Official Title: A Phase 1-2 Study of the Safety, Pharmacokinetics, and Activity of ASTX029 in Subjects With Advanced Solid Tumors

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Clinical Study Protocol — ASTX029-01

A Phase 1-2 Study of the Safety, Pharmacokinetics, and Activity of ASTX029 in Subjects With Advanced Solid Tumors

Sponsor: Taiho Oncology, Inc.
101 Carnegie Center
Suite 101
Princeton, NJ 08540
USA

Medical Monitor: [redacted] MD
[redacted] (mobile)
E-mail: [redacted]

Pharmacovigilance Group: E-mail: drugsafety@taihooncology.com

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Amendment 1.0 (21 February 2019)
Amendment 2.0 (12 July 2019)
Amendment 3.0 (31 December 2019)
Amendment 4.0 (21 July 2020)
Amendment 4.1 UK (12 March 2021)
Amendment 4.2 France (08 June 2021)
Amendment 5.0 (23 May 2024)

This clinical study will be conducted in accordance with the International Council for Harmonisation of Technical Requirements for Pharmaceuticals for Human Use (ICH), Good Clinical Practice (GCP) Guidelines, EU CTR536/2014, and applicable regulatory requirements.

SUMMARY OF CHANGES

The rationale for this substantial amendment is to update "Astex Pharmaceuticals, Inc." and associated references to Astex to "Taiho Oncology, Inc.", "Taiho", or "the Sponsor", as a result of Astex Pharmaceuticals, Inc. becoming a wholly-owned subsidiary of Taiho Oncology Inc.as of 01 January 2024, to insert the addition of the End of Study definition, and to add the Study Extension phase.

In addition to minor edits, the summary of changes for the current amendment are shown in the table below:

Section Number and Title	**Description of Change**	**Rationale**
Throughout	Sponsor name was changed	Astex Pharmaceuticals, Inc. is now a wholly-owned subsidiary of Taiho Oncology Inc.as of 1 January 2024.
Section 1.3 Summary of Nonclinical and Clinical Data for ASTX029/1.3.3 Clinical Data and Human Pharmacokinetics	Updated with current data available in IB.	
Section 4.1 Overall Study Design	Updated study duration to 5 years (61 months and 55 months for recruitment.	
Section 4.1.1 Phase 1	Added sentence to report the in vitro diagnostic (IVD) medical devices are appropriately registered for use.	
Section 4.4 Data and Safety Review Committee	Updated: The DSRC composition is detailed in the DSRC charter.	
Section 5.2 Inclusion Criteria	Updated contraception for #8: must agree to contraception requirements for at least 32 days after last treatment and updated the description of contraceptive requirements.	
	Updated contraception for #9: pregnant partner of partner who is WOCBP must agree to contraception requirements for at least 92 days after last treatment and updated the description of contraceptive requirements.	

Section Number and Title	Description of Change	Rationale
Section 5.4.3 Replacement of Subjects	Relocated last sentence to Section 12.	
Section 5.4.4 End of Study	Added entire section.	
Section 5.4.5 Study Extension	Added entire section.	
Section 7.1.5 ASTX029 Administration	Added instruction for missed dose.	
Section 7.3Dose-Escalation Guidelines and Recommended Phase 2 Dose Decision	Added statement for the DSRC decision of the RP2D.	
Section 7.7 Overdose Instructions	Updated with name change/department and timing.	
Section 9.4.9 Schedule of Events	Added Table 13 SoE for the Study Extension Phase.	
Sections 10.2.3 and 10.2.4 Reporting Requirements for Pregnancy and Abortion; Serious Adverse Events (SAEs)	Due to name change, the department name was changed.	
Section 12 Study Duration and Termination	Updated study duration to 5 years (61 months and 55 months for recruitment. Added deleted sentence from Section 5.4.3: The Sponsor may stop the study at any time. In case of this event, the Sponsor will make reasonable efforts to ensure subjects are transitioned off study in an orderly manner.	
Section 14.2.2 ASTX029 and VFR Accountability	Added: Until ASTX029 PiB was phased out, initial supplies of VFR were shipped to each study center's pharmacy when conditions as described above were met.	

PROTOCOL SYNOPSIS

Study Number and Title:
ASTX029-01: A Phase 1-2 Study of the Safety, Pharmacokinetics, and Activity of ASTX029 in Subjects With Advanced Solid Tumors

Investigational Drug: ASTX029

Clinical Phase: 1-2

Study Centers Planned/Country:

- Phase 1: up to 14 study centers in the United States and Europe.
- Phase 2: up to 30 study centers in North America and Europe.

Study Objectives:

Primary Objectives

- Phase 1 (Parts A and B): To assess safety and to identify the maximum tolerated dose (MTD), the recommended Phase 2 dose (RP2D), and the recommended dosing regimen of ASTX029.
- Phase 2: To assess preliminary clinical activity, as determined by objective response rate (ORR) in tumors characterized by gene aberrations in the mitogen-activated protein kinase (MAPK) signal pathway that may confer sensitivity to ASTX029.

Secondary Objectives

- To determine the pharmacokinetic (PK) profile of ASTX029 including the food effect on PK parameters.
- To evaluate other clinical activity parameters, such as duration of response (DOR), disease control rate (DCR), progression-free survival (PFS), and overall survival (OS).
- To evaluate relevant pharmacodynamic markers and target engagement (ie, phosphorylated ribosomal s6 kinase [pRSK] inhibition) in tumor biopsies.

Exploratory Objective

- To identify and evaluate biomarkers of ASTX029 activity.

Study Design and Investigational Plan:

This study is a first-in-human (FIH), open-label, multicenter, Phase 1-2 study to assess the safety, PK, pharmacodynamics, and preliminary clinical activity of ASTX029 administered orally to subjects ≥18 years of age with advanced solid malignancies who are not candidates for approved or available therapies.

Phase 1

The Phase 1 portion of the study will consist of Parts A and B as follows:

Part A (Dose Escalation): Dose-escalation stage to identify the MTD for up to 2 dosing regimens of ASTX029 and the recommended dose for expansion (RDE), defined as either MTD or a dose below MTD that the Data and Safety Review Committee (DSRC) agrees shows adequate safety, PK, and/or preliminary biological or clinical activity. Subjects enrolled in Regimen 1 (continuous dosing) will receive ASTX029 orally once a day on Days 1 through 21 of each 21-day cycle. If Regimen 2 (intermittent dosing) is opened to enrollment, subjects enrolled in Regimen 2 will receive ASTX029 orally once a day on Days 1 through 14 of each 21-day cycle. Initially, subjects will be allocated to Regimen 1 (continuous dosing). Subjects in the first cohort of Regimen 1 will receive a flat starting dose of 10 mg daily (QD). Planned initial escalation will be 100% (doubling the dose) until 160 mg. Smaller increments of dose escalation will be used above 160 mg. Dose doubling will also be discontinued if any 1 of the following occurs within a cohort:

- 1 subject experiences a dose-limiting toxicity (DLT).

- Any study-drug-related clinically significant ≥Grade 2 AE not adequately managed or resolved to baseline or Grade 1 by supportive treatment that, per the DSRC, indicates further dose doubling would be potentially unsafe for future subjects.
- Any study-drug-related AE or confluence of AEs that, per the DSRC, indicates further dose doubling would be potentially unsafe for future subjects.

After this point, dose escalation will proceed in smaller increments (eg, by a 50% increase initially and an ~25% increase at the higher dose levels over the previous level) after review of all available safety, PK, and biomarker data from Cycle 1 in at least 3 subjects and approval by the DSRC. Also, after this point, the sponsor, with approval of the DSRC, will determine if Regimen 2 is to be opened for enrollment. Randomization to either Regimen 1 or Regimen 2 will begin if both regimens are open for enrollment. Should Regimen 2 be evaluated, based on safety and PK data from Regimen 1 and depending on the nature, timing, and severity of observed AEs, the dose for the first cohort of subjects enrolled to Regimen 2 may be escalated to the next level pending approval by the DSRC. If the MTD is reached in 1 regimen before the other regimen, all subsequent subjects will be enrolled, without randomization, to the remaining regimen until the MTD is determined for each regimen evaluated. After reaching MTD or RDE for Regimens 1 and 2, the DSRC will also advise if it is appropriate to test an alternative intermittent regimen (Optional Regimen 3, eg, 7 days on/7 days off) and will recommend the dose and dosing regimen to be used. The total dose per cycle for the new regimen will not exceed the total safe dose per cycle already established in the first 2 regimens.

The starting dose in each regimen evaluated will be escalated stepwise in successive cohorts of at least 3 evaluable subjects each with additional allowed expansion to 6 subjects (3+3 study design) until the MTD is determined for each regimen. Dose levels and dosing regimens, the number of cohorts, and the number of subjects per cohort may be modified, as needed, in response to emerging data and recommendations from the DSRC.

Dose-escalation/de-escalation decisions will be based on the occurrence of DLTs during the first cycle of each dose level and the recommendations of the DSRC following review of all available safety, PK, and biomarker data from the completed first cycle of at least 3 subjects in each cohort. The DSRC RDE decision will be based on all available safety, PK, biomarkers, and preliminary activity data from all cycles (including potential for late or cumulative toxicity). The DSRC will also advise whether or not it is appropriate to proceed to Part B (Dose Expansion).

ASXT029 was originally introduced into the clinic in the powder-in-bottle (PiB) form and administered under fed conditions. Protocol Amendment 1.0 introduced the tablet dosage form when it became available. Protocol Amendment 2.0 introduced the evaluation of administration under fasted conditions during Phase 1 Part A dose escalation.

Part B (Dose Expansion): One or more dose levels (and regimens) may be studied in Phase 1 Part B to supplement available safety, PK, and/or clinical activity data and to evaluate target engagement in fresh tumor tissue biopsies. A total of 14 evaluable subjects will be treated at each dose/regimen selected. If more than 1 dose/regimen is selected, subjects will be randomized in a 1:1 ratio. Subjects will have to meet the following molecular eligibility criteria: documented activating mutations in BRAF (BRAF V600 mutation or activating atypical non-V600 aberrations), KRAS, NRAS, or HRAS. The RP2D decision by the DSRC will be based on all available PK, pharmacodynamic, safety, and preliminary activity data from all cycles (including the potential for late or cumulative toxicity). The RP2D could be the same or lower than the RDE.

The DSRC will advise when it is appropriate to proceed to Phase 2.

Phase 2

The Phase 2 portion of the study will explore the preliminary single-agent antitumor activity of ASTX029 at the RP2D of the selected dosing regimen identified in Phase 1 Parts A and B in tumors characterized by gene aberrations in the MAPK signal pathway that may confer sensitivity to ASTX029. The Phase 2 part of the study will consist of the following up to 6 cohorts:

- Cohort A: NRAS-mutant melanoma.
- Cohort B: KRAS-mutant or KRAS-amplified non-small cell lung cancer (NSCLC).
- Cohort C: BRAF V600-mutant cancers (non-colorectal cancers).
- Cohort D: BRAF-fusion cancers.
- Cohort E: Gynecological cancers with alterations in the MAPK pathway.
- Cohort F: Tumors characterized by other gene aberrations that upregulate the MAPK signal pathway.

In the Phase 2 part of the study, molecular eligibility will be based on the presence of documented gene aberrations in MAPK pathway.

For Phase 2, the sample size is based on a Simon's Optimal 2-stage design. Each cohort will enroll 10 subjects into the first stage of Simon's 2-stage design at the RP2D and the dosing regimen identified in Phase 1 Parts A and B. Should ≥2 first-stage subjects respond, an additional 19 subjects will be enrolled into the second stage. Therefore, up to 29 subjects will be enrolled into each cohort.

For Phase 2 Cohort F (which will enroll patients with various tumor types and gene aberrations, the sponsor, with approval of the DSRC, may expand enrollment for a particular molecularly defined subpopulation in which the most number of responses are observed to 10 or 29 subjects under the same Simon's Optimal 2-stage design as for the other cohorts for better assessment of activity in that disease subpopulation (Optional Cohort F Expansion). It is expected that no more than 2 subpopulations will be expanded in this manner.

Study Population: It is anticipated that up to 300 evaluable subjects will be enrolled if the study fully enrolls both Phases 1 and 2. This includes approximately 120 evaluable subjects in Phase 1 and up to approximately 180 evaluable subjects in Phase 2.

The number of cohorts in Phase 1 Parts A and B and the number of subjects per cohort will be based on emerging safety data, PK data, and recommendations from the DSRC. The number of subjects in Phase 2 will be based on clinical activity observed and recommendations from the DSRC. More subjects may be enrolled if more dose levels are tested in Part A, if more than 1 cohort is selected for expansion in Part B, or if more than the expected number of subpopulations in Cohort F of Phase 2 are expanded.

Inclusion Criteria

Subjects must fulfill all of the following inclusion criteria.

1. Able to understand and comply with study procedures, understand the risks involved in the study, and provide written informed consent before any study-specific procedure is performed.
2. Men or women 18 years of age or older.
3. Subjects with histologically or cytologically confirmed advanced solid tumors that are metastatic or unresectable, who are refractory or have relapsed after treatment with available therapies or for whom standard life-prolonging measures or approved therapies are not available. In Phase 1 Part B and in the Phase 2 portion of the protocol, subjects must also have documented gene alterations in the MAPK pathway.
4. In Phase 1 Part B of the protocol, subjects must have disease lesions that are amenable to biopsy.
5. In the Phase 2 portion of the protocol, subjects must have measurable disease according to Response Evaluation Criteria in Solid Tumors (RECIST) v1.1.
6. Eastern Cooperative Oncology Group performance status 0 to 2.
7. Acceptable organ function, as evidenced by the following laboratory data:
   a) Aspartate aminotransferase (AST) and alanine aminotransferase (ALT) ≤2×upper limit of normal (ULN) or ≤3 ULN in the presence of liver metastases.
   b) Total serum bilirubin ≤1.5×ULN.
   c) Absolute neutrophil count (ANC) ≥1500 cells/mm^3.
   d) Platelet count ≥100,000 cells/mm^3.

e) Calculated creatinine clearance (by the standard Cockcroft-Gault formula) of ≥50 mL/min or glomerular filtration rate of ≥50 mL/min.

8. Women of child-bearing potential (according to recommendations of the Clinical Trial Facilitation Group [CTFG]; see protocol for details) must not be pregnant or breastfeeding and must have a negative pregnancy test within 24 hours before the first dose of study treatment. While receiving study treatment and for at least 32 days (approximately 5 half-lives of ASTX029 or metabolite plus 30 days after completing treatment, women of child-bearing potential must agree to practice highly effective contraceptive measures (as described in the protocol) and must refrain from donating eggs (ova, oocytes) for the purpose of reproduction.
9. Men with a pregnant partner or nonpregnant partner who is a woman of child-bearing potential (according to recommendations of the CTFG; see protocol for details) must agree to, during the treatment period and for at least 92 days (approximately 5 half-lives of ASTX029 or metabolite plus 90 days) after completing treatment, practice highly effective contraceptive measures (as described in the protocol), not to father a child, and to refrain from donating sperm.

Exclusion Criteria

Subjects meeting any of the following exclusion criteria will be excluded from the study:

1. Hypersensitivity to ASTX029 or excipients of the drug product.
2. Poor medical risk in the investigator's opinion because of systemic diseases in addition to the cancer under study, for example, uncontrolled infections.
3. Life-threatening illness, significant organ system dysfunction, or other condition that, in the investigator's opinion, could compromise subject safety or integrity of study outcomes or interfere with the absorption or metabolism of ASTX029.
4. Prior anticancer treatments or therapies within the indicated time window prior to first dose of study treatment (ASTX029), as follows:
   a) Cytotoxic chemotherapy or radiotherapy within 3 weeks prior. Palliative radiotherapy to a single lesion within 2 weeks prior. Any encountered treatment-related toxicities (excepting alopecia) not stabilized or resolved to ≤Grade 1.
   b) Monoclonal antibodies or biologics within 4 weeks prior. Any encountered treatment-related toxicities not stabilized or resolved to ≤Grade 1.
   c) Molecularly targeted drug or other investigational drugs, without the potential for delayed toxicity, within 4 weeks of the first dose of study treatment or 5 half-lives (minimum 14 days), whichever is shorter. Any encountered treatment-related toxicities (excepting alopecia) not stabilized or resolved to ≤Grade 1.
5. Prior treatment with extracellular signal-regulated kinase (ERK) inhibitors.
6. History of, or at risk for, cardiac disease, as evidenced by 1 or more of the following conditions:
   a) Abnormal left ventricular ejection fraction (LVEF; <50%) on echocardiogram (ECHO) or multiple-gated acquisition (MUGA) scan.
   b) Congestive cardiac failure of ≥Grade 3 severity according to New York Heart Association (NYHA) functional classification defined as patients with marked limitation of activity and who are comfortable only at rest.
   c) Unstable cardiac disease including unstable angina or hypertension as defined by the need for overnight hospital admission within the last 3 months (90 days).
   d) History or evidence of long QT interval corrected for heart rate (QTc), ventricular arrhythmias including ventricular bigeminy, complete left bundle branch block, clinically significant bradyarrhythmias such as sick sinus syndrome, second- and third-degree atrioventricular (AV) block, presence of cardiac pacemaker or defibrillator, or other significant arrhythmias.
   e) Screening 12-lead electrocardiogram (ECG) with measurable QTc interval of ≥470 msec. (Fridericia's formula should be used to calculate the QTc interval throughout the study.)

7. Known history of human immunodeficiency virus (HIV) infection or seropositive results consistent with active hepatitis B virus (HBV) or active hepatitis C virus (HCV) infection.
8. Known brain metastases, unless previously treated and stable for at least 3 months with or without steroids.
9. Known significant mental illness or other conditions, such as active alcohol or other substance abuse that, in the opinion of the investigator, predispose the subject to high risk of noncompliance with the protocol treatment or assessments.
10. History or current evidence/risk of retinal vein occlusion (RVO) or central serous retinopathy (CSR) including:
    a) Presence of predisposing factors to RVO or CSR (eg, uncontrolled glaucoma or ocular hypertension, uncontrolled diabetes mellitus) or
    b) Visible retinal pathology as assessed by ophthalmic examination at screening that is considered a risk factor for RVO or CSR such as:
        – Evidence of optic disc cupping or
        – Evidence of new visual field defects on automated perimetry or
        – Intraocular pressure >21 mmHg as measured by tonography.

Study Treatment:

In the dose-escalation part of the study (Phase 1 Part A), subjects will receive 1 of up to potentially 2 ASTX029 dosing regimens (Regimen 1 or Regimen 2). Subjects enrolled in Regimen 1 (continuous dosing) will receive ASTX029 orally once a day on Days 1 through 21 of each 21-day cycle. If Regimen 2 (intermittent dosing) is opened to enrollment, subjects enrolled in Regimen 2 will receive ASTX029 orally once a day on Days 1 through 14 of each 21-day cycle. Initially, subjects will be allocated to Regimen 1 (continuous dosing). Subjects in the first cohort of Regimen 1 will receive a flat starting dose of 10 mg QD. Dose levels for subsequent cohorts will be determined by the DSRC. Planned initial escalation will be 100% (doubling the dose) until 160 mg. Smaller increments of dose escalation will be used above 160 mg. Dose doubling will also be discontinued if any 1 of the following occurs within a cohort:

- 1 subject experiences a DLT.
- Any study-drug-related clinically significant ≥Grade 2 AE not adequately managed or resolved to baseline or Grade 1 by supportive treatment that, per the DSRC, indicates further dose doubling would be potentially unsafe for future subjects.
- Any study-drug-related AE or confluence of AEs that, per the DSRC, indicates further dose doubling would be potentially unsafe for future subjects.

Dose escalation will then proceed in smaller increments (eg, by a 50% increase initially and an ~25% increase at the higher dose levels over the previous level) after review of safety and PK data from Cycle 1 in at least 3 subjects and recommendations from the DSRC. Also, after this point, the sponsor, with approval of the DSRC, will determine if Regimen 2 is to be opened for enrollment.

At any point after Cycle 1, the dose level may be reduced for individual subjects in the event of unacceptable treatment-related toxicity. One or more dose levels (and regimens) may be studied in Phase 1 Part B to supplement available safety, PK, and/or clinical activity data and to evaluate target engagement in fresh tumor tissue biopsies.

The dose level and dosing regimen used in Phase 2 will be determined by the results of Parts A and B of the Phase 1 portion of the study.

Study Endpoints:

Primary Endpoints

- Phase 1: Incidences of DLTs and AEs to determine the MTD of up to 2 dosing regimens of ASTX029 and the RP2D and regimen to be taken to Phase 2.
- Phase 2: Clinical activity assessed by ORR according to RECIST v1.1 criteria.

Secondary Endpoints

- PK parameters of ASTX029, including area under the curve (AUC), maximum concentration (C_{max}), minimum concentration (C_{min}), time to reach maximum concentration (T_{max}), elimination half-life ($t_{½}$), food effect on ASTX029 PK parameters, and other secondary PK parameters of ASTX029 if data permit; analysis of ASTX029 metabolites if applicable.
- Inhibition of pRSK protein in response to ASTX029 treatment in tumor biopsies.
- PFS.
- OS.
- DCR.
- DOR.

Exploratory Endpoints

- Suppression of mutant clones in circulating tumor DNA (ctDNA).
- Explore additional biomarkers of ASTX029 activity.

Study Assessments and Procedures:

Efficacy Assessments:

The ORR, PFS, and DOR endpoints will be based on the investigator's assessment of target and non-target lesions according to RECIST v1.1; computed tomography (CT) or magnetic resonance imaging (MRI) scans (or other appropriate disease evaluation method, including tumor marker measurement, as applicable) will be performed at baseline and every 2 cycles for the first 4 cycles, and then every 4 cycles (±1 cycle) thereafter until clinical and/or radiographic disease progression, death, or the subject withdraws consent. Subjects will be followed for OS.

Pharmacokinetics Assessments:

Serial blood sampling (up to 24 hours postdose) on the following study days will allow assessment of systemic exposures of ASTX029:

- Phase 1: Cycle 1 Day 1 (C1D1), Cycle 1 Day 2 (C1D2), Cycle 2 Day 1 (C2D1), and Cycle 2 Day 2 (C2D2) for Regimen 1 and C1D1, C1D2, Cycle 1 Day 14 (C1D14), and Cycle 1 Day 15 (C1D15) for Regimen 2.
- Phase 2: C1D1, C1D2, C2D1, and Cycle 3 Day 1 (C3D1) for Regimen 1 and C1D1, C1D2, C1D14, C1D15, and C3D1 for Regimen 2.

At specified study visits, blood samples, including predose and trough samples, will be collected. Additional ad hoc blood sample(s) may be collected per investigator discretion, for PK measurement at any time, including after the last dose, if there is a suspected safety issue. Plasma drug concentration data will be used to determine the PK parameters listed under Secondary Endpoints in all subjects during Cycle 1 and Cycle 2 if data are evaluable.

Pharmacodynamic and Biomarker Assessments:

The pharmacodynamic modulation and target engagement will be explored in fresh tumor tissue biopsies (when available). Identification and monitoring of potential biomarkers (DNA, RNA, and protein) of ASTX029 activity will be assessed in ctDNA, blood, and tumor tissue biopsies.

Safety Assessments:

At each study visit, safety will be monitored by recording AEs, serious adverse events (SAEs), DLTs, and concomitant medications; additional safety assessments at selected visits include complete or symptom-directed physical examinations (PEs), weight and height, vital signs, Eastern Cooperative Oncology Group (ECOG) performance status, 12-lead ECGs, ECHO/MUGA scans, and clinical laboratory tests (hematology, coagulation, serum chemistry, and urinalysis). All AEs will be graded by National Cancer Institute (NCI) Common Terminology Criteria for Adverse Events (CTCAE) v4.03.

Sample Size and Statistical Analyses:

Sample Size Calculation:

The dose-escalation part of the study (Phase 1 Part A) follows a 3+3 study design, with a cohort size of either 3 or 6 evaluable subjects. Dose escalation will continue until an MTD is determined for each dosing regimen evaluated.

For Phase 1 Part B, a sample size of 14 evaluable subjects will ensure a 90% probability of observing at least 1 adverse reaction to treatment for any adverse reaction with a ≥15% incidence. Evaluable subjects for Part B are all subjects who receive any amount of study drug.

For Phase 2, the sample size is based on a Simon's Optimal 2-stage design. Each cohort will enroll 10 subjects into the first stage. Should ≥2 first-stage subjects respond, an additional 19 subjects will be enrolled into the second stage. Therefore, up to 29 subjects will be used for each treatment cohort. The sample size, (10+19) 29, under this Simon's Optimal 2-stage design, will achieve a power of 80% to test the null hypothesis of ORRp_0 ≤0.1 at a 1-sided alpha of 0.05 assuming the response rate p_1 is 0.3. For Stage 2, the null hypothesis will be rejected if ≥6 responses are observed in a cohort of 29 subjects. For Phase 2 Cohort F (which will enroll patients with various tumor types and gene aberrations), the sponsor, with approval of the DSRC, may expand enrollment for a particular molecularly defined subpopulation in which the most number of responses are observed to 10 or 29 subjects under the same Simon's Optimal 2-stage design as for the other cohorts for better assessment of activity in that disease subgroup (Optional Cohort F Expansion). It is expected that no more than 2 subgroups will be expanded in this manner.

Efficacy:

Efficacy analysis (ORR) will be conducted on all subjects who had disease assessment at baseline and who received study treatment and had at least 1 follow up disease assessment visit or subjects who died or stopped treatment before the first scheduled disease assessment due to clinical progression or toxicity. Objective response (complete response [CR] + partial response [PR]) rate will be calculated, and its 90% Clopper-Pearson exact confidence interval (CI) will be provided. Disease control (CR + PR + stable disease [SD]) rate will be analyzed similarly. Subjects who receive any amount of study treatment will be included for PFS and OS analyses using the Kaplan-Meier procedure. Estimates and the 90% CIs for the median PFS and OS will also be provided. The DOR will be summarized with descriptive statistics, including arithmetic mean, standard deviation, median, and range, for subjects who have overall responses.

Pharmacokinetics/Pharmacodynamics:

The PK parameters for ASTX029 will be derived for each subject using a non-compartmental approach and will be summarized using descriptive statistics, including mean, standard deviation, median, and range. Values at baseline and changes from baseline (if appropriate) of the pharmacodynamic parameters and biomarkers assessed will be summarized descriptively using mean, standard deviation, median, minimum, and maximum for continuous variables and counts and percentages for categorical variables.

Safety:

Safety analyses will be performed on all subjects who receive any amount of study treatment (Safety Analysis Set). Safety will be assessed by subject-reported and investigator-observed AEs, along with concomitant medications, PEs, clinical laboratory tests (hematology, coagulation, serum chemistry, and urinalysis), vital signs, ECOG performance status, ECGs, and ECHO/MUGA scans. All AEs will be graded according to the NCI CTCAE, v4.03. Treatment exposure, AEs (including relatedness and severity), SAEs, reasons for treatment discontinuation, will be tabulated. Concomitant medication will be coded using the World Health Organization (WHO) Drug Dictionary. The number and proportion of subjects who have DLTs will be summarized by cohort and regimen in Phase 1 Part A. No interim analysis is planned.

Study Duration and Termination:

The expected study duration is approximately 5 years (61 months), including approximately 55 months for recruitment and approximately 6 months for safety follow-up.
The Sponsor may stop the study at any time. In case of this event, the Sponsor will make reasonable efforts to ensure subjects are transitioned off study in an orderly manner. Reasons for early termination include, but are not limited to, lack of preliminary clinical activity or safety concerns.

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ABBREVIATIONS AND DEFINITIONS

%CV	percent coefficient of variation
ADL	activities of daily living
ADME	absorption, distribution, metabolism, and excretion
AE	adverse event
AKT	protein kinase B
ALP	alkaline phosphatase
ALT	alanine aminotransferase (serum glutamic pyruvic transaminase [SGPT])
ARAF	A isoform of RAF
AST	aspartate aminotransferase (serum glutamic oxaloacetic transaminase [SGOT])
ATC	Anatomical Therapeutic Chemical
AUC	area under the curve
$AUC_{0\text{-}inf}$	area under concentration-time curve from time 0 to infinity
$AUC_{0\text{-}t}$	area under the plasma concentration-time curve from the start of dosing (0) to the last quantifiable time point (t)
AUC_{last}	area under concentration-time curve from time 0 to the last data point
AV	atrioventricular
BID	twice a day
BRAF	B isoform of RAF kinase
BRAT	bananas, rice, applesauce, toast
BSA	body surface area
BSEP	bile salt export pump
CCND1	cyclin D1
ctDNA	circulating tumor DNA
CFR	Code of Federal Regulations
CI	confidence interval
C_{max}	maximum concentration
C_{min}	minimum concentration
CRAF	C isoform of RAF
CR	complete response
CRC	colorectal cancer
CRO	contract research organization
CSR	central serous retinopathy
CT	computed tomography
CTCAE	Common Terminology Criteria for Adverse Events
CTFG	Clinical Trial Facilitation Group
CxDx	Cycle x Day x
CYP3A	cytochrome P450, family 3, subfamily A
DCR	disease control rate
DDI	drug-drug interactions
DLT	dose-limiting toxicity
DNA	deoxyribonucleic acid
DOS	duration of response
DRF	dose-range finding
DSRC	Data and Safety Review Committee
DUSP	dual specificity phosphatase
ECG	electrocardiogram
ECHO	echocardiogram
ECOG	Eastern Cooperative Oncology Group
eCRF	electronic case report form
EGFR	epidermal growth factor receptor
EMEA	European Agency for the Evaluation of Medicinal Products

ERK	extracellular signal-regulated kinase
FDA	Food and Drug Administration
FFPE	formalin-fixed paraffin embedded
FIH	first-in-human
FU	follow-up
g-tube	gastrostomy tube
GCP	Good Clinical Practice
GI	gastrointestinal
GLP	Good Laboratory Practice
GNA11	G protein subunit alpha 11
GNAQ	G protein subunit alpha q
GRAS	generally recognized as safe
GRB2	growth factor receptor-bound protein 2
GTPase	guanosine-5'-triphosphate enzyme
HBV	hepatitis B virus
HCV	hepatitis C virus
HED	human equivalent dose
hERG	human ether-a-go-go-related gene
HIV	human immunodeficiency virus
HNSTD	highest non-severely toxic dose
[redacted]	
HRAS	Harvey RAS
IB	Investigator Brochure
IC_{50}	concentration giving half-maximal inhibition
ICF	informed consent form
ICH	International Council for Harmonisation
ID	identification
IEC	Independent Ethics Committee
IMP	investigational medicinal product (ASTX029 in this protocol)
INR	international normalized ratio
IRB	Institutional Review Board
IRT	Interactive Response Technology
IV	intravenous
IVD	in vitro diagnostic
LLN	lower limit of normal
LVEF	left ventricular ejection fraction
KRAS	Kirsten RAS
m	minute(s)
MAPK	mitogen-activated protein kinase
MedDRA	Medical Dictionary for Regulatory Activities
MEK	mitogen-activated extracellular signal-regulated kinase
MHRA	Medicines and Healthcare Products Regulatory Agency
MRI	magnetic resonance imaging
MTD	maximum tolerated dose
MUGA	multiple-gated acquisition
NCI	National Cancer Institute
NE	inevaluable
NOAEL	no-observable adverse effect level
NRAS	neuroblastoma RAS
NSCLC	non-small cell lung cancer
NYHA	New York Heart Association
ORR	overall response rate
OS	overall survival

P	phosphorylated
PBMC	peripheral blood mononuclear cell
PD	progressive disease
PFS	progression-free survival
PK	pharmacokinetic(s)
PiB	powder in bottle
PR	partial response
pRSK	phosphorylated ribosomal s6 kinase
PT	Preferred Term
PTT	partial thromboplastin time
QD	daily
QT	measure of time between the start of the Q wave and the end of the T wave in the heart's electrical cycle
QTc	QT interval corrected for heart rate
RAF	rapidly accelerated fibrosarcoma
RAS	rat sarcoma virus
RDE	recommended dose for expansion
RECIST	Response Evaluation Criteria in Solid Tumors
RNA	ribonucleic acid
RP2D	recommended Phase 2 dose
rSDV	remote source data verification
RSK	ribosomal s6 kinase
RTK	receptor tyrosine kinase
RT-PCR	reverse transcription polymerase chain reaction
RVO	retinal vein occlusion
SAE	serious adverse event
SD	stable disease
SDD	spray-dried dispersion
SOC	System Organ Class
SOS	Son of Sevenless
SPRY	sprouty
STD_{10}	severely toxic dose in 10% of the animals
SUSAR	serious unexpected suspected adverse reaction
$t_{1/2}$	elimination half-life
TEAE	treatment-emergent adverse event
THP	tetrahydropyran
t_{max}	time to reach maximum concentration
TPGS	d-α-tocopherol polyethylene glycol 1000 succinate
Tx Term	Treatment Termination
ULN	upper limit of normal
US	United States
VFR	vehicle for reconstitution
V_{ss}	volume of distribution at steady state
WHO	World Health Organization

1. INTRODUCTION AND BACKGROUND

ASTX029 is a synthetic small molecule inhibitor of extracellular signal-regulated kinases (ERKs) 1/2 that has been shown to have potent tumor growth inhibitory activity in nonclinical cancer models with oncogenic activation of the Ras-Raf-MEK-ERK signal transduction cascade (also referred to as the mitogen-activated protein kinase [MAPK] signal pathway) (Section 1.3.2). The main objectives of this Phase 1-2 study are to identify a safe and tolerated dose and regimen of ASTX029 and to evaluate preliminary clinical activity of ASTX029 in subjects with advanced or refractory solid malignancies who are not candidates for approved or available therapies, and for whom standard life-prolonging measures are not available. Initially, patients with any type of solid tumor will be eligible for enrollment in this study. In later parts of this study, preliminary single-agent antitumor activity of ASTX029 will be assessed in tumors characterized by gene aberrations in the MAPK signal pathway that may confer sensitivity to ASTX029.

1.1. Background of the Disease

Approximately 1.69 million new cancer cases and 600,920 cancer deaths are projected to occur in the US in 2017 (Siegel et al 2017). Although the combined cancer death rates have been continuously declining for 2 decades, the outlook remains bleak for patients with advanced malignancies.

