BLACK DIAMOND THERAPEUTICS

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BDTX-189-01

MasterKey-01: A Phase 1/2, Open-label, Two-part, Multicenter Study to Assess the Safety, Tolerability, Pharmacokinetics, and Antitumor Activity of BDTX-189, an Inhibitor of Allosteric *ErbB* Mutations, in Patients with Advanced Solid Malignancies

SPONSOR STUDY NUMBER:	BDTX-189-01
DEVELOPMENT INNOVATIONS STUDY NUMBER:	REFMAL 648
STUDY DRUG:	BDTX-189
SPONSOR:	Black Diamond Therapeutics, Inc.
EUDRACT NUMBER:	2020-005492-12
IND NUMBER:	144515
KEY SPONSOR CONTACT:	[redacted] Black Diamond Therapeutics, Inc. [redacted]
CONTRACT RESEARCH ORGANIZATION:	[redacted]
MEDICAL MONITOR:	[redacted] Black Diamond Therapeutics, Inc. [redacted]
FINAL PROTOCOL (Version 1.0)	14 November 2019
AMENDMENT 1 (Version 2.0)	12 December 2019
AMENDMENT 2 (Version 3.0)	14 July 2020
AMENDMENT 2 (Version 3.1)	30 November 2020
AMENDMENT 3 (Version 4.0)	08 June 2021
VERSION NUMBER:	4.0
ClinicalTrials.gov Reference	**NCT04209465**

BLACK DIAMOND THERAPEUTICS

[redacted]

Clinical Study Statement of Compliance

BDTX-189-01

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This clinical study shall be conducted in compliance with the protocol, as referenced herein, and all applicable local, national, and international regulatory requirements to include, but not be limited to:

- **International Council for Harmonisation (ICH) Guidelines on Good Clinical Practice (GCP)**
- **Ethical principles that have their origins in the Declaration of Helsinki**
- **Food and Drug Administration (FDA) Code of Federal Regulation (CFR):**
  - **Title 21CFR Part 50 & 45 CFR Part 46, Protection of Human Subjects**
  - **Title 21CFR Part 54, Financial Disclosure by Clinical Investigators**
  - **Title 21CFR Part 56, Institutional Review Boards (IRBs)**
  - **Title 21CFR Part 312, Investigational New Drug (IND) Application**
  - **Title 45 CFR Parts 160, 162, and 164, Health Insurance Portability and Accountability Act (HIPAA)**

0The EU Clinical Trials Directive (2001/20/EC)

As the Principal Investigator, I understand that my signature on the protocol constitutes my agreement and understanding of my responsibilities to conduct the clinical study in accordance with the protocol and applicable regulations. Furthermore, it constitutes my understanding and agreement that any changes initiated by myself, without prior agreement in writing from the Sponsor, shall be defined as a deviation from the protocol, and shall be formally documented as such.

As the Sponsor Representative, I understand that my signature constitutes agreement and understanding of acceptance of the defined and contracted Sponsor responsibilities to the CRO and the Principal Investigator as defined by the protocol, applicable clinical trial agreements (CTA), and/or business contracts, but does not in any capacity relieve me of my responsibilities as the Sponsor Representative. Additionally, my signature constitutes my understanding and agreement that any changes to the protocol, CTA, or contracts shall be implemented timely with my review and approval prior to implementation.

[redacted]

BLACK DIAMOND THERAPEUTICS

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Clinical Study Approval Page

BDTX-189-01

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[redacted]

DocuSigned by:

[redacted]

BLACK DIAMOND THERAPEUTICS

Clinical Study Principal Investigator Signature Form

BDTX-189-01

MasterKey-01: A Phase 1/2, Open-label, Two-part, Multicenter Study to Assess the Safety, Tolerability, Pharmacokinetics, and Antitumor Activity of BDTX-189, an Inhibitor of Allosteric *ErbB* Mutations, in Patients with Advanced Solid Malignancies

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AMENDMENT 2 (Version 3.1)	30 November 2020
AMENDMENT 3 (Version 4.0)	08 June 2021

By signing this protocol acceptance page, I confirm I have read, understand, and agree to conduct the study in accordance with the current protocol.

Principal Investigator Name Insert Site Name and ID info as applicable Insert Site Location	**Principal Investigator Signature**	**Date**

Please retain a copy of this page for your study files and return the original signed and dated form to:

[redacted]

[redacted]

BDTX-189-01 CONTACT INFORMATION

Sponsor Contact Address and Phone Number:	[redacted]
Development Innovations Contact Address and Phone Number:	[redacted]
Medical Monitor:	[redacted] Black Diamond Therapeutics, Inc. [redacted]
Safety Department Fax #: **Safety Department Email:**	[redacted]
Regulatory Department Phone #: **Regulatory Department Email:**	[redacted]
Development Innovations Enrollment Fax #:	[redacted]

BDTX-189-01 PROTOCOL SYNOPSIS

Title of Study:	MasterKey-01: A Phase 1/2, Open-label, Two-part, Multicenter Study to Assess the Safety, Tolerability, Pharmacokinetics and Antitumor Activity of BDTX-189, an Inhibitor of Allosteric *ErbB* Mutations, in Patients with Advanced Solid Malignancies	
Sponsor/ Development Innovations Study Numbers:	BDTX-189-01/REFMAL 648	
Sponsor:	Black Diamond Therapeutics, Inc.	
Study Duration:	The total duration of the study is planned to be approximately 48 months. Patients will continue to receive treatment until disease progression or unacceptable toxicity.	**Phase of Study:** 1/2
Study Centers:	Part A: Phase 1 - approximately 20 centers in the United States (US) and approximately 20 centers from select European Union (EU) countries Part B: Phase 2 - approximately 80 centers globally	
Number of Patients:	A total of approximately 619 patients are anticipated to be enrolled in this study. In Part A, the Phase 1 portion of the trial, approximately 128 patients may be enrolled. The Dose Escalation portion will enroll approximately 60 DLT-evaluable patients, excluding the accelerated titration portion, the Safety Expansion will enroll up to approximately 48 patients, and the Food-Effect portion will enroll approximately 16 PK-evaluable patients. In Part B, the Phase 2 portion of the trial, up to approximately 491 patients will be enrolled. Part B patients will be split into cohorts; Cohort 1 and Cohort 2 will enroll approximately 85 patients each, Cohort 3 will enroll approximately 145 patients, Cohort 4 will enroll approximately 87 patients, and Cohort 5 will enroll 89 patients.	
Objectives:	**Primary Objectives** The primary objectives of this study are to: Part A: • Determine the recommended Phase 2 dose (RP2D) and schedule of BDTX-189 as a single agent administered orally (PO) in patients with advanced solid malignancies Part B: • Assess the antitumor activity of BDTX-189 as a single agent in patients with [redacted] mutations, including [redacted] mutations **Secondary Objectives** The secondary objectives of this study are to: Part A and B: • Assess the safety and tolerability of BDTX-189 as an oral single agent • Investigate the pharmacokinetics (PK) of BDTX-189 using population PK (PopPK) methods and explore correlations between PK, response, and/or safety findings Part A: • Establish the PK of BDTX-189 and circulating metabolite profile after a single dose and at steady state • Assess the preliminary efficacy and antitumor activity of BDTX-189 as a single oral agent. • Assess the effect of food on the PK of BDTX-189	

	Part B: • Assess additional measures of efficacy and antitumor activity of BDTX-189 as a single agent. • Assess patient outcome by evaluation of electronic patient reported outcomes (ePRO) **Exploratory Objectives** The exploratory objectives of this study are to: Part A and B: • Evaluate allosteric *ErbB* mutations, gene amplifications, and possible markers of drug sensitivity and resistance in plasma using circulating tumor deoxyribonucleic acid (ctDNA) Part A: • Evaluate the pharmacodynamic (PDx) effects of BDTX-189 in tumor tissue as determined by *ErbB* signaling pathway proteins
Study Design:	Part A is a Phase 1, first-in-human, open-label dose-escalation study to determine the RP2D and dosing schedule of BDTX-189. The safety, tolerability, maximum-tolerated dose (MTD), PK parameters (including food effect), and preliminary antitumor activity of BDTX-189 will be assessed in adult patients with advanced solid tumors. Part A consists of: • Accelerated titration with single-patient cohorts at 25, 50, 100, and 200 mg QD. • Dose-escalation portion to evaluate two dosing schedules (once daily [QD] and twice daily [BID]). • A food-effect cohort. • Once MTD has been determined, the Safety Expansion cohort(s) will be opened at the MTD or lower dose for the QD and/or BID schedule. Part B is a Phase 2, open-label, multicenter basket study to determine antitumor activity and safety in adult patients who have a solid tumor harboring an oncogenic mutation from one of the [redacted] mutational clusters (MTC-A to MTC-G; see Appendix I) in the *ErbB* tyrosine kinase receptor. MTCs contain oncogenic mutations [redacted] and are grouped together based upon 3 criteria [redacted]: 1. mutations that occur in close proximity within the 3-dimensional protein conformation 2. mutations that occur in common dynamic domains of the target protein 3. mutations that relate to similar local conformational changes in protein structure Patients will be enrolled into one of the following 5 cohorts within Part B: **Cohort 1**: Non-small cell lung cancer (NSCLC) with an [redacted] mutation from MTC-A. **Cohort 2**: NSCLC with [redacted] mutation from MTC-B or point mutation from MTC-C. **Cohort 3**: Breast cancer with [redacted] mutation from MTC-B, MTC-C, MTC-D, MTC-E, or MTC-F. **Cohort 4**: NSCLC, biliary tract cancer, or cervical cancer with [redacted] mutation from MTC-D. **Cohort 5**: Any solid tumor type with any allosteric *ErbB* mutation from any of the 7 MTCs (MTC-A to MTC-G), excluding patients who are otherwise eligible for Cohorts 1-4.

Study Drugs, Doses, and Modes of Administration:	BDTX-189 will be supplied as 100 mg and 200 mg tablets. Treatment cycles will be 21 days. A smaller and reformulated 200 mg tablet may be administered to some patients enrolling at select sites during the Safety Expansion cohort(s) of Part A, and to all patients enrolling onto Part B. Prior to exceeding the MTD for the QD schedule, patients received BDTX-189 in a fasted state. With the implementation of Amendment 3 all patients enrolling in Part A and Part B must take BDTX-189 immediately after or with a standard meal. Patients in Part A who initiated treatment with the larger 200 mg tablet may be switched to the smaller and reformulated 200 mg tablet at the beginning of their subsequent cycles at the discretion of the Sponsor. During the Dose Escalation portion of Part A the starting dose was 25 mg BDTX-189 PO QD; an alternative dosing schedule (BID) was implemented based on the analysis of emerging PK and safety/tolerability. After the 400 mg QD dose regimen was declared tolerable by the Safety Review Committee (SRC) a separate cohort of patients was assessed for food effect in a randomized, single-dose crossover fashion in the fed/fasted state (see Section 4.3). For Part B, BDTX-189 will be administer PO at the RP2D (800 mg, daily total).
Main Inclusion Criteria:	**Part A and Part B:** • Histologically- or cytologically-confirmed locally advanced or metastatic solid tumor with documented recurrence or disease progression from standard anticancer therapy in the advanced/metastatic setting **Part A Dose Escalation Only:** • No standard therapy available according to the Investigator • Patients with solid tumor with alterations that may be associated with antitumor activity based on preclinical data for BDTX-189 such as: - [redacted] mutation(s) - [redacted] mutation - [redacted] mutation Mutations must have been determined by a validated next-generation sequencing (NGS) test routinely used by each institution using tissue and/or plasma and performed in a Clinical Laboratory Improvement Amendments (CLIA)-certified or equivalent laboratory. A list of eligible validated oncogenic mutations from 1 of the 7 MTCs is provided in Appendix I. **Part A Safety Expansion Only:** • No standard therapy available according to the Investigator • Patients with one of the following mutations and tumor pairs: - [redacted] mutation in patients with NSCLC, breast cancer, biliary tract cancer, or cervical cancer - [redacted] mutation in patients with NSCLC - [redacted] tumor from the following cancer types: breast, gastric, gastroesophageal, colorectal, endometrial, biliary tract, cancer of unknown primary (CUP), and NSCLC Mutations must have been determined by a validated NGS test routinely used by each institution using tissue and/or plasma and performed in a CLIA-certified or equivalent laboratory. A list of eligible validated oncogenic mutations from 1 of the 7 MTCs are provided in Appendix I. Note: The Sponsor reserves the right to prioritize tumor/genomic alteration pairs and to cap enrollment for any of these based on the Sponsor's portfolio decision-making process.

	• Mandatory archival tumor tissue or willing to undergo pretreatment biopsy if no archival tissue available (Section 5.7.1). • Measurable disease according to RECIST version 1.1 (Appendix B).
	Part B Only: • Patients with locally advanced or metastatic: - NSCLC who have received at least one prior platinum-containing regimen (with or without an anti-programmed death-ligand 1 [PD-(L)1] antibody) and no more than 2 prior regimens for advanced NSCLC. Patients with no prior therapy who refuse standard therapy may also be eligible following discussion and approval by the Sponsor's Medical Monitor. - Solid tumor other than NSCLC who have received at least one and no more than 3 prior regimens for advanced cancer. • Patients with solid tumor(s) harboring an: - [redacted] mutation - [redacted] mutation or [redacted] mutation Mutations must have been determined by a validated NGS test routinely used by each institution using tissue and/or plasma and performed in a CLIA-certified or equivalent laboratory. A list of eligible validated oncogenic mutations from 1 of the 7 MTCs is provided in Appendix I. **Eligible patients will be assigned to one of the 5 following cohorts:** **Cohort 1**: NSCLC with [redacted] mutation from MTC-A **Cohort 2**: NSCLC with [redacted] mutation from MTC-B or point mutation from MTC-C **Cohort 3**: Breast cancer with [redacted] mutation from MTC-B, MTC-C, MTC-D, MTC-E, or MTC-F **Cohort 4**: NSCLC, biliary tract cancer, or cervical cancer with [redacted] mutation from MTC-D **Cohort 5**: Any solid tumor type with any allosteric *ErbB* mutation from any of the 7 MTCs (MTC-A to MTC-G), excluding patients who are otherwise eligible for Cohorts 1-4. Note: The Sponsor reserves the right to prioritize Cohorts (ie, tumor/mutation pairs) and to cap enrollment for any Cohort based on the Sponsor's portfolio decision-making process. • Mandatory archival tumor tissue or willing to undergo pretreatment biopsy if no archival tissue available (Section 5.7.1). • Measurable disease according to RECIST version 1.1 (Appendix B)
Main Exclusion Criteria:	**Part A and Part B:** • Clinical laboratory values meeting the following criteria within 4 weeks (28 days) prior to baseline: - Serum creatinine ≥1.5 × upper limit of normal (ULN) AND calculated creatinine clearance ≤60 mL/min using Cockcroft-Gault equation. - Total bilirubin ≥1.5 × ULN or ≥3.0 × ULN in the presence of documented Gilbert's syndrome

	- Aspartate aminotransferase (AST) or alanine aminotransferase (ALT) ≥2.5 × ULN, or AST or ALT ≥5.0 × ULN in the presence of liver metastases - Hematologic function: a. Absolute neutrophil count ≤1000 cells/μL b. Hemoglobin ≤8.5 g/dL or 5.28 mmol/L c. Platelet count ≤75,000/μL • Significant cardiovascular disease, including: - Cardiac failure New York Heart Association Class III or IV (Appendix D), or left ventricular ejection fraction (LVEF) <50% or below the lower limit of the Institution's normal range - Myocardial infarction, severe or unstable angina within 6 months prior to baseline - Significant thrombotic or embolic events within 3 months prior to baseline, including, but not limited to, stroke or transient ischemic attack. Catheter-related thrombosis and deep vein thrombosis are not a cause for exclusion - History or presence of any uncontrolled cardiovascular disease - Personal or family history of long QT syndrome • Electrocardiogram (ECG) findings obtained using the study site's ECG machine-derived measurements, meeting any of the following criteria: - Evidence of second- or third-degree atrioventricular block - Clinically significant arrhythmia (as determined by the Investigator) - QTc interval of >470 msec as calculated according to Fridericia's formula (QTcF = QT/R to R interval$^{0.33}$) • Leptomeningeal or untreated central nervous system (CNS) malignancies (primary or metastatic); patients with asymptomatic CNS metastases who have undergone surgery or radiotherapy 4 weeks prior to Cycle 1 Day 1 and who are on a dose of prednisone of no more than 10 mg or equivalent will be eligible for **Part A** of the trial. • Taking or unable to discontinue proton pump inhibitors within 1 week prior to baseline • Known concurrent [redacted] mutation • Known tumor-harboring resistance mutations including [redacted] mutations • Prior documented treatment response (i.e., complete response [CR], partial response [PR], or stable disease [SD] lasting ≥24 weeks by RECIST v1.1) to approved or investigational [redacted] therapies (e.g., afatinib, lapatinib, dacomitinib, neratinib, trastuzumab deruxtecan, poziotinib, mobocertinib, amivantamab) - Patients with or without tumor response discontinuing after 8 weeks or less of therapy due to toxicity may be considered after discussion with the Sponsor Medical Monitor - Patients with an NGS test (tissue or plasma) obtained within 8 weeks of Baseline which does not include any mutations listed in exclusion criteria #7 or #8 may be considered after discussion with the Sponsor Medical Monitor. • Women who are pregnant or breast-feeding
Correlative Testing:	Archival tumor samples or tumor tissue from a new pretreatment biopsy will be collected during the screening period for retrospective confirmation of allosteric *ErbB* mutations using a diagnostic test that is being developed. Archival tumor samples or tumor tissue from a new pretreatment biopsy is <u>required</u> for all patients enrolled in the Safety Expansion portion of Part A and in Part B. Archival tumor samples or tissue from a new pretreatment biopsy is <u>requested</u> for patients with allosteric *ErbB* mutations in the Dose Escalation portion of Part A. Samples should be provided as a tissue block. If the quantity of archival tumor tissue available is insufficient to obtain 12-20 unstained slides or unavailable, a new tumor tissue biopsy sample

	must be obtained prior to starting study treatment. Alternatively, if a tissue block cannot be provided, 12-20 freshly cut formalin-fixed paraffin-embedded unstained slides may be submitted. Fresh on-treatment tumor tissue samples will be collected from patients in the dose-escalation cohorts in Part A starting at dose level 5 (400 mg QD) at baseline and Cycle 2, if the tumor is amenable for biopsy in the opinion of the Investigator (paired biopsies are not mandatory in the Food-Effect, Safety Expansion cohort(s), or Part B). An optional on-treatment tumor biopsy will be requested from all patients (Part A and Part B) at disease progression. Blood samples will be collected longitudinally for exploratory analysis of ctDNA mutations to assess correlations with disease activity, effects of study drug, and clinical outcomes (including the presence of circulating *ErbB* mutations and other activating mutations, as well as other markers of drug sensitivity and resistance). Blood samples will be collected for calculation of PK parameters (using non-compartmental analysis and PopPK methods) to explore correlations between PK/PDx, PK/efficacy, and/or PK/safety findings.
Statistical Methodology:	**Part A: Phase 1** The Phase 1 dose-escalation portion of the study will utilize the Bayesian optimal interval design (BOIN). Once the Dose Escalation is completed, the MTD will be selected based on isotonic regression. Specifically, the dose for which the isotonic estimate of the toxicity rate is closest to the target toxicity rate is the MTD that will be selected. If there are ties, the higher dose level will be selected when the isotonic estimate is lower than the target toxicity rate and the lower dose level will be selected when the isotonic estimate is greater than or equal to the target toxicity rate. Approximately 16 patients will also be evaluated in a fed/fasted randomized crossover, single-dose lead-in phase to assess the effect of food on the PK of BDTX-189 400 mg. **Part B: Phase 2** **Sample Size Considerations**: The target objective response rate (ORR) is defined to be 30% or greater for Cohorts 1 and 2, and 20% or greater for Cohorts 3, 4, and 5. The null ORR (i.e., an ORR of no interest) is determined to be 17.5% or less for Cohorts 1 and 2, 5% or less for each subgroup in both Cohorts 3 and 4, and 10% for Cohort 5. Sample sizes were estimated based on a Simon 2-stage optimal design with some modifications. That is, a 3-stage design will be created for Cohorts 1 and 2, while a 2-stage design will be created for each of five subgroups in Cohort 3, each of three subgroups in Cohort 4, and Cohort 5. The sample size for a cohort/subgroup was estimated using a 1-sided test at the nominal 5% level of significance, with a nominal power of 80% to detect the target ORR. A total of up to 491 patients will be enrolled to Part B: approximately 85 to each of Cohort 1 and Cohort 2, approximately 29 in each of the five subgroups in Cohort 3 and each of the three subgroups in Cohort 4, and approximately 89 to Cohort 5. **Futility Analysis**: Decision rules are created separately for each cohort (subgroup) to support the primary objectives of that cohort (subgroup). Assessment of the early termination futility analysis will be based upon the response assessments conducted up to and including 6 weeks after first dose of study drug (Section 7.3.3) and will not require confirmation. **Final Analysis**: Disposition summary will be based on the intent to treat population that will include all patients that signed informed consent. Safety and efficacy analyses will be based on the full analysis set that includes all patients enrolled and who received at least 1 dose of study drug treatment. The final analysis of ORR will be based on the best overall response of CR or PR observed during the study, as per RECIST v1.1. All categorical parameters will be presented by number and percent of patients for each category, along with 2-sided 95% confidence intervals (CIs). Time-to-event endpoints will be evaluated using Kaplan-Meier survival analysis. Kaplan-Meier curves will be generated, and the median time-to-event and

	the associated 2-sided 95% CIs will be provided. Additional exploratory and confirmatory analysis may be performed.

Table 1 BDTX-189-01 Schedule of Assessments Part A-Dose Escalation Including Food-Effect Cohorts

Flow Chart (Part A Dose Escalation including food-effect cohorts) Study period	**Screening**	**Lead-in Phase Food Effect-Dose level 5 (400 mg QD) or higher**		**Part A Dose Escalation BDTX-189 Treatment Period**									
Study Procedures[a]				**Cycle 1 (±1 day for Days 8, 15)**			**Cycle 2 (±2 days)**			**Cycle 3, 4, 5 and every other cycle thereafter (±2 days)**	**End of Treatment [c]**	**30-Day Safety Follow-up Visit[d]**	**Un-scheduled Visits[e]**
Study Day	**≤28 days prior to C1D1**	**-4**	**-1**	**1[b]**	**8**	**15**	**1**	**8**	**15**	**1**	**Within 3 days of decision to discontinue study drug**	**30 days after last dose (±3)**	
Informed consent	X[f]												
Inclusion / exclusion criteria	X												
Medical and disease history	X												
Demographics	X												
Complete physical exam[g]	X			X			X			X	X		
Directed physical exam[g]					X	X		X	X			X	X
Weight	X			X[h]						X	X	X	
ECOG Performance Status	X			X[h]			X			X	X	X	X
Vital signs[i]	X			X	X	X	X	X	X	X	X	X	X
12-lead ECG[j]	X			X[k]		X[k]	X			X	X	X	X
ECHO/MUGA[l]	X									X[l]	X		X
Hematology (CBC with 5-part differential and platelets)[m]	X			X[h,m]	X	X	X			X	X	X	X
Clinical chemistry[m,n]	X			X[h]	X	X	X	X	X	X	X	X	X

Flow Chart (Part A Dose Escalation including food-effect cohorts) **Study period**	**Screening**	**Lead-in Phase Food Effect-Dose level 5 (400 mg QD) or higher**		**Part A Dose Escalation BDTX-189 Treatment Period**									
Study Procedures[a]				**Cycle 1 (±1 day for Days 8, 15)**			**Cycle 2 (±2 days)**			**Cycle 3, 4, 5 and every other cycle thereafter (±2 days)**	**End of Treatment [c]**	**30-Day Safety Follow-up Visit[d]**	**Un-scheduled Visits[e]**
Study Day	**≤28 days prior to C1D1**	**-4**	**-1**	**1[b]**	**8**	**15**	**1**	**8**	**15**	**1**	**Within 3 days of decision to discontinue study drug**	**30 days after last dose (±3)**	
Coagulation (PT, aPTT, INR)[h,m]	X			X[h]			X			X	X		
Urinalysis[m,o]	X			X[h]			X			X	X	X	X
Pregnancy test[p]	X						X			X	X		X
PK sample collection[q]				X		X	X			X			
ctDNA sample collection[r]				X			X			X[r]	X[r]		
Food administration for food effect[s]		X	X										
PK sample collection for food effect[t]		X	X			X	X			X			
Archival tissue sample[u]	X												
Fresh tumor biopsy[v]				X[v]			X[v]				X[v] (optional)		
Tumor assessment (CT or MRI)[w]	X[x]			Every 6 weeks (±3 days) from C1D1 for 1st 8 cycles and every 12 weeks (±7 days) thereafter							X		X
Response assessment using RECIST v1.1[x]	X			Every 6 weeks (±3 days) from C1D1 for 1st 8 cycles and every 12 weeks (±7 days) thereafter							X		X
Concomitant medications	X			**Collected from 14 days prior to C1D1 until 30-Day Safety Follow-up visit**									X

Flow Chart (Part A Dose Escalation including food-effect cohorts) **Study period**	**Screening**	**Lead-in Phase Food Effect-Dose level 5 (400 mg QD) or higher**		**Part A Dose Escalation BDTX-189 Treatment Period**									
Study Procedures[a]				**Cycle 1 (±1 day for Days 8, 15)**			**Cycle 2 (±2 days)**			**Cycle 3, 4, 5 and every other cycle thereafter (±2 days)**	**End of Treatment [c]**	**30-Day Safety Follow-up Visit[d]**	**Un-scheduled Visits[e]**
Study Day	**≤28 days prior to C1D1**	**-4**	**-1**	**1[b]**	**8**	**15**	**1**	**8**	**15**	**1**	**Within 3 days of decision to discontinue study drug**	**30 days after last dose (±3)**	
Monitoring of AEs	X			**Collected from date when ICF is signed until 30 days after last dose of study drug**									X
Study drug dosing review		X	X	X			X			X			

Abbreviations: AE = adverse event; ALT = alanine aminotransferase; ANC = absolute neutrophil count; aPTT = activated partial thromboplastin time; AST = aspartate aminotransferase; β-hCG = beta-human chorionic gonadotropin; BUN = blood urea nitrogen; C = cycle; CBC = complete blood count; CT = computed tomography; ctDNA = circulating tumor deoxyribonucleic acid; D = day; ECG = electrocardiogram; ECHO = echocardiogram; ECOG = Eastern Cooperative Oncology Group; EOT = End-of-Treatment; ICF = informed consent form; INR = International Normalized Ratio; LDH = lactate dehydrogenase; MRI = magnetic resonance imaging; MUGA = multigated acquisition scan; OS = overall survival; PFS = progression-free survival; PK = pharmacokinetic; PS = performance status; PT = prothrombin time; QD = once daily; QTc = QT interval corrected for heart rate; QTcF = QT interval corrected by Fridericia's formula; RECIST = Response Evaluation Criteria for Solid Tumors; SRC = Safety Review Committee; WOCBP = women of child-bearing potential.

[a] Perform all assessments prior to dosing unless otherwise specified.

[b] **The C1D1 visit will determine the visit calendar for the study**, and all projected visits will be based on the C1D1 visit date. Study visits must occur according to the study visit schedule and within the allowed protocol windows. Missed doses or dose interruptions should not alter the patient's study visit schedule.

[c] Patients starting any new anti-cancer therapy after the last dose of study drug must complete the EOT visit assessments in advance of starting a new anti-cancer therapy.

[d] All patients must complete the Safety Follow-up visit. If the EOT visit is more than 30 days after the last dose of study treatment, the 30-Day Safety Follow-up visit is not required. Patients starting any new anti-cancer therapy after the EOT visit must complete the 30-Day Safety Follow-up visit assessments in advance of starting the new anti-cancer therapy. Thirty-Day Safety Follow-up visit assessments do not need to be repeated if the new anti-cancer therapy is initiated within 7 days of the EOT visit, unless further study drug was administered or there was a new abnormal test result when last assessed (including an abnormal test result which has worsened from previous). Following the administration of any new anti-cancer therapy, patients will be followed until 30 days (±3 days) after the last dose of study drug for AEs and concomitant medications associated with these AEs only.

[e] If additional visits are needed, these assessments may be obtained/performed/measured as clinically indicated.

[f] Informed consent may be obtained during the 28-day window; however, the signed ICF must be obtained before any protocol-specific assessments are performed. Tumor assessments (CT or MRI) and/or ECHO/MUGA may occur prior to signing of the ICF if completed at the clinical site as part of standard of care and performed in compliance with the protocol requirements.

[g] A complete physical examination includes an exam of all body components; a directed physical examination is focused on a specific body part or disease, at the discretion of the Investigator. The directed physical exam will include an ophthalmological exam if clinically indicated.

[h] The following baseline assessments do not need to be reassessed at C1D1 if conducted within the prior 7 days and as part of the screening assessments: weight, ECOG PS, hematology (CBC with differential and platelets), clinical chemistry, coagulation, and urinalysis.

[i] Vital sign measurements (heart rate, systolic and diastolic blood pressure, pulse oximetry, and oral or axillary temperature) will be performed prior to dosing of study drug.

[j] Single ECGs are to be performed prior to dosing of study drug. ECGs (single) will be obtained after the patient has been resting quietly in semi-supine position for at least 5 minutes before the ECG. ECG parameters (PR interval, QRS interval, QT interval corrected for heart rate by Fridericia's formula [QTcF], and heart rate) will be recorded. When multiple assessments coincide, ECGs must be done immediately before the scheduled PK sample and/or any other blood draw.

[k] Additional triplicate ECGs (**time-matched to coincide with detailed PK assessments**) beginning with dose level 4 (200 mg) and onwards will be obtained on C1D1 and C1D15 pre-dose and 1.0, 2.0, 3.0, and 4.0 hours (+/- 5 minutes) post-dose to evaluate QTc exposure effects. For each time point, three standard resting 12-lead ECGs will be obtained in close succession and not more than 2 minutes apart (i.e., 4 minutes total for 3 ECGs). ECGs will be obtained after the patient has been resting quietly in semi-supine position for at least 5 minutes before the first ECG and during the triplicate.

[l] MUGA or ECHO should be performed at Screening (if not performed ≤6 weeks prior to patient signing informed consent), ≤7 days before dosing on C4D1, C7D1, C13D1, EOT, and as clinically indicated. ECHO/MUGA may occur prior to signing of the ICF if completed at the clinical site as part of standard of care and performed in compliance with the protocol requirements.

[m] Hematology will include CBC with hemoglobin, red blood cell count, total white blood cell count with ANC, absolute lymphocyte count, 5-part differential [% neutrophils, % lymphocytes, % or absolute value of: monocytes, basophils, eosinophils] and platelet count). The Investigator (or designee) is responsible for reviewing available lab results for each patient prior to their first dose to ensure that there are no lab abnormalities or values worsening from screening that are clinically significant.

[n] Clinical chemistry (±2 days) will include sodium, potassium, chloride, bicarbonate, BUN or blood urea, creatinine, glucose, bilirubin (total and direct), AST, ALT, LDH, alkaline phosphatase, amylase, lipase, calcium, magnesium, phosphorous, albumin, and total protein.

[o] Urinalysis will include protein, glucose, ketones, urobilinogen, occult blood, and microscopic sediment evaluation. A 24-hour urine collection for assessment of urine protein will be performed whenever the urinalysis reveals ≥3+ protein.

[p] Negative serum ß-hCG pregnancy test within 7 days prior to the first dose of study drug will be required as an entry criterion for WOCBP. For WOCBP, a urine sample or serum pregnancy test will be performed on Day 1 of Cycle 2-Cycle 5, then at each subsequent in-person visit while patient is on treatment (including the EOT visit).

[q] See Section 5.6 and Table 10 for full PK profile and sparse PK sampling schemes. On PK collection days, patients should be instructed to wait until they arrive at the study center and receive instructions from study staff prior to taking their dose of study medication. Sparse PK will also be collected (sampling scheme: C2D1, C3D1, C4D1, C5D1 and every other cycle thereafter [± 2 days], 1 pre-dose sample and 2 post-dose blood draws: the 1st draw at 0.5-1.5 hours post-dose and the 2nd draw at 2-4 hours post-dose.) Refer to Table 10. Patients participating in the initial Dose Escalation where BDTX-189 was evaluated fasting should also take the study drug fasting for the detailed PK assessment. Patients receiving BDTX-189 in the non-fasting state should be provided a meal of their choice in connection with the detailed PK assessment as instructed in Section 6.1.2.

[r] ctDNA samples will be obtained pre-dose on C1D1, C2D1, C3D1, and at the EOT visit and/or time of disease progression for all patients enrolling onto Part A, including Food-Effect patients. If not collected at the EOT visit, these samples may be collected at the 30-day Safety Follow-up visit as long as no new anticancer therapy has commenced. (See Section 5.7.3)

[s] After dose level 5 (400 mg QD) has been deemed tolerable by the SRC, or a later cohort has been deemed tolerable based on emerging data, Food Effect will be assessed during a lead-in phase for patients in that cohort. On Day -4, patients will be randomized to receive BDTX-189 as a single oral dose after fasting for at least 10 hours before dosing or immediately after consuming breakfast. Patients receiving the study drug in the fasted state will continue to fast for at least 4 hours after the dose. Patients will receive BDTX-189 in the opposite prandial state on Day-1 (see Section 5.3.1).

[t] Pharmacokinetic blood samples for the Food-Effect cohort will be taken at the time points listed in Table 11. Full PK profiles will be collected on Day-4, Day 1, and C1D15. Sparse PK will also be collected (sampling scheme: C2D1, C3D1, C4D1, C5D1 and every other cycle thereafter [± 2 days], 1 pre-dose sample and 2 post-dose blood draws: the 1st draw at 0.5-1.5 hours post-dose and the 2nd draw at 2-4 hours post-dose.) Refer to Table 10. On the days of PK collection, patients should be instructed to wait until they arrive at the study center and receive instructions from the research staff prior to taking their dose of study medication. Patients participating in the initial Dose Escalation where BDTX-189 was evaluated fasting should also take the study drug fasting for the detailed PK assessment. Patients receiving BDTX-189 in the non-fasting state should be provided a meal of their choice in connection with the detailed PK assessment as instructed in Section 6.1.2.

[u] Archival tissue sample is only required for patients in Part A who have allosteric *ErbB* mutations and archival tissue available; tissue block is preferred. For patients in the Safety Expansion portion of Part A, please see Table 2.

[v] Patients in the Dose Escalation and Food-Effect portions of Part A will be required to undergo a fresh baseline and on-treatment tumor biopsy if the tumor is amenable for biopsy in the opinion of the Investigator. The on-treatment biopsy will be obtained from dose level 5 (400 mg) and continue at higher dose levels until data supports target engagement in downstream signaling. Fresh tumor biopsies will be collected at baseline (or within 28 days prior to C1D1), on C2D1 (±5 days), and at the time of disease progression (the on-treatment tumor biopsy collected at disease progression will be optional for all patients who consent). On C2D1 (±5 days), patients must be dosed in the clinic at least 2 hours prior to collecting the biopsy. The biopsy may be collected up to 8 hours after dosing. Depending on emerging data, C2D1 biopsies may be collected pre-dose (see Section 5.7.2).

[w] Tumor assessment (CT or MRI of chest, abdomen, and pelvis, plus other sites of known disease at baseline) will be performed every 6 weeks (±3 days) for the first 8 cycles, then every 12 weeks (±7 days) thereafter, at EOT, and at the discretion of the Investigator. Imaging should be completed within a window of -3 days prior to D1 of odd cycles and should be reviewed before study drug administration on D1 for dosing determination. Tumor assessment/imaging must be performed at the time of treatment discontinuation, unless it has been done within the past 4 weeks. If disease progression according to RECIST (version 1.1) is documented at any time, no further tumor/response assessment will be required.

[x] May be performed any time within 28 days prior to C1D1 and includes assessments completed at the clinical site as part of standard of care, and prior to the signing of the informed consent, if the assessments were performed in compliance with the protocol requirements. Baseline assessment must include CT or MRI imaging of the chest and abdomen, through the level of the adrenals, and brain, if clinically indicated, as well as other sites of known disease.

Table 2 BDTX-189-01 Schedule of Assessments Part A-Safety Expansion

Flow Chart (Part A Safety Expansion) Study period	**Screening**	**Part A Safety Expansion BDTX-189 Treatment Period**										
Study Procedures[a]		**Cycle 1 (±1 day for Days 8, 15)**			**Cycle 2 (±2 days)**			**Cycle 3, 4, 5 and every other cycle thereafter (±2 days)**	**End of Treatment[c]**	**30-Day Safety Follow-up Visit[d]**	**Un-scheduled Visits[e]**	**PFS/OS[x]**
Study Day	**≤28 days prior to C1D1**	**1[b]**	**8**	**15**	**1**	**8**	**15**	**1**	**Within 3 days of decision to discontinue study drug**	**30 days after last dose (±3)**		
Informed consent	X[f]											
Inclusion / exclusion criteria	X											
Medical and disease history	X											
Demographics	X											
Complete physical exam[g]	X	X			X			X	X			
Directed physical exam[g]			X	X		X	X			X	X	
Weight	X	X[h]						X	X	X		
ECOG Performance Status	X	X[h]			X			X	X	X	X	
Vital signs[i]	X	X	X	X	X	X	X	X	X	X		
12-lead ECG[j,k]	X	X[k]		X[k]	X			X	X	X	X	
ECHO/MUGA[l]	X							X[l]	X		X	

Flow Chart (Part A Safety Expansion) Study period	**Screening**	**Part A Safety Expansion BDTX-189 Treatment Period**										
Study Procedures[a]		**Cycle 1 (±1 day for Days 8, 15)**			**Cycle 2 (±2 days)**			**Cycle 3, 4, 5 and every other cycle thereafter (±2 days)**	**End of Treatment[c]**	**30-Day Safety Follow-up Visit[d]**	**Un-scheduled Visits[e]**	**PFS/OS[x]**
Study Day	**≤28 days prior to C1D1**	**1[b]**	**8**	**15**	**1**	**8**	**15**	**1**	**Within 3 days of decision to discontinue study drug**	**30 days after last dose (±3)**		
Hematology (CBC with 5-part differential and platelets)[m]	X	X[h,m]	X	X	X			X	X	X	X	
Clinical chemistry[m,n]	X	X[h]	X	X	X	X	X	X	X	X	X	
Coagulation (PT, aPTT, INR)[m]	X	X[h]			X			X	X			
Urinalysis[m,o]	X	X[h]			X			X	X	X	X	
Pregnancy test[p]	X				X			X	X		X	
PK sample collection[q]		X		X	X			X				
ctDNA sample collection[r]		X			X			X[r]	X[r]			
Archival tissue sample[u]	X											
Fresh tumor biopsy sample (optional)[s]									X			
Tumor assessment (CT or MRI)[t]	X[v]	Every 6 weeks (±3 days) from C1D1 for 1st 8 cycles, every 12 weeks (±7 days) thereafter, and as part of PFS/OS[x]							X		X	X

Flow Chart (Part A Safety Expansion) Study period	**Screening**	**Part A Safety Expansion BDTX-189 Treatment Period**										
Study Procedures[a]		**Cycle 1 (±1 day for Days 8, 15)**			**Cycle 2 (±2 days)**			**Cycle 3, 4, 5 and every other cycle thereafter (±2 days)**	**End of Treatment[c]**	**30-Day Safety Follow-up Visit[d]**	**Un-scheduled Visits[e]**	**PFS/OS[x]**
Study Day	**≤28 days prior to C1D1**	**1[b]**	**8**	**15**	**1**	**8**	**15**	**1**	**Within 3 days of decision to discontinue study drug**	**30 days after last dose (±3)**		
Response assessment using RECIST v1.1[v]	X[v]	Every 6 weeks (±3 days) from C1D1 for 1st 8 cycles, every 12 weeks (±7 days) thereafter, and as part of PFS/OS[x]							X		X	X
Concomitant medications	X	**Collected from 14 days prior to C1D1 until 30-day Safety Follow-up visit, and as part of PFS/OS[d,x]**									X	X
Monitoring of AEs	X	**Collected from date when ICF is signed through 30 days after the last dose of study drug[d,x]**									X	
Study drug dosing review[w]		X			X			X				

Abbreviations: AE = adverse event; ALT = alanine aminotransferase; ANC = absolute neutrophil count; aPTT = activated partial thromboplastin time; AST = aspartate aminotransferase; β-hCG = beta-human chorionic gonadotropin; BUN = blood urea nitrogen; C = cycle; CBC = complete blood count; CT = computed tomography; ctDNA = circulating tumor deoxyribonucleic acid; D = day; ECG = electrocardiogram; ECHO = echocardiogram; ECOG = Eastern Cooperative Oncology Group; EOT = End-of-Treatment; ICF = informed consent form; INR = International Normalized Ratio; LDH = lactate dehydrogenase; MRI = magnetic resonance imaging; MUGA = multigated acquisition scan; OS = overall survival; PFS = progression-free survival; PK = pharmacokinetic; PS = performance status; PT = prothrombin time; QTc = QT interval corrected for heart rate; QTcF = QT interval corrected by Fridericia's formula; RECIST = Response Evaluation Criteria for Solid Tumors; WOCBP = women of child-bearing potential.

[a] Perform all assessments prior to dosing unless otherwise specified.

[b] **The C1D1 visit will determine the visit calendar for the study**, and all projected visits will be based on the C1D1 visit date. Study visits must occur according to the study visit schedule and within the allowed protocol windows. Missed doses or dose interruptions should not alter the patient's study visit schedule.

[c] Patients starting any new anti-cancer therapy after the last dose of study drug must complete the EOT visit assessments in advance of starting a new anti-cancer therapy.

[d] All patients must complete the Safety Follow-up visit. If the EOT visit is more than 30 days after the last dose of study treatment, the 30-Day Safety Follow-up visit is not required. Patients starting any new anti-cancer therapy after the EOT visit must complete the 30-Day Safety Follow-up visit assessments in advance of starting the new anti-cancer therapy. Thirty-Day Safety Follow-up visit assessments do not need to be repeated if the new anti-cancer therapy is initiated within 7 days of the EOT visit, unless further study drug was administered or there was a new abnormal test result when last assessed (including an abnormal test result which has worsened from previous). Following the administration of any new anti-cancer therapy, patients will be followed until 30 days (±3 days) after the last dose of study drug for AEs and concomitant medications associated with these AEs only.

[e] If additional visits are needed, these assessments may be obtained/performed/measured as clinically indicated.

[f] Informed consent may be obtained during the 28-day window; however, the signed ICF must be obtained before any protocol-specific assessments are performed. Tumor assessments (CT or MRI) and/or ECHO/MUGA may occur prior to signing of the ICF if completed at the clinical site as part of standard of care and performed in compliance with the protocol requirements.

[g] A complete physical examination includes an exam of all body components; a directed physical examination is focused on a specific body part or disease, at the discretion of the Investigator. The directed physical exam will include an ophthalmological exam if clinically indicated.

[h] The following baseline assessments do not need to be reassessed at C1D1 if conducted within the prior 7 days and as part of the screening assessments: weight, ECOG PS, hematology (CBC with differential and platelets), clinical chemistry, coagulation, and urinalysis.

