Official Protocol Title:	A Phase 1/2 Study of ARQ 092 (Miransertib) in Subjects with PIK3CA-related Overgrowth Spectrum and Proteus Syndrome
NCT number:	NCT03094832
Document Date:	05-MAR-2021

STUDY TITLE	A Phase 1/2 Study of ARQ 092 (Miransertib) in Subjects with PIK3CA-related Overgrowth Spectrum and Proteus Syndrome
Study Number:	ARQ 092-103 / MK-7075-002
Study Phase:	1 / 2
Product Name:	ARQ 092 (miransertib)
IND Number:	130784
EudraCT Number:	2016-000558-37
Sponsor:	ArQule, Inc. (A Wholly Owned Subsidiary of Merck, Sharp and Dohme, a subsidiary of Merck & Co., Inc., hereafter referred to as the Sponsor or MSD) One Merck Drive PO Box 100 Whitehouse Station, New Jersey, 08889-0100, USA
Medical Monitor:	PPD
Date of Protocol:	Original: 25 August 2016 Amendment 1: 21 October 2016 Amendment 2: 18 May 2017 Amendment 3: 25 September 2017 Amendment 4: 01 August 2018 Amendment 5: 14 December 2018 Amendment 6: 07 March 2019 Amendment 7: 05 March 2021

CONFIDENTIALITY STATEMENT

Summary of Changes from Amendment 6 to Amendment 7

Type of change	Rationale	Sections affected
Administrative changes to replace ArQule contact personnel and contact information with Merck address, compound number, personnel, and contact information	ArQule now part of Merck	• Title page • All headers and footers • 8.4 Serious Adverse Event Reporting • Sponsor Signature Page
Redacted potentially identifiable patient information; deleted Section 1.3.2.2 Expanded Access Program/Compassionate Use	To maintain patient privacy	• Throughout the document • Removed patient narratives from 1.3.2.1 A Phase 1 Dose-Finding Trial of ARQ 092 in Children and Adults with Proteus Syndrome.
Removal of primary objectives related to efficacy, removal of secondary and tertiary endpoints	Accurate assessment of efficacy no longer considered possible from the data set, only evaluation of safety and tolerability achievable	• Synopsis table • 2.1 Study Objectives • 2.2 Overall Study Design • 2.3 Study Endpoints • 9 Planned Statistical Methods
Updated primary objective of the entire study to reflect safety and tolerability of miransertib; endpoints for Part A and Part B have been combined.	Safety and tolerability (originally secondary endpoints) remain a valid assessment	• Synopsis table • 2.1 Study Objectives • 9.3 Study Endpoints

Type of change	Rationale	Sections affected
Removal of imaging-based efficacy assessments	Procedures that will not be used for safety and may pose additional risk to patients will not be assessed and should not be performed (eg, MRI used for comparison for efficacy on treatment) have been removed	• Synopsis table • 2.2 Overall Study Design • 2.3 Study Endpoints • 4.1 Informed Consent • 5.1 Medical History • Table 3 Schedule of Events Part B, Cohorts 1, 2, and 3 • Table 4 Schedule of Events Part B, Cohort 4
Removal of PK sample collections	PK assessments to assess efficacy will no longer be performed as there will not be efficacy assessments to support.	• 2.2 Overall Study Design • 2.3 Study Endpoints • 5.4 Pharmacokinetic Assessments • Table 3 Schedule of Events Part B, Cohorts 1, 2, and 3 • Table 4 Schedule of Events Part B, Cohort 4 • 9.5 Pharmacokinetic Analysis
Removal of preclinical efficacy data	Efficacy assessment is no longer an objective for this study, so this efficacy data is no longer relevant	• 1 Introduction