1.2. Background of Treatment Options

Historically, medical approaches to treat advanced malignancies have typically involved surgery, radiotherapy, and/or cytotoxic chemotherapy. Advances in genomics and molecular biology have led to successful development of therapies targeting specific driver mutations in cancer cells (eg, epidermal growth factor receptor [EGFR], B isoform of RAF kinase [BRAF], ALK, BCR-ABL, KIT) (Friedman et al 2015; Xu et al 2014). More recently, cancer immunotherapy has also been shown to significantly improve the outcomes of many cancers. However, a significant proportion of patients eventually relapse due to acquired resistance, and others present intrinsic resistance mechanisms (Farkona et al 2016). Thus, there is an unmet need for new approaches to stop the uncontrolled growth of cancer cells in patients whose tumors have progressed despite currently available treatments (Section 2.1).

1.2.1. Mechanism of Action of ERK Inhibitors

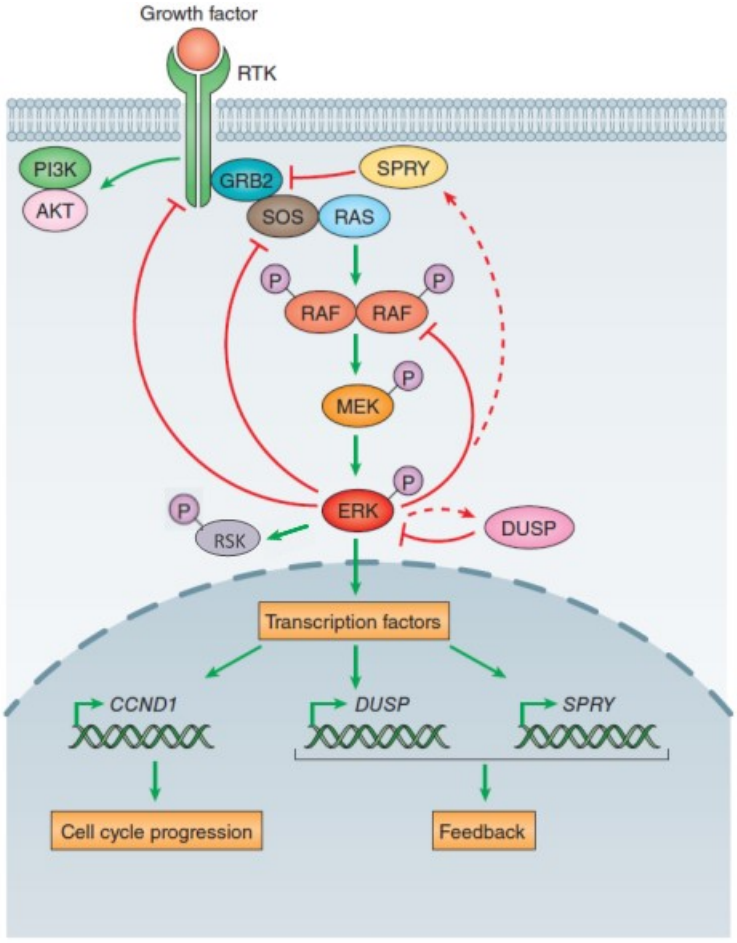
ERK1/2 are ubiquitously expressed protein serine/threonine kinases that comprise a key component of the MAPK signaling pathway) (Figure 1). The MAPK signaling pathway regulates a variety of cellular processes including cell cycle progression, cell survival, and proliferation. The pathway responds to the extracellular stimulation of cell-surface receptor tyrosine kinases (RTKs). Upon activation of RTKs, the rat sarcoma virus (RAS) guanosine-5'-triphosphate enzymes (GTPases) (Kirsten RAS [KRAS], neuroblastoma RAS [NRAS], and Harvey RAS [HRAS]) are converted from an inactive GDP-bound state to an active GTP-bound state. Activated RAS promotes the activation of rapidly accelerated fibrosarcoma (RAF) kinases (A isoform of RAF [ARAF], B isoform of RAF [BRAF], and C isoform of RAF [CRAF]), which, in turn, phosphorylate and activate the dual-specificity mitogen-activated extracellular signal-regulated kinases (MEKs) MEK1/2. Subsequently, MEK phosphorylates and activates ERK1/2,

which, upon activation, phosphorylate multiple nuclear and cytoplasmic substrates including ribosomal S6 kinase (RSK), which promotes cell proliferation and survival, and multiple transcription factors that promote cell proliferation and differentiation (Roskoski 2012; Anjum and Blenis 2008; Murphy et al 2002; Figure 1).

ERK is commonly upregulated in cancer, as a result of activating mutations within upstream components of the MAPK pathway, such as RAS and RAF. Activating RAS mutations are contained in 30% of human cancers (Roberts and Der 2007). KRAS mutations are particularly prevalent in pancreatic adenocarcinoma, non-small cell lung cancer (NSCLC), and colorectal cancer (CRC) (Neuzillet et al 2014; Prior et al 2012). NRAS and HRAS mutations have high prevalence in melanoma and bladder cancer, respectively (Prior et al 2012). $BRAF^{V600E}$ is the most common activating BRAF mutation and is found in melanoma, CRC, and NSCLC (Neuzillet et al 2014; Wan et al 2004).

Two distinct classes of ERK inhibitor have been described to date (Blake et al 2016; Morris et al 2013). Both classes directly inhibit the kinase activity of ERK. In addition, the second class also prevents the phosphorylation of ERK itself. Two examples of the first class of ERK inhibitor (which solely inhibit the phosphorylation of downstream ERK substrates) have been tested clinically and have shown some preliminary clinical activity in MAPK-activated cancers; namely ulixertinib (BVD-523) and GDC-0994 (Sullivan et al 2018; Li et al presentation 2017; Varga et al 2020; Infante et al abstract 2015; Infante et al presentation 2015). SCH772984 is an example of the second class of ERK inhibitor, which, in addition to inhibiting ERK kinase activity, also prevents the phosphorylation of ERK (Morris et al 2013). ASTX029 belongs to this second class of ERK inhibitor and is able to modulate the phosphorylation of ERK as well as directly inhibit kinase activity (as presented in the current ASTX029 Investigator Brochure [IB] Section 4.1.1.3). An ERK inhibitor with this profile (dual mechanism of MAPK pathway inhibition) may prove to be more efficacious than the first class of ERK inhibitor in tumors driven by this pathway, which provides the rationale for clinically testing ASTX029 in this study.

Figure 1: The MAPK Signaling Pathway



AKT=protein kinase B; CCND1=cyclin D1; DUSP=dual specificity phosphatase; ERK=extracellular signal-regulated kinase; GRB2=growth factor receptor-bound protein 2; MAPK=mitogen-activated protein kinase; MEK=mitogen-activated extracellular signal-regulated kinase; P=phosphorylated; RAF=rapidly accelerated fibrosarcoma; RAS=rat sarcoma virus; RSK=ribosomal s6 kinase; RTK=receptor tyrosine kinase; SOS=Son of Sevenless; SPRY=sprouty.
Source: Adapted from Lito et al 2013

1.2.2. ERK Inhibition as Potential Antitumor Treatment Option

Targeting the MAPK pathway has been clinically validated by BRAF inhibitors (eg, vemurafenib and dabrafenib) and MEK inhibitors (eg, trametinib and cobimetinib) (https://www.accessdata.fda.gov/scripts/cder/daf/). These agents elicit profound antitumor responses in $BRAF^{V600E}$-mutant melanoma patients, although responses are often short-lived, due to the onset of acquired drug resistance (Flaherty et al 2012; Hauschild et al 2012; Little et al 2012; Chapman et al 2011; Solit and Rosen 2011). A common feature of RAF or MEK inhibitor resistance mechanisms is the reactivation of ERK signaling, which drives proliferation and survival of the cells, even in the presence of BRAF and MEK inhibitors (Little et al 2012; Wagle et al 2011; Nazarian et al 2010; Emery et al 2009).

As ERK is the primary downstream effector of the MAPK pathway, it is hypothesized that ERK inhibitors may prove to be less susceptible to oncogenic bypass than RAF and MEK inhibitors and, therefore, have the potential to improve clinical outcomes in these patient populations (Nissan et al 2013).

Several ERK inhibitors have recently entered clinical development, although none have gained regulatory approval yet. ERK inhibitors in clinical development include GDC-0994 (Genentech; oral route), ulixertinib (BioMed Valley; oral route), LY3214996 (Eli Lilly; oral route) CC-90003 (Celgene; oral route) LTT462 (Novartis; oral route), KO-947 (Kura Oncology; intravenous [IV] route) and MK-8353 (Merck Sharp & Dohme Corp; oral route) (https://clinicaltrials.gov/). Notably, in the Phase 1 study of GDC-0994 (an ERK1/2 inhibitor), partial responses were observed in 2 subjects with BRAF mutant CRC (Varga et al 2020). Responses were also observed in subjects with BRAF and NRAS mutations enrolled in a Phase 1-2 study of ulixertinib (Sullivan et al 2018; Li et al presentation 2017; Infante et al abstract 2015; Infante et al presentation 2015).

ASTX029 is a synthetic small molecule that was developed using fragment-based drug discovery platform. Unlike most ERK inhibitors currently in the clinic, ASTX029 both prevents the phosphorylation of ERK and directly inhibits ERK kinase activity, which is expected to produce a more effective blocking of the MAPK pathway. Please refer to the current ASTX029 IB Section 4.1.

1.3. Summary of Nonclinical and Clinical Data for ASTX029

The following nonclinical data are summarized in this section. Please refer to the current ASTX029 IB for complete information.

- Absorption, distribution, metabolism, and excretion (ADME) properties in mouse, rat, dog, non-human primate, and human studies (Section 1.3.2.1).
- Pharmacokinetic (PK) properties in mouse, rat, and dog studies (Section 1.3.2.1).
- Nonclinical pharmacology properties of ASTX029 (Section 1.3.2.2).
- In vitro safety pharmacology studies and in vivo cardiovascular safety pharmacology of ASTX029 in dogs (Section 1.3.2.3).

1.3.1. Toxicology in rat and dog studies (single-dose and repeat-dose studies) (Section 1.3.2.4).

1.3.1.1. Chemical Name of Compound

Refer to Section 7.1.1 for the molecular formula of ASTX029.

The oral and IV routes of administration were used in the animal studies. Oral administration is proposed for this FIH study.

1.3.2. Nonclinical Data

1.3.2.1. Absorption, Distribution, Metabolism, and Excretion Studies and Nonclinical Pharmacokinetics

ASTX029 in vitro ADME properties were evaluated in mouse, rat, dog, non-human primate, and human studies, and in vivo PK properties were evaluated in mouse, rat, and dog studies.

ASTX029 was moderately permeable in Caco-2 cell monolayer model and displayed efflux that was not inhibited with a p-glycoprotein inhibitor. ASTX029 showed very high plasma protein binding across species (≥99.4%) and was highly bound to human serum albumin (≥98.5%). However, ASTX029 did not appear to bind to human red blood cells. Intrinsic clearance of ASTX029 in hepatic microsomes was low (dog) to moderate (mouse, rat, and human) across species, but was high in the non-human primate. In hepatic microsomes, 4 metabolites of ASTX029 were detected across the 5 species. ASTX029 underwent oxidation of the tetrahydropyran (THP) ring and O-demethylation of the methoxyphenyl group to the O-desmethyl metabolite (AT37200). The O-desmethyl metabolite was detectable in all species. The in vivo metabolite profile in the rat was similar to that defined in vitro.

ASTX029 was a CYP3A4 substrate in expressed human CYPs and human liver microsomes demonstrating concentration dependent clearance in both test systems. The inhibition of the metabolism of ASTX029 by ketoconazole supported the conclusion that metabolic clearance was principally CPY3A4 mediated. In human liver microsomes, ASTX029 was a weak to moderate inhibitor of CYP3A4 metabolism, which was substrate dependent. The inhibition of CYP3A4 increased after a pre-incubation step, indicating time-dependent inhibition of CYP3A4. Weak inhibition of CYP2C9 and CYP2C19 by ASTX029 was also observed in human liver microsomes.

In a preliminary assessment of transporter interactions, ASTX029 showed moderate inhibition of probe substrate uptake by OATP1B1 and weak inhibitory action on uptake of a bile salt export pump (BSEP) substrate.

ASTX029 administered via the IV route in mouse, rat, and dog exhibited a low clearance of ≤25% of liver blood flow across species, with the dog showing the lowest clearance. The volume of distribution at steady state (V_{ss}) was low for all species, which is consistent with the very high plasma protein binding observed across species. ASTX029 had a short half-life in all species following IV administration. Following oral administration, ASTX029 was bioavailable in all species with the highest bioavailability being achieved in the dog. There was evidence of pre-systemic metabolism and low bioavailability in rats at a dose of 1 mg/kg. Separate studies showed there was a supra-proportional relationship between dose and exposure in rats at oral doses of 1 mg/kg and 100 mg/kg. Evaluation of the elimination routes of ASTX029 in the rat showed that 10% of an IV dose was excreted in the bile, with minimal renal elimination. These results indicate that the primary mechanism of clearance is likely via metabolism.

In general, dose proportional PK were observed in mice for oral doses between 50 and 150 mg/kg. Furthermore, the PK showed no accumulation on repeat administration.

ASTX029 distributed into tumor xenografts with a plasma to tumor ratio of 0.3 to 0.5. The higher plasma concentrations compared to tumor concentrations are likely due to very high plasma protein binding of ASTX029. Evaluation of ASTX029 in multiple studies where

75 mg/kg was administered orally to male Balb/c nude mice bearing xenografts, indicated the PK of ASTX029 were variable.

Determination of the plasma concentrations in dogs following oral administration of ASTX029 in formulations consisting of d-α-tocopherol polyethylene glycol 1000 succinate (TPGS), ethanol, and propylene glycol in different ratios showed that the presence of TPGS was important for achieving good exposure. The optimal formulation for maximum exposure was determined to be 80% propylene glycol, 10% ethanol, and 10% TPGS.

The ASTX029 spray-dried dispersion (SDD)-based tablet ("tablet") formulation, the SDD formulation (suspension), and the powder-in-bottle (PiB) formulation were administered to cynomolgus monkeys at a single dose of 20 mg/kg to compare the overall systemic exposures. Systemic exposures, as measured by mean area under concentration-time curve from time 0 to the last data point (AUC_{last}), were comparable between the tablet and the SDD suspension, whereas exposure was 2-fold higher following tablet administration compared to following PiB administration, although variability was also higher for SDD-based forms. Please refer to the current ASTX029 IB for more information.

Food-effect studies were recently conducted in monkeys and dogs following a single dose of ASTX029 tablets at 10 mg/kg or 2 mg/kg, respectively. In 2 monkey studies, animals were dosed after having been fed 30 minutes previously or after having been fasted overnight. In a dog study, animals were dosed after having been fed a high-fat diet 30 minutes previously or after having been fasted overnight. Data from these food-effect studies demonstrate increased ASTX029 exposures in monkeys (~3.8- to ~4.3-fold) and dogs (~5.6-fold) following fasted-state dosing compared to fed-state dosing. Based on these findings, food may have a negative effect on the exposure of ASTX029 in humans.

1.3.2.2. Nonclinical Pharmacology Studies

In vitro studies with ASTX029 have shown that the compound inhibits ERK2 and ERK1 catalytic kinase activity with nanomolar potency (2.7 nM and ~3 nM, respectively). The inhibition of ERK kinase activity has been demonstrated in cancer cells and in vivo models by measuring the effect of ASTX029 on the phosphorylation levels of the ERK substrate RSK. Furthermore, experiments with isolated enzymes and cell-based assays confirmed that ASTX029 prevents the phosphorylation of ERK by MEK without directly inhibiting MEK activity.

Cellular studies have shown that ASTX029 inhibits proliferation in a wide variety of MAPK-activated tumor cell lines derived from multiple tumor types. In vivo, oral administration of ASTX029, over a range of doses, confers antitumor activity in a number of tumor cell line xenograft models with MAPK pathway activation (BRAF-mutant melanoma and CRC, KRAS-mutant lung cancer and CRC, and NRAS-mutant melanoma); tumor regression was achieved in several of these models. Please refer to the ASTX029 IB for a more detailed description.

1.3.2.3. Safety Pharmacology

ASTX029 was tested for inhibition of the hERG (human ether-a-go-go-related gene) ion channel using an automated patch clamp and a manual patch clamp assay and was shown to inhibit hERG channel with a half-maximal inhibition (IC_{50}) concentration of 11 μM. As ASTX029 is highly

protein bound (greater than 99%), the free fraction or circulating ASTX029 in vivo is unlikely to approach these levels. No QT interval corrected for heart rate (QTc) prolongation was observed in the Good Laboratory Practice (GLP) in vivo acute cardiovascular safety pharmacology study in dogs, in which ASTX029 was administered to telemetered dogs at doses up to 30 mg/kg. No relevant effects were noted on arterial blood pressure, heart rate, core body temperature, or lead II electrocardiogram (ECG) intervals at any dose level. A higher incidence of second degree atrioventricular (AV) block was noted in 1 animal after a 30 mg/kg dose. This may have been due to a higher background incidence of arrhythmia in this animal compared to the other animals in the study, but this could not be confirmed as this dog did not receive vehicle control or any lower doses. Therefore, an association with ASTX029 cannot be completely ruled out at this time.

1.3.2.4. Toxicology Studies

The initiation of the FIH study of ASTX029 (also known as AT35029) is supported by 2 pivotal GLP toxicology studies. ASTX029 refers to any form of AT35029, AT35029X refers to the free base form, and AT35029W is the monohydrate. These studies used oral twice a day (BID) and daily (QD) dosing with ASTX029 for 28 days (followed by a 2-week recovery) in rats and dogs and are intended to support the initial clinical regimen to be investigated in late-stage cancer patients. Earlier, non-GLP, studies in both species were conducted to enable the design for the pivotal GLP studies. The toxicology program for ASTX029 followed ICH and FDA Guidance *S9 Nonclinical Evaluation for Anticancer Pharmaceuticals*, dated March 2010 (FDA S9 2010), ICH and FDA Guidance *M3(R2) Nonclinical Safety Studies for the Conduct of Human Clinical Trials and Marketing Authorization for Pharmaceuticals*, dated January 2010 (FDA M3(R2) 2010), and FDA Guidance *Nonclinical Safety Studies for the Conduct of Human Clinical Trials and Marketing Authorization for Pharmaceuticals Questions and Answers (R2)*, dated March 2013 (FDA 2013).

As the intended initial clinical population consists of patients with advanced cancer, in accordance with the ICH Tripartite S9 guidance (FDA S9 2010), certain toxicology studies, such as stand-alone neurobehavioral, respiratory safety pharmacology, and genotoxicity studies with ASTX029 have not yet been conducted. A GLP cardiovascular safety pharmacology study in dogs has been completed and is included in the Safety Pharmacology section above (Section 1.3.2.3).

In rats, repeat-dose toxicity of ASTX029 was evaluated first in 3 dose-range finding (DRF) studies of 14-days duration using BID and QD dosing, followed by a pivotal 28-day GLP study with continuous QD dosing for 28 days (followed by a 2-week recovery period). In the initial BID DRF study in male rats, doses above 60 mg/kg/day (30 mg/kg BID) were not tolerated, leading to severe body weight loss and early termination. Subsequent studies were conducted using QD dosing, based on efficacy data indicating that QD dosing is adequate. The DRF studies using either BID or QD dosing consistently showed that dose levels above 60 mg/kg/day were not tolerated in either male or female rats. Key findings across all DRF studies were reproducible and were consistent with the known class effects of inhibitors of the MAPK pathway (Diaz et al 2012; Yanochko et al 2013). Changes in hematology (indicative of anemia and/or inflammation) and clinical chemistry parameters (indicating changes in liver and kidney function) were seen, including changes in serum phosphate levels.

Histopathological changes at 60 mg/kg/day included mineralization of the aorta and stomach (glandular portion) and other effects in the colon/cecum and lymph nodes. The mineralization seen is likely to be related to the pharmacology of ASTX029. Widespread mineralization affecting the stomach, kidney, colon, and arteries has been described to be related to MEK inhibition through FGF-23 signal blockade (Diaz 2012; Yanochko et al 2013). The resulting increased levels of the active form of vitamin D (1,25-dihydroxyvitamin D3) and, in turn, of Ca and P are considered the cause of metastatic calcification (Diaz 2012; Yanochko et al 2013). Although no changes in serum Ca and P were seen in the GLP study in rats, they were seen in the preceding DRF studies, and changes in these cations are considered relevant to the proposed pathogenesis of soft tissue calcification seen in this study. Based on the DRF studies, high doses of 60 mg/kg/day for males and 50 mg/kg/day for females were selected as the top doses for GLP studies to account for the gender difference in exposure and sensitivity.

In the pivotal rat GLP study, ASTX029 administered orally to male and female Sprague Dawley rats QD for 28 consecutive days at 0, 6, 18, 50 (females), or 60 (males) mg/kg/day caused morbidity and severe clinical signs including scabs and body weight loss at the high dose of 50 mg/kg/day in females with 6 animals prematurely euthanized between Days 19 and 22. The rest of the group were either euthanized on Day 22 or assigned to the recovery group with no further doses administered. In males given 60 mg/kg/day, 2/15 males were also euthanized on Day 22 in poor condition, showing decreased body weight. At the high dose, which was clearly above tolerated level for the duration of this study, histopathology changes were present in multiple organs with the changes being grouped into soft tissue mineralization affecting the gastrointestinal (GI) tract, arterial system throughout, and the kidneys; degenerative ulcerative changes in the tongue and GI tract; bone and marrow changes due to infection and remodeling as a consequence of altered mineral homeostasis; and degenerative changes in the liver in the form of necrosis and inflammation. Hepatic periportal hypertrophy was also present.

Changes in hematology (indicative of anemia and inflammation) and clinical chemistry parameters (liver and kidney function parameters) were consistent with those seen in the DRF studies in rats given the high dose. Microscopic findings in the high dose (above levels of tolerability) animals were extensive and severe, with a number of target organs being identified that included the aorta, stomach, and colon/cecum (as seen previously in the DRF studies), plus skin, bone, liver, and kidney. At the intermediate dose of 18 mg/kg/day, minimal changes in hematology and clinical chemistry parameters were seen, all of which were consistent with those seen in DRF studies and recovered by the end of the treatment-free period. Microscopically, the only target organ in rats given 18 mg/kg/day was the skin, with lesions, seen only in females at this dose, that did not fully recover by the end of the 2-week treatment-free period. Based on the severity of the skin lesions in females given 18 mg/kg/day and the lack of findings in males, the no-observable adverse effect level (NOAEL) was considered to be 18 mg/kg/day, with systemic exposures on Day 28 in males of maximum concentration (C_{max}) 138 ng/mL and area under the plasma concentration-time curve from the start of dosing (0) to the last quantifiable time point (t) (AUC_{0-t}) 1,860 ng•h/mL and in females of C_{max} 3,340 ng/mL and AUC_{0-t} of 14,700 ng•h/mL. Given the difference in sensitivity between males and females at doses 18 mg/kg/day and above, the severely toxic dose in 10% of the animals (STD_{10}) (defined as the highest dose level that does not produce evidence of lethality, life-threatening toxicities, or irreversible findings) was considered to be above 18 but below 50/60 mg/kg/day. The exposure ratios for C_{max} and AUC_{0-t} were 0.01 and 0.14 for male rats and 0.25 and 1.13 for female rats, respectively, relative to

average exposures from the lowest dose tested (25 mg/kg) and shown to be efficacious in xenograft mouse studies (Colo205).

In dogs, repeat-dose toxicity was first evaluated in a DRF study of 14 day's duration using QD dosing, followed by a pivotal 28-day GLP study using continuous QD dosing (plus a 2-week recovery period). In the DRF study, morbidity/early terminations occurred at the highest dose tested (16 and 30 mg/kg/day, respectively, in male and female dogs) manifested by severe clinical signs and reduced body weight, suggesting males to be more sensitive to the toxic effects of ASTX029, albeit with limited number of animals (1 per dose) evaluated. This was reflected in the higher systemic exposures achieved in males versus females for a given dose. Key findings were changes in hematology and clinical chemistry parameters consistent with those seen in studies with rats. Macroscopically, findings were seen in the gastric mucosa of the stomach. The maximum tolerated dose (MTD) was considered to be ≥12 mg/kg/day in this study, but given the longer duration of the GLP study, the high dose of 10 mg/kg/day was selected for the pivotal 4-week toxicology study. In the DRF study, the dose level of 12 mg/kg/day in the male dog was associated with C_{max} and AUC_{0-t} values of 32,400 ng/mL and 120,000 ng•h/mL, respectively, on Day 14. For the female dog receiving 16 mg/kg/day, the C_{max} and AUC_{0-t} values on Day 14 were 24,200 ng/mL and 66,800 ng.hr/mL, respectively.

In the pivotal GLP dog study, dose levels were 0, 1.5, 3.5, and 10 mg/kg. One male at the mid-dose of 3.5 mg/kg/day was euthanized early on Day 20 due to severe clinical symptoms and body weight loss. Microscopic evaluation revealed significant findings in the GI tract that were believed to be the cause of the clinical condition of the animal leading to early termination. Exposure achieved in in this animal was high for the group, overlapping with those achieved at the highest dose of 10 mg/kg/day. In animals surviving to scheduled termination, key findings included changes in hematology parameters consistent with anemia and inflammation, changes in coagulation parameters (increased fibrinogen), and minimal changes in clinical chemistry (decreased albumin at ≥1.5 mg/kg/day and total protein at 10 mg/kg/day). The ECG measurements revealed incidence of second degree AV block in 1 female and premature ventricular complex in another female dog given 10 mg/kg/day on scheduled measurement on Day 23. A second measurement taken on Day 29 showed the same findings (but in reverse with respect to the 2 animals affected). These animals were retained for further measurements at the end of the recovery period and showed no findings. In this study, the period of recording was short (1 to 2 minutes), and these arrhythmias are also reported to be common background findings in beagle dogs (Cools et al 2011; Tilley 1992). The incidences of arrhythmias observed in this study with ASTX029 were within ranges reported in normal dogs. Of note, dogs have high cardiac vagal tone compared to humans and sinus arrhythmia and sinus pauses can be quite pronounced in normal dogs (Cools et al 2011). Second degree AV block is also found in normal animals and is often associated with sinus arrhythmia and high vagal tone (Cools et al 2011). The potential for ASTX029-related cardiac arrhythmia was further investigated in a dedicated standalone GLP cardiovascular safety pharmacology study in dogs, in which some evidence for this was seen, with 1 dog showing high incidence of arrhythmias at the high dose (30 mg/kg. However, this animal did not receive other doses or vehicle treatment in the study and, as such, although a clear relationship to study treatment could not be conclusively established, based on available evidence from both studies, a relationship to ASTX029 could not be completely ruled out since they were only observed in animals in the high dose group.

In the dog pivotal study, ASTX029-related microscopic findings were present in the esophagus and spleen. In 1 female dog, given 10 mg/kg/day, inflammation and ulceration were seen in the esophagus, which may have correlated with episodes of vomiting recorded on Days 17 and 18 in this animal and were considered adverse due to the severity. In addition, extramedullary hematopoiesis was observed in both sexes at 10 mg/kg/day and correlated with changes in hematology parameters indicative of anemia. This change was considered to be a physiological response to the anemia and, therefore, was considered nonadverse. Overall, based on the nontolerability seen at 3.5 mg/kg/day in 1 male dog, the highest non-severely toxic dose (HNSTD) was considered to be 1.5 mg/kg/day, which also coincided with the NOAEL for this study. The exposure ratios for C_{max} and AUC_{0-t} were 0.51 and 1.04 for male dogs and 0.07 and 0.21 for female dogs, respectively, relative to average exposures from the lowest dose tested (25 mg/kg) and shown to be efficacious in xenograft mouse studies (Colo205).

Although the toxicities seen and target organs identified at the NOAEL dose in rats (mid-dose level, skin) and HNSTD/NOAEL in dogs (low-dose level, GI tract), these dose levels in these species were toxicologically meaningful as they produced toxicities that have been seen with compounds in this class. More severe toxicities observed at higher dose levels that were above tolerability are likely also explained by exaggerated pharmacology consistent with class effect. With the exception of the 1 dog at the intermediate dose (3.5 mg/kg) level that terminated early due to severe clinical signs explained by severe GI toxicities, other findings in the dog study were minimal including those in animals from the high-dose level, and were fully recovered following the 2-week treatment-free period. However, in rats, the high dose (60 mg/kg in males or 50 mg/kg in females) was clearly not tolerated due to a multitude of target organs being affected due to exaggerated pharmacology as well as secondary infections due to severe skin lesions.

Data from a bacterial reverse mutation test in *Salmonella typhimurium* and *Escherichia coli* ("Ames test"), an in vivo mammalian erythrocyte micronucleus test in the mouse, an in vitro chromosomal aberration assay in human peripheral blood lymphocytes reveal no evidence of genotoxicity.

In conclusion, the main findings in toxicity evaluation studies in both species tested were consistent with the expected pharmacological action of ASTX029 (ie, findings in bone, soft tissue mineralization, skin lesions, and ulceration of the GI tract). Other findings, such as minimal effects on liver function with no associated histopathology correlates, may be due to the chemical toxicity of ASTX029. For an ERK inhibitor, tissue mineralization is a known class effect relating to perturbation of phosphate handling linked to vitamin D levels and FGF-23 inhibition (Diaz et al 2012; Yanochko et al 2013). In addition, delayed skin lesions (rash) have also been seen clinically with ERK and MEK inhibitors (Sullivan et al 2018; Li et al presentation 2017; Varga et al 2020; MacDonald et al 2015; Manousaridis et al 2013). Since the lower (in terms of human equivalent dose) NOAEL (and the HNSTD) was seen in the dog, this species is considered more sensitive than the rat to the toxicity of ASTX029 based on dose alone. However, considering the overlapping observed systemic exposures in rat and dog pivotal studies at the HNSTD in dogs and the NOAEL in rats and also the apparent gender differences seen in both species, the distinction of the dog as the more sensitive species is tentative. In addition, some key findings in the rats (tissue mineralization, skin lesions), which are consistent with known class effects of MAPK pathway inhibitors, can be considered relevant to the clinic.

Therefore, due to the overlapping exposures at toxicologically meaningful doses in rats and dogs, both species have been considered for calculation of the proposed starting dose for the FIH clinical trial.

1.3.3. Clinical Data and Human Pharmacokinetics

This is an FIH study for ASTX029. For current data, please refer to the ASTX029 IB.

1.4. Summary of Data for Other Study Treatment

This is a clinical study of ASTX029 as a single agent (monotherapy). No active control treatments are planned.

1.5. Potential Risks and Benefits to Human Subjects

The MAPK pathway is a key regulator of cellular proliferation and survival. Somatic alterations in MAPK pathway components that deregulate the pathway are highly prevalent in human cancer (Santarpia et al 2012; Kim and Choi 2010; Dhillon et al 2010; Roberts and Der 2007). Agents targeting the MAPK pathway (eg, BRAF and MEK inhibitors) have demonstrated clinical efficacy and have attained regulatory approval for BRAF-mutated metastatic melanoma (Bollag et al 2012) and BRAF mutated NSCLC (FDA 2017). Recently, several ERK inhibitors have entered clinical testing (https://clinicaltrials.gov/); however, none have yet attained regulatory approval.

In the FIH Phase 1-2 trial of the ERK inhibitor ulixertinib at oral doses up to 900 mg administered twice a day (BID), treatment-related dose limiting toxicities (DLTs) included Grade 3 rash, Grade 3 pruritus, Grade 3 aspartate aminotransferase (AST) elevation, Grade 3 and Grade 2 diarrhea, Grade 3 vomiting, Grade 3 dehydration, Grade 3 elevated creatinine, and Grade 2 hypotension. At the recommended Phase 2 dose (RP2D) of 600 mg BID, ulixertinib was commonly associated with cutaneous adverse events (AEs) (rash, pruritus, dermatitis acneiform, and dry skin), GI AEs (diarrhea, nausea, and vomiting), decreased appetite, fatigue, and peripheral edema (Sullivan et al 2018; Li et al presentation 2017; Infante et al abstract 2015; Infante et al presentation 2015), with 32% of subjects requiring dose reductions. One event each of retinal vein occlusion (RVO) and cardiac failure and 2 events of acute renal failure were reported. Responses were observed in subjects with typical and atypical BRAF mutations and NRAS mutations.

In an FIH Phase 1 trial of another ERK inhibitor, GDC-0994 at oral doses up to 800 mg once a day for the first 21 days of a 28-day cycle, was associated with rash, diarrhea, visual disturbances, and asymptomatic LVEF decrease. At the RP2D of 400 mg, GDC-0994 was commonly associated with cutaneous AEs (rash, dry skin, and dermatitis acneiform); GI AEs (diarrhea, nausea, and vomiting), decreased appetite, fatigue, visual disturbances (blurred vision) and peripheral and periorbital edema (Varga et al 2020). Responses were observed in 2 subjects with CRC and BRAF mutations.

This study represents the first use of ASTX029 in humans, and, as with any investigational medicinal product (IMP), subjects may experience reactions or complications that are unknown and, therefore, unpredictable. Risks to subjects participating in this first evaluation of ASTX029 in a human clinical trial include the potential for adverse reactions. Due to its mechanism of

action, ASTX029 may have a toxicity profile similar to that of other ERK inhibitors in clinical development with the main findings in toxicity evaluation studies in both species tested being consistent with the expected pharmacological action of ASTX029, ie, findings in bone, soft tissue mineralization, skin lesions, and ulceration of the GI tract, and the main findings at the STD_{10}/NOAEL dose in rats and HNSTD dose in dogs being skin lesions (rats), GI lesions (dogs), and potential arrhythmias based on unconfirmed evidence from studies in dogs at higher doses (ASTX029 IB).

The potential for these AEs warrants frequent monitoring of subjects participating in this Phase 1-2 study of ASTX029 until the safety profile is further understood. In particular, clinical signs and/or symptoms of skin, ocular, GI, and liver toxicities and LVEF decrease (see Appendix 4, Appendix 5, Appendix 6, Appendix 7, and Appendix 8, respectively) as well as hematology and clinical chemistry parameters will be closely monitored during clinical studies that employ ASTX029.

These and other risks of ASTX029 in humans are described further in Section 8, Risks/Precautions. For more detailed information, please refer to the ASTX029 IB.

2. RATIONALE

2.1. Rationale for the Study

The MAPK pathway is a key regulator of cellular proliferation and survival. Somatic alterations in MAPK pathway components that deregulate the pathway are highly prevalent in human cancer (Dhillon et al 2007; Roberts and Der 2007). Activation of the ERK pathway in tumors can result from mutations in RAS genes (KRAS, NRAS, HRAS), mutations in BRAF and MEK, or activation of RAS by cell surface receptors (Nissan et al 2013).

