counsel the subject on the importance of maintaining the assigned visit schedule, to ascertain whether the subject wishes to or should continue in the study.
- Before a subject is deemed lost to follow-up, the investigator or designee must make every reasonable effort to regain contact with the subject (where possible, 3 telephone calls, e-mails, fax, and, if necessary, a certified letter to the subject's last known mailing address, or local equivalent methods). Locator agencies may also be used as local regulations permit. These contact attempts should be documented in the subject's medical records.
- Should the subject continue to be unreachable, they will be considered to have withdrawn from the study.

Should a study site close, eg, for operational, financial, or other reasons, and the investigator cannot reach the subject to inform them, their contact information will be transferred to another study site.

8. STUDY ASSESSMENTS AND PROCEDURES

The study comprises molecular eligibility, screening, treatment, follow-up, and LTE phases. The frequency and timing of assessments and procedures to be performed are outlined in the Schedule of Activities (Section 1.3) and further discussed within this section.

All PRO assessments should be conducted and completed before any other tests, procedures, or consultations to prevent influencing subject perceptions. Note: PRO assessment/data collection is no longer required for all subjects in all phases.

Assessments and procedures should be completed on the day indicated (± window indicated); if this is not possible because of a weekend, holiday, or emergency, the assessment or procedure should be completed within 48 hours of the scheduled day.

The amount of blood drawn from each subject in this study will be approximately 24 mL during screening; 241 mL from C1D1 through Cycle 6; 288 mL from Cycle 6 through Cycle 24; 37 mL at the EoT Visit; 12 mL during the safety follow-up; and 80 mL for subjects who have disease assessments after recurrence/progression during the Follow-up Phase, for a total volume of 682 mL. Repeat or unscheduled samples may be taken for safety reasons. Serum or urine pregnancy tests should be performed for women of childbearing potential, 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. The calculated volume of blood is an estimate; the actual amount may vary depending on local laboratory standard procedures, a subject's visit schedule, and childbearing potential.

The actual dates and times of sample collection must be recorded in the source document and laboratory requisition form. Instructions for the collection, handling, storage, and shipment of samples are found in the Laboratory Manual that will be provided. Collection, handling, storage, and shipment of samples must be under the specified, and where applicable, controlled temperature conditions as indicated in the Laboratory Manual.

8.1. Study Procedures

8.1.1. Screening

Screening will consist of a Molecular Eligibility Screening Phase and a Full-study Screening Phase. Also, subjects being considered for the study before the TURBT, will provide a voided urine sample after disease recurrence and before TURBT. These subjects must sign the ICF for Assay Development prior to collection of this urine sample.

8.1.1.1. Molecular Eligibility Screening Phase (Cohort 1 and Cohort 2)

Molecular eligibility can be established either by central laboratory testing or local testing. Consent for molecular eligibility screening (but not full-study screening) may be performed remotely including consent by telephone or video consultation, unless not permitted according to local guidance.

The molecular eligibility informed consent process may occur in 1 of 3 ways:

- If archived tissue is available, the Molecular Eligibility ICF is signed.
- If a new tissue biopsy is required, the Main-study ICF is signed.
- If a historical report (local testing) is available indicating the subject is molecularly eligible for the study, the Molecular Eligibility Requirement is determined complete and the subject will sign the Main-study ICF.

  If tissue is insufficient at the first molecular eligibility assessment, another tissue sample may be submitted to the central laboratory (this is not considered rescreening).
- During the Molecular Eligibility Screening Phase, tissue from 2 different times points may be used to determine eligibility for this study, ie, pre-BCG Tissue specimen (tumor tissue collected before subject receives BCG treatment for NMIBC) or post-BCG Tissue specimen (tumor tissue collected from recurrence after BCG treatment) (see Figure 2):

Pre-BCG Tissue Molecular Screening

1) Archival tissue sample will be sent to the central laboratory for testing if the subjects meet both of the following criteria:

   a) Have had prior history of high or intermediate risk NMIBC

   b) Have completed a minimum of initial BCG induction (at least 5 of 6 full doses of an initial induction).

   The central laboratory will evaluate subjects for molecular eligibility by analyzing specimens for the presence of FGFR mutations and gene fusions. The sponsor or central laboratory/designee will communicate results of the molecular eligibility testing to the site. If the subject is deemed molecularly eligible for the study, the subject will be followed at the site with routine standard of care. If the subject has a recurrent high risk NMIBC within 12 months of last dose of BCG, then the subject may sign the Main-study ICF. If the subject does not have a recurrent high risk NMIBC at less than 12 months of last dose of BCG, then the subject is molecularly ineligible for the study and is considered a molecular screen failure.

2) Subject with a historical report (local testing) indicating the subject is molecularly eligible for the study will be determined to have completed Molecular Eligibility Requirement. If the subject has a recurrent high risk NMIBC within 12 months of last dose of BCG, then subjects may sign the Main-study ICF.

Post-BCG Tissue Molecular Screening

1) Subjects with archival post-BCG tissue specimen with recurrent high risk NMIBC within 12 months of last dose of BCG will have a specimen sent to the central laboratory for testing. The central laboratory will evaluate molecular eligibility by analyzing specimens for the presence of FGFR mutations and gene fusions. The sponsor or central laboratory/designee will communicate results of the molecular eligibility testing to the site. If a subject is deemed molecularly eligible for the study, then the subject may sign the Main-study ICF.

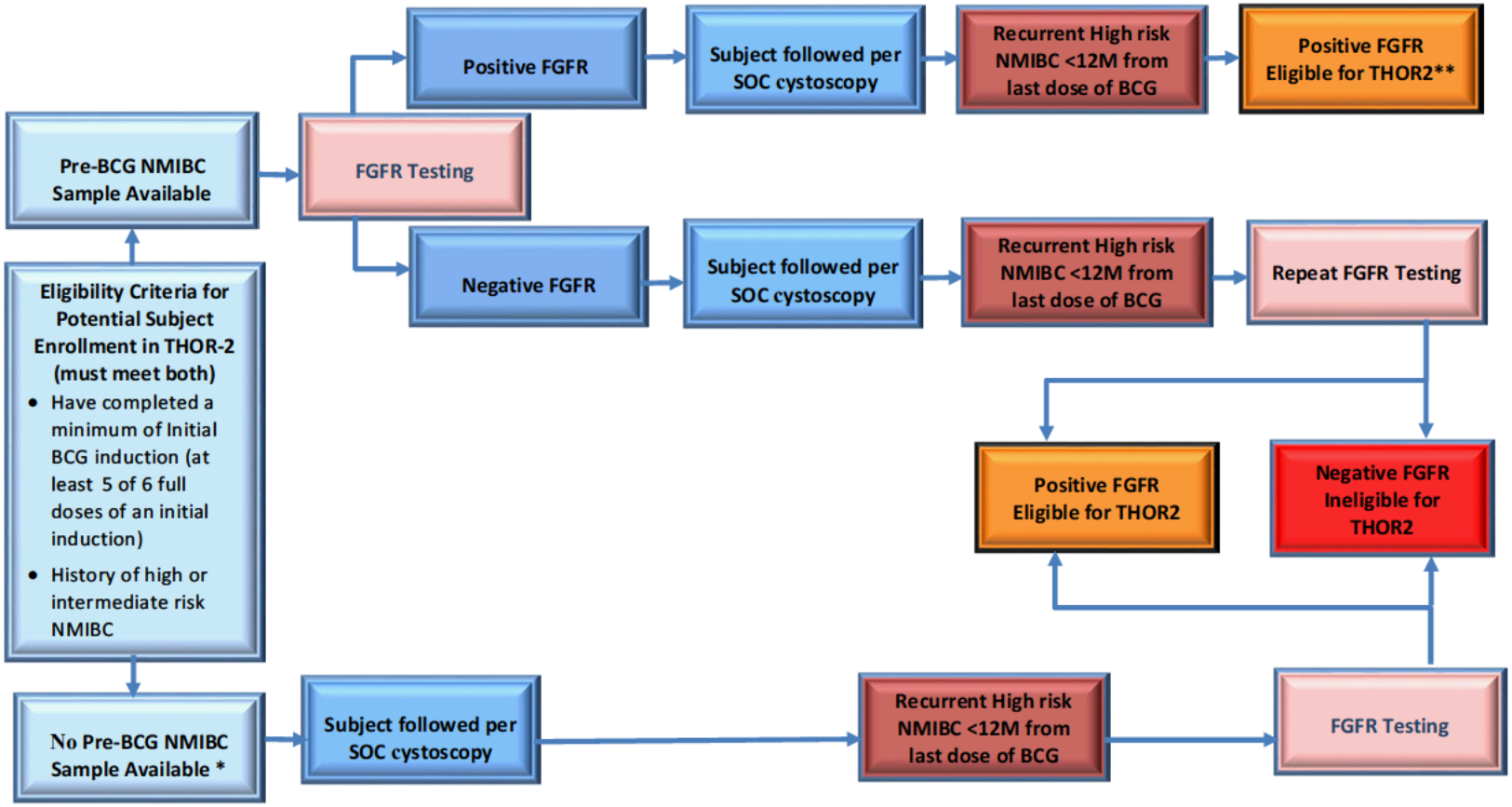
2) Subjects with recurrent high risk NMIBC within 12 months of last dose of BCG and a historical report (local testing) indicating the subject is molecularly eligible for the study will be determined to have completed Molecular Eligibility Requirement. These subjects may sign the Main-study ICF.

   For subjects with both pre-BCG and post-BCG tissue specimen available, the site pathologist will determine best tissue for molecular testing. Additional tissue may be requested if a specimen is not adequate for testing. If FGFR status is known from a locally tested NGS/PCR assay, a subject will need to sign the Main-study ICF in order for tissue to be submitted to the central laboratory for retrospective molecular eligibility confirmation.

Eligibility must be determined before randomization (Cohort 1) or the first dose of study drug (Cohort 2 and Cohort 3). See Section 5.1, inclusion criteria for requirements regarding FGFR mutations or fusions. For subjects in Cohort 2 with concurrent papillary disease, molecular

eligibility can be determined from either the CIS specimen or the papillary lesion. Figure 2 provides an overview of testing for molecular eligibility.

Figure 2: Study 42756493BLC2003 (THOR2) Tissue Testing Paradigm



*Subjects without any pre-BCG sample available, please submit post-BCG sample
**Tissue for repeat FGFR testing for concurrence if available
Key: BCG=bacillus Calmette-Guérin, FGFR=fibroblast growth factor receptor, M=months, NMIBC= non-muscle-invasive bladder cancer, SOC=standard of care.

Subjects enrolling in the study based on Molecular eligibility from pre-BCG tissue specimen and post-BCG local NGS/PCR testing must also submit the post-BCG tissue specimen tissue for central confirmation of Molecular eligibility status. The results of this retrospective central confirmation do not affect the subject's eligibility for the study. Results of retrospective testing will not be communicated to the site. Please refer to the Laboratory Manual for instructions.

In countries/territories where the ANNAR protocol pre-screening has received approval to be implemented, as required by health authorities or ethics, subjects may be identified for this study by participation in the ANNAR pre-screening protocol (Study 42756493BLC0002), during which subjects with urothelial carcinoma undergo molecular eligibility testing. Those subjects who test positive for the select FGFR mutations or fusions required for this study, will sign the Main-study ICF and proceed to the Screening Phase. Tissue for central confirmation of FGFR status is not submitted for these subjects as this step was completed as part of the ANNAR pre-screening protocol.

8.1.1.2. Cohort 3 Molecular Eligibility

Additional provisions have been put in place to limit the possibility that subjects will be enrolled into Cohort 3 without meeting molecular eligibility criteria.

1) It is anticipated that investigators will identify subjects with low-grade /intermediate-risk, multi-focal papillary-only disease for possible enrollment into Cohort 3.
2) Identified subjects will sign the Molecular Eligibility ICF to determine FGFR status from archived tissue sample, if available.
3) Subjects whose archived tissue sample meets the Molecular Eligibility Requirement will sign the Main-study ICF before the next planned TURBT and before any study-specific procedures take place once routine surveillance cystoscopy shows multi-focal papillary only recurrence (see Section 1.3). Eligibility criteria will be assessed prior to the TURBT, so that a marker lesion can be left behind after resection of other papillary lesions as appropriate. Submit tissue from on-study TURBT for central confirmation of FGFR status. The results of this retrospective central confirmation do not affect the subject's eligibility for the study. Also, results of retrospective confirmation studies will not be communicated to the site.
4) Subjects identified by the investigator but without archived tissue samples available for molecular eligibility testing will sign the Main Study ICF before any study-specific procedure takes place once routine surveillance cystoscopy shows multi-focal papillary-only recurrence (see Section 1.3). Before the TURBT is performed, the site will assess that the subject will meet the other inclusion and exclusion criteria prior to leaving behind a marker lesion. Molecular eligibility testing will be performed on recurrent papillary disease tissue collected during the on-study TURBT. Subjects who fail the Molecular Eligibility Requirement at the time of recurrence, will have the marker lesion resected.

8.1.1.3. Full-study Screening Phase

During the Full-study Screening Phase all subjects who have qualifying FGFR mutations or fusions, as determined during the Molecular Eligibility Phase, will consent to the main study by signing the Main-study ICF. The Full-study Screening Phase includes the interval between signing the Main-study ICF and the day the subject is randomized (Cohort 1) or receives the first dose of

study drug (Cohort 2 and Cohort 3). The Full-study Screening Phase should not exceed 35 days. Assessments that are required to demonstrate eligibility may be performed over the course of 1 or more days during the screening process. Molecular screening must start within 12 weeks after the last TURBT done for high risk recurrence if molecular testing is being done on post-BCG specimen.

The first HRQoL assessments will occur during the Screening Phase using the following PRO measures: PGIS, EORTC QLQ-C30, EORTC QLQ-NMIBC24, and EQ-5D-5L. Assessment of PGIC will only occur during the Treatment Phase. The PRO measures will be electronically (ePRO) collected, according to the Schedule of Activities (Section 1.3), to understand change over time (all cohorts) and difference between treatment groups (Cohort 1). Patient-reported outcome questionnaires should be completed before any other assessments at each clinic visit. Subjects should be provided a private, quiet area to complete the questionnaires. The study site staff should instruct the subject to carefully read the instructions and questions of the PRO instrument before marking responses, that there are no right or wrong answers, and that their responses to the questionnaire will not be used to determine their study eligibility. If a subject cannot read for any reason, it is acceptable for the subject to have the questions read and responses marked on the ePRO by an independent witness. Note: PRO assessment/data collection is no longer required for all subjects in all phases.

Procedures conducted, before signing the Main-study ICF, as part of the subject's routine clinical management (eg, blood count, disease assessment) may be used for screening or baseline purposes provided the procedure meets the protocol-defined criteria and has been performed within 35 days prior to dosing (see Section 1.3). All information associated with eligibility requirements must be entered onto the appropriate eCRF. Requirements for biopsy specimens for histologic assessment at screening are provided in Section 8.2.1. The subject's previous anticancer therapies and TURBT details, the dose and timing of administrations, and the subject's responses to each therapy will be collected and recorded in source documents and the eCRF.

Results from the screening evaluations will be reviewed to confirm subject eligibility before enrollment. Tests with results that fail eligibility requirements may be repeated once during screening if the investigator believes that the results suspected to be due to test error or that the underlying issue has been resolved. For screening assessments that are repeated, the most recent available results before initiation of study drug will be used to determine subject eligibility.

8.1.2. Treatment Phase

The Treatment Phase will begin on Cycle 1 Day 1 following randomization or enrollment into the study. Subjects may be randomized up to 1 day before C1D1 but no later than C1D1 predose. With the exceptions noted below for Cohort 2 and Cohort 3, treatment may continue until the subject has high risk disease recurrence or progression, intolerable toxicity, withdraws consent, there is a decision by the investigator to discontinue treatment, or the study is closed, whichever occurs first. For subjects receiving erdafitinib, treatment may continue for a maximum of 2 years.

- For Cohort 2, erdafitinib must be discontinued if CR is not observed within 3 months.

- For Cohort 3, after 3 months of study treatment: 1) Subjects with stable disease or progression of the marker lesion must discontinue erdafitinib and a TURBT of the marker lesion must be performed. 2) Subjects with CR may continue erdafitinib. 3) Subjects with PR may, at the investigator's discretion, either continue treatment with erdafitinib or discontinue erdafitinib and undergo TURBT of the marker lesion.

For Cohort 1 and Cohort 2, during the Treatment Phase, subjects who demonstrate a positive urine cytology with a negative cystoscopy will remain on study drug until the next disease assessment. If both the urine cytology and cystoscopy are positive for high-risk recurrence (high-grade Ta, T1 or CIS) or progression at the next disease assessment, the subject will discontinue study drug.

For subjects randomized to Investigator's Choice, refer to Section 6.1.2 for study drug administration.

Adverse events occurring any time after the subject signs the Main-study ICF until 30 days after the last dose of study drug in the Treatment Phase are to be recorded for all subjects. With the exception of hyperphosphatemia (see Table 3), adverse event information will be graded using the National Cancer Institute Common Terminology Criteria for Adverse Events (NCI-CTCAE), Version 5.0. See Section 10.3 for complete details on adverse event reporting. Concomitant medications will also be recorded following the discontinuation of treatment until 30 days after last dose of study drug in the Treatment Phase.

Throughout the Treatment Phase, the investigator will assess response to study drug using findings from cystoscopy, bladder mapping, urine cytology, and CT/MRI urogram. Biopsy of visible lesions will be performed during cystoscopy or TURBT. Tissue slides/blocks from subjects in Cohort 1 with any locally confirmed recurrence or progression will be sent for central histopathologic review. In addition, tissue from any positive biopsy (any grade of recurrence or bladder mapping) should be sent to central laboratory for exploratory biomarker analysis (all cohorts). For subjects receiving erdafitinib only, tissue from all biopsies performed (normal and abnormal) will be sent to central laboratory for determination of erdafitinib level. On Cycle 1 Day 14, the first approximately 20 subjects receiving erdafitinib (from any cohort) will have 24-hour urine PK samples collected. Efficacy assessments are described further in Section 8.2. For subjects who discontinue study drug without documented disease recurrence or progression, every effort should be made to continue monitoring their disease status according to the disease assessment schedule, until (1) the start of new anticancer treatment, (2) high risk disease recurrence or progression, (3) withdrawal of consent, (4) death, or (5) 18 months have elapsed since the first dose of study treatment (ie, Cycle 1 Day 1), whichever occurs first.

End-of-Treatment Visit

An EoT Visit will be performed within 7 days after a subject's permanent discontinuation of erdafitinib or Investigator's Choice, either at the end of the Treatment Phase or for any other reason before then. If the EoT Visit coincides with a regular study visit, the EoT evaluations will be conducted in lieu of the regular visit assessments, and the data will be entered into the EoT Visit in the eCRF. The subject should be encouraged to return for the Safety Follow-up Visit.

Subjects who have an EoT Visit following treatment with Investigators Choice and then cross over to treatment with erdafitinib will have an EoT Visit performed when erdafitinib is stopped (See Section 10.10).

8.1.3. Follow-up Phase

8.1.3.1. Safety Follow-up

The safety follow-up period is the interval between the EoT Visit and 30 days (+7 days) after the last dose of study drug. Reasonable efforts should be made to have the subject return for the Safety Follow-up Visit, to be scheduled 30 to 37 days after the EoT Visit (or after the last dose of treatment if the EoT Visit was not performed), and to report any adverse events and new concomitant medications that occur during that time. Adverse events and serious adverse events must be reported up until at least 30 days (+7 days) after the last dose of study drug, the date of the Safety Follow-up Visit, or until toxicities resolve, return to baseline, or are deemed irreversible, whichever is longer. If a subject begins new anticancer therapy, the adverse event reporting period for non-serious adverse events ends at the time the new treatment started.

8.1.3.2. Long-term Follow-up

Required follow-up for subjects in Disease Assessment Follow-up and Survival Follow-up at the time of Amendment 6 implementation is described in Section 10.14 (Appendix 14).

8.1.3.2.1. Disease Assessment Follow-up

For subjects who discontinue study drug without documented disease recurrence or progression, every effort should be made to continue monitoring their disease status according to the disease assessment schedule and continue to perform other assessments during this period (see Section 1.3) until (1) the start of new anticancer treatment, (2) high risk disease recurrence or progression, (3) withdrawal of consent, (4) death, or (5) 18 months have elapsed since the first dose of study treatment (ie, Cycle 1 Day 1), whichever occurs first. The results of the disease assessments will be documented in the eCRF. At the time of recurrence or progression, tissue sampling will be sent to the central laboratory for blinded independent central review (BICR).

8.1.3.2.2. Survival Follow-up

Once a subject has confirmed disease recurrence or progression or starts a new anticancer therapy, he or she will begin the follow-up for survival status for a maximum of 2 years. New anticancer therapy will be collected in the eCRF. The subject will be contacted by telephone or email, or the subject will visit the study site, at least every 12 weeks (±2 weeks) from the confirmed date of disease recurrence or progression or start of new anticancer therapy to assess for survival status until death, withdrawal of consent, or study discontinuation following Amendment 6 implementation, whichever occurs first. The results of standard-of-care follow-up cystoscopy will also be collected during this period.

8.1.4. Unscheduled Visits

Clinic visits or diagnostic laboratory visits not prescribed in the protocol may be performed at any time as clinically indicated. Results of assessments performed at these visits will be entered as "unscheduled" visit in the eCRF. The sponsor may also request that an additional visit be performed, if needed, based on emerging safety data.

8.1.5. Long-term Extension Phase

The LTE Phase will allow continued access to study drug for subjects who continue to derive benefit from treatment, as determined by their investigator. Subjects may enter the LTE Phase following implementation of Amendment 6, provided they meet the criteria for entry specified in LTE Figure 1. Limits for continuation of study drug in this phase are described in Section 6.7. No data will be collected in the eCRF during the LTE Phase, and only SAEs will be reported to the company safety repository. As an alternative to entering the LTE Phase, subjects receiving erdafitinib may exit the study and continue to receive treatment on any other post-trial access program, when permitted by local regulations. Detail regarding the LTE Phase (including a Schedule of Activities) is provided in Section 10.14, Appendix 14.

8.2. Efficacy Assessments

8.2.1. Disease Assessments

8.2.1.1. Cohort 1

Cohort 1, papillary tumors only, subjects with T1 disease must undergo TURBT of the base of the lesion (the biopsy should contain muscle fibers) before study entry (baseline) to ensure the absence of muscle-invasive disease and to determine histopathology staging at the time the subject was deemed to have recurred after BCG therapy. If there are no muscle fibers in the biopsy, subjects must undergo re-TURBT before randomization.

8.2.1.2. Cohort 2

Cohort 2, CIS, is not expected to be completely excised at baseline, but concurrent papillary disease must be completely excised before enrollment and documented at baseline cystoscopy. Urine cytology is not expected to be negative for malignant cells.

8.2.1.3. Cohort 3

Cohort 3, marker lesion, must have recurrent intermediate-risk disease with all previous tumors being low grade (G1-G2) Ta or T1 and no previous CIS at baseline. Additionally, subjects must have a risk of progression less than 5% in the next 2 years and a risk of recurrence greater than 50%, calculated using the EORTC risk calculator.[19] All tumors must be removed except for a single untouched 5 to 10 mm lesion (marker lesion).

Cohort 3 will perform a urine cytology during bladder washing or from a voided urine specimen (bladder wash specimen is preferred) at time of CR only. Subjects in Cohort 3 with PR or CR within 3 months after start of treatment may continue erdafitinib for up to 2 years until progression, intolerable toxicity, withdrawal of consent, there is a decision by the investigator to discontinue

treatment, or the study is closed, whichever occurs first. Subjects with stable disease or disease progression must undergo TURBT of the marker lesion and discontinue erdafitinib. Subjects with PR may, at the investigator's discretion, either continue treatment with erdafitinib, or discontinue erdafitinib and undergo TURBT of the marker lesion.

8.2.1.4. Histopathologic Assessment and FGFR (All Cohorts)

For all cohorts, the histopathology assessment will be performed per local standard practice, and subjects may be enrolled based on local histopathology results If a subject has a positive local result of FGFR status either by NGS or by PCR, the subject may be enrolled in the Main Study based on those results. Otherwise, a subject must wait for central FGFR results from the central laboratory to meet molecular eligibility criteria. For subjects in Cohort 1, after a positive FGFR status is known, tissue slides/blocks from the post-BCG specimen may be submitted to the central laboratory for central histopathologic review. A detailed outline for collection, handling, and evaluation of bladder tissue and interpretation of biopsy specimens will be provided in the Laboratory Manual. Blinded independent central histopathological review (BICR) will not have any bearing on enrollment status of the subject. If the central histopathological assessment reveals T2 or higher disease, the results will be communicated by the medical monitor to the principal investigator.

During the Treatment Phase and Follow-up Phase, tissue slides/blocks from subjects in Cohort 1 with any locally confirmed recurrence or progression will be sent for BICR.

8.2.1.5. Cystoscopy, Urine Cytology, Bladder Mapping, and CT/MRI Urogram

Cystoscopy (Cohort 1 and Cohort 2) will be performed as indicated in the Schedule of Activities to assess disease response. Whenever possible, the same individual should perform cystoscopy throughout the study for a given subject. For subjects in Cohort 1 and Cohort 2, cystoscopy will be done at screening, at C3D1, then every 12 weeks (±1 week) for up to 2 years of treatment or until high risk disease recurrence or progression. After treatment has stopped, cystoscopies will be performed every 24 weeks (every 6 months) (±2 weeks) for an additional 2 years or until high risk disease recurrence /progression. Note that if a TURBT was done within 6 weeks before randomization, then the findings of the complete resection from TURBT can be used instead of a screening cystoscopy.

Cystoscopy (Cohort 3) will be done at screening, and then at C2D1, C3D1, and C4D1 (±1 week) or until CR, whichever occurs first. After a subject experiences CR, cystoscopy will be performed every 12 weeks (±1 week) for up to 2 years of treatment or until disease recurrence or progression. After treatment has stopped, cystoscopies will be performed every 24 weeks (every 6 months) (±2 weeks) for an additional 2 years or until disease recurrence/progression. If the subject experiences stable disease or progression of the marker lesion, study drug will be discontinued, an EoT Visit will be conducted, and the subject will undergo TURBT of the marker lesion. Subjects with PR after 3 months of treatment may, at the investigator's discretion, either continue treatment with erdafitinib or discontinue erdafitinib and undergo TURBT of the marker lesion. Subjects with PR who continue treatment with erdafitinib will have cystoscopy and other study assessments performed, as specified in the Schedule of Activities (Section 1.3).

Urine for cytology will be collected from bladder washing or from a voided urine specimen (bladder wash specimen is preferred) during cystoscopy for local assessment for subjects in Cohort 1 and Cohort 2. Urine cytology results for subjects being screened for Cohort 1 must be negative for high-grade urothelial carcinoma before randomization; for Cohort 2, urine cytology does not have to be negative at screening. Urine for cytology will be collected from bladder washing or from a voided urine specimen (bladder wash specimen is preferred) for local assessment for Cohort 3 at the time of CR only.