Type of change	Rationale	Sections affected
Removal of functional assessments, including deletion of the following: Section 5.6 Pain Assessment (Part B Cohorts 1, 2, and 3), Section 5.7 Physical Function Assessment (Part B Cohorts 1, 2, and 3) Appendix 2: Wong-Baker FACES® Pain Rating Scale / Numerical Rating Scale, Appendix 3: Physical Function Assessment by PROMIS, Appendix 7: Study Visits for Part B	Efficacy no longer a study objective	• 2.3 Study Endpoints • 5.5 Other Assessments • Table 3 Schedule of Events, Cohorts 1, 2, and 3 • Table 4 Schedule of Events, Cohort 4
Assessment of response modified based on removal of efficacy assessments, including deletion of the following; Section 9.4 Efficacy Analysis	No longer relevant; efficacy no longer assessed	• 8 Assessment of Response • 8.1 Measurable Disease • 8.2 Response Evaluation
Deleted statistical analysis of efficacy data and exploratory endpoints, including deletion of the following: Section 9.3.1 Primary Endpoint, Section 9.3.2 Secondary Endpoints, Section 9.3.3 Exploratory Endpoints, Section 9.3.4 Part A Study Endpoints; Subsequent sections renumbered.	Efficacy no longer a study objective.	• 9 Planned Statistical Methods

Type of change	Rationale	Sections affected
Removed discussion of AKT signaling and preclinical data	Streamlined the Introduction for focus to issues of clinical importance	• Synopsis table • 1 Introduction • Figures 1-5 removed • Table 1 revised • 8 Assessment of Response
Copied details regarding study population including inclusion and exclusion criteria from Section 3 to the synopsis	Makes information more accessible. No new information added.	• Synopsis table
Moved description of inactive Part A to Annex 1	Information on the closed Part A is left only for reference. Changes to Annex 1 are not described in detail.	• Annex 1
Replaced the name “ARQ 092” with “miransertib”	Miransertib is the approved generic name for the compound	Throughout the document
Addressed issued related to spelling, grammar, and formatting. These changes had no impact on the content of the document	Improved document quality and readability	Throughout the document

Table of Contents

List of In-Text Tables

List of In-Text Figures

No table of figures entries found.

SYNOPSIS

Study Title:	A Phase 1/2 Study of ARQ 092 (Miransertib) in Subjects with PIK3CA-related Overgrowth Spectrum and Proteus Syndrome
Study Number:	ARQ 092-103 / MK-7075-002
Study Phase:	1/2
IND Number:	130784
EudraCT Number:	2016-000558-37
Rationale for the Study	Phosphatidylinositol-4,5-bisphosphate 3-kinase, catalytic subunit alpha / v-Akt murine thymoma viral oncogene homolog (PIK3CA/AKT) genetic alterations have been identified in many solid and hematologic malignancies as well as in overgrowth diseases and vascular anomalies, including PIK3CA-related Overgrowth Spectrum (PROS) and Proteus Syndrome (PS). In contrast to cancer, which is characterized by multiple genetic aberrations, a single activating mutation has been identified in both PROS and PS. This single postzygotic PIK3CA or serine-threonine protein kinase (AKT1) mutation leads to cellular overgrowth characterized by somatic mosaicism. The severity of the disease varies from patient to patient and ranges from a single overgrowth lesion to life-threatening, progressively debilitating multiorgan disorders. Both PROS and PS are very rare disorders with no specific treatment and, in general, a poor survival rate. Many PI3K/AKT inhibitors, including miransertib, are being evaluated in cancers that are driven by PI3K/AKT pathway activation. Miransertib is an oral, allosteric, selective pan-AKT inhibitor that potently inhibits both active and inactive forms of AKT. In in vitro and in vivo experiments, it showed antiproliferative activity in cancer and in cells derived from PROS and PS patients. Safety, tolerability, and preliminary efficacy data of miransertib at doses ranging from 10 mg up to 350 mg at varying frequencies (ie, qod, qd, bid, and qw) have been evaluated in more than 150 adult participants with advanced solid tumors and recurrent malignant lymphoma (NCT#01473095; NCT#02476955). In this oncology patient population, miransertib at doses up to 60 mg qd showed a manageable safety profile. The National Institutes of Health / National Human Genome Research Institute (NIH / NHGRI) has conducted the first clinical study of miransertib in patients with PS (“Dose Finding Trial of