The primary objectives of the Phase 1 portion of this study are to assess safety and to identify the MTD, the RP2D, and the recommended dosing regimen of ASTX029 administered orally.

The primary objective of the Phase 2 portion of this study is to assess preliminary clinical activity, as determined by objective response rate (ORR) in tumors characterized by gene aberrations in the MAPK signal pathway that may confer sensitivity to ASTX029.

2.2. Rationale for ASTX029 Dose and Regimen and Justification of the Starting Dose

The starting dose for the FIH trial in cancer patients is proposed using available nonclinical data, following ICH and FDA Guidance *S9 Nonclinical Evaluation for Anticancer Pharmaceuticals*, dated March 2010 (FDA S9 2010), and using dose conversions in accordance with FDA Guidance *Estimating the Maximum Safe Starting Dose in Initial Clinical Trials for Therapeutics in Adult Healthy Volunteers*, dated July 2005 (FDA 2005), using data from GLP studies in the rat and dog. As dose levels slightly above the NOAEL are possibly in the low end of the range of STD_{10} for rats as a conservative estimate, the NOAEL of 18 mg/kg derived from 28-day continuous daily dosing in rats corresponds to the human equivalent dose (HED) of 108 mg/m^2, which, converted to a fixed dose based on an average body surface area (BSA) of 1.7 m^2 and applying a 1/10th safety factor adjustment, suggests a starting human dose of 18.36 mg. The 1.5 mg/kg NOAEL/HNSTD dose from the dog GLP study corresponds to an HED of 30 mg/m^2 and translates to approximately 8.5 mg fixed dose based on BSA conversion and applying a 1/6th adjustment (Table 1).

Table 1: Proposed Human Starting Dose

	HED, mg/m^2	Implied Starting Dose, mg[a]	Proposed Starting Dose, mg (Fixed)
Rat NOAEL, 18 mg/kg	108	18.36	10
Dog NOAEL/HNSTD, 1.5 mg/kg	30	8.5	

BSA=body surface area; HED=human equivalent dose; HNSTD=highest non-severely toxic dose; NOAEL=no-observable adverse effect level.

[a] Based on average human BSA of 1.70 m^2 and applying a safety factor of 1/10 for STD_{10} and 1/6 for HNSTD (per ICH S9 [FDA S9 2010]).

In view of the variability in the toxicokinetic data in the 28-day GLP studies and the overlapping exposures seen in rats and dogs at the NOAEL and HNSTD, a fixed dose of 10 mg is proposed for the starting dose in FIH clinical trials in cancer patients (ie, an intermediate dose between the implied starting doses calculated using dog and rat data but, conservatively, closer to the low end of the range).

ASTX029 has been shown to be efficacious in immunocompromised mouse xenograft models. At the lowest dose tested of 25 mg/kg (Colo205) systemic exposures as measured by C_{max} and AUC_{last} in the range of 9,618 to 16,880 ng/mL and 8,553 to 17,490 ng•h/mL, respectively, produced significant tumor growth inhibition as well as maximum inhibition of the RSK pharmacodynamic biomarker. The averages of these exposure values, 13,249 ng/mL for C_{max} and 13,022 ng•h/mL for the AUC_{last}, were used for exposure comparisons with toxicokinetic data from toxicology studies. However, in xenograft studies following oral administration at 25 mg/kg, ASTX029 caused near maximal inhibition of the phosphorylation of ribosomal S6 kinase (RSK) in Colo205 tumors and, on repeat administration, produced significant tumor growth inhibition. Therefore, inhibition of extracellular signal-regulated kinases (ERK) is also anticipated at lower doses and lower exposures (AUC) of ASTX029.

The proposed clinical starting dose of 10 mg is less than $1/50^{th}$ of projected human dose of 500 mg estimated to produce AUC exposures in the presumed targeted therapeutic range, assuming translation from immunocompromised xenograft mouse pharmacology models.

As in most targeted cancer therapy with kinase inhibitors, a continuous target engagement through continuous dosing is usually recommended, which will be the first regimen tested for ASTX029. However, ERK inhibitors are predicted to have a narrow therapeutic window when given continuously; therefore, an intermittent regimen (2 weeks on/1 week off) may also be tested in this FIH study. The regimen may be further adjusted (eg, 1 week on/1 week off) based on emerging clinical data and DSRC recommendations.

The rationale for the RP2D and regimen is discussed in Section 7.3.

3. STUDY OBJECTIVES

3.1. Primary Objectives

- Phase 1 (Parts A and B): To assess safety and to identify the MTD, the RP2D, and the recommended dosing regimen of ASTX029.
- Phase 2: To assess preliminary clinical activity, as determined by ORR in tumors characterized by gene aberrations in the MAPK signal pathway that may confer sensitivity to ASTX029.

3.2. Secondary Objectives

- To determine the PK profile of ASTX029 including the food effect on PK parameters.
- To evaluate other clinical activity parameters, such as duration of response (DOR), disease control rate (DCR), progression-free survival (PFS), and overall survival (OS).
- To evaluate relevant pharmacodynamic markers and target engagement (ie, phosphorylated ribosomal s6 kinase [pRSK] inhibition) in tumor biopsies.

3.3. Exploratory Objectives

- To identify and evaluate biomarkers of ASTX029 activity.

4. INVESTIGATIONAL PLAN

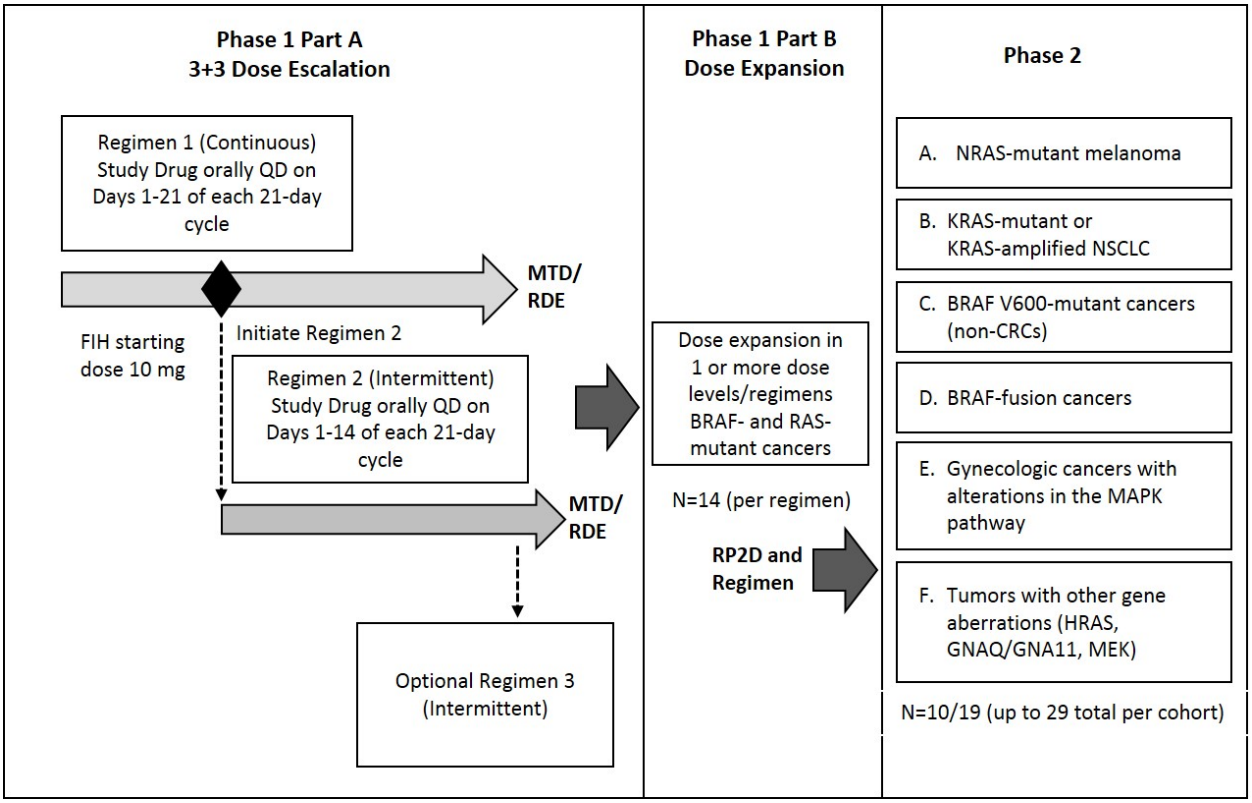
4.1. Overall Study Design

This is an FIH, open-label, multicenter, Phase 1-2 study to assess the safety of ASTX029, determine the MTD, RP2D, and recommended dosing regimen for ASTX029, and to obtain preliminary clinical activity, PK, and pharmacodynamic data in subjects with advanced solid tumors for whom standard life-prolonging measures or approved therapies are not available.

It is anticipated that up to 300 evaluable subjects will be enrolled in this study if the study fully enrolls both Phases 1 and 2. This includes approximately 120 subjects in Phase 1 at up to 14 study centers in the US and Europe and up to approximately 180 evaluable subjects in Phase 2 at up to 30 study centers in North America and Europe. The expected study duration is approximately 5 years (61 months), including approximately 55 months for recruitment and approximately 6 months for safety follow-up.

This study consists of 2 phases, as shown in the study schema below (Figure 2).

Figure 2: Study Schema



BRAF=B isoform of RAF kinase; CRC=colorectal cancer; DSRC=Data Safety Review Committee; FIH=first in human; GNA11=G protein subunit alpha 11; GNAQ=G protein subunit alpha q; KRAS=Kirsten RAS; MEK=mitogen-activated extracellular signal-regulated kinase; MTD=maximum tolerated dose; NRAS=neuroblastoma RAS; NSCLC=non-small cell lung cancer; PK=pharmacokinetic; RAS=rat sarcoma virus; QD=daily; RDE=recommended dose for expansion; RP2D=recommended Phase 2 dose.
Notes: After reaching MTD or RDE for Regimens 1 and 2, the DSRC will advise if it is appropriate to test an alternative intermittent regimen (Optional Regimen 3) and will recommend the dose and dosing regimen to be used. One or more dose levels (and regimens) may be studied in Phase 1 Part B to supplement available safety, PK, and/or clinical activity data and to evaluate target engagement in fresh tumor tissue biopsies. In Phase 2 Cohort D, the sponsor, with approval of the DSRC, may expand enrollment for a particular molecularly defined subpopulation in which the most number of responses are observed to 10 or 29 subjects for better assessment of activity in that disease subpopulation (Optional Cohort D expansion). It is expected that no more than 2 subpopulations will be expanded in this manner.

ASXT029 was originally introduced into the clinic in the PiB form (Section 7.1.1) and administered under fed conditions (Section 7.1.5). Protocol Amendment 1.0 introduced the tablet dosage form (Section 7.1.6) when it became available. Protocol Amendment 2.0 introduced the evaluation of administration under fasted conditions during Phase 1 Part A dose escalation (Section 7.1.7).

At the time of writing Protocol Amendment 4.0, the COVID-19 pandemic is altering the way clinical studies are being conducted such that alternative measures are being implemented to ensure the safety of subjects and maintain the integrity of clinical trial data. Appendix 9 details information regarding potential modifications to the conduct of the study during the pandemic.

4.1.1. Phase 1

The Phase 1 portion of the study will consist of Parts A and B as follows:

Part A (Dose Escalation): The dose-escalation stage will identify the MTD of up to 2 dosing regimens of ASTX029 and the recommended dose for expansion (RDE), defined as either the MTD or a dose below the MTD that the DSRC agrees shows adequate safety, PK, and/or preliminary biological or clinical activity.

Subjects will receive 1 of up to potentially 2 ASTX029 dosing regimens. Subjects in Regimen 1 will receive ASTX029 orally once a day on Days 1 through 21 of each 21-day cycle (Regimen 1; continuous dosing), and, if Regimen 2 is opened to enrollment, subjects in Regimen 2 will receive ASTX029 orally once a day on Days 1 through 14 of each 21-day cycle (Regimen 2; intermittent dosing, 2 weeks on/1 week off).

Initially, subjects will be allocated to Regimen 1 (continuous dosing). Subjects in the first cohort of Regimen 1 will receive a flat starting dose of 10 mg QD. Dose levels for subsequent cohorts will be determined by the DSRC. Planned initial escalation will be 100% (doubling the dose) until 160 mg. Smaller increments of dose escalation will be used above 160 mg. Dose doubling will also be discontinued if any 1 of the following occurs within a cohort:

- 1 subject experiences a DLT (Section 7.4).
- Any study-drug-related clinically significant ≥Grade 2 AE not adequately managed or resolved to baseline or Grade 1 by supportive treatment that, per the DSRC, indicates further dose doubling would be potentially unsafe for future subjects.
- Any study-drug-related AE or confluence of AEs that, per the DSRC, indicates further dose doubling would be potentially unsafe for future subjects.

After this point, dose escalation will then proceed in smaller increments (eg, by a 50% increase initially and an ~25% increase at the higher dose levels over the previous level) (Section 7.1.4) after review of all available safety, PK, and biomarker data from Cycle 1 in at least 3 subjects and approval by the DSRC.

Also, after this point, the sponsor, with approval of the DSRC, will determine if Regimen 2 is to be opened for enrollment. Randomization to either Regimen 1 or Regimen 2 will begin if both regimens are open for enrollment. Should Regimen 2 be evaluated, based on safety and PK data from Regimen 1 and depending on the nature, timing, and severity of observed AEs, the dose for the first cohort of subjects enrolled to Regimen 2 may be escalated to the next level pending approval by the DSRC. If the MTD is reached in 1 regimen before the other regimen, all subsequent subjects will be enrolled, without randomization, to the remaining regimen until the MTD is determined for each regimen evaluated.

After reaching MTD or RDE for Regimens 1 and 2, the DSRC will also advise if it is appropriate to test an alternative intermittent regimen (Optional Regimen 3, eg, 7 days on/7 days off) and will recommend the dose and dosing regimen to be used. The total dose per cycle for the new regimen will not exceed the total safe dose per cycle already established in the first 2 regimens. Dose levels and dosing regimens, the number of cohorts, and the number of subjects per cohort may be modified, as needed, in response to emerging data and recommendations from the DSRC.

The starting dose in each regimen evaluated will be escalated stepwise in successive cohorts of at least 3 evaluable subjects each with additional allowed expansion to 6 subjects (standard 3+3 study design) (Section 7.3) until the MTD is determined for each regimen.

Dose-escalation/de-escalation decisions will be based on the occurrence of DLTs (defined in Section 7.4) during the first 21-day cycle of each dose level, and the recommendations of the DSRC following review of all available safety, PK, and biomarker data from the completed first cycle of at least 3 subjects in each cohort (as described in Section 7.3). The DSRC will also advise whether or not it is appropriate to proceed to Part B (Dose Expansion).

Part B (Dose Expansion) will commence upon identification of the RDE for at least 1 regimen. The DSRC RDE decision will be based on all available safety, PK, biomarkers, and preliminary activity data from all cycles (including the potential for late or cumulative toxicity).

Part B (Dose Expansion): One or more dose levels (and regimens) may be studied in Phase 1 Part B to supplement available safety, PK, and/or clinical activity data to establish the RP2D and to evaluate target engagement in fresh tumor tissue biopsies. Subjects will have to meet the following molecular eligibility criteria: documented activating gene mutations in BRAF (BRAF V600 mutation or activating atypical non-V600 aberrations), KRAS, NRAS, or HRAS. The in vitro diagnostic (IVD) medical devices used in this study to determine genetic abnormalities are appropriately registered for use. A total of 14 evaluable subjects will be treated at each dose/regimen selected. If more than 1 dose/regimen is open for enrollment, subjects will be randomized in a 1:1 ratio. The DSRC will advise when it is appropriate to proceed to Phase 2 and will recommend the dose level and dosing regimen to be used. The RP2D decision by the DSRC will be based on all available PK, pharmacodynamic, safety, and preliminary activity data from all cycles (including the potential for late or cumulative toxicity). The RP2D could be the same or lower than the RDE.

4.1.2. Phase 2

The Phase 2 portion of the study will explore the preliminary single-agent antitumor activity of ASTX029 at the RP2D of the selected dosing regimen identified in Phase 1 Parts A and B in tumors characterized by gene aberrations in the MAPK signal pathway that may confer sensitivity to ASTX029. The Phase 2 part of the study will consist of the following up to 6 cohorts:

- Cohort A: NRAS-mutant melanoma.
- Cohort B: KRAS-mutant or KRAS-amplified NSCLC.
- Cohort C: BRAF V600-mutant cancers (non-CRCs).
- Cohort D: BRAF-fusion cancers.
- Cohort E: Gynecological cancers with alterations in the MAPK pathway.
- Cohort F: Tumors characterized by other gene aberrations that upregulate the MAPK signal pathway listed in Table 2.

Molecular eligibility will be based on the presence of documented gene aberrations in the MAPK pathway. The selection of these molecularly defined study populations is based on a comprehensive evaluation of ASTX029 nonclinical biology (as presented in the current

ASTX029 IB) and available literature (Table 2). In the first stage (Stage 1), 10 evaluable subjects will be enrolled into each cohort based on a Simon's Optimal 2-stage design (Simon 1989) at the RP2D and the dosing regimen identified in Phase 1 Parts A and B. If ≥2/10 responses are observed in a cohort, it will be expanded to a total of 29 subjects (Stage 2). For Cohort F (which will enroll patients with various tumor types and gene aberrations [Table 2]), the sponsor, with approval of the DSRC, may expand enrollment for a particular molecularly defined subpopulation in which the most number of responses are observed to 10 or 29 subjects under the same Simon's Optimal 2-stage design as for the other cohorts for better assessment of activity in that disease subpopulation (Optional Cohort F Expansion). It is expected that no more than 2 subpopulations will be expanded in this manner.

Table 2: Gene Aberrations Selected for Inclusion in Cohort F

Gene Aberration	Rationale	References
Activating HRAS mutations	ERK activity is commonly upregulated in cancer as a result of activating mutations within the RAS family of GTPases (KRAS, NRAS, and HRAS).	Kiessling et al 2015 Prior et al 2012
Activating GNA11 and GNAQ mutations	Activating mutations in the heterotrimeric G protein alpha subunit q (GNAQ) and 11 (GNA11) confer activation of the MAPK pathway.	Ambrosini et al 2012 Van Raamsdonk et al 2009
Atypical activating BRAF aberrations	Atypical (non-V600E) BRAF mutations can signal as constitutively active dimers (class 2) and can confer activation of the MAPK pathway. BRAF variants with in-frame deletions in the β3-αC-loop (ie, within or adjacent to residues L485-P490) can confer constitutive activation of BRAF.	Yao et al 2015 Chen et al 2016 Foster et al 2016
Activating MEK mutation	Activating MEK mutations confer upregulation of MAPK signaling.	Marks et al 2008

BRAF= B isoform of RAF kinase; ERK= extracellular signal-regulated kinase; GNA11= G protein alpha subunit 11; GNAQ=G protein alpha subunit q; GTPase=guanosine-5'-triphosphate enzyme; HRAS=Harvey RAS; KRAS=Kirsten RAS; MAPK=mitogen-activated protein kinase; MEK=mitogen-activated extracellular signal-regulated kinase; NRAS= neuroblastoma RAS; RAS=rat sarcoma virus.
Note: Other gene aberrations that in the investigator's opinion may confer sensitivity to ASTX029 may be included in Cohort F after obtaining approval from the Sponsor's medical monitor.

For each potential subject, there is an up to 21-day screening and eligibility assessment period before enrollment; the first dose of study treatment will be administered on Cycle 1 Day 1 (C1D1). Subjects will continue to receive their assigned treatments throughout the study until the occurrence of disease progression, death, or unacceptable treatment-related toxicity; they elect to discontinue study treatment or withdraw consent to continue study participation; or until the study is closed by the sponsor.

Study visits will take place weekly during Cycles 1 and 2 and less frequently thereafter (see Table 11 and Table 12 for the complete schedules of events for the Regimen 1 and Regimen 2, respectively). Serial blood samples will be collected for PK and biomarker analyses at specified time points. If a formalin-fixed paraffin-embedded (FFPE) archived tumor biopsy is available, it will be obtained for use in this study during screening. In addition, in Phase 1 Part A and Phase 2, fresh tumor biopsies are optional during screening and posttreatment during Cycle 2. In

Phase 1 Part B, fresh tumor biopsies are mandatory during screening and posttreatment during Cycle 2.

Upon permanent discontinuation of study treatment, there is a Treatment Termination (Tx Term) visit and a 30-day (±5 days or within 3 days before starting new treatment) Safety Follow-up visit. Subjects who remain on study after the 30-day Safety Follow-up visit will be contacted periodically by telephone for collection of long-term health status information.

Tolerability and safety of study treatment will be evaluated throughout the study by collection of clinical and laboratory data. Antitumor response will be assessed according to standard Response Evaluation Criteria in Solid Tumors (RECIST) v1.1 using computed tomography (CT) or magnetic resonance imaging (MRI) scans. Subjects whose disease is not measurable using RECIST v1.1 will be evaluated using another appropriate method.

4.2. Discussion of Study Design

Phase 1 Part A of the study uses a standard dose-escalation design for an FIH study of a new anticancer IMP. The primary objectives of the Phase 1 portion of this study are to assess safety, and to identify the MTD of up to 2 dosing regimens of ASTX029, the RP2D, and the recommended dosing regimen of ASTX029 in subjects who became refractory or relapsed after treatment with available therapies and/or for whom standard life-prolonging measures or approved therapies are not available. The primary objective of the Phase 2 portion of the study is to assess preliminary clinical activity, as determined by ORR in tumors characterized by gene aberrations in the MAPK signal pathway that may confer sensitivity to ASTX029. Other objectives of the study are to determine the PK profile of ASTX029 administered orally and to evaluate other clinical activity parameters, such as DOR, DCR, PFS, and overall survival (OS); to evaluate relevant pharmacodynamic markers and target engagement (ie, phosphorylated pRSK inhibition) in tumor biopsies; and identify and evaluate potential biomarkers of ASTX029 activity. This study is open-label, with no placebo or active control group.

The Phase 1 Part A dose-escalation process will be guided by safety and PK data and input from the DSRC (see Section 4.4, Section 7.3, and Section 7.4). The starting dose in each regimen evaluated will be escalated stepwise in successive cohorts of at least 3 subjects each with additional allowed expansion to 6 subjects (3+3 study design) until the MTD is determined for each regimen (see Section 4.1.1).

Phase 1 Dose Expansion (Part B) will commence upon identification of the RDE for at least 1 regimen. One or more dose levels (and regimens) may be studied in Phase 1 Part B to supplement available safety, PK, and/or clinical activity data to establish the RP2D and to evaluate target engagement in fresh tumor tissue biopsies.

The Phase 2 portion of the study will explore the preliminary single-agent antitumor activity of ASTX029 at the RP2D of the selected dosing regimen identified in Phase 1 Parts A and B.

At any point, the dose level may be reduced for individual subjects in the event of unacceptable treatment-related toxicity (Section 7.5).

Planned dose levels and dosing regimens, the number of cohorts, and the number of subjects per cohort may be modified, as needed, in response to emerging data and recommendations from the DSRC.

Initially, patients with any type of solid tumor will be eligible for enrollment in this study. In later parts of this study (ie, Phase 1 Part B and Phase 2), preliminary single-agent antitumor activity of ASTX029 will be assessed in tumors characterized by gene aberrations in the MAPK signal pathway that may confer sensitivity to ASTX029 (Section 4.1.2 and Table 2).

ASXT029 was originally introduced into the clinic in the PiB form (Section 7.1.1) and administered under fed conditions (Section 7.1.5). Protocol Amendment 1.0 introduced the tablet dosage form (Section 7.1.6) when it became available. Protocol Amendment 2.0 introduced the evaluation of ASXT029 administration under fasted condition during Phase 1 Part A dose escalation (Section 7.1.7) as a result of data available from food-effect studies in animals (Section 1.3.2.1) and preliminary PK data available from Phase 1 Part A (Section 7.1.7).

4.3. Study Endpoints

4.3.1. Primary Endpoints

- Phase 1: Incidences of DLTs and AEs to determine the MTD of up to 2 dosing regimens of ASTX029 and the RP2D and regimen to be taken to Phase 2.
- Phase 2: Clinical activity assessed by ORR according to RECIST v1.1 criteria.

4.3.2. Secondary Endpoint(s)

- PK parameters of ASTX029, including AUC, C_{max}, minimum concentration (C_{min}), time to reach maximum concentration (T_{max}), elimination half-life ($t_{½}$), food effect on ASTX029 PK parameters, and other secondary PK parameters of ASTX029 if data permit; analysis of ASTX029 metabolites if applicable.
- Inhibition of pRSK protein in response to ASTX029 treatment in tumor biopsies.
- PFS.
- OS.
- DCR.
- DOR.

4.3.3. Exploratory Endpoint(s)

- Suppression of mutant clones in circulating tumor DNA (ctDNA).
- Explore additional biomarkers of ASTX029 activity.

4.4. Data and Safety Review Committee

For Phase 1, the DSRC will include the principal investigator at each study center; for Phase 2, the DSRC composition will be detailed in the DSRC charter. The DSRC for both phases will also include the Sponsor's medical monitor and other subject matter experts (eg, clinical pharmacologist) as needed. The purpose of the DSRC is to review emerging safety, PK, pharmacodynamic, and preliminary clinical activity data, discuss any safety concerns, and recommend changes in the protocol intended to enhance the safety of subjects or increase the

chances that the study will meet its objectives. Unanimous recommendations for which the only purpose is to enhance the safety of subjects will be implemented immediately, and all investigators and Institutional Review Boards (IRBs)/Independent Ethics Committees (IECs) will be notified regarding such changes.

The DSRC will meet principally by teleconference at least once a month during Phase 1 and at least every 3 months during Phase 2. Additionally, during Phase 1 Part A, it will meet when complete Cycle 1 safety data are available from at least 3 subjects treated at the dose level and regimen being evaluated. After reviewing all available safety, PK, biomarker, and preliminary activity data from at least 3 subjects in each cohort, the DSRC will recommend either increasing the cohort size to 6 or proceeding with either dose escalation or reduction, as appropriate; it will also advise if recruitment into Regimen 2 may be initiated and the dose to be used and if an alternative regimen (Optional Regimen 3) is to be evaluated. The DSRC will also advise when to proceed to Part B (Dose Expansion) and when the Phase 2 portion of the study may be initiated and will recommend the dose and dosing regimen(s) to be used (RDE and RP2D for Phase 1 Part B and Phase 2, respectively).

5. SELECTION AND WITHDRAWAL OF SUBJECTS

5.1. Number of Subjects and Centers

It is anticipated that approximately 300 evaluable subjects will be enrolled in this study if the study fully enrolls both Phases 1 and 2. This includes approximately evaluable 120 subjects in Phase 1 at up to 14 study centers in the US and Europe and up to approximately 180 evaluable subjects in Phase 2 at up to 30 study centers in North America and Europe.

The number of cohorts in Phase 1 Parts A and B and the number of subjects per cohort will be based on emerging safety and PK data and recommendations from the DSRC. The number of subjects in Phase 2 will be based on clinical activity observed and recommendations from the DSRC. More subjects may be enrolled if more dose levels are tested in Part A of the study, if more than 1 cohort is selected for expansion in Part B or if more than the expected number of subpopulations in Cohort F of Phase 2 are expanded.

5.2. Inclusion Criteria

To be eligible for the study, subjects must fulfill all of the following inclusion criteria:

1. Able to understand and comply with the study procedures, understand the risks involved in the study, and provide written informed consent before any study-specific procedure is performed.
2. Men or women 18 years of age or older.
3. Subjects with histologically or cytologically confirmed advanced solid tumors that are metastatic or unresectable, who are refractory or have relapsed after treatment with available therapies or for whom standard life-prolonging measures or approved therapies are not available. In Phase 1 Part B and in the Phase 2 portion of the protocol, subjects must also have documented gene alterations in the MAPK pathway as detailed in Section 4.1.1, Section 4.1.2, and Table 2.
4. In Phase 1 Part B of the protocol, subjects must have disease lesions that are amenable to biopsy.
5. In the Phase 2 portion of the protocol, subjects must have measurable disease according to Response Evaluation Criteria in Solid Tumors (RECIST) v1.1.
6. Eastern Cooperative Oncology Group performance status 0 to 2.
7. Acceptable organ function, as evidenced by the following laboratory data:
    a. AST and alanine aminotransferase (ALT) ≤2×upper limit of normal (ULN) or ≤3 ULN in the presence of liver metastases.
    b. Total serum bilirubin ≤1.5×ULN.
    c. Absolute neutrophil count (ANC) ≥1500 cells/mm^3.
    d. Platelet count ≥100,000 cells/mm^3.
    e. Calculated creatinine clearance (by the standard Cockcroft-Gault formula) of ≥50 mL/min or glomerular filtration rate of ≥50 mL/min.

8. Women of child-bearing potential (according to recommendations of the Clinical Trial Facilitation Group [CTFG]; see below* for details) must not be pregnant or breastfeeding and must have a negative pregnancy test (urine or serum as required by local regulations) within 24 hours before the first dose of study treatment. Women of child-bearing potential must agree to the following during the treatment period and for at least 32 days (approximately 5 half-lives of ASTX029 or metabolite plus 30 days) after receipt of last dose of study treatment:
    a. Refrain from donating eggs (ova, oocytes) for the purpose of reproduction.
    b. Use a contraceptive method** that is highly effective with a failure rate of <1% per year), with low user dependency. The investigator should evaluate the effectiveness of the contraceptive method before the first dose of study treatment. The investigator is responsible for review of medical history, menstrual history, and recent sexual activity to decrease the risk for inclusion of a woman with an early undetected pregnancy.
9. Men with a pregnant partner or non-pregnant partner who is a woman of childbearing potential must agree to the following during the treatment period and for at least 92 days (approximately 5 half-lives of ASTX029 or metabolite plus 90 days) after receipt of last dose of study treatment:
    a. Refrain from donating sperm.
    b. Be abstinent from heterosexual intercourse as their preferred and usual lifestyle (abstinent on a long term and persistent basis) and to remain abstinent OR to use a male condom when having sexual intercourse with a woman of childbearing potential (according to recommendations of the CTFG; see below* for details) who is not currently pregnant, and the female partner should be advised of the benefit of using an additional highly effective contraceptive method** with a failure rate of <1% per year as a condom may break or leak. The investigator should evaluate the effectiveness of the contraceptive method before the first dose of study treatment.

*According to recommendations of the CTFG (http://www.hma.eu /fileadmin/dateien /Human_Medicines/01-About_HMA/Working_Groups/CTFG/2020_09_HMA_ CTFG_Contraception_guidance_Version_1.1_updated.pdf), a woman is considered of childbearing potential (ie, fertile) following menarche and until becoming postmenopausal, unless permanently sterile. Permanent sterilization methods include hysterectomy, bilateral salpingectomy, and bilateral oophorectomy. A man is considered fertile after puberty unless permanently sterile by bilateral orchidectomy.
**Contraceptive measures that may be considered highly effective comprise combined hormonal contraception (oral, vaginal, or transdermal) or progestogen-only hormonal contraception (oral, injectable, implantable) associated with inhibition of ovulation, intrauterine device, intrauterine hormone-releasing system, bilateral tubal occlusion, sexual abstinence, and surgically successful vasectomy. Abstinence is acceptable only if it is consistent with the preferred and usual lifestyle of the subject. Periodic abstinence (eg, calendar, ovulation, symptothermal, or postovulation methods) and withdrawal are not acceptable methods of birth control.

5.3. Exclusion Criteria

Subjects meeting any of the following criteria will be excluded from the study:

1. Hypersensitivity to ASTX029 or excipients of the drug product.

2. Poor medical risk in the investigator's opinion because of systemic diseases in addition to the cancer under study, for example, uncontrolled infections.
3. Life-threatening illness, significant organ system dysfunction, or other condition that, in the investigator's opinion, could compromise subject safety or the integrity of study outcomes or interfere with the absorption or metabolism of ASTX029.
4. Prior anticancer treatments or therapies within the indicated time window prior to first dose of study treatment (ASTX029), as follows:
    a. Cytotoxic chemotherapy or radiotherapy within 3 weeks prior. Palliative radiotherapy to a single lesion within 2 weeks prior. Any encountered treatment-related toxicities (excepting alopecia) not stabilized or resolved to ≤Grade 1.
    b. Monoclonal antibodies or biologics within 4 weeks prior. Any encountered treatment-related toxicities not stabilized or resolved to ≤Grade 1.
    c. Molecularly targeted drug or other investigational drugs, without the potential for delayed toxicity, within 4 weeks of the first dose of study treatment or 5 half-lives (minimum 14 days), whichever is shorter. Any encountered treatment-related toxicities (excepting alopecia) not stabilized or resolved to ≤Grade 1.
5. Prior treatment with ERK inhibitors.
6. History of, or at risk for, cardiac disease, as evidenced by 1 or more of the following conditions:
    a. Abnormal left ventricular ejection fraction (LVEF; <50%) on echocardiogram (ECHO) or multiple-gated acquisition (MUGA) scan.
    b. Congestive cardiac failure of ≥Grade 3 severity according to New York Heart Association (NYHA) functional classification defined as patients with marked limitation of activity and who are comfortable only at rest.
    c. Unstable cardiac disease including unstable angina or hypertension as defined by the need for overnight hospital admission within the last 3 months (90 days).
    d. History or evidence of long QT interval corrected for heart rate (QTc), ventricular arrhythmias including ventricular bigeminy, complete left bundle branch block, clinically significant bradyarrhythmias such as sick sinus syndrome, second- and third-degree atrioventricular (AV) block, presence of cardiac pacemaker or defibrillator, or other significant arrhythmias.
    e. Screening 12-lead ECG with measurable QTc interval of ≥470 msec. (Fridericia's formula should be used to calculate the QTc interval throughout the study.)
7. Known history of human immunodeficiency virus (HIV) infection or seropositive results consistent with active hepatitis B virus (HBV) or active hepatitis C virus (HCV) infection.
8. Known brain metastases, unless previously treated and stable for at least 3 months with or without steroids.
9. Known significant mental illness or other conditions, such as active alcohol or other substance abuse that, in the opinion of the investigator, predispose the subject to high risk of noncompliance with the protocol treatment or assessments.

10. History or current evidence/risk of retinal vein occlusion (RVO) or central serous retinopathy (CSR) including:
    a. Presence of predisposing factors to RVO or CSR (eg, uncontrolled glaucoma or ocular hypertension, uncontrolled diabetes mellitus) or
    b. Visible retinal pathology as assessed by ophthalmic examination at screening that is considered a risk factor for RVO or CSR such as:
        – Evidence of optic disc cupping or
        – Evidence of new visual field defects on automated perimetry or
        – Intraocular pressure >21 mmHg as measured by tonography.