Bladder mapping will include biopsies of any suspicious mucosal area (if noted); otherwise, biopsies should be taken from normal looking mucosa. Samples must be taken from each of the following regions: 1) dome, 2) anterior wall, 3) right lateral wall, 4) left lateral wall, 5) posterior wall, and 6) bladder neck/trigone (See Section 10.11). For Cohort 1 subjects bladder mapping at screening will be only done if there is prior history of CIS. Furthermore, during treatment or follow-up phase repeat bladder mapping will only be done if urine cytology is positive for malignant cells and cystoscopy is negative. In Cohort 2, all subjects will have bladder mapping at screening and at Cycle 12. No bladder mapping will be done for subjects in Cohort 3. Biopsy samples collected during bladder mapping will be evaluated by the local histopathology laboratory.

Computed tomography/MRI urograms (contrast enhanced) or retrograde pyelograms (if applicable) will be performed to evaluate subjects for the presence of locally advanced disease to the upper urinary tract or prostatic urethra. If a subject cannot tolerate intravenous contrast, a retrograde pyelogram is acceptable. All scheduled CT/MRI urograms will be performed as indicated in the Schedule of Activities (Section 1.3). CT/MRI urograms should be evaluated by the same individual throughout the study to limit inter-reviewer variability.

Additionally, unscheduled cystoscopy or CT/MRI urograms may be performed if clinically indicated. Other diagnostic modalities should not be used exclusively to assess disease status in the absence of cystoscopy or CT/MRI urogram confirmation. Identical methodology should be used for disease assessment at baseline and throughout the course of the study.

Local histopathologic findings will be used for the following assessments of recurrence, progression, and disease response.

Recurrence is defined as follows:

- Histologically proven first appearance of high-grade Ta or T1 lesion bladder cancer in patients with papillary disease only.

Complete response for Cohort 2 is defined as at least one of the following:

- Negative cystoscopy and negative (including atypical) urine cytology
- Positive cystoscopy with biopsy-proven benign or low-grade NMIBC and negative cytology

Complete response for Cohort 3 is defined as the following:

- Complete disappearance of the marker lesion without any new lesions; and if any remnant of the marker lesion, no viable tumor seen on histopathological examination.
- Negative urine cytology

Partial response for Cohort 3 is defined as the following:

- Marker Lesion reduction by 50% [35]

For subjects in Cohort 1 and Cohort 2, a new low-risk/low-grade papillary lesion may be resected by TURBT if deemed appropriate by investigator. A new low-risk/low-grade papillary lesion does not constitute recurrence. Subjects with a positive urine cytology (not atypical cells) but with negative cystoscopy will continue treatment until next scheduled evaluation in 12 weeks. Tissue slides/blocks from subjects in Cohort 1 with any locally confirmed recurrence or progression will be sent for central histopathologic review.

However, tissue from any positive biopsy (any grade of recurrence) should be sent to the central laboratory for exploratory biomarker analysis (all cohorts) and determination of erdafitinib level (subjects receiving erdafitinib only). Refer to the Laboratory Manual for instruction on sample handling.

8.2.2. Patient-Reported Outcomes

Note: PRO assessment/data collection is no longer required for all subjects in all phases.

The PGIS and PGIC are single-item questionnaires to evaluate a patient's global impression of severity and global impression of change of cancer, respectively.

The EORTC QLQ-C30 is a core questionnaire for evaluating the HRQoL of patients participating in cancer clinical studies. It is a 30-item questionnaire with 9 multi-item subscales and 6 single items. It incorporates 5 functional scales (physical, role, cognitive, emotional, and social functioning), 3 symptom scales (fatigue, pain, and nausea or vomiting), and a global health status or HRQoL scale. The single items assess dyspnea, appetite loss, sleep disturbance, constipation, diarrhea, and perceived financial impact of disease and treatment. Ratings for each item range from 1 (not at all) to 4 (very much). The QLQ-C30 is designed to be used across cancer populations and takes about 11 minutes to complete.

The EORTC QLQ-NMIBC24 is a 24-item questionnaire for evaluating the HRQoL of patients with superficial (non-muscle-invasive) bladder cancer. The questionnaire is designed to supplement the QLQ-C30 and incorporates 6 multi-item scales and 5 single items. Ratings for each item range from 1 (not at all) to 4 (very much). The scales cover urinary symptoms, malaise, worries about the future, bloating and flatulence, sexual function, and male sexual problems. The single items assess intravesical treatment issues, sexual intimacy, sexual enjoyment, risk of contaminating partner, and female sexual problems. The EORTC QLQ-NMIBC24 takes about 8 minutes to complete.

EQ-5D-5L is a standardized measure of health status developed by the EuroQol Group to provide a simple, generic measure of health for clinical and economic appraisal. The EQ-5D-5L descriptive system comprises the following 5 dimensions: mobility, selfcare, usual activities, pain/discomfort, and anxiety/depression, as well as the EQ Visual Analogue Scale (EQ VAS). The EQ-5D-5L can be completed in under 5 minutes.

8.3. Safety Assessments

Safety assessments will be based on medical review of adverse event reports and the results of vital sign measurements, 12-lead ECG, physical examinations, clinical laboratory tests, ophthalmologic examinations, and other safety evaluations at specified time points as described in the Schedule of Activities.

Any clinically significant abnormalities or toxicities persisting at the time of study discontinuation or transition to the LTE Phase will be followed by the investigator until resolution or until reaching a clinically stable endpoint. For adverse events such as skin/nail and mucosal toxicity, upon subject consent, photographs may be taken for assessment and monitoring of the toxicity.

Details regarding the IDMC are provided in Committees Structure in Section 10.2, Regulatory, Ethical, and Study Oversight Considerations. Due to the company decision to terminate study enrollment and considering the recent IDMC review (6 July 2022) found the safety of erdafitinib in this study to be consistent with the known safety profile of erdafitinib, no further monitoring by the IDMC will be conducted.

8.3.1. Physical Examinations

A full physical examination, including height and weight, will be performed at screening. Subjects should have a repeated physical examination at Cycle 1 Day 1 before dosing if the previous physical examination during screening occurred more than 14 days previously. Targeted physical examinations, including involved organs of the disease state, will be performed at subsequent visits as listed in the Schedule of Activities (Section 1.3). Height and weight measurements are not required after screening. The investigator must review physical examination results and record any clinically relevant changes occurring during the study in the adverse event section of the eCRF.

8.3.2. Vital Signs

Vital signs will be assessed per the Schedule of Activities (Section 1.3). Blood pressure (systolic and diastolic), heart rate, and temperature will be assessed. The investigator must review vital signs results and record any clinically relevant changes occurring during the study in the adverse event section of the eCRF.

8.3.3. Electrocardiograms

12-lead electrocardiograms will be performed as specified in the Schedule of Activities (Section 1.3). Additional ECGs may be performed as clinically indicated. During the Treatment Phase, ECGs should be performed before study drug is taken for the day. The subject should rest in a supine position for at least 5 minutes before ECG recording and should refrain from talking or moving arms or legs. The 12-lead ECG recorder device used should have been recently serviced

and calibrated. The following intervals should be measured: PR, QRS, QT, QTcF (Fridericia), RR. QTcF (Fridericia) will be used for assessment of QTc interval. It is recommended that all ECGs be performed at approximately the same time each day to minimize circadian variation in QT interval. The investigator will comment on the clinical relevance and document this in the eCRF (along with details of clinically significant findings).

8.3.4. Clinical Safety Laboratory Assessments

Blood samples for serum chemistry and hematology will be collected for all subjects as indicated in the Schedule of Activities (Section 1.3). Subjects receiving erdafitinib will have additional assessments of phosphate and parathyroid hormone as described separately in the Schedule of Activities. More frequent clinical laboratory tests may be performed, as indicated by the overall clinical condition of the subject and for abnormalities that warrant more frequent monitoring. The investigator must review the laboratory results, document this review, and record any clinically relevant changes occurring during the study in the adverse event section of the eCRF.

Laboratory test results completed on Cycle 1 Day 1 (except parathyroid hormone and 1,25-dihydroxyvitamin D) should be reviewed prior to dosing, and subjects should continue to meet eligibility requirements per the inclusion/exclusion criteria.

The following tests will be performed by the local laboratory:

Hematology Panel (All subjects)

-hemoglobin
-platelet count
-white blood cell count
-absolute neutrophil count

Comprehensive Metabolic Panel (All subjects)

-alanine aminotransferase (ALT)
-aspartate aminotransferase (AST)
-total bilirubin
-creatinine
-sodium
-magnesium
-calcium
- potassium
- albumin
- bicarbonate (if feasible)
- alkaline phosphatase

1,25-dihydroxyvitamin D (All subjects)

Parathyroid Hormone: All subjects at screening and only subjects receiving erdafitinib from C1D1.

Phosphate: All subjects at screening and only subjects receiving erdafitinib from C1D1.

8.3.5. Ophthalmologic Examination

All subjects must have an ophthalmologic examination performed regardless of symptoms during the Screening Phase and during the Treatment Phase as specified in the Schedule of Activities (Section 1.3). Ophthalmologic assessment must include visual acuity, fundoscopy (examination of both central and peripheral zones should be performed), slit lamp biomicroscopy, and Optical Coherence Tomography (OCT). The Amsler grid test will also be administered by the treating

study physician or nurse at screening and other timepoints, as indicated in the Schedule of Activities (Section 1.3). Any additional follow-up examination may be performed by the ophthalmologist as clinically necessary based on the findings of the Amsler grid tests and clinical assessment. A repeat OCT scan may be done in case of quality issue.

When central serous retinopathy (CSR)/retinal pigment epithelial detachment is suspected, or fundoscopic retinal abnormalities are observed, as well as each time ocular adverse events lead to the subject being referred to an ophthalmologist, an OCT should be performed. Fluorescein angiography could be considered appropriate in conditions such as suspected retinal vein occlusion. In subjects with suspected retinal pathology such as CSR or retinal vein occlusion, a consultation with a retina specialist should be considered.

Data from all fluorescein angiograms, retinal photographs, and all OCT scans should be added to the subject's case report form. All images of the OCT scan, photographs, and/or fluorescein angiograms must be stored in the subject's records and a redacted copy sent to the sponsor-selected central vendor for possible future independent assessment. Additionally, when OCT is abnormal, any retinal imaging or angiographic studies conducted must also be stored in the subject's records and a redacted copy sent to the sponsor-selected central vendor for possible future independent assessment. Note: sending redacted copies to the sponsor-selected central vendor is no longer required.

Amsler Grid Testing

Amsler grid (Section 10.8) testing will be administered to all subjects according to the Schedule of Activities (Section 1.3). Additional assessments should be performed as clinically indicated. Observation of wavy, broken or distorted lines, or a blurred/missing area of vision is equivalent to a positive Amsler grid test. For any positive Amsler grid test, subject should be referred for full ophthalmologic examination within 7 days.

8.3.6. Pregnancy Testing: Urine or Serum β-hCG

Urine or serum samples will be obtained for β-hCG pregnancy testing in female subjects of child bearing potential at time points indicated in the Schedule of Activities (Section 1.3). Pregnancy tests will be performed to establish the absence of pregnancy at any time during the subject's participation in the study.

8.3.7. ECOG Performance Status

Eastern Cooperative Oncology Group performance status grade will be determined as part of screening evaluations. The scoring information is provided in Section 10.5.

8.4. Adverse Events and Serious Adverse Events

Timely, accurate, and complete reporting and analysis of safety information from clinical studies are crucial for the protection of subjects, investigators, and the sponsor, and are mandated by regulatory agencies worldwide. The sponsor has established Standard Operating Procedures in conformity with regulatory requirements worldwide to ensure appropriate reporting of safety

information; all clinical studies conducted by the sponsor or its affiliates will be conducted in accordance with those procedures.

Adverse events will be reported by the subject (or, when appropriate, by a caregiver, surrogate, or the subject's legally acceptable representative) for the duration of the study. During the LTE Phase, only SAEs will be reported to the company safety repository (see Section 10.14, Appendix 14).

For further details on adverse events and serious adverse events (Definitions and Classifications; Attribution Definitions; Severity Criteria; Special Reporting Situations; Procedures) as well as product quality complaints, refer to Section 10.3, Adverse Events: Definitions and Procedures for Recording, Evaluating, Follow-Up, and Reporting.

8.4.1. Time Period and Frequency for Collecting Adverse Event and Serious Adverse Event Information

All Adverse Events

All adverse events and special reporting situations, whether serious or non-serious, will be reported from the time a signed and dated Main-study ICF is obtained until 30 days after the subject's last dose of study drug or before the start of subsequent anticancer therapy, whichever is longer. Serious adverse events, including those spontaneously reported to the investigator within 30 days after the last dose of study drug, must be reported using the Serious Adverse Event Form. The sponsor will evaluate any safety information that is spontaneously reported by an investigator beyond the time frame specified in the protocol.

Serious Adverse Events

All serious adverse events occurring during the study must be reported to the appropriate sponsor contact person by study-site personnel immediately but no later than 24 hours of their knowledge of the event.

Information regarding serious adverse events will be transmitted to the sponsor using the Serious Adverse Event Form and Safety Report Form of the case report form (CRF), which must be completed and reviewed by a physician from the study site and transmitted to the sponsor within 24 hours. The initial and follow-up reports of a serious adverse event should be transmitted electronically or by facsimile (fax).

8.4.2. Method of Detecting Adverse Events and Serious Adverse

Care will be taken not to introduce bias when detecting adverse events or serious adverse events. Open-ended and nonleading verbal questioning of the subject is the preferred method to inquire about adverse event occurrence.

8.4.3. Follow-up of Adverse Events and Serious Adverse Events

Adverse events, including pregnancy, will be followed by the investigator as specified in Section 10.3, Adverse Events: Definitions and Procedures for Recording, Evaluating, Follow-up, and Reporting.

8.4.4. Regulatory Reporting Requirements for Serious Adverse Events and Anticipated Events

The sponsor assumes responsibility for appropriate reporting of adverse events to the regulatory authorities. The sponsor will also report to the investigator (and the head of the investigational institute where required) all suspected unexpected serious adverse reactions (SUSARs). The investigator (or sponsor where required) must report SUSARs to the appropriate Independent Ethics Committee/Institutional Review Board (IEC/IRB) that approved the protocol unless otherwise required and documented by the IEC/IRB.

An anticipated event is an adverse event that commonly occurs in the study population independent of exposure to the drug under investigation. For the purposes of this study the following serious adverse events will be considered anticipated events:

- hematuria
- dysuria
- nocturia
- bladder perforation
- ureteric stenosis
- urinary incontinence
- urinary hesitation
- stranguria
- ureteric obstruction
- urine flow decreased
- urinary retention
- urinary tract obstruction
- urinary tract pain
- urinary tract infection
- urosepsis

Reporting of Anticipated Events

These anticipated events will be periodically analyzed in aggregate by the sponsor during study conduct. The sponsor will prepare a safety report in narrative format if the aggregate analysis indicates that the anticipated event occurs more frequently in the treatment group than in the control group and the sponsor concludes there is a reasonable possibility that the drug under investigation caused the anticipated event.

The plan for monitoring and analyzing the anticipated events is specified in a separate Anticipated Events Safety Monitoring Plan. The assessment of causality will be made by the sponsor's unblinded safety assessment committee.

The sponsor assumes responsibility for appropriate reporting of the listed anticipated events according to the requirements of the countries/territories in which the studies are conducted.

8.4.5. Pregnancy

All initial reports of pregnancy in female subjects or partners of male subjects must be reported to the sponsor by the study-site personnel within 24 hours of their knowledge of the event using the appropriate pregnancy notification form. Abnormal pregnancy outcomes (eg, spontaneous abortion, fetal death, stillbirth, congenital anomalies, ectopic pregnancy) are considered serious

adverse events and must be reported using the Serious Adverse Event Form. If a subject becomes pregnant during the study, the investigator should discuss discontinuation of study drug for the subject with the sponsor's medical monitor. Follow-up information regarding the outcome of the pregnancy and any postnatal sequelae in the infant will be required. Male subjects receiving gemcitabine or mitomycin C will refrain from sperm donation or fathering a child until 6 months after the last dose of study drug.

8.4.6. Disease-Related Events and Disease-Related Outcomes Not Qualifying as Adverse Events or Serious Adverse Events

All events that meet the definition of a serious adverse event (SAE) will be reported as SAEs, regardless of whether they are protocol-specific assessments.

Progression of disease should not be considered nor should be reported as an AE (or SAE). However, signs and symptoms of disease progression or of clinical sequelae resulting from disease progression/lack of efficacy that are determined by the investigator to be of clinical significance should be reported per the usual reporting requirements (Section 8.4 and Section 10.3).

8.4.7. Adverse Events of Special Interest

Central serous retinopathy (CSR) is considered an adverse event of special interest. Instructions for assessing vision abnormalities during the study are provided in Section 8.3.5.

8.5. Treatment of Overdose

There is no information on overdosage with erdafitinib. There is no known specific antidote for erdafitinib overdose. In the event of an overdose, stop erdafitinib and undertake general supportive measures until clinical toxicity has diminished or resolved. See Section 10.3 (Special Reporting Situations) for additional information.

8.6. Pharmacokinetics

8.6.1. Evaluations

Subjects who receive erdafitinib will have biological specimens collected for measurement of erdafitinib concentration as follows:

- Scheduled collection of venous blood during Cycle 1 and Cycle 2
- Tissue specimens from newly detected or progressing lesions during the Treatment Phase
- Matching venous blood samples collected at the time tissue specimens are collected from new or progressing lesions
- A 24-hour urine collection, first approximately 20 subjects who receive erdafitinib (from any cohort).

Erdafitinib Pharmacokinetic Assessment in Blood

Venous blood samples (2 mL per visit) will be collected for the determination of plasma concentrations of erdafitinib at the time points specified on the Schedule of Activities (Section 1.3)

for all subjects who receive erdafitinib. The Laboratory Manual provides detailed information on the handling and shipment of blood/plasma samples.

- Predose PK sample: On Cycle 1 Day 14 and Cycle 2 Day 1, erdafitinib should be taken in the clinic after the predose PK sample. The time of dosing, and the collection time of the PK sample must be recorded accurately.
- Postdose PK sample: On Cycle 2 Day 1, a 4-mL venous blood sample will be taken together with a 3-hour (±1 hour) postdose blood sample for the determination of erdafitinib plasma protein binding (ie, alpha-1-acid glycoproteins, total protein, and fraction unbound) (see Schedule of Activities, Section 1.3). The time of dosing, and the time of the protein binding sample must ±be recorded accurately.
- If indicated by the emerging safety findings or if the scheduled PK samples are not collected due to treatment interruption, blood samples may be collected at a later site visit (on Cycle 2 Day 14, Cycle 3 Day 1, or Cycle 3 Day 14). The total number of samples and blood volume will not be substantially increased without approval of the IEC or IRB.

Erdafitinib Pharmacokinetic Assessment in Urine

A 24-hour urine sample will be collected from the first approximately 20 subjects who received erdafitinib enrolled (from any cohort) at specified time point in the schedule of assessments.

8.6.2. Analytical Procedures

Analytical procedures to determine erdafitinib concentration in blood and tissue are provided in this section.

Erdafitinib Pharmacokinetic Blood Samples

Blood samples will be processed to obtain plasma for measurement of erdafitinib concentration by a validated analytical method under the direction of the sponsor. Plasma protein binding, if needed, will be determined by equilibrium dialysis. After dialysis, the buffer and plasma samples will be analyzed for erdafitinib content using a qualified liquid chromatography/mass spectrometry method by the sponsor's Bioanalytical Laboratory. Alpha-1 acid glycoprotein (α1-AGP) will also be measured in the plasma.

Pharmacokinetic Tissue Samples

Biopsy tissue concentrations of erdafitinib will be determined with a qualified liquid chromatography/mass spectrometry method by the sponsor's Bioanalytical Laboratory. Refer to the Laboratory Manual for details on sample handling.

8.6.3. Pharmacokinetic Parameters and Evaluations

Erdafitinib pharmacokinetic data in different metrices (plasma and tissue) will be listed for all subjects with available plasma erdafitinib concentrations. Subjects will be excluded from the pharmacokinetic analysis if their data do not allow for accurate assessment (eg, missing dosing and sampling time information; concentration data are not sufficient for pharmacokinetic parameter calculation). All concentrations below the lowest quantifiable concentration or missing

data will be labeled as such in the concentration database. All subjects and samples excluded from the analysis will be clearly documented in the study report.

Population pharmacokinetic analysis of plasma concentration-time data of erdafitinib may be performed using nonlinear mixed-effect modeling. Previously developed pharmacokinetic models may be used and updated as considered appropriate. Relationships between plasma concentrations or metrics of systemic exposure and CYP2C9 polymorphism, markers of pharmacological activities (serum phosphate), efficacy, or treatment-emergent adverse events may also be explored as data allow using population approaches. Results of the analyses will be provided in a separate report.

8.7. Pharmacodynamics

Predictive and pharmacodynamic biomarker analyses are described in Section 9.4.6.1.

8.8. Genetics

Germline DNA will be collected for subjects receiving erdafitinib (see Section 1.3) from a blood sample for CYP2C9 genotyping. This will be used to explore the effect of CYP2C9 polymorphism on the pharmacokinetics of erdafitinib.

8.9. Biomarkers

Biomarker investigations in this study include, but are not limited to, assessment of the following:

- Assessment of CCI in archival tissue and paired tumor biopsies where available
- Assessment of CCI in pretreatment and longitudinal voided urine samples
- Circulating tumor DNA from plasma to determine the CCI at screening, to assess changes in the levels or types of CCI observed over time, and to monitor for the CCI
- Next-generation sequencing for genetic alterations in pretreatment/archival samples and association of genetic alterations with CCI
- Serum phosphate levels as a marker of CCI

Tissue Biomarkers

Tumor tissue collected on study will be used to assess the CCI status and identify the CCI of the subjects' tumors, as well as to identify CCI to treatment with erdafitinib or Investigator's Choice. Tumor tissue from any positive biopsy (any grade of recurrence) should be sent for exploratory biomarker analysis to the central laboratory. Refer to the Laboratory Manual for instruction on sample handling.

Archival or fresh tumor tissue collected at screening will be used to assess the status of CCI CCI, via IHC.

Urothelial cancer can be classified, via molecular signature, into basal, luminal, and p53-like subtypes, which may inform patient prognosis and response to treatment in the advanced disease setting.[37] The utility of bladder cancer molecular subtyping in the CCI CCI will be assessed. Gene expression analysis, determined by RNAseq analysis or alternate method, will be utilized to assess the CCI e CCI subjects. Changes in CCI upon erdafitinib treatment will also be evaluated in paired tumor biopsies utilizing tissue from lesions biopsied during cystoscopy, where available. The correlation of bladder molecular subtype CCI CCI will be evaluated.

Urine for CCI (ie, for biomarker research)

Urine samples will be collected at multiple time points on study to provide a noninvasive method for CCI and to CCI. This would especially benefit patients with CIS, where due to tumor architecture, diagnosis is performed from cells derived from urine cytology rather than tumor biopsy. Voided urine specimen will be assessed to determine the sensitivity of CCI from urine.

Longitudinal urine sample collections will be obtained and analyzed in order to determine the optimal timepoint(s) for CCI in this population. CCI from urine will be assessed at baseline and longitudinally on all subjects from the study, with the understanding that subjects with papillary disease may not have enough tumor cells present in urine for CCI Understanding whether CCI in patients with papillary disease who have had all visible tumor resected, and whether and when CCI can be detected in these patients in relation to CCI is an important scientific question to be addressed in the context of this study.

A voided urine sample for biomarker research will be obtained from the urine cytology sample.

Circulating Biomarkers

Blood samples for circulating biomarkers should be collected predose at timepoints specified in the Schedule of Activities (Section 1.3).

Serum phosphate levels will be monitored in subjects treated with erdafitinib locally as a marker of target engagement. The Phase 1 (42756493EDI1001) and Phase 2 (42756493BLC2001) studies of erdafitinib demonstrated that phosphate levels are a robust PD biomarker of erdafitinib target engagement, and that achieving target increases in serum phosphate may be associated with clinical response to erdafitinib.

Circulating Tumor DNA

Blood for analysis of ctDNA will be collected at multiple time points to assess feasibility of CCI in the NMIBC disease setting. The ability to detect ctDNA increases with tumor stage. The utility of CCI in ctDNA from subjects with non-muscle-invasive disease will be assessed and compared with FGFR status determination from tissue and urine.

Circulating tumor DNA are fragments of DNA shed in the bloodstream during cell turnover. In cancer, a fraction of the circulating DNA is from DNA shed by tumor cells. This ctDNA often harbors somatic alterations which are reflective of the original tumor.

Circulating tumor DNA may be used to identify patients for targeted therapies, track response to treatment and the emergence of resistance by monitoring changes in target ctDNA levels over time. Samples collected prior to and during treatment will be screened for changes in the levels or types of CCI observed over time, and to monitor for the CCI CCI .

Urine for Assay Development

The ability to detect FGFR mutations or fusions in pretreatment urine samples and concordance of urine FGFR status with archival tissue-based testing will be performed. The sensitivity and utility of urine-based FGFR testing compared with tumor-based and blood-based (ctDNA, see above) analyses will be assessed.

Two voided urine samples will be collected; one sample will be collected before the subject is selected for this study (after disease recurrence and before the TURBT, except for patients being considered for study after TURBT) and another sample will be collected at the time of high-risk disease recurrence (before the TURBT procedure at the End of Treatment Visit). As noted in the Schedule of Activities (Section 1.3), the collection at the time of high-risk recurrence is no longer required.

Sample Collection and Analysis

Additional biomarkers (DNA, RNA, and protein) relevant to cancer may also be assessed in blood, urine, and tumor tissue samples collected during the study to better understand the disease and the CCI .

Adjustments in the timing of biomarker collections may be made during the study based on emerging data, and some biomarker collections may be ceased if emerging data show lack of utility for the associated sample collections.

Biomarker analyses are dependent upon the availability of appropriate biomarker assays and emerging data. Biomarker analyses may be ceased or deferred if, during or at the end of the study, it becomes clear that the analysis will have no scientific value, that there are not enough samples, or that there are not enough responders to allow for adequate biomarker evaluation. In the event the study is stopped early or shows poor clinical efficacy, completion of biomarker assessments is based on justification and intended utility of the data.

If it is determined at any time before study completion that additional material is needed from a formalin-fixed, paraffin-embedded tumor sample for the successful completion of the protocol-specified analyses, the sponsor may request that additional material be retrieved from existing samples. Also, based on emerging scientific evidence, the sponsor may request additional material from previously collected tumor samples during or after study completion for a retrospective

analysis. In this case, such analyses would be specific to research related to the study drug(s) or diseases being investigated.

8.10. Medical Resource Utilization and Health Economics

MRU and health economics data collection is no longer required for all subjects in all phases. Medical Resource Utilization data, associated with medical encounters, will be collected in the eCRF by the investigator and study-site personnel for subjects in Cohort 1 and Cohort 2 as specified in the Schedule of Activities (see Section 1.3). Protocol-mandated procedures, tests, and encounters are excluded. The data collected may be used to conduct exploratory economic analyses and will include:

- Number and duration of medical care encounters, including surgeries, and other selected procedures (inpatient and outpatient)
- Duration of hospitalization (total days length of stay, including duration by wards; eg, intensive care unit)
- Number and character of diagnostic and therapeutic tests and procedures
- Outpatient medical encounters and treatments (including physician or emergency room visits, tests and procedures, and medications)

9. STATISTICAL CONSIDERATIONS

Statistical analysis will be done by the sponsor or under the authority of the sponsor. A general description of the statistical methods to be used to analyze the efficacy and safety data is outlined below. Specific details will be provided in the Statistical Analysis Plan.