[i] Vital sign measurements (heart rate, systolic and diastolic blood pressure, pulse oximetry, and oral or axillary temperature) will be performed prior to dosing of study drug.

[j] Single ECGs are to be performed prior to dosing of study drug. ECGs (single) will be obtained after the patient has been resting quietly in semi-supine position for at least 5 minutes before the ECG. ECG parameters (PR interval, QRS interval, QT interval corrected for heart rate by Fridericia's formula [QTcF], and heart rate) will be recorded. When multiple assessments coincide, ECGs must be done immediately before the scheduled PK sample and/or any other blood draw.

[k] Approximately 12-24 patients receiving the smaller and reformulated 200 mg tablet will have blood drawn at C1D1 and C1D15 to evaluate QTc exposure effects. These patients will undergo **additional triplicate ECGs** (**time-matched to coincide with detailed PK assessments**) will be obtained at C1D1 and C1D15 pre-dose and 1.0, 2.0, 3.0, and 4.0 hours (+/- 5 minutes) post-dose to evaluate QTc exposure effects. For each time point, three standard resting 12-lead ECGs will be obtained in close succession and not more than 2 minutes apart (i.e., 4 minutes total for 3 ECGs). ECGs will be obtained after the patient has been resting quietly in semi-supine position for at least 5 minutes before the first ECG and during the triplicate. On the PK collection day, patients should be instructed to wait until they arrive at the study center and receive instructions from study staff prior to taking their dose of study medication. Refer to Section 5.6 for further details.

[l] MUGA or ECHO should be performed at Screening (if not performed ≤6 weeks prior to patient signing informed consent), ≤7 days before dosing on C4D1, C7D1, C13D1, EOT, and as clinically indicated. ECHO/MUGA may occur prior to signing of the ICF if completed at the clinical site as part of standard of care and performed in compliance with the protocol requirements.

[m] Hematology will include CBC with hemoglobin, red blood cell count, total white blood cell count with ANC, absolute lymphocyte count, and 5-part differential [% neutrophils, % lymphocytes, % or absolute value of: monocytes, basophils, eosinophils] and platelet count). The Investigator (or designee) is responsible for reviewing available lab results for each patient prior to their first dose to ensure that there are no lab abnormalities or values worsening from screening that are clinically significant.

[n] Clinical chemistry (±2 days) will include sodium, potassium, chloride, bicarbonate, BUN or blood urea, creatinine, glucose, bilirubin (total and direct), AST, ALT, LDH, alkaline phosphatase, amylase, lipase, calcium, magnesium, phosphorous, albumin, and total protein.

[o] Urinalysis will include protein, glucose, ketones, urobilinogen, occult blood, and microscopic sediment evaluation. A 24-hour urine collection for assessment of urine protein will be performed whenever the urinalysis reveals ≥3+ protein.

[p] Negative serum ß-hCG pregnancy test within 7 days prior to the first dose of study drug will be required as an entry criterion for WOCBP. For WOCBP, a urine sample or serum pregnancy test will be performed on Day 1 of Cycle 2-Cycle 5, then at each subsequent in-person visit while patient is on treatment (including the EOT visit).

[q] Approximately 12-24 selected patients in the Safety Expansion may initiate treatment with smaller reformulated 200 mg tablets. These patients will undergo detailed PK evaluation at C1D1 and C1D15 as outlined in Table 10 and Section 5.6. All patients enrolling onto the Safety Expansion will have blood drawn for sparse PK (sampling scheme: C2D1, C3D1, C4D1, C5D1 and every other cycle thereafter [± 2 days] 1 pre-dose sample and 2 post-dose blood draws: the 1st draw at 0.5-1.5 hours post-dose and the 2nd draw at 2-4 hours post-dose.) On the PK collection day(s), patients should be instructed to wait until they arrive at the study center and receive instructions from study staff prior to taking their dose of study medication.

[r] ctDNA samples will be obtained pre-dose on C1D1, C2D1, C3D1, C5D1, and at the EOT visit and/or time of disease progression. If not collected at the EOT visit, these samples may be collected at the 30-Day Safety Follow-up visit as long as no new anticancer therapy has commenced. (See Section 5.7.3).

[s] Fresh tumor biopsies will be optional; refer to Section 5.7.2 for collection details.

[t] Tumor assessment (CT or MRI of chest, abdomen, and pelvis, plus other sites of known disease at baseline) will be performed every 6 weeks (from Cycle 1 Day 1) for the first 8 cycles, then every 12 weeks thereafter, at EOT, and at the discretion of the Investigator. Imaging should be completed within a window of -3 days prior to D1 of odd cycles and should be reviewed before study drug administration on D1 for dosing determination. Tumor assessment/imaging must be performed at the time of treatment discontinuation, unless it has been done within the past 4 weeks. If disease progression according to RECIST (version 1.1) is documented at any time, no further tumor/response assessment will be required.

[u] Archival tissue sample is required for patients in the Safety Expansion who have allosteric *ErbB* mutations and archival tissue available; tissue block is preferred. In the event that a tissue block is unavailable, 12-20 formalin-fixed paraffin-embedded unstained slides may be submitted. If there is not enough archival tumor tissue, a new tumor tissue biopsy sample must be obtained during screening, prior to starting study treatment. (See Section 5.7.1)

[v] May be performed any time within 28 days prior to C1D1 and includes assessments completed at the clinical site as part of standard of care, and prior to the signing of the informed consent, if the assessments were performed in compliance with the protocol requirements. Baseline assessment must include CT or MRI imaging of the chest and abdomen, through the level of the adrenals, and brain, if clinically indicated, as well as other sites of known disease.

[w] A smaller and reformulated 200 mg tablet may be introduced and supplied to some patients during the Safety Expansion of Part A; these tablets will be available to all patients enrolling onto Part B. Patients in Part A who initiated treatment with the larger-200 mg tablet may be switched to the smaller and reformulated 200 mg tablet at the beginning of their subsequent cycles. Detailed PK sampling will be collected on Day 15 (i.e., after 14 days of daily treatment with the smaller 200 mg tablet) of that subsequent cycle according to Table 8.

[x] From the 30-Day Safety Follow-up visit, follow-up for OS, PFS, and first subsequent anti-cancer therapy, if available, will be obtained every 3 months (±14 days) until 2 years after the patient's first dose of study drug, death, loss to follow-up, withdrawal of consent, or end of the whole trial. Follow-up information about overall survival may be obtained by phone.

Table 3 BDTX-189-01 Schedule of Assessments Part B

Flow Chart (Part B) Study period	**Screening**	**Part B BDTX-189 Treatment Period**										
Study Procedures[a]		**Cycle 1**			**Cycle 2 (±2 days)**			**Cycle 3, 4, 5 and every other cycle thereafter (±2 days)**	**End of Treatment[c]**	**30-Day Safety Follow-up Visit[d]**	**Unscheduled Visits[e]**	**PFS/OS[u]**
Study Day	**≤28 days prior to C1D1**	**1[b]**	**8**	**15**	**1**	**8**	**15**	**1**	**Within 3 days of decision to discontinue study drug**	**30 days after last dose (±3)**		
Informed consent	X[f]											
Inclusion / exclusion criteria	X											
Medical and disease history	X											
Demographics	X											
Complete physical exam[g]	X	X			X			X	X			
Directed physical exam[g]										X	X	
Weight	X	X[h]						X	X	X		
ECOG Performance Status	X	X[h]			X			X	X	X	X	
Vital signs[i]	X	X			X			X	X	X	X	
ePRO[w]		X	X		X			X	X	X		
12-lead ECG[j]	X	X			X			X	X	X	X	
ECHO/MUGA	X							X[k]	X		X	
Hematology (CBC with 5-part differential and platelets)[l]	X	X[h,l]			X			X	X	X	X	
Clinical chemistry[l,m]	X	X[h]	X	X	X	X	X	X	X	X	X	
Coagulation (PT, aPTT, INR)[l]	X	X[h]			X			X	X			
Urinalysis[l,n]	X	X[h]			X			X	X	X	X	
Pregnancy test[o]	X				X[o]			X[o]	X[o]		X	

Flow Chart (Part B) **Study period**	**Screening**	**Part B BDTX-189 Treatment Period**										
Study Procedures[a]		**Cycle 1**			**Cycle 2 (±2 days)**			**Cycle 3, 4, 5 and every other cycle thereafter (±2 days)**	**End of Treatment[c]**	**30-Day Safety Follow-up Visit[d]**	**Unscheduled Visits[e]**	**PFS/OS[u]**
Study Day	**≤28 days prior to C1D1**	**1[b]**	**8**	**15**	**1**	**8**	**15**	**1**	**Within 3 days of decision to discontinue study drug**	**30 days after last dose (±3)**		
PK samples[p]		X			X			X				
ctDNA sample collection[q]	X	X			X			X	X			
Archival/new tumor tissue sample[v]	X											
Fresh tumor biopsy (optional)									X[r]			
Tumor assessment (CT or MRI)[s,u]	X[t]	Every 6 weeks (±3 days) from C1D1 for 1st 8 cycles, every 12 weeks (±7 days) thereafter, and as part of PFS/OS[u]							X		X	X
Response assessment using RECIST v1.1[t]	X	Every 6 weeks (±3 days) from C1D1 for 1st 8 cycles, every 12 weeks (±7 days) thereafter, and as part of PFS/OS[u]							X		X	X
Concomitant medications[u]	X	**Collected from 14 days prior to C1D1 until 30-Day Safety Follow-up visit and as part of PFS/OS[u] **									X	X
Monitoring of AEs[u]	X	**Collected from date when ICF is signed until 30 days after last dose of study drug **									X	
Study drug dosing review		X			X			X				

Abbreviations: AE = adverse event; ALT = alanine aminotransferase; ANC = absolute neutrophil count; aPTT = activated partial thromboplastin time; AST = aspartate aminotransferase; β-hCG = beta-human chorionic gonadotropin; BUN = blood urea nitrogen; C = cycle; CBC = complete blood count; CT = computed tomography; ctDNA = circulating tumor deoxyribonucleic acid; D = day; ECG = electrocardiogram; ECHO = echocardiogram; ECOG = Eastern Cooperative Oncology Group; ePRO= electronic patient reported outcomes; ICF = informed consent form; INR = International Normalized Ratio; LDH = lactate dehydrogenase; MRI = magnetic resonance imaging; MUGA = multigated acquisition scan; OS = overall survival; PD = progressive disease; PFS = progression-free survival; PK = pharmacokinetic; PS = performance status; PT = prothrombin time; QTc = QT interval corrected for heart rate; QTcF = QT interval corrected by Fridericia's formula; RECIST = Response Evaluation Criteria for Solid Tumors; WOCBP = women of child-bearing potential.

[a] Perform all assessments prior to dosing unless otherwise specified.

[b] **The C1D1 visit will determine the visit calendar for the study**, and all projected visits will be based on the C1D1 visit date. Study visits must occur according to the study visit schedule and within the allowed protocol windows. Missed doses or dose interruptions should not alter the patient's study visit schedule.

[c] Patients starting any new anti-cancer therapy after the last dose of study drug must complete the End of Treatment (EOT) visit assessments in advance of starting a new anti-cancer therapy.

[d] Patients starting any new anti-cancer therapy after the EOT visit must complete the 30-Day Safety Follow-up visit assessments in advance of starting the new anti-cancer therapy. Thirty-Day Safety Follow-up visit assessments do not need to be repeated if the new anti-cancer therapy is initiated within 7 days of the EOT visit, unless further study drug was administered or there was a new abnormal test result when last assessed (including an abnormal test result which has worsened from previous). If the EOT visit is more than 30 days after the last dose of study treatment, the 30-Day Safety Follow-up visit is not required. Following the administration of any new anti-cancer therapy, patients will be followed until 30 days (±3 days) after the last dose of study drug for AEs and concomitant medications associated with these AEs only.

[e] If additional visits are needed, these assessments may be obtained/performed/measured as clinically indicated.

[f] Informed consent may be obtained during the 28-day window; however, the signed ICF must be obtained before any protocol-specific assessments are performed.

[g] A complete physical examination includes an exam of all body components; a directed physical examination is focused on a specific body part or disease, at the discretion of the Investigator. The directed physical exam will include an ophthalmological exam if clinically indicated.

[h] The following baseline assessments do not need to be reassessed at C1D1 if conducted within the prior 7 days and as part of the screening assessments: weight, ECOG PS, hematology (CBC with differential and platelets), clinical chemistry, coagulation, and urinalysis.

[i] Vital sign measurements will be performed prior to dosing.

[j] Single ECGs are to be performed prior to dosing of study drug. ECG parameters (PR interval, QRS interval, QT interval corrected for heart rate by Fridericia's formula [QTcF], and HR) will be recorded. Single ECGs will be performed unless triplicate is clinically indicated in the opinion of the Investigator (i.e., borderline QTc prolongation). If a triplicate ECG is clinically indicated, three standard resting 12-lead ECGs will be obtained in close succession and not more than 2 minutes apart (i.e., 4 minutes total for 3 ECGs). ECGs will be obtained after the patient has been resting quietly in semi-supine position for at least 5 minutes before the first ECG and during the triplicate. When multiple assessments coincide, ECGs must be done immediately before the scheduled PK sample and/or any other blood draw.

[k] MUGA/ECHO should be performed at Screening (if not performed ≤6 weeks prior to patient signing informed consent), ≤7 days before dosing C4D1, C7D1, C13D1, EOT, and as clinically indicated. ECHO/MUGA may occur prior to signing of ICF if completed at the clinical site as part of standard of care and performed in compliance with the protocol requirements (see Section 5.2).

[l] Hematology will include CBC with hemoglobin, red blood cell count, total white blood cell count with ANC, absolute lymphocyte count, 5-part differential [% neutrophils, % lymphocytes, % or absolute value of: monocytes, basophils, eosinophils] and platelet count). The Investigator (or designee) is responsible for reviewing available lab results for each patient prior to their first dose to ensure that there are no lab abnormalities or values worsening from screening that are clinically significant.

[m] Clinical chemistry (±2 days) will include sodium, potassium, chloride, bicarbonate, BUN or blood urea, creatinine, glucose, bilirubin (total and direct), AST, ALT, LDH, alkaline phosphatase, amylase, lipase, calcium, magnesium, phosphorous, albumin, and total protein.

[n] Urinalysis will include protein, glucose, ketones, urobilinogen, occult blood, and microscopic sediment evaluation. A 24-hour urine collection for assessment of urine protein will be performed whenever the urinalysis reveals ≥3+ protein.

[o] Negative serum ß-hCG pregnancy test within 7 days prior to the first dose of study drug will be required as an entry criterion for WOCBP. A urine sample or serum pregnancy test will be performed on Day 1 of Cycle 2-Cycle 5, then at each subsequent in-person visit while patient is on treatment (including the EOT visit).

[p] On PK collection days, patients should be instructed to wait until they arrive at the study center and receive instructions from study staff prior to taking their dose of study medication. Sparse PK will be collected (sampling scheme: C1D1, C2D1, C3D1, C4D1, C5D1 and every other cycle thereafter [± 2 days], 1 pre-dose sample and 2 post-dose blood draws: the 1st draw at 0.5-1.5 hours post-dose and the 2nd draw at 2-4 hours post-dose.).

[q] ctDNA samples will be obtained at Screening and pre-dose on C1D1, C2D1, C3D1, C5D1, C7D1, C9D1, subsequently every 4th cycle (C13D1, C17D1, C21D1, etc.), and at the EOT visit and/or time of disease progression. If not collected at the EOT visit, these samples may be collected at the 30-day Safety Follow-up visit as long as no new anticancer therapy has commenced. (See Section 5.7.3)

[r] An optional on-treatment tumor biopsy will be collected at the time of disease progression for all patients who consent.

[s] Tumor assessment (CT or MRI of chest, abdomen, and pelvis, plus other sites of known disease at baseline) will be performed every 6 weeks for the first 8 cycles, and then every 12 weeks thereafter. Imaging should be completed within a window of -3 days prior to D1 of odd cycles and should be reviewed before study drug administration on D1 for dosing determination. Patients who discontinue treatment for reasons other than PD will undergo tumor assessment in accordance with the original schedule relative to C1D1. Tumor assessment/imaging must be performed at the time of treatment discontinuation, unless it has been done within the past 4 weeks. If disease progression according to RECIST (version 1.1) is documented at any time, no further tumor/response assessment will be required.

[t] May be performed any time within 28 days prior to C1D1 and includes assessments completed at the clinical site as part of standard of care, and prior to the signing of the informed consent, if the assessments were performed in compliance with the protocol requirements. Baseline assessment must include CT or MRI imaging of the chest and abdomen, through the level of the adrenals, and brain, if clinically indicated, as well as other sites of known disease.

[u] From the 30-Day Safety Follow-up visit, follow-up for OS, PFS, and first subsequent anti-cancer therapy, if available, will be obtained every 3 months (±14 days) until 2 years after the first dose of study drug, death, loss to follow-up, withdrawal of consent, or end of the whole trial. Follow-up information about overall survival may be obtained by phone.

[v] Archival tissue sample is mandatory for patients in Part B who have archival tissue available; a tissue block is preferred. In the event that a tissue block is unavailable, 12-20 formalin-fixed paraffin-embedded unstained slides may be submitted. If there is not enough archival tumor tissue, a new tumor tissue biopsy sample must be obtained during screening, prior to starting study treatment. (See Section 5.7.1).

[w] ePROs collection will occur C1D1, C1D8 and on Day 1 of every cycle from C2-C9. After C9D1 collection will occur every 3 months (±14 days), at the EOT visit, and 30-Day Safety Follow-up visit. Continue to collect ePROs even if the patient has discontinued taking the study drug until subsequent anti-tumor therapy is initiated. Please note ePROs should be provided to the patient as soon as they arrive at the site for their visit, ideally before any other assessments are performed. Refer to Section 5.3.4.

LIST OF ABBREVIATIONS

Abbreviation or special term	Explanation
AE	Adverse event
ALP	Alkaline phosphatase
ALT	Alanine aminotransferase
ANC	Absolute neutrophil count
aPTT	Activated partial thromboplastin time
AST	Aspartate aminotransferase
ATP	Adenosine triphosphate
AUC	Area under the plasma concentration-time curve
BCRP	Breast cancer resistant protein
BDTX	Black Diamond Therapeutics
BICR	Blinded independent central review
BID	Twice daily
BOIN	Bayesian optimal interval
BP	Blood pressure
BUN	Blood urea nitrogen
CBC	Complete blood count
CFR	Code of Federal Regulations
CI	Confidence interval
CLIA	Clinical Laboratory Improvement Amendments
C_{max}	Maximum plasma concentration
CNS	Central nervous system
CR	Complete response
CT	Computed tomography
CTCAE	Common Terminology Criteria for Adverse Events
ctDNA	Circulating tumor deoxyribonucleic acid
DCR	Disease control rate
Development Innovations	Sarah Cannon Development Innovations
DLT	Dose-limiting toxicity
DMC	Data Monitoring Committee
DOR	Duration of response
ECG	Electrocardiogram
ECHO	Echocardiogram
ECOG	Eastern Cooperative Oncology Group
eCRF	Electronic Case Report Form
EDC	Electronic data capturing system
EGFR	Epidermal growth factor receptor
EOT	End-of-Treatment
ePRO	Electronic patient reported outcome
EQ-5D	EuroQol Group's 5-domain 5-level questionnaire
FA	Full analysis
FACT	Functional Assessment of Cancer Therapy

Abbreviation or special term	Explanation
FACT-G	Functional Assessment of Cancer Therapy-General
FBSI	Functional Assessment of Cancer Therapy Breast Symptom Index
FDA	Food and Drug Administration
FFPE	Formalin-fixed paraffin-embedded
FLSI	Functional Assessment of Cancer Therapy Lung Cancer Symptom Index
FSH	Follicle stimulating hormone
GCP	Good Clinical Practice
GLP	Good Laboratory Practice
HER2	Human epidermal growth factor receptor 2
HIPAA	Health Insurance Portability and Accountability Act
HIV	Human immunodeficiency virus
HNSTD	Highest non-severely toxic dose
IB	Investigator's Brochure
IC_{50}	Half-maximal inhibitory concentration
ICF	Informed consent form
ICH	International Council for Harmonisation
IEC	Independent Ethics Committee
IND	Investigational New Drug
INR	International Normalized Ratio
IRB	Institutional Review Board
ISF	Investigator Study File
LVEF	Left ventricular ejection fraction
mAb	Monoclonal antibody
MRI	Magnetic resonance imaging
MTC	Mutational cluster
MTD	Maximum tolerated dose
MUGA	Multigated acquisition scan
NCCN	National Comprehensive Cancer Network
NCI	National Cancer Institute
NE	Non-evaluable
NGS	Next-generation sequencing
NSCLC	Non-small cell lung cancer
NTL	Non-target lesion
ORR	Objective response rate
OS	Overall survival
PD	Progressive disease
PD-1	Programmed cell death protein 1
PD-L1	Programmed death-ligand 1
PDx	Pharmacodynamic
PET	Positron emission tomography
PFS	Progression-free survival
P-gp	P-glycoprotein

Abbreviation or special term	Explanation
PHI	Protected health information
PK	Pharmacokinetic
PO	Orally/by mouth
PopPK	Population pharmacokinetics
PR	Partial response
PRO	Patient reported outcome
PROMIS	Patient Reported Outcomes Measurement Information System
PT	Prothrombin time
QD	Once daily
QT	ECG interval measured from the onset of the QRS complex to the end of the T wave
QTc	QT interval corrected for heart rate
QTcF	QT interval corrected for heart rate by Fridericia's formula
R to R interval	ECG interval measured between two R waves of the QRS signal
RECIST	Response Evaluation Criteria in Solid Tumors
RP2D	Recommended Phase 2 Dose
SAE	Serious adverse event
SAP	Statistical Analysis Plan
SAR	Suspected adverse reaction
SCRI	Sarah Cannon Research Institute
SD	Stable disease
SRC	Safety Review Committee
SUSAR	Suspected unexpected serious adverse reaction
$t_{1/2}$	Median elimination half-life
TEAE	Treatment-emergent adverse event
TGI	Tumor growth inhibition
TKI	Tyrosine-kinase inhibitor
ULN	Upper limit of normal
WBC	White blood cell
WOCBP	Women of child-bearing potential
WT	Wild type

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1. INTRODUCTION

1.1 Background

Deregulation of the [redacted] family [redacted] by mutation or amplification has been observed across multiple cancer types and is often responsible for oncogenic transformation and tumor growth. Amplification of wild-type [redacted] (i.e., non-mutated) is observed in approximately 20% of patients with breast, gastric, and esophageal cancer (Stern 2012).

Mutations are found across all exons of the [redacted] gene (Figure 1).

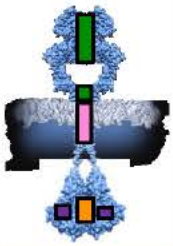
Figure 1 Diagram of [redacted] Mutations

Recurring anchor [redacted] mutations, defined as missense mutations in coding sequences that occur at a frequency >1 per 10,000 (0.01%) cases are expressed in 1-2% of solid tumors (Pahuja et al. 2018; Chmielecki et al. 2015; C-BioPortal). Activating oncogenic mutations in [redacted] and [redacted] have been identified in the extracellular domain, transmembrane or juxtamembrane domains, as well as the kinase domain in multiple solid malignancies, predominantly in those lacking [redacted] gene amplification (i.e., [redacted]) (Wen et al. 2015; Pahuja et al. 2018; Arcila et al. 2013; Bose et al. 2013). Many *ErbB* mutations affect allosteric sites outside of the adenosine triphosphate (ATP)-binding in the kinase domain. Allosteric refers to mutations located at a distance from the ATP site. A unifying feature of oncogenic allosteric mutations is that they primarily cluster to sites that are involved in receptor dimerization or pairing.

BDTX-189 is a potent and selective inhibitor of a spectrum of oncogenic [redacted] and [redacted] mutations, including those mutations that occur at allosteric sites outside of the active site. BDTX-189 is able to inhibit all these mutations by covalently binding to the ATP -binding site as described in Section 1.1.5.1. Targeted mutations comprise recurrent anchor [redacted] mutations, including [redacted] mutations, [redacted] mutations, and clusters of

allosteric [redacted] mutations. Oncogenic *ErbB* mutations occurring at allosteric sites range in frequency between 1% and more than 6% across a number of different solid tumors (e.g., bladder, breast, endometrial, gastric, lung, and brain). The distribution pattern for targeted *ErbB* mutations varies by tumor type, as reflected in Figure 2 (C-BioPortal; data on file). Within a collection of 154,414 cases of solid tumors that were molecularly profiled, various oncogenic [redacted] mutations were found to be expressed by 0.1% to 0.5% of tumors. The most commonly occurring anchor mutations include [redacted], expressed by 0.5% of tumors, and small insertions within exon 20, collectively expressed by 0.4% of tumors. The most commonly occurring [redacted] insertion is YVMA, expressed by 0.3% of tumors. The distribution of [redacted] allosteric oncogenes varies depending on tumor type; in lung adenocarcinoma the most common mutations are [redacted], while in bladder the most common mutation is the anchor mutation [redacted]. [redacted] mutations have been reported in about 6% and 4% of patients, respectively, with non-small cell lung cancer (NSCLC) (Takeda et al. 2018). They are typically mutually exclusive with mutations in [redacted] (Lindeman et al. 2018). The most common [redacted] mutation in NSCLC is in-frame insertions in [redacted] (Chmielecki et al. 2015). [redacted] comprise more than ten distinct mutations, with insertions of SVD, ASV, NPH, and FQEA being most frequent (Robichaux et al. 2018).

Figure 2 Distribution of Allosteric [redacted] Mutations by Most Common Cancer



	All Solid Tumors (154,414 cases)	Lung Adeno (22,413 cases)	CRC (19,050 cases)	Breast NOS (9,549 cases)	Bladder (3,147 cases)	Gastric (2,696 cases)
[redacted]	0.5	0.3	0.3	0.5	4.6	1.1
[redacted]	0.3	1.5	0	0.2	0.4	0
[redacted]	0.4	2.1	0	0.4	0.4	0
[redacted]	0.2	0.1	0.6	0.1	0.3	1.3
[redacted]	0.2	0.1	0.1	0.9	0.3	0.4
[redacted]	0.2	0.1	0.2	0.7	0.2	0.2
[redacted]	0.1	0	0.3	0.1	0.1	0.3
Total	**1-2%**	**2-3%**	**1-2%**	**2-3%**	**6-7%**	**3-4%**

Abbreviations: CRC = colorectal cancer; breast NOS = breast cancer not otherwise specified; [redacted]; lung adeno = lung adenocarcinoma.

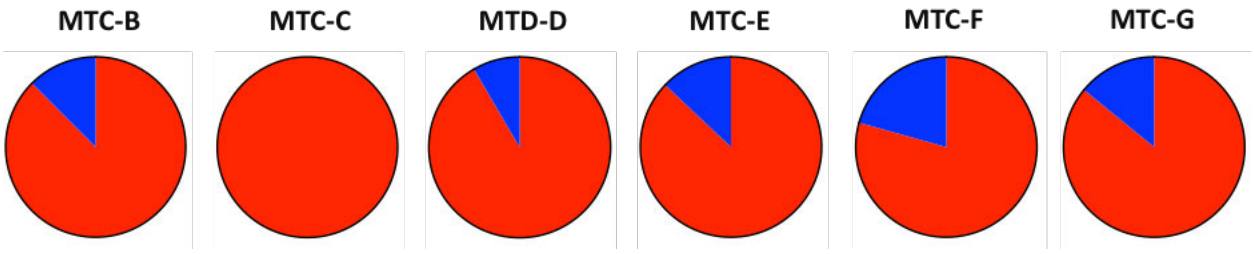
Over the past decade, the identification of specific oncogenic driver alterations (e.g., mutations, rearrangements, and amplifications) has become more efficient and cost-effective due to the increased availability of molecular testing methods, especially next-generation sequencing (NGS) technologies because of their sensitivity and tissue efficiency. Next-generation sequencing allows a relatively small amount of tumor DNA to be analyzed in parallel to identify

potentially actionable alterations with improved sensitivity and reduced tissue requirements compared to serial polymerase chain reaction (PCR) or immunohistochemistry (IHC). Tumor tissue may not always be available for testing by NGS due to lack of adequate material or because it is not possible to obtain new biopsy material. Moreover, tumor tissue may not reflect the intratumoral heterogeneity which could result in false negative test results. Liquid biopsies are a less burdensome approach which is becoming more commonly used for circulating tumor deoxyribonucleic acid (ctDNA) analysis by NGS to identify genomic alterations and for longitudinal monitoring of disease response and early relapse (Neumann et al. 2018). Although not all detected alterations represent actionable molecular targets, molecular testing has become standard in some disease settings such as NSCLC, because driver mutations are identified in up to 55% of lung adenocarcinoma (Hirsch et al. 2017). Since the Food and Drug Administration (FDA) approval of pembrolizumab, larotrectinib, and entrectinib for tumor agnostic indications, patients with a wide range of solid malignancies are now candidates for sequencing by NGS. However, these diagnostic tests have outpaced the development of precision therapies. The majority of patients diagnosed today have tumors with genetic profiles for which there are no targeted therapies.

1.1.1. Allosteric *ErbB* Oncogenic Mutations: Clustering at the Structural Hotspots

BDTX-189 also targets groups of mutations expressed at lower frequency, termed tail mutations. The clusters of mutations (MTCs) targeted by BDTX-189 comprise both anchor and tail mutations (refer to Figure 3).

Figure 3 Anchor (red) and Tail (blue) [redacted] Mutations Expressed in Human Tumors



Abbreviations: [redacted]; MTC = mutational cluster.

The anchor and tail driver mutations are often found aggregated within several functionally critical regions of [redacted]. For MTC-A, which comprises the [redacted] mutation, the most common insertions of ASV, SVD, NPH, and FQEA account for 40-50% while the remaining are much less frequent (Oxnard et al. 2013, Arcila et al. 2013). Black Diamond Therapeutics, Inc. (BDTX) has used this structural and functional information to group the family of allosteric oncogenic [redacted] mutations into MTCs, which will enable their clinical assessment in the BDTX-189-01 study. The clustering scheme of validated oncogenic [redacted] mutations is based on three criteria relating to protein structure and dynamics:

1) mutations that occur in close proximity within the 3-dimensional protein conformation
2) mutations that occur in common dynamic domains of the target protein, and
3) mutations that relate to similar local conformational changes in protein structure.

Grouping these allosteric [redacted] oncogenic mutations into clusters for clinical evaluation allows BDTX to test for differences in response rates between groups of targeted mutations that may

emerge as a result of variances in oncogenic behavior in patients' tumors, predictive significance, receptor turnover rate, pharmacology, or other factors.

Each MTC is composed of common "anchor mutations" (≥0.1% prevalence) and rare or uncommon "tail mutations" (<0.1% prevalence). Many of these tail mutations may not be represented in the current study and if they are, the number of patients with each is not expected to be adequate to fully characterize the antitumor activity. In addition, it is expected that there will be more tail oncogenic driver mutations identified as more patients have their tumors sequenced. Providing target therapies to the broadest patient population necessitates identifying both anchor and tail mutations. Given the similarities in structure and function for all mutations within a given MTC, and *in vitro* as well as *in vivo* demonstration of sensitivity to BDTX-189 (e.g., with half-maximal inhibitory concentration [IC_{50}] ≤80 nM), the anti-oncogenic activity observed in one or more mutations within the MTC is expected to translate to anti-cancer activity in patients with the rare tail mutations. Therefore, it is expected that the patients with advanced solid tumors harboring tail mutations may derive clinical benefit. However, it will be impossible to fully characterize the clinical benefit of BDTX-189 in a substantial number of patients with each tail mutation due to their rare occurrence.

Mutational clusters are grouped as follows:

Mutation Cluster A (MTC-A) - allosteric [redacted] are the short insertions in this cluster which are all located in the [redacted] of the [redacted] domain and alter a molecular hinge motif between the αC-helix and the β4-strand. Stabilization of the αC-helix in an IN conformation induced by the extended hinge motif promotes the formation of an asymmetric dimer of kinase domains that contributes to aberrant signaling by oncogenic [redacted] receptors. Some of the most common mutations within this cluster include [redacted] accounting for about 40-50% of insertions.

Mutation Cluster B (MTC-B) - [redacted] are the [redacted] mutations in this cluster which are all located in the [redacted] of the [redacted] kinase domain and alter a molecular hinge motif between the αC-helix and the β4-strand. Stabilization of the αC-helix in an IN conformation induced by the extended hinge motif promotes the formation of an asymmetric dimer of kinase domains that contributes to aberrant signaling by oncogenic *ErbB* receptors. The most commonly occurring mutation in this cluster is [redacted], accounting for more than 75% of the insertions.

Mutation Cluster C (MTC-C) - allosteric [redacted] mutations are the mutations in this cluster which are located in the [redacted] and alter a molecular hinge motif between the αC-helix and the β4-strand. Stabilization of the αC-helix in an IN conformation induced by the rigidified hinge motif promotes the formation of an asymmetric dimer of kinase domain that contributes to aberrant signaling by oncogenic *ErbB* receptors. The most commonly occurring mutations in this cluster are [redacted].

Mutational Cluster D (MTC-D) - [redacted] mutations are the mutations in this cluster which are all located in the extracellular domain of [redacted] and alter the structural stability of the extracellular domain to promote a constitutively active dimer conformation. Many of these mutations are located in either of two cysteine-rich regions that comprise the extracellular dimer interface. The presentation of free cysteines on the extracellular domain surface increases the propensity of these receptors to form covalently linked homodimers, oncogenic conformations of

ErbB receptors. The most commonly occurring site of mutation in this cluster affects [redacted], which is mutated to [redacted].

Mutational Cluster E (MTC-E) - [redacted] mutations are the mutations in this cluster which are all located in the β-sheet that comprises the N-terminal lobe of the kinase domain with the αC-helix. These mutations alter the β-sheet/αC-helix interface to promote an active kinase domain conformation. The activated N-terminal lobe promotes the formation of an asymmetric dimer of kinase domain that contributes to aberrant signaling by oncogenic *ErbB* receptors. The most commonly occurring mutation in this cluster is [redacted].

Mutational Cluster F (MTC-F) - [redacted] mutations are the mutations in this cluster which are located in either the αC-helix or A-loop of the kinase domain and alter the αC-helix/A-loop interface. Stabilization of the αC-helix in an IN conformation and the A-loop in an active conformation promotes the formation of an asymmetric dimer of kinase domain that contributes to aberrant signaling by oncogenic *ErbB* receptors. The most commonly occurring mutations in this cluster are [redacted].

Mutational Cluster G (MTC-G) - [redacted] mutations are the mutations in this cluster which are located in either the transmembrane or juxtamembrane region of [redacted]. These mutations alter the dimer interfaces of these regions to stabilize an active dimer conformation without covalent interactions. The reinforced dimer interfaces in these regions promote a constitutively active state of the kinase domain that contributes to aberrant signaling by oncogenic *ErbB* receptors. The most commonly occurring mutation in this cluster is [redacted].

1.1.2. Approved Therapies for Patients with Allosteric *ErbB* Oncogenic Mutations

Current [redacted] directed targeted therapies provide clinical benefit to patients expressing [redacted] mutations or amplified [redacted], respectively.

While [redacted] targeted therapies for NSCLC have proven to be effective in patients with ATP-site mutations, limited response to these inhibitors has been observed when treating patients with cancers expressing other types of oncogenic [redacted] mutations, including those expressed at allosteric sites outside of the ATP site, such as [redacted] mutations. [redacted] mutations are generally resistant to [redacted] tyrosine-kinase inhibitors (TKIs). *In vitro*, *in vivo*, and clinical data support the conclusion that standard first, second, and third generation [redacted] inhibitors have no or only suboptimal efficacy against the [redacted] mutations; the reported objective response rate (ORR) has been from 0% to 8% (Kim et al. 2019; Robichaux et al. 2018). In a single arm Phase 2 trial (NCT03191149), a high dose of osimertinib was assessed in 17 patients with advanced NSCLC harboring [redacted] who had received at least one prior treatment line. Osimertinib (160 mg daily, double the approved dose) showed clinical activity against [redacted] mutant NSCLC with a confirmed ORR of 24%, with 82% of patients achieving disease control and median progression-free survival (PFS) of 9.6 months. The most common toxicities were diarrhea, fatigue, cytopenia, and anorexia with low rates of Grade ≥3 events, and skin toxicity adverse events (AEs) of Grade 1. One patient discontinued study treatment due to Grade 3 anemia and another experienced Grade 4 respiratory failure (Piotrowska et al. 2020).

Approved treatment options for patients with [redacted] mutations in the first-line setting are limited to platinum-containing chemotherapy with or without bevacizumab or immune checkpoint inhibitors. Single-agent pembrolizumab in first-line or other checkpoint inhibitors in

second-line have emerged as treatment options, especially in patients whose expression levels of the programmed cell death protein 1 (PD-1) death-ligand PD-L1 are elevated; however, [redacted] mutations appear to be a negative predictive factor for clinical benefit (Gainor et al. 2016; Garassino et al. 2018). It is not yet known if the same negative correlation exists in patients with uncommon mutations ([redacted]). Retrospective data suggest patients with [redacted] mutations are less likely to benefit from nivolumab therapy (Takeda et al. 2018). Only 1 of 7 patients achieved a partial response (PR) despite tumor proportion scores of 50% in 2 patients and 10%, 5%, 0% in 3 patients, respectively, while 2 patients had unknown scores.

While there are approved treatments for patients with [redacted] amplified or overexpressing breast, gastric, or esophageal cancer, which include several monoclonal antibodies (mAbs) and small-molecule TKIs such as trastuzumab, pertuzumab, trastuzumab emtansine, lapatinib, and neratinib, these agents have minimal activity in patients with [redacted] mutations. Neratinib demonstrated a modest clinical activity in patients with advanced cancers of breast, bladder, bile duct, colon/rectum, and cervix harboring [redacted] mutations in the SUMMIT trial (Hyman et al. 2018). In this study, the highest response was observed in patients with advanced breast cancer, with an ORR of 32% at week 8 (8/25 patients) and 24% overall (6/25 patients), with responders harboring [redacted] kinase domain mutations (including [redacted]) or extracellular domain mutations ([redacted]). Recent data from the SUMMIT study have demonstrated that, in patients with metastatic/recurrent endocervical adenocarcinoma harboring [redacted] mutations, neratinib had a confirmed ORR of 25% with median PFS of 7.0 months (Oaknin et al. 2020). However, the safety of neratinib is characterized by toxicities related to [redacted] events, with 22% of SUMMIT trial patients developing Grade 3 or higher diarrhea even with mandatory anti-diarrheal prophylaxis treatment. As mentioned in Section 1.1, allosteric [redacted] mutations typically occur in patients without [redacted] amplification or overexpression (i.e., [redacted]). Approved [redacted]-directed therapies have been investigated in small prospective trials or anecdotal reports in patients with allosteric [redacted] mutations, with limited to no benefit as determined by tumor response (Connell and Doherty 2017). Tyrosine kinase inhibitors targeting [redacted] have demonstrated ORRs of 12% or below in many studies in [redacted]-mutant tumors (Robichaux et al. 2018). Breast cancer patients with [redacted] negative disease and patients with other solid tumors in the advanced and metastatic setting who are identified with an [redacted] mutation are left without therapeutic options once they progress from mostly cytotoxic standard therapies.

The largest dataset with a [redacted]-directed therapy from a prospective study was generated with neratinib in the SUMMIT trial (Hyman et al. 2018). In this study, clinical response was variable, depending on tumor type and mutation variant. When stratified by mutant allele, responses were observed in patients with tumors containing [redacted] mutations. Tumor responses were observed in patients with the following allosteric mutations: [redacted] (n=3/30 [breast, cervical, biliary]), [redacted] (n=1/11 [breast]), [redacted] (n=4/15 [breast, cervical, other]), and [redacted] (n=2/28 [breast]). Notably, no responses were seen in patients with lung cancer harboring [redacted], in which this class of alteration is most common. Overall, tumor responses for patients harboring these [redacted] mutation alleles were modest (8 of 56 patients [14%]).

1.1.3. Investigational Therapies for Patients with Allosteric *ErbB* Oncogenic Mutations

The most recent meta-analysis of 3,920 records (including 5 clinical and 32 real-world evidence studies) suggest that the outcome of treatments in patients with NSCLC harboring [redacted] mutations with currently approved TKIs and immune-oncology agents remains poor to sub-optimal (Tomaras et al. 2020). However, several investigational agents such as [redacted] and [redacted] directed TKIs and mAbs are being evaluated in clinical studies. Mobocertinib/TAK-788 is a small molecule TKI that has demonstrated activity in NSCLC patients with [redacted] mutations with an ORR of 43% (12/28 patients) and median PFS of 7.3 months in a Phase 1/2 trial (Riely et al. 2020). Preliminary data from a single-center study for poziotinib, another small molecule TKI, showed an ORR of 58% at week 8 and median PFS of 5.6 months in NSCLC patients with [redacted] mutations (Heymach et al. 2018). However, data from the larger multi-center Phase 2 ZENITH20 study in 115 NSCLC patients with [redacted] mutations showed poorer results, with ORR of 15% and a median PFS of 4.2 months (Le et al. 2020). Amivantamab, a bispecific anti-[redacted] and anti-[redacted] antibody, showed activity in NSCLC patients with [redacted] mutations with an ORR of 28% (14/50 patients) and median PFS of 8.3 months (Park et al. 2020). The safety of mobocertinib and poziotinib has been characterized by toxicities, including typical [redacted] events such as diarrhea (Grade 3 or higher in 32% of patients treated with mobocertinib, and in 26% of patients treated with poziotinib), and skin rash (Grade 3 or higher in 1% of patients for mobocertinib, and in 28% for poziotinib). Amivantamab had Grade 3 or higher events in 36% of patients, with 1 Grade 3 diarrhea event.

In NSCLC patients harboring [redacted] mutations, poziotinib has shown an ORR of 28% and PFS of 5.5 months in the Phase 2 ZENITH20 study (Socinski et al. 2020). Interim results from the DESTINY trial have shown that trastuzumab deruxtecan/DS-8201, an antibody drug conjugate, had an ORR of 62% (26/42 patients) and median PFS of 14.0 months in NSCLC patients harboring [redacted] mutations predominantly in the kinase domain (Smit et al. 2020). But as with poziotinib, trastuzumab deruxtecan/DS8201 also had high levels of toxicity, with 64% Grade 3 or higher events and 38% of patients with dose reductions.

There is a critical unmet medical need for precision treatment of patients with locally advanced or metastatic solid tumors harboring an allosteric *ErbB* mutation domain.

1.1.4. BDTX-189

BDTX-189 is an orally available, highly potent and selective irreversible inhibitor of *ErbB* allosteric mutations and kinase domain active site mutations. These mutations are constitutively activated, ligand-independent receptors that are resistant to currently approved [redacted] or [redacted] TKIs or mAbs at therapeutically relevant and tolerable systemic exposure levels. BDTX-189 binds covalently to the ATP-binding site of the mutant receptor at very low concentrations. The drug has been designed to minimize or eliminate the typical dose-limiting AEs such as rash and diarrhea associated with [redacted] TKIs by sparing [redacted] receptors.