5.4. Treatment Discontinuation and Withdrawal of Subjects

Subjects who discontinue study treatment will be followed up for important study data, as described below, unless they withdraw consent from further follow-up.

5.4.1. Discontinuation From Study Treatment

Subjects may permanently discontinue study treatment at any time (**note: subjects who experience disease progression while receiving ASTX029 should not remain on study treatment**). Subjects who discontinue study treatment will still continue study follow-up procedures until death, or until they withdraw consent or the study is closed. Investigators are encouraged to assess all subjects according to the study protocol even after discontinuation from study treatment. Possible reasons for discontinuation of study treatment include the following:

- Investigators can discontinue subjects from study treatment in case of unacceptable toxicity, non-compliance, disease progression requiring alternative therapy, or if the investigator determines it is in the subject's best interest.
- The Sponsor may require that a subject is discontinued from treatment for safety reasons or for noncompliance.

In all cases, the reason(s) for discontinuation from study treatment must be recorded in the source document and on the relevant page of the subject's electronic case report form (eCRF).

It is important to obtain protocol-specified follow-up information on any subject discontinued from study treatment. For subjects who discontinue study treatment, the investigator should review the follow-up procedures with the subject, including the number of visits, the specific procedures to be done, and the total length of the follow-up period. If at all possible, subjects should undergo all safety and preliminary clinical activity evaluations at the Tx Term visit (Section 9.4.13) and the 30-day Safety Follow-up visit (Section 9.4.14). Section 10 describes follow-up for AEs. At minimum, subjects should be followed up for safety until 30 days after the last dose of study treatment (see Section 10.3).

Subjects who agree to remain enrolled in the study after discontinuing study treatment and completing the 30-day Safety Follow-up visit will be contacted by telephone for health status information every 3 months until death, withdrawal of consent, or the end of study, whichever occurs first (see Section 9.4.15).

5.4.2. Withdrawal From the Study

Subjects may withdraw consent for the study at any time or subjects may be lost to follow-up. It is important to obtain follow-up information, according to standard medical practice, on any subject withdrawn prematurely from the study. Every effort must be made to undertake at least standard assessments that are critical for clinical activity or safety evaluation, such as disease progression (if the subject did not withdraw because of disease progression), subsequent anticancer treatment, survival information, and safety data.

If a subject withdraws consent from the study, the sponsor may retain and continue to use any information and data collected or generated up to the time of withdrawal of consent.

Additionally, if a subject withdraws consent, they may request destruction of any samples taken and not tested yet, and the investigator must document this in the site study records and inform the sponsor within 24 hours.

5.4.3. Replacement of Subjects

Subjects will be replaced in this study as needed to achieve the planned number of evaluable subjects in each part of the protocol. See Section 11.1 for the definition of evaluable subjects.

5.4.4. End of Study

The study will be considered complete (that is, scientific evaluation will be complete [study completion]) following evaluation of safety and efficacy as determined by the Sponsor. Investigators will continue to follow the Schedule of Activities (Table 13) for all patients until notified by the Sponsor that study completion has occurred.

End of the study is the date of the last visit or last scheduled procedure for the last patient.

5.4.5. Study Extension

Following Study Completion (see above Section 5.4.4), all patients who are on study treatment and deriving clinical benefit with no undue risk may continue to receive study treatment in a study extension phase or a rollover study until any of the study treatment discontinuation criteria (Section 5.4.1) are met.

During study extension, assessments are to be conducted according to the Schedule of Activities in Table 13. Data collection will be limited and will include (at a minimum):

- Study drug administration
- Study drug accountability
- AEs
- SAEs
- Any cases of pregnancy or overdose

Investigators will perform any other standard procedures and tests needed to treat and evaluate patients; however, the choice and timing of the tests will be at the investigator's discretion. The Sponsor will not routinely collect the results of these assessments.

If an SAE occurs, the Sponsor may request additional information (eg, local laboratory results, concomitant medications, hospitalizations) to evaluate the reported SAE.

6. ENROLLMENT AND RANDOMIZATION PROCEDURES

Subjects will be screened at each study center for assessment of eligibility for the study. The investigator or designated staff will be responsible for allocating and recording subject identification numbers. Each subject who signs the informed consent form (ICF) will be assigned a unique identification (ID) number that reflects the study center number assigned to the investigator and the subject at that site. The same subject ID number will be used to identify the subject from screening throughout the study and will be entered on all study documents.

A given subject ID number will not be assigned to more than 1 subject. If a subject is not eligible to receive treatment or if the subject discontinues from the study, the subject number will not be reassigned to another subject. A centralized allocation procedure will be used.

See Section 7.3 for the dose-escalation guidelines.

6.1. Randomization

This is an open label study. All enrolled subjects will receive ASTX029. In Phase 1 Part A (dose escalation), initially, only a single dosing regimen (Regimen 1) will be evaluated. Following the occurrence of event(s) meeting prespecified criteria (Section 7.1.4), a second dosing regimen (Regimen 2) may be activated. If the second dosing regimen becomes active, subjects will be assigned following a simple randomization procedure (eg, computerized random numbers) to Regimen 1 (continuous dosing) or Regimen 2 (intermittent dosing).

When only a single regimen is active (eg, the cohort for 1 regimen has completed enrollment, or is on hold), randomization will be suspended, and all subjects will be allocated to the active regimen.

In Phase 1 Part B, if more than 1 dose/regimen is selected, subjects will be randomized in a 1:1 ratio.

When a qualified subject is identified (ie, meets all eligibility criteria), site staff will confirm the subject's eligibility in the Interactive Response Technology (IRT) system. The IRT system will automatically enroll/randomize the subject to the appropriate treatment regimen/cohort and allocate study drug. Details of randomization/enrollment are described in the IRT User Guide.

7. STUDY TREATMENTS

ASTX029 (the IMP) will be the only study treatment administered.

7.1. Investigational Medicinal Product (ASTX029)

7.1.1. Drug Substance, Drug Product, and Packaging

ASTX029 is a synthetic small molecule and a new chemical entity.

The molecular formula of the ASTX029 drug substance is [redacted]

Powder-in-Bottle Dosage Form

One form of the drug product was supplied as a PiB containing 1.0 g or 5.3 g ASTX029 free-base equivalents for reconstitution with a vehicle for reconstitution (VFR), which had been formulated for this compound and was suitable for oral or gastrostomy tube (g-tube) administration.

ASTX029 PiB was supplied in amber glass bottles with screw caps. The bottles were labeled as IMP, in accordance with applicable regulations. There are no inactive ingredients formulated with ASTX029 PiB. The VFR was also supplied in amber glass bottles with screw caps. Each bottle of VFR contained a fill volume of 110 mL. The inactive ingredients in the VFR are: propylene glycol, ethanol, and TPGS (80:10:10%w/w).

Note: The PiB dosage form was phased out after sufficient PK and safety data were collected and with approval from the DSRC. See Section 7.1.6 for further information on the transition to tablets.

Tablet Dosage Form

Amendment 1.0 introduced a tablet dosage form of ASTX029. **(Note: tablets cannot be administered by g-tube.)** The tablets are provided in sealed bottles with child-resistant closures. Each bottle contains 21 tablets. Bottles are labeled with the tablet strength and are further distinguished by differently colored labels. Please refer to the current ASTX029 IB for further information. The bottles are labeled as IMP, in accordance with applicable regulations. In addition to the tablets, each bottle contains a small white plastic canister built into the cap that contains a desiccant.

The film-coated tablets include the following excipients: [redacted] These excipients are of compendial grade and are generally recognized as safe (GRAS).

7.1.2. Storage

Store ASTX029 tablets per instructions in the pharmacy manual. In the study center, storage should be in a secure, locked facility accessible only to authorized study personnel. ASTX029 tablets will be evaluated under stability protocols designed according to ICH guidelines for shelf-life assignment and, if warranted, shelf life may be extended.

7.1.3. ASTX029 Reconstitution

Tablets are provided in bottles containing 21 tablets each. A sufficient quantity of tablets will be dispensed to the subject to permit oral self-administration at the required dose level for the required number of days.

Records of the receipt and dispensing of drug will be kept at the study centers and reconciled at the end of the study to provide a complete accounting of all used and unused IMP.

7.1.4. ASTX029 Regimens and Dose Levels

In this open-label study, all subjects will receive ASTX029 orally according to the assigned treatment regimen and dose. At any point in the study, the dose of ASTX029 may be reduced, withheld, or discontinued for individual subjects in the event of unacceptable treatment-related toxicity, as described in Section 7.5. No active comparator or placebo is planned for this study.

In Phase 1 Part A, subjects will receive 1 of up to potentially 2 ASTX029 dosing regimens. Subjects in Regimen 1 will receive ASTX029 orally once a day on Days 1 through 21 of each 21-day cycle (Regimen 1; continuous dosing), and, if Regimen 2 is opened to enrollment, subjects in Regimen 2 will receive ASTX029 orally once a day on Days 1 through 14 of each 21-day cycle (Regimen 2; intermittent dosing, 2 weeks on/1 week off).

Initially, subjects will be allocated to Regimen 1 (continuous dosing). Subjects in the first cohort of Regimen 1 will receive a flat starting dose of 10 mg QD (Section 2.2). Dose levels for subsequent cohorts will be determined by the DSRC. Planned initial escalation will be 100% (doubling the dose) until 160 mg. Smaller increments of dose escalation will be used above 160 mg. Dose doubling will also be discontinued if any 1 of the following occurs within a cohort:

- 1 subject experiences a DLT (Section 7.4).
- Any study-drug-related clinically significant ≥Grade 2 AE not adequately managed or resolved to baseline or Grade 1 by supportive treatment that, per the DSRC, indicates further dose doubling would be potentially unsafe for future subjects.
- Any study-drug-related AE or confluence of AEs that, per the DSRC, indicates further dose doubling would be potentially unsafe for future subjects.

After this point, dose escalation will proceed in smaller increments (eg, by a 50% increase initially and an ~25% increase at the higher dose levels over the previous level), after review of all available safety, PK, and biomarker data from Cycle 1 in at least 3 subjects and approval by the DSRC. The DSRC will determine the need to expand to 6 subjects per cohort if 1 subject in the first 3 subjects or if multiple subjects have Grade 2 events that require additional subjects in order to collect additional safety data and better inform dose-escalation decisions. If more than 1 subject has DLTs in any cohort of 3 or 6 subjects, no further escalation should occur of that regimen and exploration of lower dose regimens may be recommended by the DSRC to refine the MTD and the RDE.

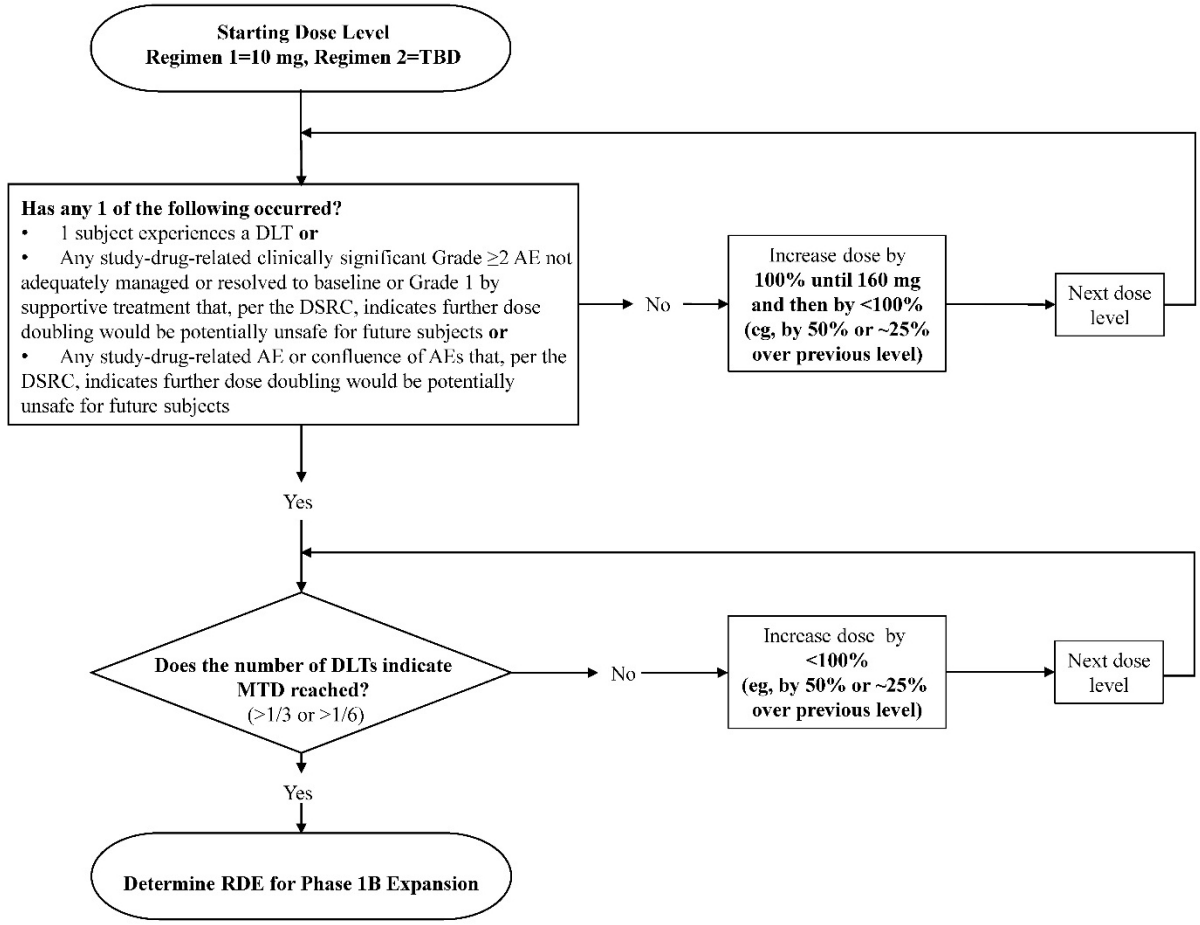
An example of a possible dose-escalation plan is shown in Table 3, and a possible dose escalation flowchart is shown in Figure 3.

Table 3: Example of Possible ASTX029 Dose Levels in Part A

Cohort	Dose Level (mg/day)	Number of Evaluable Subjects Planned	Comments
1	10 mg	3 or 6	Starting dose based on toxicology data (Section 2.2)
2	20 mg	3 or 6	Increase Starting dose by 100%
3	40 mg	3 or 6	Increase Cohort 2 dose by 100%
4	80 mg	3 or 6	Increase Cohort 3 dose by 100%
5	160 mg	3 or 6	Increase Cohort 4 dose by 100%
6	240 mg	3 or 6	Increase Cohort 5 dose by 50%
7	360 mg	3 or 6	Increase Cohort 6 dose by 50%
8	450 mg	3 or 6	Increase Cohort 7 dose by 25%

Note: The dose levels and escalation shown in this table are for purposes of example only. The Data and Safety Review Committee will decide on actual dose levels and may recommend escalation increments based on emerging safety and pharmacokinetic data or operational concerns. Planned initial escalation will be 100% (doubling the dose) until 160 mg. Smaller increments of dose escalation will be used above 160 mg.

Figure 3: ASTX029-01 Phase 1 Part A Dose Escalation Flowchart



AE=adverse event; DLT=dose-limiting toxicity; DSRC=Data and Safety Review Committee; MTD=maximum tolerated dose; RDE=recommended dose for expansion; TBD=to be determined.

See Section 7.3 for dose-escalation guidelines.

Also, after this point, the sponsor, with approval of the DSRC, will determine if Regimen 2 is to be opened for enrollment. Randomization to either Regimen 1 or Regimen 2 will begin if both regimens are open for enrollment. Should Regimen 2 be evaluated, based on safety and PK data from Regimen 1 and depending on the nature, timing, and severity of observed AEs, the dose for the first cohort of subjects enrolled to Regimen 2 may be escalated to the next level pending approval by the DSRC. If the MTD is reached in 1 regimen before the other regimen, all subsequent subjects will be enrolled, without randomization, to the remaining regimen until the MTD is determined for each regimen evaluated.

After reaching MTD or RDE for Regimens 1 and 2, the DSRC will also advise if it is appropriate to test an alternative intermittent regimen (Optional Regimen 3, eg, 7 days on/7 days off) and will recommend the dose and dosing regimen to be used. The total dose per cycle for the new regimen will not exceed the total safe dose per cycle already established in the first 2 regimens.

The starting dose in each regimen evaluated will be escalated stepwise in successive cohorts of at least 3 evaluable subjects each with additional allowed expansion to 6 subjects (3+3 study design) until the MTD is determined for each regimen.

Dose-escalation/de-escalation decisions will be based on the occurrence of DLTs (defined in Section 7.4) during the first 21-day cycle of each dose level, and the recommendations of the DSRC following review of all available safety, PK, and biomarker data from the completed first cycle of at least 3 subjects in each cohort (as described in Section 7.3). The DSRC will also advise whether or not it is appropriate to proceed to Part B (Dose Expansion).

Part B (Dose Expansion) will commence upon identification of the RDE for at least 1 regimen. The DSRC RDE decision will be based on all available safety, PK, biomarkers, and preliminary activity data from all cycles (including the potential for late or cumulative toxicity).

At any point, the dose level may be reduced for individual subjects in the event of unacceptable treatment-related toxicity (Section 7.5). Planned dose levels, the number of cohorts, and the number of subjects per cohort, may be modified as needed, in response to emerging PK and safety data, and recommendations from the DSRC.

7.1.5. ASTX029 Administration

Subjects will receive instructions for the storage and self-administration of the IMP by oral administration at home (also see Section 9.4.11). However, on visit days, subjects will be asked to wait until they arrive at the study center and are under the supervision of the study staff before they ingest the study drug to ensure accurate recording and timing of blood draws relative to IMP ingestion. When subjects self-administer IMP at home, they are expected to record the date and time of ingestion in their dosing diary, along with any pertinent notes (eg, vomiting after ingestion of the dose).

If a patient forgets to take or misses a dose, they may take the dose up to 4 hours late. After that time, the patient should skip the dose for that day and wait until the next day to resume the normal dosing schedule. The VFR of ASTX029 contains ethanol and propylene glycol (Section 7.1.1). The maximum amount of the alcohol intake from the VFR is estimated to be 3.7 g. (Refer to the pharmacy manual for further information.)

ASTX029 should be ingested at approximately the same time of day on each dosing day, and the actual dosing time should be recorded as above.

Study treatment compliance will be assessed periodically throughout the treatment period. Subjects will be required to return all study treatment syringes (used, unused, and partially used) and all unused tablets to the study center, and to share their dosing diaries with study staff.

ASXT029 was originally introduced into the clinic in the PiB form (Section 7.1.1) and administered under fed conditions (Section 7.1.5). Protocol Amendment 1.0 introduced the tablet dosage form (Section 7.1.6) when it became available. Protocol Amendment 2.0 introduced the evaluation of administration under fasted conditions during Phase 1 Part A dose escalation (Section 7.1.7).

Drug Administration Under Fed Conditions

Based on available preliminary data and the properties of ASTX029, it was expected that doses would be better tolerated and absorbed when consumed with food. Hence, although food-effect studies had not yet been conducted with ASTX029, subjects enrolled in the early stages of dose escalation were requested to ingest the IMP with food, ie, within 30 minutes after a breakfast meal. Subjects receiving ASTX029 under fed conditions are requested to have a balanced breakfast meal. Examples of breakfast meals are:

- Egg(s), toast (or potatoes), and juice (orange, apple, cranberry, or tomato) or coffee/tea.
- Bacon (2 strips), toast (or potatoes), and juice (as above) or coffee/tea.
- Sausage, toast (or potatoes), and juice (as above) or coffee/tea.
- Breakfast sandwich with eggs/sausage/bacon; juice (as above) or coffee/tea.

Other varieties/substitutions can be made as long as the meal provides a similar amount of calories from protein, carbohydrate, and fat and has comparable meal volume and viscosity.

Note: grapefruit juice is not allowed during treatment with ASTX029.

Drug Administration Under Fasted Conditions

Amendment 2.0 introduced the evaluation of fasted administration during Phase 1 Part A. Subjects receiving ASTX029 under fasted conditions will be requested to ingest the study treatment after fasting for at least 2 hours, typically in the morning before breakfast, and to also fast for 2 hours after ingestion of study drug. During the 4-hour fasting period, clear liquids (such as tea, coffee, and water) are allowed; milk, juice, and soup are not allowed. **Note: grapefruit juice is not allowed during treatment with ASTX029.** Please see Section 7.1.7 for further details of transition to fasted administration during Phase 1 Part A.

7.1.6. Transition From Powder-in-Bottle Dosage Form to Tablet Dosage Form

With Protocol Amendment 1.0, the tablet form was introduced and replaced the PiB formulation. Transition to the tablet dosage form occurred by dosing a tablet-bridging cohort of 6 subjects at 80 mg/day, a dose that did not exceed the highest PiB dose level in Regimen 1 at which no DLTs were observed as determined by the DSRC assessment of all safety and PK data at the time of initiation of the tablet-bridging cohort. Because the tablet dose was shown to be safe and no

other issues were identified, dose escalation using the tablet dosage form proceeded in subsequent cohorts as described in Section 4.1.1, Table 3, with approval of the DSRC. If the tablet dosing form had not been safely tolerated, dose de-escalation could have occurred as described in Section 7.3 and Section 7.5. Based on review of safety and PK data, the DSRC could have allowed transition of ongoing subjects still receiving PiB to tablets. At the time of Amendment 4.0, all subjects who received ASTX029 PiB had discontinued study drug.

7.1.7. Transition From Fed to Fasted Administration

At the time of Amendment 2.0, dose escalation (Phase 1 Part A) was ongoing. In Phase 1 Part A, ASXT029-01 dose was escalated in sequential cohorts from 10 mg/day to 200 mg/day QD using the PiB form in fed subjects. One DLT (Grade 3 nonserious maculo-papular rash) was reported in the 200-mg/day PiB cohort. Six subjects were enrolled in the tablet-bridging cohort at 80 mg/day QD under fed conditions with no DLTs being reported, and enrollment was ongoing in the 120-mg/day QD tablet cohort.

Preliminary PK data at the time of Amendment 2.0, showed relatively high variability for systemic exposures after ASTX029 was dosed with food. The geometric mean (CV%) plasma $AUC_{0\text{-}inf}$ values on C1D1 were 2377(170) ng•h/mL for the 80-mg tablet-bridging cohort (n=4), compared with 4053(83) ng•h/mL for the 120 mg PiB (n=5) cohort and 8304(53) ng•h/mL for the 200 mg PiB cohort (n=9).

With Protocol Amendment 2.0, administration under fasted conditions was introduced. Fasted administration may result in higher exposure of ASTX029 at lower doses (Section 1.3.2.1) and potentially reduce intersubject variability compared with administration with food.

Transition to fasted-state dosing occurred during Phase 1 Part A by dosing a bridging cohort of 3 subjects at a dose of 40 mg/day tablets QD. Starting with Amendment 3.0, dose escalation under fed conditions was discontinued, and dose escalation under fasted conditions is ongoing. Please refer to the current ASTX029 IB for preliminary PK and safety data.

7.2. Active Comparator or Placebo

No active comparator or placebo is planned for this study.

7.3. Dose-Escalation Guidelines and Recommended Phase 2 Dose Decision

Dose-escalation/de-escalation decisions will be based on the occurrence of DLTs (defined in Section 7.4) during the first cycle of each dose level, and the recommendations of the DSRC following review of all available safety, PK, and biomarker data from the completed first cycle of at least 3 subjects in each cohort (Section 4.4). The DLT-based dose-escalation guidelines are summarized below.

Intrasubject escalations will not be allowed; however, once an MTD or RDE dose level is determined, active subjects may be allowed to receive their subsequent cycles at that dose level at the investigator's discretion with prior Sponsor approval.

First 3 Subjects in a Cohort

- If no subjects among the first 3 (<33%) experience a DLT, the dose may be escalated to the next higher level for the next cohort of 3 subjects.
- If 1 subject among the first 3 (33%) experiences a DLT, the cohort size will be increased to 6 subjects.
- If 2 subjects among the first 3 (>33%) experience a DLT, the previous dose level (ie, 1 step below) would be declared the MTD.

Expanded Cohort of 6 Subjects

- If no more than 1 subject in the cohort of 6 (ie, a total of 1 out of 6, <33%) experience a DLT, the dose may be cautiously escalated (~25% increase) to the next higher level for the next cohort of 3 subjects.
- If 2 subjects in the cohort of 6 (33%) experience a DLT, that dose level or the previous dose level (ie, 1 step below) would be declared the MTD for the regimen. The DSRC may recommend exploration of intermediate doses before an MTD is declared.
- If more than 2 subjects in the cohort of 6 (>33%) experience a DLT, the previous dose level (ie, 1 step below) would be declared the MTD for the regimen. The DSRC may recommend exploration of intermediate doses before an MTD is declared.

Recommended Dose for Expansion

The RDE is defined as either the MTD or a dose below the MTD that the DSRC agrees shows adequate safety, PK and/or preliminary biological activity, or clinical activity for a regimen. One or more dose levels (and regimens) may be studied in Phase 1 Part B to supplement available safety, PK, and/or clinical activity data and to evaluate target engagement in fresh tumor tissue biopsies. The RDE decision by the DSRC will be based on all available safety, PK, biomarkers, and preliminary activity data from all cycles (including potential for late or cumulative toxicity) from Phase 1 Part A.

Recommended Phase 2 Dose

The RP2D is defined as the dose that the DSRC agree shows adequate safety, PK, pharmacodynamic, and/or biological or clinical activity to warrant further investigation in the Phase 2 part of this study. The RP2D decision by the DSRC will be based on all available PK, biomarker, safety, and preliminary clinical activity data from all cycles, including potential for late or cumulative toxicity from Phase 1 Parts A and B. The RP2D could be the same or lower than the RDE.

Based on the data presented in Section 1.3.3, the DSRC determined the RP2D to be 200 mg administered orally daily, continuously, in 21-day cycles under fasting conditions.

7.4. Definition of Dose-Limiting Toxicities

Dose-limiting toxicities are AEs (graded by National Cancer Institute (NCI) Common Terminology Criteria for Adverse Events (CTCAE) v4.03 criteria [Appendix 2]) that occur

during the first cycle of treatment and represent any 1 of the following, unless there is a clear alternative cause of the event (eg, disease progression, disease-related):

- Grade 4 thrombocytopenia of any duration.
- ≥Grade 3 hematologic toxicity with complications (eg, Grade 3 thrombocytopenia with bleeding or transfusion requirement).
- Febrile neutropenia of any duration or Grade 4 neutropenia of 5 days or more duration.
- Liver-associated abnormalities defined as:
  - ≥Grade 3 bilirubin, ALT, or AST elevation, except ALT or AST elevation >5×ULN and <8×ULN for <7 days.
  - ALT or AST >3×ULN AND either total bilirubin >2×ULN OR international normalized ratio (INR) >1.5.
  - ALT or AST >3×ULN with clinical indications of liver toxicity (signs, symptoms, or other diagnostic findings).
- ≥Grade 2 eye disorders (ocular toxicities) that do not improve to ≤Grade 1 within 7 days despite treatment discontinuation or documented RVO.
- Symptomatic Grade 2 cutaneous toxicities (including skin rash) that do not improve to ≤Grade 1 within 7 days despite supportive treatment and treatment discontinuation.
- Any other ≥Grade 3 nonhematologic AE except Grade 3 nausea, vomiting, or diarrhea that resolves to ≤Grade 1 by symptomatic treatment within 24 hours.
- Any event that, in the opinion of the DSRC, would suggest that further dose escalation would put subjects at unacceptable risk.

7.5. Guidelines for Adjusting, Withholding, or Discontinuing Study Treatment

ASTX029 dosing should be withheld in the case of a DLT in Cycle 1 or toxicity in subsequent cycles that would have qualified as a DLT if it had occurred in Cycle 1. Dosing may resume, at the investigator's discretion, if and when study-treatment-related toxicity has:

- Completely resolved or
- Returned to baseline or partially recovered to ≤Grade 2 (anemia, fatigue, malaise, and alopecia) or returned to baseline or partially recovered to ≤Grade 1 (all other toxicities).

If and when a decision is made to resume dosing, the individual's dose should be adjusted to the previously assessed lower dose level that was considered safe by the DSRC. A maximum of 2 dose reductions are permitted for any single subject. In the event of further unacceptable toxicity, the investigator should consider discontinuation of study treatment for that subject.

If toxicity has not resolved as described above within 21 days, the investigator should permanently discontinue study treatment unless the subject is receiving compelling benefit, the

benefit of the study treatment exceeds the risks, and no alternative therapy is available. Approval by the Sponsor's medical monitor is required to restart study treatment after an interruption ≥21 days, and study treatment must be administered at a dose approved by the Sponsor's medical monitor when toxicity has resolved as described above.

Suggested guidelines and criteria for adjusting, withholding, or discontinuing study treatment as a result of skin toxicities, ocular toxicities, diarrhea, liver toxicities, and LVEF decrease are provided in Appendix 4, Appendix 5, Appendix 6, Appendix 7, and Appendix 8, respectively. The institutional standards for the management of these toxicities can differ from the suggested guidelines. In this case, best clinical judgment should be applied.

7.6. Concomitant Treatment

On the concomitant medication eCRF, document all medications a subject takes starting from 14 days before study treatment initiation and ending 30 days after the last dose of study treatment. Include supportive or palliative treatment (see below) whether prescription or nonprescription, and medications taken for procedures (eg, biopsy). Include start and stop dates and indication.

7.6.1. Supportive, Prophylactic, or Other Treatments

All subjects receiving treatment with ASTX029 should continue to receive appropriate supportive care for the treatment of their cancer, according to the institutional standard practice or other established standard of care guidelines. Antiemetics and loperamide may be given to alleviate ASTX029-related toxicity on an as-required basis, and GI toxicity should not be considered to be dose limiting in the absence of maximal supportive therapy. Subjects receiving treatment with a bisphosphonate are not excluded from participating in the trial; bisphosphonate therapy may be initiated while maintaining treatment with ASTX029 provided the subject does not have disease progression according to RECIST v1.1 criteria. The subject may receive palliative radiotherapy to a symptomatic lesion during the study. All efforts should be made to reduce the radiation field to the smallest possible area of exposure. ASTX029 treatment should be interrupted during radiotherapy and resumed upon completion.

Any supportive treatment should be documented in the provided eCRFs.

7.6.2. Prohibited Medications and Substances

Other anticancer treatments, including other investigational drugs or therapies, unless specified in the protocol, are prohibited.

ASTX029 is a substrate and inhibitor of cytochrome P450, family 3, subfamily A (CYP3A). Therefore, concomitant administration of drugs known to be strong CYP3A4 inhibitors or inducers has the potential to result in drug-drug interactions (DDIs) with ASTX029. Careful consideration should be given to balancing the medical needs of the subject and the potential effect on ASTX029 before coadministering a drug that is known to be a strong CYP3A4 inhibitor or inducer. It is strongly recommended that subjects avoid strong CYP3A4 inhibitors and inducers at ASTX029 dose levels that display clinical effects (toxicity or activity). Particular caution should be exercised when coadministering drugs with ASTX029 that are sensitive

CYP3A substrates with narrow therapeutic windows until the potential liability of ASTX029 for DDIs is fully qualified.

ASTX029 is an inhibitor of the liver uptake transporter OATP1B1. Therefore, concomitant administration of drugs known to be OATP1B1 substrates has the potential to result in DDIs with ASTX029. Particular caution should be exercised when coadministering drugs with ASTX029 that are sensitive OATP1B1 substrates with narrow therapeutic windows until the potential for DDIs via inhibition of OATP1B1 is fully understood.

Examples of CYP3A4 inhibitors and inducers and OATP1B1 substrates and inhibitors may be found on the following websites; note that the published lists are not comprehensive. Refer to the specific product information for an intended concomitant drug.

- FDA.gov: http://www.fda.gov/Drugs/DevelopmentApprovalProcess/DevelopmentResources/DrugInteractionsLabeling/ucm093664.htm (FDA 2020).
- Pharmacytimes.com: http://www.pharmacytimes.com/publications/issue/2015/december2015/drug-interactions-with-cyp3a4-an-update (Horn and Hansen 2015).

Medications known to increase the risk of torsades de pointes should be used with caution. A list of such medications is provided at the following website and discussed in Drew et al (2010), https://www.crediblemeds.org/ (Woosley et al 2022). Any AV-nodal blocking medications (ie, beta-blockers, non-dihydropyridine calcium-channel blockers, and digitalis) should be used with caution. A list of such medications is provided and discussed in Wooten 2002 and by Vogler et al (Vogler et al 2012).

The VFR of ASTX029 contains ethanol and propylene glycol (Section 7.1.1). It is advisable to review concomitant medications that may interact with VFR ingredients.

Any medication considered necessary for the subject's safety and well-being may be given at the discretion of the investigator(s). However, if a subject requires treatment with a drug known to prolong the QT interval while on study and there is no alternative medication, the subject should be carefully monitored for potential QT prolongation for at least 24 hours. Investigators should also be aware that the list of medications that prolong the QT interval provided in the cited references is not exhaustive and there are other medications with a possible or conditional risk of causing QT prolongation and/or torsades de pointes.

Investigators should consult with the Sponsor's medical monitor regarding the potential concomitant use of QTc-prolonging agents with a known risk of torsades de pointes while on study treatment in individual subjects on a case-by-case basis.

Concomitant St. John's Wort, grapefruit, and grapefruit juice are also prohibited during treatment with ASTX029.

7.7. Overdose Instructions

Record the actual dose of study drug administered in the source document and on the Dosing eCRF. Record any adverse clinical signs and symptoms associated with a potential overdose on the AE eCRFs. Report signs and symptoms of a potential overdose that meet SAE criteria

(defined in Section 10.1.2) to the Sponsor's Pharmacovigilance group or its designee within 24 hours from the time the investigator first becomes aware of the SAE (see Section 10.2.4). Treat any AE (including SAE) based on standard care for the specific signs and symptoms.

8. RISKS/PRECAUTIONS

Refer to the ASTX029 IB for the most current risks and precautions, as well as a list of potential AEs associated with ASTX029 therapy based on nonclinical toxicology studies and clinical findings with other investigational agents in this drug class.