9.1. Statistical Hypothesis

For Cohort 1, the hypothesis is that erdafitinib treatment will delay the onset of tumor recurrence for subjects with papillary disease only, who recurred after BCG treatment, with FGFR mutations or fusions, and with all lesions removed.

Due to early enrollment termination and change in study's regulatory intent from registrational to non-registrational, formal hypothesis testing will no longer be performed for Cohort 1. No hypothesis testing will be performed for Cohort 2 or Cohort 3.

9.2. Sample Size Determination

Cohort 1 was originally planned to enroll approximately 240 subjects in a 2:1 randomization ratio (approximately 160 subjects assigned to the erdafitinib treatment arm; 80 subjects assigned to the control arm, Investigator's Choice of treatment). The termination of Cohort 1 enrollment resulted in a sample size of 73 subjects for the purpose of summarizing the data descriptively. With a total number of 73 subjects under the 2:1 randomization ratio, the 95% CIs for the possible hazard ratios assumed to be observed at the end of the study are presented as follows (Table 12):

Table 12: Hazard Ratio Confidence Intervals

	Number of Events			
	20	30	40	50
Hazard Ratio				
0.4	(0.16, 1.01)	(0.19, 0.85)	(0.21, 0.77)	(0.22, 0.72)
0.5	(0.20, 1.27)	(0.23, 1.07)	(0.26, 0.96)	(0.28, 0.90)
0.6	(0.24, 1.52)	(0.28, 1.28)	(0.31, 1.16)	(0.33, 1.08)

Cohort 2 was planned to enroll approximately 20 subjects. As suggested by the International Bladder Cancer Group,[27] a 40% CR rate at 6 months would be clinically meaningful. With 20 subjects, the cohort will produce a 2-sided 95% CI of (16%, 64%) when the observed CR rate is 40%. The termination of enrollment resulted in a Cohort 2 sample size of 16.

Cohort 3 was planned to enroll approximately 20 subjects. A CR rate of 30% to 50% has been reported in most previous marker lesion studies.[22] With 20 subjects, the lower bound of the 95% CIs will exclude 0 if the observed CR rate is at least 30%. The 95% CIs for different observed CR rates based on 20 subjects are as follows:

Observed rate	95% CI
30%	(7%, 53%)
40%	(16%, 64%)
50%	(26%, 74%)
60%	(36%, 84%)

The termination of enrollment resulted in a Cohort 3 sample size of 18.

9.3. Populations for Analyses

For purposes of analysis, the following populations are defined:

Population	Description
Intent-to-treat	All randomized (Cohort 1) or treated (Cohort 2 and Cohort 3) subjects. Subjects in this population will be analyzed according to the treatment to which they are assigned.
PK-evaluable	Subjects in the intent-to-treat (ITT) who received at least 1 dose of erdafitinib and had at least 1 pharmacokinetic sample obtained post-treatment.
Biomarker	Subjects in the ITT whose biomaterial is available and who have consented to participate in the study's biomarker evaluations.
Safety	Subjects in the ITT who received at least 1 dose of study drug. Safety data will be analyzed according to the actual treatment received.

The ITT population will be used to summarize the study population and characteristics, and efficacy data; the Safety Population will be used to summarize the safety data, unless otherwise specified.

9.4. Statistical Analyses

The Statistical Analysis Plan will be finalized prior to database lock and it will include a more technical and detailed description of the statistical analyses described in this section. This section is a summary of the planned statistical analyses of the most important endpoints including primary and key secondary endpoints.

9.4.1. General Considerations

The cohorts will be analyzed separately. Descriptive statistics and subject listings will be used to summarize the data. For continuous variables, number of observations, means, standard deviations, medians, interquartiles (IQs), and ranges will be used. For discrete variables, frequency will be summarized. The comparisons between the 2 treatment groups in Cohort 1 will be performed using descriptive statistics.

9.4.2. Primary Endpoint (Cohort 1)

For Cohort 1, the primary endpoint is RFS. Recurrence-free survival is defined as the time from the date of randomization until the date of the reappearance of high-risk disease (high-grade Ta, T1 or CIS), or death, whichever is reported first. Subjects who are recurrence-free and alive or have unknown status will be censored at the last tumor assessment.

The primary efficacy analysis will be based on the ITT population. The Kaplan-Meier method will be used to estimate the distribution of overall RFS for each treatment group.

The primary estimand, the main clinical quantity of interest to be estimated in the study, is defined by the following 4 components:

- Population: all randomized subjects, with high-risk NMIBC who harbor FGFR mutations or fusions, and who recurred after BCG therapy.
- Variable: time to event, RFS.
- Intercurrent event:
  - Treatment discontinuation. Treatment policy approach is used, where the occurrence of the intercurrent event is irrelevant: the value of the event is used regardless of treatment discontinuation occurring.
  - Subsequent anticancer therapy. While on treatment strategy will be used, that is, RFS will be censored at the start date of anticancer therapy. Note that for subjects randomized to Investigator's Choice in Cohort 1, the treatment of erdafitinib after cross over is considered as use of subsequent therapy and the while on treatment strategy will be used.
- Population-level summary: descriptive statistics.

9.4.3. Secondary Efficacy Endpoints (Cohort 1)

Secondary endpoints for Cohort 1 include the following:

- Time to progression: the time from the date of randomization until the date of first documented evidence of any of the following:
  - Development of or increase in stage to lamina propria invasion (eg, increase from Ta to T1)
  - Development of or increase in stage to muscle-invasive disease (stage ≥T2)
  - Development of or increase in stage to lymph node (N+) or distant metastasis (M1) disease (subject must have previously been diagnosed with N0 and/or M0 disease)

- Increase in tumor grade from low to high (including CIS)
- Death

Subjects who are progression-free and alive or have unknown status will be censored at the date of the last tumor assessment.

- Overall survival: the time from the date of randomization to the date of the subject's death resulting from any cause. Subjects who are alive or have unknown vital status will be censored at the date the subject was last known to be alive.
- RFS rate at 6 months and 12 months.

Descriptive statistics will be used to summarize the secondary efficacy endpoints of time to progression, OS, and RFS rate at 6 months and 12 months for the ITT population in Cohort 1. Kaplan-Meier methods will be used to estimate the distribution of these endpoints for each treatment group.

9.4.4. Tertiary/Exploratory Endpoints

For Cohort 2, the exploratory endpoints are CR rate at 8 weeks, CR rate at 32 weeks, and DOR. Complete response is defined as at least one of the following: 1) negative cystoscopy and negative (including atypical) urine cytology; or 2) positive cystoscopy with biopsy-proven benign or low-grade NMIBC and negative cytology. The CR rate at 8 weeks and the CR rate at 32 weeks will be calculated with their associated 2-sided 95% CIs. Duration of response will be analyzed for subjects in Cohort 2 with a BOR of CR only and is defined as the interval between the date of initial documentation of a response and the first documented evidence of PD, recurrence, or death due to any cause. The Kaplan-Meier method will be used to estimate the median DOR with 95% CI.

For Cohort 3, the exploratory endpoints are CR rate, BOR, and DOR. Complete response is defined as the disappearance of the marker lesion without any new lesions; and if any remnant of the marker lesion, no viable tumor seen on histopathological examination. The CR rate will be calculated with its associated 2-sided 95% CI. For Cohort 3, the best overall response (BOR) is defined as the best response documented after start of study treatment. CR for Cohort 3 is defined above. A partial response (PR) for Cohort 3 is defined as marker lesion reduction by 50%. Stable disease (SD) for Cohort 3 is defined as marker lesion reduction by less than 50%. Progressive disease (PD) for Cohort 3 is defined as any marker lesion growth beyond baseline. Duration of response will be analyzed for subjects in Cohort 3 with a BOR of CR or PR and is defined as the interval between the date of initial documentation of a response and the first documented evidence of PD, recurrence, or death due to any cause. The Kaplan-Meier method will be used to estimate the median DOR with 95% CI.

9.4.5. Safety Analyses

All safety analyses will be made on the Safety Population.

Adverse Events

The verbatim terms used in the eCRF by investigators to identify adverse events will be coded using the Medical Dictionary for Regulatory Activities (MedDRA). Treatment-emergent adverse events are adverse events with onset during the Treatment Phase or that are a consequence of a pre-existing condition that has worsened since baseline. All reported treatment-emergent adverse events will be included in the analysis. For each adverse event, the percentage of subjects who experience at least 1 occurrence of the given event will be summarized by treatment group. In addition, comparisons between treatment groups will be provided if appropriate.

Summaries, listings, datasets, or subject narratives may be provided, as appropriate, for those subjects who die, who discontinue treatment due to an adverse event, or who experience a severe or a serious adverse event.

Clinical Laboratory Tests

Laboratory data will be summarized by type of laboratory test. Reference ranges and markedly abnormal results (specified in the Statistical Analysis Plan) will be used in the summary of laboratory data. Frequency tabulations of the abnormalities will be made. A listing of subjects with any markedly abnormal laboratory results will also be provided. Parameters with predefined NCI-CTCAE toxicity grades will be summarized.

Electrocardiograms

All clinically relevant abnormalities in ECG waveform that are changes from the baseline readings will be reported (eg, changes in T wave morphology or the occurrence of U waves). Clinically relevant ECG abnormalities are defined in the SAP.

ECOG Performance Status

Screening ECOG performance status scores will be summarized for each cohort.

9.4.6. Other Analyses

9.4.6.1. Pharmacokinetic Analyses

The pharmacokinetic analysis of erdafitinib will be performed on data from the PK-evaluable Population (see Section 9.3). All concentrations below the lowest quantifiable concentration or missing data will be labeled as such in the concentration database.

Erdafitinib pharmacokinetic data in different metrices (plasma, urine, and tissue) will be listed for all subjects with available erdafitinib concentrations. Concentrations values below the lower limit of quantitation will be displayed in listings as zero with a flag and handled as zero in the calculations for mean, coefficient of variation (CV) for mean, standard deviation, minimum, median, maximum, but handled as missing for the calculation of the geometric means and their CV. Subjects will be excluded from the pharmacokinetic analysis if their data do not allow for accurate assessment of the pharmacokinetic (eg, incomplete administration of the study drug; missing information of dosing and sampling times; concentration data not sufficient for

pharmacokinetic parameter calculation). All subjects and samples excluded from the analysis will be clearly documented in the study report.

If appropriate, descriptive statistics, including arithmetic and geometric mean, median, standard deviation, CV, geometric CV, minimum and maximum, will be tabulated for erdafitinib PK concentrations and protein binding data by time point if provided.

9.4.6.2. Biomarkers Analyses

Changes in CCI [redacted] over time will be summarized by treatment group. Associations between baseline levels and changes from baseline in select markers and CCI [redacted] will be explored.

Results of exploratory biomarker analyses may be presented in a separate report. Planned biomarker analyses may be deferred if emerging study data show no likelihood of providing useful scientific information.

9.5. Interim Analysis

Two interim analyses were originally planned for Cohort 1. Due to the change in the conduct of the study, they will no longer be conducted.

9.6. Independent Data Monitoring Committee

An IDMC will be commissioned for reviewing safety data at various intervals outlined in the IDMC Charter (Section 10.2). Due to the company decision to terminate study enrollment and considering the recent IDMC review (6 July 2022) found the safety of erdafitinib in this study to be consistent with the known safety profile of erdafitinib, no further monitoring by the IDMC will be conducted.

10. SUPPORTING DOCUMENTATION AND OPERATIONAL CONSIDERATIONS

10.1. Appendix 1: Abbreviations

ADL	activities of daily living
ANC	absolute neutrophil count
AUA	American Urological Association
AUC	area under the curve
BCG	bacillus Calmette-Guérin
β hCG	β-human chorionic gonadotropin
BICR	blinded independent central review
BSA	body surface area
CI	confidence interval
CIS	carcinoma in situ
CLIA	Clinical Laboratory Improvement Amendments
CR	complete response
CSR	central serous retinopathy
CT	computed tomography
ctDNA	circulating tumor DNA
CV	coefficient of variation
CYP	Cytochrome
DCR	disease control rate
DDI	drug-drug interaction
DoR	duration of response
EAU	European Association of Urology
ECG	Electrocardiogram
ECOG	Eastern Cooperative Oncology Group
eCRF	electronic case report form
eDC	electronic data capture
EMA	European Medicines Agency
EoT	end of treatment
ePRO	electronic patient-reported outcome
EORTC	European Organisation for Research and Treatment of Cancer
FGFR	fibroblast growth factor receptor
FDA	Food and Drug Administration
GCP	Good Clinical Practice
HR	hazard ratio
HRQoL	health-related quality of life
IB	Investigator's Brochure
ICF	informed consent form
ICH	International Conference on Harmonisation
IDMC	Independent Data Monitoring Committee
IEC	Independent Ethics Committee
IPPI	Investigational Product Preparation Instructions
IPPM	Investigational Product Procedures Manual
IRB	Institutional Review Board
ITT	intent-to-treat
IWRS	interactive web response system
LCIS	lobular carcinoma in situ
LTE	Long-term Extension
MedDRA	Medical Dictionary for Regulatory Activities
MMC	mitomycin C
MRI	magnetic resonance imaging
MRU	medical resource utilization
NCI-CTCAE	National Cancer Institute Common Terminology Criteria for Adverse Events
NGS	next-generation sequencing
NMIBC	non-muscle-invasive bladder cancer
ORR	overall response rate

OS	overall survival
PCR	polymerase chain reaction
PD	Pharmacodynamic
PFS	progression-free survival
P-gp	P-glycoprotein
PGIC	Patient's Global Impression of Change (of cancer)
PGIS	Patient's Global Impression of Severity (of cancer)
PK	pharmacokinetic(s)
PR	partial response
PRO	patient-reported outcome(s) (paper or electronic as appropriate for this study)
PQC	product quality complaint
RFS	recurrence-free survival
RFS2	recurrence-free survival on subsequent anticancer therapy
SUSAR	suspected unexpected serious adverse reaction
TURBT	transurethral resection of bladder tumor
ULN	upper limit of normal
US	United States

Definitions of Terms

Duration of Study Drug	Period from first dose of study treatment (erdafitinib or Investigator's Choice) until the last dose. The duration of erdafitinib study treatment is a maximum of 2 years.
Electronic source system	Contains data traditionally maintained in a hospital or clinic record to document medical care or data recorded in an eCRF as determined by the protocol. Data in this system may be considered source documentation.
Investigator's Choice	For Cohort 1, subjects not assigned to receive erdafitinib will receive either intravesical gemcitabine or intravesical MMC/hyperthermic MMC.

10.2. Appendix 2: Regulatory, Ethical, and Study Oversight Considerations

REGULATORY AND ETHICAL CONSIDERATIONS

Investigator Responsibilities

The investigator is responsible for ensuring that the study is performed in accordance with the protocol, current ICH guidelines on Good Clinical Practice (GCP), and applicable regulatory and country/territory-specific requirements.

Good Clinical Practice is an international ethical and scientific quality standard for designing, conducting, recording, and reporting studies that involve the participation of human subjects. Compliance with this standard provides public assurance that the rights, safety, and well-being of study subjects are protected, consistent with the principles that originated in the Declaration of Helsinki, and that the study data are credible.

Protocol Clarification Communications

If text within a final approved protocol requires clarification (eg, current wording is unclear or ambiguous) that does not change any aspect of the current study conduct, a protocol clarification communication (PCC) may be prepared. The PCC Document will be communicated to the Investigational Site, Site Monitors, Local Trial Managers, Clinical Trial Managers, and/or Contract Research Organizations who will ensure that the PCC explanations are followed by the investigators.

The PCC Document may be shared by the sites with IECs/IRBs per local regulations.

The PCC Documents must NOT be used in place of protocol amendments, but the content of the PCC Document must be included in any future protocol amendments.

Protocol Amendments

Neither the investigator nor the sponsor will modify this protocol without a formal amendment by the sponsor. All protocol amendments must be issued by the sponsor and signed and dated by the investigator. Protocol amendments must not be implemented without prior IEC/IRB approval, or when the relevant competent authority has raised any grounds for non-acceptance, except when necessary to eliminate immediate hazards to the subjects, in which case the amendment must be promptly submitted to the IEC/IRB and relevant competent authority. Documentation of amendment approval by the investigator and IEC/IRB must be provided to the sponsor. When the change(s) involve only logistic or administrative aspects of the study, the IEC/IRB (where required) only needs to be notified.

During the study, in situations where a departure from the protocol is unavoidable, the investigator or other physician in attendance will contact the appropriate sponsor representative listed in the Contact Information page(s), which will be provided as a separate document. Except in emergency situations, this contact should be made before implementing any departure from the protocol. In all cases, contact with the sponsor must be made as soon as possible to discuss the situation and agree on an appropriate course of action. The data recorded in the CRF and source documents will

reflect any departure from the protocol, and the source documents will describe this departure and the circumstances requiring it.

Regulatory Approval/Notification

This protocol and any amendment(s) must be submitted to the appropriate regulatory authorities in each respective country/territory, if applicable. A study may not be initiated until all local regulatory requirements are met.

Required Prestudy Documentation

The following documents must be provided to the sponsor before shipment of study drug to the study site:

- Protocol and amendment(s), if any, signed and dated by the principal investigator
- A copy of the dated and signed (or sealed, where appropriate per local regulations), written IEC/IRB approval of the protocol, amendments, ICF, any recruiting materials, and if applicable, subject compensation programs. This approval must clearly identify the specific protocol by title and number and must be signed (or sealed, where appropriate per local regulations) by the chairman or authorized designee.
- Name and address of the IEC/IRB, including a current list of the IEC/IRB members and their function, with a statement that it is organized and operates according to GCP and the applicable laws and regulations. If accompanied by a letter of explanation, or equivalent, from the IEC/IRB, a general statement may be substituted for this list. If an investigator or a member of the study-site personnel is a member of the IEC/IRB, documentation must be obtained to state that this person did not participate in the deliberations or in the vote/opinion of the study.
- Regulatory authority approval or notification, if applicable
- Signed and dated statement of investigator (eg, Form FDA 1572), if applicable
- Documentation of investigator qualifications (eg, curriculum vitae)
- Completed investigator financial disclosure form from the principal investigator, where required
- Signed and dated Clinical Trial Agreement, which includes the financial agreement
- Any other documentation required by local regulations

The following documents must be provided to the sponsor before enrollment of the first subject:

- Completed investigator financial disclosure forms from all subinvestigators
- Documentation of subinvestigator qualifications (eg, curriculum vitae)
- Name and address of any local laboratory conducting tests for the study, and a dated copy of current laboratory normal ranges for these tests, if applicable (eg, CLIA or equivalent certification and laboratory director curriculum vitae)
- Local laboratory documentation demonstrating competence and test reliability (eg, accreditation/license), if applicable

Independent Ethics Committee or Institutional Review Board

Before the start of the study, the investigator (or sponsor where required) will provide the IEC/IRB with current and complete copies of the following documents (as required by local regulations):

- Final protocol and, if applicable, amendments
- Sponsor-approved ICF (and any other written materials to be provided to the subjects)
- IB (or equivalent information) and amendments/addenda
- Sponsor-approved subject recruiting materials
- Information on compensation for study-related injuries or payment to subjects for participation in the study, if applicable
- Investigator's curriculum vitae or equivalent information (unless not required, as documented by the IEC/IRB)
- Information regarding funding, name of the sponsor, institutional affiliations, other potential conflicts of interest, and incentives for subjects
- Any other documents that the IEC/IRB requests to fulfill its obligation

This study will be undertaken only after the IEC/IRB has given full approval of the final protocol, amendments (if any, excluding the ones that are purely administrative, with no consequences for subjects, data or study conduct, unless required locally), the ICF, applicable recruiting materials, and subject compensation programs, and the sponsor has received a copy of this approval. This approval letter must be dated and must clearly identify the IEC/IRB and the documents being approved.

During the study the investigator (or sponsor where required) will send the following documents and updates to the IEC/IRB for their review and approval, where appropriate:

- Protocol amendments (excluding the ones that are purely administrative, with no consequences for subjects, data or study conduct)
- Revision(s) to ICF and any other written materials to be provided to subjects
- If applicable, new or revised subject recruiting materials approved by the sponsor
- Revisions to compensation for study-related injuries or payment to subjects for participation in the study, if applicable
- New edition(s) of the IB and amendments/addenda
- Summaries of the status of the study at intervals stipulated in guidelines of the IEC/IRB (at least annually)
- Reports of adverse events that are serious, unlisted/unexpected, and associated with the study drug
- New information that may adversely affect the safety of the subjects or the conduct of the study
- Deviations from or changes to the protocol to eliminate immediate hazards to the subjects

- Report of deaths of subjects under the investigator's care
- Notification if a new investigator is responsible for the study at the site
- Development Safety Update Report and Line Listings, where applicable
- Any other requirements of the IEC/IRB

For all protocol amendments (excluding the ones that are purely administrative, with no consequences for subjects, data or study conduct), the amendment and applicable ICF revisions must be submitted promptly to the IEC/IRB for review and approval before implementation of the change(s).

At least once a year, the IEC/IRB will be asked to review and reapprove this study, where required.

At the end of the study, the investigator (or sponsor where required) will notify the IEC/IRB about the study completion (if applicable, the notification will be submitted through the head of investigational institution).

Country/Territory Selection

This study will only be conducted in those countries/territories where the intent is to launch or otherwise help ensure access to the developed product if the need for the product persists, unless explicitly addressed as a specific ethical consideration in Section 4.2.1, Study-Specific Ethical Design Considerations.

Other Ethical Considerations

For study-specific ethical design considerations, refer to Section 4.2.1.

FINANCIAL DISCLOSURE

Investigators and subinvestigators will provide the sponsor with sufficient, accurate financial information in accordance with local regulations 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 study and for 1 year after completion of the study.

Refer to Required Prestudy Documentation (above) for details on financial disclosure.

INFORMED CONSENT PROCESS

Each subject (or a legally acceptable representative) must give written consent according to local requirements after the nature of the study has been fully explained. The ICF(s) must be signed before performance of any study-related activity. The ICF(s) that is/are used must be approved by both the sponsor and by the reviewing IEC/IRB and be in a language that the subject can read and understand. The informed consent should be in accordance with principles that originated in the Declaration of Helsinki, current ICH and GCP guidelines, applicable regulatory requirements, and sponsor policy.

Informed consent for molecular eligibility may be obtained remotely unless not allowed by local regulations. Also, subjects being considered for the study before the TURBT, will provide a voided urine sample after disease recurrence and before TURBT. These subjects must sign the ICF for Assay Development prior to collection of this urine sample.

Before enrollment in the study, the investigator or an authorized member of the study-site personnel must explain to potential subjects or their legally acceptable representatives the aims, methods, reasonably anticipated benefits, and potential hazards of the study, and any discomfort participation in the study may entail. Subjects will be informed that their participation is voluntary and that they may withdraw consent to participate at any time. They will be informed that choosing not to participate will not affect the care the subject will receive for the treatment of his or her disease. Subjects will be told that alternative treatments are available if they refuse to take part and that such refusal will not prejudice future treatment. Finally, they will be told that the investigator will maintain a subject identification register for the purposes of long-term follow up if needed and that their records may be accessed by health authorities and authorized sponsor personnel without violating the confidentiality of the subject, to the extent permitted by the applicable law(s) or regulations. By signing the ICF the subject or legally acceptable representative is authorizing such access, which includes permission to obtain information about his or her survival status. It also denotes that the subject agrees to allow his or her study physician to recontact the subject for the purpose of obtaining consent for additional safety evaluations, and subsequent disease-related treatments, if needed.

The subject or legally acceptable representative will be given sufficient time to read the ICF and the opportunity to ask questions. After this explanation and before entry into the study, consent should be appropriately recorded by means of either the subject's or his or her legally acceptable representative's personally dated signature. After having obtained the consent, a copy of the ICF must be given to the subject.

A subject who is rescreened is not required to sign another Main-study ICF if the rescreening occurs within 35 days from the previous Main-study ICF signature date. Subjects who fall outside of the 35 days from the previous Main-study ICF date, will need to sign a new Main-study ICF and have all eligibility criteria re-assessed. Subjects undergoing molecular screening do not need to re-sign a new Molecular Eligibility ICF to submit historical samples to the central laboratory.

If the subject or legally acceptable representative is unable to read or write, an impartial witness should be present for the entire informed consent process (which includes reading and explaining all written information) and should personally date and sign the ICF after the oral consent of the subject or legally acceptable representative is obtained.

DATA PROTECTION

Privacy of Personal Data

The collection and processing of personal data from subjects enrolled in this study will be limited to those data that are necessary to fulfill the objectives of the study.

These data must be collected and processed with adequate precautions to ensure confidentiality and compliance with applicable data privacy protection laws and regulations. Appropriate technical and organizational measures to protect the personal data against unauthorized disclosures or access, accidental or unlawful destruction, or accidental loss or alteration must be put in place. Sponsor personnel whose responsibilities require access to personal data agree to keep the identity of subjects confidential.

The informed consent obtained from the subject or his or her legally acceptable representative includes explicit consent for the processing of personal data and for the investigator/institution to allow direct access to his or her original medical records (source data/documents) for study-related monitoring, audit, IEC/IRB review, and regulatory inspection. This consent also addresses the transfer of the data to other entities and to other countries/territories.

The subject has the right to request through the investigator access to his or her personal data and the right to request rectification of any data that are not correct or complete. Reasonable steps will be taken to respond to such a request, taking into consideration the nature of the request, the conditions of the study, and the applicable laws and regulations.

Exploratory biomarker and pharmacokinetic research is not conducted under standards appropriate for the return of data to subjects. In addition, the sponsor cannot make decisions as to the significance of any findings resulting from exploratory research. Therefore, exploratory research data will not be returned to subjects or investigators, unless required by law or local regulations. Privacy and confidentiality of data generated in the future on stored samples will be protected by the same standards applicable to all other clinical data.

LONG-TERM RETENTION OF SAMPLES FOR ADDITIONAL FUTURE RESEARCH

Samples collected in this study may be stored for up to 15 years (or according to local regulations) for additional research. Samples will only be used to understand erdafitinib, to understand NMIBC, to understand CCI [redacted], and to develop CCI [redacted] CCI [redacted]. The research may begin at any time during the study or the post-study storage period.

Stored samples will be coded throughout the sample storage and analysis process and will not be labeled with personal identifiers. Subjects may withdraw their consent for their samples to be stored for additional future research (refer to Section 7.2.1, Withdrawal From the Future Use of Research Samples).

COMMITTEES STRUCTURE

An IDMC composed of at least 1 medical expert in the relevant therapeutic area and at least 1 statistician will be established to monitor data on an ongoing basis to ensure the safety of the subjects enrolled in this study. The safety review will focus on deaths, treatment discontinuations, serious adverse events, Grade ≥3 events, and events of special interest. Based on the results from these scheduled safety review meetings, the IDMC chair may request additional analyses and more frequent monitoring. All deaths, treatment discontinuations and serious adverse events will be reviewed by the sponsor's medical monitor on an ongoing basis to identify safety concerns, and

the IDMC will be informed of any new potential signals. The plan for monitoring subject safety and evaluating efficacy, and the roles and responsibilities of the IDMC, are detailed in the IDMC Charter. Due to the company decision to terminate study enrollment and considering the recent IDMC review (6 July 2022) found the safety of erdafitinib in this study to be consistent with the known safety profile of erdafitinib, no further monitoring by the IDMC will be conducted.