	ARQ 092 in Children and Adults with Proteus Syndrome"; NCT02594215). The primary endpoint of the study was to determine the biological effect of miransertib measured by changes of phosphorylated AKT (pAKT) levels in the affected tissue. Secondary endpoints included safety, tolerability, and disease specific evaluations (volumetric magnetic resonance imaging [MRI], photography of the cerebriform connective tissue nevus [CCTN], quality of life [QoL], and functional assessments). The study initially enrolled 3 adult patients. Once miransertib was shown to be well tolerated, additional 3 younger patients (<18 years of age) were enrolled. All participants were treated at a daily dose of 5 mg/m^2 and were expected to complete 12 cycles of treatment, with a cycle being defined as a 28-day period. Of the 6 enrolled participants, 2 discontinued treatment after 8 cycles (due to withdrawal of consent and an adverse event of transaminase increase), 3 participants completed 12 cycles, and 1 participant continues treatment after completion of 12 cycles. In 5 participants, a reduction of 50% or greater of tissue pAKT levels was reported, and the primary endpoint of the study was met. The clinical efficacy measurements showed reduction in size of the CCTN at Cycle 12 by quantitative standardized photography. The 3 younger participants reported an improvement in pain as assessed by a standardized pain scale. The drug was well tolerated with most adverse events (AEs) being mild to moderate in severity.
Study Objective:	Originally, the ARQ 092-103 study was entitled "A Phase 1/2 Study of ARQ 092 in Patients with Overgrowth Diseases and/or Vascular Anomalies with Genetic Alterations of the PI3K/AKT Pathway" (NCT03094832) and was initiated as a dose-finding, safety, and tolerability study. Subsequently, this study was amended to enroll only patients with PROS or PS with PIK3CA or AKT1 mutations ("A Phase 1/2 Study of ARQ 092 in Subjects with PIK3CA-related Overgrowth Spectrum and Proteus Syndrome"). The current protocol (Amendment 6) was designed to assess safety of miransertib in patients with PROS and PS. The study consists of 2 parts: Part A that includes all participants enrolled before Amendment 6 and Part B that enrolled participants after Amendment 6. Enrollment in Part A was closed on approval of Amendment 6. Part B consists of 4 cohorts. Cohort 1 enrolled patients with PROS; Cohort 2 enrolled patients with PS; Cohort 3 enrolled patients with either PROS or PS who did not meet the eligibility criteria for Cohorts 1 or 2; and Cohort 4 enrolled patients previously treated with miransertib or currently receiving miransertib under Compassionate Use/Expanded Access.

	Amendment 7 will complete the final enrollment into the MOSAIC study and Compassionate Use/Expanded Access Program. In the future, patients will be transitioned to new miransertib programs.
Study Design and Treatment:	Global, multicenter open-label, two-part Phase 1 /2 study testing miransertib in PROS and PS patients. All participants enrolled in Part B Cohorts 1, 2, and 3 will receive miransertib at the starting dose of 15 mg/m^2 qd for the first 3 cycles, (a cycle of therapy is 28 days), and then the dose will be increased to 25 mg/m^2 qd, provided no clinically significant drug-related toxicity is observed.
Study Endpoints:	Under this amendment, the endpoints for Part A and Part B have been combined to assess the safety and tolerability of miransertib in participants with PROS and PS based on the frequency, duration, and severity of AEs from the first dose of the drug through 90 days after the last dose of the drug.
Study Population:	Participants diagnosed with PROS or PS with documented PIK3CA or AKT1 somatic mutation will be enrolled. Participants who are eligible for enrollment must meet ALL of the inclusion and NONE of the exclusion criteria. Enrollment in Part A was closed on approval of Amendment 6. **Inclusion Criteria - Part B** • Signed informed consent, and when applicable, signed assent <u>Cohort 1 (PROS)</u> • Male or female participants ≥2 years and ≤30 years of age with BSA of ≥0.33 m^2 • Have clinical diagnosis of PROS per Diagnostic Criteria for PROS and documented somatic PIK3CA variant • Have at least one lesion that can be measured by standardized volumetric MRI <u>Cohort 2 (Proteus)</u> • Male or female participants ≥2 years and ≤18 years of age with body surface area (BSA) of ≥0.33 m^2 • Have clinical diagnosis of PS per Diagnostic Criteria for PS and documented somatic AKT1 variant • Have at least one plantar CCTN and pre-CCTN lesion that can be evaluated by standardized digital photography.