This study represents the first use of ASTX029 in humans, and as with any investigational medicinal product (IMP), subjects may experience reactions or complications that are unknown and therefore unpredictable. Risks to subjects participating in this first evaluation of ASTX029 in a human clinical trial include the potential for adverse reactions.

Based on nonclinical toxicology studies with this molecule, and clinical findings with other investigational agents in this drug class (ERK inhibitors; ie, ulixertinib and GDC-0994) (Sullivan et al 2018; Li et al presentation 2017; Varga et al 2020; Infante et al abstract 2015; Infante et al presentation 2015), the ASTX029 mechanism of action may result in cutaneous AEs (eg, rash, pruritus, dry skin), GI AEs (eg, diarrhea, nausea, vomiting, and esophagitis), fatigue, peripheral and periorbital edema, LVEF decrease, potential arrhythmias, visual disturbances, and liver enzyme elevation.

The potential for these AEs warrants frequent monitoring of subjects participating in clinical trials of ASTX029 until the safety profile is further understood. In particular, clinical signs and/or symptoms of cutaneous, ocular, GI, and liver toxicities and LVEF decrease will be closely monitored, evaluated, and managed during the study (Appendix 4, Appendix 5, Appendix 6, Appendix 7, and Appendix 8 respectively).

9. STUDY ASSESSMENTS AND PROCEDURES

9.1. Preliminary Clinical Activity Assessments

Measurable disease according to RECIST v1.1 (Appendix 3) will be assessed using CT or MRI scans at baseline (screening), every 2 cycles (±7 days) for the first 4 cycles, and then every 4 cycles (±1 cycle) thereafter until clinical and/or radiographic disease progression, death, or the subject withdraws consent. Tumor markers (if applicable) should be measured at the same time points as the time points for radiological assessments.

For subjects whose disease is not measurable using RECIST v1.1, disease status must be reliably and consistently followed using another generally acceptable method.

9.2. Pharmacokinetic/Pharmacodynamic/Biomarker Assessments

9.2.1. Pharmacokinetic Assessments

Serial blood samples for Phase 1 will be collected over a 24-hour period at specified time points postdose for PK analysis on C1D1, Cycle 1 Day 2 (C1D2), Cycle 2 Day 1 (C2D1), and Cycle 2 Day 2 (C2D2) for Regimen 1 (Table 4) and on C1D1, C1D2, Cycle 1 Day 14 (C1D14), and Cycle 1 Day 15 (C1D15) for Regimen 2 (Table 5).

Serial blood samples for Phase 2 will be collected on C1D1, C1D2, C2D1, and Cycle 3 Day 1 (C3D1) for Regimen 1 (Table 6) and on C1D1, C1D2, C1D14, C1D15, and C3D1 for Regimen 2 (Table 7).

Additional ad hoc blood sample(s) may be collected, per investigator discretion, for PK measurement at any time, including after the last dose, if there is a suspected safety issue.

ASTX-029 plasma concentration data will be used to determine PK parameters, including AUC, C_{max}, C_{min}, T_{max}, and $t_{½}$, in all subjects initially during Cycle 1 (both regimens) and Cycle 2 (Regimen 1), if data are evaluable. Metabolites of ASTX029 may be investigated if applicable. It is essential that the actual time and date of sample collection relative to the administration of study treatment be recorded in the subject's eCRF. Nominal PK blood sampling times and collection windows should be adhered to as closely as possible.

During the course of the study, as data emerge and improve the understanding of PK of ASTX029, sample collection times may be modified. Blood sample preparation and plasma sample storage details are provided in the laboratory manual.

Table 4: Phase 1: Plasma Collection Schedule for Pharmacokinetic Analysis (Regimen 1)

Study Day	Dosing Day?	Time Point[a]	Hours Postdose
C1D1	Yes	Predose	0.5 (±5 m), 1.0 (±5 m), 2.0 (±10 m)[b], 3.0 (±10 m), 4.0 (±10 m), 6.0 (±20 m), 8.0 (±30 m)
C1D2	Yes	24 ±1.0 h after C1D1 dose (prior to C1D2 dose)	

Study Day	Dosing Day?	Time Point[a]	Hours Postdose
C2D1	Yes	Predose	0.5 (±5 m), 1.0 (±5 m), 2.0 (±10 m)[b], 3.0 (±10 m), 4.0 (±10 m), 6.0 (±20 m), 8.0 (±30 m)
C2D2	Yes	24 ±1.0 h after C2D1 dose (prior to C2D2 dose)	
Ad hoc PK sample (including trough sample, ie, ~24 h post last dose if safety event suspected)			Per investigator discretion

CxDx=Cycle x Day x; ECG=electrocardiogram; h=hour(s); m=minute(s); PK=pharmacokinetic.
[a] On dosing days, collect predose samples within 60 minutes prior to administration of study treatment.
[b] It is recommended that the 2-hour postdose ECG be performed before PK sample collection.

Table 5: Phase 1: Plasma Collection Schedule for Pharmacokinetic Analysis (Regimen 2)

Study Day	Dosing Day?	Time Point[a]	Hours Postdose
C1D1	Yes[a]	Predose	0.5 (±5 m), 1.0 (±5 m), 2.0 (±10 m)[b], 3.0 (±10 m), 4.0 (±10 m), 6.0 (±20 m), 8.0 (±30 m)
C1D2	Yes[a]	24 ±1.0 h after C1D1 dose (prior to C1D2 dose)	
C1D14	Yes[a]	Predose	0.5 (±5 m), 1.0 (±5 m), 2.0 (±10 m)[b], 3.0 (±10 m), 4.0 (±10 m), 6.0 (±20 m), 8.0 (±30 m)
C1D15	No	24 ±1.0 h after C1D14 dose	
Ad hoc PK sample (including trough sample, ie, ~24 h post last dose if safety event suspected)			Per investigator discretion

CxDx=Cycle x Day x; ECG=electrocardiogram; h=hour(s); m=minute(s); PK=pharmacokinetic.
[a] On dosing days, collect predose samples within 60 minutes prior to administration of study treatment.
[b] It is recommended that the 2-hour postdose ECG be performed before PK sample collection.

Table 6: Phase 2: Plasma Collection Schedule for Pharmacokinetic Analysis (Regimen 1)

Study Day	Dosing Day?	Time Point[a]	Hours Postdose
C1D1	Yes	Predose	0.5 (±5 m), 1.0 (±5 m), 2.0 (±10 m)[b], 3.0 (±10 m), 4.0 (±10 m), 6.0 (±20 m), 8.0 (±30 m)
C1D2	Yes	24 ±1.0 h after C1D1 dose (prior to C1D2 dose)	
C2D1	Yes	Predose	2.0 (±10 m)[b]
C3D1	Yes	Predose	0.5 (±5 m), 1.0 (±5 m), 2.0 (±10 m), 4.0 (±10 m), 8.0 (±30 m)

Study Day	Dosing Day?	Time Point[a]	Hours Postdose
Ad hoc PK sample (including trough sample, ie, ~24 h post last dose if safety event suspected)			Per investigator discretion

CxDx=Cycle x Day x; ECG=electrocardiogram; h=hour(s); m=minute(s); PK=pharmacokinetic.
[a] On dosing days, collect predose samples within 60 minutes prior to administration of study treatment.
[b] It is recommended that the 2-hour postdose ECG be performed before PK sample collection.

Table 7: Phase 2: Plasma Collection Schedule for Pharmacokinetic Analysis (Regimen 2)

Study Day	Dosing Day?	Time Point[a]	Hours Postdose
C1D1	Yes[a]	Predose	0.5 (±5 m), 1.0 (±5 m), 2.0 (±10 m)[b], 3.0 (±10 m), 4.0 (±10 m), 6.0 (±20 m), 8.0 (±30 m)
C1D2	Yes[a]	24 ±1.0 h after C1D1 dose (prior to C1D2 dose)	
C1D14	Yes[a]	Predose	0.5 (±5 m), 1.0 (±5 m), 2.0 (±10 m)[b], 3.0 (±10 m), 4.0 (±10 m), 6.0 (±20 m), 8.0 (±30 m)
C1D15	No	24 ±1.0 h after C1D14 dose	
C3D1	Yes	Predose	0.5 (±5 m), 1.0 (±5 m), 2.0 (±10 m), 4.0 (±10 m), 8.0 (±30 m)
Ad hoc PK sample (including trough sample, ie, ~24 h post last dose if safety event suspected)			Per investigator discretion

CxDx=Cycle x Day x; ECG=electrocardiogram; h=hour(s); m=minute(s); PK=pharmacokinetic.
[a] On dosing days, predose samples are to be collected within 60 minutes prior to administration of study treatment
[b] It is recommended that the 2-hour postdose ECG be performed before PK sample collection.

9.2.2. Pharmacodynamic and Biomarker Assessments

Assessment of target engagement and biomarker analyses will be performed in blood and tumor tissue biopsies. Biomarker investigations will include the following:

- Demonstration of target engagement in fresh tumor tissue biopsies (when available) (eg, pRSK and pERK inhibition following ASTX029 treatment).
- Evaluation of cancer cell proliferation and induction of apoptosis in fresh tumor tissue biopsies (when available).
- Suppression of mutant clones in ctDNA.
- Identification of potential biomarkers of ASTX029 activity (DNA, RNA, or protein) in blood and tumor tissue biopsies (archival and fresh biopsies, when available).

Biomarker analyses will be performed by methods including immunohistochemistry, reverse transcription polymerase chain reaction (RT-PCR), next-generation sequencing, and possibly others.

Blood samples will be collected for biomarker analysis at the time points indicated in Table 8. Details of blood sample collection and handling procedures are provided in the laboratory manual.

If a FFPE archived tumor tissue is available, it will be obtained for use in this study during screening. In addition, collection of new (or fresh) tumor biopsies is encouraged (optional) in Phase 1 Part A and Phase 2 and mandatory in Phase 1 Part B of the study at the time points indicated in Table 9.

Archived tissue and fresh biopsies collected at screening will be used to characterize the genetic background of the tumor, confirm mutational status, and identify potential additional biomarkers of response to ASTX029; biopsies collected on treatment will be used to establish target engagement in tumor tissue and changes induced by ASTX029 treatment. At each time point (if safe and feasible), at least 2 biopsy cores will be collected (1 to be fresh-frozen and 1 to be FFPE). The subject must sign a biopsy ICF. A posttreatment biopsy sample need not be collected if a pretreatment biopsy (fresh) is not available for comparison. Details of biopsy tissue collection and handling procedures are provided in the laboratory manual.

Table 8: Sample Collection Schedule for Biomarker Analyses

Study Day	Dosing Day?	Samples	Time Point
Screening	No	Germline DNA (PBMC), ctDNA	
C1D1	Yes	ctDNA	Predose[a]
C2D1	Yes	ctDNA	Predose[a]
Day 1 of every cycle thereafter	Yes	ctDNA	Predose[a]
Treatment Termination visit	No	ctDNA	

CxDx=Cycle x Day x; ctDNA=circulating tumor DNA; PBMC=peripheral blood mononuclear cell.
[a] On dosing days, predose samples are to be collected within 60 minutes prior to administration of study treatment.

Table 9: Tumor Tissue Collection Schedule for Biomarker Analyses

Study Day	Dosing Day?	Samples	Time Point
Archival	No	FFPE	
Screening	No	FFPE, Frozen	
C2D8 (±1 day)	Yes	FFPE, Frozen	4.0 h (±1 h) postdose

C2D8=Cycle 2 Day 8; h=hour(s); FFPE=formalin-fixed paraffin embedded.
If archived tumor tissue (FFPE) is available, it will be requested for use in this study during screening. In addition, collection of fresh tumor biopsies is encouraged (optional) in Phase 1 Part A and Phase 2, and mandatory in Phase 1 Part B.

9.2.3. Total Volume of Blood Samples to Be Drawn

The estimated amount of blood to be collected for PK, biomarker investigations, and routine monitoring of hematology, coagulation, and serum chemistry during any cycle will not exceed 165 mL.

9.3. Safety Assessments

At each study visit, safety will be monitored by recording AEs, SAEs, DLTs, and concomitant medications; additional assessments that may be performed at selected visits include complete or symptom-directed physical examinations (PEs), weight, height, vital signs, ECOG performance status, 12-lead ECGs, clinical laboratory tests (including hematology, serum chemistry, urinalysis, and other tests [coagulation tests] as applicable), and ECHO/MUGA scans (see Table 11 and Table 12 for the complete schedules of events for Regimen 1 and Regimen 2, respectively). General information regarding the definition, evaluation, recording, and reporting of AEs and SAEs is provided in Section 10. Additional information regarding AEs specific to this protocol are provided below.

9.3.1. Adverse Events

The AEs should be captured from the time of first dose until 30 days after the last dose of study treatment or the start of an alternative treatment, whichever occurs first. The AEs that occur during the screening period and are considered related to screening procedures, as well as all related SAEs occurring beyond 30 days from the last dose of study treatment, will also be captured. Any SAEs will be followed until they have resolved or are stable.

The following events will be recorded in the eCRF as AEs:

- Adverse events of any severity grade (including changes from screening).
- Clinically significant abnormal findings during clinical assessments, including PEs and vital signs.
- Clinically significant abnormal ECG readings and any clinically significant ECHO/MUGA results.
- Spontaneous subject reports.
- Baseline medical conditions and AEs, other than the primary disease under evaluation, that worsen in severity or frequency during the study.

Clinical hematology, coagulation, serum chemistry, and urinalysis results that are outside of normal ranges but are not considered by the investigator to be clinically significant will not be reported as AEs.

9.4. Study Procedures

9.4.1. Physical Examination

Complete or symptom-directed PEs should be performed during the course of the study as outlined in the schedules of events (Section 9.4.9). At screening, a complete PE will be performed per the institutional standard practice but must include a skin examination. After

screening, symptom-directed PEs will be performed at the time points indicated in the schedules of events and at the investigator's discretion. The subject's height and weight should be measured and recorded at screening, and the subject's weight should be recorded on Day 1 of each cycle.

If a clinically significant abnormality is observed, the investigator will record it as part of the subject's medical history if it occurs prior to the start of study treatment on C1D1 and as an AE if it occurs after the commencement of study treatment.

9.4.2. Vital Signs

At screening and predose at the time points specified in the schedules of events (Section 9.4.9), resting systolic and diastolic blood pressure, resting heart rate, resting respiration rate, and body temperature are to be recorded; postdose at the specified time points, resting blood pressure and heart rate are to be recorded.

Assess vital signs after the subject has rested in a sitting or semirecumbent position for at least 3 minutes.

On each study day, blood pressure and heart rate will be measured using a blood pressure recording device with an appropriate cuff size. The date and time of collection and measurements will be recorded on the appropriate eCRF.

9.4.3. ECOG Performance Status

ECOG performance status (Appendix 1) should be assessed at screening and during the course of the study at the time points outlined in the schedules of events (Section 9.4.9).

9.4.4. 12-Lead ECG

The 12-lead ECGs are to be performed at screening and predose and 2 hours (±30 minutes) postdose on C1D1 and C2D1 in Regimen 1 and on C1D1 and C1D14 in Regimen 2; the 12-lead ECGs are to be performed predose at all other time points on the dosing days and at the Tx Term visit as indicated in the schedules of events (Section 9.4.9). All ECGs will be recorded at 25 mm/second in triplicate, with each recording separated by at least 30 seconds while the subject is resting in a semirecumbent position. Two copies of the ECG tracing should be obtained at the time of the ECG; the first copy will be kept in the subject's medical chart and the second copy will be kept in the study file for retrospective collection by the sponsor if necessary.

The following ECG data will be collected: rhythm, atrial rate, ventricular rate, PR interval, QRS duration, QT/QTc, morphology, and overall interpretation. The QTc is measured as the mean of the 3 values.

The investigator or designated physician will review the timed 12-lead ECGs on C1D1, before ASTX029-01 dosing to ensure ECG findings meet study entry criteria, and, otherwise within 24 hours of when they are collected, unless a critical value is observed. If subjects have a clinically significant abnormal ECG reading following treatment with ASTX029, their electrolytes should be checked and, if appropriate, serum potassium, calcium, and magnesium levels corrected and concomitant medications should be reviewed. Subjects may be discharged, if appropriate, later in the day, providing their ECG findings are no longer clinically significant.

If a clinically significant abnormal finding is observed, the investigator will record it as part of the subject's medical history if it occurs prior to the start of study treatment on C1D1 and as an AE if it occurs after the commencement of study treatment.

9.4.5. ECHO or MUGA Scan

Echo or MUGA scan assessments will be performed at screening, every 2 cycles for the first 4 cycles and every 4 cycles thereafter (±7 days), and at the Tx Term visit as outlined in the schedules of events (Section 9.4.9). The same diagnostic method should be used throughout the study.

If a clinically significant abnormal finding is observed, the investigator will record it as part of the subject's medical history if it occurs prior to the start of study treatment on C1D1 and as an AE if it occurs after the commencement of study treatment.

9.4.6. Ophthalmic Examination

Subjects will be required to have a standard ophthalmic examination performed by an ophthalmologist at screening. The exam will include indirect fundoscopic evaluation, visual acuity (with correction), visual field examination, and tonometry with special attention to retinal abnormalities that are predisposing factors for RVO or CSR. Direct fundoscopy may be performed if indicated. Additional ophthalmic examinations (as detailed above) will be performed only as symptomatically warranted. In subjects with clinical suspicion of RVO or CSR, fluorescein angiography and/or optical coherence tomography are recommended.

If a clinically significant abnormal finding is observed, the investigator will record it as part of the subject's medical history if it occurs prior to the start of study treatment on C1D1 and as an AE if it occurs after the commencement of study treatment.

9.4.7. Clinical Laboratory Tests

Clinical laboratory assessments should be performed at screening and during the course of the study as outlined in the schedules of events (Section 9.4.9). All clinical laboratory tests will be performed at local laboratories. Specific tests that will be performed for hematology, serum chemistry, urinalysis, serology, and other tests are listed in Table 10.

Table 10: Clinical Laboratory Tests

Hematology	Serum Chemistry	Urinalysis[a]	Serology	Other Tests
CBC -Hemoglobin -Hematocrit -RBC counts -WBC counts -Platelet count -WBC differential[b] -Neutrophils -Eosinophils -Basophils -Lymphocytes -Monocytes	Albumin Alkaline phosphatase ALT AST BUN Calcium Chloride CO_2 Creatinine Direct bilirubin Gamma-GT Glucose Lactate dehydrogenase	Dipstick -Specific gravity -pH -Protein -Glucose -Ketones -Leukocyte esterase -Blood	Pregnancy test[c]	Coagulation parameters -PTT -prothrombin time (or INR)

Hematology	Serum Chemistry	Urinalysis[a]	Serology	Other Tests
	Magnesium Phosphorus Potassium Sodium Total bilirubin Total cholesterol Total protein Uric acid			

ALT=alanine aminotransferase; AST=aspartate aminotransferase; BUN=blood urea nitrogen; CBC=complete blood count; CO_2=carbon dioxide; eCRF=electronic case report form; GT=glutamyl transferase; INR=international normalized ratio; PTT=partial thromboplastin time; RBC=red blood cell; WBC=white blood cell.
[a] A microscopic examination is to be performed if indicated.
[b] Either manual or automated differential counts may be performed; if both are done, the manual counts will be entered into the eCRF.
[c] For women of child-bearing potential; either serum or urine pregnancy test may be performed.

If a clinically significant abnormal finding is observed, the investigator will record it as part of the subject's medical history if it occurs prior to the start of study treatment on C1D1 and as an AE if it occurs after the commencement of study treatment.

9.4.8. Disease Assessments

CT or MRI scan (or other appropriate disease evaluation method, including tumor marker measurement, as applicable) will be performed as indicated in the schedules of events (Section 9.4.9) and Section 9.1. Lesion assessment must be done for chest, abdomen, pelvis, and any area of known disease. The same diagnostic method must be used throughout the study to evaluate each lesion.

9.4.9. Schedules of Events

Table 11 presents the complete schedule of events for Regimen 1 Continuous Dosing, and Table 12 presents that for Regimen 2 Intermittent Dosing with details following in text. Table 13 presents the Schedule of Events for the Study Extension phase.

Clinical and diagnostic laboratory evaluations are detailed before study entry, throughout the study, and at the follow-up evaluation. The purpose of obtaining these detailed measurements is to ensure adequate assessments of preliminary clinical activity, safety, and tolerability. Repeat clinical evaluations and laboratory studies more frequently if clinically indicated.

Note any deviation from protocol procedures. Investigators are responsible for implementing appropriate measures to prevent the recurrence of violations and deviations and to report to their IRB/IEC according to policy.

Table 11: Schedule of Events Regimen 1 – Continuous (Days 1 Through 21) Dosing

Cycle (21 Days)[a]		**1**				**2**				**≥3[a]**	**Tx Term[b]**	**30-day Safety FU[c]**	**Long-term FU**
Cycle Day[d]		**1[e]**	**2**	**8**	**15**	**1**	**2**	**8**	**15**	**1**			
Study treatment dispensation		x		x	x	x		x	x	x			
Dosing compliance information				x	x	x		x	x	x	x		
Procedures	**Screening[f]**												
Informed consent	x												
Medical history	x												
Investigator's confirmation of eligibility	x	x											
PE/symptom-directed PE[g]	x	x		x	x	x		x	x	x	x	x	
Height	x												
Weight	x	x				x				x			
Vital signs[h]	x	x	x	x	x	x	x	x	x	x	x	x	
ECOG performance status	x	x		x	x	x		x	x	x	x	x	
12-lead ECG[i]	x	x	x	x	x	x				x	x		
ECHO or MUGA scan	x	Repeat every 2 cycles for the first 4 cycles and then every 4 cycles thereafter (±7 days)									x		
Ophthalmic examination[j]	x												
Concomitant medications/AEs[k]	x	x	x	x	x	x	x	x	x	x	x	x	
Randomization (if applicable), enrollment	x												
Laboratory Assessments													
Hematology[l,m]	x	x		x	x	x		x	x	x	x		
Coagulation[m,n]	x	x				x				x	x		

Cycle (21 Days)[a]		**1**				**2**				**≥3[a]**		**Tx Term[b]**	**30-day Safety FU[c]**	**Long-term FU**
Cycle Day[d]		**1[e]**	**2**	**8**	**15**	**1**	**2**	**8**	**15**	**1**				
Chemistry[m,o]	x	x		x	x	x		x	x	x		x		
Urinalysis[m,p]	x	x				x				x		x		
Serum or urine pregnancy test[m,q]	x	x				x				x		x		
Pharmacokinetics[r]		x	x			x	x[s]			x[t]				
Blood sample for ctDNA[u]	x	x				x				x		x		
Blood (PBMC) sample for germline DNA	x													
Obtain archival tumor tissue[v]	x													
Collect pretreatment biopsy[v]	x													
Collect on-treatment biopsy[v]								x						
Disease Assessments														
Response assessment[w]	x	At the end of every 2 cycles (±7 days) for the first 4 cycles and then every 4 cycles (±1 cycle) thereafter												
Health status follow-up[x]														Every 3 months

AE=adverse event; CxDx=Cycle x Day x; CBC=complete blood count; ctDNA=circulating tumor DNA; CT=computed tomography; ECG=electrocardiogram; ECOG=Eastern Cooperative Oncology Group; eCRF=electronic case report form; FFPE=formalin-fixed paraffin embedded; FU=follow-up; INR=international normalized ratio; MRI=magnetic resonance imaging; MUGA=multiple-gated acquisition; PBMC=peripheral blood mononuclear cell; PE=physical examination; PK=pharmacokinetic; PTT= partial thromboplastin time; Tx Term=Treatment Termination.

[a] After Cycle 6, the specific visit schedule and assessments are at the investigator's discretion; at a minimum, information should be collected regarding concomitant medications, AEs, dosing compliance, and, at least once a month, pregnancy tests. Continue to collect efficacy and response assessments, in the manner described in the protocol, until disease progression (for response assessment) or death (for survival assessment), or the subject withdraws consent.

[b] Perform Tx Term visit procedures when a subject permanently discontinues study treatment, regardless of whether or not the subject plans to continue participating in the study (unless consent to continue study participation is withdrawn by the subject). The visit is to occur within 7 days after the last study treatment or within 3 days before starting new anticancer treatment and before the 30-day Safety Follow-up visit. If a subject discontinues study treatment at a scheduled visit, the assessments at that visit can be used to fulfill the Tx Term visit requirements.

[c] The 30-day Safety Follow-up visit must occur 30 (+5) days after the last dose of ASTX029 or within 3 days before starting new cancer treatment.

[d] In Phase 1 starting with C2D8, study visits have a visit window of ±1 day. In Phase 2, all study visits for Cycles ≥2 have a visit window of ±2 days.

[e] On C1D1 (the first day of study treatment administration), complete the PE, vital signs, weight, and laboratory evaluations before administration of study treatment. Laboratory evaluations do not need to be repeated if screening tests are within 4 days prior to first dose of ASTX029. For subjects who had a full PE performed at screening within 4 days prior to the first dose of ASTX029, it is not necessary to repeat the full PE on C1D1; a symptom-directed PE on C1D1 can be done instead.

[f] Screening procedures must occur within 21 days prior to first dose of ASTX029.
[g] At screening, a complete PE per the institutional standard practice, but including a skin examination (Section 9.4.1), will be performed. After screening, symptom-directed PEs will be performed at the time points indicated and at the investigator's discretion.
[h] Obtain vital signs at screening; predose on Day 1 of each cycle and on C1D2, C1D8, C1D15, C2D2, C2D8, and C2D15; at the Tx Term visit; and at the Safety Follow-up visit. In addition, obtain systolic/diastolic blood pressure and heart rate at 1 hour (±30 minutes) postdose on C1D1 and C2D1. Assess all vital signs after the subject has rested in a sitting or semirecumbent position for at least 3 minutes.
[i] The 12-lead ECGs will be performed at screening and predose and 2 hours (±30 minutes) postdose on C1D1 and C2D1; they will be performed predose at all other time points on the dosing days and at the Tx Term visit as indicated. All ECGs will be recorded at 25 mm/second in triplicate, with each recording separated by at least 30 seconds, while the subject is in a semirecumbent position (Section 9.4.4). Two copies of the ECG tracing should be obtained at the time of the ECG; the first copy will be kept in the subject's medical chart and the second copy will be kept in the study file for retrospective collection by the sponsor if necessary. On C1D1, ECG findings must meet study entry criteria before dosing.
[j] An ophthalmic examination will be performed at screening. Additional ophthalmic examinations will be performed only as symptomatically warranted. Refer to Section 9.4.6 for details.
[k] Record all medications a subject takes starting from 14 days before study treatment initiation and ending 30 days after the last dose of study treatment. Record screening procedure-related AEs that occur before the start of study treatment and new AEs from the start of study treatment until 30 days after the last dose of study treatment or until the subject starts a new cancer treatment, including new investigational treatment, whichever occurs first. Also record screening procedure-related AEs that occur before the start of study treatment. Refer to Section 10.2.
[l] Hematology must include CBC with either manual or automated differential and platelet counts; if both are done, the manual counts will be entered into the eCRF (Table 10). C1D1 hematology evaluations do not need to be repeated if screening tests are within 4 days prior to first dose of ASTX029. On C1D1, all hematology evaluations must meet study entry criteria before dosing.
[m] Hematology, chemistry, coagulation, and urinalysis tests may be performed on the day before the visits and the pregnancy test may be performed within 24 hours before the start of study treatment Cycles 1-6 if more convenient.
[n] Collect PTT and prothrombin time (or INR) at screening, predose on Day 1 of each cycle, and at the Tx Term visit. The C1D1 coagulation evaluations do not need to be repeated if screening tests are done within 4 days prior to first dose of ASTX029.
[o] Serum chemistry must include the analytes listed in Table 10. The C1D1 chemistry evaluations do not need to be repeated if screening tests are within 4 days prior to first dose of ASTX029. On C1D1, all chemistry evaluations must meet study entry criteria before dosing.
[p] Urinalysis includes dipstick test (if available) and microscopic examination (if indicated) (Table 10). The C1D1 urinalysis evaluations do not need to be repeated if screening tests are within 4 days prior to the first dose of ASTX029.
[q] Pregnancy test: to be performed at screening, within 24 hours before the start of Cycles 1 through 6, at least monthly during treatment thereafter, and at the Tx Term visit (only for women of child-bearing potential).
[r] See Table 4 and Table 6, respectively (Section 9.2.1), for the complete PK blood draw schedule for Phase 1 and Phase 2.
[s] Collect PK blood samples in Phase 1 only; see Table 4.
[t] Collect PK blood samples in Phase 2 only; see Table 6.
[u] See Table 8 for the ctDNA sample collection schedule. On dosing days, predose samples are to be collected within 60 minutes prior to administration of study treatment.
[v] If archived tumor tissue (FFPE) is available, it will be requested for use in this study during screening. In addition, collection of fresh tumor biopsies is encouraged (optional) in Phase 1 Part A and Phase 2 and mandatory in Phase 1 Part B of the study during screening and on C2D8 (±1 day), 4 hours (±1 hour) postdose. See Table 9 for the biopsy collection schedule.
[w] CT or MRI scan (or other appropriate disease evaluation method, including tumor marker measurement, as applicable) will be performed at screening, at the end of every 2 cycles (±7 days) for the first 4 cycles, and then every 4 cycles (±1 cycle) thereafter until clinical and/or radiographic disease progression, or death, or the subject withdraws consent, whichever occurs first (Section 9.1, Section 9.4.8). If the last assessment was >12 weeks prior to study treatment withdrawal and disease progression had not been documented, a disease assessment should be obtained at the Tx Term visit.
[x] Beginning 3 months after discontinuation of treatment, subjects will be contacted by telephone for collection of health status information every 3 months until death, the subject withdraws consent, or end of study, whichever occurs first (Section 9.4.15).

Table 12: Schedule of Events Regimen 2 – Intermittent (Days 1 Through 14) Dosing

Cycle (21 Days)[a]		**1**					**2**			**≥3[a]**	**Tx Term[b]**	**30-day Safety FU[c]**	**Long-term FU**
Cycle Day[d]		**1[e]**	**2**	**8**	**14**	**15**	**1**	**8**	**15**	**1**			
Study treatment dispensation		x		x			x	x		x			
Dosing compliance information				x	x			x		x	x		
Procedures	**Screening[f]**												
Informed consent	x												
Medical history	x												
Investigator's confirmation of eligibility	x	x											
PE/symptom-directed PE[g]	x	x		x	x		x	x	x	x	x	x	
Height	x												
Weight	x	x					x			x			
Vital signs[h]	x	x	x	x	x	x	x	x	x	x	x	x	
ECOG performance status	x	x		x	x		x	x	x	x	x	x	
12-lead ECG[i]	x	x	x	x	x	x	x			x	x		
ECHO or MUGA scan	x	Repeat every 2 cycles for the first 4 cycles and then every 4 cycles thereafter (±7 days)									x		
Ophthalmic examination[j]	x												
Concomitant medications/AEs[k]	x	x	x	x	x	x	x	x	x	x	x	x	
Randomization (if applicable), enrollment	x												
Laboratory Assessments													
Hematology[l,m]	x	x		x	x		x	x	x	x	x		
Coagulation[m,n]	x	x					x			x	x		

Cycle (21 Days)[a]		**1**					**2**			**≥3[a]**	**Tx Term[b]**	**30-day Safety FU[c]**	**Long-term FU**
Cycle Day[d]		**1[e]**	**2**	**8**	**14**	**15**	**1**	**8**	**15**	**1**			
Study treatment dispensation		x		x			x	x		x			
Dosing compliance information				x	x			x		x	x		
Procedures	**Screening[f]**												
Informed consent	x												
Medical history	x												
Investigator's confirmation of eligibility	x	x											
PE/symptom-directed PE[g]	x	x		x	x		x	x	x	x	x	x	
Chemistry[m,o]	x	x		x	x		x	x	x	x	x		
Urinalysis[m,p]	x	x					x			x	x		
Serum or urine pregnancy test[m,q]	x	x					x			x	x		
Pharmacokinetics[r]		x	x		x	x				x[s]			
Blood sample for ctDNA[t]	x	x					x			x	x		
Blood (PBMC) sample for germline DNA	x												
Obtain archival tumor tissue[u]	x												
Collect pretreatment biopsy[u]	x												
Collect on-treatment biopsy[u]								x					
Disease Assessments													
Response assessment[v]	x	At the end of every 2 cycles (±7 days) for the first 4 cycles and then every 4 cycles (±1 cycle) thereafter											
Health status follow-up[w]													Every 3 months

AE=adverse event; CxDx=Cycle x Day x; CBC=complete blood count; ctDNA=circulating tumor DNA; CT=computed tomography; ECG=electrocardiogram; ECOG=Eastern Cooperative Oncology Group; eCRF=electronic case report form; FFPE=formalin-fixed paraffin embedded; FU=follow-up; INR=international normalized ratio; MRI=magnetic

resonance imaging; MUGA=multiple-gated acquisition; PBMC= peripheral blood mononuclear cell; PE=physical examination; PK=pharmacokinetic; PTT= partial thromboplastin time; Tx Term=Treatment Termination.

[a] After Cycle 6, the specific visit schedule and assessments are at the investigator's discretion; at a minimum, information should be collected regarding concomitant medications, AEs, dosing compliance, and, at least once a month, pregnancy tests. Continue to collect efficacy and response assessments, in the manner described in the protocol, until disease progression (for response assessment) or death (for survival assessment), or the subject withdraws consent.

[b] Perform Tx Term visit procedures when a subject permanently discontinues study treatment, regardless of whether or not the subject plans to continue participating in the study (unless consent to continue study participation is withdrawn by the subject). The visit is to occur within 7 days after the last study treatment or within 3 days before starting new anticancer treatment and before the 30-day Safety Follow-up visit. If a subject discontinues study treatment at a scheduled visit, the assessments at that visit can be used to fulfill the Tx Term visit requirements.

[c] The 30-day Safety Follow-up visit must occur 30 (+5) days after the last dose of ASTX029 or within 3 days before starting new cancer treatment.

[d] In Phase 1 starting with C2D8, study visits have a visit window of ±1 day. In Phase 2, all study visits for Cycles ≥2 have a visit window of ±2 days.

[e] On C1D1 (the first day of study treatment administration), complete the PE, vital signs, weight, and laboratory evaluations before administration of study treatment. Laboratory evaluations do not need to be repeated if screening tests are within 4 days prior to first dose of ASTX029. For subjects who had a full PE performed at screening within 4 days prior to the first dose of ASTX029, it is not necessary to repeat the full PE on C1D1; a symptom-directed PE on C1D1 can be done instead.

[f] Screening procedures must occur within 21 days prior to first dose of ASTX029.