BDTX-189 exhibits *in vitro* activity against the most commonly occurring *ErbB* family mutations (please see the Investigator's Brochure [IB]).

Preclinical pharmacology studies have also demonstrated relevant activity of BDTX-189 against targets that results in oncogenic transformation other than allosteric *ErbB* mutations. These

include inhibition of [redacted] overexpressing/amplified cells, [redacted], [redacted] mutations, and the classical [redacted] and [redacted] mutation.

The clinical development of BDTX-189 will initially focus on patients with genetically defined allosteric mutations in [redacted] and [redacted] in a tumor-agnostic fashion.

1.1.5. Non-clinical Experience

1.1.5.1. Pharmacology

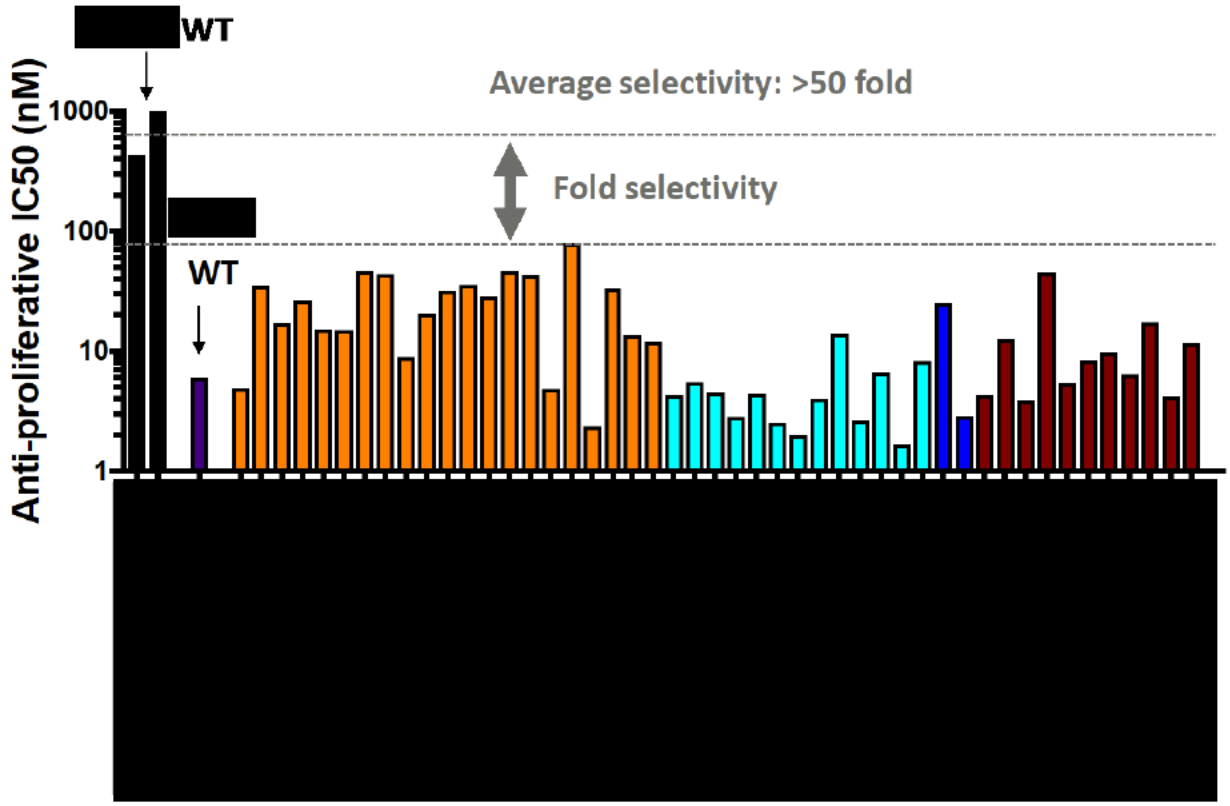
The primary pharmacology of BDTX-189 was evaluated in a series of biochemical, cellular, and *in vivo* studies. Conclusions from these studies are as follows:

- *In vitro* data demonstrate that BDTX-189 is able to inhibit an entire group or family of allosteric *ErbB* mutations, including [redacted] and [redacted] mutations.
- BDTX-189 potently and selectively inhibits the tyrosine kinase activity of allosteric [redacted] and [redacted] mutants *in vivo*.
- BDTX -189 inhibits the proliferation of and promotes regression of allografts or patient-derived tumors with allosteric [redacted] and [redacted] mutants.
- Because all allosteric *ErbB* mutations share similar pharmacology, it is expected that BDTX-189 will be able to inhibit others that have not been fully validated in nonclinical studies.

***In Vitro* Pharmacology**

BDTX-189 has been observed to potently inhibit the proliferation of BaF3 cells transformed by many oncogenic [redacted] and [redacted] mutants (Figure 4). BDTX-189 also inhibited the proliferation of patient derived cell lines expressing the [redacted] mutants [redacted]. A favorable therapeutic window over [redacted] was a key design goal in the BDTX-189 program. BDTX-189 achieved high selectivity for cells expressing the targeted allosteric [redacted] and [redacted] mutants, and BDTX-189 spares cells expressing [redacted].

Figure 4 Cellular Potency of BDTX-189

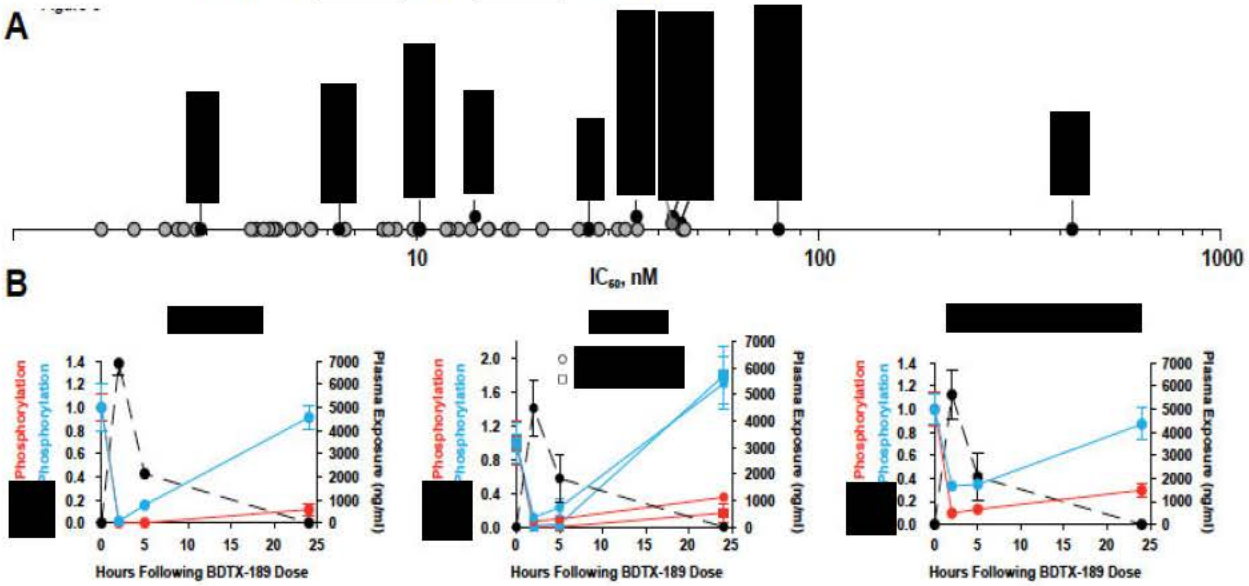


Abbreviations: [redacted]; [redacted]; IC50 = half-maximal inhibitory concentration (IC50)

In Vivo Pharmacology

The antitumor potential of BDTX-189 was determined *in vivo* in models driven by allosteric *ErbB* mutants. Relationships between dose, exposure, time, pathway-related biomarkers, and tumor growth inhibition (TGI) were established in a cell line-derived allograft model. In acute dose pharmacokinetic (PK)/pharmacodynamic (PDx) studies, oral administration of BDTX-189 to athymic nude mice bearing a range of [redacted] (both BaF3 and GBM6 patient-derived glioblastoma tumors) or [redacted] *BaF3* allograft tumors resulted in potent and sustained suppression of target phosphorylation for at least 24 hours following dosing (Figure 5). Potent activity was observed *in vivo* for [redacted], which was the least sensitive mutation *in vitro*. These data support once daily (QD) dosing of BDTX-189 due to the irreversible binding mode to the active site.

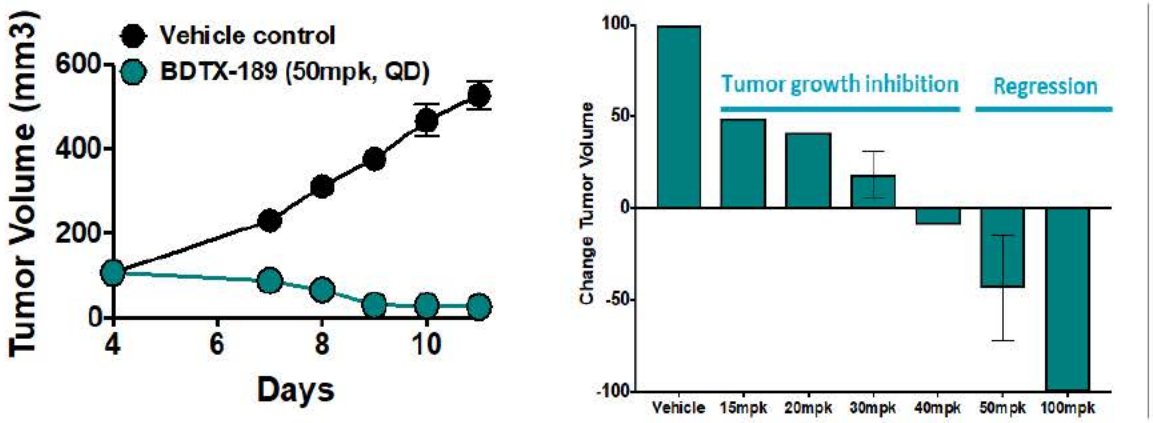
Figure 5 ***In Vitro*** **IC50 and** ***In Vivo*** **(50 mpk acute oral dose dosing) Activity Across a Range of [redacted] and [redacted] Mutants**



Abbreviations: [redacted]; IC50 =half-maximal inhibitory concentration; MTC = mutational cluster.

BDTX-189 has been shown to exhibit antitumor activity against allosteric [redacted] mutant tumors. Daily dosing of BDTX-189 was well tolerated in athymic nude mice bearing [redacted] BaF3 allograft tumors up to 100 mg/kg (Figure 6). BDTX-189 demonstrated dose-dependent TGI (median tumor volume) at daily doses ranging from 20 to 100 mg/kg. BDTX-189 also demonstrated dose-dependent tumor regression at doses ranging from 30 to 100 mg/kg.

Figure 6 **Antitumor Activity Against [redacted] BaF3 Allograft**



BDTX-189 is able to achieve regression in allo-[redacted]allografts

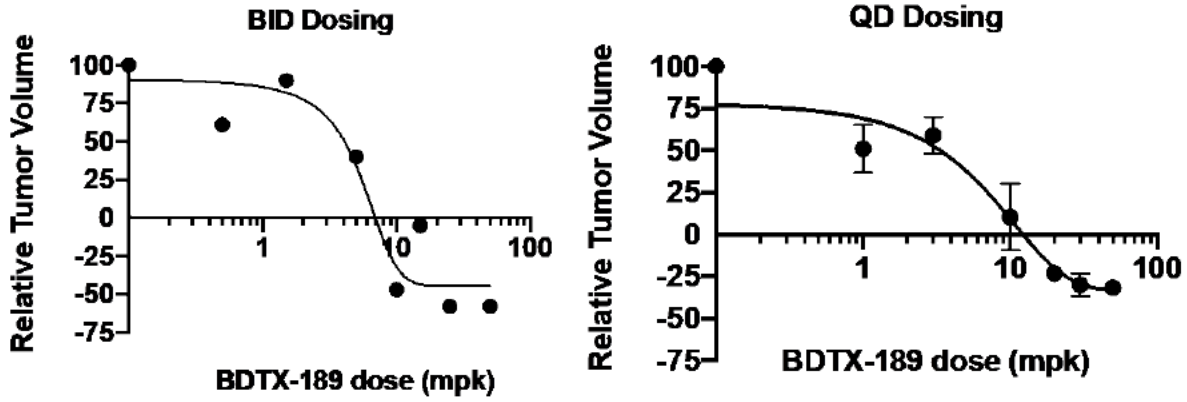
Summary of Tumor Growth Inhibition dose response (daily dose)

Abbreviations: HER2 = human epidermal growth factor receptor 2; QD = once daily

BDTX-189 has also been shown to exhibit antitumor activity against patient-derived tumors expressing allosteric [redacted] mutants. The majority of patient-derived tumor

models for allosteric *ErbB* mutations are derived from lung cancer patients, where these mutations have been most intensely studied. The Sponsor explored activity in 2 mutant models (CUTO-14 and CUTO-17), derived from 2 patients with NSCLC. In a series of dose-ranging TGI studies conducted in these 2 patient-derived tumor-expressing [redacted] mutations, BDTX-189 was found to promote complete growth stasis and/or regression at doses ranging from 10 mg/kg to 50 mg/kg. Notably, in the CUTO-14 model system (Figure 7), regressions at daily doses as low as 10-30 mg/kg on a once daily (QD) dosing schedule or 10 mg/kg on a twice-daily (BID) dosing schedule were seen. In contrast, in the A431 tumor model expressing WT [redacted], a 15 mg/kg daily dose of BDTX-189 produced only partial TGI (52%), while the non-selective inhibitor, afatinib, administered at a daily dose of 20 mg/kg produced regression (64%) in this same model system in a head-to-head comparison. These data support the highly potent and selective profile for BDTX-189 to target oncogenic *ErbB* mutations while sparing inhibition of [redacted].

Figure 7 Antitumor Activity Against CUTO-14 Patient-derived Tumor Model [redacted]



Abbreviations: BID = twice daily; mpk = mg/kg; QD =once daily

BDTX-189 exposures in the *in vivo* studies above are expected to be achievable clinically. Physiologically based PK modeling was applied to predict the PK of BDTX-189 in humans. Combining the predicted human PK with the target plasma exposure derived from the CUTO-14 model, clinical doses of ≥ 200 mg QD are expected to result in systemic exposures that could be associated with antitumor activity.

1.1.5.2. Pharmacokinetics

Based on preclinical data, the following are the predicted characteristics in humans:

- Low-to-moderate oral bioavailability
- Projected half-life of approximately 2 hours
- Once daily dose of 400 to 800 mg is expected to achieve target plasma exposures associated with antitumor activity

- Reduced solubility of BDTX-189 at increasing pH may result in decreased exposures with concomitant use of acid-reducing agents and food
- Plasma protein unbound fraction: 1.5%
- Metabolized mainly by CYP3A4, with multiple alternative pathways and glutathione conjugation; no CYP-mediated perpetrator drug interactions expected. However, the use of strong CYP3A inhibitors and inducers with BDTX-189 is prohibited.
- BDTX-189 is a substrate of P-glycoprotein (P-gp) and breast cancer resistance protein (BCRP) and coadministration with strong inhibitors of P-gp or BCRP should be used with caution. BDTX-189 is a moderate inhibitor of BCRP and sensitive substrates should be used with caution.
- Negligible excretion in urine as parent

1.1.6. Toxicology

The rat and dog were chosen as appropriate toxicology species based on the comparative metabolic profiling of BDTX-189 in the liver microsomes and hepatocytes of rats, dogs, and humans.

In the definitive good laboratory practice (GLP) study, following oral administration of BDTX - 189 QD over a period of 28 days to male and female rats, the highest non-severely toxic dose (HNSTD) was 30 mg/kg/day. This was based on BDTX-189-related clinical signs observed at 60 mg/kg/day in females, including body weight loss, piloerection, hunched posture, and reduced food intake. Males tolerated daily administration of 60 mg/kg/day for the full 28-day dosing period, but food intake was slightly lowered during the first week of treatment and the overall body weight gain was 27% less than that of concurrent controls. There were no BDTX-189-related clinical signs at 10 or 30 mg/kg/day. There were no effects on urinalysis and organ weights, nor were there ocular changes or effects on functional/behavioral observation parameters at any dose level. Microscopic changes considered related to treatment consisted of slight and reversible inflammation and hyperplasia of the mucosa in various regions of the gastrointestinal tract at all dose levels, and at the mid- and high dose levels were accompanied by elevated total white blood cell (WBC) counts (primarily neutrophils). Following a 14-day recovery period, inflammation in the gastrointestinal tract and WBC counts were completely reversed.

In the definitive GLP study, following oral administration of BDTX-189 BID over a period of 28 days to male and female dogs, the 20 mg/kg BID dose level (40 mg/kg/day) was poorly tolerated, with marked clinical signs, inappetence, and weight loss necessitating the premature termination of one animal on Day 17. Dose levels of 10 and 20 mg/kg/day were well tolerated. Based on in-life and pathology findings, the HNSTD was 20 mg/kg/day (10 mg/kg BID). Microscopic findings were consistent with a primary irritant effect to the proximal gastrointestinal tract, with associated secondary changes within the mesenteric lymph node and pancreas. Secondary changes noted in mesenteric lymph node consisted of increased sinus erythrocytes, a reaction to the gastrointestinal effect, and was not noted in other peripheral lymph nodes. In the pancreas, only edema was noted without any evidence of degeneration or inflammation. Slight inflammation of the renal papilla in one animal administered 40 mg/kg/day was of uncertain

pathogenesis and its relationship to BDTX-189 is uncertain. Complete or partial reversibility was demonstrated following the 14-day treatment-free period, with the exception of the duodenal glandular dilatation, which would be expected to resolve over a longer recovery period.

BDTX-189 did not show effects on cardiovascular or respiratory function in GLP safety pharmacology studies in dog and rat, respectively. BDTX-189 was not an inhibitor of human ether-à-go-go related gene (hERG) at concentrations up to and including 7.5 µM. BDTX-189 did not show evidence of phototoxic potential *in vitro*. BDTX-189 did not show evidence of mutagenicity or clastogenicity in *in vitro* GLP genotoxicity assays.

1.1.7. Clinical Experience

As of 02 April 2021, preliminary safety data were available for 65 patients from Part A of this study who have received at least 1 dose of BDTX-189, including 55 patients who were administered a QD schedule with doses including 25 to 200 mg (n=5, fasting), 400 mg (n=7, fasting), 800 mg (n=21, fasting), 800 mg (n=9, non-fasting [NF]), 1000 mg (n=7, NF), 1200 mg (n=6, fasting). A total of 10 patients have received the BID schedule, with doses of 600 mg (n=5, NF) and 800 mg (n=5, NF).

The DLT-evaluable population consisted of 45 patients who were enrolled into the dose-escalation cohorts. No DLTs have been reported with doses of 800 mg BDTX-189 QD (fasting or NF) or less in the dose escalation cohorts. The MTD was exceeded with 2 patients in each of the cohorts receiving either 1200 mg QD (fasting) or 1000 mg QD (NF). The 800 mg QD, NF dose was considered the MTD and the recommended phase 2 dose (RP2D). The 800 mg and 600 mg BID fasting doses also exceeded the MTD with 3 patients each experiencing DLTs. A cohort evaluating 400 mg BID, NF is currently enrolling.

The majority of DLTs were gastrointestinal in nature with diarrhea reported in 6 patients, vomiting in 5, and nausea in 4. Other DLTs reported by 1 patient included increased alanine aminotransferase (ALT) with or without increased aspartate aminotransferase (AST), increased bilirubin, increased creatinine, and dehydration. Some patients experienced more than 1 DLT, and these were either Grade 2 or 3 severity.

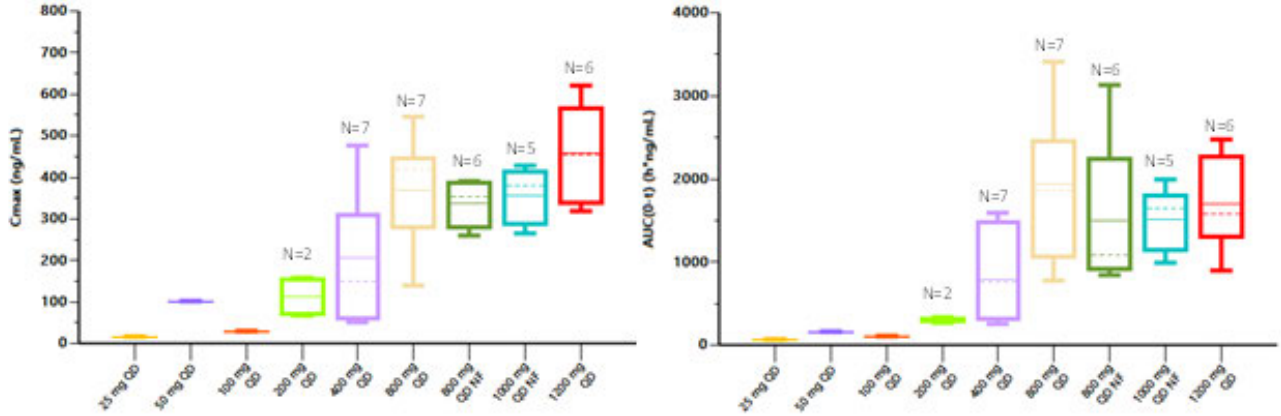
The most frequently reported treatment-emergent adverse events (TEAEs) were diarrhea (58.5%), nausea (47.7%), vomiting (44.6%), fatigue (29.2%), and increased ALT (23.1%). No dose relationship was observed in TEAEs reported. The majority of the TEAEs were Grade 1 or 2 (mild or moderate) with 43.1% of patients reporting TEAEs of Grade ≥3. The most frequently reported TEAEs Grade ≥3 included diarrhea (15.4%) and increased ALT (7.7%); all were considered by the Investigator to be related to the study treatment.

Preliminary PK data available for 43 patients showed oral absorption was generally rapid. In the multiple patient cohorts, there were dose-dependent increases in exposure (i.e., maximum concentration [C_{max}] and area under the plasma concentration-time curve [AUC]) seen with single (C1D1) and multiple (C1D15) daily administrations) up to 800 mg, before an exposure plateau was reached at 1200 mg (see Figure 8). Exposures at 800 mg QD were approximately 1.5-fold lower than projected from preclinical data. The median elimination half-life ($t_{1/2}$) across all dose levels ranged from 2.2 to 5.9 hours, which is in line with preclinical projections of approximately 2 hours. No consistent trend of accumulation or decreasing exposures on multiple dosing was indicated. In the ongoing Food Effect cohorts, evaluating the effect of a high-fat or

low-fat meal on the PK of BDTX-189, 6 patients are considered evaluable in each cohort. The effect of a high-fat meal on the PK of BDTX-189 suggests a slightly positive effect of food with geometric mean ratio for C_{max} and AUC_{0-t} of 1.0 and 2.3 respectively. Administration of BDTX-189 with food resulted in an approximately 2.5-fold increase in median t_{max} (median t_{max} 1.5 hours fasted, 3.5 hours low-fat meal, 4.0 hours high-fat meal) relative to administration in the fasted state, and no change in median $t_{1/2}$.

Based on the results described above, the Safety Review Committee (SRC) recommended that the remaining patients to be enrolled will be administered BDTX-189 following consumption of a meal (i.e., NF).

Figure 8 Relationship Between BDTX-189 Dose (mg/day QD) and Exposure (C1D1 C_{max} and AUC_{0-t})



AUC_{0-t}=area under the plasma concentration-time curve from time 0 to the time of the last measurable concentration; Cmax=maximum concentration.

1.1.8. Study Rationale and Rationale for Starting Dose

Allosteric mutations in [redacted] and [redacted] have been identified and characterized; these mutations encode molecular changes in these oncogenic targets that are not located at traditional substrate or inhibitor binding sites, but rather act at a distance to influence the binding properties of these sites. BDTX-189 is highly potent against these allosteric mutations which are found in 1% to 2% of a large variety of solid tumors but are enriched in tumors such as advanced NSCLC, invasive breast cancer, bladder cancer, and endometrial cancer. Currently available [redacted] and [redacted] TKIs or mAbs have limited or no antitumor activity against these genetic alterations either because of insufficient potency or lack of selectivity which results in toxicity before adequate exposures are achieved. Therefore, there is a high unmet medical need for a large group of patients currently not served. The goal of the development plan for BDTX-189 is to efficiently evaluate the antitumor activity across a broad range of solid tumor types expressing allosteric *ErbB* mutations.

BDTX-189 binds covalently to the ATP-binding site of the mutant receptor at very low concentrations (IC_{50} < 77 nM cellular potency). It has been demonstrated that BDTX-189 remains bound to mutant receptors for at least 24 hours, with site occupancy >50% at 24 hours after probe addition. This observation has been confirmed *in vivo,* where oral administration of BDTX-189 to athymic nude mice bearing allosteric *ErbB* mutant BaF3 allografts showed suppression of target phosphorylation for at least 24 hours. This indicates that BDTX-189 binds

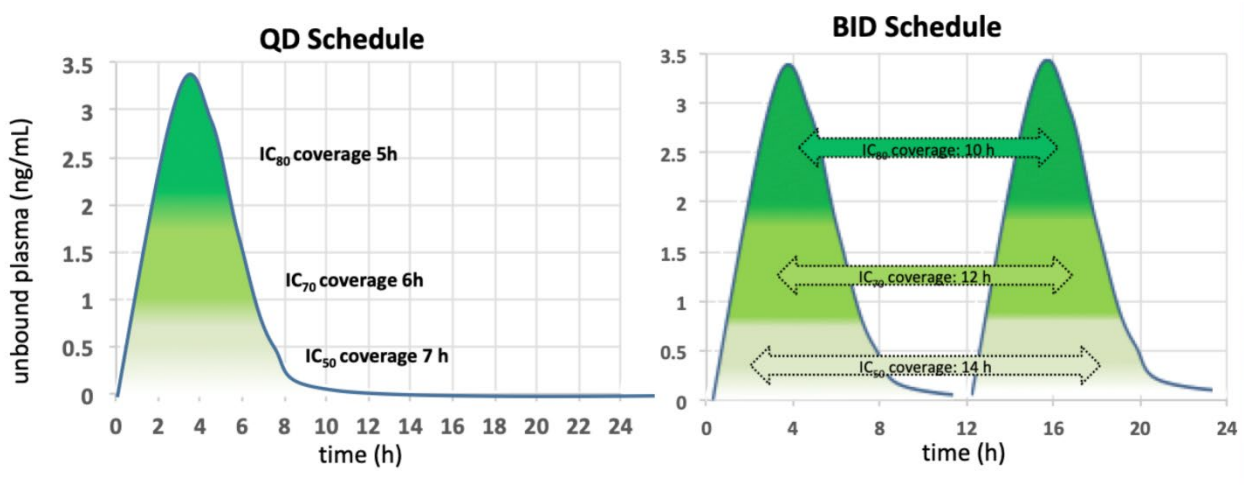
to the active site of *ErbB* allosteric mutants via a slow off-rate or covalent mechanism supporting once daily dosing in humans.

The determination of the Phase 1 starting dose in cancer patients was based on the results of the 28-day GLP toxicology studies in rat and dog. The human equivalent dose at the HNSTD in rat and dog is 180 mg/m^2 and 400 mg/m^2, respectively, and as such defined rat as the most sensitive species. The proposed maximum recommended starting dose was calculated in accordance with the International Council for Harmonisation (ICH) S9 Nonclinical Evaluation for Anticancer Pharmaceuticals (adopted by the FDA, 2010) using the toxic dose in 10% of animals (STD_{10}), which in rat was exceeded at 60 mg/kg/day and a dose of 30 mg/kg/day was the HNSTD. The starting dose was calculated as 25 mg QD as follows: 30 mg/kg/day (highest dose level < STD_{10} in rat) × 6 (human equivalent dose mg/m^2 conversion) × 1/10 (rodent safety factor) × 1.62 (human body surface area), and rounded down to the nearest multiple of 5.

With a starting dose of 25 mg QD and the projected dose to achieve exposures associated with antitumor activity in humans being 400 to 800 mg QD (see Section 1.1.5.2), this justifies using single-patient cohorts during the accelerated titration with doubling dose increments until a ≥ Grade 2 AE related to BDTX-189 is observed, or until the 200 mg QD dose cohort is complete (see Section 4.3). The projected dose range expected to be associated with antitumor activity in humans is 6.7-13 mg/kg/day which compares favorably with the HNSTD of 20 and 30 mg/kg/day observed in dog and rat, respectively.

Given that the mechanism of action of BDTX-189 is covalent/irreversible, the totality of emerging PK/PDx data will need to be considered in a scenario where the half-life is too short to achieve sufficient target engagement/pathway modulation, or where target coverage is under predicted in preclinical models (Figure 9). Therefore, a parallel Dose Escalation of one alternative dose schedule (BID) of BDTX-189 may be evaluated.

Figure 9 Predicted BDTX-189 Unbound Plasma Concentrations over Time for QD and BID Dosing Schedules



1.2. Potential Risks and Benefits of the Treatment Regimen

This is the first in-human study with BDTX-189. The risks for human patients have been estimated based on the results of the preclinical toxicology studies with BDTX-189.

The target organs of toxicology with BDTX-189 based on preclinical data include:

- Gastrointestinal Effects: Inflammation/hyperplasia/atrophy of the gastrointestinal mucosa (esophagus, stomach, duodenum, jejunum, ileum, cecum) consistent with a primary irritant effect in the proximal gastrointestinal tract in dogs with associated secondary changes within the mesenteric lymph nodes and pancreas, increases in total WBC in both species and increases in platelet counts in dogs at the higher dose levels. This was associated with clinical signs of inappetence, vomitus, and liquid/loose feces in rat and/or dog. All of these BDTX-189-related findings completely or partially resolved following a 14-day recovery period.

Toxicology findings of uncertain relationship to BDTX-189 include:

- Kidney: Slight papillary inflammation of unknown pathogenesis in 1 dog at 40 mg/kg/day.
- Pancreas: Minimal-to-slight interstitial edema in dogs at 20 and 40 mg/kg/day considered secondary to gastrointestinal inflammation.

Adverse events observed in the dose-escalation portion of the ongoing Phase 1 study:

- Gastrointestinal disorders including nausea, vomiting and diarrhea, some at Grade 3 severity
- Hepatic test abnormality, including Grade 3 ALT and/or AST elevations and Grade 2 blood bilirubin elevation

Despite the 6-fold *in vitro* selectivity of BDTX-189 for *ErbB* mutations versus WT [redacted], the potential for typical [redacted]-related class AEs such as cutaneous toxicities and diarrhea cannot be excluded. Moreover, due to the potent anti-[redacted] effects the potential for cardiac dysfunction is a theoretical possibility. The potential risks associated with BDTX-189 treatment based on observed toxicology findings and potential class-effects are considered monitorable and reversible in patients. Please refer to the BDTX-189 IB for further details regarding the potential risk associated with the use of BDTX-189.

Patients will be monitored periodically as per the Schedule of Assessments (Table 1, Table 2, and Table 3) with physical examinations, hematology, chemistry, coagulation, urinalysis, electrocardiograms (ECGs), and cardiac function. Women of child-bearing potential (WOCBP) and male patients must agree to use a highly-effective method of contraception during the study and for at least 90 days after the last dose of study treatment.

Currently, [redacted]-directed therapies are only approved for patients with tumors harboring [redacted] amplifications and not for [redacted] mutations. Allosteric *ErbB* mutations are mostly resistant to approved [redacted]-directed therapies at achievable systemic exposures in humans. There remains a significant unmet medical need for drugs that target allosteric *ErbB* mutations including [redacted]. The preclinical data for BDTX-189 demonstrate antitumor activity across a range of allosteric *ErbB* mutants both *in vitro* and *in vivo* evidenced by both TGI and regression. The data obtained to date for BDTX-189 are regarded as sufficient to justify evaluation of the objectives for the planned study in patients with advanced solid malignancies. BDTX-189 is an investigational drug and currently there are no proven benefits.

1.2.1. Precautions and Risks Associated with BDTX-189

Dose-limiting toxicities have included reversible Grade 3 ALT/AST increases, Grade 3 diarrhea (lasting >24 hours), Grade 3 dehydration, and intolerable Grade 2 and Grade 3 nausea and vomiting. Gastrointestinal disorders increased in frequency and severity with increasing doses. A total of 72% of the patients across all dose levels experienced treatment-related gastrointestinal TEAEs, of which 19% were Grade 3 severity. A total of 14% experienced a drug-related skin disorder TEAE. No patients have experienced a treatment-related TEAE of Grade 4 or 5 severity. Further details are described in the IB.

2. STUDY OBJECTIVES AND ENDPOINTS

2.1. Primary Objective

The primary objectives of this study are to:

Part A

- Determine the recommended Phase 2 dose (RP2D) and schedule of BDTX-189 as a single agent administered orally (PO) in patients with advanced solid malignancies.

Part B

- Assess the antitumor activity of BDTX-189 as a single agent in patients with allosteric [redacted] mutations, including [redacted] mutations.

2.2. Secondary Objectives

The secondary objectives of this study are to:

Part A and B

- Assess the safety and tolerability of BDTX-189 as a single oral agent.
- Investigate the PK of BDTX-189 using population PK (PopPK) methods and explore correlations between PK, response, and/or safety findings.

Part A

- Establish the PK of BDTX-189 and circulating metabolite profile after a single dose and at steady state.
- Assess the preliminary efficacy and antitumor activity of BDTX-189 as a single oral agent.
- Assess the effect of food on the PK of BDTX-189.

Part B

- Assess additional measures of efficacy and antitumor activity of BDTX-189 as a single agent.
- Assess patient outcome by evaluation of electronic patient reported outcomes (ePRO).

2.3. Exploratory Objectives

The exploratory objectives of this study are to:

Part A and B

- Evaluate allosteric *ErbB* mutations, gene amplifications, and possible markers of drug sensitivity and resistance in plasma using ctDNA.

Part A

- Evaluate the PDx effects of BDTX-189 in tumor tissue as determined by *ErbB* signaling pathway proteins.

2.4. Endpoints

The study endpoints are provided in Table 4.

Table 4 Study Objectives and Corresponding Endpoints

Primary Objective:	**Endpoint/Variable:**
Part A: Determine the RP2D and schedule of BDTX-189 administered PO in patients with advanced solid malignancies	Incidence and severity of TEAEs, including DLTs, graded according to NCI CTCAE, Version 5.0
Part B: Assess the antitumor activity of BDTX-189 as a single agent in patients with allosteric [redacted] mutations, including [redacted] mutations	Objective response defined as either a CR or PR, as determined by BICR and per RECIST version 1.1 based on CT or MRI scans
Secondary Objectives:	**Endpoint/Variable:**
Part A and B: Assess the safety and tolerability of BDTX-189 as a single oral agent	Incidence of TEAEs; changes in clinical laboratory parameters, vital signs, ECG parameters, cardiac function, and physical examination results
Part A and B: Investigate the PK of BDTX-189 using PopPK methods and explore correlations between PK, response, and/or safety findings	PopPK parameters: Cl/F, Vd/F, and Ka for BDTX-189. Cl/F will be used to generate estimates of BDTX-189 AUC. Possible PK/safety and PK/efficacy correlations, and covariate analysis of intrinsic/extrinsic factors
Part A: Establish the PK of BDTX-189 and circulating metabolite profile after a single dose and at steady-state	PK parameter estimates of BDTX-189 generated from plasma concentration-time data (e.g., C_{max}, T_{max}, AUC, and $t_{1/2}$)
Part A: Evaluate the preliminary efficacy and antitumor activity of BDTX-189 as a single oral agent	Investigator-assessed objective response, DOR, DCR, PFS as determined by RECIST v1.1, and OS (for Safety Expansion portion).
Part A: Assess the effect of food on the PK of BDTX-189	PK parameter estimates of BDTX-189 generated from plasma concentration-time data (e.g., C_{max}, T_{max}, AUC, $t_{1/2}$, Cl/F, and Vd/F). Fed/fasted geometric least squares mean ratio and 90% CI for BDTX-189 C_{max} and AUC
Part B: Assess additional measures of efficacy and antitumor activity of BDTX-189 as a single agent	Objective response (Investigator assessed), DOR (Investigator and BICR assessed), DCR (Investigator and BICR assessed), PFS (Investigator and BICR assessed) per RECIST v1.1, and OS
Part B assess patient outcome by evaluation of PROs	Change from baseline in the FACT-G subscales, NCCN-FACT FBSI-16 subscales, NCCN-FACT FLSI-17 subscales, EQ-5D-5L, PROMIS physical function score, and NCI-CTCAE scores
Exploratory Objectives:	**Endpoint/Variable:**
Part A and B: Evaluate allosteric *ErbB* mutations, gene amplifications, and possible markers of drug sensitivity and resistance in plasma using ctDNA	Presence and/or disappearance of [redacted] *ErbB* mutations and other [redacted] mutations, and other markers of drug sensitivity and resistance

Primary Objective:	Endpoint/Variable:
Part A: Evaluate the PDx effects of BDTX-189 in tumor tissue as determined by *ErbB* signaling pathway proteins	*ErbB* signaling pathway proteins in tumor tissue, such as pERK

Abbreviations: AUC = area under the concentration time curve; BICR = blinded independent central review; CI = confidence interval; Cl/F = oral clearance; C_{max} = maximum concentration; CR = complete response; CT = computed tomography; CTCAE = Common Terminology Criteria for Adverse Events; ctDNA = circulating tumor DNA; DCR = disease control rate; DLT = dose limiting toxicity; DOR = duration of response; ECG = electrocardiogram; [redacted]; ePRO = electronic patient reported outcomes; EQ-5D-5L = EuroQol Group's 5-domain 5-level questionnaire; FACT = Functional Assessment of Cancer Therapy; FACT-G = Functional Assessment of Cancer Therapy-General; FBSI = Functional Assessment of Cancer Therapy Breast Symptom Index; FLSI = Functional Assessment of Cancer Therapy Lung Cancer Symptom Index; [redacted] Ka = first-order absorption rate constant; MRI = magnetic resonance imaging; NCCN = National Comprehensive Cancer Network; NCI = National Cancer Institute; OS = overall survival; PDx = pharmacodynamics; pERK = phosphorylated extracellular regulated kinase; PFS = progression-free survival; PK = pharmacokinetics; PO = by mouth; popPK = population pharmacokinetics; PR = partial response; PROMIS = Patient Reported Outcomes Measurement Information System; RECIST = Response Evaluation Criteria in Solid Tumors; RP2D = recommended Phase 2 dose; $t_{1/2}$ = elimination half-life; TEAEs = treatment-emergent adverse events; T_{max} = time for maximum concentration; Vd/F = oral volume of distribution.

3. STUDY PATIENT POPULATION AND DISCONTINUATION

3.1. Inclusion Criteria

Patients must meet the following criteria in order to be included in the research study:

1. Signed and dated written informed consent prior to any study-specific procedures.
2. Female or male patients age ≥18 years at the time of providing voluntary written informed consent.
3. Histologically- or cytologically-confirmed locally advanced or metastatic solid tumor with documented recurrence or disease progression from standard anticancer therapy in the advanced/metastatic setting.
4. Eastern Cooperative Oncology Group (ECOG) Performance Status score of 0 or 1 (Appendix A).
5. Minimum life expectancy of ≥3 months.
6. Ability to swallow BDTX-189 tablets.
7. All toxicities from prior therapy (except alopecia, Grade 2 neuropathy, or Grade 2 hypothyroidism) must have resolved to ≤ Grade 1 according to the National Cancer Institute (NCI) Common Terminology Criteria for Adverse Events (CTCAE Version 5.0) prior to baseline. Pneumonitis due to prior therapy or radiation must be totally resolved. Patients with Grade 2 neuropathy, Grade 2 hypothyroidism, or other toxicities that are asymptomatic or adequately managed with stable medication may be eligible with approval by the Sponsor.
8. For women of child-bearing potential (WOCBP), documentation of negative serum pregnancy test (beta-human chorionic gonadotropin [β-hCG]) within 7 days prior to baseline (Appendix C).
    - **Note:** WOCBP is defined as fertile, following menarche and until becoming post-menopausal (no menses for 12 months without an alternative medical cause) unless permanently sterile (hysterectomy, bilateral salpingectomy, or bilateral oophorectomy).
9. For WOCBP and male patients whose sexual partners are WOCBP, agreement to use a highly effective method of contraception during the study and for at least 90 days after the last dose of study treatment. Male patients must also refrain from donating sperm during their participation in the study (Appendix C).
    - **Note:** Highly effective birth control includes: 1) oral, implantable, or injectable combined hormonal (estrogen and progesterone containing) or progesterone only contraceptive associated with inhibition of ovulation; 2) intrauterine device; 3) intrauterine hormone-releasing system; or 4) bilateral tubal occlusion, vasectomized partner or sexual abstinence.

Part A Only

10. No standard therapy available according to the Investigator.

11. **For the dose-escalation portion**, patients with solid tumors with alterations that may be associated with antitumor activity based on preclinical data for BDTX-189 such as:
    a. [redacted] or [redacted] mutation(s)
    b. [redacted] or [redacted] mutation
    c. [redacted] amplified or overexpressing tumor
    d. [redacted] mutation

    Mutations must have been determined by a validated NGS test routinely used by each institution using tissue and/or plasma and performed in a Clinical Laboratory Improvement Amendments (CLIA)-certified or equivalent laboratory. A list of eligible validated oncogenic mutations from 1 of the 7 MTCs is provided in Appendix I.

Part A Safety Expansion Only

12. Patients with one of the following mutations and tumor pairs:
    a. [redacted] mutation in patients with NSCLC, breast cancer, biliary tract cancer, or cervical cancer
    b. [redacted] or [redacted] mutation in patients with NSCLC
    c. [redacted] amplified or overexpressing tumor from the following cancer types: breast, gastric, gastroesophageal, colorectal, endometrial, biliary tract, cancer of unknown primary (CUP), and NSCLC

    Mutations must have been determined by a validated NGS test routinely used by each institution using tissue and/or plasma and performed in a CLIA-certified or equivalent laboratory. A list of eligible validated oncogenic mutations from 1 of the 7 MTCs are provided in Appendix I.

    Note: The Sponsor reserves the right to prioritize tumor/genomic alteration pairs and to cap enrollment for any of these based on the Sponsor's portfolio decision-making process.

13. Mandatory archival tumor tissue or willing to undergo pretreatment biopsy if no archival tissue available (Section 5.7.1).
14. Measurable disease according to RECIST version 1.1 (Appendix B).

Part B Only

15. Patients with locally advanced or metastatic:
    a. NSCLC who have received at least one prior platinum-containing regimen (with or without an anti-PD-[L]1 antibody) and no more than 2 prior regimens for advanced NSCLC. Patients with no prior therapy who refuse standard therapy may also be eligible following discussion and approval by the Sponsor's Medical Monitor.
    b. Solid tumor other than NSCLC who have received at least one and no more than 3 prior regimens for advanced cancer.

16. Patients with solid tumor(s) harboring an:
    a. [redacted] mutation.
    b. [redacted] mutation or [redacted] mutation.

    Mutations must have been determined by a validated NGS test routinely used by each institution using tissue and/or plasma and performed in a CLIA-certified or equivalent laboratory. A list of eligible validated oncogenic mutations from 1 of the 7 MTCs is provided in Appendix I.