PUBLICATION POLICY/DISSEMINATION OF CLINICAL STUDY DATA

All information, including but not limited to information regarding erdafitinib or the sponsor's operations (eg, patent application, formulas, manufacturing processes, basic scientific data, prior clinical data, formulation information) supplied by the sponsor to the investigator and not previously published, and any data, including exploratory pharmacokinetic and biomarker research data, generated as a result of this study, are considered confidential and remain the sole property of the sponsor. The investigator agrees to maintain this information in confidence and use this information only to accomplish this study and will not use it for other purposes without the sponsor's prior written consent.

The investigator understands that the information developed in the study will be used by the sponsor in connection with the continued development of erdafitinib, and thus may be disclosed as required to other clinical investigators or regulatory agencies. To permit the information derived from the clinical studies to be used, the investigator is obligated to provide the sponsor with all data obtained in the study.

The results of the study will be reported in a Clinical Study Report generated by the sponsor and will contain data from all study sites that participated in the study as per protocol. Recruitment performance or specific expertise related to the nature and the key assessment parameters of the study will be used to determine a coordinating investigator for the study. Results of exploratory pharmacokinetic or biomarker analyses performed after the Clinical Study Report has been issued will be reported in a separate report and will not require a revision of the Clinical Study Report.

Study subject identifiers will not be used in publication of results. Any work created in connection with performance of the study and contained in the data that can benefit from copyright protection (except any publication by the investigator as provided for below) shall be the property of the sponsor as author and owner of copyright in such work.

Consistent with Good Publication Practices and International Committee of Medical Journal Editors (ICMJE) guidelines, the sponsor shall have the right to publish such primary (multicenter) data and information without approval from the investigator. The investigator has the right to publish study site-specific data after the primary data are published. If an investigator wishes to publish information from the study, a copy of the manuscript must be provided to the sponsor for review at least 60 days before submission for publication or presentation. Expedited reviews will be arranged for abstracts, poster presentations, or other materials. If requested by the sponsor in writing, the investigator will withhold such publication for up to an additional 60 days to allow for filing of a patent application. In the event that issues arise regarding scientific integrity or regulatory compliance, the sponsor will review these issues with the investigator. The sponsor will not mandate modifications to scientific content and does not have the right to suppress information.

For multicenter study designs and substudy approaches, secondary results generally should not be published before the primary endpoints of a study have been published. Similarly, investigators will recognize the integrity of a multicenter study by not submitting for publication data derived from the individual study site until the combined results from the completed study have been submitted for publication, within 18 months after the study end date, or the sponsor confirms there will be no multicenter study publication. Authorship of publications resulting from this study will be based on the guidelines on authorship, such as those described in the ICMJE Recommendations for the Conduct, Reporting, Editing and Publication of Scholarly Work in Medical Journals, which state that the named authors must have made a significant contribution to the conception or design of the work; or the acquisition, analysis, or interpretation of the data for the work; and drafted the work or revised it critically for important intellectual content; and given final approval of the version to be published; and agreed to be accountable for all aspects of the work in ensuring that questions related to the accuracy or integrity of any part of the work are appropriately investigated and resolved.

Registration of Clinical Studies and Disclosure of Results

The sponsor will register and disclose the existence of and the results of clinical studies as required by law. The disclosure of the final study results will be performed after the end of study in order to ensure the statistical analyses are relevant.

DATA QUALITY ASSURANCE

Data Quality Assurance/Quality Control

Steps to be taken to ensure the accuracy and reliability of data include the selection of qualified investigators and appropriate study sites, review of protocol procedures with the investigator and study-site personnel before the study, periodic monitoring visits by the sponsor, and direct transmission of clinical laboratory data from a central laboratory into the sponsor's data base. Written instructions will be provided for collection, handling, storage, and shipment of samples.

Guidelines for CRF completion will be provided and reviewed with study-site personnel before the start of the study.

The sponsor will review CRF for accuracy and completeness during on-site monitoring visits and after transmission to the sponsor; any discrepancies will be resolved with the investigator or designee, as appropriate. After upload of the data into the study database they will be verified for accuracy and consistency with the data sources.

CASE REPORT FORM COMPLETION

Case report forms (CRF) are prepared and provided by the sponsor for each subject in electronic format. All data relating to the study must be recorded in CRF. All CRF entries, corrections, and alterations must be made by the investigator or authorized study-site personnel. The investigator must verify that all data entries in the CRF are accurate and correct.

The study data will be transcribed by study-site personnel from the source documents onto an electronic CRF, if applicable. Study-specific data will be transmitted in a secure manner to the sponsor.

Worksheets may be used for the capture of some data to facilitate completion of the CRF. Any such worksheets will become part of the subject's source documents. Data must be entered into CRF in English. Data should be entered within 3 to 5 working days of the subject visit; evaluation or assessment and queries should be answered within 5 working days of query generation, unless otherwise communicated by the team.

All participative measurements (eg, pain scale information or other questionnaires) will be completed by the same individual who made the initial baseline determinations whenever possible.

If necessary, queries will be generated in the eDC tool. If corrections to a CRF are needed after the initial entry into the CRF, this can be done in either of the following ways:

- Investigator and study-site personnel can make corrections in the eDC tool at their own initiative or as a response to an auto query (generated by the eDC tool).
- Sponsor or sponsor delegate can generate a query for resolution by the investigator and study-site personnel.

SOURCE DOCUMENTS

At a minimum, source documents consistent in the type and level of detail with that commonly recorded at the study site as a basis for standard medical care must be available for the following: subject identification, eligibility, and study identification; study discussion and date of signed informed consent; dates of visits; results of safety and efficacy parameters as required by the protocol; record of all adverse events and follow-up of adverse events; concomitant medication; study drug receipt/dispensing/return records; study drug administration information; and date of study completion and reason for early discontinuation of study drug or withdrawal from the study, if applicable.

The author of an entry in the source documents should be identifiable.

Specific details required as source data for the study and source data collection methods will be reviewed with the investigator before the study and will be described in the monitoring guidelines (or other equivalent document).

The minimum source documentation requirements for Section 5.1, Inclusion Criteria and Section 5.2, Exclusion Criteria that specify a need for documented medical history are as follows:

- Referral letter from treating physician or
- Complete history of medical notes at the site
- Discharge summaries

- Clear documentation of a subject's refusal to undergo cystectomy or medical ineligibility for cystectomy at screening must be available, and the reason for not being eligible for cystectomy or for refusing cystectomy will be entered into the eCRF.
- BCG strain will be documented in the source documents and entered into the eCRF.

Inclusion and exclusion criteria not requiring documented medical history must be verified at a minimum by subject interview or other protocol-required assessment (eg, physical examination, laboratory assessment) and documented in the source documents.

An eSource system may be utilized, which contains data traditionally maintained in a hospital or clinic record to document medical care (eg, electronic source documents) as well as the clinical study-specific data fields as determined by the protocol. These data are electronically extracted for use by the sponsor. If eSource is utilized, references made to the CRF in the protocol include the eSource system but information collected through eSource may not be limited to that found in the CRF.

MONITORING

The sponsor will use a combination of monitoring techniques (central, remote, or on-site monitoring) to monitor this study.

The sponsor will perform on-site monitoring visits as frequently as necessary. The monitor will record dates of the visits in a study site visit log that will be kept at the study site. The first post-initiation visit will be made as soon as possible after enrollment has begun. At these visits, the monitor will compare the data entered into the CRF with the source documents (eg, hospital/clinic/physician's office medical records). The nature and location of all source documents will be identified to ensure that all sources of original data required to complete the CRF are known to the sponsor and study-site personnel and are accessible for verification by the sponsor study-site contact. If electronic records are maintained at the study site, the method of verification must be discussed with the study-site personnel.

Direct access to source documents (medical records) must be allowed for the purpose of verifying that the recorded data are consistent with the original source data. Findings from this review will be discussed with the study-site personnel. The sponsor expects that, during monitoring visits, the relevant study-site personnel will be available, the source documents will be accessible, and a suitable environment will be provided for review of study-related documents. The monitor will meet with the investigator on a regular basis during the study to provide feedback on the study conduct.

In addition to on-site monitoring visits, remote contacts can occur. It is expected that during these remote contacts, study-site personnel will be available to provide an update on the progress of the study at the site.

Central monitoring will take place for data identified by the sponsor as requiring central review.

ON-SITE AUDITS

Representatives of the sponsor's clinical quality assurance department may visit the study site at any time during or after completion of the study to conduct an audit of the study in compliance with regulatory guidelines and company policy. These audits will require access to all study records, including source documents, for inspection. Subject privacy must, however, be respected. The investigator and study-site personnel are responsible for being present and available for consultation during routinely scheduled study-site audit visits conducted by the sponsor or its designees.

Similar auditing procedures may also be conducted by agents of any regulatory body, either as part of a national GCP compliance program or to review the results of this study in support of a regulatory submission. The investigator should immediately notify the sponsor if he or she has been contacted by a regulatory agency concerning an upcoming inspection.

RECORD RETENTION

In compliance with the ICH/GCP guidelines, the investigator/institution will maintain all CRF and all source documents that support the data collected from each subject, as well as all study documents as specified in ICH/GCP Section 8, Essential Documents for the Conduct of a Clinical Trial, and all study documents as specified by the applicable regulatory requirement(s). The investigator/institution will take measures to prevent accidental or premature destruction of these documents.

Essential documents must be retained until at least 2 years after the last approval of a marketing application in an ICH region and until there are no pending or contemplated marketing applications in an ICH region or until at least 2 years have elapsed since the formal discontinuation of clinical development of the investigational product. These documents will be retained for a longer period if required by the applicable regulatory requirements or by an agreement with the sponsor. It is the responsibility of the sponsor to inform the investigator/institution as to when these documents no longer need to be retained.

If the responsible investigator retires, relocates, or for other reasons withdraws from the responsibility of keeping the study records, custody must be transferred to a person who will accept the responsibility. The sponsor must be notified in writing of the name and address of the new custodian. Under no circumstance shall the investigator relocate or dispose of any study documents before having obtained written approval from the sponsor.

If it becomes necessary for the sponsor or the appropriate regulatory authority to review any documentation relating to this study, the investigator/institution must permit access to such reports.

STUDY AND SITE START AND CLOSURE

First Act of Recruitment

The first site open is considered the first act of recruitment and it becomes the study start date.

Study Closure

The sponsor reserves the right to close the study site or close the study at any time for any reason at the sole discretion of the sponsor, e.g. in case of unacceptable risk, intolerable toxicity, or change in the risk/benefit profile; this might include recurrence of adverse events of which character, severity, or frequency is new in comparison to the existing risk profile. Also, data derived from other clinical trials or toxicology studies which negatively influence the risk/benefit assessment might cause discontinuation or termination of the study. 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, provided there is reasonable cause and sufficient notice is given in advance of the intended termination.

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

- Failure of the investigator to comply with the protocol, the requirements of the IEC/IRB or local health authorities, the sponsor's procedures, or GCP guidelines
- Inadequate recruitment of subjects by the investigator
- Discontinuation of further study drug development

The sponsor may close individual study cohorts if there is inadequate recruitment of subjects within individual cohorts or within the overall study.

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

ADVERSE EVENT DEFINITIONS AND CLASSIFICATIONS

Adverse Event

An adverse event is any untoward medical occurrence in a clinical study subject administered a medicinal (investigational or non-investigational) product. An adverse event does not necessarily have a causal relationship with the study drug. An adverse event can therefore be any unfavorable and unintended sign (including an abnormal finding), symptom, or disease temporally associated with the use of a medicinal (investigational or non-investigational) product, whether or not related to that medicinal (investigational or non-investigational) product. (Definition per International Conference on Harmonisation [ICH])

This includes any occurrence that is new in onset or aggravated in severity or frequency from the baseline condition, or abnormal results of diagnostic procedures, including laboratory test abnormalities.

Note: The sponsor collects adverse events starting with the signing of the ICF (refer to All Adverse Events under Section 8.4.1, Time Period and Frequency for Collecting Adverse Events and Serious Adverse Events Information, for time of last adverse event recording).

Serious Adverse Event

A serious adverse event based on ICH and EU Guidelines on Pharmacovigilance for Medicinal Products for Human Use is any untoward medical occurrence that at any dose:

- Results in death
- Is life-threatening
  (The subject 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.)
- Requires inpatient hospitalization or prolongation of existing hospitalization
- Results in persistent or significant disability/incapacity
- Is a congenital anomaly/birth defect
- Is a suspected transmission of any infectious agent via a medicinal product
- Is Medically Important*

*Medical and scientific judgment should be exercised in deciding whether expedited reporting is also 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 subject or may require intervention to prevent one of the other outcomes listed in the definition above. These should usually be considered serious.

Unlisted (Unexpected) Adverse Event/Reference Safety Information

An adverse event is considered unlisted if the nature or severity is not consistent with the applicable product reference safety information. For erdafitinib, the expectedness of an adverse event will be determined by whether or not it is listed in the IB. For gemcitabine or MMC/hyperthermic MMC, the expectedness of an adverse event will be determined by whether or not it is listed in the applicable package insert or summary of product characteristics.

Assessment of Causality

The causal relationship to study treatment is determined by the investigator. The following selection should be used to assess all adverse events.

Related

There is a reasonable causal relationship between study treatment administration and the adverse event.

Not related

There is not a reasonable causal relationship between study treatment administration and the adverse event.

The term "reasonable causal relationship" means there is evidence to support a causal relationship.

SEVERITY CRITERIA

Adverse event severity is a clinical determination of the intensity of an adverse event. The severity assessment for an adverse event or serious adverse event should be completed using the NCI-CTCAE, Version 5.0. Any adverse event or serious adverse event not listed in the NCI-CTCAE, Version 5.0 will be graded according to the investigator clinical judgment by using the standard grades as follows:

- Grade 1: Mild; asymptomatic or mild symptoms; clinical or diagnostic observations only; intervention not indicated.
- Grade 2: Moderate; minimal, local or noninvasive intervention indicated; limiting age-appropriate instrumental activities of daily living.
- Grade 3: Severe or medically significant but not immediately life-threatening; hospitalization or prolongation of hospitalization indicated; disabling; limiting self-care activities of daily living.
- Grade 4: Life-threatening consequences; urgent intervention indicated.
- Grade 5: Death related to adverse event.

The investigator should use clinical judgment in assessing the severity of events not directly experienced by the subject (eg, laboratory abnormalities).

SPECIAL REPORTING SITUATIONS

Safety events of interest on a sponsor study drug in an interventional study that may require expedited reporting or safety evaluation include, but are not limited to:

- Overdose of a sponsor study drug
- Suspected abuse/misuse of a sponsor study drug
- Accidental or occupational exposure to a sponsor study drug
- Medication error involving a sponsor product (with or without subject/patient exposure to the sponsor study drug, eg, name confusion)
- Exposure to a sponsor study drug from breastfeeding

Special reporting situations should be recorded in the CRF. Any special reporting situation that meets the criteria of a serious adverse event should be recorded on the serious adverse event page of the CRF.

Any Grade 3 or higher treatment-emergent retinal abnormality should be reported as a serious adverse event. Instructions for assessing vision abnormalities during the study are provided in Section 6.6.2.1.5.

PROCEDURES

All Adverse Events

All adverse events, regardless of seriousness, severity, or presumed relationship to study drug, must be recorded using medical terminology in the source document and the CRF. Whenever possible, diagnoses should be given when signs and symptoms are due to a common etiology (eg, cough, runny nose, sneezing, sore throat, and head congestion should be reported as "upper respiratory infection"). Investigators must record in the CRF their opinion concerning the relationship of the adverse event to study therapy. All measures required for adverse event management must be recorded in the source document and reported according to sponsor instructions.

For all studies with an outpatient phase, including open-label studies, the subject must be provided with a "wallet (study) card" and instructed to carry this card with them for the duration of the study indicating the following:

- Study number
- Statement, in the local language(s), that the subject is participating in a clinical study
- Investigator's name and 24-hour contact telephone number
- Local sponsor's name and 24-hour contact telephone number (for medical personnel only)
- Site number
- Subject number
- Any other information that is required to do an emergency breaking of the blind

Serious Adverse Events

All serious adverse events that have not resolved by the end of the study, or that have not resolved upon discontinuation of the subject's participation in the study, must be followed until any of the following occurs:

- The event resolves
- The event stabilizes
- The event returns to baseline, if a baseline value/status is available
- The event can be attributed to agents other than the study drug or to factors unrelated to study conduct
- It becomes unlikely that any additional information can be obtained (subject or health care practitioner refusal to provide additional information, lost to follow-up after demonstration of due diligence with follow-up efforts)

Suspected transmission of an infectious agent by a medicinal product will be reported as a serious adverse event. Any event requiring hospitalization (or prolongation of hospitalization) that occurs during a subject 's participation in a study must be reported as a serious adverse event, except hospitalizations for the following:

- Hospitalizations not intended to treat an acute illness or adverse event (eg, social reasons such as pending placement in long-term care facility).
- Surgery or procedure planned before entry into the study (must be documented in the CRF).
- A standard procedure for protocol therapy administration will not be reported as a serious adverse event. (Hospitalization or prolonged hospitalization for a complication of therapy administration will be reported as a serious adverse event).
- Administration of blood or platelet transfusion. (Hospitalization or prolonged hospitalization for a complication of such transfusion remains a reportable serious adverse event.)
- Procedure for protocol/disease-related investigations (eg, surgery, scans, endoscopy, sampling for laboratory tests, bone marrow sampling) (Hospitalization or prolonged hospitalization for a complication of such procedures remains a reportable serious adverse event).
- Prolonged hospitalization for technical, practical, or social reasons, in absence of an adverse event.
- Planned procedures (ie, planned prior to starting of treatment on study; must be documented in the eCRF). (Prolonged hospitalization for a complication considered to be at least possibly related to the study drug remains a reportable serious adverse event.)

Expected progression of disease should not be considered an adverse event (or serious adverse event). However, if determined by the investigator to be more likely related to the study treatment than the underlying disease, the treatment-invoked progression (ie the treatment-invoked signs/symptoms of such progression) , should be reported per the usual reporting requirements.

Death that is attributed by the investigator explicitly to progression of disease should not be considered nor reported as an AE (or SAE). However, if determined by the investigator to be more likely related to the study treatment than being expected from the underlying disease, the treatment-invoked death due to progression should be reported per the usual reporting requirements (refer to Adverse Event Definitions and Classifications: Adverse Events: Definitions and Procedures for Recording, Evaluating, Follow-up, and Reporting).

Progression of disease and death due to disease progression should be documented on the appropriate eCRF forms (eg, the Disease Progression form and the Death form).

Signs or symptoms of disease progression that are of clinical significance, such as spinal cord compression, vena cava superior syndrome, major vessel rupture, efflux obstruction or organ failure, should be documented on the appropriate eCRF forms (eg, the Clinical Progression form).

CONTACTING SPONSOR REGARDING SAFETY

The names (and corresponding telephone numbers) of the individuals who should be contacted regarding safety issues or questions regarding the study are listed in the Contact Information page(s), which will be provided as a separate document.

PRODUCT QUALITY COMPLAINT HANDLING

A product quality complaint (PQC) is defined as any suspicion of a product defect related to manufacturing, labeling, or packaging, ie, any dissatisfaction relative to the identity, quality, durability, or reliability of a product, including its labeling or package integrity. A PQC may have an impact on the safety and efficacy of the product. Timely, accurate, and complete reporting and analysis of PQC information from studies are crucial for the protection of subjects, investigators, and the sponsor, and are mandated by regulatory agencies worldwide. The sponsor has established procedures in conformity with regulatory requirements worldwide to ensure appropriate reporting of PQC information; all studies conducted by the sponsor or its affiliates will be conducted in accordance with those procedures.

Procedures

All initial PQCs must be reported to the sponsor by the study-site personnel within 24 hours after being made aware of the event.

If the defect is combined with a serious adverse event, the study-site personnel must report the PQC to the sponsor according to the serious adverse event reporting timelines (refer to Section 8.4.1, Time Period and Frequency for Collecting Adverse Event and Serious Adverse Event Information). A sample of the suspected product should be maintained for further investigation if requested by the sponsor.

Contacting Sponsor Regarding Product Quality

The names (and corresponding telephone numbers) of the individuals who should be contacted regarding product quality issues are listed in the Contact Information page(s), which will be provided as a separate document.

10.4. Appendix 4: Contraceptive and Barrier Guidance and Collection of Pregnancy Information

Subjects must follow contraceptive measures as outlined in Section 5.1, Inclusion Criteria. Pregnancy information will be collected and reported as noted in Section 8.4.5, Pregnancy and Section 10.3 Adverse Events: Definitions and Procedures for Recording, Evaluating, Follow-up, and Reporting.

Definitions

Woman of Childbearing Potential (WOCBP)

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

Woman Not of Childbearing Potential

- **premenarchal**
  A premenarchal state is one in which menarche has not yet occurred.
- **postmenopausal**
  A postmenopausal state is defined as no menses for 12 months without an alternative medical cause. A high follicle stimulating hormone (FSH) level (>40 IU/L or mIU/mL) in the postmenopausal range may be used to confirm a postmenopausal state in women not using hormonal contraception or hormonal replacement therapy (HRT), however in the absence of 12 months of amenorrhea, a single FSH measurement is insufficient. If there is a question about menopausal status in women on HRT, the woman will be required to use one of the non-estrogen-containing hormonal highly effective contraceptive methods if she wishes to continue HRT during the study.
- **permanently sterile**
  Permanent sterilization methods for the purpose of this study include hysterectomy, bilateral salpingectomy, and bilateral oophorectomy.

Note: If the childbearing potential changes after start of the study (eg, a premenarchal woman experiences menarche) or the risk of pregnancy changes (eg, a woman who is not heterosexually active becomes active), a woman must begin a highly effective method of contraception, as described throughout the inclusion criteria.

If reproductive status is questionable, additional evaluation should be considered.

Contraceptive (birth control) use by men or women should be consistent with local regulations regarding the acceptable methods of contraception for those participating in clinical studies.

Typical use failure rates may differ from those when used consistently and correctly. Use should be consistent with local regulations regarding the use of contraceptive methods for subjects in clinical studies.

Examples of Contraceptives

EXAMPLES OF CONTRACEPTIVES[a] ALLOWED DURING THE STUDY INCLUDE:
USER INDEPENDENT **Highly Effective Methods That Are User Independent** *Failure rate of <1% per year when used consistently and correctly.*
• Implantable progestogen-only hormone contraception associated with inhibition of ovulation[b]
• Intrauterine device
• Intrauterine hormone-releasing system
• Bilateral tubal occlusion
• Vasectomized partner *(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, additional highly effective method of contraception should be used. Spermatogenesis cycle is approximately 74 days.)*
USER DEPENDENT **Highly Effective Methods That Are User Dependent** *Failure rate of <1% per year when used consistently and correctly.*
• Combined (estrogen- and progestogen-containing) hormonal contraception associated with inhibition of ovulation[b] –oral –intravaginal –transdermal –injectable
• Progestogen-only hormone contraception associated with inhibition of ovulation[b] –oral –injectable
• Sexual abstinence *(Sexual abstinence is considered a highly effective method only if defined as refraining from heterosexual intercourse during the entire period of risk associated with the study* drug*. The reliability of sexual abstinence needs to be evaluated in relation to the duration of the study and the preferred and usual lifestyle of the subject.)*
NOT ALLOWED AS SOLE METHOD OF CONTRACEPTION DURING THE STUDY (not considered to be highly effective - failure rate of ≥1% per year)
• Progestogen-only oral hormonal contraception where inhibition of ovulation is not the primary mode of action.
• Male or female condom with or without spermicide[c]
• Cap, diaphragm, or sponge with spermicide
• A combination of male condom with either cap, diaphragm, or sponge with spermicide (double-barrier methods)[c]
• Periodic abstinence (calendar, symptothermal, post-ovulation methods)
• Withdrawal (coitus-interruptus)
• Spermicides alone
• Lactational amenorrhea method (LAM)

a) Typical use failure rates may differ from those when used consistently and correctly. Use should be consistent with local regulations regarding the use of contraceptive methods for subjects in clinical studies.
b) Hormonal contraception may be susceptible to interaction with the study drug, which may reduce the efficacy of the contraceptive method. In addition, consider if the hormonal contraception may interact with the study drug.
c) Male condom and female condom should not be used together (due to risk of failure with friction).

Pregnancy During the Study

All initial reports of pregnancy in female subjects or partners of male subjects must be reported to the sponsor by the study-site personnel within 24 hours of their knowledge of the event using the appropriate pregnancy notification form. Abnormal pregnancy outcomes (eg, spontaneous abortion, fetal death, stillbirth, congenital anomalies, ectopic pregnancy) are considered serious adverse events and must be reported using the Serious Adverse Event Form. If a subject becomes pregnant during the study, the investigator should discuss discontinuation of study drug for the subject with the sponsor's medical monitor.

Because the effect of the study drug on sperm is unknown, pregnancies in partners of male subjects included in the study will be reported as noted above.

Follow-up information regarding the outcome of the pregnancy and any postnatal sequelae in the infant will be requested. Follow-up information may continue to be collected up to 12 months after the birth of a baby, if a congenital anomaly or significant medical condition is diagnosed at birth.

10.5. Appendix 5: ECOG Performance Status Scale

Grade	ECOG Performance Status Grade
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 selfcare but unable to carry out any work activities. Up and about more than 50% of waking hours
3	Capable of only limited selfcare, confined to bed or chair more than 50% of waking hours
4	Completely disabled. Cannot carry on any selfcare. Totally confined to bed or chair
5	Dead

Reference: Oken MM, Creech RH, Tormey DC, et al. Toxicity and response criteria of the Eastern Cooperative Oncology Group. Am J Clin Oncol. 1982;596:649-655.

10.6. Appendix 6: Estimated Creatinine Clearance

Cockcroft-Gault Formula

$$eCR = \frac{(140\text{-Age}) \times \text{Mass (Kilograms)} \times [0.85 \text{ if female}]}{72 \times \text{Serum Creatinine (in mg/dL}^{1})}$$

OR

$$eCcr = \frac{(140\text{-Age}) \times \text{Mass (Kilograms)} \times \text{Constant}}{\text{Serum Creatinine (in } \mu\text{mol/L)}}$$

Where Constant = 1.23 for males and 1.04 for females

Reference: http://www.mdcalc.com/creatinine-clearance-cockcroft-gault-equation/ Accessed 13 June 2019.

