A Phase Ib, Open Label, Multicenter Study to Determine the Maximum Tolerated Dose (MTD) of PARPi 2X-121 Monotherapy and the MTD of Dovitinib in Combination with 2X-121 in Patients with Advanced Solid Tumors

Protocol Number:	**Protocol #AL-2003**
Version:	**Version 2.0**
Date:	**19-July-2022**

Sponsor: **Allarity Therapeutics, Inc**
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Denmark

Confidentiality Statement

PROTOCOL APPROVAL PAGE

Protocol Number:	**Protocol #AL-2003**
Version:	**Version 2.0**
Date:	**19-July-2022**

We, the undersigned, have reviewed this protocol and agree that it contains all relevant information required to meet FDA, GCP and all applicable regulatory guidelines and statutes.

PROTOCOL APPROVAL FOR USE

Program Director; Amarex Clinical Research, LLC	Signature	Date
Pharmacovigilance; Amarex Clinical Research, LLC.	Signature	Date
Biostatistics; Amarex Clinical Research, LLC.	Signature	Date
Medical Writing; Amarex Clinical Research, LLC.	Signature	Date
CMO; Allarity Therapeutics, Inc	Signature	Date

INVESTIGATOR'S SIGNATURE PAGE

Protocol Number:	**Protocol #AL-2003**
Version:	**Version 2.0**
Date:	**19-July-2022**

I have read the protocol specified above and agree to participate in and comply with the procedures, as outlined herein for the conduct of this clinical trial. I also agree to comply with US Food and Drug Administration (FDA) regulations and Investigational Review Board/Institutional Ethics (IRB/IEC) requirements for testing on human subjects. I agree to ensure that the requirements for obtaining informed consent are met.

Principal Investigator's Signature _____ Date _____

Print Name _____

Site Number _____

SPONSOR INFORMATION

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PROTOCOL SYNOPSIS

Name of Sponsor/Company: Allarity Therapeutics, Inc	
Name of Study Product: 2X-121 **Investigational Combination Therapy:** 2X-121 + dovitinib	
Protocol Number: Protocol #AL-2003	**Indication:** Advanced Solid Tumors
Title of Study: A Phase Ib, Open Label, Multicenter Study to Determine the Maximum Tolerated Dose (MTD) of PARPi 2X-121 Monotherapy and the MTD of Dovitinib in Combination with 2X-121 in Patients with Advanced Solid Tumors	
Study Center: Up to five study centers	
Planned Number of Subjects: Part 1: Up to 16 subjects Part 2: Up to 24 subjects	**Study Development Phase:** Phase 1b
Indication for Use: Locally advanced or metastatic solid tumors.	

Study Objectives

Primary Objectives:

The primary objective of this study is:

Part 1

- To determine the maximum tolerated dose (MTD) of 2X-121 monotherapy given twice daily (BID) in patients with advanced solid tumors.

Part 2

- To determine the MTD of dovitinib given in combination with 2X-121 (MTD) in patients with advanced solid tumors.

Secondary Objectives:

The secondary objectives of this study are:

- To evaluate the anti-tumor activity of 2X-121 monotherapy (Part 1) and in combination with dovitinib (Part 2) in patients with advanced solid tumors.
- To evaluate the pharmacokinetics (PK) of 2X-121 monotherapy (Part 1) and in combination with dovitinib (Part 2) in patients with advanced solid tumors.
- To evaluate the safety and tolerability of 2X-121 monotherapy (Part 1) and in combination with dovitinib (Part 2) in patients with advanced solid tumors.

[redacted]

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Name of Study Product: 2X-121 **Investigational Combination Therapy:** 2X-121 + dovitinib	
Protocol Number: Protocol #AL-2003	**Indication:** Advanced Solid Tumors
[redacted]	

Study Outcome Measures

Primary Outcome Measure:

The primary outcome measures in this study are:

Part 1

- Determination of the MTD of 2X-121 monotherapy.

  Note: The MTD is defined as 1 dose level below the dose in which dose limiting toxicities (DLTs) were observed in ≥ 33% of the participants during the first 14 days of the main treatment period.

Part 2

- Determination of the MTD of dovitinib given in combination with 2X-121 (MTD).

  Note: The MTD is defined as 1 dose level below the dose in which dose limiting toxicities (DLTs) were observed in ≥ 33% of the participants during the first 14 days of the main treatment period.

Secondary Outcome Measures:

The secondary anti-tumor activity outcome measures in this study are:

- To evaluate the objective response rate (ORR) of 2X-121 monotherapy (Part 1) and in combination with dovitinib (Part 2).

  ORR is defined as the proportion of subjects who achieve a Complete Response (CR) or Partial Response (PR) as assessed by RECIST v1.1.

- To evaluate the duration of overall response (DOR) of 2X-121 monotherapy (Part 1) and in combination with dovitinib (Part 2).

  DOR is defined as the time in months from the first documented CR or PR per RECIST v. 1.1 to disease recurrence or disease progression (PD) whichever occurs first.

- To evaluate progression free survival (PFS) of 2X-121 monotherapy (Part 1) and in combination with dovitinib (Part 2).

  PFS is defined as the time from study treatment initiation to either first observation of progressive disease or occurrence of death.

- To evaluate overall survival (OS) of 2X-121 monotherapy (Part 1) and in combination with dovitinib (Part 2).

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OS is defined as the time from study treatment initiation to death from any cause or last day known to be alive.

Pharmacokinetic (PK) Outcome Measures:

The following pharmacokinetic parameters will be calculated for 2X-121 monotherapy at each dose level (Part 1) and for 2X-121 (MTD) in combination with dovitinib at each dose level (Part 2):

- Maximum concentration of 2X-121 (C_{max}) and dovitinib (C_{max})
- Area under the plasma-time concentration curve (AUC)
- Elimination half-life of 2X-121 ($t_{½}$) and dovitinib ($t_{½}$)
- Time to maximum plasma concentration (t_{max})
- Total body clearance of 2X-121 (Cl/F) and dovitinib (Cl/F)
- Apparent volume of distribution (Vz/F)

Safety Outcome Measures:

- The safety and overall tolerability of 2X-121 and dovitinib will be evaluated based on:
- Dose Limiting Toxicities
- Incidence and severity of treatment-emergent adverse events (TEAEs), including serious adverse events and adverse events resulting in permanent discontinuation of study treatment
- Laboratory data changes from baseline to subsequent scheduled visits
- Changes in physical examinations from baseline to subsequent scheduled visits
- Changes in vital signs from baseline to subsequent scheduled visits
- Changes in Eastern Cooperative Oncology Group (ECOG) performance status from baseline to subsequent scheduled visits
- Changes of electrocardiogram (ECG) results from baseline to subsequent scheduled visits

[redacted]

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Name of Study Product: 2X-121 **Investigational Combination Therapy:** 2X-121 + dovitinib	
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Trial Design:

This is a Phase Ib, two-part, multi-center study. In Part 1, the study will evaluate the safety and tolerability, antitumor activity, pharmacokinetics, and determine the maximum tolerated dose (MTD) of 2X-121 monotherapy (at BID regimen) in patients with advanced solid tumors. In Part 2, the study will evaluate the safety and tolerability, antitumor activity, and pharmacokinetics of 2X-121 (MTD) and dovitinib as combination therapy, and determine the MTD of dovitinib when given in combination with the MTD of 2X-121 determined in Part 1.

Part 1

This part of the study will follow an accelerated titration method followed by a standard "3+3" design to determine the MTD of 2X-121. The MTD is defined as one dose level (cohort) below the dose in which dose limiting toxicities (DLTs) were observed in ≥ 33% of the participants.

The calculation of the sample size for this trial is based on the traditional 3 + 3 dose escalation scheme which is conducted as follows:

- Subjects are treated in cohorts of one (Cohort 1) or three (Cohorts 2-3) subjects, each receiving the same dose. For the assessment of a DLT, subjects are observed for 14 days.
- In Cohort 1, if the one subject does not exhibit a DLT, the next cohort of three subjects will receive the next higher dose (Cohort 2). In Cohort 2, if none of the three subjects exhibits a DLT, the next cohort of three subjects will receive the next higher dose (Cohort 3).
- Otherwise, if at least one subject of a cohort exhibits a DLT, a further cohort of three subjects is treated at the same dose level (cohort) without escalating the dose.
- If exactly one out of the six subjects treated at this dose exhibits a DLT, the trial continues as planned at the next higher dose level (cohort).
- If two or more subjects out of the six subjects treated at this dose exhibit a DLT, the dose escalation stops at that level and the next lower dose is considered as the MTD. When the escalation has stopped, additional subjects will be treated at the MTD to a total of six subjects.

[redacted]

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The dose levels to be evaluated in Part 1 are shown below:

Dose Cohort	2X-121 Monotherapy Dose (BID)
Cohort 1	600 mg (morning dose: 200 mg + evening dose: 400 mg)
Cohort 2	800 mg (morning dose: 400 mg + evening dose: 400 mg)
Cohort 3	1000 mg (morning dose: 400 mg + evening dose: 600 mg)

On Day 1 of first treatment cycle (C1D1), patients will be administered 2X-121 monotherapy as oral capsules taken twice daily. Each treatment cycle will consist of 28 days.

[redacted]

Once the MTD has been determined, subjects enrolled in lower dose cohorts will be allowed to escalate the dose to the MTD, if acceptable per the Investigator's discretion. Subjects will be eligible for continuing treatment in absence of progressive disease or unacceptable toxicity or withdrawal of consent.

Part 2

In Part 2 of the study, patients will receive dovitinib in combination with the MTD of 2X-121 determined in Part 1. Part 2 will follow a "3+3" design to determine the MTD of dovitinib when given in combination with 2X-121. The MTD is defined as one dose level (cohort) below the dose in which dose limiting toxicities (DLTs) were observed in ≥ 33% of the participants. See Part 1 above for definition of DLTs.

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Allarity Therapeutics, Inc

Name of Study Product: 2X-121
Investigational Combination Therapy: 2X-121 + dovitinib

Protocol Number:	**Indication:**
Protocol #AL-2003	Advanced Solid Tumors

The dose levels to be evaluated in Part 2 are shown below:

Dose Cohort	Combination 2X-121 (BID administration) and Dovitinib
Cohort 1	2X-121 (MTD) + 300 mg dovitinib
Cohort 2	2X-121 (MTD) + 400 mg dovitinib
Cohort 3	2X-121 (MTD) + 500 mg dovitinib

Dovitinib will be administered once daily (morning) on a 5 days on/2 days off schedule. In a 28 day cycle, dovitinib will be administered C1D1 - C1D5, C1D8 - C1D12, C1D15 - C1D19, and C1D22 - C1D26.

[redacted]

Once the MTD has been determined, subjects enrolled in lower dose cohorts will be allowed to escalate the dose to the MTD, if acceptable per the Investigator's discretion. Subjects will be eligible for continuing treatment in absence of progressive disease or unacceptable toxicity or withdrawal of consent.

An additional 3-6 patients will receive 2X-121 in combination with dovitinib once the MTD dose is determined.

Study Duration:

- **Screening Phase:** Up to 28 days
- **Treatment Phase:**
  - First Treatment Cycle: 4 weeks
  - Subsequent Treatment Cycles: Subjects will be eligible for continuing treatment in absence of progressive disease or unacceptable toxicity or withdrawal of consent.
  - End of Treatment (EOT): EOT visit will be conducted 30 (±7) days after the last treatment visit (i.e., after last dose of 2X-121).

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- **Follow-Up Phase:** Follow-up visits will be done for survival status, by clinic visits or phone or another method of contact at least every 3 months from the date of treatment discontinuation. All subsequent anti-cancer treatments are to be reported.

All patients are to be followed for 2 years or until death whichever comes first.

Inclusion Criteria:

Subjects will be eligible for enrollment in the study only if they meet ALL the following criteria at time of Screening:

1. Age 18 years or older.
2. Histologically or cytological documented solid tumor.
3. Available tumor biopsy (most recent) for DRP® analysis.
4. Measurable disease by CT scan or MRI if possible.
5. Performance status of ECOG ≤ 1.
6. Recovered to Grade <1 or baseline from prior surgery or from acute toxicities of prior radiotherapy, or from treatment with cytotoxic, hormonal or biologic agents.
7. ≥ 2 weeks must have elapsed since any prior surgery or therapy with G-CSF and GM-CSF.
8. Patients with intracranial disease must be on stable or decreased level of steroid therapy (e.g. dexamethasone) for at least 7 days prior to baseline MRI. Non-enzymatic inducing anti-epileptic drugs are allowed.
9. Adequate conditions as evidenced by the following clinical laboratory values:
    a. Absolute neutrophils count (ANC) ≥ 1500/mm^3 (1.5 x 10^3/mL)
    b. Hemoglobin > 10.0 g/dL
    c. Platelets ≥ 100,000/mm^3 (≥ 100 x 10^9/L)
    d. Alanine aminotransferase (ALT) and aspartate aminotransferase (AST) ≤ 3 x ULN or ≤5x ULN in presence of liver metastases
    e. Serum bilirubin ≤ 1.5 ULN
    f. Alkaline phosphatase ≤ 2.5 x ULN
    g. Creatinine ≤ 1.5 ULN
    h. Blood urea nitrogen (BUN) ≤2X ULN.
10. Life expectancy equal or longer than 3 months.