    Eligible patients will be assigned to one of the 5 following cohorts:

    Cohort 1: NSCLC with an [redacted] mutation from MTC-A.

    Cohort 2: NSCLC with an [redacted] mutation from MTC-B or point mutation from MTC-C.

    Cohort 3: Breast cancer with an [redacted] mutation from MTC-B, MTC-C, MTC-D, MTC-E, or MTC-F.

    Cohort 4: NSCLC, biliary tract cancer, or cervical cancer with an [redacted] mutation from MTC-D.

    Cohort 5: Any solid tumor type with any allosteric *ErbB* mutation from any of the 7 MTCs (MTC-A to MTC-G), excluding patients who are otherwise eligible for Cohorts 1-4.

    Note: The Sponsor reserves the right to prioritize Cohorts (ie, tumor/mutation pairs) and to cap enrollment for any Cohort based on the Sponsor's portfolio decision-making process.

17. Measurable disease according to RECIST version 1.1 (Appendix B).
18. Mandatory archival tumor tissue or willing to undergo pretreatment biopsy if no archival tissue available (Section 5.7.1).

3.2. Exclusion Criteria

Patients who meet any of the following criteria will be excluded from study entry:

1. Clinical laboratory values meeting the following criteria within 4 weeks (28 days) prior to baseline:
    a. Serum creatinine ≥1.5 × upper limit of normal (ULN) AND calculated creatinine clearance ≤60 mL/min using Cockcroft-Gault equation.
    b. Total bilirubin ≥1.5 × ULN or ≥3.0 × ULN in the presence of documented Gilbert's syndrome.
    c. Aspartate aminotransferase or ALT ≥2.5 × ULN, or AST or ALT ≥5.0 × ULN in the presence of liver metastases.
    d. Hematologic function:
        i. Absolute neutrophil count (ANC) ≤1000 cells/µL.

ii. Hemoglobin ≤8.5 g/dL or 5.28 mmol/L.

iii. Platelet count ≤75,000/μL.

2. Significant cardiovascular disease, including:
    a. Cardiac failure New York Heart Association Class III or IV (Appendix D), or left ventricular ejection fraction (LVEF) <50% or below the lower limit of the Institution's normal range.
    b. Myocardial infarction, severe or unstable angina within 6 months prior to baseline.
    c. Significant thrombotic or embolic events within 3 months prior to baseline including, but not limited to, stroke or transient ischemic attack. Catheter-related thrombosis and deep vein thrombosis are not a cause for exclusion.
    d. History or presence of any uncontrolled cardiovascular disease.
    e. Personal or family history of long QT syndrome.
3. ECG findings obtained using the study site's ECG machine-derived measurements, meeting any of the following criteria:
    a. Evidence of second- or third-degree atrioventricular block.
    b. Clinically significant arrhythmia (as determined by the Investigator).
    c. QTc interval of >470 msec as calculated according to Fridericia's formula (QTcF = QT/R to R interval$^{0.33}$).
4. Leptomeningeal or untreated central nervous system (CNS) malignancies (primary or metastatic); patients with asymptomatic CNS metastases who have undergone surgery or radiotherapy 4 weeks prior to C1D1 and who are on a dose of prednisone of no more than 10 mg or equivalent will be eligible for **Part A** of the trial.
5. Received other recent antitumor therapy, including:
    a. Investigational therapy administered within the 28 days prior to baseline or 5 half-lives, whichever is shorter.
    b. Any standard chemotherapy, targeted therapy (TKI or mAB), or radiation within 14 days prior to baseline.
    c. Any antineoplastic mAbs within 21 days or checkpoint immunotherapy (including, but not limited to, pembrolizumab, nivolumab, atezolizumab, or durvalumab) within 3 months prior to baseline.
6. Taking or unable to discontinue proton pump inhibitors within 1 week prior to baseline.
7. Known concurrent [redacted] mutation.
8. Known tumor-harboring resistance mutations including [redacted] or [redacted] mutations or [redacted] mutations.
9. Prior documented treatment response (i.e., complete response [CR], partial response [PR], or stable disease [SD] lasting ≥24 weeks by Response Evaluation Criteria in Solid

Tumors [RECIST] v1.1) to approved or investigational [redacted] or [redacted] therapies (e.g., afatinib, lapatinib, dacomitinib, neratinib, trastuzumab deruxtecan, poziotinib, mobocertinib, amivantamab).

- Patients with or without tumor response discontinuing after 8 weeks or less of therapy due to toxicity may be considered after discussion with the Sponsor Medical Monitor.
- Patients with an NGS test (tissue or plasma) obtained within 8 weeks of Baseline which does not include any mutations listed in Exclusion Criteria 7 or 8 may be considered after discussion with the Sponsor Medical Monitor.

10. Major surgery within 4 weeks before baseline or scheduled for surgery during projected course of the study.
11. Received a transfusion of whole blood or red blood cells within 1 week, or platelet transfusion within 2 weeks before baseline.
12. Any history of concomitant condition (e.g., alcohol abuse or psychiatric condition) that, in the opinion of the Investigator, would compromise the patient's ability to comply with the study or interfere with the evaluation of the safety and efficacy of the study drug.
13. Known concurrent malignancy that is expected to require active treatment within 2 years and that may interfere with the interpretation of the efficacy and safety outcomes of the study in the opinion of the treating Investigator confirmed by the Medical Monitor. Prior malignancy that is at a low risk of progression or recurrence (e.g., superficial bladder cancer, non-melanoma skin cancers, or low-grade prostate cancer not requiring therapy) is allowed.
14. Known active hepatitis B or C infection and/or known human immunodeficiency virus (HIV) carrier.
15. Any history (within 6 months) or presence of poorly controlled gastrointestinal disorders that may interfere with absorption of the study drug including delayed gastric emptying, chronic diarrhea associated with intestinal malabsorption, ulcerative colitis or Crohn's disease that requires steroid therapy at any dose, refractory nausea and vomiting, and/or prior surgical procedures affecting absorption or requirement of intravenous alimentation.
16. Taking medications or herbal supplements that are known potent CYP3A4 inhibitors/inducers (including St. John's wort, kava, ephedra [ma huang], ginkgo biloba, dehydroepiandrosterone [DHEA], yohimbe, saw palmetto, ginseng, and double-strength grapefruit juice) within 14 days before the start of treatment through permanent discontinuation of study treatment (See Appendix E).
17. Taking medications that are known to have a risk to cause QT interval and/or Torsades de pointes within 14 days before the start of treatment through permanent discontinuation of study treatment (Appendix F).
18. Women who are pregnant or breast-feeding.

3.3. Discontinuation from Study Treatment

Patients will be discontinued from study treatment for any of the following reasons:

- Disease progression (patients who are receiving clinical benefit in the opinion of the treating Investigator may be allowed to stay on study after consultation with the Medical Monitor).
- Intolerable toxicity or abnormal laboratory values thought to be related to drug toxicity.
- Conditions requiring therapeutic intervention not permitted by the protocol.
- Intercurrent illness that may interfere with the patient's ongoing participation in the study (this will be at the Investigator's discretion).
- Inability of the patient to comply with study requirements.
- Patient lost to follow-up.
- Patient requests to discontinue treatment.
- Patient withdraws consent from study participation altogether.
- Pregnancy.
- Study termination.

After discontinuation from protocol treatment, patients must be followed for AEs for 30 days after their last dose of study drug. All new AEs occurring during this period must be reported and followed until resolution unless, in the opinion of the Investigator, these values are not likely to improve because of the underlying disease. In this case, the Investigator must record his or her reasoning for this decision in the patient's medical records and indicate on the AE pages of the electronic case report form (eCRF) that the outcome is not resolved.

All patients who have Grade 3 or 4 laboratory abnormalities (per NCI CTCAE Version 5.0) at the time of discontinuation must be followed until the laboratory values have returned to Grade 1 or 2 unless it is, in the opinion of the Investigator, not likely that these values are to improve. In this case, the Investigator must record his or her reasoning for making this decision in the patient's medical records and indicate on the AE pages on the eCRF that the outcome is not resolved.

4. STUDY DESIGN

This is a Phase 1/2, open-label, 2-part study of an inhibitor of allosteric *ErbB* mutations, BDTX-189, given as a single oral agent. The study schema is shown in Figure 10.

4.1. Part A (Phase 1 - Dose Escalation and Safety Expansion)

Part A (Phase 1) is designed to determine the RP2D and schedule of BDTX-189 as a single agent. The RP2D will be based on the safety, tolerability, PK, food effect, and preliminary antitumor activity of BDTX-189 and will not exceed the MTD (see Section 4.3.3).

BDTX-189 will be given PO QD on a 21-day schedule in escalating doses. Accelerated titration has been performed with single-patient cohorts at 25, 50, 100, and 200 mg QD followed by multiple-patient cohorts of 400, 800, and 1200 mg QD in fasting state. After the SRC determined 1200 mg QD fasting exceeded the MTD, 800 mg, and 1000 mg QD administered with a meal (i.e., NF) were evaluated.

In addition, a parallel, dose-escalation of BDTX-189 being administered BID is being evaluated. The SRC determined to initiate the BID evaluation at 800 mg BID, which was subsequently de-escalated to 600 mg BID. A dose of 400 mg BID will also be evaluated.

The Safety Expansion cohort(s) at the MTD or lower dose for the QD and/or BID schedule of up to approximately 48 additional patients (including a minimum of 12 patients who may receive the smaller and reformulated 200 mg tablet strength [see Section 6.1.1]) will be enrolled to further evaluate the safety, PK, and preliminary efficacy of BDTX-189 while administrative steps are taken to open enrollment in Part B of the study. Patients in Part A who initiated treatment with the larger 200 mg tablet may be switched to the smaller and reformulated 200 mg tablet at the beginning of their subsequent cycles as instructed by the Sponsor.

After the SRC deemed the 400 mg QD dose regimen was tolerable, a fed (high- or low-fat meal)/fasted randomized crossover, single-dose, lead-in phase was initiated (in up to 16 PK-evaluable patients) to assess the effect of food on the PK of 400 mg BDTX-189 (see Table 1 and Section 5.3.1). Enrollment of the Food-Effect cohort and next dose cohort (800 mg QD Dose Expansion cohort) was done in parallel with priority for enrollment given to the 800 mg QD cohort.

Patients in Part A who terminate participation in the study for any reason other than DLTs before completing Cycle 1 and patients who do not receive at least 75% of the planned doses of BDTX-189 in Cycle 1 for any reason other than DLT-related interruptions will be considered non-evaluable (NE) for DLTs, and additional patients may be enrolled to ensure an adequate number of DLT-evaluable patients. Additional patients may also be enrolled if there are patients who are deemed NE for food effect PK assessment.

Patients who experience a DLT but who, in the opinion of the Investigator, are deriving clinical benefit will be permitted to continue treatment with BDTX-189 at a lower dose that has been demonstrated to be well tolerated upon resolution of the DLT. In total approximately 128 patients will be enrolled in Part A.

4.2. Part B (Phase 2)

Part B is a Phase 2, open-label, multicenter basket study to determine the antitumor activity and safety of BDTX-189 in adult patients who have a solid tumor harboring an oncogenic allosteric [redacted] mutation or an [redacted] or [redacted] mutation from one of the 7 MTCs (Appendix I). Mutation testing, performed by a validated and CLIA-certified NGS assay routinely used by each institution, must be performed using tissue and/or plasma. Baseline tumor tissue for retrospective concordance testing by a companion diagnostic test is mandatory.

Each patient must have a tumor harboring 1 of the eligible [redacted] mutations or 1 of the eligible [redacted] or [redacted] mutations (see Appendix I). Eligible patients will be assigned to 1 of the following 5 cohorts:

Cohort 1: NSCLC with an [redacted] mutation from MTC-A

Cohort 2: NSCLC with an [redacted] mutation from MTC-B or point mutation from MTC-C

Cohort 3: Breast cancer with an [redacted] mutation from MTC-B, MTC-C, MTC-D, MTC-E, or MTC-F

Cohort 4: NSCLC, biliary tract cancer, or cervical cancer with an [redacted] mutation from MTC-D

Cohort 5: Any solid tumor type with any allosteric *ErbB* mutation from any of the 7 MTCs (MTC-A to MTC-G), excluding patients who are otherwise eligible for Cohorts 1-4

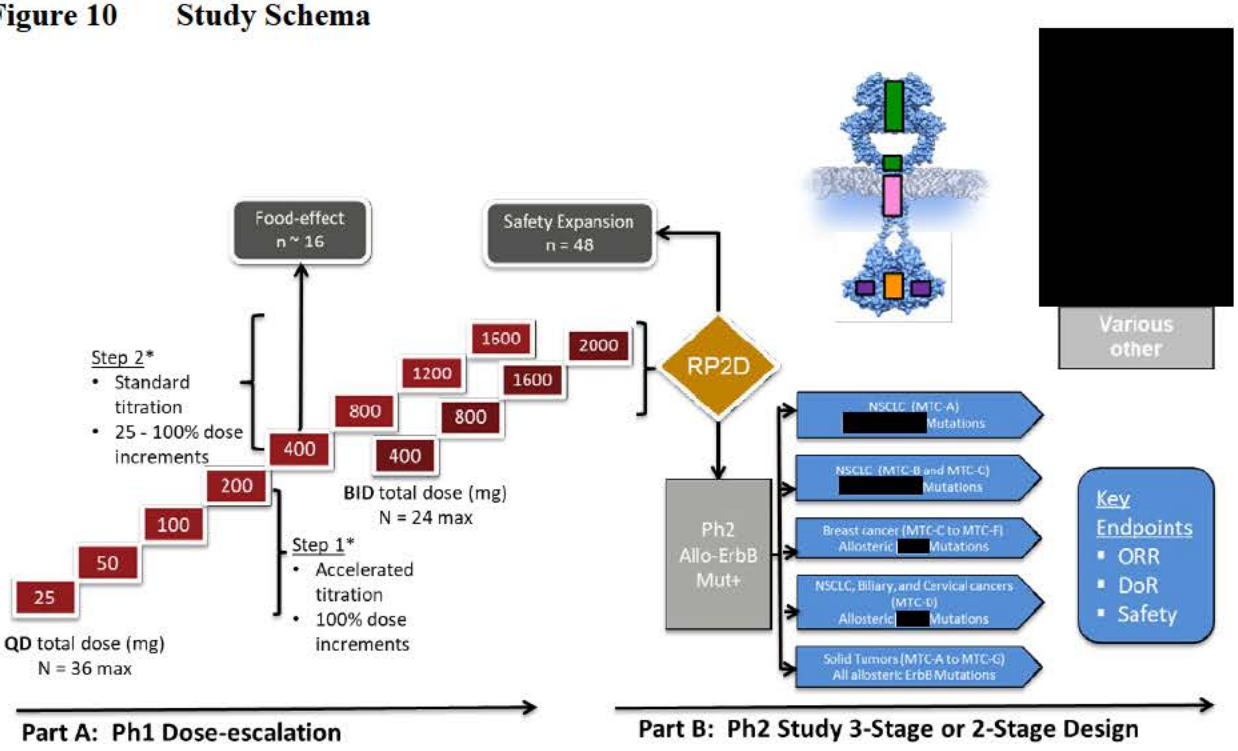
BDTX-189 will be evaluated at the RP2D determined in Part A (800 mg, daily total dose) in each of the 5 separate cohorts described above, which reflect an interest in testing the hypothesis that the drug is active against a broad range of *ErbB* allosteric mutations and cancer types, supported by the pre-clinical data (see Section 1.1.5) and the proof of principle demonstrated by other investigational drugs in the same class in patients with NSCLC harboring exon 20 insertion mutations, and breast cancer and other solid cancers harboring [redacted] mutations (see Section 1.1.4 and 1.1.5). In total approximately 491 patients will be enrolled in Part B.

Separate null hypotheses and targeted ORR values are established for each cohort (see Section 9.3.2) to permit evaluation of potentially different antitumor activity of BDTX-189 in response to different cancer and mutation pairs. The target response rates reflect several key observations: (1) patients with NSCLC harboring [redacted] or [redacted] mutations remain a cancer population with currently no approved therapies and therefore has an unmet medical need. Investigational therapies targeting NSCLC patients with [redacted] or [redacted] mutations have achieved response rates of about 20-40% in Phase 2 trials (see Section 1.1.4 and 1.1.5); (2) Patients with advanced breast cancer harboring some common [redacted] mutations have achieved a response rate of 24% with single-agent neratinib, a pan-[redacted] TKI (Hyman et al. 2017); (3) NSCLC, biliary or cervical cancers with an [redacted] mutation from MTC-D (including, but not limited to S310F and S310Y) demonstrated anecdotal responses on single-agent neratinib while other solid cancers did not (Hyman et al. 2017).

To minimize exposing patients that may be unresponsive to BDTX-189 therapy in Part B, each cohort will have either 1 or 2 futility analyses to evaluate the treatment effect before the cohort proceeds to full enrollment. The detailed futility analysis plan including sample size and

stopping rules for each cohort is described in Section 9.3.2. The study schema is presented in Figure 10.

Figure 10 Study Schema



1. The Dose Escalation in Part A will start with a QD regimen.
2. The dose evaluated for the BID regimen will be initiated at 800 mg.

* The actual number of cohorts per step will be data-driven.

Note: Up to 48 patients will be included in the Safety Expansion cohort(s).

Yuan et al. 2016.

4.3. Treatment Plan

BDTX-189

BDTX-189 will be provided as tablets for oral administration in dose strengths of 100 and 200 mg. Additionally, a smaller and reformulated 200 mg tablet will be administered to some patients at select sites enrolling in the Safety Expansion of Part A and all patients enrolling onto Part B.

Prior to exceeding the MTD for the QD schedule, patients received BDTX-189 in a fasted state. As of January 2021, based on the recommendation of the SRC (details provided in Section 1.1.7), all patients will receive BDTX-189 with approximately 240 mL water within 30 minutes of completing a meal (Section 6.1.2). The time of day for BDTX-189 administration should be consistent. For patients receiving BDTX-189 BID, the 2 doses should be separated by at least 10 hours.

Patients enrolling into the Food Effect cohort will be dosed in the fed/fasted state as per Table 1 and Section 5.3. On scheduled PK collection days (Cycle 1 Day 1 and Cycle 1 Day 15 for Part A, and Days -4 and -1 for the Food Effect Cohort), patients will be instructed to wait until they arrive at the study center to take their study drug when told.

In Part B, patients will be administered BDTX-189 at the RP2D identified during Part A (800 mg QD, non-fasting).

If the patient misses a dose of study drug, the patient should take the dose as soon as possible but not less than 12 hours before the next dose is due for QD dosing. If the next dose is due in less than 12 hours, the patient should skip the missed dose and take the next dose as scheduled. If the patient in a BID cohort misses a dose of study drug, the patient should take the dose as soon as possible but not less than 6 hours before the next dose is due for BID dosing. If the next dose is due in less than 6 hours, the patient should skip the missed dose and take the next dose as scheduled.

If vomiting occurs more than 30 minutes after taking the study treatment, the patient should be instructed not to retake that dose. Patients should take the next scheduled dose of BDTX-189. If vomiting persists, the patient should contact the Investigator.

BDTX-189 dosing compliance will be reviewed with the patient at the beginning of each new treatment cycle when the study drug is dispensed. A cycle will be 21 days. All patients will be required to complete a paper dosing diary, which must be returned to the clinic for review at each visit. The patient should be instructed to record each date and time the dose(s) were taken in the dosing diary. If a dose is missed, the reason must be noted in the diary.

Patients should be advised to return any unused BDTX-189 in the original bottles, in addition to returning any empty bottles. Any remaining empty study drug bottles and dosing diaries will be given to the study staff at the End-of-Treatment (EOT) visit.

No routine anti-diarrheal agents will be given preemptively. However anti-diarrheal agents should be administered in the event of diarrhea to manage the symptoms (see Table 8). Prophylactic anti-emetics are allowed for nausea and/or vomiting. Oral ondansetron may be used after consultation with the Sponsor.

Table 5 Dose Levels Projected for Evaluation (Part A)

QD Cohort - Dose Level	Total Daily Dose (QD)	BID Cohort – Dose Level	Total Daily Dose (BID)[a]
1 (starting dose)	25 mg		
2	50 mg		
3	100 mg		
4	200 mg		
5	400 mg	1 (earliest starting dose)	400 mg
6	800 mg	2	800 mg
7	1200 mg	3	1600 mg
8	1600 mg	4	2000 mg

Abbreviations: BID = twice daily; QD = once daily

[a] Alternative dosing schedule (BID) evaluation may or may not be initiated. If the BID schedule is evaluated, the first dose level may not be initiated until dose level 4 of the QD schedule is declared tolerable by the Safety Review Committee. The QD and BID schedule, if opened, will be assessed and escalated independently.

4.3.1. Dose-Escalation Procedure

The actual number of dose cohorts to be explored in this study will depend on determination of the MTD based on DLTs reported during the DLT evaluation period (Day 1 to Day 21 in Cycle 1 [Part A]).

In order that sufficient PK data are collected at doses below the MTD, additional patients may be enrolled at lower doses.

The Bayesian Optimal Interval Design

A Bayesian optimal interval (BOIN) design (Liu and Yuan 2015; Yuan et al. 2016) will be used to find the MTD (Appendix G). For this study, the target toxicity rate for the MTD will be $\phi = 0.3$ and the maximum sample size will be 36 evaluable patients for the QD schedule, excluding patients in the accelerated titration step. The BOIN study design is described in the following steps:

1. Accelerated titration will be performed as follows: the first patient will be treated at QD dose level 1. If no ≥Grade 2 AE related to BDTX-189 is observed during Cycle 1, the dose will be escalated to the next higher level for the next patient enrolled. One additional patient may be enrolled to ensure at least 1 patient is DLT-evaluable. This one-patient-per-dose escalation process will be continued until any ≥Grade 2 AE related to BDTX-189 is observed, and then an additional 2 patients will be treated at the dose at which the AE is observed. If no ≥Grade 2 drug-related AE is observed by dose level 4 (200 mg QD), then enrollment into dose level 5 will proceed. Thereafter, patients will be treated in cohorts as described in steps 2 and 3.
2. To assign a dose to the next cohort of patients, dose escalation/de-escalation will be conducted according to the rules in Table 6, which minimize the probability of incorrect dose assignment.

3. Step 2 will be repeated until the maximum sample size of 36 DLT-evaluable patients, without including the patients treated in the accelerated titration step, is reached or the trial will be stopped if the number of patients treated at the current dose reaches 15.

Table 6 Dose Escalation/De-escalation Rules for Bayesian Optimal Interval Design Once Daily Dosing

Actions	The number of patients treated at the current dose														
	1	2	3	4	5	6	7	8	9	10	11	12	13	14	15
Escalate if # of DLT ≤	0	0	0	0	1	1	1	1	2	2	2	2	3	3	3
De-escalate if # of DLT ≥	1	1	2	2	2	3	3	3	4	4	4	5	5	6	6
Eliminate if # of DLT ≥	NA	NA	3	3	4	4	5	5	5	6	6	7	7	8	8

Abbreviations: DLT = dose-limiting toxicity; NA = not applicable.

Please note the following:

a "Eliminate" means eliminate the current and higher doses from the trial to prevent treating any future patients at these doses because they are overly toxic.

b When a dose is eliminated, the dose is automatically de-escalated to the next lower level. When the lowest dose is eliminated, the trial is stopped for safety. In this case, no dose should be selected as the MTD.

c If the decision is to escalate the dose and the next higher dose has been eliminated due to high toxicity, new patients are treated at the current dose. Alternatively, a new intermediate dose between the current dose and the eliminated dose may be added (increment between 25% and 50% of the current dose) or if the next higher dose has not been eliminated but the current dose level is associated with non-DLTs; then new patients are treated at the added intermediate dose (increment between 50% and 75%).

d If none of the actions (i.e., escalation, de-escalation, or elimination) is triggered, new patients are treated at the current dose.

e If the current dose is the lowest dose and the rule indicates dose de-escalation, new patients are treated at the lowest dose unless the number of DLTs reaches the elimination boundary, at which point the trial is terminated for safety.

f If the current dose is the highest dose and the rule indicates Dose Escalation, new patients are treated at the highest dose. Alternatively, a new higher dose (increment not greater than 25% of current dose) may be added; then new patients are treated at the added dose.

After each cohort of a minimum of 1 patient in the accelerated titration step and 3 patients in steps 2 and 3 have been enrolled and completed Cycle 1, the SRC will review the safety data and determine whether to proceed with further dose escalation. Safety and tolerability data obtained in patients past Cycle 1 may also be considered, as appropriate. More than 3 patients per cohort may be enrolled at the current dose level, as shown in Table 6. If 1 DLT is observed at the current dose, between 5 and 8 patients must complete Cycle 1 and be evaluable for DLT assessments before a decision to proceed with further dose escalation is made.

The operating characteristics of this BOIN design based on simulations of various scenarios are shown in Appendix G.

After Part A is completed, the MTD will be selected based on isotonic regression. Specifically, the dose for which the isotonic estimate of the toxicity rate is closest to the target toxicity rate is

the MTD that will be selected. If there are ties, the higher dose level will be selected when the isotonic estimate is lower than the target toxicity rate, and the lower dose level will be selected when the isotonic estimate is greater than or equal to the target toxicity rate.

Once the MTD has been determined (MTD may be QD or BID), up to 48 additional patients (including 12-24 patients for PK evaluation of a smaller and reformulated 200 mg tablet) may be enrolled at the MTD or a lower dose if deemed relevant, to obtain additional experience with safety and efficacy. The elimination boundaries in Appendix H will be used for toxicity monitoring.

BID Dose Schedule Evaluation

In the event that PK, tolerability, or PDx analysis suggests that a more frequent daily dosing schedule should be explored, a BID dose schedule will be evaluated and a separate BOIN design will be used to find the MTD using that dosing schedule. The design parameters will depend on the specific PK/PDx and tolerability results and the cumulative observations from the QD Dose Escalation study. The BID schedule will not be initiated until dose level 4 (200 mg QD) of the QD schedule has been deemed tolerated or until the MTD has been determined for the QD schedule (see Table 5). The BID schedule may also be initiated at higher dose levels as determined by the SRC based on emerging safety and PK data. Should a Dose Escalation for the QD schedule be eliminated before reaching the highest dose, then BID Dose Escalation may be pursued independently.

The target toxicity rate for the MTD will remain $\phi = 0.3$, and patients will be enrolled and treated in cohorts with no accelerated titration phase. The Dose Escalation/de-escalation rules will be the same as shown in Table 6 and Appendix H.

If 4 dose levels are evaluated and the maximum sample size is 24, the study will continue until 24 patients have been treated or if the number of patients treated at the current dose reaches 15.

4.3.2. Dose-limiting Toxicity

Toxicity will be assessed using the NCI CTCAE Version 5.0 unless otherwise specified.

A toxicity will be considered dose-limiting (unless clearly attributable to an extraneous cause, such as underlying disease) if it occurs during the first cycle (21 days) of treatment with BDTX-189. Dose-limiting toxicities (DLTs) will be defined as follows:

- Any death not clearly due to the underlying disease or extraneous causes.
- Hematologic toxicity
  - Grade 4 neutropenia or thrombocytopenia for >7 days or febrile neutropenia.
  - Grade 3 thrombocytopenia associated with bleeding or requiring a platelet transfusion.
  - Grade ≥4 anemia.
- Non-hematologic toxicity of ≥ Grade 3 (at any time during treatment) that, in the judgment of the Investigator, is dose-limiting except for:
  - Grade 3 fatigue lasting <1 week.
  - Grade 3 nausea, vomiting, or diarrhea lasting <5 days without adequate supportive care.

- Grade 3 nausea, vomiting, or diarrhea lasting <24 hours with adequate supportive care.

- The following non-hematologic laboratory abnormalities:
  - Baseline Grade ≤1 ALT or AST: any drug -related Grade ≥3 abnormality of ALT and/or AST or increase in ALT or AST >3 × ULN with a concurrent increase in total bilirubin >2 × ULN (per Hy's Law).
  - Baseline Grade ≥2 ALT or AST due to liver metastases: any drug-related ALT and/or AST >2 × baseline or ≥10 × ULN.
- Dose reduction during Cycle 1 due to an AE related to BDTX-189.
- Delay of starting Cycle 2 for >2 weeks if due to an AE related to BDTX-189.
- Interruption of BDTX-189 dosing for more than 7 days during Cycle 1, if due to a drug-related AE.

4.3.2.1. Determination of DLT-evaluable Population

The patient population used for determination of DLTs will consist of patients who have met the minimum safety evaluation requirements of the study or who have experienced a DLT. Minimum safety requirements will be met if, during Cycle 1 of treatment, the patient receives at least 75% of planned total doses of BDTX-189 (i.e., 16 of 21 QD doses or 32 of 42 BID doses unless due to dose hold guidelines provided in Table 8) and is observed for at least 21 days following the first dose of BDTX-189. Patients receiving less than 75% of the planned doses of BDTX-189 due to drug-related AEs that are not considered a DLT may still be evaluable for determination of DLTs.

If a patient withdraws from treatment during Cycle 1 due to any reason other than DLT and does not meet the minimum requirements for inclusion in the DLT-evaluable population described above, an additional patient may be enrolled to ensure an adequate number of evaluable patients. Patients being evaluated for Food Effect will not be part of the DLT-evaluable population per the BOIN design parameters; however, the safety information from these patients will be considered when making decisions about Dose Escalation/de-escalation and determination of the RP2D.

4.3.3. Maximum-tolerated Dose

The BOIN design will be used to find the MTD in this study. The target toxicity rate for the MTD will be $\phi = 0.3$ and the maximum sample size will be 36 evaluable patients for the QD schedule and 24 patients for the BID schedule, should that be explored. Please see Section 4.3.1 and Table 6 for complete details.

4.3.4. Safety Expansion after Determination of the Maximum-Tolerated Dose

As described in Section 1.1.7, the MTD and preliminary RP2D is 800 mg for the QD schedule. Once the Safety Expansion opens for enrollment, up to 48 additional patients (including patients for PK evaluation of a smaller and reformulated tablet [see below]) will be enrolled at the MTD or a lower dose for either the QD and/or the BID schedule to further characterize the safety, PK, and efficacy profile. The MTD will be considered the recommended dose unless there is a lower dose that provides adequate exposure and biologic activity with more favorable tolerability.

A smaller and reformulated 200 mg tablet will be introduced and may be supplied to some patients during the Safety Expansion of Part A; these tablets will be available to all patients enrolling on Part B. A minimum of 12 patients from selected study sites may undergo PK evaluation on C1D1 and C1D15 (see Section 5.6) during the Safety Expansion period and/or Part B.

Should the PK parameters from these smaller and reformulated tablets be consistent with data from the larger tablets, additional PK evaluation can be performed in newly enrolled patients on C1D1 and C1D15 and/or by switching patients from the larger tablets to the smaller and reformulated 200 mg tablets to further characterize the PK. The latter subset of patients in Part A who initiated treatment with the larger 200 mg tablet may be switched to the smaller and reformulated 200 mg tablet at the beginning of the subsequent cycle. Detailed PK sampling will be collected on Day 15 of that subsequent cycle according to Table 10, to provide additional exposure data.

4.3.5. Dose Modifications

If toxicity occurs, the toxicity will be graded using the NCI CTCAE Version 5.0, and appropriate supportive care treatment will be administered to decrease the signs and symptoms thereof. Dose adjustments will be based on the organ system exhibiting the greatest degree of toxicity.

Specific criteria for interruption, re-initiation, dose reduction, and/or discontinuation of BDTX-189 are listed in Table 8. All interruptions or modifications must be recorded on the AE and drug administration eCRFs. Appropriate clinical experts must be consulted as deemed necessary.

The Investigator will evaluate which AEs are attributed to the study drug and adjust the dose of the drug as recommended below. All dose modifications must be based on the worst preceding toxicity (CTCAE Version 5.0).

Patients whose treatment is delayed due to AEs may continue treatment if the AE resolves within 21 days of onset. Any patient who requires a treatment interruption of more than 21 days due to AEs will be discontinued from study treatment unless the Investigator and the Medical Monitor agree that continued treatment at the appropriate dose is in the best interest of the patient.

A maximum of 2 dose reductions are allowed in this study. Table 7 outlines acceptable dose reductions for patients in the Safety Expansion of Part A or Part B, who are enrolling after the implementation of Amendment 3. Once the dose of BDTX-189 has been reduced because of toxicity, all subsequent cycles must be administered at that lower dose level unless further dose reduction is required. The patient will be withdrawn from study treatment if further toxicity meeting the requirement for dose reduction occurs. Dose reduction below the initial starting dose levels for QD and BID in Part A, respectively, is not allowed. Otherwise, the patient must be removed from treatment.

Recommended BDTX-189 dose modifications are presented in Table 8.

Table 7 Dose Reduction Levels for BDTX-189 Administered Once or Twice Daily

Original dose	800 mg QD	400 mg BID
Dose level –1	600 mg QD	300 mg BID

Dose level –2	400 mg QD	200 mg BID

Table 8 Dose Modification Guidelines for BDTX-189-related Adverse Events

Recommended Dose Modifications	
Worst toxicity NCI CTCAE v5.0 Grade (value)	**Recommended dose modification any time during a cycle of therapy**
Renal	
Serum creatinine	
≤1.5 × ULN	Maintain dose level
Grade 2 (>1.5 to 3 × ULN)	Omit dose until resolved to baseline, then • If resolved ≤ 7 days, then maintain dose level • If resolved > 7 days, then ↓ 1 dose level
Grade 3 (>3.0 to 6.0 × ULN)	Discontinue patient from study treatment
Grade 4 (>6.0 × ULN)	Discontinue patient from study treatment
Hepatic	
Total bilirubin	
<1.5 × ULN	Maintain dose level
Grade 2 (>1.5 to 3 × ULN if baseline was normal; >1.5 to 3.0 × baseline if baseline was abnormal)	Omit dose until resolved to baseline, then • If resolved ≤7 days, then maintain dose level • If resolved >7 days, then ↓ 1 dose level
Grade 3 (>3.0 to 10.0 × ULN if baseline was normal; >3.0 to 10.0 × baseline if baseline was abnormal)	Omit dose until resolved to baseline, then • If resolved ≤7 days, then ↓ 1 dose level • If resolved >7 days and discontinue patient from study treatment
Grade 4 (>10.0 × ULN if baseline was normal; >10.0 × baseline if baseline was abnormal)	Discontinue patient from study treatment Note: If Grade 3 or 4 hyperbilirubinemia is due to the indirect (unconjugated) component only and hemolysis has been ruled out as the etiology as per institutional guidelines (e.g., review of peripheral blood smear and haptoglobin determination), then ↓ 1 dose level and continue treatment at the discretion of the Investigator
AST or ALT	
Grade 1 (>ULN to 3.0 × ULN if baseline was normal; >1.5 to 3.0 × baseline if baseline was abnormal)	Maintain dose level
Grade 2 (>3.0 to 5.0 × ULN if baseline was normal; >3.0 to 5.0 × baseline if baseline was abnormal)	Maintain dose level
Grade 3 (>5.0 to 20.0 × ULN if baseline was normal; >5.0 to 20.0 × baseline if baseline was abnormal)	Omit dose until resolved to ≤ Grade 1 (or ≤ Grade 2 if liver metastases present), then either maintain dose level (if Grade 3 lasted ≤7 days) or ↓ 1 dose level (if Grade 3 lasted >7 days)
Grade 4 (>20.0 × ULN if baseline was normal; >20.0 × baseline if baseline was abnormal)	Discontinue patient from study treatment

Recommended Dose Modifications

Worst toxicity NCI CTCAE v5.0 Grade (value)	Recommended dose modification any time during a cycle of therapy
Combination of bilirubin and AST/ALT	
Total bilirubin ≥2.0 × ULN and ALT or AST ≥3.0 × ULN (Potential Hy's Law) See Section 8.2.4 for further details	1st occurrence: Omit dose and repeat tests 2-3 times a week until all abnormal lab results resolved to ≤ Grade 1 (or baseline), then ↓ 1 dose level 2nd occurrence: Omit dose and discontinue patient from study treatment
Diarrhea	
Grade 1	Maintain dose level. Stop treatment with concomitant medications that may cause diarrhea (e.g., laxatives). Administration of standard doses of loperamide should be initiated.
Grade 2	Optimize anti-diarrheal medication. Temporarily interrupt BDTX-189 until resolved to Grade ≤1. Resume same dose level unless associated with complicating signs/symptoms, in which case consider ↓ 1 dose level.
Grade 3	Optimize anti-diarrheal medication. Temporarily interrupt BDTX-189 until resolved to Grade ≤1. If the severity lasts <24 hours during Cycle 1, resume at the same dose level. If the severity persists for >24 hours or resumes, then ↓ 1 dose level.
Grade 4	Discontinue patient from study treatment
Skin rash	
Grade 1	Maintain dose level. Consider initiation of topical emollients, antihistamines in the case of pruritus, and/or topical (mild strength) corticosteroid creams
Grade 2	Maintain dose level at first occurrence and monitor rash closely. Initiate rash treatment if not already done. If rash worsen or reoccurs within 14 days, interrupt BDTX-189 until resolved to Grade ≤1, then ↓ 1 dose level.
Grade 3	At first occurrence, interrupt BDTX-189 administration and apply topical emollients, antihistamines, and/or high strength corticosteroid creams until it resolves to ≤ Grade 1, then the study drug can be reinstated at current dose level. At second occurrence, interrupt BDTX-189 administration until resolved to Grade ≤1, then ↓ 1 dose level.
Grade 4	Study drug administration will be discontinued. Schedule dermatologist evaluation
Prolonged QTc interval	
Grade 2 QTcF >480 msec and ≤500 msec	1. Repeat ECG in triplicate as soon as practical, no later than 7 days after the initial ECG. If the mean QTcF on repeat ECG triplicate is ≤500 msec and the patient is asymptomatic, then continue study drug at the same dose. Post-dose ECG must be monitored weekly in triplicate. 2. If the mean QTcF on repeat ECG triplicate is >480 and ≤500 msec, then consultation with cardiologist (must occur as soon as practical, no later than 7 days after the initial ECG). 3. If the cardiologist confirms a mean QTcF >480 and ≤500 msec is drug-related, then ↓ 1 dose level.
Grade 3 QTcF >500 msec or QTcF increased by ≥60 msec from baseline	1. Repeat ECG in triplicate approximately 1 hour after the initial ECG 2. If the mean QTcF on repeat ECG triplicate is >500 msec or increased by ≥60 msec from baseline, then omit dose until consultation with cardiologist (must occur as soon as practical, no later than 7 days after

Recommended Dose Modifications

Worst toxicity NCI CTCAE v5.0 Grade (value)	Recommended dose modification any time during a cycle of therapy
	the initial ECG). ECG must be monitored in triplicate at the frequency selected at Investigator's discretion. 3. If the cardiologist confirms a mean QTcF >500 msec or increase by ≥60 msec from baseline is drug-related, then ↓ 1 dose level. If second occurrence is attributed to BDTX-189, then discontinue patient from study treatment.
Left ventricular systolic dysfunction	
Asymptomatic absolute decrease of 10% – 19% in LVEF compared to baseline and the LVEF is below the Institution's LLN (e.g., a decrease from 60% to 48% is an absolute decrease of 12%)	Interrupt BDTX-189 and repeat evaluation of LVEF within 2 weeks: • If LVEF recovers to ≥50% or ≥ LLN and o absolute decrease ≤10% compared to baseline in 21 days, then maintain dose level o absolute decrease >10% compared to baseline in 21 days, then ↓ 1 dose level after approval of Medical Monitor. Monitor LVEF 2 weeks after resuming, every 4 weeks for 12 weeks and subsequently per protocol • If the LVEF does not recover in ≤21 days, permanently discontinue BDTX-189. Closely monitor LVEF until resolution or for up to 16 weeks.
Grade 3-4	Permanently discontinue BDTX-189. Closely monitor LVEF until resolution or for up to 16 weeks.
All other BDTX-189 treatment-related adverse events	
Grade 1 or 2 (except fatigue, alopecia, and laboratory abnormalities not requiring medical intervention	Maintain dose level if the event is Grade 1 or non-persistent Grade 2. If the event is persistent Grade 2 not responding to a specific therapy, consider ↓ 1 dose level.
Grade 3	Omit dose until resolved to ≤ Grade 1 or baseline level, then ↓ 1 dose level
Grade 4	Discontinue patient from study treatment

Abbreviations: ALT = alanine aminotransferase; AST = aspartate aminotransferase; ECG = electrocardiogram; LLN = lower limit of normal; LVEF = left ventricular ejection fraction; NCI CTCAE = National Cancer Institute Common Terminology Criteria for Adverse Events; QTcF = QT interval corrected according to Fridericia's formula; ULN = upper limit of normal.
Note: After the MTD was exceeded for the QD and BID schedules in fasted state, subsequent cohorts were evaluated non-fasted (fed). For Dose reduction levels refer to Table 7.

Intrapatient dose-escalation during Part A may be considered in the absence of ≥ Grade 2 toxicities related to BDTX-189 in the following circumstance: After a new higher dose level has been determined to be tolerated (≤30% DLTs), any patients remaining on study and being treated with a lower dose of BDTX-189 may, at the discretion of the Investigator and with agreement of the Sponsor, be offered treatment at the new higher tolerated dose once that dose level evaluation has been cleared. During the Safety Expansion and Part B, re-escalation of BDTX-189 following dose reduction due to toxicities may be considered following discussion and approval of Sponsor's Medical Monitor.

4.4. Treatment Duration

The **start of the study** is defined as the date when the first patient in the whole study signs informed consent.

The **end of the study** is defined as the date of the last visit (including all follow-up visits) of the last patient in the whole study.

Patients will be evaluated for toxicities through AE reporting (continuously) and other safety assessments, weekly for the first 2 cycles during Part A and at the start of each 2 subsequent cycles thereafter. During Part B, patient's toxicities will be evaluated through AE reporting (continuous) and other safety assessments, weekly for the first 2 cycles and then at the start of each cycle for the first 4 cycles and every other cycle thereafter. Restaging will occur with imaging, laboratory chemistries, and tumor markers as defined in the Schedule of Assessments (Table 1 and Table 3). Patients will continue on treatment until progressive disease (PD) as defined in Section 7 or intolerance of side effects. Patients who are receiving clinical benefit in the opinion of the treating Investigator may be allowed to stay on study after consultation with the Medical Monitor (Section 3.3).

4.5. Concomitant Medications

Patients will be asked about prior medications during screening and instructed not to take any additional medications during the course of the study without prior consultation with the study team. At each visit, the patient will be asked about any new medications he or she is taking or has taken from 14 days prior to receiving their first dose of study drug until the 30-Day Safety Follow-up visit. Additionally, for the Safety Expansion portion of Part A and Part B, first subsequent anticancer therapy, will be collected as part of PFS/overall survival (OS), from the 30-day Safety Follow-up visit, and will be obtained every 3 months (±14 days) until 2 years after the first study drug dose, death, loss to follow-up, withdrawal of consent, or end of the whole trial.