	<u>Cohort 3 specific criteria</u> Male or female PROS or PS patients ≥2 years old with BSA of ≥0.33 m^2 and who fail to meet the eligibility criteria for Cohorts 1 or 2 <u>Cohort 4 (PROS or PS) specific criteria</u> • Participants previously treated with miransertib or currently receiving miransertib under Compassionate Use/Expanded Access • Note: Participants should meet the age criterion by/on the date of the first dose, Cycle 1 Day 1. **All Cohorts:** 1. Archival or fresh overgrowth tissue sample available to be shipped to Sponsor or designee 2. Except for Cohort 4, clinically progressive or worsening disease defined as an increase in number or size of the overgrowth lesion(s) in the last 6 months as assessed by the investigator 3. Adequate organ function as indicated by the following laboratory values: <u>Hematological</u> • Hemoglobin (hgb) depending on age: 2 to 5 years male and female: ≥10.0 g/dL, 6 to 9 years male and female: ≥11.5 g/dL, 10 to 17 years female: ≥11.0 g/dL, 10 to 17 years male: ≥11.5 g/dL, ≥18 years male and female: ≥10.0 g/dL • HbA1c: ≤8% (≤64 mmol/mol) • Absolute neutrophil count (ANC): ≥1.5 x 10^9/L • Platelet count ≥150 x 10^9/L <u>Hepatic</u> • Total bilirubin ≤1.5 x ULN • AST and ALT ≤3 x ULN <u>Renal</u> • Serum creatinine depending on age: 2 to 5 years male and female: maximum 0.80 mg/dL, 6 to 10 years male and female: maximum 1.0 mg/dL, 11 to 15 years male and female: maximum 1.2 mg/dL, >15 years male and female: maximum 1.5 mg/dL • Estimated glomerular filtration rate (eGFR): ≥60 mL/min/1.73 m^2

	Metabolic (lipids) • Cholesterol: ≤400 mg/dL (≤10.34 mmol/L) • Triglyceride: ≤500 mg/dL (≤5.7 mmol/L) 4. Male or female participants of child-producing potential must agree to use double-barrier contraceptive measures, oral contraception, or avoidance of intercourse during the study and for 90 days after the last dose of miransertib. 5. Ability to complete the study questionnaires by the participant or his/her caregiver **Exclusion Criteria – Part B** 1. History of Type 1 diabetes mellitus or Type 2 uncontrolled diabetes mellitus requiring regular medication (other than metformin or other oral hypoglycemic agents) or fasting glucose ≥160 mg/dL (if >12 years old) and ≥180 mg/dL (if ≤12 years old) at the Screening Visit 2. History of significant cardiac disorders 3. Myocardial infarction (MI) or congestive heart failure defined as Class II to IV per the New York Heart Association (NYHA) classification within 6 months of the first dose of miransertib (MI occurring >6 months of the first dose of miransertib will be permitted) 4. Grade 2 (per current version of National Cancer Institute Common Terminology Criteria for Adverse Events [NCI CTCAE]) or worse conduction defect (eg, right or left bundle branch block) 5. Major surgical procedures or locoregional therapy within 4 weeks of the first dose of miransertib 6. Any experimental systemic therapy for the purposes of treating PROS or PS (eg, sirolimus, everolimus, high dose steroids) within 2 weeks of the first dose of miransertib 7. Intolerance of or severe toxicity attributed to AKT inhibitors (eg, miransertib, uprosertib, afuresertib, ipatasertib) 8. Concurrent severe uncontrolled illness not related to PROS or PS, (eg, ongoing or active infection, known human immunodeficiency virus [HIV] infection) 9. Malabsorption syndrome 10. Psychiatric illness/substance abuse/social situation that would limit compliance with study requirements 11. Pregnant or breastfeeding