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11. The subject is willing to provide written informed consent to participate in the study after reading the informed consent form and the information provided and has had the opportunity to discuss the study with the investigator or designee.
12. The subject is able to communicate satisfactorily with the investigator and to participate in, and comply with, the requirements of the study.
13. The subject is able to understand the nature of the study and any potential hazards associated with participating in it.
14. Negative pregnancy test for female subjects of childbearing potential. Women of childbearing potential (WOCBP) and Women of non-childbearing potential are eligible to participate. Both women of childbearing potential and women of non-childbearing potential should use an approved method of birth control and agree to continue to use this method for the duration of the study (and for 90 days after taking the last dose of study drug).

    Acceptable methods of contraception include abstinence, female subject/partner's use of hormonal contraceptive (oral, implanted, or injected) in conjunction with a barrier method (WOCBP only) (e.g., diaphragm, cervical cap, male condom, and female condom and spermicidal foam, sponges, and film), female subject/partner's use of an intrauterine device (IUD), or if the female subject/partner is surgically sterile for at least three months before screening or 2 years post-menopausal at time of screening. All male subjects/partners must agree to consistently and correctly use a condom for the duration of the study and for 90 days after taking the study drug. In addition, subjects may not donate sperm for the duration of the study and for 90 days after taking study drug.

Exclusion Criteria:

Subjects meeting ANY of the following criteria at time of Screening will be excluded from enrollment:

1. Concurrent chemotherapy, radiotherapy, hormonal therapy, or other investigational drug except non-disease related conditions (e.g. insulin for diabetes) during study period.
2. Other malignancy with exception of curative treated non-melanoma skin cancer or cervical carcinoma in situ within 5 years prior to entering the study.
3. Any active infection requiring parenteral or oral antibiotic treatment.
4. History of coagulation or bleeding disorder or subject currently on therapeutic anticoagulant medication.

    Note: Prophylactic doses of heparin or low molecular weight heparin are allowed.
5. Known HIV positivity.
6. Known active hepatitis B or C.

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7. Clinically significant (i.e. active) cardiovascular disease:
    a. Stroke within ≤ 6 months prior to day 1
    b. Transient ischemic attack (TIA) within ≤ 6 months prior to day 1
    c. Myocardial infarction within ≤ 6 months prior to day 1
    d. Unstable angina
    e. New York Heart Association (NYHA) Class II or greater congestive heart failure (CHF)
    f. Serious cardiac arrhythmia requiring medication.
8. Other medications or conditions, including surgery, that in the Investigator's opinion would contraindicate study participation for safety reasons or interfere with the interpretation of study results.
9. Inability to take oral medication, or malabsorption syndrome or any other uncontrolled gastrointestinal condition (e.g., nausea, diarrhea, or vomiting) that might impair the bioavailability of 2X-121 and dovitinib.
10. Requiring immediate palliative treatment of any kind including surgery and/or radiotherapy.
11. Female patients who are pregnant or breast-feeding (pregnancy test with a positive result before study entry).

Statistical Considerations:

Sample Size Determination and Rationale

A sample size of up to 16 subjects in Part 1 and up to 24 subjects in Part 2 will be used in this trial. This sample size is selected based on the conventional 3+3 study design and not based on statistical power calculation; it is deemed adequate to provide clinically meaningful descriptive results consistent with study objectives.

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LIST OF ABBREVIATIONS

Abbreviation	Definition
ADL	Activities of Daily living
AE	Adverse Event
ALT	Alanine Aminotransferase
ANC	Absolute Neutrophils Count
ASCO	American Society of Clinical Oncology
AST	Aspartate Aminotransferase
AUC	Area Under the Curve
BBB	Blood Brain Barrier
B.i.d	Twice daily
Bpm	Beats Per Minute
BRCA	Breast Cancer 1/2 Mutation
CBC	Complete Blood Count
CBR	Clinical Benefit Rate
CDK	Cyclin Dependent Kinase
CHF	Congestive Heart Failure
Cl	Clearance
Cmax	Concentration maximum
CNS	Central Nervous System
CR	Complete Response
CRA	Clinical Research Associate
CRF	Case Report Form
CSR	Clinical Study Report
CT scan	Computed Tomography scan
CTCAE	Common Toxicity Criteria for Adverse Events
DLT	Dose Limiting Toxicity
DM	Data Manager
DNA	DeoxyriboNucleic Acid
DRP®	Drug Response Predictors
EC	Ethics Committee
ECOG	Eastern Cooperative Oncology Group
eCRF	Electronic Case Report Form
EDC	Electronic Data Capture
EMA	The European Medicines Agency
EOT	End Of Treatment
GCP	Good Clinical Practice
HDL	High Density Lipoprotein
HER2	Human Epidermal growth factor Receptor 2
HIV	Human Immunodeficiency Virus

Abbreviation	Definition
HR	Homologous Recombination
IB	Investigator Brochure
ICF	Informed Consent Form
ICH	International Conference on Harmonization
ISF	Investigator Site File
ITT	Intention-To-Treat
Kg	Kilogram
LDL	Low Density Lipoprotein
Mg	Milligram
MPI	Medical Prognosis Institute
MRI	Magnetic Resonance Imaging
MTD	Maximum Tolerated Dose
NAD+	Nicotinamide-Adenine Dinucleotide
NCI	National Cancer institute
NYHA	New York Heart Association
ORR	Overall Response Rate
OS	Overall Survival
OTC	over the counter
PARP	Poly ADP Ribose Polymerase
PARPi	Poly ADP Ribose Polymerase inhibitor
PFS	Progression Free Survival
P-gp	Plasma P-Glycoprotein
PI	Principal Investigator
PIS	Patient Information Sheet
PR	Partial Response
RD	Recommended dose
RNA	RiboNucleic Acid
RP2D	Recommended phase 2 dose
s.c	Sub Cutaneous
SADR	Serious Adverse Drug Reaction
SAE	Serious Adverse Event
SD	Standard Deviation
SDV	Source Data Verification
SmPC	Summary of Products Characteristics
SOP	Standard Operating Procedure
SUSAR	Suspected Unexpected Serious Adverse Reaction
t1/2	Half time
tmax	Time maximum
TEAE	Treatment Emergent Adverse Event

Abbreviation	Definition
TIA	Transient Ischemic Attack
ULN	Upper Limit Normal
V_2	Distribution

1 INTRODUCTION AND BACKGROUND

1.1. STATEMENT OF INTENT

The design, conduct, and reporting of this study shall be conducted in compliance with the protocol, International Council for Harmonisation/Good Clinical Practice (ICH/GCP), and all appropriate regulatory requirements. Investigator(s) participating in this study will have documented training in GCP. Independent monitoring of the trial will be accomplished utilizing a Contract Research Organization (CRO).

1.2. BACKGROUND OF THE DISEASE

1.2.1. BRCA1/2 and other Homologous Recombination Genes

The genes *BRCA1* and *BRCA2* were cloned in the early 1990s. These genes encode proteins that are involved in DNA homologous recombination (HR) (3). Epidemiological studies have shown an association between germline *BRCA1/2* (*gBRCA1/2*) mutations and the development of ovarian cancer (OC) and breast cancer (BC). Mutation frequencies are estimated to be 10% for those diagnosed with BC (4). However, the estimated lifetime risk up to 70 years-old is higher for patients with germline BRCA1/2 mutations; 40% for OC patients carrying gBRCA1 mutations, 11-18% for *gBRCA2* mutation carriers and for BC patients, 57-65% for *gBRCA1* and 45-49% for *gBRCA2* mutation carriers (5, 6).

Patients harboring germline *BRCA1/2* mutations carry a defective copy of the gene in every cell, which increases the likelihood of cancer developing if the remaining copy becomes defective through somatic mutation or epigenetic inactivation (7). However, there are also patients with germline mutations in other HR pathway genes and patients who do not carry an inherited germline mutation but have tumors with sporadic HRD mutations. Data from the Cancer Genome Atlas (TCGA) demonstrates that approximately fifty percent of high grade serous ovarian cancers have aberrations in HR repair (8).

DNA repair pathways involving *BRCA1/2* engage in single or double stranded DNA breaks, which can occur from damage inflicted by ultra violet light, the generation of reactive oxygen species, ambient or therapeutic irradiation, day-to-day replication errors or chemical exposure (9). Cells lacking a functional *BRCA1/2* are also deficient in HR and show a high-degree of chromosomal instability as well as increased sensitivity to ionizing radiation and chemotherapeutic agents that lead to double-stranded breaks (10). Until recently, hereditary ovarian cancer was thought to be caused almost exclusively by mutations in *BRCA1* and *BRCA2*, with a small contribution from mutations in the DNA mismatch repair (MMR) genes (11). As mentioned above the TCGA has shown that half of the most common histologic subtype, high grade serous ovarian cancer, has aberrations in HR repair. Further investigation of the HR pathway highlights multiple other protein co-factors that are necessary for successful HR repair including RAD51C, RAD51D, BRIP1,

PALB2, BARD1 and the MMR genes (11, 12). This group of genes is collectively referred to as the HRD genes (13).

1.2.2. Ovarian Cancer and Standard Treatment

Ovarian Cancer (OC) is a lethal disease with a 5 years survival rate of 20-30% for advanced OC. It is the second leading cause of cancer related deaths in women. A large proportion of patients with OC are diagnosed at an advanced tumor stage.

The outcome after chemotherapy for advanced OC becomes poorer and poorer each time a new treatment is introduced following progression on the previous treatment. Approximately 14,000 OC patients die each year due to disease progression.

Treatment of OC and breast cancer (BC) progressed when the genes BRCA1 and BRCA2 were cloned in the early 1990s and allowing identification of high risk individuals. These genes encode proteins that are involved in DNA homologous recombination (HR) (14). Epidemiological studies have shown an association between germline BRCA1/2 (gBRCA1/2) mutations and the development of OC, (BC), and to a lesser extent pancreatic and endometrial cancers. Mutation frequencies are estimated to be approximately 15-20% for those diagnosed with OC and 5% for those diagnosed with BC (15). In a recent publication it was shown that for BRCA1 and 2 carriers, cumulative risk for BC by age 80 was 72% and 69%, respectively. For OC, cumulative risk was 44% and 17%, respectively.

The peak incidence of BC occurred in the 41-50-year age group (28.3 per 1000 person-years) for BRCA1 and in the 51-60-year group (30.6 per 1000) for BRCA2 mutation carriers. The incidence of OC was 3.6 times higher for BRCA1 than BRCA2 carriers, with the peak incidence of cancer occurring regardless of mutation type among women in the 61-70-year age group (29.4 per 1,000 in BRCA1 carriers). For BRCA1 and 2 carriers, BC risk increased with the number of first- and second- degree relatives with breast cancer. In contrast, OC risk did not vary with respect to family history of this disease (16). Patients harboring germline BRCA1/2 mutations carry a defective copy of the gene in every cell, which increases the likelihood of cancer developing if the remaining copy becomes defective through somatic mutation or epigenetic inactivation (17). DNA repair pathways involving BRCA1/2 engage in single or double stranded DNA breaks, which can occur from damage inflicted by ultra violet light, the generation of reactive oxygen species, ambient or therapeutic irradiation, day- to-day replication errors or chemical exposure (18). Cells lacking a functional BRCA1/2 are also deficient in HR and show a high-degree of chromosomal instability as well as increased sensitivity to ionizing radiation and chemotherapeutic agents that lead to double-stranded breaks (19-21).

1.2.3. PARP inhibitors PARP inhibitors in Ovarian Cancer

Poly(ADP-ribose) polymerases (PARPs) are a family of DNA-dependent nuclear enzymes catalyzing the transfer of ADP-ribose moieties from cellular nicotinamide-adenine-dinucleotide (NAD+) to a variety of target proteins. There are 17 PARP family member proteins identified through sequence homology of the catalytic domain. PARP1, 2 and 3 have all been implicated in

DNA repair, with PARP1 being the most abundant (22). PARP inhibitors are designed to compete with NAD+ for the substrate binding to PARP and inhibit PARP activity (23). Cells containing dysfunctional BRCA1 or BRCA2 have been shown to become profoundly sensitized to the inhibition of PARP enzymatic activity, resulting in chromosomal instability, cell cycle arrest and subsequent apoptosis (24). PARP inhibition is thought to induce synthetic lethality, which describes a process where at least two genetic lesions that individually are not lethal become lethal when combined in the same cell (25). For example, cells that are deficient in HR, which is not lethal in itself, are hypersensitive to a reduction in PARP activity by PARP inhibitors (14,15-21). However, disruption to other proteins involved in HR DNA repair other than in BRCA may have the same effect on PARP inhibitor sensitivity (26). A further important mechanism of action for PARPi is the trapping of the PARP1 and PARP2 enzymes at damaged DNA causing cytotoxicity (27). Recent studies have revealed a more complex web of fundamental cellular processes that PARP1 is involved other than in DNA repair such as chromatin remodeling and transcription or regulation of the cell cycle (28).