10.7. Appendix 7: The Stages of Heart Failure – New York Heart Association (NYHA) Classification

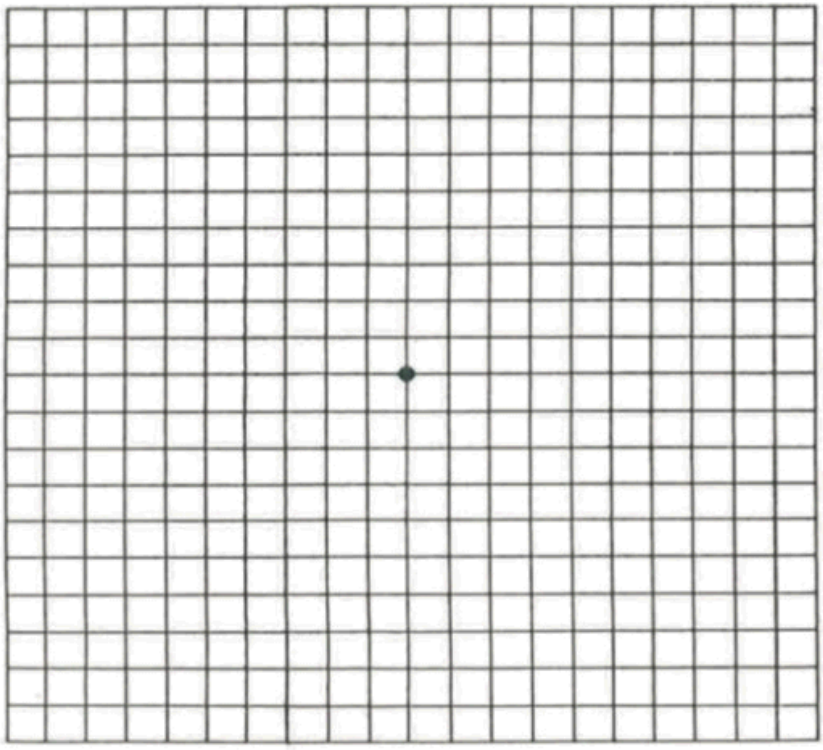
Class	Patient Symptoms
Class I (Mild)	No limitation of physical activity. Ordinary physical activity does not cause undue fatigue, palpitation, or dyspnea (shortness of breath) .
Class II (Mild)	Slight limitation of physical activity. Comfortable at rest, but ordinary physical activity results in fatigue, palpitation, or dyspnea.
Class III (Moderate)	Marked limitation of physical activity. Comfortable at rest, but less than ordinary activity causes fatigue, palpitation, or dyspnea.
Class IV (Severe)	Unable to carry out any physical activity without discomfort. Symptoms of cardiac insufficiency at rest. If any physical activity is undertaken, discomfort is increased.

Reference: Heart Failure Society of America The Stages of Heart Failure – NYHA Classification. Available at http://www.abouthf.org/questions_stages.html. Accessed October 6, 2008.

10.8. Appendix 8: Amsler Grid

AMSLER RECORDING CHART

A replica of Chart No. 1, printed in black on white for convenience of recording



Subject No.:
Date:
Examiner:
*Note: Please utilize the Amsler Recording Chart that is provided with your study materials.

10.9. Appendix 9: Drugs Classified as Strong In Vivo Inhibitors of CYP3A4/2C9 or as Moderate to Strong Inducers of CYP3A4/2C9 Enzymes

Strong CYP3A4 Inhibitors

Boceprevir	Conivaptan
Clarithromycin	Indinavir
Lopinavir	Itraconazole
Mibefradil	Ketoconazole
Nefazodone	Ritonavir
Posaconazole	Nelfinavir
Saquinavir	Erythromycin
Telaprevir	Troleandomycin
Telithromycin	Fluconazole
Voriconazole	

Strong Inhibitors: ≥5-fold increase in AUC or ≥80% decrease in CL.

Moderate to Strong CYP3A4 Inducers

Moderate CYP3A4 Inducers	
Bosentan	Efavirenz
Etravirine	Modafinil
Nafcillin	Lersivirine
Talviraline	Tipranavir
Lopinavir	
Strong CYP3A Inducers	
Avasimibe	Carbamazepine
Barbiturates eg, phenobarbital	Phenytoin
Rifabutin	Rifampin
St. John's wort	Mitotane
Enzalutamide	Apalutamide

Strong Inducers: ≥80% decrease in area under the curve (AUC). Moderate Inducers: 50% to 80% decrease in AUC.

Moderate CYP2C9 Inhibitors

Fluconazole	Amiodarone
Miconazole	Piperine
Oxandrolone	Atacigual
Tienilic acid	Azapropazone
Bucolome	Sulfaphenazole
Benzbromarone	

Moderate CYP2C9 Inducers

Carbamazepine	Rifampin
Enzalutamide	Aprepitant

Reference: University of Washington's Drug Interaction Database
http://www.fda.gov/Drugs/DevelopmentApprovalProcess/DevelopmentResources/DrugInteractionsLabeling/ucm093664.htm#4
Note: Both these references may not be exhaustive and up-to-date at any given time. Please consult the product information of ongoing and new concomitant medications for the most accurate information on potential moderate to strong inhibitors or inducers of CYP3A4 and CYP2C9.

10.10. Appendix 10: Erdafitinib Crossover

Note: no additional crossover from Investigator's Choice to erdafitinib will be permitted. Subjects who have already crossed over to erdafitinib may continue to receive study treatment and transition to the LTE Phase (please refer to Section 10.14, Appendix 14).

This appendix is intended as a supplement to the main study protocol to describe the eligibility criteria, treatment schedule, and assessments to be conducted during the Erdafitinib Crossover for subjects in Cohort 1 who have locally confirmed high-risk recurrence and who were randomized to Investigator's Choice with either intravesical gemcitabine or intravesical MMC/hyperthermic MMC. The appendix is not intended to be a stand-alone document, and rather than repeating key sections of the main protocol, cross-references back to the main protocol have been included, as applicable.

Subjects who were randomized in Cohort 1 to either gemcitabine or MMC/hyperthermic MMC, who have locally confirmed high-risk recurrence, recommendation by the investigator, and review by the sponsor's medical monitor, will be offered the option to cross over to erdafitinib, beginning with C1D1 and a more limited Schedule of Activities.

Overall Design of the Erdafitinib Crossover

Each cycle is 28 days, and administration of erdafitinib is to occur daily for up to a maximum of 2 years or until high risk disease recurrence or progression, intolerable toxicity, withdrawal of consent, there is a decision by the investigator to discontinue treatment, or the study is closed, whichever occurs first. Scheduled assessments to be performed for eligibility and treatment during the Erdafitinib Crossover are outlined in the Schedule of Activities in CO Table 1.

The amount of blood drawn from each subject during the Erdafitinib Crossover will be approximately 24 mL during screening; 241 mL through Cycle 6; 288 mL from Cycle 6 through Cycle 24; 37 mL at the EoT Visit, 12 mL during the safety follow-up, and 80 mL for subjects who have disease assessments after recurrence/progression during the Follow-up Phase for a total volume of 682 mL.

Erdafitinib Up-titration Guidelines for Crossover Subjects

The erdafitinib dose is modified to the 6-mg daily regimen (without up-titration). After review of safety and tolerability data from approximately 5 to 10 additional subjects who received the 6-mg daily regimen, the IDMC may recommend that the erdafitinib dose be modified to allow up-titration to the 8-mg daily regimen. Details of any such recommendation will be communicated separately. Should the dosing regimen be modified to include up-titration, please follow the instruction in Section 10.12, Appendix 12.

CO Table 1: Schedule of Activities: Erdafitinib Crossover

	NOTES	Screening Phase (Must begin within 60 days of recurrence)	Treatment Phase (28 days Cycle)				Follow-up Phase		
			Cycles 1, 2, 3		Cycle 4+	EoT Visit	30-day Safety Follow-up Visit	Disease Assessment Follow-up	Survival Follow-up
			Day 1	Day 14	Day1				
Visit window		- 35 days	C1:0 days C2, C3: ± 2 days	±2 days	±2 days	+7 days after last dose	30 (+7) days after last dose	Every 24 weeks ±2 weeks	Every 12 ±2 weeks
Screening/Administrative: Minimum criteria for the availability of documentation supporting the eligibility criteria are described in Section 10.2 (Appendix 2). Check clinical status again before first dose of study drug.									
Review Erdafitinib Crossover appendix of the ICF and sign to enroll		X							
Inclusion/exclusion criteria	See below for crossover inclusion and exclusion criteria.	X	X C1D1 predose						
ECOG performance status		X							
Enrollment Erdafitinib Crossover			X						
Study Drug Administration (Erdafitinib Crossover)									
Erdafitinib	The dosing regimen is 6 mg daily. (After review of safety and tolerability data from approximately 5 to 10 additional subjects dosed with the 6-mg daily regimen, the IDMC may recommend a modification of the dosing regimen to allow up-titration to the 8-mg daily regimen based on phosphate levels measured on Cycle 2 Day 1. See Section 10.12, Appendix 12.) (see guidelines in Section 6.6.1).		Once daily until 2 years of treatment have been completed, high risk recurrence or progression, intolerable toxicity, withdrawal of consent, there is a decision by the investigator to discontinue treatment, or the study is closed, whichever occurs first						
Safety Assessments: The 30-day Safety Follow-up Visit should occur before the start of any subsequent anticancer therapy, if such therapy starts within 30 days after last dose of study drug.									
Physical examination	Perform a target physical exam. See Section 8.3.1.	X	X		X C4D1, C5D1, C6D1, then every 3 cycles	X	X		
Vital Signs	See Section 8.3.2.	X	X	X	X	X	X		

	NOTES	Screening Phase (Must begin within 60 days of recurrence)	Treatment Phase (28 days Cycle)				Follow-up Phase		
			Cycles 1, 2, 3		Cycle 4+	EoT Visit	30-day Safety Follow-up Visit	Disease Assessment Follow-up	Survival Follow-up
			Day 1	Day 14	Day1				
Visit window		**- 35 days**	**C1:0 days C2, C3: ± 2 days**	**±2 days**	**±2 days**	**+7 days after last dose**	**30 (+7) days after last dose**	**Every 24 weeks ±2 weeks**	**Every 12 ±2 weeks**
12-lead ECG	ECGs should be performed at approximately the same time of day when possible. See Section 8.3.3.	X	X C2D1 only (predose)		X C4D1 only (predose)				
Review adverse events	Collected from the day the Main-study ICF is signed until 30 days after last dose of study drug (see Section 8.4).	X					X		
Concomitant medications	See Section 6.5.	X	X	X	X	X	X		
Urine or serum β-hCG pregnancy test	Women of childbearing potential only. See Section 8.3.6.	X Screening test within 7 days before treatment	X predose C1		X	X	X		
Amsler Grid Test	To be performed by treating study physician or nurse (as directed by specific site instructions) prior to beginning erdafitinib treatment. See Section 8.3.5.		X		X		X		
Ophthalmologic examination	All subjects: To be performed by an ophthalmologist; see Section 8.3.5. *During screening and then every 4 months while on study treatment up to 2 years. Ophthalmologic examinations will be performed at EOT if the last ophthalmologic examination was done ≥4 months prior to the EOT visit.	X (Only required if last ophthalmologic examination was more than 1 month prior)			C5D1 C9D1 C13D1 C17D1 C21D1 C25D1 (±2 weeks)	X *See note			
Clinical Safety Laboratory Assessments: Clinical laboratory test results (except parathyroid hormone and 1,25-dihydroxyvitamin D) must be available before the start of treatment at C1D1. Results of previous testing should be available for comparison as clinically necessary. Clinical laboratory testing will be performed at a local laboratory. The 30-day Safety Follow-up Visit should occur before the start of any subsequent anticancer therapy, if such therapy starts within 30 days after last dose of study drug.									
Hematology	Predose C1D1. For exact assessment see Section 8.3.4. After Cycle 6 Visit, perform every 3 cycles until end of treatment, eg, Cycle 6, Cycle 9, Cycle 12.	X	X		X	X			
Comprehensive metabolic panel	Predose C1D1. For exact assessment see Section 8.3.4. After Cycle 6 Visit, perform every 3 cycles until end of treatment, eg, Cycle 6, Cycle 9, Cycle 12.	X	X	X	X	X	X		

	NOTES	Screening Phase (Must begin within 60 days of recurrence)	Treatment Phase (28 days Cycle)				Follow-up Phase		
			Cycles 1, 2, 3		Cycle 4+	EoT Visit	30-day Safety Follow-up Visit	Disease Assessment Follow-up	Survival Follow-up
			Day 1	Day 14	Day1				
Visit window		**- 35 days**	**C1:0 days C2, C3: ± 2 days**	**±2 days**	**±2 days**	**+7 days after last dose**	**30 (+7) days after last dose**	**Every 24 weeks ±2 weeks**	**Every 12 ±2 weeks**
Phosphate	Prior to erdafitinib dose on C1D1. See Section 8.3.4.	X	X	X	X				
1,25-dihydroxyvitamin D	All subjects	X	X C13D1 (±1 week)			X			
Parathyroid hormone	After Cycle 6 Visit, perform every 3 cycles until end of treatment, eg, Cycle 6, Cycle 9, Cycle 12 (see Section 8.3.4).	X	X C2, C3 only	X C1 only	X				
Efficacy and other assessments									
Cystoscopy (with biopsy of visible lesions if present)	At Screening, if TURBT was done within 6 weeks before randomization, then the findings of the complete resection from TURBT can be used instead of Screening cystoscopy. During the Treatment Phase, subjects who demonstrate a positive urine cytology with a negative cystoscopy will remain on erdafitinib until the next disease assessment. If both the urine cytology and cystoscopy are positive for high-risk recurrence or progression at the next disease assessment, the subject will discontinue erdafitinib. Tissue from any positive biopsy (any grade of recurrence) should be sent for CCI to central laboratory. (see Section 8.2.1.5).	X	C3D1 then every 12 weeks (±1 week) until C26D1 or until disease recurrence or progression.			X		X For 2 years or until disease recurrence/ progression (see Section 8.1.3.2.1)	
TURBT			X When clinically indicated						
Bladder mapping	Bladder mapping at screening will be only done if there is prior history of CIS. During treatment or follow-up phase will only be done if urine	X							

	NOTES	Screening Phase (Must begin within 60 days of recurrence)	Treatment Phase (28 days Cycle)				Follow-up Phase		
			Cycles 1, 2, 3		Cycle 4+	EoT Visit	30-day Safety Follow-up Visit	Disease Assessment Follow-up	Survival Follow-up
			Day 1	Day 14	Day1				
Visit window		**- 35 days**	**C1:0 days C2, C3: ± 2 days**	**±2 days**	**±2 days**	**+7 days after last dose**	**30 (+7) days after last dose**	**Every 24 weeks ±2 weeks**	**Every 12 ±2 weeks**
	cytology is positive for malignant cells and cystoscopy is negative.								
Urine cytology	Urine sample may be collected either from bladder washing during cystoscopy or from a voided urine specimen (bladder wash specimen is preferred). Analysis will be done locally (see Section 8.2.1).	X	C3D1 then every 12 weeks (±1 week) until C26D1 or until disease recurrence or progression.			X		X For 2 years or until disease recurrence/ progression (see Section 8.1.3.2.1)	
CT/MRI Urogram	If a subject cannot tolerate intravenous contrast, a retrograde pyelogram is acceptable (see Section 8.2.1).	X			Starting from Cycle 6, every 24 weeks (±2 weeks) until recurrence/progression.				
Blood (plasma) for ctDNA	See Section 8.9.		C1D1 (predose), C3D1, then every 12 weeks (±1 week) until C26D1 or until disease recurrence or progression.			X		X For 2 years or until disease recurrence/ progression (see Section 8.1.3.2.1)	
Survival status and subsequent anticancer therapy	May be assessed via telephone call, email, or visit to the study site. Survival status, start of alternate anticancer therapy, and results of standard-of-care cystoscopy will be monitored at least every 12 weeks (±2 weeks) until death, withdrawal of consent, or end of study, whichever occurs first. See Section 8.1.3.2.2.								X

β-hCG= beta-human chorionic gonadotropin; C=cycle; CT=computed tomography; ctDNA=circulating tumor DNA; CXDX=Cycle X Day X; D=day; ECG=electrocardiogram; ECOG=Eastern Cooperative Oncology Group; EoT=End of Treatment; ICF=informed consent form; IDMC= Independent Data Monitoring Committee; MRI=magnetic resonance imaging

Eligibility Criteria for Erdafitinib Crossover

To be eligible for cross over to treatment with erdafitinib, subjects in Cohort 1 randomized to Investigator's Choice with gemcitabine or MMC/hyperthermic MMC must meet all of the following inclusion and none of the exclusion criteria.

Inclusion Criteria for Erdafitinib Crossover

Each potential subject must satisfy all of the following inclusion criteria before beginning Erdafitinib Crossover.

1. Eastern Cooperative Oncology Group (ECOG) performance status Grade 0 or 1 (Section 10.5)

2. Criterion modified per Amendment 2

   2.1 Adequate bone marrow, liver, and renal function:

   a. Bone marrow function (without the support of cytokines or erythropoiesis-stimulating agent in preceding 2 weeks):

      i. Absolute neutrophil count (ANC) ≥1,000/mm^3

      ii. Platelet count ≥75,000/mm^3

      iii. Hemoglobin ≥8.0 g/dL

   b. Liver function:

      i. Total bilirubin ≤1.5 x institutional ULN OR direct bilirubin ≤ULN for subjects with total bilirubin levels >1.5xULN

      ii. Alanine aminotransferase (ALT) and aspartate aminotransferase (AST) ≤2.5x institutional ULN

   c. Renal function:

      Creatinine clearance >30 mL/min calculated using the Cockcroft-Gault formula, (Section 10.6).

   d. Phosphate:

      <ULN within 14 days before the first dose of study drug on Cycle 1 Day 1 (medical management allowed)

3. Must sign an ICF (or their legally acceptable representative must sign) within 60 days of recurrence indicating that he or she understands the purpose of, and procedures required and is willing to participate in the Erdafitinib Crossover.

4. A woman of childbearing potential must have a negative pregnancy test (β-hCG) (urine or serum) within 7 days before first dose of erdafitinib in the Erdafitinib Crossover.

5. Contraceptive use by men or women should be consistent with local regulations regarding the use of contraceptive methods for subjects participating in clinical studies.

   a. For women of childbearing potential (defined as: fertile, following menarche and until becoming postmenopausal unless permanently sterile):

   - Highly effective method of contraception (failure rate of <1% per year when used consistently and correctly).
   - Permanent sterilization methods (for the purposes of this study) include hysterectomy, bilateral salpingectomy, and bilateral oophorectomy).
   - Examples of highly effective contraceptives include:
     - user-independent methods: implantable progestogen-only hormone contraception associated with inhibition of ovulation; intrauterine device; intrauterine hormone-releasing system; vasectomized partner; sexual abstinence: true abstinence when this is in line with the preferred and usual lifestyle of the subject (Note: periodic abstinence [eg, calendar, ovulation, symptothermal, post-ovulation methods], declaration of abstinence for the duration of exposure to study drug, and withdrawal are not acceptable methods of contraception.)
     - user-dependent methods: combined (estrogen- and progestogen-containing) hormonal contraception associated with inhibition of ovulation: oral, intravaginal, and transdermal; progestogen-only hormone contraception associated with inhibition of ovulation: oral and injectable
   - agrees to remain on a highly effective method of contraception during the study and for at least 3 months after the last dose of study drug
   - agrees to not donate eggs (ova, oocytes) for the purposes of assisted reproduction during the study and for at least 3 months after the last dose of study drug
   - not breastfeeding and not planning to become pregnant during the study and for at least 3 months after the last dose of study drug

   b. For men who are sexually active with women of childbearing potential:

   - agrees to use a condom with spermicidal foam/gel/film/cream/suppository
   - agrees to not donate sperm during the study and for at least 3 months after the last dose of study drug
   - not planning to father a child during the study or within 3 months after the last dose of study drug

6. Criterion added per Amendment 1.

Locally confirmed high-risk recurrence while receiving Investigator's Choice, and the subject has all visible tumor resected completely prior to enrollment and documented at baseline cystoscopy

Exclusion Criteria for Erdafitinib Crossover

Any individual who meets any of the following criteria will be excluded from participating in the Erdafitinib Crossover:

1. Histologically confirmed, muscle-invasive (T2 or higher stage) urothelial carcinoma of the bladder

2. Histopathology demonstrating a small cell component, pure adenocarcinoma, pure squamous cell carcinoma, or pure squamous CIS of the bladder

3. Active malignancies (ie, progressing or requiring treatment change in the last 24 months) other than the disease being treated under study. The only allowed exceptions are:

    a. skin cancer treated within the last 24 months that is considered completely cured

    b. adequately treated LCIS and ductal CIS

    c. history of localized breast cancer and receiving antihormonal agents, or history of localized prostate cancer (N0M0) and receiving androgen deprivation therapy

4. Current central serous retinopathy or retinal pigment epithelial detachment of any grade

5. History of uncontrolled cardiovascular disease including:

    a. any of the following in the preceding 3 months: unstable angina, myocardial infarction, ventricular fibrillation, Torsades de Pointes, cardiac arrest, or known congestive New York Heart Association Class III-IV heart failure (Section 10.7), cerebrovascular accident, or transient ischemic attack.

    b. QTc prolongation as confirmed by ECG assessment at screening (Fridericia; QTc >480 milliseconds).

    c. Pulmonary embolism or other venous thromboembolism within the preceding 2 months.

6. Criterion modified by Amendment 1.

    6.1. Known HIV infection, unless the subject has been on a stable anti-retroviral therapy regimen for the last 6 months or more and has had no opportunistic infections and a CD4 count >350 in the last 6 months

7. Criterion modified by Amendment 1.

7.1. Evidence of active hepatitis B or C infection (for example, subjects with history of hepatitis C infection but normal hepatitis C virus polymerase chain reaction test and subjects with hepatitis B with positive HBsAg antibody are allowed).

8. Not recovered from toxicity of prior anticancer therapy (except toxicities which are not clinically significant such as alopecia, skin discoloration, neuropathy, hearing loss)

9. Impaired wound healing capacity defined as skin/decubitus ulcers, chronic leg ulcers, known gastric ulcers, or unhealed incisions

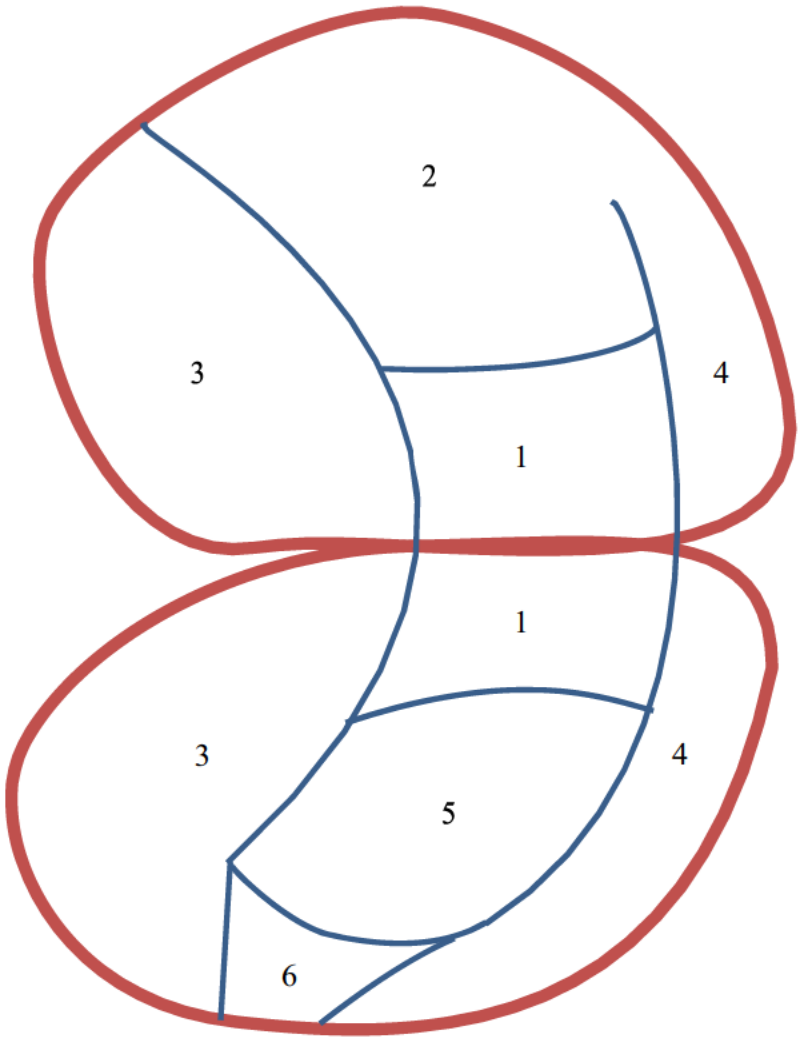
10. Major surgery within 4 weeks before Cycle 1 Day 1 of erdafitinib treatment (TURBT is not considered major surgery)

11. Criterion modified per Amendment 2

11.1 Severe hypocalcemia (corrected serum calcium of <7 mg/dl), acute and unhealed bone fractures, known underlying bone disease, or at an increased risk of bone fracture. In addition, any condition for which, in the opinion of the investigator, participation would not be in the best interest of the subjects (eg, compromise the well-being) or that could prevent, limit, or confound the protocol-specified assessments. Examples include ongoing active infection requiring systemic therapy and uncontrolled ongoing medical conditions.

12. 12.1 Criterion deleted with Amendment 3

10.11. Appendix 11: Bladder Map



1. Dome, 2. Anterior wall, 3. Right lateral wall, 4. Left lateral wall, 5. Posterior wall, 6. Bladder neck/trigone

10.12. Appendix 12: Guidance for 6 mg Daily Dose with Up-titration

DO NOT FOLLOW THIS GUIDANCE UNLESS SPECIFICALLY INSTRUCTED TO DO SO BY THE SPONSOR. After review of safety and tolerability data from approximately 5 to 10 additional subjects who received the 6 mg daily dosing regimen, the IDMC may recommend a dose modification to up-titrate from 6 mg to 8 mg daily based on phosphate levels at Cycle 2 Day 1. The details of the IDMC recommendation will be communicated in writing to the investigative sites and, per local regulation, to health authorities. The pharmacodynamic biomarker (serum phosphate) data considered in selection of the 6-mg daily starting dose (with up-titration to 8-mg daily) are summarized below.