4.5.1. Permitted Concomitant Medications

Medications may be administered for maintenance of existing conditions prior to study enrollment or for a new condition that develops while on study, including but not limited to the following:

- Bisphosphonate use or receptor activator of nuclear factor kappa-B (RANK) ligand inhibitors, as recommended according to practice guidelines.
- Oral contraceptives.
- Hormone-replacement therapy.
- Megestrol acetate administered as an appetite stimulant.
- Transfusion of blood or red blood cells and/or prophylactic erythropoietin is permitted for the treatment of anemia (transfusion of blood or red blood cells is permitted from C1D1 until the EOT visit [see Section 3.2 Exclusion Criteria #11]).
- Transfusion of platelets is permitted from C2D1 until the EOT visit for the treatment of thrombocytopenia.
- Patients may take low-dose warfarin or a Coumadin preparation for maintenance of an open port.
- Concomitant use of corticosteroids at doses up to 10 mg prednisone or equivalent for the treatment of inflammatory conditions that are not prohibited by the applicable exclusion criteria is permitted.

- Prophylactic anti-emetics and anti-diarrheals are allowed for nausea and/or vomiting and diarrhea, per Institutional standards.

Supportive care and other medications considered necessary for the patient's safety and wellbeing may be given at the discretion of the Investigator, with the exception of those listed in Section 4.5.2.

4.5.2. Prohibited Concomitant Medications

The following treatments are prohibited while in this study:

- No other investigational therapy should be given to patients. No anticancer agents other than the study treatment should be given to patients from ≤14 days prior to the first dose of BDTX-189 for standard chemotherapy and from ≤28 days or 5 half-lives, whichever is shorter, for investigational drugs until 30 days after the last dose of BDTX-189. If such agents are required for a patient, then the patient must first be withdrawn from the study.
- No routine pre-medications will be given during the DLT evaluation period (Day 1 to Day 21 in Cycle 1 [Part A]), however, based on emerging clinical experience in earlier cohorts/patients, prophylactic administration of medications may be permitted at the discretion of the Investigator.
- Concomitant treatment with any medication that is known to prolong the QT interval and/or cause Torsades de pointes is prohibited from 14 days before the start of treatment until the EOT visit (see Appendix F). After study enrollment, if a patient requires use of any of these medications, the patient must be removed from study.
- Drugs known to be strong CYP3A4 inhibitors or inducers are prohibited from ≤14 days before the start of treatment until the permanent discontinuation of treatment. Refer to Appendix E for a comprehensive list of agents in these categories. These agents include, but are not limited to:
    - CYP3A4 inhibitors: azole antifungals (ketoconazole, voriconazole and itraconazole), macrolide antibiotics (clarithromycin, erythromycin), HIV protease inhibitors (indinavir and ritonavir), cimetidine, aprepitant, nelfinavir, nefazodone, and double-strength grapefruit juice.
    - CYP3A4 inducers: phenytoin, barbiturates, and rifampicin.
- Herbal preparations/medications known to be potent inducers of CYP3A4 are not allowed from ≤14 days before the start of treatment until permanent discontinuation of treatment. These herbal medications include, but are not limited to, St. John's wort, kava, ephedra (ma huang), ginkgo biloba, dehydroepiandrosterone (DHEA), yohimbe, saw palmetto, and ginseng.
- Proton pump inhibitors are prohibited from 1 week prior to the start of treatment until the discontinuation of treatment. If the reduction of gastric acidity is essential before or during the study at the Investigator's discretion, the patients may use H_2-receptor antagonists or antacids (this will **not** be allowed for patients participating in the Food-Effect Cohort from 1 week prior to the Day -4 dose until C1D1 [Section 5.3.1]). If applicable, these agents should be taken at least 8 hours before or 2 hours after the daily dose of BDTX-189.

Some prohibited medications may be allowed at the Investigator's discretion after approval by the Medical Monitor when the patient has unmet medical need to continue receiving such prohibited medication(s), no suitable alternative treatments are available, and the benefit-risk ratio is acceptable in the Investigator's opinion. This exemption may not be applied to other anti-cancer therapies or other investigational therapies.

4.5.3. Concomitant Medications to be Used with Caution

The following treatments should be used with caution while in this study:

- Sensitive substrates of BCRP (e.g., rosuvastatin, sulfasalazine).
- Strong inhibitors of P-gp (e.g., itraconazole, ritonavir) and BCRP (e.g., curcumin, cyclosporine A, eltrombopag).

A detailed list can be found at: https://www.fda.gov/drugs/drug-interactions-labeling/drug-development-and-drug-interactions-table-substrates-inhibitors-and-inducers#table5-1.

5. STUDY ASSESSMENTS AND EVALUATIONS

5.1. Overview

All patients should visit the study center on the days specified within this protocol. **The C1D1 visit will determine the visit calendar for the study, and all projected visits will be based on the C1D1 visit date.** Study visits must occur according to the study visit schedule and within the allowed protocol windows. Missed doses or dose interruptions should not alter the patient's study visit schedule. The complete Schedule of Assessments for this study is presented at the beginning of this protocol (see Table 1, Table 2, and Table 3). The key procedures required in this study include:

- Reporting of all AEs occurring after the ICF has been signed.
- Safety hematology, chemistry, coagulation, and PK samples throughout the study.
- Baseline and on-treatment blood biomarker assessments.
- Archived tumor samples or new pretreatment tumor biopsy.
- Baseline and on-treatment tumor biopsy, if tumor amenable by biopsy (Part A).
- Tumor assessments (based on computed tomography [CT], positron emission tomography [PET], and/or magnetic resonance imaging [MRI] scan) according to RECIST Version 1.1 (see Appendix B).
- ECG measurements (including ECGs time-matched to coincide with detailed PK assessments beginning with dose level 4 [200 mg QD]) at baseline and onwards.
- Cardiac function echocardiography (ECHO) or multigated acquisition scan (MUGA).

A cycle of treatment is scheduled to last 3 weeks (21 calendar days). Multiple procedures may be scheduled at the same time point relative to BDTX-189 dosing. Priority should be given to PK collection at the time specified. Vital signs and ECG assessments should be performed prior to specimen collections (except where ECG assessments are to coincide with PK sample collection).

5.2. Screening

At enrollment, each potential patient will provide written informed consent ≤28 days prior to initiation of treatment and prior to starting any study-specific procedures. Upon signature of the ICF, patients will be assigned a unique patient number as enrollment (screening) occurs.

The screening assessments described in the Schedule of Assessments (Table 1, Table 2, and Table 3) will be collected, reviewed, and determined to be acceptable by the site Principal Investigator or designee after obtaining informed consent prior to the initiation of treatment.

The following screening parameters should be recorded prior to initiation of treatment:

- Medical history and demographics.
- Physical examination (including height and weight).
- ECOG performance status (Appendix A).

- Vital signs (heart rate, systolic and diastolic blood pressure [BP], pulse oximetry, and oral or axillary temperature) and weight.
- ECG.
- Cardiac MUGA/ECHO (within 28 days; however, no need to repeat during the screening if a comparable assessment has been performed ≤6 weeks from the date of consent).
- Hematology assessments (complete blood count [CBC] with hemoglobin, red blood cell count, total WBC count with ANC, absolute lymphocyte count, 5-part differential [% neutrophils, % lymphocytes, % or absolute value of: monocytes, basophils, eosinophils] and platelet count).
- Biochemistry assessments (sodium, potassium, chloride, bicarbonate, blood urea nitrogen (BUN) or blood urea, creatinine, calcium, albumin, total protein, AST, ALT, alkaline phosphatase [ALP], total and direct bilirubin, lactate dehydrogenase, amylase, lipase, magnesium, phosphorous, and glucose).
- Coagulation assessments (prothrombin time [PT], activated partial thromboplastin time [aPTT], and international normalized ratio [INR]).
- Urinalysis (protein, glucose, ketones, urobilinogen, occult blood, and microscopic sediment evaluation).
- Screening pregnancy test for WOCBP (serum).
- Baseline fresh tumor biopsy (or within 28 days prior to C1D1), if tumor is amenable for biopsy from dose level 5 (Part A).
- Archived or new tumor tissue sample (within 28 days if new tumor tissue sample) for patients in Part B and only for patients with allosteric *ErbB* mutations who have archival tissue in Part A.
- CT or MRI for tumor assessment.
- Genomic results
    - Part A: eligible genomic alteration and allosteric mutation and all co-occurring genomic alterations based on NGS testing.
    - Part B: some clinical sites do not routinely perform broad NGS testing of tumor tissue. These sites may need to prescreen some patients for eligible mutations which will require separate Sponsor approval and patient consent.

If the following assessments are performed within the prior 7 days and as part of the screening assessments, they do not need to be repeated pre-dose on C1D1: weight, ECOG performance status, hematology, clinical chemistry, coagulation, and urinalysis.

Tumor assessments (scans) should be performed ≤28 days prior to initiation of treatment.

Relevant concomitant diagnoses and/or therapies present at study entry and/or during screening that are relevant to the patient's safety during the study as judged by the Investigator will be recorded in the eCRF (see Section 4.5 for details on concomitant medications).

5.3. Assessments During Study Treatment

Patients will remain on treatment as long as, in the opinion of the Investigator, they are deriving benefit and the criteria listed in Section 5.5 are not met. Please refer to the Schedule of Assessments (Table 1, Table 2, and Table 3) for detailed outlines of each visit during the treatment period for each part of the study.

5.3.1. Food-effect Assessment (Dose Escalation Part A)

The effect of food on the PK of BDTX-189 will be assessed in a single dose, fed/fasted randomized crossover design. Based on the projected exposures at the various dose levels, Food Effect evaluation is planned at dose level 5 (400 mg QD). Randomization will be performed by Development Innovations at the time of patient registration. The Food Effect evaluation will be executed without disruption of the Dose Escalation and DLT evaluation to the extent feasible. Dose level 5 (400 mg QD) will therefore proceed as described in Section 4.3.1 in patients not having Food Effect assessed. Assignment of 3 or more patients to dose level 5 (400 mg QD) for DLT assessment will take place according to Section 4.3.2.

Patients (n = up to 8 per meal type) will be assigned to the Food Effect evaluation as described below. Depending on emerging data, additional patients may be enrolled to meet the requirements of a pivotal Food Effect study. The SRC will decide how to allocate patients but should prioritize assignment of patients for DLT evaluation. Patients evaluated for Food Effect will not be counted in the BOIN decision rule. Should any DLT occur in the Food-effect Cohort, this will not be included in the dose escalation/de-escalation rules in Table 6, but the SRC will take the information into account for the dose increment/decrement decisions. Once the Day -1 assessments are complete, the patients may continue study drug administration on C1D1. The dose will be 400 mg QD unless that dose level has been declared tolerated, and a decision made to escalate to dose level 6 (800 mg QD), in which case patients will be assigned to that dose level. Patients included in the Food Effect evaluation will not have additional PK samples collected on C1D1.

Patients will receive BDTX-189 as a single oral dose on Day -4 after fasting for at least 10 hours before dosing or immediately after consuming a high-fat breakfast. Patients will receive BDTX-189 in the opposite prandial state on Day -1. BDTX-189 will be administered QD in 21-day cycles starting on C1D1. On the assigned day of PK assessment in the fed state, 30 minutes prior to the planned BDTX-189 administration time, patients will be instructed to consume a high-fat meal (see below for an example breakfast) and must finish the meal within 30 minutes. Patients will be instructed to take their dose of BDTX-189 with approximately 240 mL water within 30 minutes after starting the high-fat meal. On the assigned day of PK assessment in the fasted state, BDTX-189 will be administered together with approximately 240 mL water, following an overnight fast of at least 10 hours. Patients should not consume any food for at least 4 hours after the dose. The use of agents that suppress gastric acidity (H2 receptor antagonists, proton pump inhibitors, and intraluminal antacids) and agents that delay gastric emptying are prohibited from 1 week prior to the Day -4 dose until C1D1, when only proton pump inhibitors will be prohibited, as described in Section 4.5.2. Please see Table 11 (PK Sample Collection Food Effect Part A) for specific time points.

Patients will be given a high-fat breakfast in order to assess food effects on the PK of BDTX-189. An example high-fat breakfast that will be provided is a standard McDonald's

breakfast, which might include an Egg McMuffin, bacon, hash browns, and milk.
Note: Alternative food components/quantity and/or time (i.e., lunch) may be allowed as per timing of dose administration and as approved by the Investigator/Sponsor. In addition, a low-fat breakfast may also be assessed as emerging data dictate. An example low-fat breakfast may include 8 ounces of milk (1% fat), one boiled egg, and one packet flavored instant oatmeal with water (approximately 400-500 calories).

5.3.2. Electrocardiogram Measurements

Single ECGs will be required pre-dose at the time points indicated in the Schedule of Assessments (Table 1, Table 2, and Table 3). Electrocardiograms (single) will be obtained after the patient has been resting quietly in semi-supine position for at least 5 minutes before the ECG. Electrocardiogram parameters (PR interval, QRS interval, QTcF, and heart rate) will be recorded. When multiple assessments coincide, ECGs will be done immediately before the scheduled PK sample or any other blood draw.

Time-matched triplicate ECG measurements will also be collected for patients in Part A's Dose Escalation and Food-Effect cohorts, and patients who are undergoing detailed PK assessment of a smaller and reformulated tablet in the Safety Expansion. ECG measurements will coincide with the detailed PK assessments around the projected C_{max} in patients to evaluate any corrected QT (QTc) concentration-effect relationship. These ECG measurements will be performed in triplicate pre-dose and at 1.0, 2.0, 3.0, and 4.0 hours post-dose on C1D1 and C1D15 starting with dose level 4 (200 mg) and onwards for the QD schedule and starting with dose level 1 for the BID dosing schedule, if a more frequent dosing schedule is pursued. For each set of triplicate ECGs, three standard resting 12-lead ECGs will be obtained in close succession and not more than 2 minutes apart (4 minutes total for 3 ECGs). Electrocardiograms will be obtained after the patient has been resting quietly in semi-supine position for at least 5 minutes, prior to the first ECG procedure and during the triplicate ECG collection.

Please refer to the Schedule of Assessments (Table 1 and Table 2).

5.3.3. Response Assessments

Patients will be evaluated for response to treatment after 2 cycles of treatment. Response will be assessed at 6-week intervals (±3 days) during the first 24 weeks (8 cycles) of study treatment. Thereafter, patients will be evaluated for response to treatment every 12 weeks (±7 days), at the EOT visit (if not performed within the previous 4 weeks), and at the discretion of the Investigator. Patients with PD or unacceptable toxicity should be discontinued from the study; patients with SD or response to therapy will continue treatment. However, patients who are receiving clinical benefit in the opinion of the treating Investigator may be allowed to stay on study beyond initial radiological progression after consultation with the Medical Monitor if it is felt that it is in the patient's best interest. The assessments to be performed at this time are specified in Appendix B. All target and non-target lesions documented at screening must be assessed. Please refer to Section 7 for further instructions on evaluating response (e.g., PD, SD).

The following assessments will be performed if abnormal at baseline or if clinically indicated:

- CT scan or MRI of chest, abdomen, and pelvis plus any other sites of known disease.
- CT scan head/MRI brain if history of CNS metastasis.

Investigators must ensure that images of all chest and abdomen CT/MRI scans for patients enrolled in Part B are available for transmission to the Sponsor for a future central reading by a BICR committee depending on preliminary efficacy results from Part A (see separate imaging charter).

5.3.4. Patient Reported Outcomes (Part B only)

Patient reported outcomes (PROs) will be collected at C1D1, C1D8 and on Day 1 of every Cycle C2-C9. After C9D1 continue to collect electronic patient reported outcomes (ePROs) every 3 months (±14 days), at the EOT visit, and 30-Day Safety Follow-up visit. Continue to collect ePROs even if the patient has discontinued taking the study drug until subsequent anti-tumor therapy is initiated. PROs should be provided to the patient as soon as they arrive at the site for their visit, before any other assessments are performed.

Table 9 ePRO Assessments (Part B only)

Assessments	NSCLC	Breast Cancer	Other Cancers
NCCN FACT FBSI-16 (16 questions)		X	
NCCN-FACT FLSI-17 (17 questions)	X		
FACT-G (27 questions)[a]	X	X	X
EQ-5D-5L (5 questions)	X	X	X
Physical Function PROMIS Short Form 8c (8 questions)	X	X	X
NCI-CTCAE (14 questions)	X	X	X

Abbreviations: CTCAE = common terminology criteria for adverse events; ePRO = electronic patient reported outcome; EQ-5D-5L = EuroQol Group's 5-domain 5-level questionnaire; FACT = functional assessment of cancer therapy; FACT-G = functional assessment of cancer therapy-general; FBSI = functional Assessment of Cancer Therapy Breast Symptom Index; FLSI = Functional Assessment of Cancer Therapy Lung Cancer Symptom Index; NCI = national cancer institute; NCCN = national comprehensive cancer network; PROMIS = Patient Reported Outcomes Measurement Information System.

a For Cohorts 1-3: Patients will answer only 13 of the 27 questions in the FACT-G questionnaire.

5.4. Follow-up Periods and Study Completion

5.4.1. End-of-Treatment Visit

The EOT visit will be performed as soon as possible (preferably within 3 days but no later than 14 days) after permanent discontinuation of the study treatment or when the Investigator decided with the patient to permanently discontinue the study treatment or when the Investigator became aware that the study treatment had been discontinued. The assessments of the EOT visit will then be performed instead of at the next planned visit. If the patient finishes treatment without having PD, tumor assessment/imaging must be performed at the time of treatment discontinuation unless it has been done within the past 4 weeks.

5.4.2. 30-day Safety Follow-up Visit

All patients will be followed during the off-treatment period until all treatment-related toxicity has resolved, or for at least 30 days (±3 days) post-study drug discontinuation, or until the start

of another anti-cancer treatment, in which case this visit should occur before the start of subsequent therapy. Any concomitant medications received up to 30 days after the last dose of study medication should be recorded. For Part B and the Safety Expansion portion of Part A subsequent anticancer therapy will continue to be collected as outlined in Table 2 and Table 3.

Thirty-day Safety Follow-up visit assessments do not need to be repeated if a new anti-cancer therapy was initiated within 7 days of the EOT visit, unless further study drug was administered or there was a new abnormal test result when last assessed (including an abnormal test result which had worsened from previous). If the EOT visit is more than 30 days after the last dose of study treatment, the 30-Day Safety Follow-up visit is not required.

5.4.3. Extended Follow-up Period (Safety Expansion and Part B)

For patients participating in Safety Expansion portion of Part A and all patients in Part B, additional follow-up for OS, PFS, and the first subsequent anti-cancer therapy after the 30-Day Safety Follow-up visit will be performed every 3 months (±14 days) until 2 years after the first study drug dose if the patient has stopped treatment prior to PD based on RECIST Version 1.1 as assessed by the Investigator (see Appendix B) or another withdrawal criterion is met:

- Start of a new anti-cancer therapy.
- Lost to follow-up.
- Death.
- End of the whole study.

Follow-up information for OS may be obtained by phone.

5.5. Early Patient Termination/Patient Withdrawal

Patients who discontinue treatment early due to PD, a DLT, or withdrawal will be asked to have all EOT safety evaluations performed as described in the protocol (see the Schedule of Assessments [Table 1,Table 2, and Table 3]). If a patient withdraws from treatment during Cycle 1 due to any reason other than a DLT and does not meet the minimum requirements for inclusion in the DLT-evaluable population described in Section 4.3.3, an additional patient may be enrolled to ensure an adequate number of evaluable patients.

5.6. Pharmacokinetic Assessments

The plasma PK parameters (including $AUC_{0\text{-}INF}$, $AUC_{(0\text{-}\tau)}$, C_{max}, T_{max}, $t_{1/2}$, Cl/F, and Vd/F) of BDTX-189 following oral administration will be assessed by analysis of blood plasma samples (see Table 10). Patients participating in the Dose Escalation cohorts during Part A will undergo detailed PK evaluation according to Table 10. Patients participating in the initial Dose Escalation where BDTX-189 was evaluated fasting should also take the study drug fasting for the detailed PK assessment. Patients enrolled in cohorts evaluating BDTX-189 in the non-fasting state should be provided a meal of their choice in connection with the detailed PK assessment as instructed in Section 6.1.2.

All patients enrolling into the Safety Expansion will have blood drawn on Day 1 of Cycles 2, 3, 4, 5 and every other cycle thereafter for sparse pop PK sampling. In addition, a minimum of 12 patients in the Safety Expansion will be administered a smaller and reformulated 200 mg tablet and will undergo detailed PK evaluation according to Table 10 on C1D1 and C1D15. This evaluation will be performed at selected study sites capable of performing detailed PK

procedures. Detailed PK sampling will be collected on Day 15 (i.e., after 14 days of daily treatment with the smaller and reformulated 200 mg tablet) of that subsequent cycle according to Table 10.

Table 10 BDTX-189 pharmacokinetic collection times (Part A Dose Escalation and Safety Expansion patients)

Study Day	PK draws (hours post-dose)[a]	Collection window (± mins)
C1D1	pre-dose[c]	
	0.5	5
	0.75	5
	1[c]	10
	1.5	10
	2[c]	15
	3[c]	15
	4[c]	20
	6	30
	8[d]	30
	24[e]	30
C1D15[b]	pre-dose[c]	
	0.5	5
	0.75	5
	1[c]	10
	1.5	10
	2[c]	15
	3[c]	15
	4[c]	20
	6	30
	8[d]	30
	24[e]	30
Sparse PK Sampling (Pop PK)		
Cycles 2, 3, 4, 5 and every other cycle thereafter (± 2 days)	Pre-dose 1st sample: 0.5 - 1.5 hours post-dose[a] 2nd sample: 2 - 4 hours post-dose[a]	n/a

Abbreviations: C = Cycle; D = Day; mins = minutes; n/a = not applicable; PK = pharmacokinetic.

a The actual post-dose time of collection should be recorded.

b Patients in Part A who initiated treatment with the larger 200 mg tablet may be switched to the smaller and reformulated 200 mg tablet at the beginning of their subsequent cycles. Detailed PK sampling will be collected on Day 15 (i.e., after 14 days of daily treatment with the smaller 200 mg tablet) of that subsequent cycle.

c ECG measurements will be performed in triplicate pre-dose and at 1.0, 2.0, 3.0, and 4.0 hours (+/- 5 minutes) post-dose on C1D1 and C1D15 starting with dose level 4 (200 mg) and onwards for the QD schedule and starting with dose level 1 for the BID dosing schedule. For each set of triplicate ECGs, 3 standard resting 12-lead ECGs will be obtained in close succession and not more than 2 minutes apart (4 minutes total for 3 ECGs); see Section 5.3.2.

d Patients on the BID schedule should have their 8-hour PK samples drawn prior to the second dose of the day.

e The 24-hour sample will be collected prior to the administration of study drug on Day 2 or Day 16, as appropriate.

In Part A, time-matched ECG measurements will be collected coinciding with the detailed PK assessments around the projected C_{max} in patients to evaluate any QTc concentration-effect relationship. See Table 1, Table 2, and Section 5.3.2 for specific time points.

For Part B, sparse PK blood samples will be collected at approximately the following time points:

- Cycles 1 to 5 and every other cycle thereafter (± 2 days), Day 1: One pre-dose, two post-dose blood draws, the 1st draw at 0.5 – 1.5 hours post-dose and the 2nd draw at 2 – 4 hours post-dose.

Note: An ad hoc PK sample should be drawn (whenever possible) in case of a severe adverse event or at pre-dose in the event of dose modification, to assess the safety of the patient.

5.6.1. Pharmacokinetic Assessments – Food Effect (Part A)

Plasma PK parameters (including $AUC_{0\text{-}INF}$, $AUC_{(0\text{-}\tau)}$, C_{max}, T_{max}, $t_{1/2}$, Cl/F, and Vd/F) of BDTX-189 following oral administration in a fed/fasted state will be assessed by analysis of blood samples at the time points specified in Table 11.

Table 11 BDTX-189 pharmacokinetic collection times – Lead-in phase for Food-Effect (Part A)

Study Day	PK draws (hours post-dose)	Collection window (± mins)
Day -4	pre-dose	
	0.5	5
	0.75	5
	1	10
	1.5	10
	2	15
	3	15
	4	20
	6	30
	8	30
Day -1	pre-dose	
	0.5	5
	0.75	5
	1	10
	1.5	10
	2	15
	3	15
	4	20
	6	30
	8	30

Abbreviations: mins = minutes; PK = pharmacokinetic.

Note: Beginning with Cycle 1 Day 15, PK sampling will continue as per all other patient cohorts (see Table 10). There is no PK sampling on C1D1 for patients in the Food-Effect cohort.

5.7. Biomarker Assessments

5.7.1. Archival Tumor Samples

Tumor samples will be collected during the screening period for retrospective confirmation of allosteric *ErbB* mutations using a diagnostic test that is being developed. Archival tumor samples or tumor tissue from a new pretreatment biopsy is required for all patients enrolled in the Safety Expansion portion of Part A and Part B who have allosteric *ErbB* mutations. Archival tumor samples or tissue from a new pretreatment biopsy is requested for patients with allosteric *ErbB* mutations enrolled in the Dose Escalation portion of Part A.

Samples should be provided as a tissue block. Alternatively, if a tissue block cannot be provided 12-20 freshly cut formalin-fixed paraffin-embedded (FFPE) unstained slides may be submitted. Freshly cut unstained slides are preferred, however unstained slides that were sectioned within 2 years prior to the patient enrolling in the study may be submitted only if stored in the appropriate long-term storage conditions (-80°C). If the quantity of archival tumor tissue available is insufficient to obtain 12-20 unstained slides, a new tumor tissue biopsy sample must be obtained prior to starting study treatment.

Further details on sample processing, handling, and shipment are provided in the Laboratory Manual.

5.7.2. Fresh Biopsies

Patients in the Dose Escalation portion of Part A will be required to undergo baseline and on-treatment tumor biopsies if the tumor is amenable for biopsy in the opinion of the Investigator. For patients participating in the Safety Expansion cohort(s) or any cohort in Part B an archival tumor tissue sample is required, if an archival tumor tissue sample is not available, a fresh tumor biopsy will be required at baseline.

In Part A, the on-treatment biopsy is planned to be obtained from dose level 5 (400 mg) or an earlier dose cohort (e.g., 200 mg) if emerging data suggest and continue at higher dose levels until data supports target engagement in downstream signaling. Fresh tumor biopsies will be collected at baseline (or within 28 days of baseline) and on C2D1 (±5 days). On C2D1, patients must be dosed in the clinic at least 2 hours prior to collecting the biopsy. The biopsy may be collected up to 8 hours after dosing. Depending on emerging PDx data, the C2D1 biopsy may be collected pre-dose in either the BID cohorts or both cohorts. Pre-dose biopsies may be collected 12 hours after a BID dose or 24 hours after a QD dose. This sample will be used to investigate changes in pathway signaling and potential mechanisms of resistance (e.g., ERK phosphorylation, evidence of alternative pathway activation [e.g., PI3K/AKT], and co-occurring genomic alterations). The material must include both FFPE and fresh frozen tissue. A minimum of 2 and ideally 4 core biopsies should be obtained. Detailed sample processing, handling, and shipment are provided in the Laboratory Manual.

All patients in Part A and Part B will be asked to undergo an optional on-treatment tumor biopsy at the time of disease progression if the tumor is amenable for biopsy in the opinion of the Investigator and the patient consents.

Evaluable paired on-treatment samples will be used to evaluate exploratory biomarkers. Failure to obtain a sufficient tumor sample after making best efforts to biopsy the tumor will not be considered a protocol deviation. When feasible, collection of an optional tumor biopsy at relapse is encouraged but will not be considered to be a protocol deviation if the patient does not give or withdraws consent.

Biopsies should be obtained through non-significant risk procedures. Sampling should be undertaken by experienced physicians in appropriate settings. The on-treatment biopsy can be omitted if clinically contraindicated or if the risk of the procedure for the individual patient has increased to a significant level as determined by the Investigator.

Instructions regarding sample collection, sample handling/processing, and sample shipping are provided in the Laboratory Manual. This will include instruction regarding study drug administration to be done in the clinic at least 2 hours prior to obtaining the tumor biopsy.

5.7.3. Blood Samples for Circulating Tumor DNA (ctDNA)Analysis

Blood samples will be collected for exploratory analysis of ctDNA mutations to assess correlations with disease activity, effects of study drug, and clinical outcomes. Blood samples will be collected from all patients to generate plasma samples and these samples will be used for the extraction and analysis of ctDNA. The samples will be used to explore the relationship between changes in biomarkers and response to treatment. In addition, innate and acquired resistance mechanisms may be explored. Markers tested may include, but will not be limited to, allosteric *ErbB* mutations, resistance mutations (e.g., [redacted]), and alterations in other genes involved in [redacted] and [redacted] signaling. Similarly, the relationship between other blood-borne biomarkers and drug response and/or PD may be explored. During treatment, ctDNA blood samples will be taken at the following time points:

Part A Dose Escalation (includes Food-Effect Cohort patients)

- Cycle 1 Day 1: pre-dose.
- Cycle 2 Day 1: pre-dose.
- Cycle 3 Day 1: pre-dose.
- End of study treatment/PD.

Part A Safety Expansion Cohort(s)

- Cycle 1 Day 1: pre-dose.
- Cycle 2 Day 1: pre-dose.
- Cycle 3 Day 1: pre-dose.
- Cycle 5 Day 1: pre-dose.
- End of study treatment/PD (If not collected at the EOT visit, these samples may be collected at the 30-Day Safety Follow-up visit as long as no new anticancer therapy has commenced).

Part B

- Screening
- Cycle 1 Day 1: pre-dose.
- Cycle 2 Day 1: pre-dose.
- Cycle 3 Day 1: pre-dose.
- Cycle 5 Day 1: pre-dose.
- Cycle 7 Day 1: pre-dose.
- Cycle 9 Day 1: pre-dose.
- One pre-dose sample will be collected every 4th cycle (Cycle 13 Day 1, Cycle 17 Day 1, Cycle 21 Day 1, etc.).
- End of study treatment/PD (If not collected at the EOT visit, these samples may be collected at the 30-Day Safety Follow-up visit as long as no new anticancer therapy has commenced).

Instructions regarding sample collection, handling/processing, and shipping are provided in the Laboratory Manual.

6. DRUG FORMULATION, AVAILABILITY, ADMINISTRATION, AND RISK INFORMATION

6.1. BDTX-189

Investigational Product	Dosage Form and Strength	Manufacturer
BDTX-189	100 mg and 200 mg tablets (A smaller and reformulated 200 mg tablet may be administered to some patients in select sites during the Safety Expansion of Part A and to all patients enrolling onto Part B).	Black Diamond Therapeutics, Inc.

6.1.1. Labeling, Packaging, and Supply

The Sponsor will supply the BDTX-189 as tablet formulations of 100 and 200 mg. A smaller and reformulated 200 mg tablet may be introduced during the Safety Expansion of Part A to select sites, and will also be administered to patients enrolling onto Part B. Each high density polyethylene (HDPE) bottle will contain 30 tablets. This tablet is a common granulated blend of drug substance and pharmacopeial grade excipients compressed into an immediate release form, which is half the size of the larger 200 mg tablet provided to patients in the Dose Escalation portion of Part A. The pharmacopeial grade excipients include starch, microcrystalline cellulose, croscarmellose sodium, sodium dodecyl sulfate, colloidal silicon dioxide, and magnesium stearate.

Patients in Part A who initiated treatment with the larger 200 mg tablet may be switched to the smaller and reformulated 200 mg tablet at the beginning of their subsequent cycles after instruction by the Sponsor.

At each visit, patients will be dispensed sufficient supplies until the next visit. Study drug compliance will be assessed at each patient visit by review of the dosing diary. The research staff will count and document the amount of study drug taken and returned by the patient. The batch number of the study drug dispensed to the patient should be entered on the eCRF, if applicable.

The immediate packaging will contain a statement to conform with FDA Investigational New Drug (IND) requirements as follows: “Caution: New Drug - Limited by federal (or United States) law to investigational use.” and according to the applicable local laws for labeling the investigational products

All study drugs must be kept in a secure place under appropriate storage conditions. Storage conditions for BDTX-189 are included on the investigational product label.

The Sponsor or its representative must be granted access on reasonable request to check drug storage, dispensing procedures, and accountability records.

6.1.2. Preparation and Administration of BDTX-189

BDTX-189 is administered PO. The study drug will be provided to the sites by the Sponsor.

The emerging food-effect data suggest a slight to moderate increase in systemic exposure of BDTX-189 when administered with a high fat meal. Therefore, separate cohorts (QD and BID)

at ≥800 mg/day will be evaluated in the fed state, as will the Safety Expansion cohort(s) and Part B. In this case, patients will be instructed not to take study drug on an empty stomach. Patients are allowed to take their dose of BDTX-189 with approximately 240 mL water within 30 minutes of completing a meal.

Tablets should be swallowed whole (along with up to 240 mL water), not crushed, chewed, or dissolved.

For the QD dosing schedule, patients will self-administer the study drug with approximately 240 mL water within 30 minutes of completing a meal. The time of day for administration of BDTX-189 should be as consistent as possible.

For the BID dosing schedule, BDTX-189 should be taken at approximately the same time each morning and approximately the same time each evening, approximately 10 hours after the morning dose. Patients will self-administer the study drug with approximately 240 mL water within 30 minutes of completing a meal.

For the Food-Effect Patients, study drug will be self-administered on an empty stomach following a fast of approximately 2 hours. Patients will continue to fast for approximately 1 hour after the administration of BDTX-189.

On scheduled PK collection days, C1D1 and C1D15 during Dose Escalation and Safety Expansion, the patient should be instructed to wait until he/she arrives at the study center and receives instructions from the research staff to take their morning dose of study medication.

On the scheduled on-treatment tumor biopsy day, the patient in Part A should be instructed to wait until he/she arrives at the study center and receives instructions from the research staff to take their study medication. Study drug administration will take place at least 2 hours prior to obtaining the tumor biopsy.

6.1.3. Accountability for All Study Drugs

The Principal Investigator (or designee) is responsible for accountability of all used and unused study drug supplies at the site.

All study drug inventories must be made available for inspection by the Sponsor or its representative, e.g., Development Innovations, and regulatory agency inspectors upon request.

Throughout the study and at its completion, Development Innovations Drug Accountability Record Form(s) (or an equivalent form) will be completed by the site and sent to the Development Innovations Regulatory Department. Study drug supplies must not be destroyed unless prior approval has been granted by the Sponsor or its representative. Please contact the Sponsor or its representative regarding disposal of any study drug.

7. RESPONSE EVALUATIONS AND MEASUREMENTS

Response and progression will be evaluated in this study using RECIST Version 1.1 (see Appendix B). Lesions are either measurable or non-measurable according to the criteria. The term "evaluable" in reference to measurability will not be used, as it does not provide additional meaning or accuracy.

At screening, tumor assessments should encompass all areas of known predilection for metastases in the disease under evaluation and should additionally investigate areas that may be involved based on signs and symptoms of individual patients. These assessments should be performed no more than 28 days before the start of study treatment and, ideally, should be performed as close as possible to the start of study treatment. The methods of assessment used at screening should be used at each subsequent follow-up assessment.

Follow-up assessments should be performed every 6 weeks (±3 days) after the start of BDTX-189 treatment for the first 8 cycles and every 12 weeks (±7 days) thereafter. Any other sites at which new disease is suspected should also be appropriately imaged. If an unscheduled assessment is performed and the patient has not progressed, every attempt should be made to perform subsequent assessments at the scheduled visits while the patient remains on study treatment.

Categorization of objective tumor response assessment will be based on the RECIST v1.1 criteria for response: CR (complete response), PR (partial response), SD (stable disease), and PD (progressive disease).

If the Investigator is in doubt as to whether progression has occurred, particularly with response to non-target lesions (NTLs) or the appearance of a new lesion, it is advisable to continue treatment and reassess the patient's status at the next scheduled assessment or sooner if clinically indicated.

To achieve "unequivocal progression" on the basis of non-target disease, there must be an overall level of substantial worsening in non-target disease such that, even in presence of SD or PR in target disease, the overall tumor burden has increased sufficiently to merit discontinuation of therapy. A modest increase in the size of one or more NTLs is usually not sufficient to qualify for unequivocal PD status.

8. SAFETY REPORTING AND EVALUATION

Safety assessments will consist of monitoring and recording protocol-defined AEs and SAEs, and measurement of protocol-specified hematology, clinical chemistry, and other protocol-specified tests that are deemed critical to the safety evaluation of the study drug.

The Principal Investigator is responsible for recognizing and reporting SAEs to the Development Innovations Safety Department (see Section 8.2), and the Development Innovations Safety Department in turn notifies the Sponsor (see Section 8.2). It is the Sponsor-designated 3rd party agent's responsibility to report relevant SAEs to the applicable local, national, or international regulatory bodies. In addition, Investigators must report SAEs and follow-up information to their responsible IRBs according to the policies of each IRB.

The Principal Investigator is also responsible for ensuring that every staff member involved in the study is familiar with the content of this section.

8.1. Definitions

8.1.1. Adverse Events

Adverse event means any untoward medical occurrence associated with the use of a drug in humans, whether or not considered drug related. An AE can be any unfavorable and unintended sign (e.g., an abnormal laboratory finding), symptom, or disease temporarily associated with the use of a drug, without any judgment about causality. An AE can arise with any use of the drug (e.g., off-label use, use in combination with another drug) and with any route of administration, formulation, or dose, including overdose.

8.1.2. Serious Adverse Events

An AE or a suspected adverse reaction (SAR) is considered "serious" if it results in any of the following outcomes:

- Death.
- A life-threatening AE.
- Inpatient hospitalization or prolongation of existing hospitalization.
- A persistent or significant incapacity or substantial disruption of the ability to conduct normal life functions.
- A congenital anomaly/birth defect.

Important medical events that may not result in death, be life-threatening, or require hospitalization may be considered serious when, based upon appropriate medical judgment, they may jeopardize the patient and may require medical or surgical intervention to prevent one of the outcomes listed in this definition. Examples of such medical events include allergic bronchospasm requiring intensive treatment in an emergency room or at home, blood dyscrasias or convulsions that do not result in hospitalization, or development of drug dependency or drug abuse.

It is important to distinguish between "serious" and "severe" AEs, as the terms are not synonymous. Severity is a measure of intensity; however, an AE of severe intensity need not

necessarily be considered "serious." Seriousness serves as the guide for defining regulatory reporting obligations and is based on patient/event outcome or action usually associated with events that pose a threat to a patient's life or vital functions. For example, nausea that persists for several hours may be considered "severe" nausea but may not be considered an SAE. On the other hand, a stroke which results in only a limited degree of disability may be considered only a mild stroke but would be considered an SAE. "Severity" and "seriousness" should be independently assessed when recording an AE on the eCRF.

8.1.3. Adverse Event Severity

The severity refers to the intensity of an AE, which is different from seriousness as described in Section 8.1.2. Adverse event severity will be reported at the highest experienced as described in Section 8.1.5. Adverse events severity will be graded according to NCI CTCAE v 5.0. Events not listed in NCI CTCAE will be graded according to the criteria described in Appendix J.

8.1.4. Suspected Adverse Reaction

Suspected adverse reaction (SAR) means any AE for which there is a reasonable possibility that the drug caused the AE. "Reasonable possibility" means that there is evidence to suggest a causal relationship between the drug and the AE.

8.1.5. Recording and Reporting of Adverse Events

Recording of Adverse Events

All AEs of any patient during the course of the research study will be recorded in the eCRF, and the Investigator will give his or her opinion as to the relationship of the AE to the study drug treatment (i.e., whether the event is related or unrelated to study drug administration).

All AEs should be documented in the eCRF. A description of the event, including its date of onset and resolution, whether it constitutes an SAE or not, any action taken (e.g., changes to study treatment), and its outcome should be provided, along with the Investigator's assessment of causality (i.e., the relationship to the study treatment). For an AE to be a suspected treatment-related event, there should be at least a reasonable possibility of a causal relationship between the protocol treatment and the AE. Adverse events will be graded according to the NCI CTCAE Version 5.0, and changes in severity will be documented by recording the AE as separate entries.

If the AE is serious, it should be reported within 24 hours of the Investigator site awareness or receipt of the initial SAE or any follow-up information to Development Innovations Safety Department. Other untoward events occurring in the framework of a clinical study are to be recorded as AEs (i.e., AEs that occur prior to assignment of study treatment that are related to a protocol-mandated intervention, including invasive procedures such as biopsies, medication washout, or no treatment run-in).

Test findings will be reported as an AE if the test result requires an adjustment in the study drug or discontinuation of treatment and/or test findings require additional testing or surgical intervention, a test result, or finding is associated with accompanying symptoms, or a test result is considered to be an AE by the Investigator.

Reporting Period for Adverse Events

All AEs, regardless of seriousness or relationship to study treatment, spanning from the signing of the ICF until 30 calendar days after discontinuation or completion of study treatment as defined by the study for that patient after his/her last dose of BDTX-189, are to be recorded on the AE page in the eCRF. The AEs occurring from the signing of the ICF until the first dosing with BDTX-189 will be the pre-treatment AEs. The AEs occurring at or after the first dosing will be the TEAEs.

All AEs resulting in discontinuation from the study should be followed until resolution or stabilization. All new AEs occurring during this period must be reported and followed until resolution unless, in the opinion of the Investigator, the AE or laboratory abnormality/ies is/are not likely to improve because of the underlying disease. In this case, the Investigator must record his or her reasoning for this decision in the patient's medical record.

Only drug-related SAEs that emerge 30 days or more after the last dose of study medication, as well as deaths assessed by the Investigator as treatment-related are to be reported.

8.1.6. Assessment of Adverse Events

All AEs (regardless of seriousness) whether volunteered by the patient, discovered by study personnel during questioning, or detected through physical examination, laboratory tests, or other means will be reported appropriately. Each reported AE will be described by its duration (i.e., start and end dates), regulatory seriousness criteria, suspected relationship to the study drug (see following guidance), and actions taken.

To ensure consistency of AE causality assessments, Investigators should apply the following general guideline:

> **YES:** There is a plausible temporal relationship between the onset of the AE and administration of the study treatment, and the AE cannot be readily explained by the patient's clinical state, intercurrent illness, or concomitant therapies; and/or the AE follows a known pattern of response to the study drug; and/or the AE abates or resolves upon discontinuation of the study drug or dose reduction and, if applicable, reappears upon re-challenge.
>
> **NO:** Evidence exists that the AE has an etiology other than the study drug (e.g., pre-existing medical condition, underlying disease, intercurrent illness, or concomitant medication); and/or the AE has no plausible temporal relationship to study drug administration (e.g., cancer diagnosed 2 days after first dose of study drug).

8.2. Serious Adverse Event Reporting by the Investigator

Adverse events classified by the treating Investigator as "serious" require expeditious handling and reporting to the Sponsor or designee in order to comply with regulatory requirements. Determination of "life-threatening" or "serious" is based on the opinion of either the Sponsor or the Investigator.

Serious AEs occurring at any time from the signing of the ICF through the 30-day follow-up period after the last dose of study drug must be reported as SAEs in the eCRF and followed until resolution (with autopsy report if applicable). **The Development Innovations Safety**

Department must be notified of all SAEs, regardless of causality, within 24 hours of the first knowledge of the event by the treating physician or research personnel via the paper SAE reporting form.

Paper SAE Report Forms will be submitted via fax or e-mail using the following contact information (during both business and non-business hours):

[redacted]

Safety Dept. Phone# [redacted]

Safety Dept. Fax #: [redacted]

Safety Dept. Email: [redacted]

Transmission of the SAE report should be confirmed by the site personnel submitting the report.