There are currently three PARP inhibitors approved, for either monotherapy or maintenance therapy in patients with advanced OC. Two are approved in patients with BRCA 1 and 2 mutations with advanced OC having undergone therapy with >3 chemotherapies (Olaparib) or >2 chemotherapies (Rucaparib). All three PARPi are approved as maintenance therapy in patients with advanced OC who are in complete or partial response to platinum based chemotherapy.

The effectiveness of PARP inhibitors as monotherapy or as maintenance therapy has substantially improved the progression free survival and overall survival in OC patients. PARP inhibitors as single agents or as potential enhancers of cytotoxic agents that provoke DNA damage, such as alkylating agents and chemotherapy (18) have been investigated in a number of studies.

1.3. Name and Description of the Investigational Product

[redacted]

1.4. Summary of Prior Pre-Clinical and Clinical Studies

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1.5. RISKS / BENEFITS ASSESSMENT

The inclusion and exclusion criteria, screening, and safety monitoring practices employed by this protocol, and physical examination are adequate to protect the subject's safety and detect all TEAEs.

1.5.1. Pregnancy

Any pregnancy that occurs while taking study drug should be recorded using a Pregnancy Report Form and reported immediately to Sponsor within 24 hours of learning of the pregnancy. See Section 9.5 for more information on reporting of pregnancy.

1.5.2. Unknown Risks

Research inherently carries the possibility of risks that are unknown or that cannot be foreseen based on current information.

1.5.3. 2X-121

In the phase 1 study, fatigue was the dose limiting toxicity. Apart from fatigue in the phase 1 study as well as in the two ongoing phase 2 studies, the most frequent treatment-emergent adverse events are gastrointestinal related (nausea, diarrhea, loss of appetite and vomiting). Phototoxicity and allergic reactions with maculo-papular rash and periorbital edema are seen.

Refer to the Investigator's Brochure for a complete list of risks associated with 2X-121.

1.5.4. Dovitinib

Across the various dovitinib studies, the most commonly reported non-laboratory AEs for both continuous dosing and 5 days on/2 days off dosing, were nausea, fatigue, diarrhea, vomiting and decreased appetite. Commonly reported AEs were reversible and manageable; most were mild or moderate in severity (CTCAE grade 1 or 2).

Refer to the Investigator's Brochure for a complete list of risks associated with dovitinib.

1.5.5. Benefits

Subjects participating in this study will contribute to the development of a drugs which has the potential to become a treatment option for them and others in the future.

[redacted]

1.6.2. Rationale for Dose Selection

[redacted]

[redacted]

2. STUDY OBJECTIVES AND OUTCOME MEASURES

2.1. STUDY OBJECTIVES

2.1.1. Primary Objective

The primary objective of this study is:

Part 1

- To determine the maximum tolerated dose (MTD) of 2X-121 monotherapy given twice daily (BID) in patients with advanced solid tumors.

Part 2

- To determine the MTD of dovitinib given in combination with 2X-121 (MTD) in patients with advanced solid tumors.

2.1.2. Secondary Objective

The secondary objectives of this study are:

- To evaluate the anti-tumor activity of 2X-121 monotherapy (Part 1) and in combination with dovitinib (Part 2) in patients with advanced solid tumors.
- To evaluate the pharmacokinetics (PK) of 2X-121 monotherapy (Part 1) and in combination with dovitinib (Part 2) in patients with advanced solid tumors.
- To evaluate the safety and tolerability of 2X-121 monotherapy (Part 1) and in combination with dovitinib (Part 2) in patients with advanced solid tumors.

[redacted]

2.2. STUDY OUTCOME MEASURES

2.2.1. Primary Outcome Measure

The primary outcome measures in this study are:

Part 1

- Determination of the MTD of 2X-121 monotherapy.

  Note: The MTD is defined as 1 dose level below the dose in which dose limiting toxicities (DLTs) were observed in ≥ 33% of the participants during the first 14 days of the main treatment period.

Part 2

- Determination of the MTD of dovitinib given in combination with 2X-121 (MTD).

  Note: The MTD is defined as 1 dose level below the dose in which dose limiting toxicities (DLTs) were observed in ≥ 33% of the participants during the first 14 days of the main treatment period.

2.2.2. Secondary Outcome Measures

2.2.2.1. Antitumor Activity

The secondary anti-tumor activity outcome measures in this study are:

- To evaluate the objective response rate (ORR) of 2X-121 monotherapy (Part 1) and in combination with dovitinib (Part 2).

  ORR is defined as the proportion of subjects who achieve a Complete Response (CR) or Partial Response (PR) as assessed by RECIST v1.1.

- To evaluate the duration of overall response (DOR) of 2X-121 monotherapy (Part 1) and in combination with dovitinib (Part 2).

  DOR is defined as the time in months from the first documented CR or PR per RECIST v. 1.1 to disease recurrence or disease progression (PD) whichever occurs first.

- To evaluate progression free survival (PFS) of 2X-121 monotherapy (Part 1) and in combination with dovitinib (Part 2).

  PFS is defined as the time from study treatment initiation to either first observation of progressive disease or occurrence of death.

- To evaluate overall survival (OS) of 2X-121 monotherapy (Part 1) and in combination with dovitinib (Part 2).

  OS is defined as the time from study treatment initiation to death from any cause or last day known to be alive.

2.2.2.2. Pharmacokinetic (PK) Outcome Measures

The following pharmacokinetic parameters will be calculated for 2X-121 monotherapy at each dose level (Part 1) and for 2X-121 (MTD) in combination with dovitinib at each dose level (Part 2):

- Maximum concentration of 2X-121 (C_{max}) and dovitinib (C_{max})
- Area under the plasma-time concentration curve (AUC)
- Elimination half-life of 2X-121 ($t_{½}$) and dovitinib ($t_{½}$)
- Time to maximum plasma concentration (t_{max})
- Total body clearance of 2X-121 (Cl/F) and dovitinib (Cl/F)

- Apparent volume of distribution (Vz/F)

2.2.2.3. Safety Outcome Measures

The safety and overall tolerability of 2X-121 and dovitinib will be evaluated based on:

- Dose Limiting Toxicities
- Incidence and severity of treatment-emergent adverse events (TEAEs), including serious adverse events and adverse events resulting in permanent discontinuation of study treatment
- Laboratory data changes from baseline to subsequent scheduled visits
- Changes in physical examinations from baseline to subsequent scheduled visits
- Changes in vital signs from baseline to subsequent scheduled visits
- Changes in Eastern Cooperative Oncology Group (ECOG) performance status from baseline to subsequent scheduled visits
- Changes of electrocardiogram (ECG) results from baseline to subsequent scheduled visits

[redacted]

[redacted]

- [redacted]
- [redacted]

3. STUDY DESIGN

3.1. GENERAL SCHEMA

This is a Phase Ib, two-part, multi-center study. In Part 1, the study will evaluate the safety and tolerability, antitumor activity, pharmacokinetics, and determine the maximum tolerated dose (MTD) of 2X-121 monotherapy (at BID regimen) in patients with advanced solid tumors. In Part 2, the study will evaluate safety and tolerability, antitumor activity, and pharmacokinetics of 2X-121 (MTD) and dovitinib as combination therapy, and determine the MTD of dovitinib when given in combination with the MTD of 2X-121 determined in Part 1.

Part 1

This part of the study will follow an accelerated titration method followed by a standard "3+3" design to determine the MTD of 2X-121. The MTD is defined as one dose level (cohort) below the dose in which dose limiting toxicities (DLTs) were observed in ≥ 33% of the participants.

The calculation of the sample size for this trial is based on the traditional 3 + 3 dose escalation scheme which is conducted as follows:

- Subjects are treated in cohorts of one (Cohort 1) or three (Cohorts 2-3) subjects, each receiving the same dose. For the assessment of a DLT, subjects are observed for 14 days.
- In Cohort 1, if the one subject does not exhibit a DLT, the next cohort of three subjects will receive the next higher dose (Cohort 2). In Cohort 2, if none of the three subjects exhibits a DLT, the next cohort of three subjects will receive the next higher dose (Cohort 3).
- Otherwise, if at least one subject of a cohort exhibits a DLT, a further cohort of three subjects is treated at the same dose level (cohort) without escalating the dose.
- If exactly one out of the six subjects treated at this dose exhibits a DLT, the trial continues as planned at the next higher dose level (cohort).
- If two or more subjects out of the six subjects treated at this dose exhibit a DLT, the dose escalation stops at that level and the next lower dose is considered as the MTD. When the escalation has stopped, additional subjects will be treated at the MTD to a total of six subjects.

[redacted]

[redacted]

Part 2

In Part 2 of the study, patients will receive dovitinib in combination with the MTD of 2X-121 determined in Part 1. Part 2 will follow a "3+3" design to determine the MTD of dovitinib when given in combination with 2X-121. The MTD is defined as one dose level (cohort) below the dose in which dose limiting toxicities (DLTs) were observed in ≥ 33% of the participants. See Part 1 above for definition of DLTs.

[redacted]

[redacted]

3.2. STUDY CENTER

Up to five study centers

3.3. STUDY POPULATION

The target population for this study will be patients with locally advanced or metastatic solid tumors.

3.4. ELIGIBILITY CRITERIA

3.4.1. Inclusion Criteria

Subjects will be eligible for enrollment in the study only if they meet ALL the following criteria at time of Screening:

1. Age 18 years or older.
2. Histologically or cytological documented solid tumor.
3. Available tumor biopsy (most recent) for DRP® analysis.
4. Measurable disease by CT scan or MRI if possible.

5. Performance status of ECOG ≤ 1.
6. Recovered to Grade <1 or baseline from prior surgery or from acute toxicities of prior radiotherapy, or from treatment with cytotoxic, hormonal or biologic agents.
7. ≥ 2 weeks must have elapsed since any prior surgery or therapy with G-CSF and GM-CSF.
8. Patients with intracranial disease must be on stable or decreased level of steroid therapy (e.g. dexamethasone) for at least 7 days prior to baseline MRI. Non-enzymatic inducing anti-epileptic drugs are allowed.
9. Adequate conditions as evidenced by the following clinical laboratory values:
    a. Absolute neutrophils count (ANC) ≥ 1500/mm^3 (1.5 x 10^3/mL)
    b. Hemoglobin > 10.0 g/dL
    c. Platelets ≥ 100,000/mm^3 (≥ 100 x 10^9/L)
    d. Alanine aminotransferase (ALT) and aspartate aminotransferase (AST) ≤ 3 x ULN or ≤5x ULN in presence of liver metastases
    e. Serum bilirubin ≤ 1.5 ULN
    f. Alkaline phosphatase ≤ 2.5 x ULN
    g. Creatinine ≤ 1.5 ULN
    h. Blood urea nitrogen (BUN) ≤2X ULN.
10. Life expectancy equal or longer than 3 months.
11. The subject is willing to provide written informed consent to participate in the study after reading the informed consent form and the information provided and has had the opportunity to discuss the study with the investigator or designee.
12. The subject is able to communicate satisfactorily with the investigator and to participate in, and comply with, the requirements of the study.
13. The subject is able to understand the nature of the study and any potential hazards associated with participating in it.
14. Negative pregnancy test for female subjects of childbearing potential. Women of childbearing potential (WOCBP) and Women of non-childbearing potential are eligible to participate. Both women of childbearing potential and women of non-childbearing potential should use an approved method of birth control and agree to continue to use this method for the duration of the study (and for 90 days after taking the last dose of study drug).

    Acceptable methods of contraception include abstinence, female subject/partner's use of hormonal contraceptive (oral, implanted, or injected) in conjunction with a barrier method (WOCBP only) (e.g., diaphragm, cervical cap, male condom, and female condom and

spermicidal foam, sponges, and film), female subject/partner's use of an intrauterine device (IUD), or if the female subject/partner is surgically sterile for at least three months before screening or 2 years post-menopausal at time of screening. All male subjects/partners must agree to consistently and correctly use a condom for the duration of the study and for 90 days after taking the study drug. In addition, subjects may not donate sperm for the duration of the study and for 90 days after taking study drug.