[g] At screening, a complete PE per the institutional standard practice, but including a skin examination, (Section 9.4.1) will be performed. After screening, symptom-directed PEs will be performed at the time points indicated and at the investigator's discretion.

[h] Obtain vital signs at screening; predose on Day 1 of each cycle and on C1D2, C1D8, C1D14, and C2D8; on C1D15 and C2D15; at the Tx Term visit; and at the Safety Follow-up visit. In addition, obtain systolic/diastolic blood pressure and resting heart rate at 1 hour (±30 minutes) postdose on C1D1 and C1D14. Assess all vital signs after the subject has rested in a sitting or semirecumbent position for at least 3 minutes.

[i] The 12-lead ECGs will be performed at screening and predose and 2 hours (±30 minutes) postdose on C1D1 and C1D14; they will be performed predose at all other time points on the dosing days and at the Tx Term visit as indicated. All ECGs will be recorded at 25 mm/second in triplicate, with each recording separated by at least 30 seconds, while the subject is in a semirecumbent position (Section 9.4.4). Two copies of the ECG tracing should be obtained at the time of the ECG; the first copy will be kept in the subject's medical chart and the second copy will be kept in the study file for retrospective collection by the sponsor if necessary. On C1D1, ECG findings must meet study entry criteria before dosing.

[j] An ophthalmic examination will be performed at screening. Additional ophthalmic examinations will be performed only as symptomatically warranted. Refer to Section 9.4.6 for details.

[k] Record all medications a subject takes starting from 14 days before study treatment initiation and ending 30 days after the last dose of study treatment. Record screening procedure-related AEs that occur before the start of study treatment and new AEs from the start of study treatment until 30 days after the last dose of study treatment or until the subject starts new cancer treatment, including new investigational treatment, whichever occurs first. Also record screening procedure-related AEs that occur before the start of study treatment. Refer to Section 10.2.

[l] Hematology must include CBC with either manual or automated differential and platelet counts; if both are done, the manual counts will be entered into the eCRF (Table 10). C1D1 hematology evaluations do not need to be repeated if screening tests are within 4 days prior to first dose of ASTX029. On C1D1, all hematology evaluations must meet study entry criteria before dosing.

[m] Hematology, chemistry, coagulation, and urinalysis tests may be performed on the day before the visits and the pregnancy tests may be performed within 24 hours before the start of study treatment Cycles 1-6 if more convenient.

[n] Collect PTT and prothrombin time (or INR) at screening, predose on Day 1 of each cycle, and at the Tx Term visit. The C1D1 coagulation evaluations do not need to be repeated if screening tests are done within 4 days prior to first dose of ASTX029.

[o] Serum chemistry must include the analytes listed in Table 10. The C1D1 chemistry evaluations do not need to be repeated if screening tests are within 4 days prior to first dose of ASTX029. On C1D1, all chemistry evaluations must meet study entry criteria before dosing.

[p] Urinalysis includes dipstick test (if available) and microscopic examination (if indicated) (Table 10). The C1D1 urinalysis evaluations do not need to be repeated if screening tests are within 4 days of first dose of ASTX029.

[q] Pregnancy test: to be performed at screening, within 24 hours before the start of Cycles 1 through 6, at least monthly during treatment thereafter, and at the Tx Term visit (only for women of child-bearing potential).

[r] See Table 5 and Table 7, respectively (Section 9.2.1), for the complete PK blood draw schedule for Phase 1 and Phase 2.
[s] Collect PK blood samples in Phase 2 only; see Table 7.
[t] See Table 8 for the ctDNA sample collection schedule. On dosing days, predose samples are to be collected within 60 minutes prior to administration of study treatment.
[u] If archived tumor tissue (FFPE) is available, it will be requested for use in this study during screening. In addition, collection of fresh tumor biopsies is encouraged (optional) in Phase 1 Part A and Phase 2 and mandatory in Phase 1 Part B of the study during screening and on C2D8 (±1 day), 4 hours (±1 hour) postdose. See Table 9 for the biopsy collection schedule.
[v] CT or MRI scan (or other appropriate disease evaluation method, including tumor marker measurement, as applicable) will be performed at screening, at the end of every 2 cycles (±7 days) for the first 4 cycles, and then every 4 cycles (±1 cycle) thereafter until clinical and/or radiographic disease progression, or death, or the subject withdraws consent, whichever occurs first (Section 9.1, Section 9.4.8. If the last assessment was >12 weeks prior to study treatment withdrawal and disease progression had not been documented, a disease assessment should be obtained at the Treatment Termination visit.
[w] Beginning 3 months after discontinuation of treatment, subjects will be contacted by telephone for collection of health status information every 3 months until death, the subject withdraws consent, or end of study, whichever occurs first (Section 9.4.15).

Table 13 Schedule of Events – Study Extension Phase

	Treatment Period (1 cycle = 21 days)	Safety Follow-Up	Notes
	At Least Every 3 Cycles	30 (+5 days) After Last Dose	
Physical examination	X	X	Only symptom-directed examinations required
Vital signs	X	X	Assess all vital signs after the subject has rested in a sitting or semirecumbent position for at least 3 minutes.
Weight	X	X	
Ophthalmological examination	(X)	(X)	Performed only as symptomatically warranted. Section 9.4.6
ECOG performance status	X	X	See Appendix 1
12-Lead electrocardiogram	X	X	Performed in triplicate, with each recording separated by at least 30 seconds. See Section 9.4.4.
Hematology	X	X	Must include CBC with either manual or automated differential and platelet counts. See Table 10
Coagulation	X	X	Includes PTT and prothrombin time (or INR). See Table 10
Chemistry	X	X	See Table 10
Pregnancy test	X	X	If applicable. Additional testing (urine or serum) as required per local practice.
Concomitant medications/ AEs	X	X	Collect through 30 days after administration of the last dose of study treatment or until the subject starts of new cancer treatment, whichever occurs first. See Section 7.6 and Section 9.3
Response assessment (CT/MRI)	X		Tumor assessments may be performed as necessary to determine continued benefit from treatment, every 4 cycles (± 1 cycle), or as clinically indicated, until radiologic PD or initiation of new anticancer therapy (whichever occurs first). See Section 9.4.8

AE=adverse event; ECOG=Eastern Cooperative Oncology Group

9.4.10. Screening and Baseline Procedures

After the investigator or sub-investigator confirms that a subject is eligible and willing to participate in the study, study center personnel will forward the appropriate documentation to the attention of the sponsor or sponsor delegate according to the study regulatory binder.

Within 21 days before treatment administration, perform the following study procedures and tests:

- Written informed consent. The ICF must be signed and dated by the subjects before any study-specific samples are collected or study-specific procedures are initiated.
- Complete medical history, including demographics. Record disease history, including the date of initial diagnosis and list prior treatments and responses to these treatments*)*. Document concurrent medical signs and symptoms to establish baseline conditions.
- Complete PE per the institutional standard practice, but including a skin examination, and including height and weight.
- Vital signs include resting systolic/diastolic blood pressure, resting respiration rate, resting heart rate, and body temperature. Assess vital signs after the subject has rested in a sitting or semirecumbent position for at least 3 minutes (Section 9.4.2).
- ECOG performance status assessment (Appendix 1).
- 12-lead ECG in triplicate (Section 9.4.4).
- ECHO or MUGA scan.
- Ophthalmic examination (Section 9.4.6).
- Record screening procedure-related AEs that occur before the start of study treatment and concomitant medications starting 14 days before study treatment initiation.
- Sample collection for clinical laboratory tests (hematology, coagulation, serum chemistry, and urinalysis) (Table 10).
- Serum or urine pregnancy test: for women of child-bearing potential only. Results must be negative for the subject to be eligible for enrollment into the study.
- Blood sample collection for ctDNA and blood (PBMC) sample collection for germline DNA (Section 9.2.2, Table 8).
- Archival tumor tissue (FFPE) collection (Section 9.2.2, Table 9).
- Pretreatment fresh tumor biopsy collection (optional in Phase 1 Part A and Phase 2 and mandatory in Phase 1 Part B) (Section 9.2.2, Table 9).
- CT or MRI scan (or other appropriate disease evaluation method, including tumor marker measurement, as applicable).
- Investigator's confirmation of eligibility. Perform all necessary procedures and evaluations to document that the subject meets each eligibility criterion.

- Randomize patient (Phase 1, if applicable).
- Enroll patient.

9.4.11. Treatment and Follow-up Procedures

The first day of study drug administration is C1D1. Consecutive QD oral doses of study drug will be administered (or self-administered) on Days 1 to 21 (Regimen 1) or Days 1 to 14 (Regimen 2). For details on study drug administration please refer to Section 7.1.7. Subjects should drink 1 full glass of water immediately after drug ingestion and not lay down for at least 30 minutes after drug ingestion. On scheduled visit days, subjects should wait to take the study drug until after they have checked into the study center and undergone the predose procedures. Subjects should record the time and date of each dose they self-administer in their dosing diary.

Treatment and follow-up procedures will be followed for Regimen 1 or 2, based on the regimen selected.

9.4.11.1. Cycle 1 – Week 1

Week 1 is a dosing week in both Regimen 1 and Regimen 2: consecutive QD oral doses of study treatment will be administered (or self-administered) on Days 1 to 7.

9.4.11.1.1. Cycle 1 – Week 1 – Day 1

Before administration of study treatment:

- Perform symptom-directed PE (Section 9.4.1).
- Record subject's weight.
- Record vital signs (Section 9.4.2).
- Evaluate ECOG performance status (Appendix 1).
- Perform predose 12-lead ECG in triplicate (Section 9.4.4). Note: ECG findings must meet study entry criteria before dosing.
- Record screening procedure-related AEs that occur before the start of study treatment and concomitant medications received since screening.
- Collect blood samples for hematology, coagulation, and serum chemistry laboratory tests and review results; collect urine sample for urinalysis (Table 10). Note: hematology and chemistry values must meet study entry criteria before dosing, C1D1 hematology, coagulation, serum chemistry, and urine evaluations do not need to be repeated if screening tests are done within 4 days prior to first dose of ASTX029, and these tests may be performed on the day before the visit if more convenient.
- Perform serum or urine pregnancy test for women of child-bearing potential only, and this test may be performed within 24 hours before the start of study treatment if more convenient.
- Collect predose blood sample for PK analysis (Section 9.2.1, Table 4, Table 5, Table 6, and Table 7).

- Collect predose blood sample for ctDNA (Section 9.2.2, Table 8).
- Confirm eligibility.

Subject ingests study treatment while at the clinic.

After administration of study treatment:

- Record blood pressure and heart rate 1 hour (±30 minutes) postdose (Section 9.4.2).
- Perform 12-lead ECG in triplicate 2 hours (±30 minutes) postdose (Section 9.4.4).
- Record AEs and concomitant medications.
- Collect blood samples for postdose PK analysis (Section 9.2.1, Table 4, Table 5, Table 6, and Table 7).
- Dispense study treatment (ASTX029), provide instruction for self-administration, and instruct subject to, on dosing days when there is a scheduled visit, refrain from ingesting the study drug until after being on-site at the study clinic and the predose study procedures have been performed.
- Provide a dosing diary to the subject and instructions for how to enter dosing information.

9.4.11.1.2. Cycle 1 – Week 1 – Day 2

Before administration of study treatment:

- Record vital signs (Section 9.4.2).
- Perform predose 12-lead ECG in triplicate (Section 9.4.4).
- Record AEs and concomitant medications.
- Collect post C1D1 dose blood sample for PK analysis (Section 9.2.1, Table 4, Table 5, Table 6, and Table 7).

Subject ingests study treatment while at the clinic.

After administration of study treatment:

- Record AEs and concomitant medications.

9.4.11.2. Cycle 1 – Week 2 – Day 8

Week 2 is a dosing week in both Regimen 1 and Regimen 2: consecutive QD oral doses of study treatment will be administered (or self-administered) on Days 8 to 14.

Before administration of study treatment (note: hematology and serum chemistry tests may be performed on the day before the visit if more convenient):

- Perform symptom-directed PE (Section 9.4.1).
- Record vital signs (Section 9.4.2).
- Evaluate ECOG performance status (Appendix 1).

- Record AEs and concomitant medications.
- Perform predose 12-lead ECG in triplicate (Section 9.4.4).
- Collect blood samples for hematology and serum chemistry laboratory tests (Table 10).

Subject ingests study treatment while at the clinic.

After administration of study treatment:

- Record AEs and concomitant medications.
- Review dosing diary to assess dosing compliance.
- Dispense study treatment (ASTX029), provide instruction for self-administration as needed, and instruct subject to, on dosing days when there is a scheduled visit, refrain from ingesting the study drug until after being are on-site at the study clinic and the predose study procedures have been performed.

9.4.11.3. Cycle 1 – Week 2 – Day 14 Regimen 2 Only

Week 2 Day 14 is the last day of dosing in Regimen 2.

For subjects receiving Regimen 2 treatment (before administration of study treatment) (note: hematology and serum chemistry tests may be performed on the day before the visit if more convenient):

- Perform symptom-directed PE (Section 9.4.1).
- Record vital signs (Section 9.4.2).
- Evaluate ECOG performance status (Appendix 1).
- Perform predose 12-lead ECG in triplicate (Section 9.4.4).
- Record AEs and concomitant medications.
- Review dosing diary to assess dosing compliance.
- Collect blood samples for hematology and serum chemistry laboratory tests (Table 10).
- Collect predose blood sample for PK analysis (Section 9.2.1, Table 5 and Table 7).

Subject ingests study treatment while at the clinic.

For subjects receiving Regimen 2 treatment (after administration of study treatment):

- Record blood pressure and heart rate 1 hour (±30 minutes) postdose (Section 9.4.2).
- Perform 12-lead ECG in triplicate 2 hours (±30 minutes) postdose (Section 9.4.4).
- Record AEs and concomitant medications.
- Collect postdose blood samples for PK analysis (Section 9.2.1, Table 5 and Table 7).

9.4.11.4. Cycle 1 – Week 3 – Day 15

Week 3 is a dosing week in Regimen 1 (only): consecutive QD oral doses of study treatment will be administered (or self-administered) on Days 15 to 21.

For subjects receiving Regimen 1 treatment (before administration of study treatment) (note: hematology and serum chemistry tests may be performed on the day before the visit if more convenient):

- Perform symptom-directed PE (Section 9.4.1).
- Record vital signs (Section 9.4.2).
- Evaluate ECOG performance status (Appendix 1).
- Record AEs and concomitant medications.
- Perform predose 12-lead ECG in triplicate (Section 9.4.4).
- Collect blood samples for hematology and serum chemistry laboratory tests (Table 10).

Subject receiving Regimen 1 treatment ingests study treatment while at the clinic.

After administration of study treatment for subjects receiving Regimen 1 treatment:

- Record AEs and concomitant medications.
- Review dosing diary to assess dosing compliance.
- Dispense study treatment (ASTX029), provide instruction for self-administration as needed, and instruct subject to, on dosing days when there is a scheduled visit, refrain from ingesting the study drug until after being are on-site at the study clinic and the predose study procedures have been performed.

For subjects receiving Regimen 2 treatment:

- Record vital signs (Section 9.4.2).
- Record AEs and concomitant medications.
- Perform 12-lead ECG in triplicate (Section 9.4.4).
- Collect post C1D14 dose blood sample for PK analysis (Section 9.2.1, Table 5 and Table 7).

9.4.11.5. Cycle 2 – Week 1

Week 1 is a dosing week in both Regimen 1 and Regimen 2: consecutive QD oral doses of study treatment will be administered (or self-administered) on Days 1 to 7.

9.4.11.5.1. Cycle 2 – Week 1 – Day 1

Before administration of study treatment (note: hematology, serum chemistry, coagulation, and urinalysis tests may be performed on the day before the visit and the pregnancy test may be performed within 24 hours before administration of study treatment if more convenient):

- Perform symptom-directed PE (Section 9.4.1).
- Record subject's weight.
- Record vital signs (Section 9.4.2).
- Evaluate ECOG performance status (Appendix 1).
- Perform predose 12-lead ECG in triplicate (Section 9.4.4).
- Record AEs and concomitant medications.
- Collect blood samples for hematology, coagulation, and serum chemistry laboratory tests and review results; collect urine sample for urinalysis (Table 10).
- Perform serum or urine pregnancy test for women of child-bearing potential only.
- Collect predose blood sample for ctDNA (Section 9.2.2, Table 8).

In addition, for subjects receiving Regimen 1 treatment (before administration of study treatment):

- Collect predose blood sample for PK analysis (Section 9.2.1, Table 4 and Table 6).

Subject ingests study treatment while at the clinic.

After administration of study treatment:

- Record AEs and concomitant medications.
- Dispense study treatment (ASTX029), provide instruction for self-administration as needed, and instruct subject to, on dosing days when there is a scheduled visit, refrain from ingesting the study drug until after being are on-site at the study clinic and the predose study procedures have been performed.
- Provide a dosing diary to the subject and instructions for how to enter dosing information.

In addition, for subjects receiving Regimen 1 treatment (after administration of study treatment):

- Review dosing diary to assess dosing compliance.
- Record blood pressure and heart rate 1 hour (±30 minutes) postdose (Section 9.4.2).
- Perform 12-lead ECG in triplicate 2 hours (±30 minutes) postdose (Section 9.4.4).
- Collect postdose blood samples for PK analysis (Section 9.2.1, Table 4 and Table 6).

9.4.11.5.2. Cycle 2 – Week 1 – Day 2 Regimen 1 Only

For subjects receiving Regimen 1 treatment (Before administration of study treatment):

- Record vital signs (Section 9.4.2).
- Record AEs and concomitant medications.

For subjects in Phase 1 receiving Regimen 1 treatment (before administration of study treatment):

- Collect post C2D1 blood sample for PK analysis (Section 9.2.1, Table 4).

Subject ingests study treatment while at the clinic.

For subjects receiving Regimen 1 treatment (After administration of study treatment):

- Record AEs and concomitant medications.

9.4.11.6. Cycle 2 – Week 2 – Day 8

Week 2 is a dosing week in both Regimens 1 and 2: consecutive QD oral doses of study treatment will be administered (or self-administered) on Days 8 to 14.

Before administration of study treatment (note: hematology and serum chemistry tests may be performed on the day before the visit if more convenient):

- Perform symptom-directed PE (Section 9.4.1).
- Record vital signs (Section 9.4.2).
- Evaluate ECOG performance status (Appendix 1).
- Record AEs and concomitant medications.
- Collect blood samples for hematology and serum chemistry laboratory tests (Table 10).

Subject ingests study treatment while at the clinic.

After administration of study treatment:

- Record AEs and concomitant medications.
- Collect fresh tumor biopsy (optional in Phase 1 Part A and Phase 2 and mandatory in Phase 1 Part B) 4 hours (±1 hour) postdose (Section 9.2.2, Table 9).
- Dispense study treatment (ASTX029), provide instruction for self-administration as needed, and instruct subject to, on dosing days when there is a scheduled visit, refrain from ingesting the study drug until after being are on-site at the study clinic and the predose study procedures have been performed.
- Review dosing diary to assess dosing compliance.

9.4.11.7. Cycle 2 – Week 3 – Day 15

Week 3 is a dosing week in Regimen 1 (only): consecutive QD oral doses of study treatment will be administered (or self-administered) on Days 15 to 21.

For subjects receiving Regimen 1 treatment (before administration of study treatment) (note: hematology and serum chemistry tests may be performed on the day before the visit if more convenient):

- Perform symptom-directed PE (Section 9.4.1).
- Record vital signs (Section 9.4.2).
- Evaluate ECOG performance status (Appendix 1).
- Record AEs and concomitant medications.
- Collect blood samples for hematology and serum chemistry laboratory tests (Table 10).

Subject receiving Regimen 1 treatment ingests study treatment while at the clinic.

After administration of study treatment for subjects receiving Regimen 1 treatment:

- Record AEs and concomitant medications.
- Dispense study treatment (ASTX029), provide instruction for self-administration as needed, and instruct subject to, on dosing days when there is a scheduled visit, refrain from ingesting the study drug until after being are on-site at the study clinic and the predose study procedures have been performed.
- Review dosing diary to assess dosing compliance.

For subjects receiving Regimen 2 treatment (note: hematology and serum chemistry tests may be performed on the day before the visit if more convenient):

- Perform symptom-directed PE (Section 9.4.1).
- Record vital signs (Section 9.4.2).
- Evaluate ECOG performance status (Appendix 1).
- Record AEs and concomitant medications.
- Collect blood samples for hematology and serum chemistry laboratory tests (Table 10).

9.4.11.8. Cycle 2 End of Cycle (before Cycle 3 Day 1)

- Assess subject's disease by CT or MRI scan (or other appropriate disease evaluation method, including tumor marker measurement, as applicable).

9.4.11.9. Cycles 3 Through 6 – Week 1 – Day 1

Week 1 is a dosing week in both Regimens 1 and 2: consecutive QD oral doses of study treatment will be administered (or self-administered) on Days 1 to 7.

Before administration of study treatment (note: hematology, serum chemistry, coagulation, and urinalysis tests may be performed on the day before the visits and the pregnancy tests may be performed within 24 hours before administration of study treatment Cycles 3 through 6 if more convenient):

- Perform symptom-directed PE (Section 9.4.1).
- Record subject's weight.
- Record vital signs (Section 9.4.2).
- Evaluate ECOG performance status (Appendix 1).
- Perform predose 12-lead ECG in triplicate (Section 9.4.4).
- Record AEs and concomitant medications.
- Collect blood samples for hematology, coagulation, and serum chemistry laboratory tests; collect urine sample for urinalysis (Table 10).
- Perform serum or urine pregnancy test for women of child-bearing potential only.
- Collect predose blood sample for ctDNA (Section 9.2.2, Table 8).

Before administration of study treatment for subjects in Phase 2:

- Collect predose blood sample for PK analysis for Cycle 3 only (Section 9.2.1, Table 6 and Table 7).

Subject ingests study treatment while at the clinic.

After administration of study treatment:

- Record AEs and concomitant medications.
- Review dosing diary to assess dosing compliance.
- Dispense study treatment (ASTX029), provide instruction for self-administration as needed, and instruct subject to, on dosing days when there is a scheduled visit, refrain from ingesting the study drug until after being are on-site at the study clinic and the predose study procedures have been performed.
- Provide a dosing diary to the subject and instructions for how to enter dosing information.

After administration of study treatment for subjects in Phase 2:

- Collect postdose blood samples for PK analysis for Cycle 3 only (Section 9.2.1, Table 6 and Table 7).

9.4.11.10. Cycles 3 Through 6 – Week 2 – Day 8

Week 2 is a dosing week in both Regimens 1 and 2: consecutive QD oral doses of study treatment will be administered (or self-administered) on Days 8 to 14.

9.4.11.11. Cycle 3 Through 6 – Week 3 – Day 15

Week 3 is a dosing week in Regimen 1 (only): consecutive QD oral doses of study treatment will be administered (or self-administered) on Days 15 to 21.

9.4.11.12. End of Cycle 4 and at End of Every 4 Cycles (±1 Cycle) After Cycle 4 (Before Day 1 of Cycle 5 and Before Day 1 of Every 4 Cycles [±1 Cycle] After Cycle 5)

- Assess subject's disease by CT or MRI scan (or other appropriate disease evaluation method, including tumor marker measurement, as applicable).

9.4.12. Cycle 7 and Subsequent Cycles

After Cycle 6, the specific visit schedule and assessments are at the investigator's discretion; at a minimum, information should be collected regarding concomitant medications, AEs, dosing compliance, and, at least once a month, pregnancy tests. Continue to collect efficacy and response assessments, in the manner described in the protocol, until disease progression (for response assessment) or death (for survival assessment), or the subject withdraws consent.

9.4.13. Treatment Termination Visit

This visit should occur within 7 days after the last study treatment or within 3 days before starting new cancer treatment and before the 30-day Safety Follow-up visit. (Note: hematology, serum chemistry, coagulation, urinalysis, and pregnancy tests may be performed on the day before the visit if more convenient.) If a subject discontinues study treatment at a scheduled visit, the assessments at that visit can be used to fulfill the Tx Term visit requirements.

The visit should occur when a subject permanently discontinues study treatment, regardless of whether or not the subject plans to continue participating in the study, for long term follow up of health status (unless consent to continue study participation is withdrawn by the subject).

- Perform symptom-directed PE (Section 9.4.1).
- Record vital signs (Section 9.4.2).
- Evaluate ECOG performance status (Appendix 1).
- Perform 12-lead ECG in triplicate (Section 9.4.4).
- Perform ECHO or MUGA scan.
- Record AEs and concomitant medications.
- Collect blood samples for hematology, coagulation, and serum chemistry laboratory tests; collect urine sample for urinalysis (Table 10).
- Perform serum or urine pregnancy test for women of child-bearing potential only.
- Collect blood sample for ctDNA (Section 9.2.2, Table 8).
- Review dosing diary to assess dosing compliance.
- If the last disease assessment was >12 weeks prior to study treatment withdrawal and disease progression had not been documented, assess subject's disease by CT or MRI

scan (or other appropriate disease evaluation method, including tumor marker measurement, as applicable).

9.4.14. 30-day Safety Follow-up Visit

This visit must occur 30 (±5) days after the last dose of study treatment or within 3 days before starting a new cancer treatment.

- Perform symptom-directed PE (Section 9.4.1).
- Record vital signs (Section 9.4.2).
- Evaluate ECOG performance status (Appendix 1).
- Record AEs and concomitant medications.

9.4.15. Long-Term Follow-up of Health Status

For subjects who remain on study, beginning 3 months after the discontinuation of study treatment, the subject's health status will be collected by telephone every 3 months until death, or the subject withdraws consent, or until the end of the study, whichever occurs first. The following health information will be collected and recorded in the source documents and eCRF:

- Survival information.
- Date of disease progression if subject did not have disease progression at the time they discontinued study treatment.

9.5. Missed Evaluations

Evaluations should occur within the visit window specified by the protocol. If an evaluation is missed, reschedule and perform it as close as possible to the original date. If rescheduling becomes, in the investigator's opinion, medically unnecessary because the evaluation would occur too close to the next scheduled evaluation, it may be omitted.

10. EVALUATION, RECORDING, AND REPORTING OF ADVERSE EVENTS

10.1. Definitions

10.1.1. Adverse Event (AE)

An AE is any untoward medical occurrence associated with the use of a drug in humans, whether or not considered drug related. An AE can therefore be any unfavorable and unintended sign (including a clinically significant abnormal finding in laboratory tests or other diagnostic procedures), symptom, or disease temporally associated with the use of a drug, without any judgment about causality. An AE can arise from any use of the drug and from any route of administration, formulation, or dose, including an overdose.

Disease progression is not considered to be an AE or SAE. If there are specific AEs that are always part of disease progression, these do not need to be reported as AEs or SAEs. Pre-existing medical conditions (other than natural progression of the disease being studied) judged by the investigator or subject to have worsened in severity or frequency or changed in character during the protocol-specified AE reporting period will be reported as AEs or SAEs as appropriate.

An AE or SAE can also be a complication that occurs as a result of protocol mandated procedures (eg, invasive procedures such as biopsies).

10.1.2. Serious Adverse Events (SAEs)

An AE is considered serious, if in the view of either the investigator or sponsor, it results in any of the following outcomes:

- Death.
- A life-threatening AE.

An AE is considered "life-threatening" if in the view of either the investigator, or sponsor, its occurrence places the subject at immediate risk of death. It does not include an AE that, had it occurred in a more severe form, might have caused death.

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

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

10.2. Adverse Event Reporting and Descriptions

Record new AEs from the start of study treatment until 30 days after the last dose of study treatment or until the subject starts new anticancer treatment, including new investigational treatment, whichever occurs first. Also record screening procedure-related AEs that occur before the start of study treatment. Collection of AEs may also continue until the decision is made to permanently discontinue study treatment.

Record all AEs either observed by the investigator or one of the medical collaborators, or reported by the subject spontaneously, or in response to the direct question below, in the AEs section of the subject's eCRF, in the source document, and if applicable, record on the SAE Report form. Whenever possible, the investigator should group signs and symptoms (including laboratory tests or other results of diagnostic procedures) into a single diagnosis under a single term. For example, cough, rhinitis, and sneezing might be reported as "upper respiratory infection" or a pulmonary infiltrate, positive sputum culture and fever might be reported as "pneumonia."

To optimize consistency of AE reporting across centers, ask the subject a standard, general, non-leading question to elicit any AEs (such as "Have you had any new symptoms, injuries, illnesses since your last visit?").

Death is an outcome of an SAE and usually not itself an SAE, unless it is death with no identifiable cause or event. In all other cases, record the cause of death as the SAE. Investigators will assess the status of previously reported, and occurrence of new AEs and SAEs at all subject evaluation time points during the study.

10.2.1. Severity

Use the definitions found in the CTCAE v4.03 for grading the severity (intensity) of AEs. The CTCAE v4.03 displays Grades 1 through 5 with unique clinical descriptions of severity for each referenced AE and provides guidance not listed. Should a subject experience any AE not listed in the CTCAE v4.03, use the following grading system to assess severity:

- Grade 1 – Mild; asymptomatic or mild symptoms; clinical or diagnostic observations only; intervention not indicated.
- Grade 2 – Moderate; minimal, local or noninvasive intervention indicated; limiting age-appropriate instrumental activities of daily living (ADL), such as preparing meals, shopping for groceries or clothes, using the telephone, managing money, etc.
- Grade 3 – Severe or medically significant but not immediately life-threatening; hospitalization or prolongation of hospitalization indicated; disabling; limiting self-care ADL, such as bathing, dressing and undressing, feeding self, using the toilet, taking medications, and not bedridden.
- Grade 4 – Life-threatening consequences; urgent intervention indicated.
- Grade 5 – Death related to AE.

10.2.2. Relationship to Study Treatment (Suspected Adverse Reactions)

Assess all AEs/SAEs for relationship to study treatment or if applicable, to study procedure.

If an AE/SAE occurs before the first dose of study treatment, report it only if it is considered related to a study-specific procedure (eg, bleeding or local infection after skin punch biopsy). Those events will be recorded in the study database but will not be part of the treatment-emergent AE analysis.

To ensure consistency of AE and SAE causality assessments, investigators should apply the general guideline shown below.

Related (Suspected Adverse Reaction)	A suspected adverse reaction means any AE for which there is a reasonable possibility that the drug caused the AE. Reasonable possibility means there is evidence to suggest a causal relationship between the drug and the AE such as a plausible temporal relationship between the onset of the AE and administration of the drug; and/or the AE follows a known pattern of response to the drug; and/or the AE abates or resolves upon discontinuation of the drug or dose reduction and, if applicable, reappears upon rechallenge. Further examples of type of evidence that would suggest a causal relationship between the drug and the AE: • A single occurrence of an event that is uncommon and known to be strongly associated with drug exposure (eg, angioedema, hepatic injury, Stevens-Johnson Syndrome), • One or more occurrences of an event that is not commonly associated with drug exposure, but is otherwise uncommon in the population exposed to the drug (eg, acute myocardial infarction in a young woman), • An aggregate analysis of specific events observed in a clinical study (such as known consequences of the underlying disease or condition under investigation or other events that commonly occur in the study population independent of drug therapy) that indicates those events occur more frequently in the drug treatment group than in a concurrent or historical control group.
Not Related (Not Suspected)	Adverse events that do not meet the definition above.

10.2.3. Reporting Requirements for Pregnancy and Abortion

Report any pregnancy that occurs in a subject or male subject's female partner during the time between the first study-specific procedure and 90 days after the last dose of study treatment. Record any occurrence of pregnancy on the Pregnancy Report Form Part I and email it to the Sponsor's Pharmacovigilance group or designee within 24 hours of learning of the event. After the birth of the baby, collect and report additional information on the baby until the baby is 1 year old by completing the Pregnancy Report Form Part II.

Sponsor's Pharmacovigilance Group Contact Information	
PRIMARY CONTACT: email	**DrugSafety@taihooncology.com**

A subject must immediately inform the investigator if the subject or subject's partner becomes pregnant during the time between the first study-specific procedure and 90 days after the last dose of study treatment. Any female subjects receiving ASTX029 who become pregnant must immediately discontinue study treatment. The investigator should counsel the subject, discussing any risks of continuing the pregnancy and any possible effects on the fetus.

Report any abortion and the reason for it, whether therapeutic, elective or spontaneous, to the Sponsor's Pharmacovigilance group or designee within 24 hours of learning of the event, through the SAE reporting process (Section 10.2.4).

10.2.4. Reporting Requirements for Serious Adverse Events (SAEs)

All SAEs regardless of causality will be reported by the investigator to the Sponsor through the 30-day period after the last dose of study treatment. Deaths and SAEs occurring after the 30-day safety follow-up period AND considered related to study treatment or study procedures must also be reported until the end of the study or subject death.

Report all SAEs (initial and follow-up information) on the SAE Report form and email it to the Sponsor's Pharmacovigilance group or designee, within 24 hours of learning of the event or information (see below). The Sponsor may request follow-up and other additional information from the investigator (eg, hospital admission or discharge notes, laboratory results).

Sponsor's Pharmacovigilance Group Contact Information	
PRIMARY CONTACT: email	**DrugSafety@taihooncology.com**

Report all deaths with the primary cause of death as the SAE term, as death is the outcome of the event, not the event itself. If an autopsy was performed, report the primary cause of death on the autopsy report as the SAE term. Forward autopsy and postmortem reports to the Sponsor's Pharmacovigilance group or designee, as outlined above.

If study treatment is discontinued, temporarily suspended, or dose reduced because of an SAE, include this information in the SAE Report form.

Suspected Unexpected Serious Adverse Reactions (SUSARs) are SAEs that qualify for mandatory expedited safety reporting to regulatory authorities where the SAE is suspected to be caused by the study treatment and is considered unexpected (ie, not listed as expected in the Reference Safety Information section of the current IB, clinical study protocol, or approved

labeling for marketed drugs). In this case, the Sponsor's Pharmacovigilance group or designee will report to the relevant regulatory authorities and forward a formal notification describing the SUSAR to investigators, according to regulatory requirements. Each investigator must then notify his or her IRB/IEC of the SUSAR as required by local regulatory authorities and in accordance with IRB/IEC policy.

10.3. Follow-up for Adverse Events

Follow all AEs and SAEs that are encountered during the protocol-specified AE reporting period (1) to resolution, (2) until the investigator assesses the subject as stable and the event is following a clinically expected outcome, or (3) until the subject is lost to follow-up or withdraws consent.

11. STATISTICS

Statistical analyses will be performed by the Sponsor or its designee.