Follow-up information for SAEs and information on non-serious AEs that become serious should also be reported to the Development Innovations Safety Department as soon as it is available. The detailed SAE reporting process will be provided to the sites in the SAE reporting guidelines contained in the study reference manual.

8.2.1. Diagnosis versus Signs and Symptoms

All AEs should be recorded individually in the patient's own words (verbatim) unless, in the opinion of the Principal Investigator or designated physician, the AEs constitute components of a recognized condition, disease, or syndrome. In the latter case, the condition, disease, or syndrome should be named rather than each individual sign or symptom. If a constellation of signs and/or symptoms cannot be medically characterized as a single diagnosis or syndrome at the time of reporting, each individual event should be recorded as an AE or SAE as appropriate on the relevant form(s) (AE eCRF or paper SAE Report Form). If a diagnosis is subsequently established, it should be reported as follow-up information is available. If a diagnosis is determined subsequent to the reporting of the constellation of symptoms, the signs/symptoms should be updated to reflect the diagnosis.

Progression of malignancy (including fatal outcomes), if documented by use of appropriate methods (e.g., as per RECIST criteria for solid tumors; see Appendix B), should not be reported as an SAE.

8.2.2. Persistent or Recurrent Adverse Events

A persistent AE is one that extends continuously, without resolution, between patient evaluation time points. A persistent AE should only be recorded once (i.e., a single AE) on the AE eCRF. If a persistent AE becomes more severe or lessens in severity, the event should be recorded as a separate AE. Each AE must have its own severity grade and corresponding start and stop dates. Persistent toxicity from a prior therapy should be recorded as medical history on the medical history page on the eCRF. If this toxicity has increased in severity during the study, this toxicity should be recorded as an AE on the AE eCRF with the new severity; the start date for this event should be the date when the new severity is observed.

A recurrent AE is one that occurs and resolves between patient evaluation time points and subsequently recurs. In this case, each occurrence should be recorded as a separate AE with corresponding start and stop dates.

8.2.3. Abnormal Laboratory or Vital Sign Values

Abnormal laboratory values will be reported as an AE if the laboratory result requires an adjustment in the study drug or discontinuation of treatment, and/or laboratory findings require additional testing or surgical intervention, a laboratory result or finding is associated with accompanying symptoms, or a laboratory result is considered to be an AE by the Investigator.

If an abnormal laboratory value or vital sign is associated with clinical signs and/or symptoms, the signs or symptoms should be reported as an AE or SAE, and the associated laboratory value or vital sign should be considered additional information that must be collected on the relevant eCRF (e.g., laboratory eCRF or vital sign page). If the laboratory abnormality is a sign of a disease or syndrome, only the diagnosis needs to be recorded as an AE on the AE eCRF.

8.2.4. Hy's Law

The Investigator is responsible for determining whether a patient meets potential Hy's Law criteria at any time during the study. Potential Hy's Law criteria are defined as AST or ALT $\geq 3 \times$ ULN together with total bilirubin $\geq 2 \times$ ULN without initial findings of cholestasis (elevation of ALP) at any point during the study following the start of study medication without other reason that can explain the combined ALT/AST and bilirubin elevation (e.g. viral hepatitis or underlying liver disease).

When a case meeting potential Hy's Law is identified, the Investigator will immediately notify the Sponsor. The Investigator will also request a new blood draw to repeat the test immediately and will review all previous laboratory data to determine whether potential Hy's Law criteria were met at any study visit prior to or after starting study treatment.

The Investigator will review the case with the Medical Monitor and agree on the approach for the patients' follow-up assessments, which include monitoring the patient until liver chemistry tests and clinical signs and symptoms return to normal or baseline levels, and investigating the etiology of the event including diagnostic tests, as appropriate. The SRC or DMC and other subject matter experts may also be involved in the case review and assessment, as needed. The Investigator and Medical Monitor will meet periodically to review all available and emerging data and agree upon whether there is an alternative explanation for meeting potential Hy's Law criteria other than drug induced liver injury caused by the study drug.

Standard safety reporting procedures will be followed for reporting AEs and SAEs according to the outcome of the review and assessment. If it is agreed that there is no alternative explanation that would explain the ALT or AST and total bilirubin elevations other than the study drug, then the Investigator is required to report an SAE with the term Drug-Induced Liver Injury and the causality assessment of "related."

Any potential Hy's Law case should be handled as a serious unexpected adverse event associated with the use of the drug and reported to the FDA promptly (i.e., even before all other possible causes of liver injury have been excluded). It should be promptly reported to the FDA before fully working up the patient to rule out other etiologies.

8.2.5. Deaths

Deaths occurring during the protocol-specified AE reporting period that are attributed by the Investigator solely to the progression of disease will be recorded on the "End of Study" eCRF.

All other on-study deaths, regardless of attribution, will be recorded on the SAE paper report form and expeditiously reported to the Development Innovations Safety Department.

When recording an SAE with an outcome of death, the event or condition that caused or contributed to the fatal outcome should be recorded as the single medical concept on the AE eCRF. If the cause of death is unknown and cannot be ascertained at the time of reporting, record "death, cause unknown" on the Adverse Event eCRF. During post-study survival follow-up, deaths attributed to progression of disease will be recorded on the "Follow-up Summary" and "Death Page" eCRFs.

8.2.6. Hospitalization, Prolonged Hospitalization, or Surgery

Any AE that results in hospitalization of >24 hours or prolongation of pre-existing hospitalization should be documented and reported as an SAE unless specifically instructed otherwise in this protocol. There are some hospitalizations that do not require reporting as an SAE.

Treatment within or admission to the following facilities is not considered to meet the criteria of "inpatient hospitalization" (although if any other SAE criteria are met, the event must still be treated as an SAE and immediately reported):

- Emergency department or emergency room.
- Outpatient or same-day surgery units.
- Observation or short-stay unit.
- Rehabilitation facility.
- Hospice or skilled nursing facility.
- Nursing homes, custodial care, or respite care facility.

Hospitalization during the study for a pre-planned surgical or medical procedure (one which was planned prior to entry in the study) does not require reporting as an SAE.

8.2.7. Pre-Existing Medical Conditions

A pre-existing medical condition is one that is present at the start of the study. Such conditions should be recorded on the General Medical History of the eCRF. A pre-existing medical condition should be recorded as an AE or SAE only if the frequency, severity, or character of the condition worsens during the study. When recording such events on an AE eCRF, it is important to convey the concept that the pre-existing condition has changed by including applicable descriptors, such as new start date, new severity/frequency, etc.

8.2.8. New Cancers

The development of a new primary cancer should be regarded as an AE and will generally meet at least one of the seriousness criteria (see Section 8.1.2). New primary cancers are those that are not the primary reason for the administration of the study treatment and have developed after the inclusion of the patient into the study. They do not include metastases of the original cancer. Symptoms of metastasis or the metastasis itself should not be reported as an AE/SAE, as they are considered to be PD (see Section 8.2.1).

8.2.9. Pregnancy, Abortion, Birth Defects/Congenital Anomalies

If a patient becomes pregnant while enrolled in the study, a Pregnancy Form (a paper report form, not available within the eCRF) should be completed and faxed to the Development Innovations Safety Department. The Development Innovations Safety Department should be notified expeditiously, irrespective of whether or not it meets the criteria for expedited reporting. Abortions (spontaneous, accidental, or therapeutic) must also be reported to the Development Innovations Safety Department.

If a female partner of a male patient becomes pregnant during the male patient's participation in this study, this must be reported to the Development Innovations Safety Department immediately. Every effort should be made to follow the pregnancy for the final pregnancy outcome.

A pregnancy itself is not an AE; however, congenital anomalies/birth defects always meet SAE criteria and should therefore be expeditiously reported as an SAE using the previously described process for SAE reporting. A Pregnancy Form should also have been previously completed and will need to be updated to reflect the outcome of the pregnancy.

8.2.10. BDTX-189 Overdose

Symptomatic and non-symptomatic overdose must be reported in the eCRF system. Any accidental or intentional overdose with the study treatment that is symptomatic, even if not fulfilling a seriousness criterion, is to be reported to the Development Innovations Safety Department no greater than 24 hours from first knowledge of the event following the same process described for SAE reporting (see Section 8.2).

8.3. Sponsor Serious Adverse Event Reporting Requirements

Per regulatory requirements, if an SAE is required to be submitted to a regulatory authority, the Sponsor or Sponsor-designated third party agent will report it to the competent authority and the Investigators/site, and a copy of the report will be submitted to the respective IRB or IEC in accordance with ICH guidelines, Directive 2001/20/EC, 21CFR312.32 and other local regulatory requirements.

8.3.1. Sponsor Assessment of Expectedness

The Sponsor and/or Development Innovations Safety Department is responsible for assessing an AE or suspected AE for expectedness.

An SAE or SAR is considered "unexpected" when the following conditions occur:

- Event(s) is not mentioned in the IB, Reference Safety Information Section 7.12.
- Event(s) is not listed at the specificity or severity that has been observed.

This includes SAEs or SARs that may be anticipated from the pharmacological properties of the study drug, or that occur with members of the drug class, but that have not previously been observed under investigation

Known as suspected unexpected serious adverse reactions (SUSARs), these events suspected (by the Investigator or Sponsor) to be related to the study drug are unexpected (not listed in the IB's Reference Safety Information Section 7.12), are serious (as defined by the protocol), and require

expedient submission to relevant health authorities, ECs, Investigators, and sites within 7 days (for fatal or life-threatening events) or 15 days (for all serious events), or as defined by law. The term SUSAR is used primarily in the reporting of events to regulatory authorities.

Expected SAEs are those events that are listed or characterized in the current IB (Section 7.12).

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

9. STATISTICAL CONSIDERATIONS

9.1. Statistical Design

This is a Phase 1/2, open-label, 2-part, multi-center study of BDTX-189. Part A is designed primarily to determine the RP2D and dosing schedule, and to characterize the safety, tolerability, PK profile, preliminary antitumor activity, and effect of food on BDTX-189 PK.

Part B is an open label, multi-center, Phase 2 basket study to investigate the antitumor activity of BDTX-189 as a single oral agent in patients with a tumor harboring an eligible allosteric *ErbB* mutation.

Each part will be analyzed and summarized separately. Descriptive statistics will be used to summarize the study data overall and by dose level cohort for Part A unless otherwise specified.

Additional details on statistical design and evaluation of specific endpoint variables are provided in the Statistical Analysis Plan (SAP).

9.2. Estimands

The primary estimand for Part A is the rate at which DLTs occur after treatment with BDTX-189 when administered either QD or BID. It is further described by the following attributes:

- Population: Patients with advanced solid malignancies as reflected by the inclusion/exclusion criteria outlined in Sections 3.1 and 3.2.
- Variable: DLTs, as defined in Section 4.3.2, occurring during the first 21 days of treatment (i.e., Cycle 1).
- Population-level summary: DLT rate, which is defined as the proportion of patients who experience a DLT during Cycle 1. Separate summaries will be estimated for each evaluated dose level of BDTX-189.
- Intercurrent events: Estimation will be based on the hypothetical situation that all patients either receive at least 75% of their planned doses of BDTX-189 during their first 21 days of treatment or experience a DLT during their first 21 days of treatment (i.e. are considered DLT-evaluable). Patients who are DLT-evaluable will be included in the calculation of the DLT rate. Additional patients will be enrolled, if necessary, to ensure an adequate number of DLT-evaluable patients.

The primary estimand for Part B is the effect of BDTX-189, when administered at the RP2D, on objective response rate as assessed by BICR and per RECIST v1.1. It is described by the following attributes:

- Population: Patients with solid tumors containing mutations falling into one of the MTC-A through MTC-G groupings as reflected by the inclusion/exclusion criteria outlined in Sections 3.1 and 3.2.
- Variable: Objective responses defined as CR or PR as assessed by BICR and per RECIST v1.1, which occur from the date of first dose of study treatment until the date of the first documentation of PD, death or start of new anti-cancer therapy. Objective responses must be confirmed by repeat assessments performed at least 4 weeks later.

- Population-level summary: Objective response rate, defined as the proportion of patients in the analysis population with an objective response. Separate summaries will be estimated for various combinations of MTC groupings and tumor types.
- Intercurrent events: Estimation will be based on a "while on treatment" strategy. Patients who do not have a post-baseline tumor assessment or patients who receive subsequent anti-cancer therapies, have PD, die, or otherwise stop tumor assessments prior to experiencing a CR or PR will be considered non-responders.

9.3. Sample Size Considerations

9.3.1. Phase 1 (Part A)

The Phase 1 dose-escalation portion of the study will utilize a BOIN design as described in Section 4.3.1 and Appendix G. Part A will enroll approximately 36 DLT-evaluable patients to the QD schedule, and approximately 24 additional DLT-evaluable patients may be treated in the dose-escalation portion to assess the BID schedule. The number of DLT-evaluable patients in Part A will not exceed 60, excluding patients in the accelerated titration step. Because both a QD and BID schedule are being evaluated and one RP2D and schedule will be selected, the Safety Expansion cohort(s) will include up to 48 patients, including a minimum of 12 patients for PK evaluation of a smaller and reformulated 200 mg tablet. In addition, up to 16 PK-evaluable patients will be enrolled to evaluate food-effect for a total of up to approximately 128 evaluable patients in Part A. The final sample size will depend on the dosing schedule, the number of DLTs, and the total number of cohorts treated before a DLT is observed and the MTD is determined.

9.3.2. Phase 2 (Part B)

For Cohorts 1, 2, and 5, the sample size was determined for each cohort independently. For Cohorts 3 and 4, the sample size was determined for each subgroup within a cohort independently.

The rationale for the different null hypotheses and target ORR values for each cohort/subgroup is discussed in Section 4.2.

Sample sizes for Cohorts 1-5 were estimated using nQuery version 8.6. The following sections provide the details of sample size considerations for each cohort and a summary of sample size for each cohort for various scenarios.

9.3.2.1. Sample Size Considerations for Cohorts 1 and 2

The sample size in each cohort will be based on a Simon 2-stage optimal design (Simon 1989), with the modification of adding an additional earlier assessment of futility. Therefore, Cohorts 1 and 2 will be evaluated in 3 stages.

Each cohort is designed to provide approximately 80% power to detect a true target ORR of 30%, while rejecting a null ORR of 17.5% at a nominal 1-sided alpha level of 0.05. For each cohort, 15 patients will initially be enrolled. If no patient has an objective response at the end of Stage 1, enrollment to the cohort will stop, otherwise an additional 16 patients will be enrolled. If 6 or fewer of the 31 total patients have objective responses at the end of Stage 2, enrollment to

the cohort will stop, otherwise an additional 54 patients will be enrolled. The null hypothesis will be rejected if at least 21 of the 85 total patients have objective responses.

A small number of first-line NSCLC patients may be enrolled to Cohort 1, in which case, these patients will be analyzed separately and will not count towards the numbers of patients described above.

Table 12 provides the operating characteristics for Cohorts 1 and 2.

Table 12 Operating Characteristics for Cohorts 1 and 2

	Cumulative Probability of Stopping for Futility (Number of Responders/Total N)[1]			
	Stage 1 (0/15)	Stage 2 (≤ 6/31)	Stage 3 (≤ 20/85)	
True ORR = 17.5%	0.0558	0.7081	0.9541	Overall Type I Error: 0.0459
True ORR = 30%	0.0047	0.1355	0.1992	Overall Type II Error: 0.1992

[1] Based on exact binomial distribution.

9.3.2.2. Sample Size Consideration for Cohort 3

Cohort 3 will include 5 distinct mutational type subgroups (MTC-B, MTC-C, MTC-D, MTC-E and MTC-F) with each being evaluated independently.

The sample size in each subgroup will be based on a Simon 2-stage optimal design (Simon 1989). Each subgroup is designed to provide approximately 80% power to detect a true target ORR of 20%, while rejecting a null ORR of 5% at a nominal 1-sided alpha level of 0.05. For each subgroup, 10 patients will initially be enrolled. If no patient has an objective response at the end of Stage 1, enrollment to the subgroup will stop, otherwise an additional 19 patients will be enrolled. The null hypothesis will be rejected if at least 4 of the 29 total patients have objective responses.

Table 13 provides the operating characteristics for each Cohort 3 subgroup.

Table 13 Operating Characteristics for Cohort 3

	Cumulative Probability of Stopping for Futility (Number of Responders/Total N)[1]		
	Stage 1 (0/10)	Stage 2 (≤3/29)	
True ORR = 5%	0.5987	0.9532	Overall Type I Error: 0.0468
True ORR = 20%	0.1074	0.1989	Overall Type II Error: 0.1989

[1] Based on exact binomial distribution.

9.3.2.3. Sample Size Considerations for Cohort 4

Cohort 4 will include patients from 3 distinct cancer-type subgroups (NSCLC, biliary or cervical cancer), with each being evaluated independently.

The sample size in each subgroup will be based on a Simon 2-stage optimal design (Simon 1989). Each subgroup is designed to provide approximately 80% power to detect a true target ORR of 20%, while rejecting a null ORR of 5% at a nominal 1-sided alpha level of 0.05. For each subgroup, 10 patients will initially be enrolled. If no patient has an objective response,

enrollment to the subgroup will stop, otherwise an additional 19 patients will be enrolled. The null hypothesis will be rejected if at least 4 of the 29 total patients have objective responses.

Table 14 provides the operating characteristics for each Cohort 4 subgroup.

Table 14 Operating Characteristics for Cohort 4

	Cumulative Probability of Stopping for Futility (Number of Responders/Total N)[1]		
	Stage 1 (0/10)	Stage 2 (≤3/29)	
True ORR = 5%	0.5987	0.9532	Overall Type I Error: 0.0468
True ORR = 20%	0.1074	0.1989	Overall Type II Error: 0.1989

[1] Based on exact binomial distribution.

9.3.2.4. Sample Size Considerations for Cohort 5

Cohort 5 will have a heterogeneous patient population with many cancer types and MTC subsets. This cohort will include all eligible patients who cannot be assigned to Cohorts 1-4.

The sample size will be based on a Simon 2-stage optimal design (Simon 1989). The cohort is designed to provide approximately 80% power to detect a true target ORR of 20%, while rejecting a null ORR of 10% at a nominal 1-sided alpha level of 0.05. Thirty patients will initially be enrolled. If 3 or fewer patients have an objective response, enrollment to the cohort will stop, otherwise an additional 59 patients will be enrolled. The null hypothesis will be rejected if at least 14 of the 89 total patients have objective responses.

Table 15 provides the operating characteristics for Cohort 5.

Table 15 Operating Characteristics for Cohort 5

	Cumulative Probability of Stopping for Futility (Number of Responders/Total N)[1]		
	Stage 1 (≤3/30)	Stage 2 (≤13/89)	
True ORR = 10%	0.6474	0.9522	Overall Type I Error: 0.0478
True ORR = 20%	0.1227	0.1982	Overall Type II Error: 0.1982

[1] Based on exact binomial distribution.

9.4. Analysis Population

The following analysis populations will be used:

- The Intent-To-Treat (ITT) population is defined as all patients who signed informed consent. The ITT population is the primary population for the summarization of enrollment.
- The Full Analysis (FA) population is defined as all patients who receive at least one dose of BDTX-189. The FA population is the primary population for both safety and Part A efficacy analyses.
- The Per-Protocol Efficacy (PPE) population is defined as all FA population patients who meet the eligibility criteria, receive BDTX-189, and have at least one baseline and post-baseline response assessment. The PPE population will be used for exploratory sensitivity analyses.

- The DLT-evaluable population will consist of all patients in Part A (excluding those patients in the Food-Effect Cohort) who receive at least 75% of the planned oral doses during Cycle 1 and complete all required safety evaluations or who have a DLT in Cycle 1.
- The Pharmacokinetic (PK) population is defined as all patients who receive at least one dose of BDTX-189 and have at least one post-dose PK blood collection with associated bioanalytical results.
- The Pharmacodynamic (PDx) population is defined as all patients who receive at least one dose of BDTX-189 and have post-baseline ctDNA samples or have paired on-treatment tumor tissue biopsy results.

9.5. Data Analysis

Descriptive statistics, including mean, median, standard deviations, and range for all continuous measures will be tabulated and reported. Percentages and frequencies for all categorical measures will also be presented. Time to event endpoints will be reported using Kaplan-Meier estimates, with approximate 2-sided 95% confidence intervals (CIs) for median time to event.

9.5.1. Demographics and Baseline Characteristics

Demographic and baseline disease characteristics will be summarized descriptively. Data to be tabulated will include demographic features such as age, sex, and race, as well as disease-specific characteristics.

The number and percentages of patients who were screened, registered, and treated; who completed the treatment/study; and who were withdrawn from treatment/study for any reasons will be presented overall and by treatment cohort for Part A and Part B.

9.5.2. Hypotheses to be Tested

Part B Cohorts 1 and 2 of the study are designed to test the null hypothesis that the true ORR of BDTX-189 is less than or equal to 17.5%, while having sufficient power to detect (i.e., reject the null hypothesis with) a true ORR of 30%.

Part B Cohorts 3-4 of the study are designed to test the null hypothesis that the true ORR of BDTX-189 is less than or equal to 5%, while having sufficient power to detect a true ORR of 20%.

Part B Cohort 5 of the study is designed to test the null hypothesis that the true ORR of BDTX-189 is less than or equal to 10%, while having sufficient power to detect a true ORR of 20%.

9.5.3. Efficacy Analysis

The Investigator-assessed objective response is a secondary endpoint for Part A. BICR-assessed objective response is a primary endpoint for Part B. Secondary objectives of Part B include evaluating the Investigator-assessed objective response, and evaluating both the Investigator and BICR-assessed duration of response (DOR), disease control rate (DCR), and PFS as evidence of the antitumor activity of BDTX-189. Evidence of antitumor activity for ORR, DOR, DCR, and PFS will be determined by RECIST v1.1. OS is also a secondary endpoint for Part B.

- Objective Response Rate (ORR), defined as the proportion of patients with a best overall response of CR or PR recorded from baseline until PD, start of subsequent anti-cancer therapy, or death due to any cause according to the RECIST Version 1.1 criteria (see Appendix B). The Part B primary endpoint will be based on the confirmed ORR (i.e., 2 CRs or PRs at least 4 weeks apart). Unconfirmed best overall response and response rates will also be summarized.

- Duration of Response (DOR), defined as the time between first documentation of a response (CR or PR) and first evidence of PD according to RECIST v1.1 or death due to any cause. In case a patient does not have progression or death, DOR is censored at the date of last adequate tumor assessment (defined as an assessment of CR, PR, or SD). Duration of response analysis will include only the responders.

- Disease Control Rate (DCR) is defined as the proportion of patients with a best overall response of CR, PR, or SD.

- Progression-Free Survival (PFS), defined as the time from the first day of study drug administration to PD as defined by the RECIST Version 1.1 criteria, or death. Patients who are alive and free from PD will be censored at the date of last adequate tumor assessment.

- Overall Survival (OS), defined as the time from the first day of study drug administration to death. Patients who are alive will be censored at the last date the patient was known to be alive.

For ORR and DCR, patients without an adequate post-baseline tumor assessment will be classified as NE and considered non-responders. ORR estimates and the associated 95% CIs (based on exact binomial distributions) in each cohort/subgroup will be calculated.

For PFS and OS, Kaplan-Meier curves will be generated, and the median time-to-event and the associated 2-sided 95% CIs will be provided.

Efficacy analyses in Part A will be performed using the FA Population by cohort and combined. Part B efficacy summaries will be performed by cohort/subgroup.

9.5.4. Sub-group Analyses

Subgroups will be explored for the primary efficacy endpoint based on:

- Mutation clusters within a cohort.
- Tumor types across cohorts, such as NSCLC, breast cancer, colorectal cancer, and other cancer types regardless of mutation variant.
- Mutation variants across cohorts such as [redacted], [redacted] separate, as data permit), other [redacted] mutations, and [redacted] mutations regardless of tumor type.

Other subgroups may be explored for the primary and secondary efficacy endpoint as described in the SAP.

9.5.5. Safety Analysis

Safety will be assessed through the analysis of the reported incidence of TEAEs. Treatment emergent AEs are those with an onset on or after the initiation of therapy (on or after C1D1, first dose of study drug) and will be graded according to NCI CTCAE Version 5.0.

The TEAEs will be coded using the current version of Medical Dictionary for Regulatory Activities (MedDRA; https://www.meddra.org/about-meddra/) and summarized using system organ class and preferred term for all patients in the FA population. In addition, summaries of SAEs, TEAEs leading to treatment discontinuation, TEAEs by maximum NCI CTCAE grade, and TEAEs related to study treatment will also be presented. TEAEs will be summarized separately for Part A and Part B. In Part A, the TEAE summary will be provided by dose level, cohort, and overall, whereas in Part B, the TEAE summary will be provided by cohort, subgroups within a cohort (as appropriate), and overall. Additional TEAE analysis (such as subset or pooled analysis) could be performed if data warrants.

Other safety endpoints including laboratory results, vital signs, physical examinations, ECG findings, and cardiac function will be summarized for all patients in the FA population and presented separately for Parts A and B, respectively. Descriptive summary statistics of observed values, as well as changes from baseline, will be presented. In addition, laboratory parameters will also be summarized by shift from baseline CTCAE grade to maximum post-baseline CTCAE grade (NCI CTCAE Version 5.0).

Concomitant medications will be coded using the World Health Organization Drug Dictionary (WHO DD; https://www.who-umc.org/) and they will be listed and summarized for Part A and Part B separately.

9.5.6. Pharmacokinetics

Plasma concentrations of BDTX-189 will be used to calculate the PK parameters. The plasma PK parameters to be analyzed include $AUC_{0\text{-}INF}$, $AUC_{(0\text{-}\tau)}$, C_{max}, T_{max}, and $t_{1/2}$. These parameters will be listed by individual patient and summarized by descriptive statistics (means, medians, ranges, standard deviations, geometric means, 90% CI, and coefficients of variation) as appropriate, by treatment group/cohort. Pharmacokinetic parameters will be analyzed separately for Dose Escalation and the Food-Effect Cohort.

For the Food-Effect Cohort, the following exposure measures and PK parameters will be derived and reported: $AUC_{0\text{-}INF}$, $AUC_{0\text{-}t}$, C_{max}, T_{max}, t_{lag}, $t_{1/2}$, Cl/F, and Vd/F. Individual patient measurements as well as summary statistics (e.g., group averages, standard deviation, coefficients of variation, ranges) will be reported. Exposure measurements (AUC and C_{max}) will be log-transformed. When the 90% CI for the ratio of the log-transformed population geometric means of either $AUC_{0\text{-}INF}$ ($AUC_{0\text{-}t}$ when appropriate) or C_{max} between fed and fasted treatments fails to meet the limits of 80 – 125%, specific recommendation on the clinical significance of the food effect will be provided. The clinical relevance of any difference in T_{max} and t_{lag} will be described.

Population PK parameters including CL/F, Vd/F, and K_a will also be used to investigate the PK of BDTX-189 in Part B. Oral clearance will be used to generate estimates of BDTX-189 AUC.

Further details on the PK analyses will be documented in a separate PK analysis plan.

9.5.7. Biomarkers

On-treatment paired tumor tissue will be evaluated for changes from baseline to C2D1 in pathway signaling downregulation (e.g., ERK phosphorylation) and potential mechanisms of resistance or evidence of alternative pathway activation at the time of tumor progression (e.g., PI3K/AKT and co-occurring genomic alterations).

Blood samples collected for ctDNA extraction will be analyzed for the relationship between changes in allosteric mutations, tumor mutational burden and response to treatment. In addition, innate and acquired resistance mechanisms may be explored. Markers tested may include, but will not be limited to, allosteric *ErbB* mutations, [redacted] mutations (e.g., [redacted]), and alterations in other genes involved in [redacted] and [redacted] signaling. Similarly, the relationship between other blood-borne biomarkers and drug response and/or disease progression may be explored.

9.5.8. Quality of Life

Quality of life data will be collected via ePROs. The questionnaire data from FACT-G, NCCN FACT FBSI-16, NCCN-FACT FLSI-17, EQ-5D-5L, and Physical Function PROMIS Short Form will be scored according to the corresponding scoring manual for each questionnaire. The responses from each NCI-CTCAE question will be assessed individually. Descriptive statistics will be used to summarize the scores at each visit as well as the change from baseline over time. In addition, the change from baseline values for some scores may be assessed in a longitudinal manner using a mixed-effect model for repeated measures.

9.6. Analysis Time Points

9.6.1. Final Analysis

The final analysis for a given cohort in Part B will occur once all patients in the cohort are enrolled and have either been treated for at least 6 months or discontinued treatment for any reason prior to 6 months after their first dose of study drug.

The final analysis of the entire study will occur after all patients have discontinued the study (Part A will be separate from Part B).

9.6.2. Planned Interim Analysis

To minimize exposing patients that may be unresponsive to BDTX-189 therapy in Part B, the plan is to apply the stopping rules described in Section 9.6. The interim analysis for each cohort will be conducted once the required number of patients have been enrolled and have either undergone at least 1 postbaseline tumor assessment or discontinued treatment for any reason prior to their first postbaseline tumor assessment.

10. QUALITY ASSURANCE AND QUALITY CONTROL

10.1. Monitoring

Site monitoring shall be conducted to ensure that patient protection, study procedures, laboratory, study intervention administration, and data collection processes are of high quality and meet Sponsor, Good Clinical Practice (GCP), ICH and, when appropriate, regulatory guidelines.

10.2. Audits and Inspections

The Investigator will permit study-related quality audits and inspections by Development Innovations or its representative(s), government regulatory authorities, and the IRB(s) of all study-related documents (e.g., source documents, regulatory documents, data collection instruments, case report forms). The Investigator will ensure the capability for review of applicable study-related facilities. The Investigator will ensure that the auditor or inspector or any other compliance or Quality Assurance reviewer is given access to all study-related documents and study-related facilities.

At the discretion of the Sponsor or its delegate, Source Document Verification may be performed on partial or all data items as defined in study documents and/or plans.

Participation as an Investigator in this study implies the acceptance of potential inspection by the Sponsor or its representative, government regulatory authorities, and IRB(s)/IEC(s).

10.3. Study Committees

10.3.1. Safety Review Committee (Part A Only)

During Part A of the study, dose Escalation decisions (as per the BOIN criteria described in Section 4.3.1 and Appendix H) and determination of the RP2D and/or MTD will be evaluated by the SRC and based upon review of all safety data that occur during the first cycle of therapy (21 days), as well as longer term safety data, as appropriate. The SRC will convene approximately once monthly when there are at least 1 to 3 evaluable patients at a dose level who have completed Cycle 1 to evaluate all available safety information (including AEs and laboratory abnormalities that are not DLTs), as well as available PK and PDx information. When other patients are ongoing at the time of this review, the SRC may decide to defer their decision until these further data become evaluable.

Any patient started on treatment in error because he or she failed to comply with all of the selection criteria but who otherwise meets the criteria of an evaluable patient will be reviewed on a case-by-case basis by the SRC to determine if the patient should be included or excluded in the decision for Dose Escalation.

The SRC will make decisions with regard to escalation/de-escalation to the next planned dose or to an intermediate dose level, expand cohorts (including the Food-Effect cohort and BID schedule cohorts) to the maximum allowed, or make the decision to stop recruitment to the Dose Escalation part of the study for one or both schedules, as applicable, after review of the data from all cohorts. The decisions and decision-making of the SRC on the next dose level will be documented and provided to the Investigators prior to dosing any new patients.

Membership of the SRC will include:

- Principal Investigator from each of the investigational sites, or a medically qualified delegate from each of the investigational sites.
- Medical Safety Team representative from Sarah Cannon Development Innovations.
- Sponsor Chief Medical Officer or designee.
- Sponsor Medical Monitor.
- Sponsor Study Statistician.
- Sponsor pharmacology scientist and other technical experts, as appropriate.

10.3.2. Data Monitoring Committee (Part B Only)

To provide independent oversight of safety and efficacy, a data monitoring committee (DMC) will be instituted. The DMC will meet regularly to ensure that patient safety is carefully monitored. The DMC will convene to review relevant data determine if each stage can proceed to the next based on the futility boundaries for each cohort as described in Section 9.3.2. The DMC will convene additional ad hoc meetings if necessary. Following each meeting, the DMC will recommend continuation, modification, or discontinuation of each cohort and/or subgroup. A separate DMC charter will describe the activities of this committee in more detail.

10.3.3. Blinded Independent Central Review Committee

A blinded independent central review (BICR) committee will review all available tumor assessment scans for patients enrolled to Part B of this study. Each image will be independently reviewed. The process for review and adjudication of the images will be provided in the imaging review charter (IRC).

10.3.4. Protocol Steering Committee

The role of the Steering Committee is to provide scientific oversight of the conduct of the study. This includes oversight of the practical aspects of the study as well as ensuring that the study continues to be run in a way to ensure the study objectives can be assessed.

Specific responsibilities of the Steering Committee include, but are not limited to, the following:

- Provide overall scientific supervision of the study.
- Take steps to reduce deviations from the protocol to a minimum.
- Periodic review of the progress of the study.
- Review and discuss emerging scientific data which may impact the ongoing study and make recommendations to the Sponsor.

11. ETHICAL, FINANCIAL, AND REGULATORY CONSIDERATIONS

This research study will be conducted according to the standards of GCP outlined in the ICH E6 Tripartite Guideline and Code of Federal Regulations (CFR) Title 21 part 312, applicable government regulations, institutional research policies and procedures, and any other local applicable regulatory requirement(s).

11.1. Institutional Review Board Approval

The clinical study protocol, ICF, IB, available safety information, patient documents (e.g., study diary), patient recruitment procedures (e.g., advertisements), information about payments (i.e., Principal Investigator payments) and compensation available to the patients, and documentation evidencing the Principal Investigator's qualifications should be submitted to the IRB for ethical review and approval, if required by local regulations, prior to the study start.

The Principal Investigator/Sponsor and/or designee will follow all necessary regulations to ensure appropriate, initial, and on-going IRB study review. The Principal Investigator/Sponsor (as appropriate) must submit to and, where necessary, obtain approval from the IRB for all subsequent protocol amendments and changes to the ICF. Investigators will be advised by the Sponsor or designee whether an amendment is considered substantial or non-substantial and whether it requires submission for approval or notification only to an IRB.

Safety updates for BDTX-189 will be prepared by the Sponsor or its representative as required, for distribution to the Investigator(s) and submission to the relevant IRB.

11.2. Regulatory Approval

As required by local regulations, the Sponsor will ensure all legal aspects are covered, and approval of the appropriate regulatory bodies obtained, prior to study initiation. If required, the Sponsor will also ensure that the implementation of substantial amendments to the protocol and other relevant study documents happen only after approval by the relevant regulatory authorities.

For European Union (EU) Only: If applicable, the Principal Investigator will notify the IEC within 90 days of the end of the study (as defined in Section 4.4). If the study terminates early, the Principal Investigator must notify the IEC within 15 days of the termination. A reason for the early termination must be provided (as defined in Directive 2001/20/EC).

11.3. Study Registration

The patient must willingly consent after being informed of the procedures to be followed, the experimental nature of the treatment, potential benefits, alternatives, side-effects, risks, and discomforts. Human protection committee (Institutional Review Board/Independent Ethics Committee [IRB/IEC]) approval of this protocol and any associated informed consent forms (ICFs) is required. Eligible patients who wish to participate in the study will be enrolled in the study.

Registration must occur prior to the initiation of protocol-related procedures and therapy. Patient registration and dose level assignment will be performed by Sarah Cannon Development Innovations (Development Innovations). The Development Innovations designee will document the patient identification number, dose level (Part A) or cohort number (Part B), and date of enrollment on the registration form and in the electronic data capturing (EDC) system and will

send the completed form back to the site as soon as possible, but no later than 24 hours following the registration request.

For additional information regarding study registration, please refer to the Study Reference Manual.

11.4. Informed Consent

Informed consent is a process by which a patient voluntarily confirms his or her willingness to participate in a particular study after having been informed of all aspects of the study that are relevant to the patient's decision to participate. Informed consent is documented by means of a written, signed, and dated ICF.

The ICF will be submitted for approval to the IRB that is responsible for review and approval of the study. Each ICF must include all of the relevant elements currently required by the FDA, as well as local county authority or state regulations and national requirements.

Before recruitment and enrollment into the study, each prospective candidate will be given a full explanation of the research study. Once the essential information has been provided to the prospective candidate and the Investigator is sure that the individual candidate understands the implications of participating in this research study, the candidate will be asked to give consent to participate in the study by signing an ICF. A notation that written informed consent has been obtained will be made in the patient's medical record. A copy of the ICF, to include the patient's signature, will be provided by the Investigator to the patient.

If an amendment to the protocol substantially alters the study design or the potential risks to the patient, the patient's consent to continue participation in the study should be obtained.

11.4.1. Confidentiality

11.4.1.1. Patient Confidentiality

Confidentiality of patients' personal data will be protected in accordance with the Health Insurance Portability and Accountability Act of 1996 (HIPAA). HIPAA regulations require that, in order to participate in the study, a patient must sign an authorization form for the study that he or she has been informed of the following:

- What protected health information (PHI) will be collected from patients in this study.
- Who will have access to that information and why.
- Who will use or disclose that information.
- That health information may be further disclosed by the recipients of the information, and that if the information is disclosed, the information may no longer be protected by federal or state privacy laws.
- That the information collected about the research study will be kept separate from the patient's medical records, but the patient will be able to obtain the research records after the conclusion of the study.
- Whether the authorization contains an expiration date.

- The rights of a research patient to revoke his or her authorization.

In the event that a patient revokes authorization to collect or use his or her PHI, the Investigator, by regulation, retains the ability to use all information collected prior to the revocation of patient authorization. For patients that have revoked authorization to collect or use PHI, attempts should be made to obtain permission to collect at least vital status (i.e., that the patient is alive) at the end of their scheduled study period.

In compliance with ICH GCP guidelines and applicable parts of 21 CFR it is a requirement that the Investigator and institution permit authorized representatives of the Sponsor, Development Innovations, the regulatory authorities, and the IRB direct access to review the patient's original medical records at the site for verification of study-related procedures and data.

One measure to protect confidentiality is that only a unique study number will identify patients in the eCRF database system or other documents submitted to the Sponsor or delegate and Development Innovations. This information, together with the patient's year of birth, will be used in the database for patient identification. Patient names or addresses will not be entered in the eCRF database system. No material bearing a patient's name will be kept on file by the Sponsor or Development Innovations. Patients will be informed of their rights within the ICF.

11.4.1.2. Investigator and Staff Information

Personal data of the Investigators and sub-Investigators may be included in the Sponsor and/or Development Innovations databases and shall be treated in compliance with all applicable laws and regulations. When archiving or processing personal data pertaining to the Investigator or sub-Investigator, the Sponsor and/or Development Innovations shall take all appropriate measures to safeguard and prevent access to this data by any unauthorized party.

11.5. Financial Information

The finances for this clinical study will be subject to a separate written agreement between the Sponsor and applicable parties. Any Investigator financial disclosures as applicable to 21CFR Part 54 shall be appropriately provided.

12. RESEARCH RETENTION AND DOCUMENTATION OF THE STUDY

12.1. Amendments to the Protocol

Amendments to the protocol shall be planned, documented, and signature-authorized prior to implementation.

If an amendment to the protocol is required, the amendment will be originated and documented by the Sponsor or its representative. All amendments require review and approval of all pharmaceutical companies and the Principal Investigator supporting the study. The written amendment must be reviewed and approved by the Sponsor and submitted to the IRB at the Investigator's facility for the board's approval.

Amendments specifically involving change to study design, risk to patient, increase in dosing or exposure, patient number increase, or addition or removal of new tests or procedures shall be reviewed and approved by the IRB of record for the Investigator's facility.

The amendment will be submitted formally to the FDA or other regulatory authorities by the Sponsor as applicable, and IRB/IEC approval obtained, specifically when an increase to dosing or patient exposure and/or patient number has been proposed; or, when the addition or removal of an Investigator is necessitated.

Items requiring a protocol amendment with IRB, IEC, and/or the FDA or other regulatory authorities' approval include, but are not limited to, the following:

- Change to study design.
- Risk to patients.
- Increase in dose or patient exposure to drug.
- Patient number increase.
- Addition or removal of tests and/or procedures.
- Addition/removal of an Investigator.

It should be further noted that if an amendment to the protocol substantially alters the study design or the potential risks to the patients, their consent to continue participation in the study should be obtained.

12.2. Documentation Required to Initiate the Study

Before the study can begin, certain documentation required by FDA regulations and ICH GCP must be provided by the Investigator. The required documentation should be submitted to:

Documents required at a minimum to begin a study include, but are not limited to, the following:

- A signature-authorized protocol and contract.

- A copy of the official IRB/IEC approval of the study and the IRB/IEC members list.
- Current curricula vitae for the Principal Investigator and any associate Investigator(s) who will be involved in the study.
- Indication of appropriate accreditation for laboratories (as required) to be used in the study and the normal ranges for tests to be performed by those laboratories.
- Original Form FDA 1572 (Statement of Investigator), appropriately completed and signed.
- A copy of the IRB/IEC-approved ICF containing permission for audit by representatives of the Sponsor, Development Innovations, the IRB/IEC, and the FDA and other regulatory agencies (as applicable).
- Financial disclosure forms for all Investigators listed on Form FDA 1572 (if applicable, i.e., for covered trials).
- Verification of Principal Investigator acceptability from local and/or national debarment list(s).

12.3. Study Documentation and Storage

The Principal Investigator must maintain a list of appropriately qualified persons to whom he/she has delegated study duties and should ensure that all persons assisting in the conduct of the study are informed of their obligations. All persons authorized to make entries and/or corrections on the eCRFs are to be included on this document. All entries in the patients' eCRFs are to be supported by source documentation where appropriate.

Source documents are the original documents, data, records, and certified copies of original records of clinical findings, observations, and activities from which the patients' eCRF data are obtained. These can include, but are not limited to, hospital records, clinical and office charts, laboratory, medico-technical department and pharmacy records, diaries, microfiches, ECG traces, copies or transcriptions certified after verification as being accurate and complete, photographic negatives, microfilm or magnetic media, x-rays, NGS testing results, and correspondence.

The Principal Investigator and study staff members are responsible for maintaining a comprehensive and centralized filing system (e.g., regulatory binder or Investigator study file [ISF]) of all essential study-related documentation, suitable for inspection at any time by representatives from the Sponsor and/or applicable regulatory authorities. The ISF must consist of those documents that individually or collectively permit evaluation of the conduct of the study and the quality of the data produced. The ISF should contain at a minimum all relevant documents and correspondence as outlined in ICH GCP Section 8 and 21 CFR Part 312.57, including key documents such as the IB and any amendments, the protocol and any amendments, signed ICFs, copies of completed eCRFs, IRB/IEC approval documents, Financial Disclosure forms, patient identification lists, enrollment logs, delegation of authority log, staff qualification documents, laboratory normal ranges, and records relating to the study drug including accountability records. Drug accountability records should, at a minimum, contain information regarding receipt, shipment, and disposition. Each form of drug accountability record, at a minimum, should contain Principal Investigator name, date drug shipped/received, and the date,

quantity, and batch/code or lot number for the identity of each shipment. In addition, all original source documents supporting entries in the eCRF must be maintained and readily available.