3.4.2. Exclusion Criteria

Subjects meeting ANY of the following criteria at time of Screening will be excluded from enrollment:

1. Concurrent chemotherapy, radiotherapy, hormonal therapy, or other investigational drug except non-disease related conditions (e.g. insulin for diabetes) during study period.
2. Other malignancy with exception of curative treated non-melanoma skin cancer or cervical carcinoma in situ within 5 years prior to entering the study.
3. Any active infection requiring parenteral or oral antibiotic treatment.
4. History of coagulation or bleeding disorder or subject currently on therapeutic anticoagulant medication.

   Note: Prophylactic doses of heparin or low molecular weight heparin are allowed.
5. Known HIV positivity.
6. Known active hepatitis B or C.
7. Clinically significant (i.e. active) cardiovascular disease:
   a. Stroke within ≤ 6 months prior to day 1
   b. Transient ischemic attack (TIA) within ≤ 6 months prior to day 1
   c. Myocardial infarction within ≤ 6 months prior to day 1
   d. Unstable angina
   e. New York Heart Association (NYHA) Class II or greater congestive heart failure (CHF)
   f. Serious cardiac arrhythmia requiring medication.
8. Other medications or conditions, including surgery, that in the Investigator’s opinion would contraindicate study participation for safety reasons or interfere with the interpretation of study results.
9. Inability to take oral medication, or malabsorption syndrome or any other uncontrolled gastrointestinal condition (e.g., nausea, diarrhea, or vomiting) that might impair the bioavailability of 2X-121 and dovitinib.

10. Requiring immediate palliative treatment of any kind including surgery and/or radiotherapy.
11. Female patients who are pregnant or breast-feeding (pregnancy test with a positive result before study entry).

4. STUDY SCHEDULE

4.1. OVERVIEW

The study Schedule of Assessments in presented in Table 4-3 and Table 4-4. See Section 7 for a detailed description of each protocol assessment and procedure. The study is divided into three phases: Screening Phase, Treatment Phase, and Follow-Up Phase.

Part 1

The dose levels to be evaluated in Part 1 are shown below:

Table 4-1: Part 1 Dose Cohorts

Dose Cohort	2X-121 Monotherapy Dose (BID)
Cohort 1	600 mg (morning dose: 200 mg + evening dose: 400 mg)
Cohort 2	800 mg (morning dose: 400 mg + evening dose: 400 mg)
Cohort 3	1000 mg (morning dose: 400 mg + evening dose: 600 mg)

On Day 1 of first treatment cycle (C1D1), patients will be administered 2X-121 monotherapy as oral capsules taken twice daily. Each treatment cycle will consist of 28 days.

[redacted]

Once the MTD has been determined, subjects enrolled in lower dose cohorts will be allowed to escalate the dose to the MTD, if acceptable per the Investigator's discretion. Subjects will be eligible for continuing treatment in absence of progressive disease or unacceptable toxicity or withdrawal of consent.

Part 2

The dose levels to be evaluated in Part 2 are shown below:

Table 4-2: Part 2 Dose Cohorts

Dose Cohort	Combination 2X-121 (BID administration) and Dovitinib
Cohort 1	2X-121 (MTD) + 300 mg dovitinib
Cohort 2	2X-121 (MTD) + 400 mg dovitinib
Cohort 3	2X-121 (MTD) + 500 mg dovitinib

Dovitinib will be administered once daily (morning) on a 5 days on/2 days off schedule. In a 28 day cycle, dovitinib will be administered C1D1 - C1D5, C1D8 - C1D12, C1D15 - C1D19, and C1D22 - C1D26.

[redacted]

Once the MTD has been determined, subjects enrolled in lower dose cohorts will be allowed to escalate the dose to the MTD, if acceptable per the Investigator's discretion. Subjects will be eligible for continuing treatment in absence of progressive disease or unacceptable toxicity or withdrawal of consent.

An additional 3-6 patients will receive 2X-121 in combination with dovitinib once the MTD dose is determined.

Table 4-3: Schedule of Assessments – Part 1

Study Phase	Screening Phase	Treatment Phase								Follow-up Phase	
		Treatment Cycle 1 (28 Days)			Treatment Cycle 2 (28 Days)			Subsequent Treatment Cycles (28 Days)			
Visit	SV	C1D1	C1D7	C1D15	C2D1	C2D7	C2D15	CXD1	CXD15	EOT	FU [15]
Window	Within 28 Days of C1D1		±1 Day	±1 Day	±1 Day	±1 Day	±1 Day	±1 Day	±1 Day	30 Days (±7) after last treatment dose	Every 3 months after EOT
[redacted]											
[redacted]	X										
[redacted]	X										
[redacted]	X										
[redacted]	X										
[redacted]	X	X	X	X	X		X	X		X	
[redacted]	X	X [5]	X [5]	X [5]	X [5]	X [5]	X [5]	X [5]	X [5]	X [5]	
[redacted]	X	X		X[6]	X[6]		X[6]	X[6]	X[6]	X	
[redacted]	X	X			X			X		X	
[redacted]	X	X			X			X		X	
[redacted]		X									X
[redacted]	X	X	X	X	X	X	X	X	X	X	X
[redacted]		X	X	X	X	X	X	X	X	X	X
[redacted]											
[redacted]	X [8]							X [7]		X [7]	
[redacted]	X [8]							X [7]		X [7]	
[redacted]	X [8]							X [7]		X [7]	
[redacted]											
[redacted]	X	X	X	X	X	X	X	X	X	X	
[redacted]	X	X		X	X		X	X	X	X	
[redacted]	X	X			X			X		X	
[redacted]	X	X								X	
[redacted]		X	X	X	X			X			
[redacted]	X										
[redacted]											
[redacted]											

[redacted]

[redacted]

Table 4-4: Schedule of Assessments – Part 2

Study Phase	Screening Phase	Treatment Phase								Follow-Up Phase	
		Treatment Cycle 1 (28 Days)			Treatment Cycle 2 (28 Days)			Subsequent Treatment Cycles (28 Days)			
Visit	SV	C1D1	C1D7	C1D15	C2D1	C2D7	C2D15	CXD1	CXD15	EOT	FU [16]
Window	Within 28 Days of C1D1		±1 Day	±1 Day	±1 Day	±1 Day	±1 Day	±1 Day	±1 Day	30 Days (±7) after last treatment dose	Every 3 months after EOT
[redacted]											
[redacted]	X										
[redacted]	X										
[redacted]	X										
[redacted]	X										
[redacted]	X	X	X	X	X		X	X		X	
[redacted]	X	X [5]	X [5]	X [5]	X [5]	X [5]	X [5]	X [5]	X [5]	X [5]	
[redacted]	X	X		X[6]	X[6]		X[6]	X[6]	X[6]	X	
[redacted]	X	X			X			X		X	
[redacted]	X	X			X			X		X	
[redacted]		X									X
[redacted]	X	X	X	X	X	X	X	X	X	X	X
[redacted]		X	X	X	X	X	X	X	X	X	X
[redacted]											
[redacted]	X [8]							X [7]		X [7]	
[redacted]	X [8]							X [7]		X [7]	
[redacted]	X [8]							X [7]		X [7]	
[redacted]											
[redacted]	X	X	X	X	X	X	X	X	X	X	
[redacted]	X	X		X	X		X	X	X	X	
[redacted]	X	X			X			X		X	
[redacted]	X	X								X	
[redacted]		X	X	X	X			X			
[redacted]	X										
[redacted]											
[redacted]											
[redacted]		X		X	X		X	X	X		

[redacted]

4.2. SCREENING PHASE

The subject (or Legally Acceptable Representative (LAR)) will sign and date the informed consent form (ICF) and Health Insurance Portability Accountability Act (HIPAA) authorization (according to site policy and practices) prior to any study-related procedures. All study centers will be instructed to maintain the study-specific screening and enrollment logs at their sites.

4.2.1. Screening Visit: Up to 28 days

Subjects will be screened for enrollment within 28 days prior to Treatment Cycle 1, Day 1.

The assessments described in this section will be the same for both Part 1 and Part 2 of the study, unless otherwise noted.

Subjects will be screened in accordance with predefined entrance criteria as described in Section 3.4. The following procedures will be performed at Screening:

[redacted]

All subjects who fail to meet eligibility criteria are considered screen failures and are exited from the study without further evaluation.

Note: If a subject initially fails to meet inclusion/exclusion criteria and is later reconsidered for participation, the subject will be re-consented and assigned a new unique identification number at the time of re-screening. Subjects who fail their first screening attempt may be re-screened a maximum of once and may be enrolled if they are found to meet all inclusion and no exclusion criteria when re-screened.

All screening information for subjects who meet eligibility criteria will be transcribed onto the appropriate page of the Case Report Form (CRF). See Section 7.2.1 for procedures for documenting screening failures.

4.3. TREATMENT PHASE

Subjects who meet all eligibility criteria during Screening are to be treated.

Each treatment cycle will consist of 28 days.

4.3.1. Treatment Cycle 1

[redacted]

[redacted]

[redacted]

- [redacted]
- [redacted]
- [redacted]
- [redacted]

[redacted]

[redacted]

- [redacted]
- [redacted]
- [redacted]
- [redacted]
  - [redacted]
- [redacted]

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- [redacted]
- [redacted]
- [redacted]
  - [redacted]
- [redacted]
- [redacted]
- [redacted]

4.3.2. Treatment Cycle 2

[redacted]

[redacted]

4.3.3. Subsequent Treatment Cycles

Subjects will be eligible for continuing treatment in absence of progressive disease or unacceptable toxicity or withdrawal of consent.

[redacted]

- [redacted]

4.4. FOLLOW-UP PHASE

4.4.1. End of Treatment Visit (EOT)

An end of treatment visit will be conducted 30 (± 7) days after last treatment dose (i.e., after last dose of 2X-121).

The assessments performed at this visit will include:

- [redacted]
- [redacted]
- [redacted]
- [redacted]
  - [redacted]
  - [redacted]
  - [redacted]
- [redacted]
- [redacted]
- [redacted]
- [redacted]
  - [redacted]
  - [redacted]
  - [redacted]

4.4.2. Follow Up Visit (FU)

Follow-up visits will be done for survival status, by clinic visits or phone or another method of contact at least every 3 months from the date of treatment discontinuation. All subsequent anti-cancer treatments are to be reported.

All patients are to be followed for 2 years or until death whichever comes first.

The assessments performed at these visits will include:

- [redacted]
- [redacted]
- [redacted]

4.5. UNSCHEDULED VISITS

In the event that the subject will return to clinic at a time other than a regularly scheduled study visit, the visit will be regarded as an unscheduled visit. This includes when subjects require rescue therapy or need interim care due to chronic illness. Assessments at unscheduled visits are at the discretion of the Investigator. All pertinent findings, including adverse events or changes in medications, will be noted in the CRF.

5. SUBJECT COMPLETION, WITHDRAWAL AND CRITERIA FOR STOPPING THE STUDY

5.1. SUBJECT COMPLETION

5.1.1. Definition of Study Treatment Completion

5.1.1.1. End of Treatment (EOT) Completion

A subject is considered to have completed the treatment phase once they complete the EOT visit conducted 30 (±7) days after the last treatment visit (i.e., after last dose of 2X-121).

5.1.1.2. End of Follow-Up (EOFU) Completion

A subject is considered to have completed the follow-up phase once all survival follow-up visit assessments after treatment discontinuation have been performed or until death, whichever occurs first.

5.2. SUBJECT WITHDRAWAL

At any point during the study all subjects have the right to withdraw without prejudice to future care. Documentation to whether or not each subject completed the clinical study will be recorded. If for any subject, study treatment was discontinued, the reason(s) will be documented.

5.2.1. Subject Discontinuation

The Investigator can discontinue a subject at any time if in their clinical judgment considers to be medically necessary. Investigators considering discontinuing study treatment should contact the medical monitor prior to such discontinuation. Subjects who have study treatment discontinued will continue to be followed, per protocol, whenever possible. Subjects who have study treatment discontinued due to a serious adverse event will be followed until resolution or stabilization of the event as described in Section 9.4.1 (SAE Follow-Up).

5.2.2. Subject Replacement

This study will follow a 3+3 design during Part 1 and Part 2. Three subjects within a dose level must be observed for one cycle (14 days) before accrual to the next higher dose level may begin. If a subject is withdrawn from the study prior to completing one cycle of therapy for any reason other than experiencing a DLT, an additional subject may be added to that dose level.

Note: Subjects who discontinue treatment prior to completing one cycle of therapy due to experiencing a DLT will not be replaced.

5.2.3. Data Collected from Withdrawn Subjects

In the case of subject withdrawal, the appropriate disposition CRF page will be completed for Treatment or Follow-Up, as applicable.