Data summaries and listings will be generated using SAS version 9.4 or a more recent version (SAS Institute Inc., Cary, NC, USA).

The statistical analysis plan and/or the clinical study report will provide additional details of the analysis, which may include details of missing and, if applicable, unused data, as well as additional sensitivity analyses of the primary and secondary variables. The clinical study report will describe deviations from the statistical analysis plan, if any.

11.1. Sample Size

The dose-escalation part of the study (Phase 1 Part A) follows a standard 3+3 study design, with a cohort size of 3 or 6 evaluable subjects. Dose escalation will continue until the MTD for each regimen evaluated is determined. Evaluable subjects for dose-escalation decisions in Part A are those who have completed the first cycle and have received at least 85% of planned doses in the first cycle of treatment (or were not able to receive at least 85% of planned doses due to safety concerns).

For Part B (of Phase 1), a sample size of 14 evaluable subjects will ensure a 90% probability of observing at least 1 adverse reaction to treatment for any adverse reaction with a ≥15% incidence. Evaluable subjects for Part B are all subjects who receive any amount of study drug.

For Phase 2, the sample size is based on a Simon's Optimal 2-stage design (Simon 1989). Each cohort will enroll 10 subjects into the first stage. Should ≥2 first-stage subjects respond, an additional 19 subjects will be enrolled into the second stage. Therefore, up to 29 subjects will be used for each treatment cohort. The sample size, (10+19) 29, under this Simon's Optimal 2-stage design, will achieve a power of 80% to test the null hypothesis of ORR $p_0 \leq 0.1$ at a 1-sided alpha of 0.05 assuming the response rate p_1 is 0.3. For Stage 2, the null hypothesis will be rejected if ≥6 responses are observed in a cohort of 29 subjects. For Cohort F (which will enroll patients with various tumor types and gene aberrations [Table 2]), the sponsor, with approval of the DSRC, may expand enrollment for a particular molecularly defined subpopulation in which the most number of responses are observed to 10 or 29 subjects under the same Simon's Optimal 2-stage design as for the other cohorts for better assessment of activity in that disease subpopulation (Optional Cohort F expansion). It is expected that no more than 2 subpopulations will be expanded in this manner.

11.2. Analysis Sets to Be Analyzed

11.2.1. All Subject Analysis Set

The All Subject Analysis Set will include information from all screened subjects, including those who did not meet the study entry criteria or did not receive a study treatment. This data set will only be used for disposition in which all screened subjects are accounted for.

11.2.2. Efficacy Analysis Set

The Efficacy Analysis Set will include all subjects who receive any amount of study treatment for efficacy analyses. Efficacy analyses will be based on the actual treatment received. The ORR and DCR analysis will be based on subjects who are in the Efficacy Analysis Set and who had disease assessment at baseline and at least 1 follow up disease assessment or subjects who died or stopped treatment before the first scheduled disease assessment due to clinical progression or toxicity.

11.2.3. Safety Analysis Set

The Safety Analysis Set will include data from all subjects who receive any amount of study drug. Safety analysis will be based on the actual treatment received. All data will be included, and no subjects excluded because of protocol violations.

11.2.4. PK Analysis Set

The PK Analysis Set will consist of all available plasma concentrations and PK parameters for ASTX029 from subjects who have received study drug and for whom PK samples were collected and successfully analyzed.

11.2.5. Pharmacodynamic and Biomarker Analysis Set

Subjects will be included in the pharmacodynamic and biomarker analyses if they have received study drug and their samples were successfully collected and analyzed.

11.3. Schedule of Analyses

This is an open-label study. Ongoing analyses to help manage the study and support the DSRC reviews for safety and antitumor activity will be undertaken. A final analysis will be conducted after all subjects have completed the study.

11.4. Disposition

The number and percentage (n, %) of subjects enrolled, treated, lost to follow-up, and withdrawn from treatment or discontinued from the study (with reason) will be summarized. The sample sizes for the Efficacy Analysis Set, Safety Analysis Set, PK Analysis Set, and Pharmacodynamic and Biomarker Analysis Set will be clearly identified. All subjects in the All Subject Analysis Set will be included in the disposition analysis.

Summaries will be provided separately for each regimen in Phase 1 Part A, for the RDE cohort(s) in Phase 1 Part B, and for the RP2D in Phase 2.

11.5. Analysis of Demographic and Baseline Data

Subject demographic and baseline characteristics will be summarized by mean, standard deviation, median, minimum, and maximum for continuous variables; and by counts and percentages for categorical variables. All subjects who received any amount of study drug (ie, the Safety Analysis Set) will be included in the analysis of demographic and baseline characteristics.

Summaries will be provided separately for each regimen in Phase 1 Part A, for the RDE cohort(s) in Phase 1 Part B, and for each cohort in Phase 2.

11.6. Efficacy Analyses

Analyses for all efficacy endpoints will be provided separately for each treatment regimen in Phase 1 Part A and for the RDE cohort(s) in Phase 1 Part B, and for each cohort in Phase 2.

11.6.1. Objective Response and Disease Control Rate

The ORR will be calculated as the number of evaluable subjects whose best response is CR or PR, divided by the total number of subjects evaluable for ORR analysis (Section 11.2.2). The DCR will be calculated as the number of subjects whose best response is CR, PR, or stable disease (SD), divided by the total number of subjects evaluable for DCR analysis (Section 11.2.2). The 90% Clopper-Pearson confidence intervals (Cis) for the ORR and DCR will be provided.

11.6.2. Progression-free Survival

The PFS is defined as the number of days from the start of the study treatment to disease progression or death, whichever occurs first. The PFS will be analyzed using a Kaplan-Meier method, with PFS time being censored on the date of the last disease assessment. The 90% CI for median PFS will be provided using the Kaplan-Meier procedure. All subjects in the Efficacy Analysis Set will be included in the PFS analysis.

11.6.3. Overall Survival

The OS is defined as the number of days from the day the subject was randomized to the date of death (regardless of cause). Subjects without a documented death date will be censored on the last date they were known to be alive. The OS will be presented using a Kaplan-Meier estimate. The 90% CI for median OS will be provided using the Kaplan-Meier procedure. All subjects in the Efficacy Analysis Set will be included in the OS analysis.

11.6.4. Duration of Response

Duration of response will be calculated for all responders from the date of the earliest assessment of CR or PR to the date of relapse or death, whichever occurs earlier, or the last disease assessment date for subjects without a relapse or death. Duration of SD will be calculated for subjects whose best response is CR, PR, or SD from the day study drug was first taken to the date of disease progression or death, whichever occurs earlier, or the last disease assessment for subjects without disease progression or death.

Duration of response and duration of SD will be summarized with descriptive statistics including arithmetic mean, standard deviation, median, and range will be summarized for subjects who have overall responses.

11.7. Safety Analyses

Safety will be assessed by subject-reported and investigator-observed Aes along with concomitant medications, Pes, clinical laboratory tests (hematology, coagulation, serum

chemistry, and urinalysis), vital signs, ECOG performance status, ECGs, and ECHO/MUGA scans.

All Aes will be mapped to the appropriate System Organ Class (SOC) and Preferred Term (PT) according to the Medical Dictionary for Regulatory Activities (MedDRA). Severity of Aes will be graded using CTCAE v4.03 (Appendix 2). All Aes collected during the study will be presented in data listings. TEAEs are defined as events that first occur or worsen after the subject receives study drug on C1D1 until 30 days after the last dose of study treatment, or the start of an alternative anticancer treatment, whichever occurs first, to be defined in more detail in the statistical analysis plan. Summaries will be provided by SOC and PT for all Aes, Aes considered related to study treatment, SAEs, and related SAEs as follows based on the treatment period when the events occur. Similar summaries will also be generated by maximum severity. In addition, exposure to ASTX029, reasons for discontinuation, deaths, and causes of deaths will be tabulated.

The number and proportion of subjects who have DLTs, as defined in Section 7.4, will be summarized by cohort and regimen in Phase 1 Part A.

Laboratory values reported by different local labs will be listed. Shift tables will be provided for each graded laboratory test.

Concomitant medications are the medications taken with a start date on or after the start of the administration of study treatment (C1D1) or those with a start date before the start of the administration of study treatment (C1D1) and a stop date on or after the start of study drug administration (C1D1) as to be defined in more detail in the statistical analysis plan. Concomitant medication will be coded by the World Health Organization (WHO) Global List and summarized by therapeutic subgroup (Anatomical Therapeutic Chemical [ATC] level 2) and PT, sorted alphabetically, using counts and percentages.

Vital sign measurements will be summarized by visit using the proportion of subjects with each vital sign being too high or too low according to conventionally accepted vital sign normal ranges. Physical examination, ECOG performance status, and ECG findings will be listed in data listings or analyzed with summary tables.

11.8. Pharmacokinetic Analyses

The PK Analysis Set (Section 11.2.4) will be used for PK analyses.

The PK parameters will be derived for each subject using a noncompartmental approach. Descriptive statistics including mean, standard deviation, median, and range for PK parameters for ASTX029 will be summarized separately for each regimen and by dose within each regimen. Detailed and additional PK analyses are described in a separate PK analysis plan.

11.9. Pharmacodynamic/Biomarker Analyses

The Pharmacodynamic and Biomarker Analyses Set (Section 11.2.5) will be used for pharmacodynamic and biomarker analyses.

Values at baseline and changes from baseline (if appropriate) of the pharmacodynamic parameters and biomarkers assessed in the study will be summarized descriptively using mean, standard deviation, median, minimum, and maximum for continuous variables and counts and

percentages for categorical variables. Summaries will be provided separately for each regimen in Phase 1 Part A, for the RDE cohort(s) in Phase 1 Part B, and for each cohort in Phase 2.

11.10. Interim Analysis

No interim analysis is planned for this open-label study. The data will be reviewed in an ongoing manner in conjunction with dose-escalation decisions and general safety monitoring.

11.11. Procedures for Handling Missing, Unused, and Spurious Data

No imputation of values for missing data will be performed unless specified otherwise in the statistical analysis plan. Data from subjects lost to follow-up will be included in statistical analyses to the day of last contact.

12. STUDY DURATION AND TERMINATION

The expected study duration is approximately 5 years (61 months), including approximately 55 months for recruitment and approximately 6 months for safety follow-up.

The Sponsor may stop the study at any time. In case of this event, the Sponsor will make reasonable efforts to ensure subjects are transitioned off study in an orderly manner. Reasons for early termination include, but are not limited to, lack of preliminary clinical activity or safety concerns.

13. STUDY COMPLIANCE AND ETHICAL CONSIDERATIONS

13.1. Compliance Statement

The study will be conducted in accordance with the ICH GCP guidelines, principles enunciated in the Declaration of Helsinki, and all human clinical research regulations in countries where the study is conducted.

13.2. Informed Consent

The ICFs used for the study must comply with the Declaration of Helsinki, federal regulations US 21 Code of Federal Regulations (CFR) Part 50, and ICH GCP guidelines and any other local regulations. The investigator, or a person delegated by the investigator, must explain the medical aspects of the study, including the nature of the study and the treatment, orally and in writing, in such a manner that the subject is aware of potential benefits and risks. Subjects must be informed that participation is voluntary and that they may withdraw from the study at any time, without prejudice. Subjects, or a legal guardian if the subject is unable to, must give informed consent in writing.

The informed consent process must be conducted, documented in the source document (including the date), and the form must be signed, before the subject undergoes any study-specific procedures.

13.3. Institutional Review Board or Independent Ethics Committee (IRB/IEC)

The investigator must submit the protocol, protocol amendments, and the ICF for the proposed study, along with any other documents required by the center's IRB/IEC to the center's duly constituted IRB/IEC for review and approval. The investigator must also ensure that the IRB/IEC reviews the progress of the study on a regular basis and, if necessary, renews its approval of the study on an annual basis. A copy of each IRB/IEC approval letter must be forwarded to the sponsor before the study is implemented. Documentation of subsequent reviews of the study must also be forwarded to the sponsor.

14. ADMINISTRATIVE PROCEDURES

14.1. Sponsor Responsibilities

The Sponsor reserves the right to terminate the study and remove all study materials from a study center at any time. The Sponsor and the investigators will assure that adequate consideration is given to the protection of the subjects' interests. Specific circumstances that may precipitate such termination are:

- Request by Health Authority to terminate the study.
- Unsatisfactory subject enrollment with regard to quality or quantity.
- Significant or numerous deviations from study protocol requirements, such as failures to perform required evaluations on subjects, maintain adequate study records or inaccurate, incomplete or late data recording on a recurrent basis.
- The incidence or severity of AEs in this or other studies indicating a potential health hazard caused by the study treatment.

14.1.1. Study Supplies

The sponsor will supply sufficient quantities of the following materials to each clinical center:

- ASTX029 as described in Section 7.
- VFR as described in Section 7.
- IB for ASTX029.
- Case report forms or data collection tools.

14.1.2. Investigator Training

All study centers will have a center-specific study initiation meeting to ensure the center staff understand the protocol, study requirements, and data capture processes. This training will take place before the first subject is enrolled. Each study center will be provided with information regarding GCP and regulations specific to the conduct of clinical studies. Each center is responsible for ensuring that new team members are adequately trained and the training is documented.

14.1.3. Ongoing Communication of Safety Information During the Study

The sponsor will provide the investigator with documentation of SAEs, from this study and other studies, that are related to ASTX029 and unexpected (see Section 10.2.4), as appropriate. The investigator must forward this documentation to the IRB/IEC, as described in Section 10.2.4.

The sponsor will also notify the investigator about any other significant safety findings that could alter the safety profile of the IMP from what is described in the protocol and significantly affect the safety of subjects, affect the conduct of the study, or alter the IRB/IEC's opinion about continuation of the study. This does not include safety issues that could be mitigated by simple changes in the protocol decided by the DSRC (Section 4.4) such as limiting some of the eligibility criteria or reducing the IMP dose or dosing schedule.

14.1.4. Study Monitoring

Representatives of the Sponsor will monitor the study. Routine monitoring visits will be conducted to:

- Assure compliance with the study protocol and appropriate regulations.
- Verify that (1) the informed consent process was conducted before initiation of any study-specific procedures (ie, performed solely for the purpose of determining eligibility for the study) and before provision of study treatment, and (2) this process is adequately documented.
- Verify that the protocol, protocol amendments, and safety information are submitted to the IRB/IECs and approved by the IRB/IECs in a timely manner.
- Review the eCRFs and source documents to ensure that reported study data are accurate, complete, and verifiable from source documents.
- Verify that study treatments are stored properly and under the proper conditions, that they are in sufficient supply, and that receipt, use, and return of ASTX029 at the study centers are controlled and documented adequately.
- Verify that the investigator and study center personnel remain adequately qualified throughout the study.
- Verify that the research facilities, including laboratories and equipment, are maintained adequately to safely and properly conduct the study.

14.1.5. Study Auditing and Inspecting

The sponsor may audit the study conduct, compliance with the protocol and accuracy of the data in 1 or more centers.

The investigator(s)/institution(s) will permit study-related monitoring, audits, and inspections by the Sponsor, IRB/IEC, government regulatory bodies and Taiho Quality Assurance personnel or its designees by providing direct access to source data/documents after appropriate notification from sponsor.

14.2. Investigator Responsibilities

14.2.1. Subject Screening Log

The investigator must keep a record that lists all subjects who signed an informed consent and the reason for non-inclusion if they were not ultimately enrolled, randomized, or treated.

14.2.2. ASTX029 and VFR Accountability

Initial supplies of ASTX029 and VFR-will be shipped to each study center’s pharmacy when all the initiation documents, including IRB/IEC approvals, IRB/IEC approved ICF, and business agreements, have been received and reviewed by the Sponsor and upon activation of the study center by the Sponsor. Resupply of ASTX029 and VFR will be managed by the IRT system. The study center will be responsible for ensuring the inventory in the IRT system is accurate to

ensure resupply occurs as needed. Until ASTX029 PiB was phased out, initial supplies of VFR were shipped to each study center's pharmacy when conditions as described above were met.

Keep ASTX029 and VFR in a locked, limited-access room. The study treatment must not be used outside the context of the protocol. Under no circumstances should the investigator or other study center personnel supply ASTX029 or VFR to other investigators, subjects, or clinics or allow supplies to be used other than as directed by this protocol without prior authorization from the Sponsor.

The monitor will regularly review and verify all ASTX029 and VFR supplies and associated documentation.

Maintain an accurate accounting of the study treatments. These records must show dates, lot numbers, quantities received, dispensed, and returned and must be available for monitoring by the sponsor. The investigator will ensure that any used and unused ASTX029, VFR, and other study material is destroyed or returned to the sponsor on completion of the study. If the ASTX029 or VFR is destroyed at the study center, there should be documentation of destruction at the study center. The sponsor and/or their representatives will verify final drug accountability. ASTX029 and VFR accountability records must be maintained and readily available for inspection by representatives of the Sponsor and are open to inspections by regulatory authorities at any time.

14.2.3. Reporting and Recording of Study Data

Data will be captured and compiled using procedures developed by the sponsor or their representatives. Clearly record all requested study data on the eCRF and other study forms as required. Whenever possible, record the reason for missing data in the source document. Only individuals who are identified on the study personnel responsibility/signature log may enter or correct data in the eCRF. Incomplete or inconsistent data on the eCRFs will result in data queries that require resolution by the investigator or designee.

The investigator must assure subject anonymity and protection of identities from unauthorized parties. On eCRFs or other documents or subject records provided to the Sponsor, identify subjects by code (subject number, initials, date of birth) and not by names. The principal investigator should maintain documents not for submission to the Sponsor (eg, subject's signed informed consent), in strict confidence.

14.2.4. Source Documentation

The investigator must maintain adequate and accurate source documents upon which eCRFs for each subject are based. They are to be separate and distinct from eCRFs, except for cases in which the sponsor has predetermined that direct data entry into specified pages of the subject's eCRF is appropriate. These records should include detailed notes on:

- The oral and written communication with the subject regarding the study treatment (including the risks and benefits of the study). Record the date of informed consent in the source documentation.
- The subject's medical history before participation in the study.

- The subject's basic identifying information, such as demographics, that links the subject's source documents with the eCRFs.
- The results of all diagnostic tests performed, diagnoses made, therapy provided, and any other data on the condition of the subject.
- The subject's exposure to study treatment.
- All AEs.
- The subject's exposure to any concomitant therapy (including start and stop dates, route of administration, and dosage).
- All relevant observations and data on the condition of the subject throughout the study.

14.2.5. Tissue and Blood Sample Collection/Storage

Tissue and blood components samples which are collected as part of routine medical care or as part of protocol procedures may be stored and analyzed for PK or pharmacodynamic and other biomarker analyses.

After the study, samples may be used for additional investigation to help identify factors that may influence response to therapy. Such samples will be used in compliance with guidelines defined by FDA Guidance on Informed Consent for In Vitro Diagnostic Device Studies Using Leftover Human Specimens that are Not Individually Identifiable (issued 25 April 2006) and European Agency for the Evaluation of Medicinal Products (EMEA)'s Reflection Paper on Pharmacogenomic Samples, Testing and Data Handling (EMEA 2007).

If a subject withdraws consent, they may request destruction of any samples taken and not tested yet, and the investigator must document this in the site study records and inform the sponsor within 24 hours.

14.2.6. Records Retention

The investigator must ensure that clinical study records are retained according to national regulations, as documented in the clinical trial agreement entered into with the sponsor in connection with this study. The investigator will maintain all records and documents pertaining to the study including, but not limited to, those outlined above (see Section 14.2.4) for a period of: at least 2 years after FDA approval of the drug or at least 2 years after withdrawal of the IND under which this study was conducted, whichever is longer. In countries outside the US, records must be kept for the period of time required by the US FDA as a minimum, and record retention should also comply with the local country regulatory requirements, if longer retention times are required than in the US. Mandatory documentation includes copies of study protocols and amendments, financial disclosures, each FDA Form 1572, IRB/IEC approval letters, signed ICFs, drug accountability records, SAE Report forms transmitted to the Sponsor, subject files (source documentation) that substantiate entries in eCRFs, all relevant correspondence, and other documents pertaining to the conduct of the study. These records must remain in each subject's study file and be available for verification by study monitors at any time.

The investigator must inform the sponsor immediately if any documents are to be destroyed, transferred to a different facility, or transferred to a different owner. The sponsor should be given the option of collecting the documents before destruction.

14.3. Clinical Trial Insurance

Clinical trial insurance has been undertaken according to the laws of the countries where the study will be conducted. An insurance certificate will be made available to the participating study centers upon request.

14.4. Study Administrative Letters and Protocol Amendments

The Sponsor may issue Study Administrative Letters (1) to clarify certain statements or correct obvious errors/typos/inconsistencies in the study protocol, (2) to change the logistical or administrative aspects of the study, such as study personnel or contact information, or (3) to instruct investigators of DSRC safety decisions for immediate implementation for safety reasons (Section 4.4).

For all other changes, the Sponsor will initiate any change to the protocol in a protocol amendment document. The study center will submit the amendment to the IRB/IEC together with, if applicable, a revised model ICF. If the change in any way increases the risk to the subject, information on the increased risk must be provided to subjects already actively participating in the study, and they must read, understand, and sign any revised ICF confirming willingness to remain in the study.

The investigator must obtain IRB/IEC approval before any protocol amendment can be implemented, except for administrative changes or changes necessary to eliminate an immediate risk to study subjects, as outlined above.

15. POLICY FOR PUBLICATION AND PRESENTATION OF DATA

The sponsor encourages the scientific publication of data from clinical research studies. However, investigators may not present or publish partial or complete study results individually without review by the sponsor. The principal investigators and the sponsor may propose appropriate scientific manuscripts or abstracts from the study data. The sponsor must review and comment on all proposed publications before submission for publication. The detailed procedures for the review of publications are set out in the clinical trial agreement entered into with the sponsor in connection with this study. These procedures are in place to ensure coordination of study data publication and adequate review of data for publication against the validated study database for accuracy. Names of all investigators and sponsor representatives responsible for designing the study and analyzing the results will be included in the publication(s).

Qualification of authorship will follow the requirements of the International Committee of Medical Journal Editors (www.icmje.org). In most cases, the principal investigators at the centers with the highest participation in the study shall be listed as lead authors on manuscripts and reports of study results. In addition, other than clinical pharmacology studies in healthy volunteers or Phase 1 studies, all clinical studies must be registered with ClinicalTrials.gov.

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17. APPENDICES

APPENDIX 1. ECOG PERFORMANCE STATUS

Score	ECOG Description
0	Fully active, able to carry on all predisease performance without restriction
1	Restricted in physically strenuous activity, but ambulatory and able to carry out work of a light or sedentary nature (eg, light house work, office work)
2	Ambulatory and capable of all self-care but unable to carry out any work activities. Up and about more than 50% of waking hours
3	Capable of only limited self-care, confined to bed or chair more than 50% of waking hours
4	Completely disabled. Cannot carry on any self-care. Totally confined to bed or chair
5	Dead

Source: ECOG Performance Status https://ecog-acrin.org/resources/ecog-performance-status/

APPENDIX 2. NATIONAL CANCER INSTITUTE COMMON TERMINOLOGY CRITERIA FOR ADVERSE EVENTS

Adverse events and/or adverse drug reactions will be graded according to the Common Terminology Criteria for Adverse Events (CTCAE) v4.03.

View the National Cancer Institute (NCI) CTCAE electronically at the following website:

https://evs.nci.nih.gov/ftp1/CTCAE/CTCAE_4.03_2010-06-14_QuickReference_8.5x11.pdf .

APPENDIX 3. RESPONSE EVALUATION CRITERIA IN SOLID TUMORS, VERSION 1.1

The information is this appendix is based on RECIST v1.1 (Eisenhauer et al 2009).

Measurability of Tumor at Baseline

Definitions

At baseline, tumor lesions/lymph nodes will be categorized as measurable or nonmeasurable, as described below:

Measurable

- Tumor lesions: Must be accurately measured in at least 1 dimension (longest diameter in the plane of measurement is to be recorded) with a minimum size of:
  - 10 mm by CT scan (CT scan slice thickness no greater than 5 mm).
  - 10 mm caliper measurement by clinical exam (lesions which cannot be accurately measured with calipers should be recorded as nonmeasurable).
  - 20 mm by chest X-ray.
- Measurable 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 (CT scan slice thickness recommended to be no greater than 5 mm). At baseline (ie, screening for this study) and in follow-up (ie, all measurements past screening for this study), only the short axis will be measured and followed. See also notes below on 'Baseline documentation of target and nontarget lesions' for information on lymph node measurement.

Nonmeasurable

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 nonmeasurable lesions. Lesions considered truly nonmeasurable include: leptomeningeal disease, ascites, pleural or pericardial effusion, inflammatory breast disease, lymphangitic involvement of skin or lung, abdominal masses/abdominal organomegaly identified by physical exam that is not measurable by reproducible imaging techniques.

Special Considerations Regarding Lesion Measurability

Bone lesions, cystic lesions, and lesions previously treated with local therapy require particular comment.

Bone Lesions

- Bone scan, PET scan, or plain films are not considered adequate imaging techniques to measure bone lesions. However, these techniques can be used to confirm the presence or disappearance of bone lesions.
- Lytic bone lesions or mixed lytic-blastic lesions, with identifiable soft tissue components, that can be evaluated by cross-sectional imaging techniques such as CT

or MRI can be considered as measurable lesions if the soft tissue component meets the definition of measurability described above.

- Blastic bone lesions are nonmeasurable.

Cystic Lesions

- Lesions that meet the criteria for radiographically defined simple cysts should not be considered as malignant lesions (neither measurable nor nonmeasurable) since they are, by definition, simple cysts.
- 'Cystic lesions' thought to represent cystic metastases can be considered as measurable lesions, if they meet the definition of measurability described above. However, if noncystic lesions are present in the same subject, these are preferred for selection as target lesions.

Lesions With Prior Local Treatment

Tumor lesions situated in a previously irradiated area, or in an area subjected to other loco-regional therapy, are not considered measurable unless there has been demonstrated progression in the lesion.

Specifications by Methods of Measurements

Measurement of Lesions

All measurements should be recorded in metric notation, using calipers if clinically assessed. All baseline evaluations should be performed as close as possible to the treatment start and NEVER more than 21 days before the beginning of the treatment.

Method of Assessment

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 should always be done rather than clinical examination unless the lesion(s) being followed cannot be imaged but are assessable by clinical exam.

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 5 mm 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. Magnetic resonance imaging (MRI) is also acceptable in certain situations (eg, for body scans).

Tumor Response Evaluation

Assessment of Overall Tumor Burden and Measurable Disease

To assess objective response or future progression, it is necessary to estimate the overall tumor burden at baseline and use this as a comparator for subsequent measurements. In this study, only subjects with measurable disease at baseline should be included in the study.

Baseline Documentation of 'Target' and 'Nontarget' Lesions

When more than 1 measurable lesion is present at baseline, all lesions up to a maximum of 5 lesions total representative of all involved organs should be identified as target lesions and will

be recorded and measured at baseline. In instances where subjects have only 1 or 2 organ sites involved, a maximum of 2 and 4 lesions respectively will be recorded.

The criteria for selection of target lesions are as follows:

Largest in size (ie, lesions with the longest diameter). If the largest lesion does not lend itself to reproducible measurement, the next largest lesion that can be measured reproducibly should be selected.

a. Representative of all involved organs.
b. Can be repeatedly measured using a reproducible method.

Lymph nodes merit special mention since they are normal anatomical structures that may be visible by imaging even if not involved by tumor. As noted above, pathological nodes that are defined as measurable and may be identified as target lesions must meet the criterion of a short axis of ≥15 mm by CT scan. Only the short axis of these nodes will contribute to the baseline sum. The short axis of the node is the diameter normally used by radiologists to judge if a node is involved by solid tumor. Nodal size is normally reported as 2 dimensions in the plane in which the image is obtained (for CT scan this is almost always the axial plane; for MRI the plane of acquisition may be axial, sagittal, or coronal). The smaller of these measures is the short axis. For example, an abdominal node that is reported as being 20 × 30 mm has a short axis of 20 mm and qualifies as a malignant, measurable node. In this example, 20 mm should be recorded as the node measurement. All other pathological nodes (those with short axis ≥10 mm but <15 mm) should be considered nontarget lesions. Nodes that have a short axis <10 mm are considered nonpathological and should not be recorded or followed.

A sum of the diameters (longest for nonnodal 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 regression in the measurable dimension of the disease.

All other lesions (or sites of disease) including pathological lymph nodes should be identified as nontarget lesions and should also be recorded at baseline. Measurements are not required and these lesions should be followed as ‘present,’ ‘absent,’ or in rare cases ‘unequivocal progression.’ In addition, it is possible to record multiple nontarget lesions involving the same organ as a single item on the case record form (eg, ‘multiple enlarged pelvic lymph nodes’ or ‘multiple liver metastases’).

Response Criteria

This section provides the definitions of the criteria used to determine objective tumor response for target lesions.

Evaluation of Target Lesions

Complete response (CR): Disappearance of all target lesions. Any pathological lymph nodes (whether target or nontarget) must have reduction in short axis to <10 mm.

Partial response (PR): At least a 30% decrease in the sum of diameters of target lesions, taking as reference the baseline sum diameters.

Progressive disease (PD): At least a 20% increase in the sum of diameters of target lesions, taking as reference the smallest sum on study (this includes the baseline sum if that is the smallest on study). In addition to the relative increase of 20%, the sum must also demonstrate an absolute increase of at least 5 mm. (Note: the appearance of 1 or more new lesions is also considered progression).

Stable disease (SD): Neither sufficient shrinkage to qualify for PR nor sufficient increase to qualify for PD, taking as reference the smallest sum diameters while on study.

Special Notes on the Assessment of Target Lesions

Lymph nodes: Lymph nodes identified as target lesions should always have the actual short axis measurement recorded (measured in the same anatomical plane as the baseline examination), even if the nodes regress to below 10 mm on study. This means that when lymph nodes are included as target lesions, the 'sum' of lesions may not be zero even if CR criteria are met, since a normal lymph node is defined as having a short axis of <10 mm. For PR, SD, and PD, the actual short axis measurement of the nodes is to be included in the sum of target lesions.

Target lesions that become 'too small to measure': While on study, all lesions (nodal and nonnodal) recorded at baseline should have their actual measurements recorded at each subsequent evaluation, even when very small (eg, 2 mm). However, sometimes lesions or lymph nodes which are recorded as target lesions at baseline become so faint on CT scan that the radiologist may not feel comfortable assigning an exact measure and may report them as being 'too small to measure.' When this occurs, it is important that a value be recorded on the eCRF. If it is the opinion of the radiologist that the lesion has likely disappeared, the measurement should be recorded as 0 mm. If the lesion is believed to be present and is faintly seen but too small to measure, a default value of 5 mm should be assigned (Note: it is less likely that this rule will be used for lymph nodes since they usually have a definable size when normal and are frequently surrounded by fat such as in the retroperitoneum; however, if a lymph node is believed to be present and is faintly seen but too small to measure, a default value of 5 mm should be assigned in this circumstance as well). This default value is derived from the 5-mm thickness of CT scan slices (but should not be changed with varying CT slice thickness). The measurement of these lesions is potentially nonreproducible; therefore providing this default value will prevent false responses or progressions based upon measurement error. To reiterate, however, if the radiologist is able to provide an actual measure, that value should be recorded, even if it is below 5 mm.

Lesions that split or coalesce on treatment: When nonnodal lesions 'fragment,' the longest diameters of the fragmented portions should be added together to calculate the target lesion sum. Similarly, as lesions coalesce, a plane between them may be maintained that would aid in obtaining maximal diameter measurements of each individual lesion. If the lesions have truly coalesced such that they are no longer separable, the vector of the longest diameter in this instance should be the maximal longest diameter for the 'coalesced lesion'.

Evaluation of Nontarget Lesions

This section provides the definitions of the criteria used to determine the tumor response for the group of nontarget lesions. While some nontarget lesions may actually be measurable, they need

not be measured, and instead should be assessed only qualitatively at the time points specified in the protocol.

CR: Disappearance of all nontarget lesions and normalization of tumor marker level. All lymph nodes must be nonpathological in size (<10 mm short axis).

Non-CR/Non-PD: Persistence of 1 or more nontarget lesion(s) and/or maintenance of tumor marker level above the normal limits.

PD: Unequivocal progression (see comments below) of existing nontarget lesions (Note: the appearance of 1 or more new lesions is also considered progression).

Special Notes on Assessment of Progression of Nontarget Disease

The concept of progression of nontarget disease requires additional explanation as follows, when the subject also has measurable disease. In this setting, to achieve 'unequivocal progression' on the basis of the nontarget disease, there must be an overall level of substantial worsening in nontarget 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 1 or more nontarget lesions is usually not sufficient to qualify for unequivocal progression status. The designation of overall progression solely on the basis of change in nontarget disease in the face of SD or PR of target disease will therefore be extremely rare.

New Lesions

The appearance of new malignant lesions denotes disease progression; therefore, some comments on detection of new lesions are important. There are no specific criteria for the identification of new radiographic lesions; however, the finding of a new lesion should be unequivocal: ie, not attributable to differences in scanning technique, change in imaging modality or findings thought to represent something other than tumor (for example, some 'new' bone lesions may be simply healing or flare of preexisting lesions). This is particularly important when the subject's baseline lesions show PR or CR. For example, necrosis of a liver lesion may be reported on a CT scan report as a 'new' cystic lesion, which it is not.

A lesion identified on a follow-up study in an anatomical location that was not scanned at baseline is considered a new lesion and will indicate disease progression. An example of this is the subject who has visceral disease at baseline and while on study has a CT or MRI brain ordered that reveals metastases. The subject's brain metastases are considered to be evidence of PD even if they did not have brain imaging at baseline.

If a new lesion is equivocal, for example because of its small size, continued therapy and follow-up evaluation will clarify if it represents truly new disease. If repeat scans confirm there is definitely a new lesion, then progression should be declared using the date of the initial scan.

<u>Evaluation of Best Overall Response</u>

The best overall response is the best response recorded from the start of the study treatment until the end of treatment. No confirmatory measurement for CR, PR, or SD is required in the study.

The subject's best overall response assignment will depend on the findings of both target and nontarget disease and will also take into consideration the appearance of new lesions.

Time Point Response

Please follow the per-protocol time point response assessments. Table 14 below provides a summary of the overall response status calculation at each time point for subjects who have measurable disease at baseline.

Table 14: Overall Response

Time Point Response: Subjects with Target (±Nontarget) Disease			
Target Lesions	**Nontarget Lesions**	**New Lesions**	**Overall Response**
CR	CR	No	CR
CR	Non-CR/Non-PD	No	PR
CR	Not evaluated	No	PR
PR	Non-PD or not all evaluated	No	PR
SD	Non-PD or not all evaluated	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

CR=complete response, NE=inevaluable, PD=progressive disease, PR=partial response; SD=stable disease.