The Sponsor shall maintain adequate investigational product and financial interest records as per 21 CFR Part 54.6 and Part 312.57 for no less than 2 years after the last marketing application has been approved by the FDA or, in the event that the marketing application has not been approved by the FDA, for no less than 2 years after the last shipment/delivery of the drug for investigational use or the drug is discontinued, and the FDA has been notified of the discontinuation.

The IRB shall maintain adequate documentation/records of IRB activities as per 21 CFR Part 56.115 for at least 3 years after completion of the research.

The Investigator shall maintain adequate records of drug disposition, case histories, and any other study-related records as per 21 CFR Part 312.62 for no less than 2 years after the last marketing application has been approved by the FDA or, in the event that the marketing application has not been approved by the FDA, for no less than 2 years after the last shipment/delivery of the drug for investigational use or the drug is discontinued, and the FDA has been notified of the discontinuation.

To enable evaluations and/or audits from regulatory authorities or from the Sponsor or its representative, the Investigator additionally agrees to keep records, including the identity of all participating patients (sufficient information to link records, e.g., eCRF and medical records), all original signed ICFs, copies of all eCRF records, SAE reporting forms, source documents, detailed records of treatment disposition, and related essential regulatory documents. The documents listed above must be retained by the Investigator for as long as needed to comply with national and international regulations (generally 2 years after discontinuing clinical development or after the last marketing approval). The Sponsor or its representative will notify the Investigator(s)/institutions(s) when the study-related records are no longer required.

If the Investigator relocates, retires, or for any reason withdraws from the study, the Sponsor or its representative must be prospectively notified. The study records must be transferred to an acceptable designee, such as another Investigator, another institution, or to Development Innovations. The Investigator must obtain the Sponsor's written permission before disposing of any records, even if retention requirements have been met. All study files will be maintained by the Sponsor or its representative throughout the study and will be transferred to the Sponsor at the conclusion of the study, if applicable.

12.4. Data Collection

The study eCRF is the primary data collection instrument for the study. Case report forms will be completed using the English language, except for patient questionnaires for non-English speaking patients, and should be kept current to enable the Sponsor to review the patients' status throughout the course of the study.

In order to maintain confidentiality, only study number, patient number, and year of birth will identify the patient in the eCRF. If the patient's name appears on any other document (e.g., laboratory report), it must be obliterated on the copy of the document to be supplied to Development Innovations and be replaced instead with the patient number and other identifier (i.e., patient initials), as allowed per institutional policy. The Investigator will maintain a

personal patient identification list (patient numbers with corresponding patient identifiers) to enable records to be identified and verified as authentic. Patient data/information will be kept confidential and will be managed according to applicable local, state, and federal regulations.

All data requested by the eCRF must be supported by and be consistent with the patient's source documentation. All missing data must be explained. When a required laboratory test, assessment, or evaluation has not been done, or an "Unknown" box is not an option on the eCRF, a note should be created verifying that the test was "Not Done," or the result was "Unknown." For any entry errors made, the error(s) must be corrected, and a note explaining the reason for change should be provided.

The Investigator will electronically sign and date the patient eCRF indicating that the data in the eCRF has been assessed. Each completed eCRF will be signed and dated by the Principal Investigator once all data for that patient is final.

12.5. Disclosure and Publication Policy

All information provided regarding the study, as well as all information collected/documented during the course of the study, will be regarded as confidential. The Sponsor reserves the right to release literature publications based on the results of the study. Results from the study will be published/presented as per the Sponsor's publication process.

For EU Only: The Sponsor will disclose the study results in the form of a clinical study report synopsis to the IEC and the applicable regulatory authorities within one year of the end of the study (as defined in Section 4.4). The format of this synopsis and that of the clinical study report should comply with ICH E3 guidelines for structure and content of a clinical study report.

Inclusion of the Investigator in the authorship of any multi-center publication will be based upon substantial contribution to the study design, the analysis or interpretation of data, or the drafting and/or critically revising of any manuscript(s) derived from the study. The Investigator acknowledges that the study is part of a multi-center study and agrees that any publication by the Investigator of the results of the study conducted at the research site shall not be made before the first multi-center publication. In the event there is no multi-center publication within 15 months after the study has been completed or terminated at all study sites and all data has been received, the Investigator shall have the right to publish his/her results from the study, subject to the notice requirements described herein and subject to acknowledgement of the Sponsor as appropriate. The Investigator shall provide the Sponsor 30 days to review a manuscript or any poster presentation, abstract or other written or oral material which describes the results of the study for the purpose only of determining if any confidential or patentable information is disclosed thereby. If the Sponsor requests in writing, the Investigator shall withhold any publication or presentation an additional 60 days solely to permit the Sponsor to seek patent protection and to remove any Development Innovations confidential information from all publications.

REFERENCES

Arcila et al. 2013

Arcila M, Khedoudja N, Chaft J, Rekhtman N, Lau C, Reva B, et al. *EGFR* exon 20 insertion mutations in lung adenocarcinomas: prevalence, molecular heterogeneity, and clinicopathologic characteristics. Mol Cancer Ther. 2013;12(2):220-9

Bose et al. 2013

Bose R, Kavuri SM, Searleman AC, et al. Activating *HER2* mutations in *HER2* gene amplification negative breast cancer. Cancer Discov. 2013;3(2):224-37.

C-BioPortal

C-BioPortal. [Internet]. Available from: http://www.cbioportal.org

Chmielecki et al. 2015

Chmielecki J, Ross JS, Wang K, et al. Oncogenic alterations in *ERBB2/HER2* represent potential therapeutic targets across tumors from diverse anatomic sites of origin. Oncologist. 2015;20(1):7-12.

Connell and Doherty 2017

Connell CM, Doherty GJ. Activating *HER2* mutations as emerging targets in multiple solid cancers. ESMO Open. 2017;2(5):e000279.

CTCAE Version 5.0

Common terminology criteria for adverse events (CTCAE): Version 5.0 (v5.0: Published 27 November 2017). Available from: https://ctep.cancer.gov/protocolDevelopment/electronic_applications/docs/CTCAE_v5_Quick_Reference_5x7.pdf

Eisenhauer et al. 2009

Eisenhauer EA, Therasse P, Bogaerts J, et al. New response evaluation criteria in solid tumours: revised RECIST guideline (Version 1.1). Eur J Cancer. 2009;45(2):228-47.

Gainor et al. 2016

Gainor JF, Shaw AT, Sequist LV, Fu X, Azzoli CG, Piotrowska Z, et al. *EGFR* mutations and ALK rearrangements are associated with low response rates to PD-1 pathway blockade in non–small cell lung cancer: a retrospective analysis. Clin Cancer Res. 2016;22(18):4585-93.

Garassino et al. 2018

Garassino MC, Cho BC, Kim JH, Mazières J, Vansteenkiste J, Lena H, et al. Durvalumab as third-line or later treatment for advanced non-small-cell lung cancer (ATLANTIC): an open-label, single-arm, phase 2 study. Lancet Oncol. 2018;19(4):521-36.

Heymach et al. 2018

Heymach JV, Negrao MV, Robichaux, et al. A Phase II trial of poziotinib in *EGFR* and *HER2* exon 20 mutant non-small cell lung cancer (NSCLC). 2018 IASLC World Conference on Lung Cancer. 2018;13(10 suppl.):S323-S324. OA02.06.

Hirsch et al. 2017

Hirsch FR, Scagliotti GV, Mulshine JL, et al. Lung cancer: current therapies and new targeted treatments. Lancet. 2017;389(10066):299-311.

Hyman et al. 2017

Hyman DM, Piha-Paul SA, Rodon J, Saura C, Shapiro GI, Quinn DI, et al. Abstract CT001: Neratinib in *HER2* or *HER3* mutant solid tumors: SUMMIT, a global, multi-histology, open-label, phase 2 "basket" study. Cancer Res. 2017;77(13 suppl);CT001

Hyman et al. 2018

Hyman DM, Piha-Paul SA, Won H, et al. HER kinase inhibition patients with *HER2*- and *HER3*-mutant cancers. Nature. 2018;554(7691):189-94.

Kim et al. 2019

Kim T, Ock CY, Kim M, Kim S, Keam B, Kim Y, et al. Phase II study of osimertinib in NSCLC patients with *EGFR* exon 20 insertion mutation: a multicenter trial of the Korean Cancer Study Group (LU17-19). Ann of Oncol. 2019:30(5 suppl):v628.

Le et al. 2020

Le X, Goldman JW, Clarke JM, Tchekmedyian N, Piotrowska Z, Chu D, et al. Poziotinib shows activity and durability of responses in subgroups of previously treated *EGFR* exon 20 NSCLC patients. J Clin Oncol. 2020:38(15 suppl):9514.

Lindeman et al. 2018

Lindeman NI, Cagle PT, Aisner DL, et al. Updated molecular testing guideline for the selection of lung cancer patients for treatment with targeted tyrosine kinase inhibitors: guideline from the College of American Pathologists, the International Association for the Study of Lung Cancer, and the Association for Molecular Pathology. J Thorac Oncol. 2018;13(3):323-58.

Liu and Yuan 2015

Liu S, Yuan Y. Bayesian optimal interval designs for Phase I clinical trials. J Soc: Series C. 2015;64:507-23.

Neumann et al. 2018

Neumann MHD, Bender S, Krahn T, et al. ctDNA and CTCs in liquid biopsy current status and where we need progress. Comput Struct Biotechnol J. 2018;16:190-95.

Oaknin et al. 2020

Oaknin A, Friedman CF, Roman LD, D'Souza A, Brana I, Bidard FC, et al. Neratinib in patients with *HER2*-mutant, metastatic cervical cancer: findings from the phase 2 SUMMIT basket trial. Gynecol Oncol. 2020;159(1):150-6.

Oxnard et al. 2013

Oxnard G, Lo P, Nishino M, Dahlberg S, Lindeman N, Butaney M, et al. Natural history and molecular characteristics of lung cancers harboring EGFR exon 20 insertions. J Thorac Oncol. 2013;8(2):179-84.

Pahuja et al. 2018

Pahuja KB, Nguyen TT, Jaiswal BS, et al. Actionable activating oncogenic *ERBB2/HER2* transmembrane and juxtamembrane domain mutations. Cancer Cell. 2018;34(5):792-806.

Park et al. 2020

Park K, John T, Kim S, Lee JS, Shu CA, Kim DW, et al. Amivantamab (JNJ-61186372), an anti-*EGFR*-MET bispecific antibody, in patients with *EGFR* exon 20 insertion (exon20ins)-mutated non-small cell lung cancer (NSCLC). J Clin Oncol. 2020;38(15 suppl):9512.

Piotrowska et al. 2020

Piotrowska Z, Wang Y, Sequist LV, Ramalingam SS. ECOG-ACRIN 5162: A phase II study of osimertinib 160 mg in NSCLC with *EGFR* exon 20 insertions. J Clin Oncol. 2020;38(15 suppl):9513.

Riely et al. 2020

Riely G, Neal J, Camidge D, Spira A, Piotrowska Z, Horn L, et al. 1261MO Updated results from a phase I/II study of mobocertinib (TAK-788) in NSCLC with *EGFR* exon 20 insertions (exon20ins). Ann of Oncol. 2020;31:S815-S816.

Robichaux et al. 2018

Robichaux JP, Elamin YY, Tan Z, et al. Mechanisms and clinical activity of an *EGFR* and *HER2* exon 20 selective kinase inhibitor in non small cell lung cancer. Nat Med. 2018;24(5):638-46.

Simon 1989

Simon, R. Optimal two-stage designs for Phase II clinical trials. Controlled Clin Trials. 1989;10(1):1–10.

Smit et al. 2020

Smit EF, Nakagawa K, Nagasaka M, Felip E, Goto Y, Li BT, et al. Trastuzumab deruxtecan (T-DXd; DS-8201) in patients with *HER2*-mutated metastatic non-small cell lung cancer (NSCLC): Interim results of DESTINY-Lung01. J Clin Oncol. 2020;38(15 suppl):9504.

Socinski et al. 2020

Socinski M, Cornelissen R, Garassino M, Clarke J, Tchekmedyian N, Molina J, et al. LBA60 ZENITH20, a multinational, multi-cohort phase II study of poziotinib in NSCLC patients with *EGFR* or *HER2* exon 20 insertion mutations. Ann of Oncol. 2020;31(4 suppl):S1188.

Stern 2012

Stern HM. Improving treatment of *HER2*-positive cancers: opportunities and challenges. Sci Transl Med. 2012;4:127.

Takeda et al. 2018

Takeda M, Sakai K, Hayashi H, et al. Clinical characteristics of non small cell lung cancer harboring mutations in exon 20 of *EGFR* or *HER2*. Oncotarget. 2018;9(30):21132-40.

Tomaras et al. 2020

Tomaras D, Lin H, Forsythe A, Crossland V, Ou SI. 1362P Clinical and real-world outcomes in patients with epidermal growth factor receptor (*EGFR*) exon 20 insertions in non-small cell lung cancer (NSCLC): meta-analysis. Ann of Oncol. 2020;31:S871.

Wen et al. 2015

Wen W, Chen WS, Xiao N, et al. Mutations in the kinase domain of the *HER2/ERBB2* gene identified in a wide variety of human cancers. J Mol Diagn. 2015;17(5):487-95.

Yuan et al. 2016

Yuan Y, Hess KR, Hilsenbeck SG, et al. Bayesian optimal interval design: A simple and well-performing design for phase I oncology trials. Clin Cancer Res. 2016;22(17):4291-301

Appendix A Eastern Cooperative Oncology Group Performance Status Criteria

ECOG Performance Status Scale		Karnofsky Performance Scale	
Grade	**Descriptions**	**Percent**	**Description**
0	Normal activity. Fully active, able to carry on all pre-disease performance without restriction.	100	Normal, no complaints, no evidence of disease.
		90	Able to carry on normal activity; minor signs or symptoms of disease.
1	Symptoms, but ambulatory. Restricted in physically strenuous activity, but ambulatory and able to carry out work of a light or sedentary nature (e.g., light housework, office work).	80	Normal activity with effort; some signs or symptoms of disease.
		70	Cares for self, unable to carry on normal activity or to do active work.
2	In bed <50% of the time. Ambulatory and capable of all self-care, but unable to carry out any work activities. Up and about more than 50% of waking hours.	60	Requires occasional assistance, but is able to care for most of his/her needs.
		50	Requires considerable assistance and frequent medical care.
3	In bed >50% of the time. Capable of only limited self-care, confined to bed or chair more than 50% of waking hours.	40	Disabled, requires special care and assistance
		30	Severely disabled, hospitalization indicated. Death not imminent.
4	100% bedridden. Completely disabled. Cannot carry on any self-care. Totally confined to bed or chair.	20	Very sick, hospitalization indicated. Death not imminent.
		10	Moribund, fatal processes progressing rapidly.
5	Dead	0	Dead

Appendix B Response Evaluation Criteria in Solid Tumors (RECIST) Version 1.1

Definitions

Response and progression will be evaluated in this trial using the RECIST v1.1 (Eisenhauer et al. 2009). Lesions are either measurable or non-measurable using the criteria provided below. The term "evaluable" in reference to measurability will not be used, as it does not provide additional meaning or accuracy.

Baseline Eligibility

Measurable Disease:	**Tumor lesions:** Must be accurately measured in at least one dimension (longest diameter in the plane of measurement is to be recorded) with a minimum size of: • 10 mm by CT by computed tomography (CT scan slice thickness no greater than 5 mm). • 10 mm caliper measurement by clinical exam (lesions that cannot be accurately measured with calipers should be recorded as non-measurable). • 20 mm by chest x-ray. **Skin lesions:** Documentation by color photography, including a ruler to estimate the size of the lesion, is recommended. **Malignant lymph nodes:** To be considered pathologically enlarged and measurable, a lymph node must be ≥15 mm in short axis when assessed by CT scan. At baseline and in follow-up, only the short axis will be measured and followed.
Non-Measurable Disease:	All other lesions, including small lesions (longest diameter <10 mm or pathological lymph nodes with ≥10- to <15-mm short axis) as well as truly non-measurable lesions. Lesions considered truly non-measurable include: leptomeningeal disease, ascites, pleural or pericardial effusion, inflammatory breast disease, lymphangitic involvement of skin or lung, abdominal masses, and abdominal organomegaly identified by physical exam that is not measurable by reproducible imaging techniques.

Target Lesions:	The most reproducible measurable lesions, up to a maximum of 2 lesions per organ and 5 lesions in total, representative of all involved organs should be identified as target lesions and recorded and measured at baseline. Target lesions should be selected on the basis of their size (lesions with the longest diameter), should be representative of all involved organs, and in addition should be those that lend themselves to reproducible repeated measurements. Pathological nodes which are defined as measurable and that may be identified as target lesions must meet the criterion or a short axis of ≥15 mm by CT scan. A sum of the diameters (longest for non-nodal lesions, short axis for nodal lesions) for all target lesions will be calculated and reported as the baseline sum diameters. If lymph nodes are to be included in the sum, then as noted above, only the short axis is added into the sum. The baseline sum diameters will be used as reference to further characterize any objective tumor response.
Non-Target Lesions:	**All other lesions should be identified as non-target lesions at baseline. Measurements of these lesions are not required, but the presence or absence of each should be noted throughout follow-up.**

Guidelines for Evaluation of Measurable Disease

All measurements should be taken and recorded in metric notation, using a ruler or calipers. All baseline evaluations should be performed as closely as possible to the beginning of treatment, as per protocol screening requirements.

The same method of assessment and the same technique should be used to characterize each identified and reported lesion at baseline and during follow-up. Imaging-based evaluation is preferred to evaluation by clinical examination when both methods have been used to assess the antitumor effect of a treatment.

Clinical Lesions:	Clinical lesions will only be considered measurable when they are superficial (e.g., skin nodules and palpable lymph nodes) and ≥10 mm in diameter. In the case of skin lesions, documentation by color photography, including a ruler to estimate the size of the lesion, is recommended.
Chest X-ray:	Lesions on chest X-ray are acceptable as measurable lesions when they are clearly defined and surrounded by aerated lung. However, a CT scan is preferable.

Conventional CT and MRI:	CT, MRI: CT is the best currently available and reproducible method to measure lesions selected for response assessment. This guideline has defined measurability of lesions on CT scan based on the assumption that CT slice thickness is 5mm or less. When CT scans have slice thickness greater than 5 mm, the minimum size for a measurable lesion should be twice the slice thickness. MRI is also acceptable in certain situations (e.g., for body scans).
Ultrasound:	When the primary trial endpoint is objective response, ultrasound should not be used to measure tumor lesions. It is, however, a possible alternative to clinical measurements of superficial palpable lymph nodes, subcutaneous lesions, and thyroid nodules. Ultrasound may also be useful to confirm the complete disappearance of superficial lesions usually assessed by clinical examination.
Endoscopy and Laparoscopy:	Use of endoscopy and laparoscopy for objective tumor evaluation has not yet been fully and widely validated. Therefore, use of these techniques for objective tumor response should be restricted to validation purposes in specialized centers. Such techniques can be useful in confirming complete pathological response when biopsies are obtained.
Tumor Markers:	Tumor markers alone cannot be used to assess response. If markers are initially above the upper limit of normal, they must normalize for a patient to be considered in complete clinical response when all lesions have disappeared.
Cytology and Histology:	Cytology and histology can be used to differentiate between partial response (PR) and complete response (CR) in rare cases (e.g., after treatment to differentiate between residual benign lesions and residual malignant lesions in tumor types such as germ cell tumors).

Response Criteria

Evaluation of Target Lesions

Complete Response (CR):	Disappearance of all target lesions.
Partial Response (PR):	At least a 30% decrease in the sum of diameters of target lesions, taking as reference the baseline sum diameters.
Stable Disease (SD):	Neither sufficient shrinkage to qualify for PR nor sufficient increase to qualify for PD, taking as reference the smallest (nadir) sum of diameters since the treatment started.
Progressive Disease (PD):	At least a 20% increase in the sum of the diameters of target lesions, taking as reference the smallest (nadir) sum since the treatment started, or the appearance of one or more new lesions. Requires not only 20% increase, but absolute increase of a minimum of 5 mm over sum.

Evaluation of Non-Target Lesions

Complete Response (CR):	Disappearance of all non-target lesions and normalization of tumor markers. All lymph nodes must be non-pathological in size (<10 mm short axis).
Non-CR/Non-PD:	Persistence of one or more non-target lesions and/or persistence of tumor marker level above the normal limits.
Progressive Disease (PD):	Appearance of one or more new lesions and/or unequivocal progression of existing non-target lesions. When the patient also has measurable disease, to achieve "unequivocal progression" on the basis of the non-target disease, there must be an overall level of substantial worsening in non-target disease such that, even in presence of SD or PR in the target disease, the overall tumor burden has increased sufficiently to merit discontinuation of therapy.

Evaluation of Best Overall Response

The best overall response is the best response recorded from the start of the treatment until disease progression/recurrence (taking as reference for PD the smallest measurements recorded since the treatment started). In general, the patient's best response assignment will depend on the achievement of both measurement and confirmation criteria.

Confirmation of response (by repeat scans after 4 weeks or as specified in the protocol) is required for trials in which response rate is the primary endpoint but is not required in randomized trials or trials with primary survival endpoints (i.e., where response is not a primary endpoint).

Note that a best overall response of SD requires an assessment of SD or better at the time of the first protocol-specified post-baseline tumor assessment (i.e., 42 days +/- 3 days after first dose) or later.

Target Lesions	Non-Target Lesions	New Lesions	Overall Response
CR	CR	NO	CR
CR	NON-CR/NON-PD	NO	PR
CR	NE	NO	PR
PR	NON-CR/NON-PD OR NE	NO	PR
SD	NON-CR/NON-PD OR NE	NO	SD
NOT ALL EVALUATED	NON-PD	NO	NE
PD	ANY	YES OR NO	PD
ANY	PD	YES OR NO	PD
ANY	ANY	YES	PD

In some circumstances, it may be difficult to distinguish residual disease from normal tissue. When the evaluation of a CR depends upon this determination, it is recommended that the residual lesion be investigated by fine needle aspirate or biopsy to confirm the CR status.

When nodal disease is included in the sum of target lesions, and the nodes decrease to "normal" size (<10 mm), they may still have a measurement reported on scans. This measurement should be recorded even though the nodes are normal in order not to overstate progression, should it be based on increase in size of the nodes. As noted earlier, this means that patients with CR may not have a total sum of "zero" on the eCRF.

Appendix C Guidelines for Women of Childbearing Potential and Fertile Male Patients

Acceptable Contraception Methods:

Women of childbearing potential, defined as all women physiologically capable of becoming pregnant, must use highly effective contraception during the study and for at least 90 days after stopping treatment.

Highly effective contraception is defined as either:

True Abstinence	When this is in line with the preferred and usual lifestyle of the patient. Periodic abstinence (e.g., calendar, ovulation, symptothermal, post-ovulation methods) and withdrawal are not acceptable methods of contraception.
Sterilization	When a woman of childbearing potential has had surgical bilateral oophorectomy (with or without hysterectomy) or tubal ligation at least six weeks prior to study entry. In case of oophorectomy alone, only when the reproductive status of the woman has been confirmed by follow-up hormone level assessment.
Male Partner Sterilization	When there is appropriate post-vasectomy documentation of the absence of sperm in the ejaculate.

Use of the following:

Placement of an intrauterine device (IUD) or intrauterine system (IUS) or established use of oral, injected or implanted hormonal methods of contraception, bilateral tubal occlusion, vasectomized partner.

Fertile male patients, defined as all males physiologically capable of conceiving offspring, with female partners of childbearing potential must use condoms plus a spermicidal agent during the study treatment period and for at least 90 days after the last dose of study drug, and should not father a child during this period.

Male patients must also refrain from donating sperm during their participation in the study.

Unacceptable Contraception Methods for women of childbearing potential include:

- IUD progesterone T.
- Female condom.
- Natural family planning (rhythm method) or breast-feeding.
- Fertility awareness.
- Withdrawal.
- Cervical shield.

Pregnancies

To ensure patient safety, each pregnancy in a patient on study treatment must be reported to the Development Innovations Safety Department within 24 hours of learning of its occurrence. The

pregnancy should be followed up for 3 months after the termination of the pregnancy to determine outcome, including spontaneous or voluntary termination, details of the birth, and the presence or absence of any birth defects, congenital abnormalities, or maternal and/or new-born complications.

Pregnancy should be recorded on a Clinical Study Pregnancy Form and reported by the Investigator to the **Development Innovations Safety Department**. Pregnancy follow-up should be recorded on the same form and should include an assessment of the possible relationship to the study drug of any pregnancy outcome. Any SAE experienced during pregnancy must be reported on the SAE paper report form.

Pregnancy outcomes must be collected for the female partners of any males who took study treatment in this study. Consent to report information regarding these pregnancy outcomes should be obtained from the mother.

Women Not of Childbearing Potential are defined as follows:

- Women are considered post-menopausal and not of childbearing potential if they have had continuous 12 months of natural (spontaneous) amenorrhea with an appropriate clinical profile (e.g., age appropriate, history of vasomotor symptoms).
- Women who are permanently sterilized (e.g., tubal occlusion, hysterectomy, bilateral salpingectomy, bilateral oophorectomy).
- Women who are >45 years-of-age, not using hormone-replacement therapy and who have experienced total cessation of menses for at least 12 months OR who have a follicle stimulating hormone (FSH) value >40 mIU/mL and an estradiol value <40 pg/mL (140 pmol/L).
- Women who are >45 years-of-age, using hormone-replacement therapy and who have experienced total cessation of menses for at least 1 year OR who have had documented evidence of menopause based on FSH >40 mIU/mL and estradiol <40 pg/mL prior to initiation of hormone-replacement therapy.

Appendix D New York Heart Association Classification of Cardiac Disease

The following table presents the New York Heart Association classification of cardiac disease.

Class	Functional Capacity	Objective Assessment
I	Subjects with cardiac disease but without resulting limitations of physical activity. Ordinary physical activity does not cause undue fatigue, palpitation, dyspnea, or anginal pain.	No objective evidence of cardiovascular disease.
II	Subjects with cardiac disease resulting in slight limitation of physical activity. They are comfortable at rest. Ordinary physical activity results in fatigue, palpitation, dyspnea, or anginal pain.	Objective evidence of minimal cardiovascular disease.
III	Subjects with cardiac disease resulting in marked limitation of physical activity. They are comfortable at rest. Less than ordinary activity causes fatigue, palpitation, dyspnea, or anginal pain.	Objective evidence of moderately severe cardiovascular disease.
IV	Subjects with cardiac disease resulting in inability to carry on any physical activity without discomfort. Symptoms of heart failure or the anginal syndrome may be present even at rest. If any physical activity is undertaken, discomfort is increased.	Objective evidence of severe cardiovascular disease.

Source: The Criteria Committee of New York Heart Association. Nomenclature and Criteria for Diagnosis of Diseases of the Heart and Great Vessels. 9th Ed. Boston, MA: Little, Brown & Co; 1994:253-256.

Appendix E Common Inhibitors and Inducers of Cytochrome P450 Isozymes

The following list describes medications and foods that are common inhibitors and inducers of CYP3A4.

Consult the following link for a complete list: http://medicine.iupui.edu/clinpharm/ddis.

Drugs known to be strong inhibitors/inducers of CYP3A4 are excluded within 14 days before the start of treatment through permanent discontinuation of study treatment.

Some of the medications listed below may be allowed at the Investigator's discretion after approval by the Medical Monitor when the patient has unmet medical need to continue receiving prohibited medication(s), no suitable alternative treatments are available, and the benefit-risk ratio is acceptable in the Investigator's opinion.

Cytochrome P450 CYP3A4 Inhibitors and Inducers

Inhibitors	Inducers
STRONG Boceprevir, clarithromycin, grapefruit juice, indinavir, itraconazole, ketoconazole, lopinavir/ritonavir, mibefradil, nefazodone, nelfinavir, posaconazole, ritonavir, saquinavir, telaprevir, telithromycin **MODERATE** Aprepitant, cimetidine, ciprofloxacin, clotrimazole, conivaptan, crizotinib, cyclosporine, dronedarone, erythromycin, fluconazole, fluvoxamine, imatinib, verapamil, voriconazole	**STRONG** Apalutamide, carbamazepine, enzalutamide, mitotane, phenytoin, rifampin, St. John's wort **MODERATE** Bosentan, efavirenz, etravirine, phenobarbital, primidone

Appendix F Drugs That Induce Torsades De Pointes

Drugs with a known risk of Torsades de pointes should be avoided for all patients from screening through permanent discontinuation of study treatment.

Some of the medications listed may be allowed at the Investigator's discretion after approval by the Medical Monitor when the patient has unmet medical need to continue receiving prohibited medication(s), no suitable alternative treatments are available, and the benefit-risk ratio is acceptable in the Investigator's opinion.

CredibleMeds® (www.crediblemeds.org) is the standard reference for drugs with known or possible risk of Torsades de Pointes. Since CredibleMeds® constantly assesses new drug information and updates its lists, sites should go directly to the crediblemeds.org website in real-time for reference. Patients receiving drugs listed in the "known" or "possible" categories at the time of eligibility assessment are prohibited from 14 days before the start of treatment until permanent discontinuation of treatment.

Appendix G Operating Characteristics of the Bayesian Optimal Interval Design

Operating Characteristics of the BOIN Design for QD Dosing Schedule

	Dose Level (mg)								Mean # of Patients	% Early Stopping
	1 (25)	**2 (50)**	**3 (100)**	**4 (200)**	**5 (400)**	**6 (800)**	**7 (1200)**	**8 (1600)**		
					Scenario 1					
True DLT Rate	0.11	**0.30**	0.46	0.48	0.51	0.53	0.56	0.58		
Selection %	19.3	**53.5**	16.7	6.5	2.6	0.9	0.2	0.2		0.1
# Pts Treated	4.9	**9.5**	5.6	2.6	1.3	0.5	0.2	0.1	24.70	
					Scenario 2					
True DLT Rate	0.04	0.08	0.12	0.16	**0.30**	0.47	0.54	0.60		
Selection %	0.1	1.4	4.8	22.3	**50.0**	16.8	3.6	1.0		0.0
# Pts Treated	1.3	1.8	2.7	5.7	**8.8**	5.0	1.9	0.7	27.92	
					Scenario 3					
True DLT Rate	0.04	0.07	0.10	0.12	0.15	**0.30**	0.48	0.68		
Selection %	0.4	0.8	2.3	4.5	19.9	**54.8**	16.0	1.3		0.0
# Pts Treated	1.2	1.6	2.2	2.7	5.2	**9.2**	5.2	1.3	28.59	
					Scenario 4					
True DLT Rate	0.02	0.04	0.06	0.08	0.10	0.12	**0.30**	0.45		
Selection %	0.0	0.1	0.8	1.9	3.2	20.5	**51.7**	21.8		0.0
# Pts Treated	1.1	1.3	1.6	2.0	2.3	5.3	**8.9**	5.9	28.33	

Abbreviations: DLT = dose-limiting toxicity; Pts = patients.

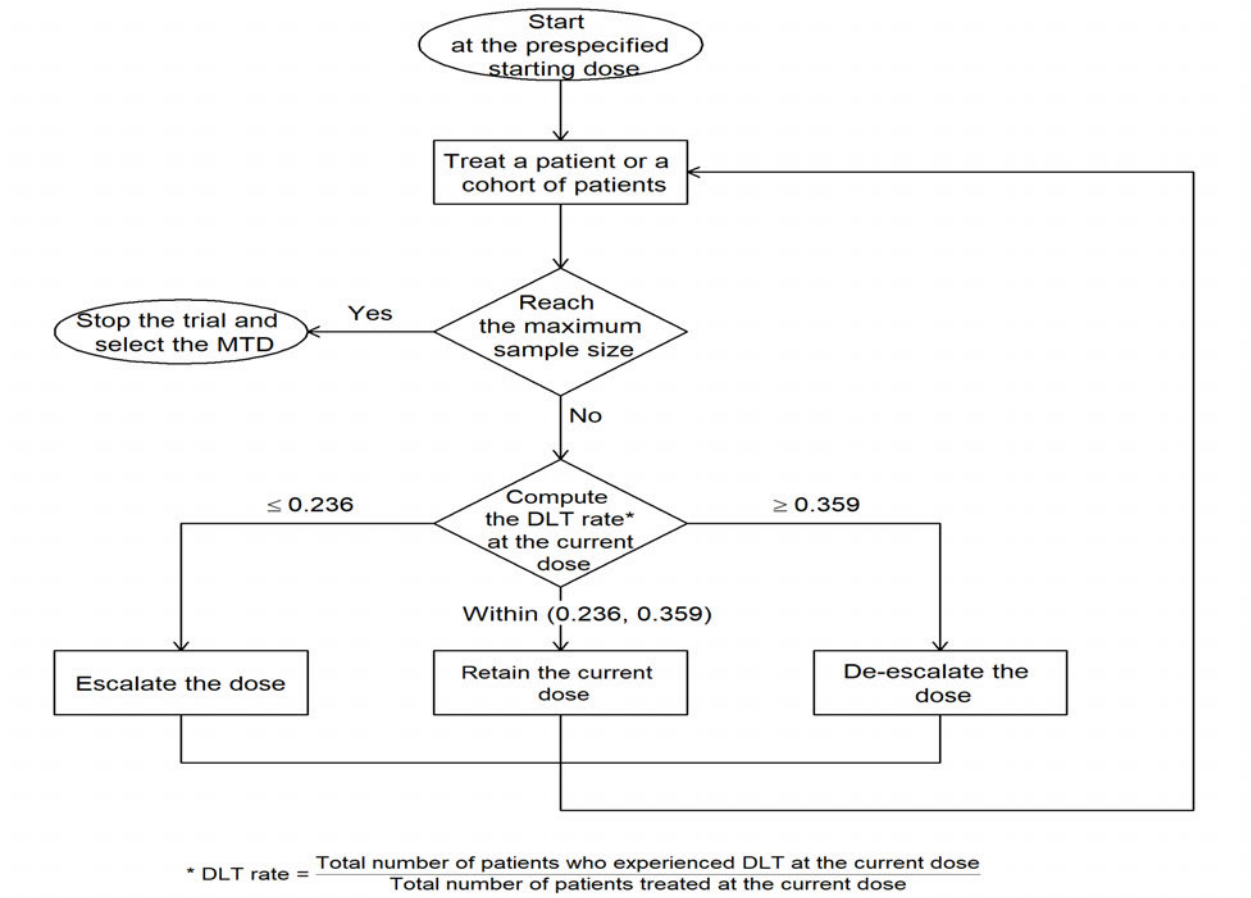
Operating Characteristics of the BOIN Design for BID Dose Schedule

	Dose Level				Number of Patients	% Early Stopping
	1	2	3	4		
Scenario 1						
True DLT Rate	0.30	0.47	0.55	0.64		
Selection %	68.1	16.1	2.3	0.0		13.5
# Pts Treated	12.1	5.1	0.8	0.1	18.12	
Scenario 2						
True DLT Rate	0.11	0.30	0.45	0.67		
Selection %	21.8	55.0	21.2	1.6		0.4
# Pts Treated	7.4	9.7	4.7	0.8	22.55	
Scenario 3						
True DLT Rate	0.02	0.13	0.30	0.47		
Selection %	0.6	24.0	55.5	19.9		0.0
# Pts Treated	3.5	7.1	8.8	4.2	23.56	
Scenario 4						
True DLT Rate	0.05	0.10	0.15	0.30		
Selection %	0.9	5.4	26.3	67.4		0.0
# Pts Treated	3.7	4.7	6.3	9.0	23.75	

Abbreviations: DLT = dose-limiting toxicity; Pts = patients.

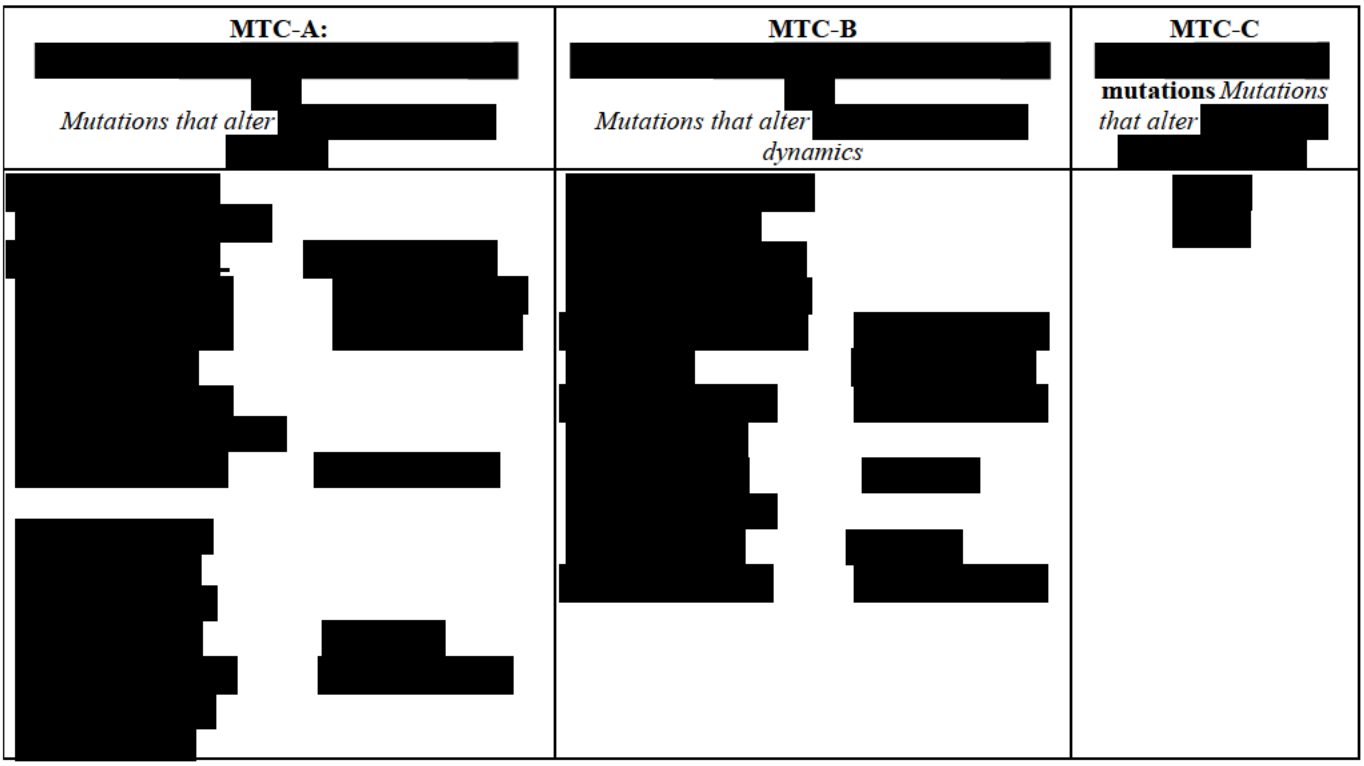
Appendix H Flowchart for Trial Conduct

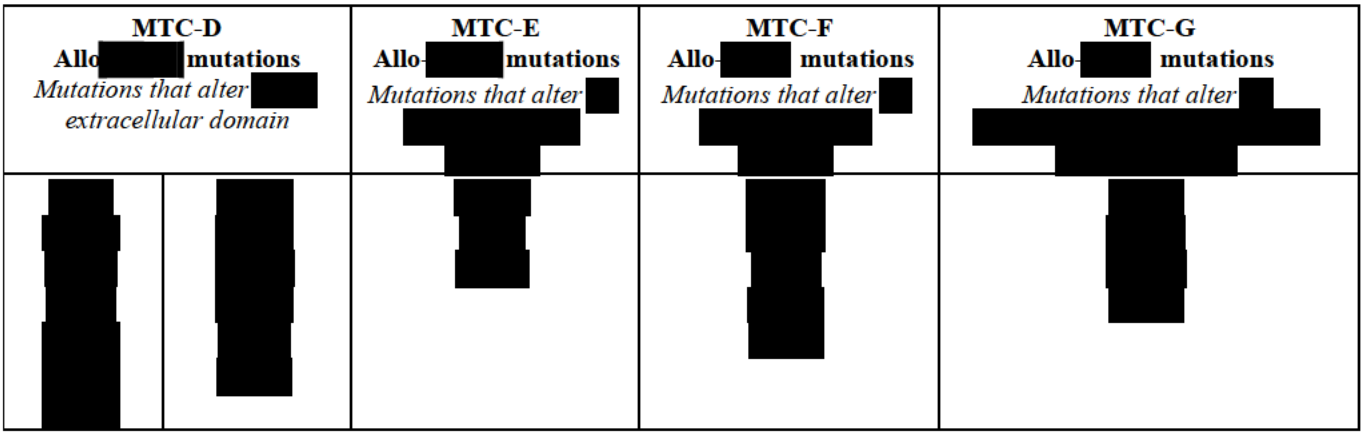
Flowchart for Trial Conduct Using the BOIN Design



Abbreviations: BOIN = Bayesian optimal interval; DLT = dose-limiting toxicity; MTD = maximum tolerated dose

Appendix I Eligible [redacted] Mutations, [redacted] Point Mutations, and Allosteric [redacted] Mutations





Most Prevalent Mutations in each category are in Bold

Note: Eligible mutations will be determined by a validated next-generation sequencing (NGS) test routinely used by each institution and performed in a Clinical Laboratory Improvement Amendments (CLIA)-certified or equivalent laboratory. In the rare event a patient presents with more than 1 eligible mutation, the following allocation is the priority: NSCLC patients with an [redacted] mutation will be assigned to MTC-A or -B, respectively, regardless of co-occurring mutation; any other solid tumor patient will be allocated according to the following priority: MTC-D, MTC-E, MTC-F, MTC-G.

Appendix J Adverse Events Severity Grading Guideline

Adverse events will be reported at the highest experienced. Adverse events severity will be graded according to the National Cancer Institute Common Terminology Criteria for Adverse Events (NCI CTCAE v 5.0.) A copy of the document will be provided to investigational sites and an electronic version is available at:

https://ctep.cancer.gov/protocolDevelopment/electronic_applications/docs/CTCAE_v5_Quick_Reference_8.5x11.pdf

Events not listed in NCI CTCAE will be graded according to the criteria described in the table below:

Severity Grading Guideline for Adverse Events not listed in NCI CTCAE V5.0

Adverse Events not Listed in NCI CTCAE V5.0	
Grade	**Description**
1	Mild; Asymptomatic or mild symptoms; Clinical or diagnostic observations only; Intervention not indicated
2	Moderate; Minimal, local or noninvasive intervention indicated; Limiting age-appropriate instrumental ADL*
3	Severe or medically significant but not immediately life threatening; Hospitalization or prolongation of hospitalization indicated; Disabling; Limiting self-care ADL**
4	Life-threatening consequences; Urgent intervention indicated
5	Death related to AE

Abbreviations: ADL = activity of daily living; AE = adverse event
Adapted from NCI-CTCAE V5.0
Note: A Semicolon indicates 'or' within the description of the grade.
*Instrumental ADL refer to preparing meals, shopping for groceries or clothes, using the telephone, managing money, etc.
**Self-care ADL refer to bathing, dressing and undressing, feeding self, using the toilet, taking medications, and not bedridden.