Every attempt should be made to collect follow-up information. The reason for withdrawal from the study will be recorded in the source documents and on the appropriate page of the CRF.

Before a subject is identified as lost-to-follow up, the site should make all reasonable efforts to contact the subject. These attempts must be documented and should include at a minimum one phone call and one certified letter.

In the event that a subject is withdrawn from the study at any time due to an AE or SAE, the procedures stated in Section 9.2 (AE) or Section 9.4 (SAE) must be followed.

5.3. STUDY STOPPING CRITERIA

[redacted]

6. STUDY TREATMENT

6.1. 2X-121

2X-121 is novel dual PARP1/2 and tankyrase supplied as hard gelatin capsules each containing 200 mg investigational medicine product (IMP).

Subjects will receive twice daily oral administration of 2X-121 monotherapy in Part 1 of the study.

Dose Cohort	2X-121 Monotherapy Dose (BID)
Cohort 1	600 mg (morning dose: 200 mg + evening dose: 400 mg)
Cohort 2	800 mg (morning dose: 400 mg + evening dose: 400 mg)
Cohort 3	1000 mg (morning dose: 400 mg + evening dose: 600 mg)

6.1.1. Packaging and Labeling

Study treatment will be labeled, according to the regulatory guidelines, as an investigational product to ensure that it will not be used outside of the clinical investigation. The Sponsor, protocol number, expiry date and time, and any additional relevant information will appear on the pack label.

6.1.2. Storage and Handling

[redacted]

All study treatment materials will be stored in their original packaging in a safe and secure location at the investigational site. Study treatment material will be disposed of in accordance with institutional and /or local requirements.

6.1.3. Drug Interactions

[redacted]

[redacted]

6.2. DOVITINIB

Dovitinib (TKI258), a pan-TKI, is an inhibitor of type III-V receptor tyrosine kinases (RTKs) that mediate both endothelial and tumor cell proliferation and survival. Dovitinib is formulated as a film-coated tablet of 100 mg strength.

Subjects will receive daily oral administration of dovitinib in combination with 2X-121 in Part 2 of the study.

Dose Cohort	Combination 2X-121 (BID administration) and Dovitinib
Cohort 1	2X-121 (MTD) + 300 mg dovitinib
Cohort 2	2X-121 (MTD) + 400 mg dovitinib
Cohort 3	2X-121 (MTD) + 500 mg dovitinib

6.2.1. Packaging and Labeling

[redacted]

Study treatment will be labeled, according to the regulatory guidelines, as an investigational product to ensure that it will not be used outside of the clinical investigation. The Sponsor, protocol number, expiry date and time, and any additional relevant information will appear on the pack label.

6.2.2. Storage and Handling

[redacted]

All study treatment materials will be stored in their original packaging in a safe and secure location at the investigational site. Study treatment material will be disposed of in accordance with institutional and /or local requirements.

6.2.3. Drug Interactions

[redacted]

6.3. ADMINISTRATION

6.3.1. 2X-121

A twice daily dose of 2X-121 will be administered as hard gelatin capsules, independent of food intake in a 28 days cycle. The capsules are to be administered twice a day about the same time each treatment day. In Part 2 of the study, the 2X-121 morning dose will be administered at the same time as dovitinib.

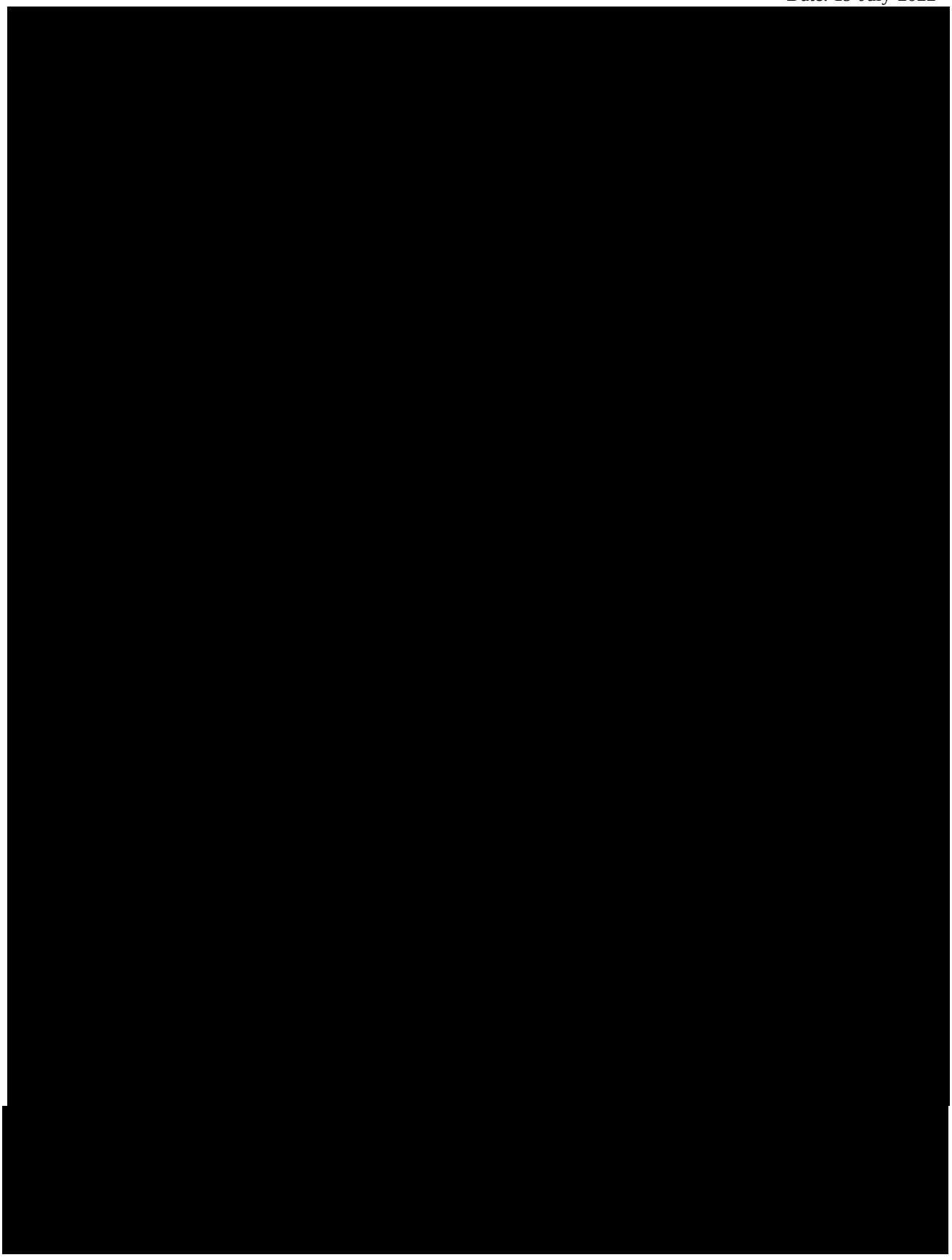
6.3.2. Dovitinib

Dovitinib will be administered once daily (morning) on a 5 days on/2 days off schedule independent of food intake at the same time as the 2X-121 morning dose. In a 28 day cycle, dovitinib will be administered C1D1 - C1D5, C1D8 - C1D12, C1D15 - C1D19, and C1D22 - C1D26.