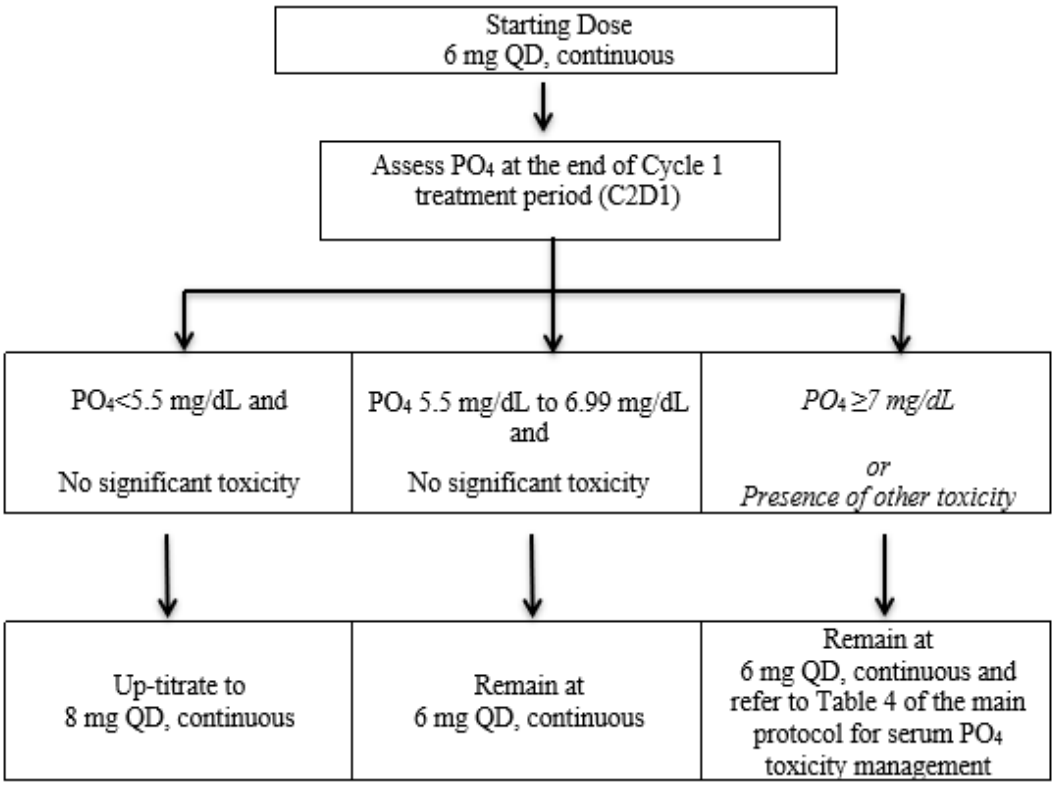
Data supporting Up-titration to the 8-mg Daily Dosing Regimen

Data from Phase 1 Study 42756493EDI1001 indicate that an increase in the serum phosphate level of at least 35% over the baseline level may be associated with antitumor response. Therefore, a pharmacodynamic (PD) objective of a 50% increase in the serum phosphate level over baseline is considered clinically meaningful. Given the median serum phosphate level of 3.6 mg/dL at baseline in the Phase 1 study, and the phosphate level of 3.3 mg/dL at baseline in the Phase 2 Study BLC2001 (BLC2001 Interim Analysis 1 data), an increase of at least 50% for the majority of subjects would correspond to an absolute serum phosphate level of approximately 5.5 mg/dL (which is also 35% over the upper limit of normal [ULN] for serum phosphate). Overall, 6 mg is the lowest sustained dose that achieves, in 77.8% of subjects in the Phase 1 study, hyperphosphatemia consistent with a biologically significant inhibition of FGFR. Emerging pharmacokinetic/pharmacodynamic modeling suggests that CCI [redacted] CCI [redacted] and would potentially benefit from dose up-titration.

Guidelines for Dose Titration of Erdafitinib from 6-mg Daily to 8-mg Daily Regimen

Erdafitinib treatment may be up-titrated or maintained based on the phosphate level measured on Cycle 2 Day 1 taking into account any toxicity to that day, as described in in the figure below. The dose reduction schedule is provided in the table on the following page.

Appendix 12, Figure 1: Dose Titration of Erdafitinib from 6-mg to 8-mg Daily Regimen



Appendix 12, Table 1: Dose Schedule and Dose Reductions - 6 mg Daily Dosing (with Up-titration)

Category	With Up-titration
Starting dose	6 mg
Up-titration	8 mg
1st dose reduction	6 mg
2nd dose reduction	5 mg
3rd dose reduction	4 mg
4th dose reduction	STOP

10.13. Appendix 13: Guidance on Study Conduct During a National Disaster for Enrolled Subjects

It is recognized that a national disaster, eg, pandemic, may have an impact on the conduct of this clinical study. In alignment with the recent health authority guidances, the Sponsor is providing guidance for study-related patient management in the event of disruption to the per-protocol conduct of the study as outlined throughout the protocol. These measures are to be followed on a temporary basis. Once the national situation allows, the usual study conduct methods will resume. This guidance does not supersede any local or government requirements or the clinical judgement of the Investigator to protect the health and well-being of patients and site staff. If at any time a subject's safety is considered to be at risk, study drug will be discontinued, and study follow-up will be conducted, as outlined in the protocol. (Note: These measures do not apply to subjects who have not initiated study treatment.)

Scheduled visits for safety monitoring and other protocol-required assessments that cannot be conducted in-person will be performed remotely/virtually (eg, telephone contact, telemedicine, remote nursing, remote administration of study drug), where feasible, or delayed until the time at which access is determined to be appropriate by the Investigator and Sponsor. Study assessments requiring investigator judgement, should be conducted by the investigator. At each contact, subjects will be interviewed to collect adverse events data and any changes to concomitant medications. Subjects will also be questioned regarding general health status to fulfill the physical examination requirement.

Flexibility for all protocol-required assessments will be provided on a case by case basis, and with agreement between the Sponsor and Investigator. However, every effort should be made to adhere to protocol-specified assessments, including follow-up, if it is in the best interest of the subject. The Sponsor will continue to monitor the conduct and progress of the clinical study and any changes (eg, delay or discontinuation in recruitment) will be communicated to the sites and health authorities.

Guidance specific to this protocol:

- Missed assessments or change to protocol assessments will be documented in the source documentation and in the case report form. All study conduct performed outside of the protocol should be documented in the source documentation.
- If a site visit is not feasible, the Investigator may discuss with the Sponsor other mechanisms for the subject to receive study drug (eg, direct to patient shipment, obtain from another Investigative Site participating in the study). Any change in dispensing study drug must be documented in the source documentation and eCRF.
- Safety assessments may be conducted at a local facility after discussion with the Sponsor.
- Critical laboratory tests, imaging or other diagnostic tests may be done at an authorized/certified (as legally required nationally) local laboratory or clinical facility. A copy of the laboratory report must be reviewed by the Investigator and retained, along with the reference ranges, for the source documentation and provided with the eCRF.

- Consenting of subjects for full-study screening and for molecular eligibility screening will be performed as applicable (including also remote consenting by telephone or video consultation) according to local guidance for the informed consent.

Note: Administration of non-live vaccines approved or authorized for emergency use (eg, COVID-19) by local health authorities are allowed before or during this study. For guidance on vaccination, please refer to National Comprehensive Cancer Network (NCCN). Preliminary recommendations of the NCCN COVID-19 Vaccination Advisory Committee* Version 1.0 1/22/2021. NCCN https://www.nccn.org/covid-19/pdf/COVID-19_Vaccination_Guidance_V1.0.pdf (2021), Garassino, M. C. et al. The European Society for Medical Oncology call to action on COVID-19 vaccinations and patients with cancer: Vaccinate. Monitor. Educate. Ann. Oncol. https://doi.org/10.1016/j.annonc.2021.01.068 (2021), and Desai et al COVID-19 vaccine guidance for patients with cancer participating in oncology clinical trials Nature Reviews Vol18; 313 https://doi.org/10.1038/s41571-021-00487-z.

10.14. Appendix 14: Long-term Extension Phase

The purpose of the Long-term Extension (LTE) Phase is to provide continued access to study drug, while minimizing data collection burden. Subjects who are continuing to derive benefit from erdafitinib or Investigator's Choice of either intravesical gemcitabine or intravesical MMC/hyperthermic MMC, as determined by their investigator, may have continued access to their assigned study drug in the LTE Phase of this study (see Section 6.7). Note:

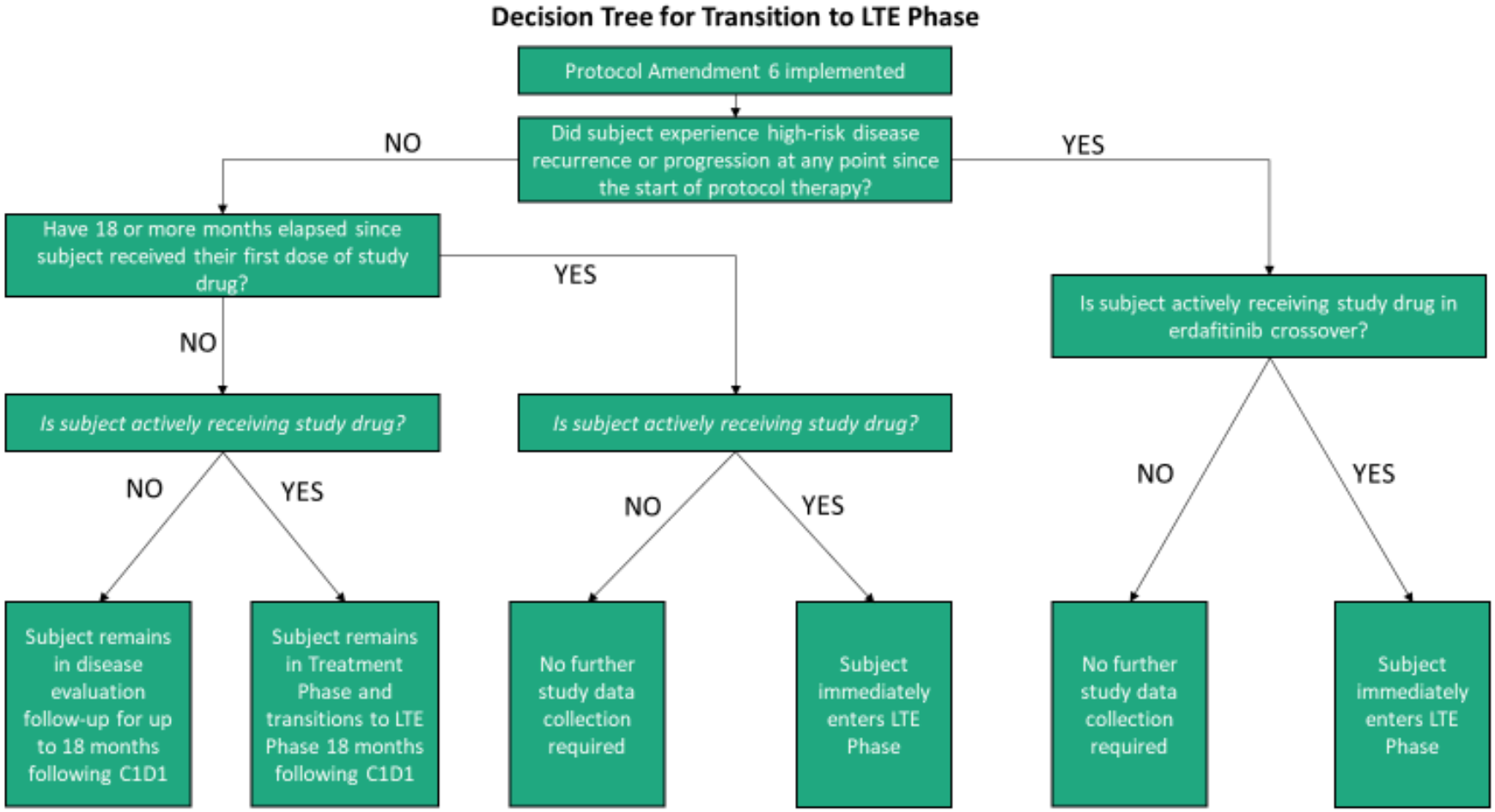
- Subjects must be actively receiving study treatment to be able to transition to the LTE Phase. Subjects who have already permanently discontinued treatment will not be permitted to enter the LTE Phase.
- Subjects eligible to enter the LTE Phase will continue to receive the study drug that they were receiving at the time of Amendment 6 implementation; no additional crossover from Investigator's Choice to erdafitinib will be permitted (including in the LTE Phase).
- Subjects who elect not to continue in the LTE Phase will be discontinued from the study.

As an alternative to entering the LTE Phase, subjects receiving erdafitinib may continue to receive treatment on any other post-trial access program, when permitted by local regulations, or by receiving commercially available drug.

Subjects may enter the LTE Phase following implementation of Amendment 6, provided they meet the criteria for entry. LTE Figure 1 is a decision tree which depicts transition to the LTE Phase at the individual subject level, according to the following factors: whether the subject has experienced high-risk disease recurrence or progression at any point since the start of protocol therapy, whether 18 or more months have elapsed since the subject received their first dose of study drug (ie, Cycle 1 Day 1), and whether the subject is actively receiving study drug.

No data will be collected in the eCRF during the LTE Phase, and only SAEs will be reported to the company safety repository. No analyses other than routine periodic safety review encompassing reported SAEs are planned for the LTE Phase.

LTE Figure 1: Decision Tree for Transition to LTE Phase



Study Treatment Administration

Study treatment (erdafitinib or investigator's choice of either intravesical gemcitabine or intravesical MMC/hyperthermic MMC) may continue to be administered as described in Section 6.1.1 Erdafitinib, Section 6.1.2.1 Gemcitabine Administration, and Section 6.1.2.2 Mitomycin C Administration of the protocol.

Prohibitions and Restrictions

Refer to protocol Sections 6.5.2 and 6.5.3.

Study Procedures for the Long-term Extension

All subjects continuing in the LTE Phase will follow the schedule of activities provided in LTE Table 1.

Clinical assessments will be conducted according to the standard of practice or to other country regulation. SAEs will be reported to the Company safety repository as specified in LTE Table 1. Specific safety assessments may be performed if required by local Health Authorities.

Assessment of Anticipated Events will cease at start of the LTE Phase.

Discontinuation Criteria for the Long-term Extension

Subjects continue on study drug as defined in Section 6.7.

Case Report Form Completion

Instructions will be provided in the CRF completion guidelines, for specific CRF pages that need to be completed upon subject transition to the LTE Phase. No data will be collected in the eCRF for subjects in the LTE Phase. However, documentation of assessments performed should be done in the subject file/source notes.

LTE Table 1: Schedule of Activities

Procedures	**Continuing to Receive Erdafitinib or Investigator's Choice of Either Intravesical Gemcitabine or Intravesical MMC/Hyperthermic MMC in the LTE Phase**
Informed Consent	
	Upon implementation of Amendment 6, subjects will be required to sign the updated Main-study ICF prior to transitioning to the LTE Phase.
Study Drug Dispensing	
Erdafitinib or Investigator's Choice of either intravesical gemcitabine or intravesical MMC/hyperthermic MMC	Continuous. See Section 6.1.1 Erdafitinib, Section 6.1.2.1 Gemcitabine Administration, Section 6.1.2.2 Mitomycin C Administration, and Section 6.7 Access to Study Drug in the Long-term Extension Phase.

Study drug accountability	Drug accountability procedures must be performed for all treatment administered during the LTE Phase of the study (see Section 6.2).
Safety	
Hematology and blood chemistry	Safety laboratory assessments for erdafitinib and investigator's choice of either intravesical gemcitabine or intravesical MMC/hyperthermic MMC will be performed as per local prescribing information or standard of care. (If erdafitinib is not approved in a country/territory, the erdafitinib Investigator's Brochure will be utilized.) In addition, safety laboratory assessments will be performed as clinically indicated.
Other safety assessments	Safety assessments for erdafitinib and investigator's choice of either intravesical gemcitabine or intravesical MMC/hyperthermic MMC will be performed as per local prescribing information or standard of care. (If erdafitinib is not approved in a country/territory, the erdafitinib Investigator's Brochure will be utilized.) In case of drug-related toxicity, refer to dose modification guidance provided in Section 6.6. In addition, safety assessments will be performed as clinically indicated. During the LTE Phase, only SAEs will be reported to the company safety repository. Pregnancy reporting should continue as described in Section 8.4.5. No other safety data will be collected.
Efficacy	
	Per local practice. No data is collected.

LTE=Long-Term Extension; MMC=mitomycin C

10.15. Appendix 15: Protocol Amendment History

The Protocol Amendment Summary of Changes Table for the current amendment is located directly before the Table of Contents (TOC).

Amendment 5 (24 September 2021)

Overall Rationale for the Amendment: A CCI [redacted] utilizing CCI [redacted] is under development. The collection of an additional urine sample after disease recurrence and before the TURBT, and another urine sample before the TURBT procedure at the End of Treatment Visit were added to aid the CCI [redacted].

Section Number and Name	Description of Change	Brief Rationale
1.3, Schedule of Activities; 4.1, Overall Design; 8.1.1, Screening; 8.9, Biomarkers; 10.2, Regulatory, Ethical, and Study Oversight Considerations	In the Schedule of Activities (under the new "Voided urine sample for CCI [redacted]" row) and Section 8.9 (under the new subheader "Urine for CCI [redacted] (ie, for biomarker research)"), instruction regarding collection of 2 voided urine samples was added: one sample will be collected after disease recurrence and before the TURBT (except for patients being considered for study after TURBT) and another sample will be collected at the time of high-risk disease recurrence before the TURBT procedure at the End of Treatment Visit. In the Schedule of Activities added in the notes that the pre-study urine samples for subjects who are found to have low or intermediate risk disease recurrence (except for eligible Cohort 3 subjects) must be discarded as these patients would not be eligible for the study. Also, an additional row for the "Urine Sample for Assay Development ICF" was added to the Schedule of Activities. In section 4.1, added that subjects being considered for the study before the TURBT, will provide a voided urine sample after disease recurrence and before TURBT. These subjects must sign the Informed Consent Form (ICF) for Urine Sample for Assay Development. Subjects being considered for study after TURBT will not provide this urine sample Also, mentioned at the end of the overview that additional urine samples will be collected for assay development. The consent for the urine sample before screening is added to Section 8.1.1 and Section 10.2 (Informed Consent Process subheader). In Section 8.9, the instrumented urine sample was changed to voided urine sample.	The collection of 2 additional urine samples, as described under the "Description of Change" were added to aid the CCI [redacted]
1.3, Schedule of Activities; 4.1, Overall Design; 8.9, Biomarkers	In the Schedule of Activities, the row "Urine for CCI [redacted] was expanded to add "(ie, for biomarker research") and in the notes of this row CCI [redacted] was replaced with	Revisions were made to distinguish urine samples for biomarker research from urine samples for assay development.

Section Number and Name	Description of Change	Brief Rationale
	"biomarker research" (as well as in the text of Section 8.9). In Section 4.1, mentioned that additional urine samples may be collected for exploratory biomarker research (these are not new samples, already listed on the Schedule of Activities). In Section 8.9, the subsection title CCI CCI From Urine" was revised to "Urine for CCI (ie, for Biomarker Research)" and information related to the CCI CCI was moved to the new subjection titled "Urine for Assay Development" described earlier in this amendment table. As, a voided sample will be collected rather than an instrumented urine sample this notation was also made. Mentioned the urine sample collected at the time of high-risk disease recurrence before the TURBT procedure during the study treatment phase. (This is not a new sample, ie, previously shown on the Schedule of Activities.)	
8.1.1.1, Molecular Eligibility Screening Phase (Cohort 1 and Cohort 2); 8.9, Biomarkers	Under the "Post-BCG Tissue Molecular Screening" subsection, removed the mention of signing the Molecular Eligibility ICF, as this is not required for patients for whom molecular eligibility was determined based on a local (historical) report. In Section 8.9 ("Circulating Biomarkers" subsection), corrected the Phase 2 study number (ie, 42756493BLC2001).	Corrections
6.6.2.1.5, Guidelines for the Management of Eye Toxicity Associated with Vision Changes; 8.4.7, Adverse Events of Special Interest; 10.3 Appendix 3 Adverse Events: Definitions and Procedures for Recording, Evaluating, Follow-up, and Reporting	In Section 8.4.7, corneal or retinal abnormalities were removed as adverse events of special interest, as the adverse event of special interest is the combined term Central Serous Retinopathy. In Section 6.6.2.1.5, information regarding the adverse event of special interest and the special reporting requirement was removed as not applicable to this section. The reporting requirement for treatment-emergent retinal abnormalities (ie, Grade 3 or higher reported as a serious adverse event) was placed in Section 10.3, under Special Reporting Situations. Also, a reference to instructions for assessing visual abnormalities with a reference to the applicable section was added. The special reporting requirement was removed from Section 8.4.7.	The adverse event of special interest (AESI) termed "Corneal or retinal abnormalities" was replaced with the AESI term "central serous retinopathy". Retinal toxicities have been characterized as an adverse AESI in the Erdafitinib Clinical Development Program. Central serous retinopathy is an umbrella term being used to capture treatment-emergent retinal toxicities. However, retinal abnormalities should continue to be reported as serious adverse events if the severity is Grade 3 or higher.
6.1.1, Erdafitinib	Guidance for subjects with CYP2C9 *3/*3 genotype added.	To provide guidance for subjects with CYP2C9 *3/*3 genotype
6.5.3 Precautions for Concomitant Medications	Edited precaution language in the first bullet for consistency with current Investigator Brochure. Guidance for use with CYP3A4 substrates and OCT2 substrates added.	Aligned with updates to the current Investigator's Brochure.

Section Number and Name	Description of Change	Brief Rationale
6.5.1 Permitted Medications	Text added relating to coronavirus disease 2019 (COVID-19) vaccination.	Guidance added relating to COVID-19 vaccination.
6.6.2.1.2 Guidelines for the Management of Dry Mouth and Mucositis; 6.6.2.1.3 Guidelines for the Management of Dry Skin and Skin Toxicity; 6.6.2.1.4 Guidelines for the Management of Nail Toxicity (Onycholysis, Onychodystrophy, and Paronychia); 6.6.2.1.5 Guidelines for the Management of Eye Toxicity Associated With Vision Changes	Minor edits were added throughout these tables.	Harmonization of presentation of toxicity management guidance across the development program.
4.2.2, Participant Input Into Design	Explanation of how the results of the study may be made available to participants.	To comply with an update to the company template.
10.2, Regulatory and Ethical Considerations	Addition of text relating to protocol clarification communications	Per update to company protocol template.
10.3 Appendix 3 Regarding Adverse Events	Clarification of text regarding disease progression.	Per update to company protocol template.
10.13 Appendix 13: Guidance on Study Conduct During a National Disaster for Enrolled Subjects	Guidance relating to administration of non-live vaccines added.	Per program-wide change.
1.3, Schedule of Activities; 6.1.2, Investigator's Choice of Treatment - Cohort 1 Only	In the Schedule of Activities (under the "Investigator Choice" row) and in Section 6.1.2, provided instruction regarding additional induction and maintenance doses and the timing of pre-dose assessments, if >4 induction doses are given and the start of the monthly maintenance dose falls on Day 8, Day 15, or Day 22 of subsequent cycles.	Added information from the clarification memorandum issued 30 July 2021. This memorandum clarifies the flexibility of giving additional induction and maintenance doses and the timing of the corresponding predose assessments.
Synopsis; 4.1, Overall Design	In the Synopsis and Section 4, removed text regarding no application of electricity around the tumor.	Removed text that is no longer applicable, as tumors are now excised per standard practice as mentioned in an earlier amendment.
Throughout the protocol	Minor grammatical, formatting, or spelling changes were made.	Minor errors were noted.

Amendment 4 (08 February 2021)

Overall Rationale for the Amendment: The erdafitinib dose is modified to 6 mg daily to improve tolerability while maintaining activity to prevent disease recurrence in the non-muscle invasive bladder cancer (NMIBC) population. The Independent Data Monitoring Committee (IDMC) for this study reviewed safety data for the first 4 subjects treated with erdafitinib and recommended that the change in dosing to 6 mg daily be implemented effective immediately to prevent any new or ongoing subjects from discontinuing study treatment prematurely due to intolerance to therapy. Further, the IDMC plans to review safety and tolerability data from approximately 5 to 10 additional subjects treated with the erdafitinib 6-mg daily regimen (without up-titration) and with at least 2 months of data after initiation of study drug to determine whether up-titration is feasible in this population. The erdafitinib dose of 6 mg daily (with and without up-titration) has demonstrated clinical activity with lower rates of Grades 3 and 4 drug-related treatment-emergent adverse events (TEAEs), drug-related TEAEs leading to dose interruptions, and drug-related TEAEs leading to discontinuation in subjects with advanced or metastatic urothelial carcinoma in Study 42756493BLC2001 (hereafter referred to as Study BLC2001). Therefore, the lower dosing regimen of 6 mg daily (without up-titration) may be better suited, with respect to the CCI CCI for this patient population without advanced, life-threatening disease. Due to the modification to the dose of erdafitinib, the drug-drug interaction (DDI) substudy was removed, as it was designed specifically for the 8-mg dosing regimen.

Section Number and Name	Description of Change	Brief Rationale
Synopsis, Treatment Groups and Duration; 1.3 Schedule of Activities; 2.2.2 Erdafitinib; 4.1 Overall Design; 4.3.1 Erdafitinib Dose Selection; 6.1.1, Erdafitinib; 6.6.1 Erdafitinib Up-titration Guidelines; Table 2; Appendix 10: Erdafitinib Crossover, CO Table 1; Appendix 12: Guidance for 6 mg Daily Dose with Up-titration	In the Synopsis, Schedule of Activities, Section 4.1 (Overall Design), Section 4.3.1 (Erdafitinib Dose Selection), Section 6.1.1 (Erdafitinib), Section 6.6.1 (Erdafitinib Up-titration Guidelines) and Appendix 10 (the Crossover Schedule of Activities), the dosing regimen was modified to 6 mg daily. These sections also state that after review of safety and tolerability data from approximately 5 to 10 additional subjects dosed with the 6-mg daily regimen (without up-titration), the IDMC may recommend a modification of the dosing regimen to allow up-titration to the 8-mg daily regimen. Sections 6.1.1 and 6.6.1 refer to information regarding up-titration to the 8-mg daily dosing regimen in Section 10.12 (Appendix 12) and in Section 6.6.1 the former up-titration information was removed. The Synopsis (Overall Design) and Section 4.1 also mention that the details of the IDMC recommendation will be communicated in writing to the investigative sites and, per local regulation, to health authorities. Also, Table 2 (Erdafitinib Dose Reduction Levels) was amended to provide the sequence of reduction for the new dosing regimen. Section 2.2.2 provides data from BLC2001 reviewed in consideration of the dose modification to 6 mg daily, ie, data showing clinical activity in the dosing regimens (6-and 8-mg daily regimens) with CCI tolerability for the 6-mg daily compared with the 8-mg daily dosing regimen. Also, data from an analysis for subjects who received the 6-mg daily dosing regimen (with and	The dosing regimen was modified to 6 mg daily without up-titration (previously 8 mg daily with up-titration to 9 mg daily) based on IDMC recommendation after review of safety data from subjects enrolled in the BLC2003 study, thus far, and data from the BLC2001 study.

Section Number and Name	Description of Change	Brief Rationale
	without up-titration) were provided showing comparable results regardless of up-titration. In addition to the dose modification, Section 4.3.1 also highlights that based on efficacy and safety data from patients with advanced or metastatic urothelial carcinoma (BLC2001), the 6-mg dosing regimen may be better suited with respect to CCI for the early bladder cancer population of NMIBC. Data in Section 2.2.2 that support this position are referenced. Background on the IDMC review is mentioned. The former information supporting the original 8-mg dosing regimen was removed.	
Synopsis, Other secondary objectives for all cohorts; Synopsis, Overall Design; Synopsis, Statistical Methods; Schedule of Activities; 3 Objectives and Endpoints; 4 Overall Design; 4.2.1 Study-specific Ethical Design Considerations; 5 Study Population; 5.1 Inclusion Criteria; 5.2 Exclusion Criteria; 6 Study Drug;	The DDI Substudy presented in Appendix 10 (Section 10.10) was removed. As a result, Inclusion Criteria 7.1 was modified to remove the creatinine requirement for the DDI substudy. Also, the note, after the list of exclusion criteria in Section 5.2, regarding ensuring that enrollment criteria have been met at screening was revised to remove instruction for the DDI substudy. The information related to the DDI substudy was removed from the Schedule of Activities, ie, Inclusion/Exclusion Criteria, Randomization Cohort 1, and Erdafitinib rows were modified to remove mentions of the DDI substudy; and the DDI-substudy specific rows were deleted. Throughout the protocol, the mention of elements related to the DDI substudy have been removed.	Due to the modification in the starting dose of erdafitinib (to 6 mg daily), the DDI substudy was removed as it was designed for an 8-mg dose.