Appendix K Clinical Protocol Amendment Summary of Changes

Amendment 3, Version 4.0, 08 June 2021		
Section(s)	**Description of Change**	**Rationale for Change**
Global Changes	The study protocol document has been placed in a new clinical protocol template to improve flow and readability. In addition, new content was added or the content was revised based on emerging data. It should be noted not all of the changed content was transcribed verbatim into this summary. Primary safety, eligibility and toxicity details are mostly described. Please review the track change version for all section renumbering and content updates and revisions. The following sections were added: **Section 1.1.1** ***Allosteric ErbB Oncogenic Mutations: Clustering at Structural Hotspots*** **Section 1.1.2** ***Approved Therapies for Patients with Allosteric ErbB Oncogenic Mutations*** **Section 1.1.3** ***Investigational Therapies for Patients with Allosteric ErbB Oncogenic Mutations.*** **Section 1.1.5.2** ***Pharmacokinetics*** was added. **Section** ***1.1.6 Toxicology*** was updated. **Section 1.1.7** ***Clinical Experience*** was updated. ***Sections* 4.0 *through* 12 *were moved and renumbered.*** ***Figure 3: Anchor (red) and Tail (blue)*** [redacted] ***Mutations Expressed in Human Tumors*** was updated ***Figure 4: Cellular Potency of BDTX-189*** was updated ***Figure 5: In Vitro IC50 and In Vivo (50 mpk acute oral dose dosing) Activity Across a Range of*** [redacted] ***and*** [redacted] ***Mutants*** was updated ***Figure 8: Relationship between BDTX-189 dose (mg/day QD) and exposure (C1D1 C_{max} and AUC_{0-t})*** was updated Throughout the protocol the word ***"subject" has been replaced with the word "patient"***	Added to define and differentiate anchor and tail mutations in mutational clusters, and to describe the safety and efficacy limitations of approved and investigational therapies for patients with allosteric ErbB Oncogenic Mutations.
Title Page, Page 3, and Page 5	**BDTX-189 Key Contact and Medical Monitor Information** The Key Sponsor Contact for Black Diamond has changed to: ***Rachel Humphrey, MD*** ***Chief Medical Officer*** The Medical Monitor for Black Diamond has changed to: ***Melinda Merchant, MD, PhD.*** ***Vice President Clinical Development and Medical Affairs***	Updates made to Sponsor contact information

Amendment 3, Version 4.0, 08 June 2021		
Section(s)	**Description of Change**	**Rationale for Change**
Title Page, Page 3, and Page 4	**EUDRACT NUMBER: 2020-005492-12**	Update
Title Page, Page 3, and Page 4	**IND NUMBER: 144515**	Update
Synopsis: Study Duration	Modified to clarify patients may continue to receive treatment until disease progression or unacceptable toxicity.	Clarification
Synopsis: Study Centers	Revised to reflect an increase in the number of centers Part A: Phase 1 - ***approximately 20 centers in the United States (US) and approximately 20 centers from select European Union (EU) countries*** Part B: Phase 2 - ***approximately 80 centers globally***	Increase in number of participating sites
Synopsis: Numbers of Patients	***A total of approximately 619 patients are anticipated to be enrolled in this study. In Part A, the Phase 1 portion of the trial, approximately 128 patients may be enrolled. In Part B, the Phase 2 portion of the trial, up to approximately 491 patients will be enrolled.***	Increase in number of patients to be enrolled.
Section 1.2	**Section 1.2** was updated to provide the data from ***AEs observed during the dose-escalation portion of the ongoing Phase 1 study***. These include: ***Gastrointestinal disorders including nausea, vomiting and diarrhea, some at Grade 3 severity*** ***Hepatic test abnormality, including Grade 3 ALT and/or AST elevations and Grade 2 blood bilirubin elevation***	Updated to reflect available clinical data
Section 1.2.1	**Section 1.2.1** Precautions and Risks Associated with BDTX-189 was added. ***Dose-limiting toxicities have included reversible Grade 3 ALT/AST increases, Grade 3 diarrhea (lasting >24 hours), Grade 3 dehydration, and intolerable Grade 2 and Grade 3 nausea and vomiting. Gastrointestinal disorders increased in frequency and severity with increasing doses. A total of 72% of the patients across all dose levels experienced treatment-related gastrointestinal TEAEs, of which 19% were Grade 3 severity. A total of 14% experienced a drug-related skin disorder TEAE. No patients have experienced a treatment-related TEAE of Grade 4 or 5 severity.***	Revised to reflect available clinical data
Section 2 Study Objectives and Endpoints, Table 4 Synopsis: Objectives	Text related to study endpoint information was removed from the study objectives section as it was duplicative ***(e.g., ~~evaluation of OR~~).***	Editorial changes made to improve clarity and to correct errors
	Patient reported outcomes have been added as a secondary objective and endpoint for Part B.	New secondary objective and endpoint added to Part B to analyzing patient outcomes.

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Section(s)	**Description of Change**	**Rationale for Change**
	Endpoints were updated to add investigator-assessed objective response as a secondary endpoint to Part A.	Capture preliminary efficacy and antitumor activity
	A secondary endpoint to Part B was revised to specify: Objective response (***Investigator assessed***), DOR (***Investigator and BICR assessed***), DCR (***Investigator and BICR assessed***), and PFS (***Investigator and BICR assessed***), per RECIST v1.1; ***and OS***	Assess additional measures of efficacy and antitumor activity of BDTX-189 as a single agent
	Pharmacodynamics was listed as a secondary objective in Table 4, this was in error and has been removed, as ***PDx is exploratory.***	Correction
Section 3.1 Inclusion Criteria	**Inclusion criteria (IC)** #7 for prior therapies, added text to clarify that ***pneumonitis must have been totally resolved***.	Clarification
Synopsis: Main Inclusion Criteria	**IC #8** clarified that ***WOCBP*** must have a negative pregnancy test ***7 days prior to screening*** **IC #9** clarified that highly effective contraception must be used during the study and for **at least 90 days** after stopping treatment.	Clarification
	IC #10 (formerly #4) is for patients enrolling onto **Part A only**. ***No standard therapy available according to the Investigator.***	Clarification
	IC #11 Part A Dose-Escalation portion: has been revised to allow patients ***with solid tumors*** with alterations that may be associated with antitumor activity based on preclinical data for BDTX-189 such as: ***a.*** [redacted] ***or*** [redacted] ***mutation(s)*** ***b.*** [redacted] ***or*** [redacted] ***mutation*** ***c.*** [redacted] ***amplified or overexpressing tumor*** ***d.*** [redacted] ***mutation***	Preclinical data was used to update the solid tumor patient population
	Mutations must have been determined by a validated NGS test routinely used by each institution using tissue and/or plasma and performed in a CLIA-certified or equivalent laboratory. A list of eligible validated oncogenic mutations from 1 of the 7 MTCs is provided in Appendix I. **Part A Safety Expansion Only** **IC #12** ***Patients with one of the following mutations and tumor pairs:*** [redacted] ***mutation in patients with NSCLC, breast cancer, biliary tract cancer, or cervical cancer*** [redacted] ***or*** [redacted] ***mutation in patients with NSCLC*** [redacted] ***amplified or overexpressing tumor from the following cancer types: breast, gastric, gastroesophageal, colorectal,***	To better characterize antitumor activity and efficacy

Amendment 3, Version 4.0, 08 June 2021		
Section(s)	**Description of Change**	**Rationale for Change**
	endometrial, biliary tract, cancer of unknown primary (CUP), and NSCLC **Mutations must have been determined by a validated NGS test routinely used by each institution using tissue and/or plasma and performed in a CLIA-certified or equivalent laboratory. A list of eligible validated oncogenic mutations from 1 of the 7 MTCs is provided in Appendix I.** **Note: The Sponsor reserves the right to prioritize tumor/genomic alteration pairs and to cap enrollment for any of these based on the Sponsor's portfolio decision-making process.** **IC #13** added to required ***(mandatory) archival tumor tissue or pretreatment biopsy if archival tissue is not available.*** This is only applicable to patient's enrolling into **the Safety Expansion cohort(s) of Part A**. **IC #14** added ***measurable disease according to RECIST v***1.1. This is only applicable to patient's enrolling onto the **Part A Safety Expansion Only**.	
Section 3.1 Inclusion Criteria Synopsis: Main Inclusion Criteria	**PART B Only** **IC #15** permissible prior therapies for solid tumors has been added and is applicable **for Part B Only.** ***Patients with locally advanced or metastatic:*** ***a. NSCLC who have received at least one prior platinum-containing regimen (with or without an anti-PD-[L]1 antibody) and no more than 2 prior regimens for advanced NSCLC. Patients with no prior therapy who refuse standard therapy may also be eligible following discussion and approval by the Sponsor's Medical Monitor.*** ***b. Solid tumor other than NSCLC who have received at least one and no more than 3 prior regimens for advanced cancer.***	Patient population clarification

Amendment 3, Version 4.0, 08 June 2021		
Section(s)	**Description of Change**	**Rationale for Change**
	IC#16 clarification made for patients enrolling onto Part B that they must have a solid tumor harboring an [redacted] ***mutation,*** or an [redacted] **mutation,** or an [redacted] mutation. ***Mutations must have been determined by a validated NGS test routinely used by each institution using tissue and/or plasma and performed in a CLIA-certified or equivalent laboratory. A list of eligible validated oncogenic mutations from 1 of the 7 MTCs is provided in Appendix I.*** Revised to only allow certain types of solid tumors with mutations and MTCs that may be associated with antitumor activity based on preclinical data. **Eligible patients will be assigned to one of the 5 following cohorts:** **Cohort 1**: NSCLC with ***an*** [redacted] mutation ***from MTC-A***. **Cohort 2**: ***NSCLC with an*** [redacted] ***mutation from MTC-B or point mutation from MTC-C.*** ***Cohort 3:*** Breast cancer with an [redacted] mutation ***from MTC-B, MTC-C, MTC-D, MTC-E, or MTC-F.*** **Cohort 4**: ***NSCLC, biliary tract cancer, or cervical cancer with an*** [redacted] mutation ***from MTC-D***. **Cohort 5**: ***Any solid tumor type with any allosteric ErbB mutation from any of the 7 MTCs (MTC-A to MTC-G), excluding patients who are otherwise eligible for*** **Cohorts 1-*4*.** ***Note: The Sponsor reserves the right to prioritize Cohorts (ie, tumor/mutation pairs) and to cap enrollment for any Cohort based on the Sponsor's portfolio decision-making process.***	Patient population clarification
Section 3.2 Exclusion Criteria Synopsis: Main Exclusion Criteria	**Exclusion criteria (EC) #1** revised: for creatinine revised patients who have elevated serum ***AND*** calculated creatinine will be excluded.	Patient safety
	EC #4 leptomeningeal or untreated central nervous system (CNS) malignancies (primary or metastatic); patients with asymptomatic CNS metastases who have undergone surgery or radiotherapy ***4 weeks prior to C1D1***and who are on a dose of prednisone of no more than 10 mg or equivalent will be eligible for ***Part A*** the trial	Clarification
	EC #5 antitumor therapy revised to exclude ***tyrosine kinase inhibitors or monoclonal antibodies*** within 14 days prior to baseline. Further revised to exclude antineoplastic monoclonal antibodies ***within 21 days or checkpoint immunotherapy within 3 months prior to baseline.***	Clarification

Amendment 3, Version 4.0, 08 June 2021		
Section(s)	**Description of Change**	**Rationale for Change**
	EC #6 through EC #9 and EC #12.	EC numbering rearranged
Section 3.2 Exclusion Criteria Synopsis: Main Exclusion Criteria	**EC #8** added mutations to known tumor-harboring resistance mutations including [redacted] or [redacted] mutations or [redacted] ***mutations.***	Updated based on emerging data
	EC #9 Second bullet added as follows: ***Patients with an NGS test (tissue or plasma) obtained within 8 weeks of Baseline which does not include any mutations listed in Exclusion Criteria 7 or 8 may be considered after discussion with the Sponsor Medical Monitor.***	Clarification
	EC #17 Taking medications that are known ***to have*** a risk to cause ***QT interval and/or*** Torsades de pointes within 14 days before the start of treatment through permanent discontinuation of study treatment (Appendix F)	Clarification
Section 4 Study Design Section 4.1 Part A (Phase 1 – Dose Escalation and Safety Expansion) Synopsis: Study Design	**Section 4.1** Part A was revised as follows: Part A (Phase 1) is designed to determine the RP2D and schedule of BDTX-189 as a single agent. The RP2D will be based on the safety, tolerability, PK, food effect, and preliminary antitumor activity of BDTX-189 and ***will not exceed the MTD.*** BDTX-189 will be given ***PO*** QD on a 21-day schedule in escalating doses. ***Accelerated*** titration ***has been*** performed with single-patient cohorts at 25, 50, 100, and 200 mg QD ***followed by multiple-patient cohorts of 400, 800, and 1200 mg QD in fasting state. After the SRC*** determined ***1200 mg QD fasting exceeded the MTD, 800 mg, and 1000 mg QD administered with a meal (i.e., NF) were evaluated.***	To provide preliminary information for Part A Dose Escalation. To clarify the Safety Expansion
	In addition, a parallel, dose-escalation of BDTX-189 being administered BID is being evaluated. The SRC determined to initiate the BID evaluation at 800 mg, which was subsequently de-escalated to 600 mg BID. A dose of 400 mg BID will also be evaluated. ***The Safety Expansion cohort(s) at the MTD or lower dose for the QD and/or BID schedule of up to approximately 48 additional patients (including a minimum of 12 patients who may receive the smaller and reformulated 200 mg tablet strength*** will be enrolled to further evaluate the safety, PK, and preliminary efficacy of BDTX-189 while administrative steps are taken to open enrollment in Part B of the study. ***Patients in Part A who initiated treatment with the larger 200 mg tablet may be switched to the smaller and reformulated 200 mg tablet at the beginning of their subsequent cycles as instructed by the Sponsor.*** ***After the SRC deemed the 400 mg QD dose regimen was tolerable, a fed (high- or low-fat meal)***/fasted randomized	

Amendment 3, Version 4.0, 08 June 2021		
Section(s)	**Description of Change**	**Rationale for Change**
	crossover, single-dose, lead-in phase ***was initiated (in up to 16 PK-evaluable patients)*** to assess the effect of food on the PK of ***400 mg*** BDTX-189 (see Table 1 and Section 5.3.1). Enrollment of the Food-Effect cohort and next dose cohort ***(800 mg QD Dose Expansion cohort)*** was done in parallel with priority for enrollment given to ***the 800 mg QD cohort.*** Patients in Part A who terminate participation in the study for any reason other than DLTs before completing Cycle 1 and patients who do not receive at least 75% of the planned doses of BDTX-189 in Cycle 1 for any reason other than DLT-related interruptions will be considered nonevaluable ***(NE) for DLTs***, and ***additional patients may be enrolled to ensure an adequate number of DLT-evaluable patients. Additional patients may also be enrolled if there are patients who are deemed NE for food effect PK assessment.*** ***In total approximately 128 patients will be enrolled in Part A.*** Please refer to the section to review the added content.	
Section 4.2 Part B (Phase 2) Synopsis: Study Design	**Section 4.2** Part B (Phase 2) The design of Part B has been revised to enroll solid tumor patients harboring an ***oncogenic*** [redacted] mutation or an [redacted] or [redacted] mutation from one of the 7 MTCs (Appendix I). Eligible patients will be assigned to one of the following 5 cohorts: **Cohort 1**: NSCLC with ***an*** [redacted] ***mutation from MTC-A*** ***Cohort 2: NSCLC with an*** [redacted] ***mutation from MTC-B or point mutation from MTC-C*** **Cohort 3**: Breast cancer with an allosteric [redacted] mutation ***from MTC-B, MTC-C, MTC-D, MTC-E, or MTC-F*** **Cohort 4**: ***NSCLC, biliary tract cancer, or cervical cancer with an allosteric*** [redacted] ***mutation from MTC-D*** **Cohort 5**: ***Any solid tumor type with any allosteric ErbB mutation from any of the 7 MTCs (MTC-A to MTC-G), excluding patients who are otherwise eligible for Cohorts 1-4*** ***BDTX-189 will be evaluated at the RP2D determined in Part A (800 mg, daily total dose) in each of the 5 separate cohorts described above, which reflect an interest in testing the hypothesis that the drug is active against a broad range of ErbB allosteric mutations and cancer types, supported by the pre-clinical data (see Section 1.1.5) and the proof of principle demonstrated by other investigational drugs in the same class in patients with NSCLC harboring exon 20 insertion mutations, and breast cancer and other solid cancers harboring allosteric HER2 mutations (see Section 1.1.4 and 1.1.5).*** ***In total approximately 491 patients will be enrolled in Part B.***	To determine the antitumor activity and safety of BDTX-189 in adult patients who have a solid tumor harboring an oncogenic [redacted] mutation or [redacted] mutation

Amendment 3, Version 4.0, 08 June 2021		
Section(s)	**Description of Change**	**Rationale for Change**
	Please refer to the sections to review the added content.	
Figure 10 Study Schema	Figure 10 Study Schema has been updated.	Revised to reflect the changes made to the number of patients enrolling onto additional cohort(s) and to remove the null and alternative hypotheses as they were incorrect
Section 4.3 Treatment Plan Synopsis: Study Drugs, Doses, and Modes of Administration	**Section 4.3** Treatment Plan The following modifications have been made: BDTX-189 will be provided as tablets for oral administration in dose strengths of 100 and 200 mg. ***Additionally, a smaller and reformulated 200 mg tablet will be administered to some patients at select sites enrolling in the Safety Expansion of Part A and all patients enrolling onto Part B.*** ***Prior to exceeding the MTD for the QD schedule, patients received BDTX-189 in a fasted state. As of January 2021, based on the recommendation of the SRC (details provided in Section 1.1.7)***, all patients will receive BDTX-189 with ***approximately*** 240 mL water ***within 30 minutes of completing a meal (Section 6.1.2***). The time of day ***for BDTX-189*** administration should be consistent. ***For patients receiving BDTX-189 BID, the 2 doses should be separated by at least 10 hours.*** ***Patients enrolling into the Food Effect cohort will be dosed in the fed/fasted state as per Table 1 and Section 5.3***. ***In Part B, patients will be administered BDTX-189 at the RP2D identified during Part A (800 mg QD, non-fasting).*** No routine ***anti-diarrheal agents*** will be given ***pre-emptively.*** However, ***anti-diarrheal agents should*** *be administered in the event of* ***diarrhea to manage the symptoms (see Table 8). Prophylactic anti-emetics are allowed*** for nausea and***/or*** vomiting. ***Oral ondansetron may be used after consultation with*** the ***Sponsor.*** Please refer to the section for complete information.	A smaller and reformulated 200 mg tablet will be administered in the Safety Expansion and to all patients in Part B. Emerging food-effect data suggest a slight to moderate increase in systemic exposure of BDTX 189 when administered with a high fat meal. Revisions made in response to available clinical data
Section 4.3.1 Dose-Escalation Procedure	***The Bayesian Optimal Design*** ***Step 3 added.*** Please refer to the sections to review the added content.	Clarification
Section 4.3.2.1 Determination of	Clarification added to **Section 4.3.2.1**	Clarification

Amendment 3, Version 4.0, 08 June 2021		
Section(s)	**Description of Change**	**Rationale for Change**
DLT-evaluable Population	Please refer to the section to review the added content.	
Section 4.3.4 Safety Expansion after Determination of the MTD	**Section 4.3.4** updates made as follows: ***As described in Section 1.1.7 the MTD and preliminary RP2D is 800 mg for the QD schedule. Once the Safety Expansion opens for enrollment,*** up to ***48*** additional patients ***(including patients for PK evaluation of a smaller and reformulated tablet [see below])*** will be enrolled at the MTD or a lower dose for either the QD and/or the BID schedule to further characterize the safety, PK, and efficacy profile. The MTD will be considered the recommended dose unless there is a lower dose that provides adequate exposure and biologic activity with more favorable tolerability. ***A smaller and reformulated 200 mg tablet will be introduced and may be supplied to some patients during the Safety Expansion of Part A; these tablets will be available to all patients enrolling on Part B. A minimum of 12 patients from selected study sites may undergo PK evaluation on C1D1 and C1D15 (see Section 5.6) during the Safety Expansion period and/or Part B.*** ***Should the PK parameters from these smaller and reformulated tablets be consistent with data from the larger tablets, additional PK evaluation can be performed in newly enrolled patients on C1D1 and C1D15 and/or by switching patients from the larger tablets to the smaller and reformulated 200 mg tablets to further characterize the PK. The latter subset of patients in Part A who initiated treatment with the larger 200 mg tablet may be switched to the smaller and reformulated 200 mg tablet at the beginning of the subsequent cycle. Detailed PK sampling will be collected on Day 15 of that subsequent cycle according to Table 10, to provide additional exposure data.***	Guidance for Safety Expansion
Section 4.3.5 Dose Modifications	***Table 7*** added to Section **4.3.5** ***Dose Reduction Levels for BDTX-189 Administered Once or Twice Daily***	For patients in Part A Safety Expansion or Part B, Table 7 provides dose reduction levels for patients
Table 8 Dose Modifications Guidelines for BDTX-189-related AEs	***Table 8 Updates to the guidance for combination of bilirubin and AST/ALT, and diarrhea dose modification guidelines.*** Please refer to the table for information.	Safety update.
Section 4.3.5 Dose Modifications	**Section 4.3.5** During ***the Safety Expansion and*** Part B, re - escalation of BDTX-189 following dose reduction due to toxicities ***may be considered following discussion and approval of Sponsor's Medical Monitor***	Allows for flexibility in dose-reduced patients

Amendment 3, Version 4.0, 08 June 2021		
Section(s)	**Description of Change**	**Rationale for Change**
		when deemed appropriate
Section 4.4 Treatment Duration	**Section 4.4** Treatment Duration was updated to specify Patients will be evaluated for toxicities ***through AE reporting (continuously) and other safety assessments***, weekly for the first 2 cycles during Part A and at the start of each 2 subsequent cycles thereafter. During Part B, patients will be evaluated toxicities ***through AE reporting (continuous) and other safety assessments, weekly for the first 2 cycles and then*** at the start of each cycle for the first 4 cycles and every other cycle thereafter.	To align with the other sections of the protocol including "Statistical Design" and "Schedule of Assessments"
Section 4.5.1 Permitted Concomitant Medications	**Section 4.5.1** The following is now permitted ***Prophylactic anti-emetics and anti-diarrheals are allowed for nausea and/or vomiting and diarrhea, per Institutional standards.***	Promotes the ability to provide supportive care without asking Medical Monitor
Section 5.2 Screening and Study Assessments and Evaluations Table 1, Table 2, Table 3	**Section 5.2** clarifications: Percent ***or absolute values*** are acceptable for the following hematologic assessments: neutrophils, lymphocytes, monocytes, basophils, eosinophils Biochemistry assessments (sodium, potassium, chloride, bicarbonate, blood urea nitrogen (BUN) ***or blood urea***...	Clarification
Section 5.2 Screening and Study	Genomic Results Part B: ***some clinical sites do not routinely perform broad NGS testing of tumor tissue. These sites may need to prescreen some patients for eligible mutations which will require separate Sponsor approval and patient consent***	To harmonize with eligibility criteria
Section 5.3.2 ECG Measurements Table 1, Table 2	**Section 5.3.2** updated for patients receiving smaller reformulated tablet as follows: ***Time***-matched triplicate ECG measurements will also be collected ***for patients in Part A's Dose Escalation and Food-Effect cohorts, and patients who are undergoing detailed PK assessment of a smaller and reformulated tablet in the Safety Expansion. ECG measurements will coincide*** with the detailed PK assessments around the projected C_{max} in patients to evaluate any corrected QT (QTc) concentration-effect relationship.	Safety measurement
Section 5.3.4 Table 3	**Section 5.3.4** Patient Reported Outcomes (PRO) Part B Only and ***Table 9*** added. ***Patient reported outcomes (PROs) will be collected at C1D1, C1D8 and on Day 1 of every Cycle C2-C9. After C9D1 continue to collect electronic patient reported outcomes (ePROs) every 3 months (±14 days), at the EOT visit, and 30-Day Safety Follow-up visit.*** Please refer to the section for complete information.	To harmonize with secondary objectives

Amendment 3, Version 4.0, 08 June 2021		
Section(s)	**Description of Change**	**Rationale for Change**
Section 5.4.3 Table 2, Table 3	**Section 5.4.3** Extended follow-up Period (Safety Expansion and Part B) Updated to extend follow-up from 1 year to ***2 years***.	To expand the follow-up period in patients with a potential response
Section 5.6 Pharmacokinetic Assessments Table 2, Table 10	**Section 5.6** Pharmacokinetic Assessments The PK section has been updated to include instructions and time-points for patients in Part A Dose-Escalation and Safety Expansion and Part B of the trial. ***A 24-hour post dose PK draw has been added and time-matched ECGs will be collected for the Safety Expansion and Dose Escalation patients of Part A. For Part B Sparse PK blood samples will be collected.*** Separate instructions for Food-Effect patients PK are in Section **5.6.1** Please refer to the sections to review the added content.	To establish the PK of BDTX-189
Section 5.7.1 Archival tumor Samples Synopsis: Correlative Testing Table 1, Table 2, Table 3	**Section 5.7.1** has been updated as follows: ***Tumor samples will be collected during the screening period for retrospective confirmation of allosteric ErbB mutations using a diagnostic test that is being developed.*** Archival tumor samples or tumor tissue from a new pretreatment biopsy is required for all patients enrolled in ***the Safety Expansion portion of Part A*** and Part B ***who have allosteric ErbB mutations. Archival tumor samples or tissue from a new pretreatment biopsy is requested for patients with allosteric ErbB mutations enrolled in the Dose Escalation portion of Part A.*** ***Samples*** should be provided as a tissue block. ***Alternatively, if a tissue block cannot be provided 12-20 freshly cut formalin-fixed paraffin-embedded (FFPE) unstained slides may be submitted. Freshly cut unstained slides are preferred, however unstained slides that were sectioned within 2 years prior to the patient enrolling in the study may be submitted only if stored in the appropriate long-term storage conditions (-80°C). If the quantity of archival tumor tissue available is insufficient to obtain 12-20 unstained slides, a new tumor tissue biopsy sample must be obtained prior to starting study treatment.*** Please refer to the section for complete information.	To evaluate allosteric ErbB mutations.
Section 5.7.2 Fresh Biopsies Table 1, Table 2, Table 3	**Section 5.7.2** has been updated as follows: Patients in the ***Dose Escalation portion of Part A*** will be required to undergo baseline and on-treatment tumor biopsies if the tumor is amenable for biopsy in the opinion of the Investigator. For patients participating in the ***Safety Expansion cohort(s) or any cohort in Part B an archival tumor tissue sample is required, if an archival tumor tissue sample is not available, a fresh tumor biopsy will be required at baseline.*** All patients in Part A and Part B will be asked to undergo an ***optional*** on-treatment tumor biopsy at the time of ***disease***	To evaluate allosteric ErbB mutations.

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Section(s)	**Description of Change**	**Rationale for Change**
	progression if the tumor is amenable for biopsy in the opinion of the Investigator and the patient consents.	
Section 5.7.3, Table 2, Table 3	**Section 5.7.3** - Circulating Tumor DNA time-points for ctDNA collection during the ***Safety Expansion portion of Part A at end of study have been added***. In addition, ***Part B's time-points*** have been modified and a screening time-point has been added.	Evaluation of and possible markers of drug sensitivity and resistance in plasma using ctDNA
Table 1, Table 2, and Table 3	**Table 1** Title expanded to indicate the table is for patients ***Part A Dose Escalation Including Food Effect Cohorts*** **Table 2** Summary of Assessments is a new table created for ***Part A Safety Expansion.*** **Table 3** ***Part B (previously Table 2) has been revised. Cycle 1 Day 1 and Cycle 2 Day 1 clinic visits have been expanded. Patients will return for a clinic visit on Cycle 1 and Cycle 2 on Days 1, 8 and 15. Additional testing and progression-free and overall survival follow-up was added.***	Safety and efficacy evaluations
Table 3	***Part B: pregnancy testing added to Day 1 of all subsequent cycles after Cycle 1 Day 1 and the EOT visit.***	Correction
Section 6 Drug Formulation, Availability, Administration, and Risk Information Section 6.1 Table 2, Table 3	**Section 6.1 BDTX-189** ***100 mg and 200 mg tablets (25 mg and 50 mg tablets will no longer be provided. (A smaller and reformulated 200 mg tablet may be administered to some patients in select sites during the Safety Expansion of Part A and to all patients enrolling onto Part B).***	Drug strength and formulation update
Section 6.1.1 Labeling, Packaging, and Supply Table 2, Table 3	**Section 6.1.1** updated ***The Sponsor will supply the BDTX-189 as tablet formulations of 100 and 200 mg. A smaller and reformulated 200 mg tablet may be introduced during the Safety Expansion of Part A to select sites, and will also be administered to patients enrolling onto Part B. Each high density polyethylene (HDPE) bottle will contain 30 tablets. This tablet is a common granulated blend of drug substance and pharmacopeial grade excipients compressed into an immediate release form, which is half the size of the larger 200 mg tablet provided to patients in the Dose Escalation portion of Part A. The pharmacopeial grade excipients include starch, microcrystalline cellulose, croscarmellose sodium, sodium dodecyl sulfate, colloidal silicon dioxide, and magnesium stearate.*** ***Patients in Part A who initiated treatment with the larger 200 mg tablet may be switched to the smaller and reformulated 200 mg tablet at the beginning of their subsequent cycles after instruction by the Sponsor.***	Drug strength and formulation update

Amendment 3, Version 4.0, 08 June 2021		
Section(s)	**Description of Change**	**Rationale for Change**
Section 6.1.2 Preparation and Administration of BDTX-189	**Section 6.1.2** modified based on clinical data. ***The emerging food-effect data suggest a slight to moderate increase in systemic exposure of BDTX-189 when administered with a high fat meal. Therefore, separate cohorts (QD and BID) at ≥800 mg/day will be evaluated in the fed state, as will the Safety Expansion cohort(s) and Part B. In this case, patients will be instructed not to take study drug on an empty stomach. Patients are allowed to take their dose of BDTX-189 with approximately 240 mL water within 30 minutes of completing a meal.*** Tablets should be swallowed whole (along with up to 240 mL water), not crushed, chewed, or dissolved. **For the QD dosing schedule**, ***patients will self-administer the study drug with approximately 240 mL water within 30 minutes of completing a meal***. The time of day for administration of BDTX-189 should be as consistent as possible. **For the BID dosing schedule**, BDTX-189 should be taken at approximately the same time each morning and approximately the same time each evening, approximately 10 hours after the morning dose. ***Patients will self-administer the study drug with approximately 240 mL water within 30 minutes of completing a meal.*** ***For the Food-Effect Patients, study drug will be self-administered on an empty stomach following a fast of approximately 2 hours.*** Patients will continue to fast for approximately 1 hour after the administration of BDTX-189. ***On scheduled PK collection days, C1D1 and C1D15 during Dose Escalation and Safety Expansion, the patient should be instructed to wait until he/she arrives at the study center and receives instructions from the research staff to take their morning dose of study medication.***	BDTX-189 administration update
Section 8.2 SAE Reporting by the Investigator	**Section 8.2** was revised so that SAEs are reported through paper report forms and AEs are reported through eCRFs.	SAEs must be disclosed through paper report forms
Section 8.2.2. Persistent or Recurrent AE	**Section 8.2.2**.the term ***"persistent AE"*** definition was clarified.	Editorial revisions to clarify text
Section 8.2.4 Hy's Law	**Section 8.2.4** "Hy's Law" explanation and reporting guidelines added to protocol Please refer to the section to review the added content.	Safety criteria added.
Section 8.2.10 BDTX-189 Overdose	**Section 8.2.10** "BDTX-189 Overdose" guidelines have been clarified	Clarification

Amendment 3, Version 4.0, 08 June 2021		
Section(s)	**Description of Change**	**Rationale for Change**
Section 8.1.2 Serious Adverse Event	**Section 8.1.2** SAE criteria revised. Inpatient hospitalization ~~***of at least 24 hours***~~ or prolongation of existing hospitalization.	Safety
Section 8.1.5 Recording of AE	**Section 8.1.5** If the AE is serious, it should be reported ***within 24 hours of the Investigator site awareness or receipt of the initial SAE or any follow-up information to Development*** Innovations Safety Department.	Safety
Section 8.3 Sponsor Serious Adverse Event Reporting	**Section 8.3** clarification of Sponsor SAE reporting requirements.	Rewritten for clarity.
Section 9.2 Estimands	**Section 9.2** has been updated. Estimands for Part A and Part B have been added to the protocol. Revisions were made to the Statistical Design of Part B so that it now characterizes Cohorts 1-5 (includes sample size considerations),	The statistical plan was revised to align with changes made to other Sections of the protocol, including Study Objectives and Endpoints and Study Design.
Section 9.3 Sample Size Considerations Synopsis: Number of Patient Synopsis: Statistical Methodology Section 9.5 Data Analysis	**Section 9.3** updates include: ***The number of patients has been updated.*** ***The statistical design has been updated*** ***Section 9.3.1 Phase 1 (Part A) and Section 9.3.2 Phase 2 (Part B) updates.*** ***Sample size considerations for Cohorts 1-5 were added.*** Please refer to the sections to review the added content.	
Section 9.5.2 Hypotheses to be Tested Section 9.5.3 Efficacy Analysis Section 9.5.4 Sub-group Analysis Section 9.5.5 Safety Analysis Section 9.5.8 Quality of Life	***Sections 9.5.2 through 9.5.5 and Section 9.5.8 were revised*** to harmonize with the changes made to study design. Please refer to the sections to review the added content.	
Section 9.6 Analysis Time Points	***Section 9.6.1 Final Analysis and Section 9.6.2 Planned Interim Analysis*** were updated. Please refer to the sections to review the added content.	Revised to harmonize with the changes made to study design.
Section 10.3.2	New Section **10.3.2** "Data Monitoring Committee (Part B only)" has been added to the protocol.	Independent oversight of safety,

Amendment 3, Version 4.0, 08 June 2021		
Section(s)	**Description of Change**	**Rationale for Change**
		efficacy, and study conduct.
Section 10.3.3	New Section **10.3.3** "Blinded Independent Central Review Committee" has been added the protocol.	For determination of ORR and PFS endpoints
Section 10.3.4	New Section **10.3.4** "Protocol Steering Committee" added to the protocol.	Added to provide scientific oversight of the conduct of the study.
References	Reference added to the study protocol	Cite literature referenced throughout the trial
Appendix B Response Evaluation Criteria in Solid Tumors (RECIST) Version 1.1	Revisions made to "Evaluation of Best Overall Response" including revisions to a reference table and addition of a new statement: ***"Note that a best overall response of SD requires an assessment of SD at the time of the first protocol-specified post-baseline tumor assessment (i.e., 42 days +/- 3 days after first dose) or later."***	Describe guidelines for best overall response
Appendix C Guidelines for Women of Childbearing Potential and Fertile Male Patients	Clarified that highly effective contraception must be used during the study and for at least ***90 days*** after stopping treatment	Clarification
Appendix I Eligible [redacted] Mutations, Mutations, and [redacted] Mutations	The table has been revised to include MTC A- MTC G eligible allosteric [redacted] Mutations and [redacted] Mutations. Footnotes have also been updated.	Provide parameters for eligibility criterion
Clinical Protocol Amendment Summary of Changes	The header for Amendment 2 version 3.0 contained a typographical error. The final version date for that amendment has been corrected to 14 July 2020	Correction of typographical error
Clinical Protocol Amendment	Minor typographical and editorial errors were corrected/clarified throughout the protocol. Innovations change to Development Innovations.	Correction

Amendment 2, Version 3.1, 30 November 2020

Changes to the protocol are summarized below:

- Addition of the EudraCT number 2020-005492-12
- Section 7.2 was updated to include axillary as a method to collect the patient's temperature. "Vital signs (heart rate, systolic and diastolic blood pressure (BP), pulse oximetry, and oral **or axillary** temperature) and weight."

Amendment 2, Version 3.0, 14 July 2020

Changes to the protocol are summarized below:

- The number of centers and sites involved in the study was updated (Synopsis).
- The Schedule of Assessments column header was updated to add Cycle 5 (Cycle 3, 4, **5** and every other cycle thereafter [±2 days]) in order to adjust assessments to odd cycles.
- The Schedule of Assessments was updated to reflect the change from urine pregnancy sample collection to urine or **serum** sample collection on Day 1 of each treatment cycle (Table 1, footnote p and Table 3, footnote o).
- The Schedule of Assessments was updated to clarify the difference between a complete physical examination (includes an exam of all body components) and a directed physical examination (focused on a specific body part or disease, at the discretion of the Investigator) (Table 1 and Table 3 footnote g).
- The Schedule of Assessments was updated to reflect that a brain scan is not required at baseline unless the patient has a history or if clinically indicated (Table 1, footnote x and Table 3, footnote t).
- Non-clinical Experience (Section 1.1.5 and Figure 7) was updated with new data from CUTO-14 patient-derived tumor models.
- Clinical Experience (Section 1.1.7) was updated with preliminary safety and pharmacokinetic (PK) information.
- Exclusion criteria #3c (Synopsis and Section 3.2) was updated to change the acceptable QTc interval from ~~>480 msec~~ to **>470 msec**.
- Exclusion criteria (Synopsis and Section 3.2) for Part B only (previously Exclusion criteria #16b: Known concurrent [redacted] mutation and previously Exclusion criteria #16c: Known tumor-harboring resistance mutations including [redacted] or [redacted] mutations or [redacted] mutation) were modified to include all patients in Part A and Part B (now Exclusion criteria #6 and 8, respectively).
- Exclusion criteria #5 (Section 3.2) was updated to specify that any targeted therapy will have a 14-day washout period (Exclusion criteria 5b).
- Exclusion criteria #18 (Synopsis and Section 3.2) was updated to remove ~~TAK-788~~ and add **amivantamab, mobocertinib**, and **trastuzumab deruxtecan** to the documented treatment response.
- The Treatment Plan for BDTX (Section 4.3) was updated as follows:
    - Clarified that BDTX tablets may be taken with up to 240 mL of water and that additional fluids should be avoided 2 hours prior to dose and for 1 hour post-dose.
    - The following sentence was removed "~~The total daily dose of the BID schedule will not initially exceed the separate QD schedule~~" to allow for greater flexibility. Preliminary PK data

Amendment 2, Version 3.0, 14 July 2020

show lower than predicted human exposures and the probability of accumulation with the BID schedule is negligible.
  - BDTX BID dosing instructions were clarified to include instructions in the event of a missed dose.

- Prohibited Concomitant Medications (Section 4.5.2) were updated to match Appendix E (Common Inhibitors and Inducers of Cytochrome P450 Isozymes) by removing fluconazole and calcium channel blockers as strong CYP3A4 inhibitors.
- Food-effect Assessment (Section 5.3.1 and Table 1, footnote s) was updated to allow the assessment of a low-fat meal if emerging data dictate and to provide an example.
- Electrocardiogram Measurements (Section 5.3.2) was updated to clarify that all single ECGs in Part A are obtained pre-dose.
- The BDTX Pharmacokinetic Collection times (Section 5.6, Table 10, footnote a and Table 3, footnote p) were updated as follows:
  - Additional PK sampling times were added at 45 minutes and 1.5 hours post-dose on C1D1 and C1D15.
  - PK sampling times were removed at 10 hours on C1D1 and C1D15, and 24 hours on C1D1 (C1D2) and C1D15 (C1D16).
  - Actual timing of post-dose PK samples for Cycles 2, 3, and 4 in Part A and for Part B was added (1st sample: 0.5 – 1.5 hours post-dose; 2nd sample: 2 – 3 hours post-dose).
  - Footnote a was added to Table 7 indicating that the actual post-dose time of collection should be recorded.
- BDTX-189 Pharmacokinetic Collection Times – Lead-in phase for food-effect (Part A) (Table 11) was updated to remove the 10 and 24 hour draws and add 45 minute and 1.5hour post-dose draws on Days -4 and -1. Added a footnote clarifying the PK sampling beyond Day -1.
- Biomarker Tissue Samples (Section 1.1.1) was updated to include pre-dose biopsies if data suggests and to clarify timing of pre-dose biopsies based on QD or BID dosing schedules.
- Fresh Biopsies (Section 5.7.2) was updated as follows:
  - Clarified that for patients in the food-effect cohort, fresh tumor biopsies are optional (Table 1, footnote v).
  - Clarified that for patients in Part A, baseline and on-treatment fresh tumor biopsies may be collected up to 8 hours after dosing with BDTX (Table 1, footnote v).
- Preparation and Administration of BDTX (Section 6.1.2) was updated to clarify that BDTX tablets should be dispensed from the original bottle and that tablets should be swallowed whole, not crushed, chewed, or dissolved.
- Sample Size Considerations (Synopsis, Section 4.3.1, and Section 9.2) were updated to enable a safety expansion of approximately 12 patients with each schedule or a total 24 patients which results in an increase of the approximate number of patients that may participate in the study.
- Final Analysis (Section 9.6.1) was updated to include the following sentence: **Follow-up analysis for OS may be performed if data are immature at the time of final analysis**.
- Common Inhibitors and Inducers of Cytochrome P450 Isozymes (Appendix E) was updated.
- The Operating Characteristics for the BOIN Design for the BID Dosing Schedule (Appendix G) was updated using the trial and model specifications for a cohort size of 3. The original specifications used a default cohort size of 1.

Amendment 2, Version 3.0, 14 July 2020

- Eligible [redacted], and [redacted] Mutations (Appendix I) was updated with additional eligible mutations per emerging data. Specific mutations were updated throughout protocol.
- BDTX-189 tablet strength was updated to include 200 mg tablets throughout protocol.
- Page numbering was added to the protocol.
- Minor typographical and editorial errors were corrected/clarified throughout the protocol.

Amendment 1, Version 2.0, 12 December 2019

Implementation of Amendment 1 occurred prior to the first patient enrollment. These changes were made to the protocol in response to comments from the FDA.

- The directed physical examination was replaced with a complete physical examination on Day 1 of each treatment cycle (Table 1 and Table 3). Footnote "g" was edited as follows: The ~~directed~~ physical exam will include an ophthalmological exam if clinically indicated.
- The Dose Modification Guidelines (Section 1.1.1, Table 8) were updated to correct inconsistencies in prolonged QTc interval modification guidelines as follows (**bold**):
  - Repeat ECG in triplicate as soon as practical, no later than 7 days after the initial ECG. If the mean QTcF on repeat ECG triplicate is **≤500** msec **and the patient is asymptomatic**, then continue study drug at the same dose. Post-dose ECG must be monitored weekly in triplicate.
  - If the mean QTcF on repeat ECG triplicate is **>480 and ≤500** msec, then ~~omit dose until~~ consultation with cardiologist (must occur as soon as practical, no later than 7 days after the **repeat** ECG). ~~ECG must be monitored in triplicate at the frequency selected at Investigator's discretion.~~
  - If the cardiologist confirms a mean QTcF **>480 and** ≤500 msec is drug-related, then **↓ 1 dose level** ~~discontinue patient from study treatment~~.
- Typographical errors in the dose escalation criteria, exceptions for non-hematologic toxicity, (Section 4.3.2) were corrected.
- Inconsistencies in final protocol dates were corrected on pages 3 and 4.