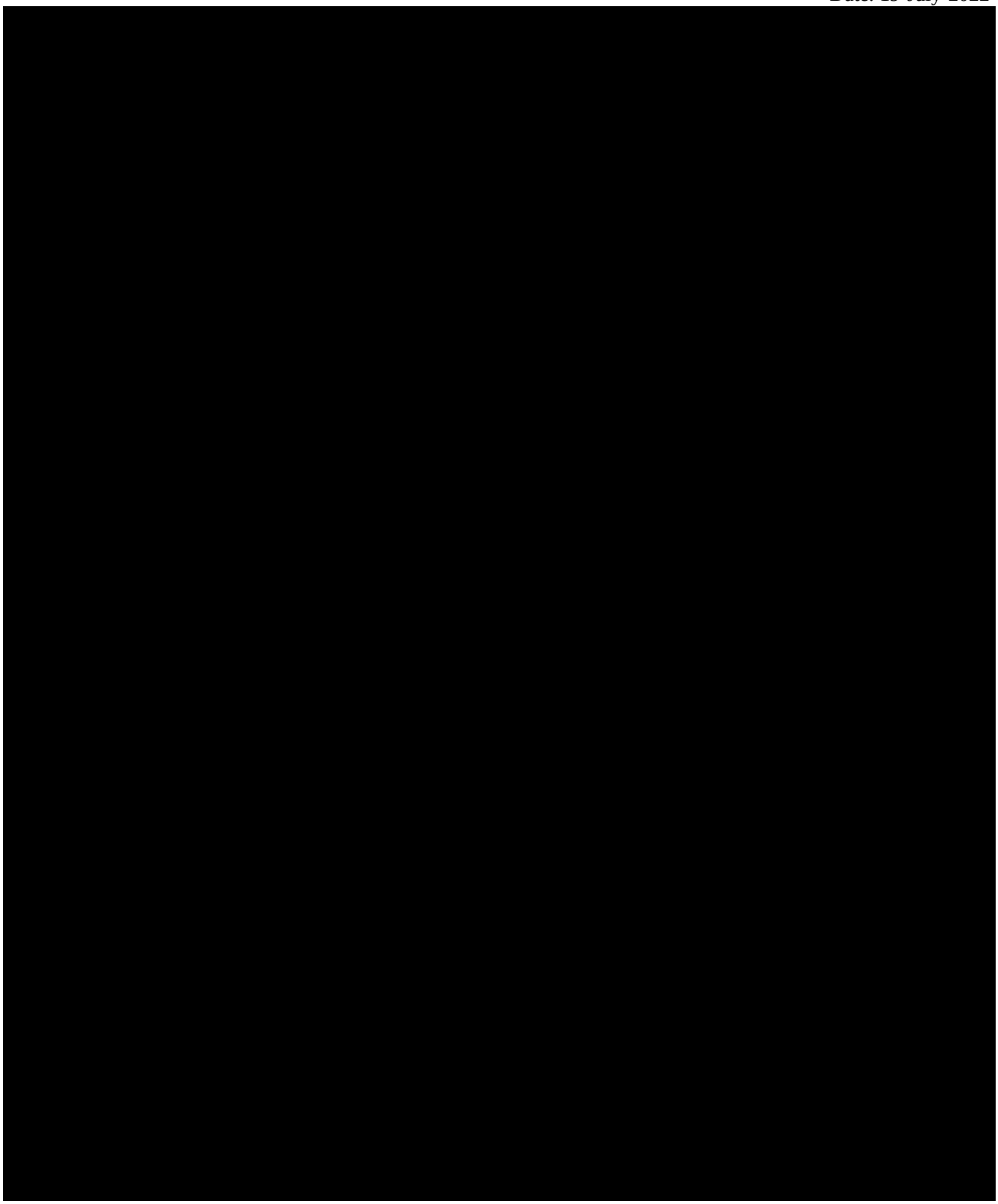
6.3.3. Toxicity Management

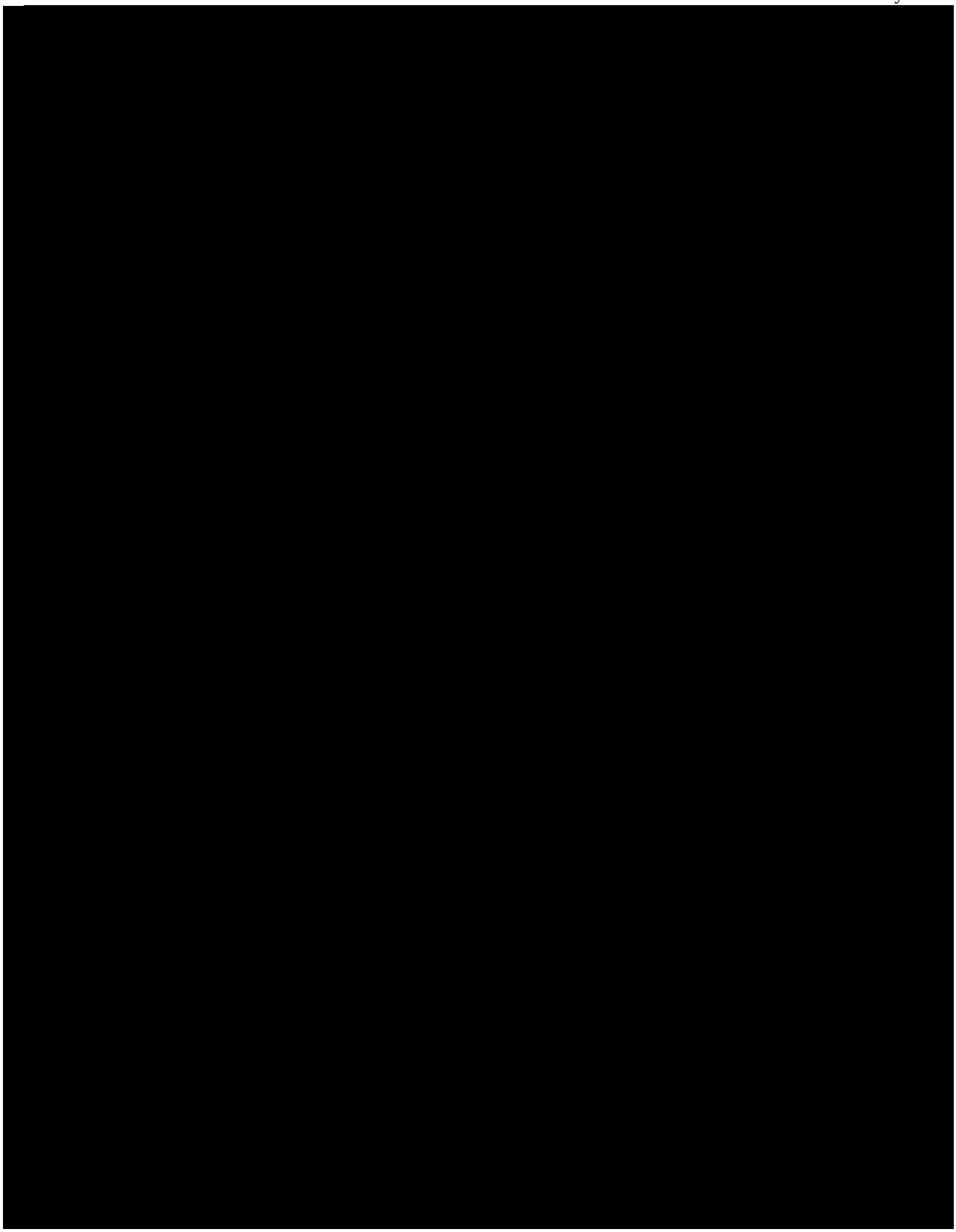
[redacted]

[redacted]



[redacted]





6.4. PRODUCT ORDERING

Investigational products will be provided to the investigational site by the sponsor for the duration of the study.

6.4.1. Product Disposition

All drug supplies are to be used only for this protocol and not for any other purpose. The investigator must not destroy any drug labels or any partially used or unused drug supply until instructed by the Sponsor. At the conclusion of the study and as appropriate during the course of the study, the investigator will return all used and unused drug containers and drug labels to the drug distributor as directed by the Sponsor.

6.4.2. Product Accountability

The Investigator or designee will verify the contents of each shipment against the shipping documents. Verification of IP receipt will be documented according to the Sponsor's requirements.

An accountability log will be provided to the site for use by the Investigator to maintain current and accurate inventory records (batch, expiry, and quantity) covering the dispensing and the destruction of the IP.

At the conclusion of the study the Investigator must return or destroy all IP as instructed by the

Sponsor. Further details will be provided in the Pharmacy Manual.

6.5. CONCOMITANT MEDICATIONS

6.5.1. Prohibited Medications and Therapies

[redacted]

6.5.2. Allowable Medications and Therapies

The following medications and therapies are allowed during the study, if in the judgment of the Investigator, they are required for proper care of the study subject:

- Other medications/therapies that are not otherwise prohibited and, in the judgment of the Investigator, are required for proper medical care.

7. DESCRIPTION OF PROTOCOL ASSESSMENTS AND PROCEDURES

7.1. INFORMED CONSENT

A written informed consent will be obtained for this study by the Investigator or designee from all subjects prior to performance of any protocol-specific procedure. This study will be conducted in accordance with the provisions of the Declaration of Helsinki.

The Investigator must comply with applicable regulatory requirements and must adhere to the Good Clinical Practice (GCP) in the process of obtaining and documenting the informed consent. The Investigator, or designee, must also inform subjects of all pertinent aspects of the study. Before written informed consent is obtained from the subject, the Investigator or a person designated by the Investigator, must provide the subject enough time and opportunity to inquire about the details of the study and to decide whether or not to participate in the trial. All questions addressed by the subject about the study must be answered to the satisfaction of the subject. Prior to the subject's participation in the trial, the written informed consent must be signed and personally dated by the subject and by the person who conducted the informed consent discussion. Authorization for release of protected health information must also be obtained, as per local policies.

7.2. ASSESSMENT OF ELIGIBILITY

The Investigator must assess subject' continued eligibility for the study as per the Inclusion and Exclusion criteria, during the Screening Phase. The eligibility criteria are described in Section 3.4.1 (Inclusion Criteria) and Section 3.4.2 (Exclusion Criteria). In the event that the subject is not suitable or eligible for the study, the subject will be considered "screen failure".

7.2.1. Re-screening

A subject who signed a consent form but did not meet the inclusion/exclusion criteria is classified as a screen failure.

Note: If a subject initially fails to meet inclusion/exclusion criteria and is later reconsidered for participation, the subject will be re-consented and assigned a new unique identification number at the time of re-screening. Subjects who fail their first screening attempt may be re-screened a maximum of once and may be enrolled if they are found to meet all inclusion and no exclusion criteria when re-screened.

For consented subjects who do not meet eligibility criteria, a Screen Failure Case Report Form (CRF) will be completed. The Screen Failure CRF will contain the following details: the subject identification number, the date of ICF signature, demographic information (see Section 7.3), and the reason for screen failure. No additional information will be required for subjects who fail screening.

7.3. DEMOGRAPHIC INFORMATION

In this study the demographic information will include:

- Dates of ICF signature
- Date of birth
- Gender
- Race (American Indian or Alaska Native, Asian, Black or African American, Native Hawaiian or Other Pacific Islander, White, Not Reported, or Unknown)
- Ethnicity (Hispanic or Latino, Not Hispanic or Latino, Not Reported, or Unknown)
- Use of tobacco or nicotine replacement products and e-cigarettes

7.4. MEDICAL HISTORY

A medical history will be recorded during the Screening Phase and will include:

- All ongoing medical conditions
- All previously resolved medical conditions that are relevant in the judgment of the Investigator
- Any prior medical conditions that have resolved within the last year

Events that emerge prior to the first treatment will be recorded in the medical history and not as AEs. Aside from being used to determine subject eligibility, this information will permit the Investigator to record the nature, duration, and severity of any ongoing baseline medical conditions prior to the subject's receiving investigational product treatment.

For each relevant history, the following will be documented:

- Disease/disorder/condition
- Date of diagnosis
- History status (resolved or ongoing).

7.5. PHYSICAL EXAMINATION

The physical examination will include routine examinations for the following:

- Constitutional/General Appearance
- Head, Ears, Eyes, Nose, Throat (HEENT)
- Neurologic

- Cardiovascular
- Musculoskeletal and Extremities
- Dermatologic
- Respiratory
- Gastrointestinal
- Genitourinary
- Lymphatic
- Psychiatric

Each abnormality will be recorded and the Investigator will record an assessment of its clinical significance.

7.6. VITAL SIGNS, HEIGHT AND WEIGHT

The following vital signs will be collected:

- Systolic and Diastolic Blood Pressure
- Heart Rate
- Respiratory Rate
- Oral Temperature

Blood pressure and heart rate will be obtained in the supine position after subject has been resting for 5 minutes.

In addition, the following will be recorded:

- Height (Only performed at Screening visit)
- Weight
- Body Mass Index

7.7. CONCOMITANT MEDICATION

The subject may be applied any medications judged necessary by the Investigator, provided such medications are not listed in Section 6.5.1.

All medications and therapies administered or taken by the subject beginning 30 days prior to Screening Visit and throughout the study will be recorded in the source documents and on the appropriate page of the Case Report Form (CRF). Subjects must be questioned at each study visit

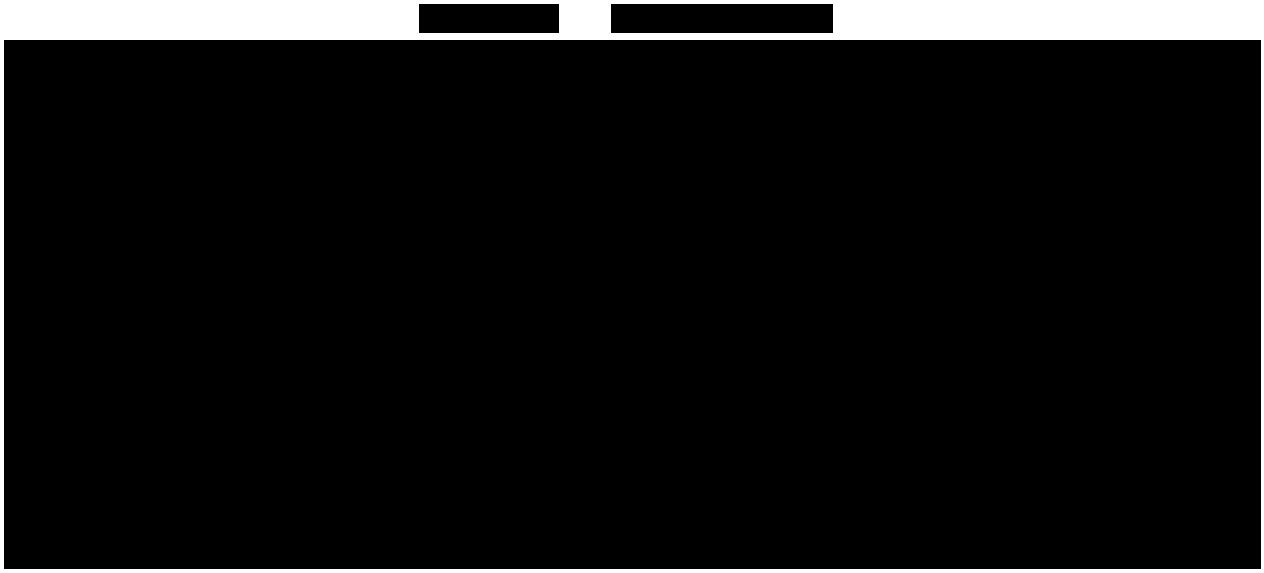
concerning any new medications or changes in current medications including over-the-counter medication and topical medication.

For each medication and non-study treatment, the following will be documented:

- Medication/treatment name (generic name may be used if trade name is unknown)
- Dose, unit, and frequency of dosing (individual dosages, not total daily dose).
    - **Note:** *Each new dose of medication should be recorded as a separate entry, with the exception of medications that are given on a sliding scale. For these, it is acceptable to enter the range of the dosage, including the start and stop dates for which the specified dosage range was used.*
- Route of dosing
- Indication for use
- The start date
- The stop date (if medication/therapy is not ongoing).

7.8. CLINICAL LABORATORY ASSESSMENTS

All laboratory assessments will be reviewed by the Investigator. If clinically significant findings, as determined by the Investigator, are recorded for a particular symptom, sign or abnormal measurement, that measurement will be repeated at medically appropriate intervals until the value returns to an acceptable range, a specific diagnosis is established, or the condition is otherwise explained.



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[redacted]

7.9.1.1. [redacted]

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[redacted]

7.10. 12-LEAD ELECTROCARDIOGRAM

12-Lead ECG will be performed per the site standard procedures. [redacted]

[redacted]

[redacted]

8. STATISTICAL CONSIDERATIONS

This section presents general information about statistical considerations and concepts such as randomization, covariates/stratification, statistical power, sample size, and a brief discussion on analysis methodology, as well as some data conventions. Detailed descriptions of the statistical analysis methods and data conventions will be included in a separate document; i.e., the Statistical Analysis Plan (SAP).

8.1. TREATMENT GROUPS

Refer to Table 4-1 and Table 4-2 for description of treatment groups.

8.2. STUDY OUTCOME MEASURES

Refer to Section 2.2 for list of study outcome measures.

8.3. SAMPLE SIZE DETERMINATION AND RATIONALE

A sample size of up to 16 subjects in Part 1 and in up to 24 subjects in Part 2 will be used in this trial. This sample size is selected based on the conventional 3+3 study design and not based on statistical power calculation; it is deemed adequate to provide clinically meaningful descriptive results consistent with study objectives.

8.4. RANDOMIZATION AND STRATIFICATION

Not applicable.

8.5. BLINDING AND PREVENTION OF BIAS

Not applicable.

8.6. INTERIM ANALYSIS

Not applicable.

8.7. GENERAL STATISTICAL CONSIDERATIONS

All collected study data will be presented in subject data listings and/or will be summarized. Statistical analyses will be performed using SAS® for Windows, version 9.4 or later.

A Statistical Analysis Plan (SAP) will be developed and approved before the database is locked. The SAP will present the detailed statistical methodology to be used in analyzing the efficacy and safety data from this trial.