Section Number and Name	Description of Change	Brief Rationale
8 Study Assessments and Procedures; 8.1.2 Treatment Phase; 8.6.1 Evaluations; 8.6.2 Analytical Procedures; 9.4.6.1 Pharmacokinetic Analyses; 10.10 (Appendix 10) Erdafitinib Crossover		
10.10 Drug-drug interaction study	Due to the removal of the DDI substudy (Section 10.10, Appendix 10) and the addition of the appendix for up-titration if recommended by the IDMC (as Section 10.12, Appendix 12) the remaining sections (appendices) have been renumbered.	Renumbering of the appendices due to removal of Appendix 10 containing the DDI substudy

Amendment 3 (26 October 2020)

Overall Rationale for the Amendment: The time point of the tissue collection for molecular eligibility testing has been expanded to time before treatment with BCG (ie, previously required at the time of recurrence after BCG therapy) to provide more opportunity for collection of a sufficient tumor sample. Clarifications for histopathology sampling, bladder mapping for cross over study and acquisition of good quality Optical Coherence Tomography (OCT) scan were added. Instructions on combination with moderate CYP2C9 and strong CYP3A inhibitors or inducers was added. Other minor clarifications and alignment with updated oncology protocol template text were also included.

Section number and Name	Description of Change	Brief Rationale
1.3, Schedule of Activities; 5.1, Inclusion Criteria; 8.1.1.1 Molecular Eligibility Phase; Figure 2 (new); 8.1.1.2, Cohort 3 Molecular Eligibility	Inclusion Criterion 3 (now numbered 3.2) was revised to allow testing of molecular eligibility to occur any time prior to enrollment by removing the text, "at the time of recurrence after BCG therapy." This change was also reflected in the Schedule of Activities (Notes for "Tumor tissue for molecular eligibility...") and in the sections regarding molecular eligibility (8.1.1.1 and 8.1.1.2). In Section 8.1.1.1, added that tissue obtained before BCG treatment must also be submitted for central confirmation of fibroblast growth factor receptor (FGFR) status. A figure to depict the tissue testing paradigm for this study (Figure 2) was also added to Section 8.1.1.1.	To allow tissue testing for molecular eligibility any time prior to enrollment to provide more opportunity for collection of a sufficient tumor sample. The consent instruction was changed accordingly.
8.2.1.4, Histopathologic Assessment and FGFR (All Cohorts)	In Section 8.2.1.4, revised instruction for Cohort 1 to add that it is the post-BCG specimen that will be submitted to the central laboratory for central histopathologic testing. Enrollment information was removed. Added that if the central histopathological assessment reveals T2 or higher disease, the results will be communicated by the medical monitor to the principal investigator.	Tissue samples for central histopathologic assessment for subjects in Cohort 1 will be post-BCG specimens.

Section number and Name	Description of Change	Brief Rationale
1.3, Schedule of Activities 8.1.2, Treatment Phase; 8.2.1.5, Cystoscopy, Urine Cytology, Bladder Mapping, and CT/MRI Urogram; 8.9, Biomarkers; CO Table 1, Schedule of Activities	In Section 1.3, the notes section of the cystoscopy and bladder mapping rows, specified that only positive biopsy samples should be sent for exploratory biomarker analysis and clarified that this is for any grade of recurrence. This instruction was also added to the last paragraphs of Sections 8.1.2 and 8.2.1.5. Due to the above change and sentence structure in Section 8.1.2, it was clarified that any tissue should be sent for determination of the erdafitinib level.	Only tissue from positive biopsy samples should be sent for exploratory biomarker analysis.
CO Table 1, Schedule of Activities	In Table 1, added that bladder mapping at screening will be done only if a prior history of carcinoma in situ (CIS). Also, note was moved to the "Note" column.	For the cross over study, only subjects with a history of CIS will have bladder mapping performed at screening.
CO Table 1, Schedule of Activities	In Table 1, Cystoscopy, deleted the requirement to send tissue slides/blocks from subjects with locally confirmed recurrence for central histopathologic review.	Central histopathologic review not required in the crossover study
8.1.1.1 Molecular Eligibility Phase (Cohort1 and Cohort2)	For Cohort 2 with concurrent papillary disease, molecular eligibility can be determined from either the CIS specimen or the papillary lesion.	For Cohort 2, clarified the type of tissue specimens that may be used to determine molecular eligibility.
1.3, Schedule of Activities (footnote b); 8.1.1.1 Molecular Eligibility Screening Phase (Cohort1 and Cohort2); Figure 2 (new)	In Section 8.1.1.1 removed the requirement to obtain sponsor approval prior to submitting a local next-generation sequencing (NGS)/tissue sample for confirmation of FGFR status. Also added that pre-BCG tissue specimen and post-BCG local NGS/PCR testing must also submit the post-BCG tissue specimen tissue for central confirmation of Molecular eligibility status. The need for sponsor review and approval prior to completion of the molecular eligibility requirement and for resubmission of tissue that was of insufficient quantity was removed.	Removed the requirement to have sponsor approval for aspects of molecular eligibility testing.
6.5.3 Precautions for Concomitant Medications; 10.9, Drug Classified ...	In Section 6.5.3, instruction for precaution with concomitant medications has been updated, ie, the combination of erdafitinib with moderate CYP2C9 inhibitors or inducers or strong CYP3A inhibitors or inducers should be avoided. Also, additional information regarding erdafitinib and moderate CYP2C9 inhibitors or inducers and strong CYP3A inducers or inducers were added.	The combination of erdafitinib with moderate CYP2C9 inhibitors or inducers or strong CYP3A inhibitors or inducers should be avoided. Instruction for precaution with concomitant medications was updated.

Section number and Name	Description of Change	Brief Rationale
5, Study Population; 5.2, Exclusion Criteria; 10.10, Drug-drug Interaction Substudy; 10.11, Erdafitinib Crossover	In Section 5.2, deleted Exclusion Criterion 13 from the main study and the crossover study (Exclusion Criterion 12). and updated the Drug-drug Interaction (DDI) Substudy (Exclusion Criterion 1) to read "Use of strong CYP3A4 inhibitors or inducers" or "moderate CYP2C9 inhibitors or inducers" (previously "Medications known to induce or inhibit CYP3A or CYP2C9"). Also edited the DDI Exclusion Criterion 1 for clarity regarding OCT2 use. In Section 5, noted that additional eligibility criteria for entry into the DDI Substudy is provided in Appendix 10 under the "Subject Population" subsection.	To remove Exclusion Criterion 13 (main study) and Exclusion Criterion 12 (crossover study), as this exclusion applies only to those entering the DDI Substudy, to align the DDI exclusion with the update for CYP3A4/CYP2C9 inhibitors and inducers, and to add a reminder that additional eligibility criteria for participation in the DDI Substudy is provided in the substudy appendix.
5.2, Exclusion Criteria	Exclusion Criterion 15 was added to ensure washout of any other investigational agent in another clinical study within 30 days prior to randomization.	To clarify that subjects should have adequate washout from prior use of an investigational agent.
8.3.2, Vital Signs	For the assessment of temperature, removed "oral or tympanic".	Temperature may be performed by any method.
1.3, Schedule of Activities; 4.1, Overall Design; 8.1.2, Treatment Phase; 8.6.1, Evaluations	Added that the 24-hour PK urine sample for subjects receiving erdafitinib is done for the first 20 subjects in any cohort (previously all subjects in Cohorts 2 and 3). Also added "approximately" 20 subjects will have the sample obtained.	As 20 subjects is sufficient for PK evaluation of the 24-hour urine sample, the requirement to test further subjects was removed. Testing was expanded to all cohorts.
1.3, Schedule of Activities; CO Table 1, Schedule of Activities	In the "Notes" column for the row "Ophthalmologic examination" the following text was added: "Repeat OCT scan in case of quality issue."	To ensure a quality OCT scan is obtained.
1.3, Schedule of Activities; 8.3.4, Clinical Safety Laboratory Assessments; CO Table 1, Schedule of Activities	In Section 1.3, the "Notes" column for the rows "Phosphate" and "Parathyroid hormone", noted that these tests are done for all subjects at screening and for only subjects assigned to receive erdafitinib after Cycle 1 Day 1 (C1D1). This instruction was also added to Section 8.3.4. In Section 1.3 (in the "Clinical Safety Laboratory Assessments" subheader row) noted that results for 1,25-dihydroxyvitamin D do not need to be available prior to the start of treatment at C1D1. In Section 1.3 (screening results confirmed prior to randomization) and Section 8.3.4, noted the exception for parathyroid hormone and 1,25-dihydroxyvitamin D.	The clinical laboratory tests for phosphate and parathyroid hormone will be conducted for all subjects at screening, as the treatment assignment is not known at this time. It is not necessary to have results of the 1,25-dihydroxyvitamin D and parathyroid hormone tests prior to dosing.
1.3, Schedule of Activities;	In the "Notes" for the row "Cystoscopy (with biopsy of visible lesions if present)" the following change was made: ". . . Send tissue slides/blocks from subjects with locally confirmed ("high-risk" removed from this location) recurrence or progression for central histopathologic review . . . "	Tissue slides/blocks from subjects with locally confirmed recurrence or progression of any grade will be sent for central histopathologic review.
1.3, Schedule of Activities	Reordered the PK sample assessments to list blood sampling first followed by tissue specimen collection.	To improve readability.

Section number and Name	Description of Change	Brief Rationale
8.4.4, Regulatory Reporting Requirements for Serious Adverse Events and Anticipated Events; 8.4.6, Disease-related Events and Disease-related Outcomes Not Qualifying as Adverse Events or Serious Adverse Events; 10.3, Appendix 3, Severity Criteria subheader	The Section 8.4.4 header was revised to include Anticipated Events (per template); this topic is already provided in this section. In Section 8.4.6, the description of disease-related events was updated. In Section 10.3, the definitions of Grades 1 to 5 were added (the mild, moderate, and severe definitions were removed).	Aligned wording in several sections with updated text common to the oncology protocol template.
10.3, Appendix 3, Serious Adverse Events subheader	Removed instructions for reporting of serious and unexpected adverse events that are a component of the study endpoint.	Not applicable to this study based on study endpoints.
Synopsis, Overall Design; 1.3, Schedule of Activities; 8.1.1.3, Full-study Screening Phase	Clarified that the requirement for molecular screening to start within 12 weeks of transurethral resection of bladder tumor (TURBT) was done for "high risk" recurrence "if molecular testing is being done on post-BCG specimen".	To clarify molecular screening requirements.
5.4, Screen Failures	In the last paragraph, it was clarified that subjects may be rescreened once for the main study. Also, the sentence was simplified by removing some of the detail that may result in rescreening. Instruction was added that for samples with insufficient tissue, another sample may be submitted, and this submission is not considered rescreening.	Clarified that a subject may be rescreened once for the main study. Provided instruction for resubmitting a tumor sample with insufficient tissue.
1.3, Schedule of Activities; Section 8.1.1.1, 8.1.1.1 Molecular Eligibility Screening Phase (Cohort1 and Cohort2); 10.2, Appendix 2, Informed Consent Process	Added that consent for molecular eligibility screening may be performed remotely including consent by telephone or video consultation, unless not permitted according to local guidance. In Section 10.2, noted that informed consent for molecular eligibility may be obtained remotely.	Added remote consent to provide more options for obtaining consent for molecular eligibility.
8.2.1.3, Cohort 3	Removed the following sentence from the first paragraph, "No electricity should be applied to a 1 cm circumference around the tumor."	Tumors will be excised per standard practice; therefore, extra detail was removed.
Synopsis, Overall Design; 4.1, Overall Design; 6.5.1, Permitted Medications	Moved the sentence regarding peri-operative intravesical chemotherapy prior to study entry per local standard of care from Section 6.5.1 to Section 4.1 (for Cohort 2) and added that prior immunotherapy (eg, PD1 inhibitor etc) are also allowed (for Cohort1 and Cohort 2). Also added that for Cohort 2, subjects may receive chemotherapy as bridging therapy after adequate BCG therapy while being considered for trial.	

Section number and Name	Description of Change	Brief Rationale
1.3, Schedule of Activities; 8.9, Biomarkers	In the Notes for "Urine for [redacted]" added urine can be taken from excess "bladder washing sample/" urine/cells remaining after urine cytology "sample amount is aliquoted for testing: . . . In 8.9, FGFR alteration detection subsection, included that voided urine specimen could be assessed, although instrumented specimen is preferred.	Clarified permitted methods of urine sampling for diagnostic development.
10.13, Appendix 13, Guidance . . . During a National Disaster	Added text to the first paragraph to clarify that the measures in this appendix are temporary and that usual study conduct will resume once the national situation allows. The following text was added to clarify the consent process during a national disaster: Consenting of subjects for full-study screening and for molecular eligibility screening will be performed as applicable (including also remote consenting by telephone or video consultation) according to local guidance for the informed consent.	Clarified in the National Disaster attachment that usual study conduct resumes once the national situation allows and added guidance for consent during a national disaster.
Table 9	For Grade 2 Management of Nail Discoloration/ Loss/Ridging (Onycholysis/ Onychodystrophy, the instruction was changed as follows "Continue holding study drug (previously "continue study drug") with reassessment in 1-2 weeks".	Correction to Grade 2 instruction for study drug management.
1.3, Schedule of Activities; 8.1.1.3, Full-study Screening Phase	In Section 1.3, added a notation to the Main-study Informed Consent Form (ICF) row of the table that procedures conducted, before signing the Main-study ICF, as part of the subject's routine clinical management (eg, blood count, disease assessment) may be used for screening or baseline purposes provided the procedure meets the protocol-defined criteria and has been performed within 35 days prior to dosing. In Section 8.1.1.3, added that test results may be repeated once during screening if the underlying issue has been resolved, as well as if the results are believed to be in error.	Clarified the timing of procedures conducted as part of patients' routine clinical management that can be used for screening purposes.
4.3.2, Gemcitabine Dose Selection	Removed the lead sentence of the second paragraph of this section: "Although gemcitabine and the aforementioned dose is not labeled for use in bladder cancer, it is considered standard to use as an intravesical therapy and it is generally well-tolerated.[16]"	General information was removed from this section.
Table 3; Table 4	Revised the serum phosphate levels in these tables to align with the program-wide levels used for the erdafitinib program. The "Symptom Management" column for Grade 3 was revised as follows: Sevelamer up to 1,600 mg TID with food until serum phosphate level "is" [added "is" and deleted "returns to" <7.00 mg/dL.	Aligned rounding with other protocols within the erdafitinib program. A minor correction was made to the guidelines for the management of elevated phosphate levels.

Section number and Name	Description of Change	Brief Rationale
Figure 1; 8.1.1, Screening; 8.1.1.1, Molecular Eligibility Screening Phase (Cohort1 and Cohort2); 8.1.1.2, Cohort 3 Molecular Eligibility; Section 8.1.1.3, Full-study Screening Phase	Updated Figure 1 to reorder screening to display "Screening for FGFR . . ." first, followed by "NMIBC subjects . . ." second. Reorganized the description for Screening (now Section 8.1.1) as follows: Section 8.1.1.1, "Molecular Eligibility Screening Phase (Cohort 1 and Cohort 2)"; Section 8.1.1.2, "Cohort 3 Molecular Eligibility"; and Section 8.1.1.3, "Full-study Screening Phase." Numbering for subsequent headings in Section 8.1.1 were updated accordingly (Section 8.1.2, Treatment Phase [was 8.1.3]; Section 8.1.3, Follow-up Phase [was 8.1.4]; and 8.1.4, Unscheduled Visits [was 8.1.5]).	To clarify molecular screening and full-study screening procedures and improve readability.
1.1 Synopsis; 3 Objectives and Endpoints; 9.4.3 Secondary Efficacy Endpoints;	Switched order of secondary efficacy endpoints in instances where "Time to progression" preceded "Time to disease worsening."	To align with the order in hierarchical testing.
9.4.2 Primary Endpoints	Added description of primary estimand.	To align with ICH E9(R1) Harmonised Guideline on Estimands and Sensitivity Analysis in Clinical Trials issued in 2019.
9.4.3 Secondary Efficacy Endpoints	Modified Time to Disease Worsening definition to clarify components as (1) first documented evidence of cystectomy, (2) change in therapy indicative of more advanced disease, including systemic chemotherapy or radiotherapy, (3) death. Also, changed phrase "radiation therapy" to "radiotherapy" for consistency with case report form (CRF).	To reduce ambiguity in the definition of this endpoint.
9.4.5 Safety Analyses	Added the sentence: "Clinically relevant ECG abnormalities are defined in the SAP."	To clarify that these abnormalities have been defined in the SAP.
9.4.6.1 Pharmacokinetic Analyses	Included urine along with plasma and tissue as a potential source of PK data.	To clarify that PK urine sample will be included in listings.
9.4.6.1 Pharmacokinetic Analyses	Added description for how PK concentrations below the lower limit of quantitation will be displayed in listings.	To clarify display of PK concentrations below the lower limit of quantitation.
9.4.6.3 Medical Resource Utilization Analyses (new)	Added a separate section number for Medical Resource Utilization Analyses (formerly included the Biomarkers Analyses section).	Minor correction.
9.5 Interim Analysis	Added that if the hazard ratio at the interim analysis is ≥1, "the Independent Data Monitoring Committee (IDMC) may recommend" Cohort 1 to be stopped for futility.	To clarify that that the IDMC recommendation is not binding.
9.5 Interim Analysis	Changed reference from interim analysis plan to statistical analysis plan.	For consistency in including the interim analysis plan in the statistical analysis plan.
2.2.1, Fibroblast Growth Factor Receptors	In the "FGFR Alterations in High-risk NMIBC" subsection, added recent data from the Breyer et al study regarding the prognostic and predictive value of FGFR alterations in NMIBC for the real-world patients.	To provide additional background information.

Section number and Name	Description of Change	Brief Rationale
6.1.2, Investigator's Choice of Treatment (Cohort 1 Only)	Add that subjects in Cohort 1 are not candidate for re-treatment with BCG.	To clarify treatment options for Cohort 1 subjects.
9.6 Independent Data Monitoring Committee	Renamed the section from "Data Monitoring Committee or Other Review Board" to "Independent Data Monitoring Committee."	To reflect the type of review board used for the study.
10.2, Appendix 2, Committees Structure subsection	Changed the number of medical experts on the IDMC from at least 2 to "at least 1."	Updated to reflect the required number of medical experts (1) for IDMC.
11, References	Added references for Breyer 2020 and Gallagher 2008.	Updated to support protocol revisions.
Title page and footer	Updated confidentiality information added.	To align with updated statements.
Throughout the protocol; 4.3.3, Mitomycin C Dose Selection; 8.1.1.1, Molecular Eligibility Phase (Cohort 1 and Cohort 2); 8.1.1.2, Cohort 3 Molecular Eligibility; 10.9, Drug Classified . . .	Minor grammatical corrections were made. Added recurrence refers to "high risk" recurrence as applicable throughout the protocol. In Section 4.3.3, removed redundant sentence: "Additional doses of induction or maintenance are allowed per local standard of care." In Section 8.1.1.1, moved the first paragraph regarding the ANNAR protocol to the end of this section. In Section 8.1.1.2 the instruction in Number 5 regarding resection of the marker lesion when molecular eligibility is not met was added to Number 4. In Section 10.9, provided correction to the Strong CYP3A4 Inhibitor table, ie, Strong Inhibitors: ≥5-fold increase in area under the curve (AUC) or ≥80 % (previously >80%) decrease in CL. In Section 10.10 under the Prohibition and Restrictions subsection of the DDI substudy, clarified subjects should not consume alcohol on Day -3 and Day 12 (deleted "Day -3" and "Day 12" from text regarding "no more than 1 drink").	Minor clarifications and corrections were made.

Amendment 2 (26 March 2020)

Overall Rationale for the Amendment: To address the shortage of Mitomycin C/MMC supply

Section number and Name	Description of Change	Brief Rationale
Throughout the protocol	The following bolded phrase was added: The reason for not being eligible for cystectomy **or for refusing cystectomy**…	As requested by the European Medicines Agency (EMA)
Throughout the protocol	The word "terminated" was replaced with "closed" when referring to study discontinuation.	To provide clarity relative to European guidance
Section 1.1 Synopsis; Section 4.1 Overall Design	The following sentence was added: **BCG strain administered will also be documented in the eCRF.**	As requested from the EMA
Section 1.1 Synopsis; Section 4.1 Overall Design	A statement was added to indicate that peri-operative intravesical chemotherapy prior to study entry is allowed per local standard of care.	To align with standard of care practice
Section 1.3 Schedule of Activities; Section 10.11 Appendix 11: Erdafitinib Crossover	Additional ocular examinations were added to the ophthalmologic examination assessment.	As requested from the FDA
Section 1.3 Schedule of Activities	The days of administration for the Investigator's Choice treatment were changed from C1D7, C1D14, and C1D21 to C1D**8**, C1D1**5**, and C1D2**2,** respectively. The day for assessment was changed to C2**6**D1 for the following: cystoscopy, urine cytology, MRU data collection, urine for CCI [redacted], and blood (plasma) for ctDNA. The notes section was modified for tumor tissue for molecular eligibility, histopathology staging, and biomarker testing.	To align with weekly 7-day dosing To address that each cycle is 28 days, and there are 13 cycles in 1 year To add clarity
Section 1.3. Schedule of Activities; Section 8.3.4 Clinical Safety Laboratory Assessments; Section 10.11 Appendix 11: Erdafitinib Crossover	Measurement of 1,25-dihydroxyvitamin D was added for all subjects at specified time points.	To address a request from the Italian regulatory authority
Section 1.3. Schedule of Activities; Section 8.6.1 Evaluations	PK urine sample was added for subjects in Cohorts 2 and 3.	To assess erdafitinib concentration levels between tissue and urine
Section 1.3 Schedule of Activities (footnote a)	A footnote was added to refer to Appendix 13 for guidance on national disasters.	To add instructions to be used during national disasters
Section 4.3.2 Gemcitabine Dose Selection	Clarified the dose of gemcitabine and removed language that was already included in the IPPI, which is referenced in this section.	To align and provide clarity with the IPPI

Section number and Name	Description of Change	Brief Rationale
Section 4.3.3 Mitomycin C Dose Selection	Clarified the dose of MMC and added instruction to follow the IPPI.	To address a shortage of MMC .
Section 5.1 Inclusion Criteria	For criterion #3, the following text was added: **Subjects enrolling as referrals from ANNAR study do not need to submit tissue for central confirmation.**	Per the ANNAR protocol procedures/processes
Section 5.1 Inclusion Criteria	For criteria #10, the time period was changed to 6 months after the last dose of study drug for the following: to remain on a highly effective method of contraception, to not donate eggs, not breastfeeding, not planning to become pregnant, not donate sperm, not planning to father a child.	Per the SmPC for gemcitabine. To address a request from the regulatory authorities in Germany and Belgium
Section 5.1 Inclusion Criteria	For criteria #7, the calculation of renal function was modified.	To add clarity
Section 5.2 Exclusion Criteria	An additional criterion was added relating to contraindications to the use of gemcitabine or MMC/hyperthermic MMC.	To address a request from the German regulatory authority
Section 5.3 Lifestyle Considerations	The following was added: **Male and female subjects should be advised on sperm banking and egg preservation, respectively, prior to entering the study, if appropriate.**	To address a request from the Belgium regulatory authority
Section 6.1.3 Continuation of Treatment After Disease Recurrence	Text was added and deleted as shown below: **Subjects will not continue erdafitinib treatment after disease recurrence or progression.** ~~In Cohort 1, erdafitinib may be continued after disease recurrence if by the assessment of the investigator it is the best treatment for the subject. This should be discussed with and agreed to by the sponsor's medical monitor. Additionally, the subject must agree to continue treatment and be clinically stable.~~	To address a request from the French regulatory authority
Section 6.3 Measures to Minimize Bias: Randomization and Blinding	The following text was added: **All tissue samples with a local investigator assessment of any recurrence will be sent to central lab for an independent pathologic assessment regardless of risk category in order to decrease bias.**	To address a request from the FDA to decrease bias
Section 6.5.3 Precautions for Concomitant Medications; Section 10.9 Appendix 9: Drugs Classified as Strong In Vivo Inhibitors of CYP3A4/2C9 or as Moderate to Strong Inducers of CYP3A4/2C9 Enzymes; Section 10.10 Appendix 10: Drug-drug Interaction Substudy	Text related to CYP3A4 and CYP2C9 inhibitors and inducers was added. Other edits were made to the CYP3A4 and CYP2C9 tables.	To address a request from FDA by adding a list of known CYP2C9 inhibitors and inducers; To indicate that tables of inhibitors and inducers provided is not an exhaustive list. To reduce duplicity.

Section number and Name	Description of Change	Brief Rationale
Section 6.6.2.1.1 Guidelines for the Management of Elevated Phosphate Levels; Throughout the protocol	The values for grading of hyperphosphatemia have been revised throughout the protocol to include 2 decimals, for consistency with the CRF. Toxicity Grade 0 was added to Table 3.	To ensure consistency between the protocol and case report form (CRF) guidelines, harmonize rounding of phosphate values.
Section 6.6.2.1.2 Guidelines for the Management of Dry Mouth and Mucositis	Guidelines for general prophylaxis and management of mucositis (Table 6) were updated.	To provide updated guidance for specific erdafitinib toxicities for additional clarification, and for consistency with National Cancer Institute Common Terminology Criteria for Adverse Events (NCI-CTCAE) guidelines.
Section 6.6.2.1.4 Guidelines for Management of Nail Toxicity (Onycholysis, Onychodystrophy, and Paronychia)	Guidelines for general prophylaxis and management of nail toxicities (Table 9) were updated.	To provide updated guidance for specific erdafitinib toxicities for additional clarification, and for consistency with National Cancer Institute Common Terminology Criteria for Adverse Events (NCI-CTCAE) guidelines
Section 7.1 Discontinuation of Study Drug, Section 10.2 Appendix 2: Regulatory, Ethical, and Study Oversight Considerations	Text related to the sponsor's right to discontinue the study was added.	To address a request from the German regulatory authority to add criteria for discontinuation of the study
Section 8.1.1.1, Molecular Eligibility Phase (Cohort 1 and Cohort 2)	Instructions for subjects from the ANNAR study were added.	To indicate that FGFR testing may come from the ANNAR study
Section 8.1.3 Treatment Phase	Text was deleted as shown: ~~Subjects in Cohort 1 assessed with recurrent disease, but for whom the treating physician strongly believes that continuation of study treatment is in their best interest, may be allowed to continue treatment with erdafitinib after consultation with the sponsor's medical monitor (see Section 6.1.3). The subject will continue to follow procedures as outlined in the Schedule of Activities and receive treatment until the treating physician and the sponsor's medical monitor agree that further continuation of treatment is no longer providing benefit to the subject.~~	To address a request from the French regulatory authority
Section 8.3.5 Ophthalmologic Examination	The following text was modified: All subjects ~~should~~ **must** have an ophthalmologic examination performed regardless of symptoms during the Screening Phase and during the Treatment Phase as specified in the Schedule of Activities (Section 1.3).	To clarify that assessments must be performed according to the Schedule of Activities
Section 8.3.5 Ophthalmologic Examination	Instructions for handling of angiograms, photographs, and OCT scans were added and the frequency of ophthalmic examinations was increased.	To address a request from the FDA

Section number and Name	Description of Change	Brief Rationale
Section 8.4.5 Pregnancy	The following text was added: **Male subjects receiving gemcitabine or MMC will refrain from sperm donation or fathering a child until 6 months after the last dose of study drug.**	To address a request from the Belgium and German regulatory authorities
Section 10.10 Appendix 10: Drug-drug Interaction Substudy	An additional exclusion criterion was added for the DDI substudy.	To address a request from the German regulatory authority
Section 10.11 Appendix 11: Erdafitinib Crossover	Text was added to specify that the Amsler Grid Test is to be performed prior to beginning erdafitinib treatment.	To add clarity regarding requirements
Section 10.11 Appendix 11: Erdafitinib Crossover	Cross-over assessment timepoints at screening were added for the following: bladder mapping, urine cytology.	These timepoints were missing from the schedule
Section 10.11 Appendix 11: Erdafitinib Crossover; Section 5.2 Exclusion Criteria	Exclusion criterion #12 was modified to add severe hypocalcemia (corrected serum calcium of <7 mg/dL), acute and unhealed bone fractures, known underlying bone disease, or at an increased risk of bone fracture.	To address a request from the Italian regulatory authority
Appendix 13	This appendix was added and provides guidance on study conduct in the event of a national disaster.	To add instructions to be used during national disasters
Throughout the protocol	Minor grammatical, formatting, or spelling changes were made.	Minor errors were noted

Amendment 1 (06 November 2019)

Overall Rationale for the Amendment: To indicate that collection of a blood (plasma) sample for ctDNA evaluation is required at specific time points before and during the first 2 years of the Treatment Phase. This clarification is required to ensure relevant data are available for analysis. Additional revisions were made throughout the protocol to facilitate study conduct.