Missing Assessments and Inevaluable Designation

When no imaging/measurement is done at a particular time point, the subject is not evaluable at that time point. If only a subset of lesion measurements are made at an assessment, usually the case is also considered not evaluable at that time point, unless a convincing argument can be made that the contribution of the individual missing lesion(s) would not change the assigned time point response. This would be most likely to happen in the case of PD. For example, if a subject had a baseline sum of 50 mm with 3 measured lesions and at follow-up only 2 lesions were assessed, but those gave a sum of 80 mm, the subject will have achieved PD status, regardless of the contribution of the missing lesion.

Best Overall Response: All Time Points

The best overall response is determined once all the data for the subject is known.

Best response determination in studies where confirmation of CR or PR is not required: Best response in these studies is defined as the best response across all time points (eg, if a subject has SD at first assessment, PR at second assessment, and PD on last assessment, he or she will have a best overall response of PR). When SD is believed to be best response, it must also meet the protocol-specified minimum time from baseline (6 weeks). If the minimum time is not met when SD is otherwise the best time point response, the subject's best response depends on the subsequent assessments. For example, if a subject has SD at first assessment, but PD at the second assessment, and does not the meet minimum duration for SD, he or she will have a best response of PD. The same subject lost to follow-up after the first SD assessment would be considered inevaluable.

Special Notes on Response Assessment

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 subjects with CR may not have a total sum of 'zero' on the eCRF.

Subjects with a global deterioration of health status requiring discontinuation of treatment without objective evidence of disease progression at that time should be reported as 'symptomatic deterioration.' Every effort should be made to document objective progression even after discontinuation of treatment. Symptomatic deterioration is not a descriptor of an objective response: it is a reason for stopping study therapy. The objective response status of such subjects is to be determined by evaluation of target and nontarget disease.

For equivocal findings of progression (eg, very small and uncertain new lesions; cystic changes or necrosis in existing lesions), treatment may continue until the next scheduled assessment. If at the next scheduled assessment, progression is confirmed, the date of progression should be the earlier date when progression was suspected.

Frequency of Tumor Re-evaluation

In this study, tumor measurement will be conducted at the end of every 2 cycles (±7 days) for the first 4 cycles and then every 4 cycles (±1 cycle) thereafter until clinical and/or radiographic disease progression, or death, or the subject withdraws consent. Scan dates should not be adjusted or rescheduled due to dose interruption of any type.

Baseline tumor assessments must be performed within 3 weeks (21 days) prior to the first dose of treatment.

All efforts should be made to ensure consistency between the baseline measurements and all subsequent measurements in reference to utilization of scanning method, equipment, technique (including slice thickness and field of view), and radiographic interpreter.

The radiographic evaluation must include CT or MRI scanning of the known sites of involvement, as well as the chest, abdomen, and pelvis if they are not the primary target. Any additional suspected sites of disease should also be imaged. All evaluations should meet the standard of care for imaging of lesions in the respective organ(s) and should conform to the image acquisition guidelines according to institutional standards.

All target and nontarget sites are evaluated at each time point of tumor assessment.

APPENDIX 4. MANAGEMENT OF SKIN TOXICITIES

Cutaneous adverse events have been observed in subjects receiving MEK inhibitors (ie, trametinib [Mekinist USPI] and cobimetinib [Cotellic USPI]) and ERK inhibitors (ulixertinib and GDC-0994) (de la Cruz-Merino et al 2017; Sullivan et al 2018; Li et al presentation 2017, Varga et al 2020; Infante et al abstract 2015; Infante et al presentation 2015; Macdonald et al 2015; Reyes-Habito et al 2014; Anforth et al 2013; Mandalà et al 2013; Manousaridis et al 2013).

Suggested guidelines regarding management and criteria for adjusting, withholding, and discontinuing study treatment for skin toxicities considered to be related to study treatment are provided in Table 15. The institutional standards for the management of skin-related AEs can differ from these guidelines. In this case, best clinical judgment should be applied.

Table 15: Suggested Management and Dose Modification Guidelines for Skin Toxicities

CTCAE Grade	Management	Action and Dose Modification
Grade 1	• Initiate symptomatic measures. • Use moderate strength topical steroid.[a] • Consider topical antibiotics or combined topical steroids/antibiotics if acneiform papulopustular rash. • Consider oral antibiotics. • Consider oral antihistamines if maculopapular rash. • Reassess after 1 week.	• Continue study treatment and monitor for change in severity. • If no recovery to ≤Grade 1 within 2 weeks despite best supportive care, reduce study treatment by 1 dose level.[b]
Grade 2	• Initiate symptomatic measures. • Use moderate strength topical steroid.[a] • Obtain bacterial/viral/fungal cultures if infection is suspected. • Initiate topical antibiotics and, if rash is persistently ≥Grade 2 after 1 week, initiate oral antibiotics for 6 weeks (doxycycline 100 mg BID or minocycline 100 mg BID) if acneiform papulopustular rash. Initiation of oral antibiotics at first sign of Grade 2 acneiform papulopustular rash is also appropriate. • Initiate oral antihistamines or oral steroid[c] if maculopapular rash. • Consider dermatology referral for evaluation and biopsy. • Reassess after 1 week.	• Reduce study treatment by 1 dose level. • After reduction, if recovery to ≤Grade 1, increase dose to previous dose level. • After reduction, if no recovery to ≤Grade 1 within 1 week, interrupt study treatment until recovery to ≤Grade 1 and restart with study treatment reduced by 1 dose level.[d]
Grade ≥3	• Initiate symptomatic measures. • Use moderate strength topical steroid[a] plus oral steroids. • Obtain bacterial/viral/fungal cultures if infection is suspected. • Initiate oral antibiotics (doxycycline 100 mg BID or minocycline 100 mg BID or oxytetracycline 500 mg BID) if acneiform (papulopustular) rash. • Initiate oral antihistamines if maculopapular rash. • Consider dermatology referral for evaluation and biopsy. • Reassess after 1 week.	• Interrupt study treatment until recovery to ≤Grade 1.[d] • Restart with study treatment reduced by 1 dose level.[b] • If no recovery to ≤Grade 1 within 3 weeks, permanently discontinue study treatment.

BID=twice a day; CTCAE=Common Terminology Criteria for Adverse Events.
[a] Hydrocortisone 2.5% cream or fluticasone 0.5% cream.
[b] Escalation to previous dose level may be considered if no skin toxicity is evident for 4 weeks after restarting study treatment.
[c] Prednisolone 0.5 mg/kg/day or equivalent (up to 60 mg/kg/day) for 5 to 7 days.
[d] Approval of the Sponsor's medical monitor is required to restart study treatment after interruption ≥21 days.

Preventative care measures for skin toxicities should include:

- Avoid sun exposure.
- Apply broad spectrum sunscreen twice daily (SPF >15).
- Use thick, alcohol-free emollient cream on dry areas at least twice daily.

Symptomatic care should include:

- Pruritic lesions: cool compresses and oral antihistamine.
- Paronychia: antiseptic bath, oral antibiotic, and local corticosteroids.
- Fissuring lesions: silver nitrate or zinc oxide cream.
- Desquamation: emollients and mild soap.

APPENDIX 5. MANAGEMENT OF VISUAL CHANGES

Ocular adverse events have been observed in subjects receiving MEK inhibitors (ie, trametinib [Mekinist USPI] and cobimetinib [Cotellic USPI]) and ERK inhibitors (ulixertinib and GDC-0994 [de la Cruz-Merino et al 2017; Sullivan et al 2018; Li et al presentation 2017; Maubon et al 2016; Stjepanovic et al 2016; Varga et al 2020; Duncan et al 2015; Infante et al abstract 2015; Infante et al presentation 2015; Welsh and Corrie 2015; Ho et al 2013]). Ocular toxicities include blurring and altered light perception, periorbital edema, increased lacrimation, uveitis, and visual disturbances. Retinal adverse events have also been described in subjects receiving MEK inhibitors (de la Cruz-Merino et al 2017; Stjepanovic et al 2016; Welsh and Corrie 2015).

The causal relationship between a change in vision and the study treatment should be carefully explored, and an ophthalmologist should be consulted. Special attention should be given to retinal adverse events (eg, CSR, RVO). For events of visual changes regardless of severity, a blood sample for PK analysis must be drawn as close as possible to the time of the event.

Suggested guidelines regarding management and criteria for adjusting, withholding, and discontinuing study treatment for visual changes considered to be related to study treatment are provided in Table 16. The institutional standards for the management of ocular AEs can differ from these guidelines. In this case, best clinical judgment should be applied.

Table 16: Suggested Management and Dose Modification for Visual Changes

CTCAE Grade	Management	Action and Dose Modification
Grade 1	Consult ophthalmologist within 7 days of onset	• Continue study treatment. • If dilated fundus examination cannot be performed within 7 days of onset, interrupt study drug. • If RVO or CSR excluded, continue study treatment at the same dose level. • If CSR suspected or diagnosed, continue study treatment at the same dose level. If RVO diagnosed, permanently discontinue study treatment and report as an SAE.
Grade 2	Interrupt study treatment and consult ophthalmologist immediately	• If RVO or CSR excluded, resume study treatment at the same dose level. • If CSR diagnosed, withhold study treatment. If improved to ≤Grade 1, resume at a lower dose level[a] with close monitoring following treatment re-initiation. • If RVO diagnosed, permanently discontinue study treatment and report as an SAE.
Grade 3	Interrupt study treatment and consult ophthalmologist immediately	• If RVO or CSR excluded, withhold study treatment. If improved to ≤Grade 1, resume at a lower dose level. • If CSR diagnosed, withhold study treatment. If improved to ≤Grade 1, resume at a lower dose level[a] with close monitoring following treatment re-initiation. • If RVO diagnosed, permanently discontinue study treatment and report as an SAE.
Grade 4	Interrupt study treatment and consult ophthalmologist immediately	• Permanently discontinue study treatment and report as an SAE.

CSR=central serous retinopathy; CTCAE=Common Terminology Criteria for Adverse Events; RVO=retinal vein occlusion; SAE=serious adverse event.

[a] Dose level depends on the nature of the ocular toxicity. Approval of the Sponsor's medical monitor is required to restart study treatment after interruption ≥21 days.

APPENDIX 6. MANAGEMENT OF DIARRHEA

Episodes of diarrhea have occurred in subjects receiving MEK inhibitors (ie, trametinib [Mekinist USPI] and cobimetinib [Cotellic USPI]) and ERK inhibitors (ulixertinib and GDC-0994) (Adjei et al, 2017; Sullivan et al 2018; Li et al presentation 2017; Varga et al 2020; Infante et al abstract 2015; Infante et al presentation 2015; Welsh and Corrie 2015).

Suggested guidelines regarding management and criteria for adjusting, withholding, and discontinuing study treatment for diarrhea considered to be related to study treatment are provided in Table 17. The institutional standards for the management of GI AEs can differ from these guidelines. In this case, best clinical judgment should be applied.

Table 17: Suggested Management and Dose Modification for Diarrhea

CTCAE Grade	Management	Action and Dose Modification
Uncomplicated[a] Grade 1 or 2	• Diet: stop lactose-containing products; BRAT diet recommended. • Hydration: 8 to 10 large glasses per day. • Loperamide[b]: Initially 4 mg followed by 2 mg every four hours; maximum 16 mg/day. Continue until diarrhea-free for 12 hours. • Diarrhea >24 hours: loperamide every 2 hours, maximum 16 mg/day. Consider adding oral antibiotics. • Diarrhea >48 hours: loperamide every 2 hours; maximum 16 mg/day. Consider second-line therapies (budesonide, tincture of opium, or octreotide) and oral antibiotics. • Rule out other causes (eg, infection).	• Continue study treatment. • If diarrhea is Grade 2 for >48 hours, interrupt study treatment until diarrhea resolves to ≤Grade 1.[c] • Resume study treatment at the same dose level.
Uncomplicated[a] Grade 3	• Diet: stop lactose-containing products; BRAT diet recommended. • Hydration: 8 to 10 large glasses per day. • Loperamide[b]: Initially 4 mg followed by 2 mg every four hours; maximum 16 mg/day. Continue until diarrhea-free for 12 hours. • Second-line therapies and antibiotics if clinically indicated. • Hydration: IV fluids if clinically indicated. • Rule out other causes (eg, infection).	• Inform the Sponsor's medical monitor • Interrupt study treatment until diarrhea resolves to ≤G1.[c] • Resume with study treatment at a lower dose level.[e]
Grade 4 Any complicated[d] diarrhea	• Urgent intervention indicated. • Intervention may require hospitalization for subjects at risk of life-threatening complications.	• Inform the Sponsor's medical monitor. • Permanently discontinue study treatment and report as an SAE.

BRAT=bananas, rice, applesauce, toast; CTCAE=Common Terminology Criteria for Adverse Events; IV=intravenous; SAE=serious adverse event.

[a] Uncomplicated diarrhea defined by the absence of symptoms.

[b] Loperamide should be made available before study treatment so that administration can start at the first signs of diarrhea.

[c] Approval of the Sponsor's medical monitor is required to restart study treatment after ≥21 days interruption

[d] Complicated diarrhea defined by the presence of symptoms such as pyrexia, sepsis, neutropenia ≥Grade 3, frank bleeding, and/or dehydration requiring IV fluid substitution.

[e] Escalation of study treatment to previous dose level may be allowed after consultation with the Sponsor's medical monitor and in the absence of another episode of complicated or severe diarrhea in the 4 weeks subsequent to dose reduction.

APPENDIX 7. LIVER STATUS MONITORING AND MANAGEMENT OF POTENTIAL LIVER INJURY

Liver enzyme elevation has been observed in patients receiving ERK inhibitors (Sullivan et al 2018; Li et al presentation 2017; Varga et al 2020; Infante et al abstract 2015; Infante et al presentation 2015). Clinical symptoms and laboratory test values that are potential signals of liver injury must be regularly reviewed by investigators and by the Sponsor's medical monitor for the study.

Discontinuation of study treatment should occur if a subject shows potential signals of liver injury, indicated by the occurrence of any of the following liver function test values. (Note: liver toxicity or injury may be confirmed with a liver biopsy, if clinically indicated.)

- ALT or AST ≥8×ULN.
- ALT or AST >5×ULN but <8×ULN for ≥7 days.
- ALT or AST >3×ULN and either total bilirubin >2×ULN or INR >1.5, if INR measured.
- ALT or AST >3×ULN with clinical indications of liver toxicity (signs, symptoms, or other diagnostic findings).
- ALT or AST >5×ULN but <8×ULN and subject cannot be closely monitored as described below.

Subjects with potential signals of liver injury must be closely monitored as described below:

- Report the event to the Sponsor's medical monitor.
- Repeat liver enzymes, total bilirubin, and INR at least twice weekly until liver function test elevations resolve or stabilize or the values return to baseline. (The frequency of retesting can decrease to once a week or less if abnormalities stabilize and the subject is asymptomatic.)
- Obtain a detailed history of symptoms, including any prior and concurrent diseases.
- Obtain a history of concomitant drug use (including nonprescription medications and herbal and dietary supplement preparations), alcohol and recreational drug use, and any special diets consumed.
- Rule out acute viral hepatitis (types A, B, C, D, and E), autoimmune or alcoholic hepatitis, nonalcoholic steatohepatitis, hypoxic/ischemic hepatopathy, and biliary tract disease.
- Obtain a history of exposure to environmental chemical agents.
- Review additional tests to evaluate liver status, as appropriate. If alkaline phosphatase (ALP) is elevated, perform an analysis of ALP isoenzymes to determine if the origin of the ALP elevation is bone or liver.
- Consider scheduling the subject for gastroenterology or hepatology consultation.
- Collect ad hoc PK samples.

Subjects who experience ALT or AST values >3× to <5×ULN, with total bilirubin <2×ULN and INR <1.5 (and have no clinical symptoms indicative of liver toxicity) may continue to receive study drug. However, ALT, AST, and total bilirubin tests should be repeated twice weekly until liver function test elevations resolve or stabilize or the values return to baseline. These repeat results will be discussed with the Sponsor's medical monitor. If, at any time, the subject meets any of the above stopping criteria for potential liver injury, study drug treatment should be discontinued and the subject should be monitored as described above.

APPENDIX 8. DOSE MODIFICATION FOR DECREASE IN LEFT VENTRICULAR EJECTION FRACTION

Decreases of LVEF have been observed in patients receiving the MEK inhibitors trametinib (Mekinist USPI) and cobimetinib (Cotellic USPI) and the ERK inhibitor GDC-0994 (Varga et al 2020). ECHO or MUGA scans will be performed to assess cardiac ejection fraction in regular intervals as outlined in the schedule of events tables (Table 11 and Table 12).

Suggested guidelines regarding management and criteria for adjusting, withholding, and discontinuing study treatment for LVEF decrease are provided in Table 18. In the event that institutional standard practice differs from these suggested guidelines, institutional practices may be followed with best clinical judgement applied.

Table 18: Suggested Action and Dose Modification for LVEF Decrease

LVEF Decrease (%)	Action and Dose Modification
Resting LVEF 49% to 40%; absolute decrease of >10% but <19% in LVEF from baseline and LVEF below the institution's LLN	• Interrupt study treatment and perform ECHO within 3 weeks. • If ECHO recovers within 3 weeks: – Consult with the Sponsor's medical monitor and request approval to restart ASTX029 dosing. – If approval is obtained, restart at a lower dose level. – If ASTX029 is restarted, repeat ECHO after 3, 6, and 9 weeks after restart; continue in intervals of every 12 weeks thereafter. • If ECHO does not recover within 3 weeks: – Consider cardiology consultation. – Permanently discontinue study treatment. – Repeat ECHO after 3, 6, and 9 weeks or until resolution or plateau.
Resting LVEF 39% to 20% or >20% absolute reduction from baseline	• Inform the Sponsor's medical monitor. • Permanently discontinue study treatment.
Resting LVEF <20%	• Consult with a cardiologist. • Repeat ECHO after 3, 6, and 9 weeks or until resolution.

ECHO=echocardiogram; LVEF=left ventricular ejection fraction; LLN=lower limit of normal.

APPENDIX 9. MODIFICATIONS DURING THE COVID-19 HEALTH EMERGENCY

1.0 GENERAL INFORMATION

This section describes modifications to the study protocol to allow flexibility in conducting this study during the COVID-19 public health emergency while maintaining safety of trial participants, maintaining compliance with Good Clinical Practice (GCP), and minimizing risks to trial integrity. These modifications are intended to remain in effect only for the duration of the public health emergency related to COVID-19 and only in instances in which the study cannot be conducted per the protocol.

Any modifications to the study protocol must be discussed with the Sponsor's medical monitor before implementation.

2.0 STUDY STATUS

The feasibility of continuing this clinical study in the presence of the COVID-19 pandemic was assessed by the Sponsor to ensure subject safety and data integrity. The Sponsor decided to:

- Continue to enroll/treat participants in this study with temporary modifications including:
  - Conversion of physical visits to telephone or video visits.
  - Modification to ensure that only strictly necessary visits are performed at study centers.
  - Allow laboratory test and/or diagnostic tests (excluding pharmacokinetic [PK] and biomarker analyses and disease assessments) to be conducted at a local laboratory, authorized certified to perform such tests, close to the subject's residence, to reduce COVID-19 exposure, if needed.
  - Remote monitoring.
  - Remote source data verification (rSDV), where permitted by regulations.*
  - Changes to the informed consent process.*
- Temporarily pause recruitment of new trial participants (at some study centers).
- Extend the duration of the study, if needed, by 6 months.

* Where required, submitted as a substantial amendment.

3.0 COVID-19 BENEFIT/RISK ASSESSMENT

The safety of each trial participant is of primary importance, and the risks of participating in this clinical trial, given the challenges due to COVID-19, were carefully weighed against the anticipated benefit for trial participants.

The Sponsor will reassess the risks of conducting this study as the situation develops and will document assessments as part of the sponsor's trial master file. It is possible that local circumstances may lead to a local change in risk assessment (eg, an escalation of the pandemic within a certain region); therefore, the need to implement additional measures may arise.

Investigators may be asked to complete a risk assessment questionnaire or other document provided by the Sponsor(or designee. This assessment should be documented in the investigator's site master file and communicated to the Sponsor.

Benefits

The benefits of participating in this study during the COVID-19 pandemic include treatment of a life-threatening disease for which there are limited or no alternate therapies with new drugs or new drug combinations and include the added benefit of participating in a study with an oral formulation of the study drug administered for conditions for which only intravenous (IV) or subcutaneous therapy is available.

Risks

Additional risks to participating in this trial during the COVID-19 pandemic may include:

- Visiting the study center may increase the risk of exposure to COVID-19, depending on the status of the pandemic in the area near the study center.
- As a result of the disease and treatment, there may be risk of greater morbidity and mortality if COVID-19 is contracted. Additional measures implemented to mitigate this will depend on the individual study center.
- In the event that, as a result of the pandemic, local health officials require shelter in place, alternative arrangements (eg, dosing at home on study days when study drug is to be taken in the clinic) may need to be made to assure subjects continue to receive treatment. Arrangements will be made in collaboration with each study center physician to minimize any such associated risks.

COVID-19 Benefit/Risk Summary

With the life-threatening nature of the condition being treated in this study and because there are no approved alternative treatments for such conditions, the potential anticipated benefits of continuation of this study justify the risks. Study centers will only be allowed to participate in this study during the COVID-19 outbreak if they are able to ensure they can monitor subject safety, ensure data integrity, and continue to oversee study conduct.

4.0 MODIFICATIONS TO STUDY CONDUCT

4.1 Alternative Methods for Obtaining Informed Consent

Alternative methods for obtaining informed consent may be used for re-consenting subjects if necessary and must be appropriately documented in each subject's chart. Alternative methods include, but are not limited to, contacting the subject via phone or video-calls and obtaining oral consent, supplemented with e-mail confirmation, as per Institutional Review Board (IRB)/Independent Ethics Committee (IEC) and Institutional policies or guidelines.

4.2 Alternative Methods for Drug Supply

In extenuating circumstances (eg, during the COVID-19 pandemic) under which standard approaches to dispensing study drug to subjects are not possible, alternative methods for dispensing study drug to subjects may be used. The Sponsor will work with individual centers to find acceptable alternative arrangements (eg, shipment of study drug from study center

pharmacies to subjects) that assure compliant control of study drug and acceptable safety monitoring. Alternative methods for drug dispensing must be reviewed by the Sponsor before implementation.

4.3 Study Visits and Procedures

Protocol-mandated visits and laboratory/diagnostic testing may be modified as follows:

- Telemedicine visits (ie, visits conducted via telephone and/or video, or in-person Telehealth visits with a health professional) may be permitted in lieu of in-person visits to monitor adverse events and participant safety.
  - Telemedicine visits must be approved by the Sponsor and aligned with Institutional practice and local regulations.
  - Telemedicine visits must be appropriately documented in source documents.
  - Additional details regarding how to conduct telemedicine visits will be provided by the Sponsor.

In-person visits are required to assess eligibility, perform baseline assessments, and for primary outcome measures. Telemedicine visits would generally not be permitted for the following visits/procedures unless approved by the Sponsor:

- Screening and/or predose Cycle 1 Day 1 (C1D1) assessments to determine eligibility.
- Visits with mandatory fresh tumor sample collection and sample collection for biomarker and PK analyses.
- Visits with disease assessments (eg, computed tomography [CT], magnetic resonance imaging [MRI], tumor markers).
- Visits with mandatory ophthalmic evaluations.
- Day 1 cycle visits when a subject is in early cycles of the protocol-defined treatment.
- Visits with investigator assessments of new serious or ≥Grade 3 adverse events (AEs) or suspected dose-limiting toxicity (DLT) events.

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APPENDIX 9: SUMMARY OF CHANGES FROM ORIGINAL VERSION IN AMENDMENT 1.0

Protocol: ASTX029-01

Amendment 1.0, Date: 21 February 2019

Rationale for Amendment 1.0

The protocol was amended to introduce the new tablet dosage form of ASTX029, increase the number of study centers, add Europe as a location of study centers for Phase 1, provide newly available nonclinical study results, and allow for administration of the powder-in-bottle (PiB) dosage form of ASTX029 by gastrostomy tube (g-tube). Time windows have been provided for certain assessments that are planned to occur at cycle visits to allow more scheduling flexibility for the subjects, investigators, and study centers without impacting subject safety. Additional minor editorial changes were made throughout for clarification and consistency. All changes in the body of the protocol are also reflected in the protocol synopsis, as applicable.

Summary of Changes:

1. A summary of a nonclinical pharmacokinetic study conducted in monkeys to support dosing of the tablet formulation in humans was added to the introduction (Section 1.3.2.1).
2. A summary of nonclinical genotoxicity study results, which indicate no evidence of genotoxicity, was added to the introduction (Section 1.3.2.4).
3. The numbers of study centers were increased to up to 14 for Phase 1 and to up to 30 for Phase 2, and Europe was added as a location of study centers for Phase 1 to facilitate enrollment and study completion in the Overall Study Design section (Section 4.1) and the Number of Subjects and Centers section (Section 5.1).
4. Clarified the primary endpoint by adding details of how (by determining incidences of dose limiting toxicities and adverse events) the maximum tolerated dose (MTD) will be established (Section 4.3.1).
5. Clarified that a subject who withdraws consent may request destruction of any untested samples and that this must be documented and reported to the sponsor within 24 hours in the Withdrawal From Study section (Section 5.4.2) and Tissue and Blood Sample Collection/Storage section (Section 14.2.5).
6. Added details to Exclusion Criterion #4 for clarity (Section 5.3).
7. The new ASTX029 tablet dosage form was added in multiple sections, including the Drug Substance, Drug Product, and Packaging section (Section 7.1.1), and the Transition from Powder-in-Bottle Dosage Form to Tablet Dosage Form section (Section 7.1.6) was added.
8. Administration of the PiB dosage form of ASTX029 by g-tube was added as a dosing option to the Drug Substance, Drug Product, and Packaging section (Section 7.1.1).

9. Clarified that intrasubject escalations will not be allowed but that investigators may change subjects' dose levels to the MTD or recommended dose for expansion (RDE) dose levels (once determined and with approval of Astex) in the Dose-Escalation Guidelines and Recommended Phase 2 Dose Decision section (Section 7.3).

10. Clarified that tumor marker measurements are to be performed, if appropriate, as part of disease reassessments to assess response per Appendix 3, Response Evaluation Criteria in Solid Tumors (RECIST) v1.1, in multiple subsections in the Study Assessments and Procedures section (Section 9.0).

11. To provide more flexibility for the subjects, investigators, and study centers and accommodate the time needed to obtain and review results from clinical laboratory assessment adjustments have been made in multiple subsections in the Study Assessments and Procedures section (Section 9.0).

12. Added assessment of dosing compliance information for Regimen 1 Cycle 2 Days 8 and 15 to correct an omission in study assessments and procedures sections (Section 9.4.9, Section 9.4.11.6, Section 9.4.11.7) and, for Regimen 2, moved the Cycle 2 Day 1 assessment to Cycle 1 Day 14, the last dosing day of Cycle 1 for that regimen in study assessments and procedures sections (Section 9.4.9, Section 9.4.11.3, Section 9.4.11.5.1).

13. Clarified that the Treatment Termination (Tx Term) visit is to occur within 3 days before starting new anticancer treatment (as applicable) and that, if a subject discontinues study treatment at a scheduled visit, that visit's assessments can be used to fulfill the Tx Term visit requirements in the study assessments and procedures sections (Section 9.4.9, Section 9.4.13).

14. The suggested actions and dose modifications for left ventricular ejection fraction (LVEF) decrease were clarified as being based on LVEF ranges rather than Common Terminology Criteria for Adverse Events in the Dose Modification for Decrease in Left Ventricular Ejection Fraction appendix (Appendix 8).

APPENDIX 9: SUMMARY OF CHANGES FROM AMENDMENT 1.0 TO AMENDMENT 2.0

Protocol: ASTX029-01

Amendment 2.0, Date: 12 July 2019

Rationale for Amendment 2.0

The protocol was amended to evaluate dosing of ASTX029 under fasting conditions in Phase 1 Part A as a result of nonclinical data from 3 food-effect studies conducted in monkeys or dogs and preliminary clinical pharmacokinetic (PK) data becoming available. Additional minor editorial changes were made throughout for clarification and consistency. All changes in the body of the protocol are also reflected in the protocol synopsis, as applicable.

Summary of Changes:

1. Data from 3 food-effect studies conducted in monkeys or dogs were added to the Absorption, Distribution, Metabolism, and Excretion Studies and Nonclinical Pharmacokinetics section (Section 1.3.2.1).
2. "Preliminary" was removed from the description of the data available from the in vitro chromosomal aberration assay in human peripheral blood lymphocytes in the Toxicology Studies section (Section 1.3.2.4) because the final report is now available.
3. "Food effect on PK parameters" was added to the PK secondary objective in the Secondary Objectives section (Section 3.2) and to the PK secondary endpoint in the Secondary Endpoint(s) section (Section 4.3.2).
4. Language regarding a potential food-effect cohort and a food-effect evaluation in Phase 1 Part B was removed from multiple sections.
5. A description of ASTX029 formulations (powder in bottle [PiB] and tablet) and administration conditions (fed and fasting) was added to the Overall Study Design section (Section 4.1, in place of the previous formulation descriptions), the Discussion of Study Design section (Section 4.2, along with the rationales for fed and fasted administration), and the ASTX029 Administration section (Section 7.1.5).
6. The descriptions of the bottles of ASTX029 powder-in-bottle and of the vehicle for reconstitution as being "induction-sealed" and "150-mL induction-sealed," respectively, were removed from the Drug Substance, Drug Product, and Packaging section (Section 7.1.1).
7. Administration of ASTX029 under fasted conditions was specified as being introduced with Amendment 2 the ASTX029 Administration section (Section 7.1.5).
8. The Transition From Fed to Fasted Administration section (Section 7.1.7, in which DLT and PK data as of this amendment and fasted-dose administration are described) was added.

9. "With a known risk of torsades de pointes while on study treatment" was added in the Prohibited Medications and Substances section (Section 7.6.2) to the description of QT interval corrected for heart rate (QTc)-prolonging medications of which potential concomitant use is to be discussed with Astex Pharmaceutical's medical monitor.

10. The specification that the Cycle 1 Day 1 electrocardiogram results must meet study entry criteria before ASTX029 dosing was added within Section 9.4 subsections, including Table 9 and Table 10 footnotes.

11. Discussion of administration of ASTX029 with food, still present in Drug Administration Under Fed Conditions subsection of the ASTX029 Administration section (Section 7.1.5), was removed from the Treatment and Follow-up Procedures section (Section 9.4.11).

APPENDIX 9: SUMMARY OF CHANGES FROM AMENDMENT 2.0 TO AMENDMENT 3.0

Protocol: ASTX029-01

Amendment 3.0, Date: 31 December 2019

Rationale for Amendment 3.0

The protocol was amended to modify Phase 2 cohorts and specify Phase 2 evaluations in preparation for initiation of Phase 2 and to remove ASTX029 tablet strength information to accommodate potential additional strengths, which are to be specified in the Investigator Brochure (IB). Additional minor editorial changes were made throughout for clarification and consistency. All changes in the body of the protocol are also reflected in the protocol synopsis, as applicable.

Summary of Changes:

1. The numbers of subjects in Phases 1 and 2 were adjusted per updated estimates (Section 4.1 and Section 5.1).
2. The Phase 2 cohorts for B isoform of RAF kinase (BRAF)-fusion cancers (Cohort D) and gynecological cancers with alterations in the mitogen-activated protein kinase (MAPK) pathway (Cohort E) were added; 2 previously specified cohorts (Cohort B and Cohort C) were modified; and the cohort for tumors with other gene alterations (previously Cohort D) was designated as Cohort F (Figure 2, Section 4.1; Section 4.1.2; Section 5.1; and Section 11.1).
3. ASTX029 tablet strength information was replaced with a reference to the current ASTX029 IB (Section 7.1.1).
4. Dosing information at the time of Amendment 2 was replaced with the fact that Phase 1 Part A dose escalation is ongoing under the fasted condition at the time of Amendment 3.0 (Section 7.1.7).
5. Pharmacokinetic assessments during Phase 2 were specified (Table 6 and Table 7, Section 9.2.1).
6. Biomarker assessments and tumor biopsies during Phase 2 were specified (Table 6 and Table 9, respectively, Section 9.2.2; Table 11 and Table 12, Section 9.4.9; and subsequent Section 9.4 subsections).
7. Other Phase 2 evaluations were specified (Table 11 and Table 12, Section 9.4.9 and subsequent Section 9.4 subsections).
8. Study visit windows were specified (Table 11 and Table 12, Section 9.4.9).

APPENDIX 9: SUMMARY OF CHANGES FROM AMENDMENT 3.0 TO AMENDMENT 4.0

Protocol: ASTX029-01

Amendment 4.0, Date: 21 July 2020

Rationale for Amendment 4.0

The protocol was amended to add language regarding conducting the study during the COVID-19 pandemic to enable continuation of the study during the pandemic, clarify that Regimen 2 may not need to be evaluated during Phase 1 Part A to determine the regimen to be evaluated in Phase 1 Part B, specify contraceptive use and pregnancy tests consistent with requirements of countries other than the United States (US) as well as the US, remove descriptions of the phased out ASTX029 powder-in-bottle [PiB] formulation or change the descriptions to the past tense. Additional minor editorial changes were made throughout for clarification and consistency. All changes in the body of the protocol are also reflected in the protocol synopsis, as applicable.

Summary of Changes:

1. Updated the medical monitor information.
2. Clarified that Regimen 2 may not need to be evaluated during Phase 1 Part A to determine the regimen to be evaluated in Phase 1 Part B.
3. Extended the expected duration of recruitment for the study by 6 months.
4. Changed contraceptive use specifics for women of childbearing potential and men.
5. Added language about sperm donation for men and egg (ova, oocyte) donation for women of childbearing potential.
6. Added a pregnancy test within 24 hours before the start of ASTX029 on Day 1 of Cycle 1 and specified that pregnancy tests before Cycles 2 through 6 are to be done within 24 hours before the start of treatment for those cycles.
7. Indicated the PiB dosage form was phased out and changed the descriptions of PiB dosing to the past tense.
8. Clarified that grapefruit juice is not allowed during treatment with ASTX029 rather than during subjects' participation in the study.
9. Added language regarding conducting the study during the COVID-19 pandemic.