8.7.1. Analysis Populations

[redacted]

[redacted]

[redacted]

[redacted]

[redacted]

[redacted]

8.7.2. Covariates and Subgroups

[redacted]

8.7.3. Missing Data

All efforts will be made to minimize the amount of missing data for the study. The methods of handling missing data will be detailed in the SAP.

8.1. Statistical Methods

[redacted]

[redacted]

8.1.1. Subject Disposition

The disposition of all subjects who signed an ICF will be provided. The numbers of subjects screened, received treatment, completed, and discontinued during the study, as well as the reasons for discontinuation will be summarized. Disposition and reason for study discontinuation will also be provided as a by-subject listing.

8.1.2. Demographics And Baseline Characteristics Analysis

Demographics and baseline characteristics will be summarized using appropriate descriptive statistics.

8.1.3. Concomitant Medications/Therapies

All prior and concomitant medications recorded in the case report form will be coded to all matching Anatomic Therapeutic Classification codes using the most recent version of the WHO Drug Dictionary. Descriptive summaries will be prepared using the coded term. All concomitant medications recorded in the case report form will be listed.

8.1.4. Efficacy Analyses

All efficacy data collected will be summarized and analyzed according to the variable type:

[redacted]

8.1.6. Safety Analyses

8.1.6.1. Adverse Events

Adverse events will be classified by System Organ Class (SOC) and Preferred Term (PT) according to the most recent version of MedDRA dictionary.

[redacted]

8.1.6.2. Clinical Laboratory Data

[redacted]

[redacted]

8.1.6.3. Vital signs

[redacted]

8.1.6.4. Physical Examination

[redacted]

8.1.6.5. ECG

[redacted]

8.1.6.6. Other Safety Data

[redacted]

9. SAFETY REPORTING

The Investigator is responsible for the detection and documentation of events meeting the criteria and definition of an AE or SAE, as provided in this protocol. During the study when there is a safety evaluation, the Investigator or site staff will be responsible for detecting, documenting, and reporting AEs and SAEs as detailed in this Section of the protocol.

9.1. ADVERSE EVENT (AE) DEFINITION

An adverse event (AE) is defined as any unfavorable or unintended sign, symptom, or disease that occurs or is reported by the patient to have occurred, or a worsening of a pre-existing condition. An adverse event may or may not be related to the study treatment.

AEs will be elicited through direct questioning and subject reports. Any abnormality in physical examination findings or laboratory results that the investigator believes is clinically significant (CS) to the research subject and that occurred after initiation of the first study treatment will be reported as AEs. Abnormal findings that are NOT clinically significant should not be recorded as an AE.

9.2. REPORTING OF ADVERSE EVENTS (AES)

Report initiation for all AEs and SAEs will begin at the time of the first treatment visit and continue until the end of final study visit. All events will be followed to resolution or until the subject completes the study. A final assessment of outcome will be made at that time.

All AEs must be recorded in the subject's medical records and on the CRF. AEs will be reported using customary medical terminology along with the following information: the onset and end dates, whether the event is considered to be a SAE (see Section 9.3), the impact the event had on study treatment (see Section 9.2.1), the Common Terminology Criteria for Adverse Events (CTCAE) grade (intensity) of the event (see Section 9.2.2), the causality of the event (see Section 9.2.3), whether treatment was given as a result of the event (see Section 9.2.4), and the outcome of the event (see Section 9.2.5).

9.2.1. Impact on Study Treatment

The impact the event had on the study treatment will be assessed as either: dose increased, dose not changed, dose rate reduced, dose reduced, drug interrupted, drug withdrawn, not applicable, or unknown. The "not applicable" assessment will be used only when the subject is no longer in the Treatment Phase of the protocol.

9.2.2. CTCAE Grade (Intensity) Assessment

The guidelines outlined in CTCAE v5.0 will be used for assessing the intensity of the event. The general guidelines for assessing the AE grade appear below. Full guidelines may be obtained at http://evs.nci.nih.gov/ftp1/CTCAE.

Table 9-1: CTCAE v5.0 General Guidelines

Grade	Description
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)*.
Grade 3	Severe or medically significant but not immediately life-threatening; hospitalization or prolongation of hospitalization indicated; disabling; limiting self-care ADL†.
Grade 4	Life-threatening consequences; urgent intervention indicated.
Grade 5	Death related to AE.

*Instrumental ADL refer to preparing meals, shopping for groceries or clothes, using the telephone, managing money, etc.
†Self-care ADL refer to bathing, dressing and undressing, feeding self, using the toilet, taking medications, and not bedridden.

-Common Terminology Criteria for Adverse Events (CTCAE), v5.0: November 27, 2017

9.2.3. Event Causality Assessment

AEs will be assigned a relationship (causality) to the study treatment. The Investigator will be responsible for determining the relationship between an AE and the study treatment. The type of event, organ system affected, and timing of onset of the event will be factors in assessing the likelihood that an AE is related to the study treatment. Relationship of AEs to study treatment will be classified as follows:

1. **Definitely related**: This category applies to those AEs that the Investigator feels are incontrovertibly related to the study treatment. An AE may be assigned an attribution of definitely related if or when it meets all of the following criteria: (1) it follows a reasonable temporal sequence from administration of the study treatment; (2) it could not be reasonably explained by the known characteristics of the subject's clinical state, environmental or toxic factors, or other modes of therapy administered to the subject; (3) it follows a known response pattern to treatment with the study treatment.
2. **Probably related**: This category applies to those AEs which, after careful medical consideration at the time they are evaluated, are felt with a high degree of certainty to be related to the study treatment. An AE may be considered probable if or when (must have three): (1) it follows a reasonable temporal sequence from administration of the study treatment. (2) It could not readily have been produced by subject's clinical state, environmental or toxic factors, or other therapies administered to the subject. (3) Disappears or is decreased upon discontinuation of the study treatment. (4) It follows a known response pattern to treatment with the study treatment.
3. **Possibly related**: This category applies to those AEs which, after careful medical consideration at the time they are evaluated, are judged unlikely but cannot be ruled out with certainty to the study treatment. An AE may be considered possible if or when (must have two): (1) it follows a reasonable temporal sequence from administration of the study treatment. (2) It could not

readily have been produced by subject's clinical state, environmental or toxic factors, or other therapies administered to the subject. (3) Disappears or is decreased upon discontinuation of the study treatment. (4) It follows a known response pattern to treatment with the study treatment.

4. **Unlikely related**: In general, this category can be considered applicable to those AEs which, after careful medical consideration at the time they are evaluated, are judged likely to be unrelated to the study treatment. An AE may be considered unlikely if or when (must have two): (1) it does not follow a reasonable temporal sequence from administration of the study treatment. (2) It could not readily have been produced by subject's clinical state, environmental or toxic factors, or other therapies administered to the subject. (3) Disappears or is decreased upon discontinuation of the study treatment. (4) It does not follow a known response pattern to treatment with the study treatment.
5. **Unrelated**: This category applies to those AEs which, after careful consideration at the time they are evaluated, are clearly and incontrovertibly due to extraneous causes (disease, environment, etc.) and determined with certainty to have no relationship to the study treatment.

9.2.4. Treatment Given as a Result of the Event

The event impact in terms of treatment provided will be as either: none, medication administered, non-drug therapy administered, surgery performed, hospitalization, or other (with a specification).

9.2.5. Event Outcome Assessment

The outcome of the event will be assessed as either: fatal, not recovered/not resolved, recovered/resolved, recovered/resolved with sequelae, recovering/resolving, or unknown. Only one AE per subject is allowed to have an outcome assessment as "death." If there are multiple causes of death for a given subject, only the primary cause of death will have an outcome of death.

9.3. SERIOUS ADVERSE EVENT (SAE) DEFINITION

A SAE is defined as any AE that:

- Results in death
- Is life threatening (the subject is at immediate risk of dying from the adverse experience)
- Requires subject hospitalization or prolongs existing hospitalization
- Results in persistent or significant disability/incapacity
- Is a congenital anomaly/birth defect
- Important medical events that may not result in death, be life-threatening, or require hospitalization may be considered a serious adverse effect when, based upon appropriate medical judgment, they may jeopardize the subject or subject and may require medical or surgical intervention to prevent one of the outcomes listed in this definition.

9.4. REPORTING OF SERIOUS ADVERSE EVENTS (SAES)

The Investigator is required to report all SAEs that occur during the time period specified in Section 9.2. Once the Investigator becomes aware of an SAE, he/she must report the SAE to Medical Monitor within 24 hours.

Attn: Amarex Clinical Research, LLC
20201 Century Boulevard, 4th Floor
Germantown, MD 20874
[redacted]

The Medical Monitor may request additional supporting documentation as it becomes available, such as lab reports, electrocardiogram [ECG] reports, discharge summary, hospital notes, etc., if applicable. Additional follow-up information as it becomes available must be reported to the Medical Monitor.

The Investigator is also responsible for reporting all SAEs to the appropriate Institutional Review Board (IRB) in accordance with local laws and regulations. The Investigator is responsible for maintaining documentation in the study file that indicates the IRB has been properly notified.

9.4.1. SAE Follow-Up

All subjects experiencing an SAE, including the discontinued subjects, must be closely followed until sufficient information is obtained to indicate a return to normal status or until the event stabilizes at a level acceptable to the investigator or the last study visit, whichever occurs first (i.e., recovery, return to baseline status, no further improvement expected, or death).

For each SAE indicated as an unresolved event on the initial report, regardless of whether the subject completed the study or withdrew, the site should submit a follow-up report with updated information.

9.5. PREGNANCY REPORTING

To ensure patient safety, any pregnancy that occurs while subject is taking study drug, any pregnancy that occurs in a female subject or a female partner of a male subject from the time of first study treatment administration till 30 days after the last treatment administration should be recorded using a Pregnancy Notification Report Form and reported immediately to Sponsor within 24 hours of learning of the pregnancy.

If a female subject becomes pregnant during the study before the end of treatment period, they will be a discontinued subject. If a subject becomes pregnant during the study after the end of treatment during the follow up portion, they can complete the remaining scheduled follow up visits unless there is a medical contraindication.

9.5.1. AE and SAE Reporting

Pregnancy itself is not regarded as an AE unless there is a suspicion that the IP may have interfered with the effectiveness of a contraceptive medication. Pregnancy in a subject's partner is not considered an AE. Congenital abnormalities/birth defects and spontaneous miscarriages should be reported and handled as SAEs.

9.5.1.1. Abortions

An induced elective abortion to terminate a pregnancy without medical reason is not regarded as an AE. However, an induced therapeutic abortion to terminate a pregnancy because of complications or medical reasons must be reported as an SAE. The underlying medical diagnosis for this procedure should be reported as the SAE term. A spontaneous abortion is always considered an SAE.

9.5.2. Informed Consent

The ICF will include information regarding reporting of pregnancy to the Sponsor and collection of information through the end of pregnancy that occurs in either a female subject or in a female partner of a male subject. If a female partner becomes pregnant, the Investigator will request consent from the partner to collect this information.

9.5.3. Pregnancy Follow-Up

The pregnancy will be followed-up to determine the outcome (spontaneous miscarriage, elective termination, ectopic pregnancy, normal birth, or congenital abnormality) and should include an assessment of the possible relationship to the study treatment of any pregnancy outcome. This information should also be documented on the Pregnancy Outcome Report Form and reported to the Sponsor.

10. DIRECT ACCESS TO SOURCE DATA/DOCUMENTATION

Subjects will be identified on CRFs by a unique subject identification number and on source documents by name and date of birth. No personal identifier will be used in any publication or communication used to support this research study. The subject identification number will be used if it becomes necessary to identify data specific to a single subject.

The local IRB, FDA, the monitors, auditors and personnel authorized by the Sponsor are eligible to review the medical and research records related to this study as part of their responsibility to protect human subjects in clinical research. They will be given direct access to source data and documentation (e.g., medical charts/records, printouts etc.) for source data verification, provided that subject confidentiality is maintained in accordance with local requirements. Access to electronic medical records may be governed by institution policy. Each site will be required to ensure access while remaining compliant with institutional requirements.

11. QUALITY CONTROL AND QUALITY ASSURANCE

11.1. MONITORING REQUIREMENTS

The specific obligations outlined in 21 Code of Federal Regulations (CFR) and ICH guidelines require the Sponsor to maintain current personal knowledge of the progress of a study. Therefore, the Sponsor's designated monitor will visit the site during the study as well as maintain frequent telephone and written communication. The Investigator will permit the Sponsor to monitor the study as frequently as is deemed necessary and provide access to medical records to ensure that data are being recorded adequately, that data are verifiable and that protocol adherence is satisfactory.