Section number and Name	Description of Change	Brief Rationale
Section 1.3. Schedule of Activities	For the assessment "Blood (plasma) for ctDNA", the following replacement text was provided for the description of Treatment Phase assessment timing: "All Cohorts: C1D1 (predose), C3D1, then every 12 weeks (±1 week) until C24D1 or until disease recurrence/ progression."	Text was missing from the protocol.
Synopsis (Objectives and Endpoints [Cohort 1]); Section 3. Objectives and Endpoints; Section 9.4.3. Secondary Efficacy Endpoints	The secondary endpoint of RFS by central histopathologic review was added for Cohort 1.	A supportive analysis of RFS by central histopathologic review provides additional scientific rigor.
Synopsis (Overall Design); Section 4.1. Overall Design; Section 5.1. Inclusion Criteria (No. 4) Section 5.1. Inclusion Criteria (No. 4)	Text was added to state that subjects in Cohort 3 have no predefined BCG or intravesical chemotherapy requirements. Cross reference to Section 2.3 was added for a description of "full dose" BCG. The word "OR"	To more clearly define the study population.

Section number and Name	Description of Change	Brief Rationale
	was added between items 1 and 2 of 4b. Clarification was added that maintenance doses are given weekly. Note text was revised for clarity.	
Section 5.2. Exclusion Criteria (No. 7); Section 10.11. Appendix 11 (Crossover Exclusion Criteria; No. 6) Section 5.2. Exclusion Criteria (No. 8); Section 10.11. Appendix 11 (Crossover Exclusion Criteria; No. 7) Section 10.11. Appendix 11 (Crossover Inclusion)	Clarification was added that subjects with known HIV infection will be excluded. A timeframe for CD4 count was provided (ie, in the last 6 months). Text was revised. Subjects with evidence of hepatitis B or C infection will be excluded. Erdafitinib Crossover inclusion criterion no. 6 was added: "Locally confirmed high-risk recurrence while receiving Investigator's Choice, and the subject has all visible tumor resected completely prior to enrollment and documented at baseline cystoscopy." Text was revised in the general description of the Erdafitinib Crossover: "Subjects who were randomized in Cohort 1 to either gemcitabine or MMC/hyperthermic MMC, who have ~~investigator-assessed~~ locally confirmed recurrence ~~or progression~~…" Treatment may continue for "up to a maximum of 2 years or until disease recurrence or progression…"	
Section 1.3. Schedule of Activities; Section 8.3.4. Clinical Laboratory Assessments; Section 10.11. Appendix 11 (Crossover Schedule of Activities)	Presentation of clinical laboratory assessments was reorganized to clarify timing and subjects affected. Phosphate was removed from the Comprehensive Metabolic Panel; alkaline phosphatase and magnesium were added (Section 8.3.4). Phosphate and parathyroid hormone were identified as analytes measured only for subjects receiving erdafitinib. EoT Visit assessment of phosphate and parathyroid hormone was deleted. Text describing chemistry analytes for subjects receiving erdafitinib was deleted (Section 8.3.4).	Reorganized for improved understanding.
Section 8.1.3. Treatment Phase; Section 8.2.1.5. Cystoscopy, Urine Cytology, Bladder Mapping, and CT/MRI Urogram	Clarification was added that pharmacokinetic assessment for erdafitinib level will be performed only for subjects receiving erdafitinib.	To limit the possibility of unnecessary sampling for pharmacokinetic assessment.
Section 4.3.2. Gemcitabine Dose Selection Section 6.1.2.1. Gemcitabine Administration	Text was revised: "Gemcitabine will be provided by the sponsor as 2,000 mg/vial powder in a 100 mL vial." Text was revised: "Gemcitabine will be administered as an intravesical instillation with 2,000 mg in ~~50~~ 52.6 mL NSS once weekly…"	Additional detail was added to the description of gemcitabine.
Section 1.3. Schedule of Activities Section 10.11. Appendix 11 (Crossover Schedule of Activities)	For "Main-study ICF" the "X" was removed from the Molecular Eligibility Phase column. For the task "Review Erdafitinib Crossover appendix of the ICF", the text "and sign to enroll" was added.	To clarify informed consent requirements.

Section number and Name	Description of Change	Brief Rationale
Synopsis (Overall Design); Section 1.3. Schedule of Activities; Section 8.1.2. Screening Phase	Text was revised: "Screening must ~~occur~~ start within 12 weeks after the last TURBT done for recurrence."	To clarify activity or assessment timing.
Section 1.3. Schedule of Activities; Section 10.11. Appendix 11 (Crossover Schedule of Activities)	The interval for Disease Assessment Follow-up during the Follow-up Phase was specified as every 24 weeks ±2 weeks.	
Section 1.3. Schedule of Activities	For "Inclusion/exclusion criteria" and "Randomization Cohort 1" text was added to the grid to reiterate that these activities will be done on Day -3 for subjects in the DDI substudy.	
Section 1.3. Schedule of Activities	Presentation of assessment/activity timing and cohorts affected during the Treatment Phase and Follow-up Phase (including NOTE text where applicable) was revised for clarity for the following: "Ophthalmologic evaluation", "Physical examination", "12-lead ECG", "Urine or serum β-hCG pregnancy test", "Bladder mapping", "Urine cytology", "MRU data collection", "Urine for [redacted]", and "Blood (plasma) for ctDNA".	
Section 1.3. Schedule of Activities	For "Erdafitinib", detail on erdafitinib discontinuation was replaced with cross-reference to Section 6.1.1. Clarification was added that treatment may continue until "…disease recurrence or progression…"	
Section 1.3. Schedule of Activities	For "Investigator's Choice", specific time points were given for induction doses (C1D1, C1D7, C1D14, C1D21[±2 days]) and maintenance doses (C2D1, C3D1, C4D1, C5D1, C6D1, C7D1 [±2 days]).	
Section 1.3. Schedule of Activities	For "Tumor tissue for molecular eligibility…", NOTE text was revised to provide detail on sample handling and testing requirements by cohort.	
Section 1.3. Schedule of Activities; Section 10.11. Erdafitinib Crossover (Schedule of Activities)	For "Review adverse events", detailed text in the NOTE was deleted.	
Section 1.3. Schedule of Activities; Section 8.2.1.5. Cystoscopy, Urine Cytology, Bladder Mapping, and CT/MRI Urogram; Section 10.11. Appendix 11 (Crossover Schedule of Activities)	For "Cystoscopy", NOTE text regarding activity during the Molecular Eligibility Phase was replaced with the following: "At screening, if TURBT was done within 6 weeks before randomization, then the findings of the complete resection from TURBT can be used instead of Screening cystoscopy." Corresponding text was added to Section 8.2.1.5.	

Section number and Name	Description of Change	Brief Rationale
Section 1.3. Schedule of Activities; Section 8.1.3. Treatment Phase; Section 8.2.1.4. Histopathologic Assessment; Section 8.2.1.5. Cystoscopy, Urine Cytology, Bladder Mapping, and CT/MRI Urogram; Section 8.9. Biomarkers (Tissue Biomarkers); Section 10.11. Appendix 11 (Crossover Schedule of Activities)	For "Cystoscopy", NOTE text in the Schedule of Activities regarding activity during the Treatment Phase was revised for clarity and added to Section 8.1.3 and Section 8.9. Instruction was provided for handling biopsy samples for biomarker analysis (corresponding revision to Section 8.2.1.5 and Section 8.9) and tissue for central histopathologic review (corresponding text added to Section 8.2.1.4).	
Section 1.3. Schedule of Activities (Cystoscopy); Section 8.2.1.5. Cystoscopy, Urine Cytology, Bladder Mapping, and CT/MRI Urogram	Cystoscopy assessments for Cohort 3 at C1D28, C2D28, and C3D28 (±1 week) were changed to align with planned visits on C2D1, C3D1, and C4D1 (±1 week).	
Section 1.3. Schedule of Activities (TURBT); Section 10.11. Appendix 11 (Crossover Schedule of Activities)	"TURBT" was added as an assessment.	
Section 1.3. Schedule of Activities	For "Bladder mapping", NOTE text was revised to change the word "patient" to "subject". Cross reference to Section 8.2.1.5 was added. Cohort 2 assessment at C12D1 was repositioned within the grid.	
Section 1.3. Schedule of Activities (urine cytology); Section 8.2.1.5. Cystoscopy, Urine Cytology, Bladder Mapping, and CT/MRI Urogram	Clarification was added that urine cytology is only required for Cohort 1 and Cohort 2. Urine cytology will not be done for Cohort 3.	
Section 1.3. Schedule of Activities (Urine cytology, Urine for CCI CCI); Section 8.2.1.5. Cystoscopy, Urine Cytology, Bladder Mapping, and CT/MRI Urogram; Section 8.9. Biomarkers (FGFR Alteration)	Text was added stating that "A voided urine specimen for urine cytology is acceptable at screening if no screening cystoscopy is performed (due to TURBT within 6 weeks prior)".	
Section 1.3. Schedule of Activities; Section 8.10. Medical Resource Utilization and Health Economics	For the assessment "MRU Data Collection", clarification was added that the assessment was applicable to Cohort 1 and Cohort 2 only. The start of MRU data collection was changed from C3D1 to Screening. Text was aligned in Section 8.10.	
Section 1.3. Schedule of Activities; Section 8.2.1.5.	For "CT/MRI Urogram", assessment will occur until recurrence/progression. The window for	

Section number and Name	Description of Change	Brief Rationale
Cystoscopy, Urine Cytology, Bladder Mapping, and CT/MRI Urogram; Section 10.11. Appendix 11 (Crossover Schedule of Activities)	CT/MRI urogram assessment was changed from ±1 week to ±2 weeks.	
Section 1.3. Schedule of Activities; Section 8.2.2. Patient-reported Outcomes (Follow-up Phase ePRO Assessments)	For the assessment "PGIS, EORTC QLQ-C30, EORTC QLQ-NMIBC24, EQ-5D-5L" Follow-up Phase assessment was limited to the 30-day Safety Follow-up Visit, and the following text was deleted from the NOTE: "~~In addition to the required assessments per this SoA. A total of 3 ePRO assessments will be conducted after the subject has ended treatment.~~" Corresponding text describing Follow-up Phase PRO assessment in Section 8.2.2 was deleted.	
Section 1.3. Schedule of Activities	For "Urine for [redacted]", clarification was added that urine will be collected "…during cystoscopy for all cohorts".	
Section 1.3. Schedule of Activities	For "PK: tissue specimen for erdafitinib", PK: blood sample for erdafitinib", "Protein binding blood sample" and "Blood sample for CYP2C9 genotyping", NOTE text was revised to add "Subjects receiving erdafitinib only".	
Section 2.3. Benefit-Risk Assessment	A definition of full dose of BCG therapy was added.	
Section 4.1. Overall Design; Section 10.10. Appendix 10; Section 10.11. (Erdafitinib Crossover)	Clarification was added that subjects who participate in the Erdafitinib Crossover will not participate in the DDI substudy.	
Section 4.4. End of Study Definition (Treatment and Study Completion)	The stated minimum duration of gemcitabine or MMC/hyperthermic MMC was changed from 6 months to 7 months per local standard of care ~~site practice~~.	
Section 8.2.1.5. Cystoscopy, Urine Cytology, Bladder Mapping, and CT/MRI Urogram	Text was revised: "…for Cohort 2, urine cytology does not have to be negative at screening." Text was revised: "All scheduled CT/MRI urograms ~~assessments of disease status~~ will be performed ~~within 1 week before or after the timepoint~~ as indicated in the Schedule of Activities (Section 1.3)." Text was revised: "Subjects with a positive urine cytology (not atypical cells) but with negative ~~cystoscopic biopsy~~ cystoscopy will continue treatment until next scheduled evaluation in 12 weeks."	
8.1.3. Treatment Phase	Text was revised: "Subjects in Cohort 1 assessed with recurrent or progressive disease, but for	

Section number and Name	Description of Change	Brief Rationale
	whom the treating physician strongly believes…"	
Section 8.1.4.2.2. Survival Follow-up	Text was added that survival follow-up begins when a subject has confirmed disease recurrence or progression or starts new anticancer therapy. Text was added that new anticancer therapy will be collected in the eCRF.	
Section 10.10. Appendix 10 (DDI Substudy)	Reference to metformin as a 500-mg tablet presentation was deleted.	
Section 10.11. Appendix 11 (Erdafitinib Crossover)	For "Ophthalmologic examination", screening examination is "Only required if last ophthalmologic examination was more than ~~2~~ 1 month~~s~~ prior"	
Section 10.11. Appendix 11 (Erdafitinib Crossover)	For "Cystoscopy", screening cystoscopy was added to the Schedule of Activities. The following text was added to the NOTE: "At Screening, if TURBT was done within 6 weeks before randomization, then the findings of the complete resection from TURBT can be used instead of Screening cystoscopy."	
Section 10.11. Appendix 11 (Erdafitinib Crossover)	For "Bladder mapping", screening bladder mapping was deleted. "NOTE" text was moved into the grid for the Treatment Phase.	
Synopsis (Treatment Groups); Section 6.1.2. Investigator's Choice of Treatment	Text was aligned between sections: "(All) dose modifications or omissions will be managed by the treating physician per local standard of care after discussion with the sponsor."	Consistency within the protocol.
Synopsis (Overall Design); Section 4.1. Overall Design; Section 10.2. Regulatory, Ethical, and Study Oversight Considerations	The following text was added: "(T)he reason for not being eligible for cystectomy will be entered into the eCRF."	.
Synopsis (Evaluations); Section 1.3. Schedule of Activities (Cystoscopy); Section 4.1. Overall Design; Section 8.1.3. Treatment Phase; Section 8.2.1.4. Histopathologic Assessment; Section 8.2.1.5. Cystoscopy, Urine Cytology, Bladder Mapping, and CT/MRI Urogram; Section 10.11. Appendix 11 (Crossover Schedule of Activities)	Clarification was made that biopsied tumor tissue will be sent for "central histopathologic review" for subjects in Cohort 1. Tissue slides/blocks from subjects in Cohort 1 with locally confirmed high-risk recurrence or progression will be sent for central histopathologic review.	
Section 1.2. Schema	Cohort 3 exploratory endpoint was changed to "CR Rate"	
Section 6.1.4. Erdafitinib Crossover	Text was replaced: "…~~and demonstrate a recurrence via investigator disease assessment.~~." was changed to "…and demonstrate locally confirmed high-risk recurrence while receiving study drug…"	

Section number and Name	Description of Change	Brief Rationale
Section 6.6.2.1.5. Guidelines for the Management of Eye Toxicity Associated With Vision Changes; Section 8.1.3. Treatment Phase; Section 8.1.4.2.1. Disease Assessment Follow-up	"Study therapy" or "erdafitinib therapy" was changed to "study drug".	
Section 8.1.2. Screening Phase	Clarification was added that PGIC is only assessed during the Treatment Phase. Clarification was added: "The PRO measures will be electronically (ePRO) collected, according to the Schedule of Activities (Section 1.3), to understand change over time (all cohorts) and difference between treatment groups (Cohort 1)."	
Section 8.2.1.5. Cystoscopy, Urine Cytology, Bladder Mapping, and CT/MRI Urogram	The description of cystoscopy timing was aligned with the revised Schedule of Activities. Text related to cystoscopy was kept together. The definition of recurrence was restated as histologically proven first appearance of "high-grade Ta or T1 lesion bladder cancer…"	
Section 4.1. Overview of Study Design	Text was revised: ~~"All subjects randomized and enrolled to erdafitinib~~… Subjects receiving erdafitinib…"	
Section 4.1. Overall Design.	Text was revised: "Total subject involvement in the main study is up to 4 years from the day of randomization (Cohort 1) or enrollment (Cohort 2 and Cohort 3)."	
Section 8.1.3. Treatment Phase	Clarification was made that treatment with Investigator's Choice will follow guidance in Section 6.1.2. Reference to standard local practice was deleted.	
Section 8.2.1.1. Cohort 1	Text was revised: "If there are no muscle fibers in the biopsy, subjects must undergo re-TURBT before randomization ~~or enrollment.~~"	
Section 8.2.1.3. Cohort 3	Text was revised: "Subjects with stable disease or disease progression ~~will~~ must undergo TURBT of the marker lesion and discontinue erdafitinib. Subjects with PR may, at the investigator's discretion, either continue treatment with erdafitinib or discontinue erdafitinib and undergo TURBT of the marker lesion."	
Section 8.3.5. Ophthalmologic Examination	A description of assessment timing was replaced with a cross reference to the Schedule of Activities.	
Section 8.9. Biomarkers ([redacted] From Urine)	Clarifying text was added: "Instrumented (ie, urine samples collected during cystoscopy) urine samples…"	

Section number and Name	Description of Change	Brief Rationale
Section 10.8. Appendix 8 (Amsler Grid) Section 10.11. Appendix 11 (Crossover Schedule of Activities)	Information to be collected on the Amsler Recording Chart page was limited to subject number, date, and examiner. For the assessments "Physical examination", "12-lead ECG", "Urine or serum β-hCG pregnancy test", "Ophthalmologic evaluation", "Cystoscopy", "Urine cytology", and "Blood (plasma) for ctDNA" the description of Treatment Phase and Follow-up Phase assessment timing was aligned with changes to the main Schedule of Activities. For the assessments "Cystoscopy" and "Urine cytology" reference to Cohort 1 and Cohort 2 was deleted.	
Synopsis (Overall Design, Treatment Groups); Section 4.1 (Overall Design); Section 6.1.2. Investigator's Choice; Section 6.1.3. Continuation of Treatment; Section 8.2.1.5. Cystoscopy, Urine Cytology, Bladder Mapping, and CT/MRI Urogram; Section 10.11. Appendix 11 (Erdafitinib Crossover)	Clarification was added that assessment of recurrence, progression, and disease response will be based on locally confirmed histopathologic evaluation.	To clarify an assessment, activity, analysis, or study design element
Synopsis (Overall Design, Treatment Groups); Section 1.3. Schedule of Activities (Cystoscopy); Section 4.1 (Overall Design); Section 6.1.2. Investigator's Choice; Section 6.1.3. Continuation of Treatment; Section 10.11. Appendix 11 (Erdafitinib Crossover)	Clarification was made that subjects in Cohort 1 will be monitored for high-risk ~~-grade~~ recurrence.	
Synopsis (Treatment Groups); Section 4.1. Overall Design; Section 6.1.1. Erdafitinib; Section 8.1.3. Treatment Phase; Section 8.2.1.5. Cystoscopy, Urine Cytology, Bladder Mapping, and CT/MRI Urogram	The description of treatment for Cohort 3 after the first 3 months of the Treatment Phase was revised for completeness based on response to treatment.	
Section 4.1. Overall Design	Clarification was made: "Subjects will be assessed for disease response by cystoscopy and bladder mapping for detection ~~and tracking~~ of new lesions…" Clarification was made: "An IDMC will be commissioned to review safety and efficacy data during the study primarily for Cohort 1…" Cross reference to a description of interim analysis was added, and the following text was deleted: "~~The~~	

Section number and Name	Description of Change	Brief Rationale
	~~IDMC will review safety and efficacy results of both interim analyses (see Section 9.5).~~" Clarification was made that "Subjects who receive erdafitinib during the main study will have plasma erdafitinib concentration measurements during the Treatment Phase for pharmacokinetic assessment."	
Section 4.1; Overall Design	Clarification made that biomarker assessments will be performed for all subjects ~~receiving erdafitinib~~.	
Section 4.2. Scientific Rationale (Blinding); Section 6.3. Measures to Minimize Bias	Clarification was added that the sponsor (as well as investigators and subjects) is not blinded to treatment assignment.	
Section 4.2. Scientific Rationale (MRU Data Collection)	The description of planned MRU analyses was rephrased.	
Section 4.2.1. Study-Specific Ethical Design Considerations; Section 8. Study Assessments and Procedures; Section 10.11. Appendix 11 (Erdafitinib Crossover)	The total blood volume collected during the main study was revised from 407 mL to 682 mL. Detailed collection volumes were revised in Section 8. Total blood volume for subjects also participating in the DDI substudy increased from 493 mL to 768 mL. Text was added to acknowledge that the blood volume actually collected may vary for reasons such as "a subject's visit schedule and childbearing potential". Total and detailed blood volumes collected during the Erdafitinib Crossover were added in Section 10.11.	
Section 6. Study Drug	Clarification was added that erdafitinib administered during the Erdafitinib Crossover is considered study drug.	
Section 6.5. Concomitant Therapy	Emphasis was added that all prior anticancer therapy will be recorded in the eCRF.	
Section 6.6.3. Investigator's Choice Dose Modification	Detail was added: "Changes to intravesical gemcitabine or intravesical MMC/hyperthermic MMC dose or regimen for subjects in Cohort 1 assigned to receive Investigator's Choice (ie, additional doses of induction or maintenance) will be directed by local standard ~~practice~~ of care..."	
8.1.2. Screening Phase; Section 10.10. Drug-drug Interaction Substudy	Text was added to specify the role of an independent witness to assist with PRO questionnaires during the main study and completion of diary cards during the DDI substudy.	
Section 8.1.4.2.1. Disease Assessment Follow-up	Text was added that other assessments, in addition to disease assessment, will be performed during the Disease Assessment Follow-up period.	

Section number and Name	Description of Change	Brief Rationale
Section 8.2.1.5. Cystoscopy, Urine Cytology, Bladder Mapping, and CT/MRI Urogram; Section 10.11. Appendix 11 (Crossover Schedule of Activities); Section 10.12. Appendix 12 (Bladder Map)	Detail was provided on requirements for bladder mapping, and a new Bladder Map Appendix (Appendix 12) was added.	
Section 9.4.3. Secondary Efficacy Endpoints	The definition of RFS2 was modified as follows: "RFS2 is defined as the time from the date of randomization until the date of the reappearance of high-risk disease (high-grade Ta, T1 or CIS) on the first subsequent non-surgical anticancer treatment, or death, whichever is reported first."	
Section 10.10. Appendix 10 (Drug-drug Interaction Substudy)	Statements were added stating that residual plasma samples and residual urine samples from the DDI substudy may be used for exploratory analysis of endogenous drug disposition biomarkers if there is sufficient sample remaining.	
Section 10.2. Appendix 2. Regulatory, Ethical, and Study Oversight Considerations (Committee Structure)	Text was revised: "Based on the results from these scheduled safety review meetings, the IDMC chair may request additional ~~safety~~ interim analyses and more frequent monitoring".	The IDMC chair is not limited in the type of additional interim analyses that may be requested.
Section 6.2. Preparation/Handling/Storage/ Accountability	Clarification of supplemental Investigational Product Preparation Instructions and Investigational Product Procedures Manual materials was provided.	To clearly identify all supplemental pharmacy manual material provided.
Section 7.1. Discontinuation of Study Drug	The following reason for discontinuation of study drug was deleted: "~~Investigator decision~~".	Text was redundant, no longer relevant, or unnecessary for endpoint analysis
Section 8.2.1.3. Cohort 3	The following text was deleted: "~~No biopsy will be done if the tumor is not visible and urine cytology is negative~~."	
Section 8.2.1.5. Cystoscopy, Urine Cytology, Bladder Mapping, and CT/MRI Urogram	The following text was deleted: "~~If a subject demonstrates progression, a tissue sample should be collected for biomarker analysis.~~" and "~~Additionally, at the time of disease recurrence or progression, the decision for next treatment option (therapy, cystectomy or both) will be entered in the eCRF. If the subject declines cystectomy, the reason will be entered into the eCRF.~~"	.
Section 10.13. Appendix 13 (Protocol Amendment History)	Text was modified to direct readers to the Protocol Amendment Summary of Changes Table for a description of this protocol amendment.	Document version control.
Section 10.1. Appendix 1	The list of abbreviations was updated.	To define abbreviations used in text.
Section 3. Objectives and Endpoints	For the MRU Exploratory Endpoint: "Evaluation of all the health states generated by the EQ-5D-5L utility ~~and~~ including visual analogue scale (VAS)"	Typographical error was corrected.

Section number and Name	Description of Change	Brief Rationale
Section 5.1. Inclusion Criteria (No. 2)	For inclusion criterion no. 2, part b, the following typographical error was corrected: "Papillary disease (Cohort 1) must be high-risk disease, defined as high-grade ~~disease~~ Ta/T1 lesion."	
Section 8.2.1.3. Cohort 3	Text revised: "Subjects in Cohort 3 with PR or CR ~~at~~ within 3 months…"	
Section 10.10. Appendix 10 (DDI Table 2)	The Study Day 1 time point was corrected to show it is in the DDI Treatment Phase.	
Section 4.3.3. Mitomycin C Dose Selection	"40 ~~mL~~ mg in 40 mL"	
Throughout the protocol	Minor grammatical, formatting, or spelling changes were made. Abbreviation usage was updated.	Minor errors were noted.

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INVESTIGATOR AGREEMENT

I have read this protocol and agree that it contains all necessary details for carrying out this study. I will conduct the study as outlined herein and will complete the study within the time designated.

I will provide copies of the protocol and all pertinent information to all individuals responsible to me who assist in the conduct of this study. I will discuss this material with them to ensure that they are fully informed regarding the study intervention, the conduct of the study, and the obligations of confidentiality.

Coordinating Investigator (where required):

Name (typed or printed): _____

Institution and Address: _____

_____

_____

_____

Signature: _____ Date: _____

(Day Month Year)

Principal (Site) Investigator:

Name (typed or printed): _____

Institution and Address: _____

_____

_____

_____

Telephone Number: _____

Signature: _____ Date: _____

(Day Month Year)

Sponsor's Responsible Medical Officer:

Name (typed or printed): PPD MD

Institution: Janssen Research & Development

Signature: electronic signature appended at the end of the protocol Date: _____

(Day Month Year)

Note: If the address or telephone number of the investigator changes during the study, written notification will be provided by the investigator to the sponsor, and a protocol amendment will not be required.

Signature

User	Date	Reason
PPD	13-Jul-2023 14:27:33 (GMT)	Document Approval