As delineated above, the Investigator will permit representatives of the Sponsor and/or designated CRO to inspect all CRFs and corresponding study subject original medical records (source documents) at regular intervals throughout the study. Subject original medical records and other relevant data must be available to support all data recorded in the CRF. In addition to the original medical records, these data may include but are not limited to study, laboratory reports, etc.

In accordance with federal regulations, site inspections will serve to verify strict adherence to the protocol and the accuracy of the data that is being entered on the case report forms. A Monitoring Log will be maintained at each study site. The Monitoring Log will be signed by the monitor, dated and stated the type of visit. The Investigator should be aware that the study site and subject records may be inspected by the Sponsor and or representatives of the designated CRO, FDA or other regional regulatory authority.

11.2. ACCEPTABILITY OF CASE REPORT FORMS (CRFS)

For each subject who has signed an informed consent form, a CRF must be completed. For subjects who are screen failures, this would be limited to the screen failure CRF page. All source documents and CRFs will be completed as soon as possible after the subject's visit and corrections to data on the CRFs will be documented, if applicable. The Investigator will review the CRFs to indicate that, to his/her knowledge, they are complete and accurate. CRFs will be reviewed by the Sponsor's or designated CRO's monitor, who will make a decision as to their acceptability.

11.3. MODIFICATION OF PROTOCOL

The Investigator will not modify or alter this protocol without first obtaining the concurrence of the Sponsor. Approval by the Investigator's IRB must also be obtained prior to implementation of the change, with two exceptions:

1. When necessary to eliminate apparent immediate hazard to the subject; or
2. When the modification does not involve the subject's participation in the trial.

An amendment may also require modification of the informed consent form. The Investigator will provide an approval letter for the amendment and revised informed consent form, if applicable, to the Sponsor. An amendment must be provided in writing and it must be dated by both the Sponsor and the Investigator. If necessary, the Sponsor will submit protocol amendments to FDA and other appropriate regulatory authorities and notify other Investigators using this protocol.

11.4. REPORTING PROTOCOL DEVIATIONS

The Investigator is obligated to follow the protocol without departure from the requirements written in the protocol. If the Investigator deviates from the protocol requirements, the Sponsor will make the determination as to whether the subject will continue in the study. The Sponsor also has the right to discontinue the subject for protocol violations. The IRB may also have to be contacted if safety to the subject or if the scientific soundness of the study is involved. All protocol deviations must be documented in the CRFs.

11.4.1. Major Protocol Deviation or Violation

A major protocol deviation or violation is a deviation from the IRB approved protocol that may affect the subject's rights, safety, or well-being and/or the completeness, accuracy, and reliability of the study data. Examples of this include:

- Failure to obtain informed consent prior to initiation of study-related procedures
- A research subject does not meet the protocol's eligibility criteria but was enrolled without prior approval from the sponsor.
- A research subject received the wrong treatment or incorrect dose.
- A research subject met withdrawal criteria during the study but was not withdrawn.
- A research subject received a prohibited concomitant medication.
- Failure to treat research subjects per protocol procedures that specifically relate to primary efficacy outcomes.
- Changing the protocol without prior sponsor and IRB approval.
- Multiple minor violations of the same nature after multiple warnings.

11.4.2. Minor Protocol Deviation or Violation

A minor protocol deviation is any change, divergence, or departure from the study design or procedures of a research protocol that has not been approved by the IRB and which DOES NOT have a major impact on the subject's rights, safety or well-being, or the completeness, accuracy and reliability of the study data. Examples of this include:

- Follow-up visits that occurred outside the protocol required time frame because of the participant's schedule.

- Blood samples obtained at times close to but not precisely at the time points specified in the protocol.

12. INDEPENDENT DATA MONITORING COMMITTEE (IDMC)

Not applicable.

13. ETHICS AND REGULATORY REQUIREMENTS

This study is to be conducted in accordance with the specifications of this protocol and in accordance with principles consistent with Declaration of Helsinki, GCP, 21 CFR, ICH E6, HIPAA regulations in 45 CFR Part 164 (US only), and the Belmont Principles of respect for persons, beneficence, and justice. No protocol changes will be implemented without the prior review and approval of the IRB, except when the modification does not involve the subject's participation in the trial or where it may be necessary to eliminate an immediate hazard to a research subject. In the latter case, the change will be reported to the IRB as soon as possible, according to IRB regulations.

Additionally, the study product used in this study is manufactured, handled and stored in accordance with applicable GMP. The study product provided for this study will be used only in accordance with this protocol.

13.1. INSTITUTIONAL REVIEW BOARD/INDEPENDENT ETHICS COMMITTEE (IRB/IEC)

The Principal Investigator (PI) at each site will provide the Institutional Review Board/Independent Ethics Committee (IRB/IEC) with all appropriate materials as required by their IRB/IEC, including but not limited to the clinical study protocol, informed consent form, and any advertising materials. The study will not be initiated until the IRB/IEC provides written approval of the aforementioned documents and until approval documents have been obtained by the Principal Investigator and Sponsor or Sponsor designee. The Investigator will not participate in the decision. If the Investigator is an IRB or IEC member, documentation must be provided indicating recusal from the approval process. Appropriate reports on the progress of this study by the Principal Investigator will be made to the IRB/IEC as required by local and applicable government regulations and in agreement with policy established by the Sponsor. The Investigator is required to maintain an accurate and complete record of all written correspondence to and received from the IRB/IEC and must agree to share all such documents and reports with the Sponsor.

No changes from the final approved protocol will be initiated without the IRB/IEC's prior written approval or favorable opinion of a written amendment, except when necessary to eliminate immediate hazards to the subjects or when the modification does not involve the subject's participation in the trial.

13.2. INVESTIGATOR'S RESPONSIBILITIES

The Investigators are responsible for performing the study in full accordance with the protocol and the current revision of the Declaration of Helsinki, the Good Clinical Practice: Consolidated Guideline, approved by the ICH, and any applicable national and local laws and regulations.

Information regarding to the study center participating in this study that cannot comply with these standards will be documented.

13.3. SUBJECT INFORMED CONSENT REQUIREMENTS

All subjects participating in this study will be given to by the Investigator and/or designee, written and oral information about the study in a language understandable by the subject. Written informed consent will be obtained from each subject prior any procedures or assessments that would not otherwise be required for the care of the subject are done and after the aims, methods, anticipated benefits, potential hazards, and insurance arrangements in force are explained and the subject has been given sufficient time to ask questions and consider participation in the study. It will also be explained to the subjects that they are free to refuse entry into the study and free to withdraw from the study at any time without prejudice to future treatment. It is permissible for a third person (e.g., a family member) to be present during the explanation of the study.

The written Informed Consent Form (ICF) will be in compliance with CFR 21 Part 50.27 and GCP guidelines. The Sponsor and/or designated CRO will approve the ICF and all amendments to the ICF prior to submission to the IRB/IEC. A copy of the ICF to be used will be submitted by the Investigator to the IRB/IEC for review and approval prior to the start of the study. The study site must provide the Sponsor with an unsigned copy of IRB/IEC-approved ICF along with applicable documentation to support this approval. The original signed ICF is retained in the subject's study records, and a copy is provided to the subject. A second copy may be filed in the subject's medical record, if allowed by institutional policy.

14. DATA HANDLING AND RECORD KEEPING

14.1. RECORDING AND COLLECTION OF DATA

The primary source document for this study will be the subject's medical record. If separate research records are maintained by the Investigator(s), the medical record and the research records will be considered the source documents for the purposes of auditing the study.

Applicable source data will be manually transcribed to approve case report forms (CRF). The Investigator is ultimately responsible for the accuracy of the data transcribed on the forms. All source documents and CRFs will be completed as soon as possible after the subject's visit.

The Investigator will review the CRFs to indicate that, to his/her knowledge, they are complete and accurate. Designated source documents will be signed and dated by the appropriate study personnel. The Investigator must agree to complete and maintain source documents and CRFs for each subject participating in the study.

All research data will be entered, either electronically or manually, into a computerized database. The clinical database will be designed by the clinical data manager in accordance with 21 CFR Part 11 and based on protocol requirements defined by the Sponsor in association with the Lead Investigator.

The Investigator will maintain a confidential list of study subjects that will include each subject's study number, name, date of birth, and unique hospital identification number if applicable. This list will be kept by the Investigator and will not be collected by the Sponsor. A notation will be made in the subject's case history/medical chart that he/she is participating in a clinical study and has provided a signed and dated ICF as well as a release for protected health information as required by local policies. The Investigator must also maintain a separate screening log of all the subjects screened for participation in the study; it should include gender, age, eligibility status, reason for ineligibility, if applicable; and study allocated subject number, if applicable.

14.2. CLINICAL DATA MANAGEMENT

The Sponsor and/or designated CRO will be responsible for the processing and quality control of the data. Data management will be carried out as described in the Sponsor's or CRO's standard operating procedures (SOPs) for clinical studies.

The handling of data, including data quality control, will comply with regulatory guidelines (e.g., ICH E6 GCP, and local regulations where applicable) and the Sponsor's or the CRO's SOPs as well as provisions of the study-specific Data Management Plan.

14.3. ARCHIVING

All study documentation at the Investigator site and Sponsor site will be archived in accordance with ICH GCP E6 and the Sponsor's quality standards and SOPs.

The Investigator will maintain all research records, reports, and case history reports for a period of two (2) years after regulatory approval of the investigational product. If no application is filed or if the application is not approved, records must be maintained for two (2) years after all investigations have been completed, terminated or discontinued and the FDA has been notified.

These documents should be retained for a longer period however, if required by the applicable regulatory requirements or if needed by Sponsor or its authorized representative (as per GCP 5.5.11).

At the completion of the study, details of the archival process must be provided to the Sponsor. Study records are subject to inspection by applicable health and regulatory agencies at any time.

Records to be retained by the Investigator include, but are not restricted to:

- Source data and the primary records upon which they are based (e.g., subject's progress notes, adverse event data, test results, and any other diagnostic procedures required to evaluate the progress of the study)
- Completed CRFs
- Signed protocols and protocol amendments
- Laboratory results, ranges, and certifications
- IP and accountability records
- Study personnel signature log
- Monitoring logs
- Correspondence to and from the Sponsor, designee and IRB
- Investigator and sub-investigator CVs
- Signed informed consent and protected health information consent forms
- Subject screening
- SAE reports
- IRB approval and re-approval letters
- Completed quality of life questionnaire
- Other documents pertaining to the conduct of the study

These documents must be maintained and kept on file by the Investigator so that the conduct of the study can be fully documented and monitored.

Study records should not be transferred from site or destroyed without prior written agreement between the Sponsor and the study Investigator. Study records are subject to inspection by applicable health and regulatory agencies at any time.

15. PUBLICATION PLAN

All information supplied by Allarity Therapeutics, Inc in connection with this study and not previously published, is considered confidential information. This information includes, but is not limited to, the Investigator's Brochure, clinical protocol, case report forms and other scientific data. Any data collected during the study are also considered confidential. This confidential information shall remain the sole property of Allarity Therapeutics, Inc, shall not be disclosed to others without the written consent of Allarity Therapeutics, Inc, and shall not be used except in the performance of this study.

It is understood by the Investigator that the Sponsor will use the information collected in this clinical trial in connection with the development of the investigational product. Therefore, this information may be disclosed as required to other Investigators or appropriate regulatory authorities. By agreeing to participate in this clinical trial, the Investigator understands that he/she has an obligation to provide the Sponsor with complete test results and all data developed during this trial.

Publication and Disclosure: The site and Investigator agree to submit any proposed manuscript, presentation or other public disclosure regarding the study to Sponsor for review at least thirty (30) days prior to submitting such proposed manuscript to a publisher or delivering or making such presentation or other public disclosure to any third party. Within thirty (30) days of its receipt, Sponsor shall advise the site and/or Investigator, as the case may be, in writing of any information contained therein that is confidential information (other than research results included in a proposed manuscript) or that may impair Sponsor's ability to obtain patent protection. Sponsor shall have the right to require the site and/or Investigator, as applicable, to remove specifically identified confidential information (but may not require removal of research results from a proposed manuscript) and/or to delay the proposed submission or delivery of the proposed manuscript or presentation, or other public disclosure, for an additional sixty (60) days to enable Sponsor to seek patent protection. The site and Investigator shall not publish, publicly disclose, present or discuss any results of or information pertaining to the site's and Investigator's activities prior to completion of the trial, even if the study is terminated before its completion and the final clinical study report is signed off, or with respect to any endpoints or analyses other than those specified in this protocol.

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17. APPENDIX

17.1. APPENDIX 1: COMMON TERMINOLOGY CRITERIA FOR ADVERSE EVENTS V5.03

For complete detailed information please refer to the link below:

https://ctep.cancer.gov/protocoldevelopment/electronic_applications/docs/CTCAE_v5_Quick_Reference_5x7.pdf

17.2. [redacted]

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