	12. Inability to comply with study evaluations or to follow drug administration guidelines
Study Drug, Doses, and Administration:	Miransertib is an orally administered pan-AKT inhibitor. Miransertib is supplied as 5-mg or 10-mg capsules and will be administered either 1 hour before or 2 hours after a meal. The capsules should be swallowed whole but, when medically necessary, can be opened and sprinkled onto a small amount of sweetened semiliquid food (eg, apple sauce, chocolate syrup, or ice cream). Participants will be administered miransertib at 15 mg/m^2 daily for 3 cycles and then 25 mg/m^2 daily for the remainder of the study unless unacceptable toxicity is observed. Participants in Cohort 4 will receive miransertib at the same dose they were on at the time of enrollment, the dose should not exceed 25 mg/m^2. For participants who previously received miransertib but at the time of the enrollment were not receiving the drug, miransertib administration will follow Part B miransertib administration schedule. Independent from the dose the participant is on, the actual dose should be evaluated at each study visit and adjusted when necessary based on BSA, since it is expected to change over the course of treatment due to the normal growth of the participant.
Criteria for Dose Escalation/ Reduction:	For participants enrolled in Part B Cohorts 1, 2, and 3 dose escalation to 25 mg/m^2 qd will be performed after 3 cycles of treatment at the initial dose of 15 mg/m^2 qd provided no clinically significant drug-related toxicity was observed (as assessed by the investigator and agreed on by the investigator and the Sponsor). When a miransertib-related toxicity is observed, dose delays and/or reductions are allowed. Dose re-escalation will not be permitted.
Duration of Treatment:	For an individual participant, treatment will continue for up to 48 cycles or until disease progression, unacceptable toxicity, or another discontinuation criterion is met. It is expected that most participants will receive between 3 and 48 cycles of treatment.
Data Monitoring Committee:	The DMC will monitor participants' safety by reviewing and evaluating study data, reviewing study conduct and progress, and making recommendations concerning the continuation, modification, or termination of the study. Data Monitoring Committee (DMC) meetings will take place at least 2 times per year.

Statistical Analysis:	All participants who receive at least 1 dose of miransertib will be included in the analysis of safety. For Part A and Part B: The safety and tolerability of miransertib for all participants enrolled in Part A and Part B will be determined and summarized as a clinical narrative. Further details including data handling rules will be provided in the Statistical Analysis Plan (SAP).

LIST OF ABBREVIATIONS

Note: The terms subject, patient, or study participant may be used interchangeably.

AE	adverse event
AKT	v-Akt murine thymoma viral oncogene homolog
AKT1	serine-threonine protein kinase
ALT	alanine aminotransferase
ANC	absolute neutrophil count
AST	aspartate aminotransferase
AUC	area under the curve
AUC_{0-24}	area under the curve from time 0 to 24 hours after dose administration
AVM	arteriovenous malformation
bid	twice daily
BSA	body surface area
BUN	blood urea nitrogen
C	cycle (eg, C1 = Cycle 1)
CBC	complete blood count
CCTN	cerebriform connective tissue nevus
CFR	Code of Federal Regulations
CLOVES	Congenital Lipomatous Overgrowth, Vascular Malformations, Epidermal Nevis, Spinal/Skeletal Anomalies/Scoliosis syndrome
C_{max}	maximum plasma drug concentration
CT	computed tomography
CTCAE	Common Terminology Criteria for Adverse Events
CYP	cytochrome
D	day (eg, D1 = Day 1)
DDI	drug-drug interaction
DIC	disseminated intravascular coagulation
DLT	dose-limiting toxicity
DMC	Data Monitoring Committee
DVT	deep vein thrombosis
ECG	electrocardiogram

eCRF	electronic case report form
EDC	electronic data capture
eGFR	estimated Glomerular Filtration Rate
EOT	end of treatment
FAO	fibroadipose hyperplasia or overgrowth
FDA	Food and Drug Administration
FOB	Functional Observational Battery
GCP	Good Clinical Practice
GDPR	General Data Protection Regulation
GI	gastrointestinal
HbA1C	glycated hemoglobin
HDL	high-density lipoprotein
Hgb	hemoglobin
HHML	Hemihyperplasia Multiple Lipomatosis
HIPAA	Health Information Portability and Accountability Act
HIV	human immunodeficiency virus
HNSTD	highest non-severely toxic dose
IB	Investigator's Brochure
IC_{50}	inhibitor concentration required for 50% inhibition
ICF	informed consent form
ICH	International Council for Harmonisation of Technical Requirements for Pharmaceuticals for Human Use
IEC	Independent Ethics Committee
INR	international normalized ratio
IRB	Institutional Review Board
LDH	lactate dehydrogenase
LDL	low-density lipoprotein
MCAP	megalencephaly-capillary malformation
MedDRA	Medical Dictionary for Regulatory Activities
MI	myocardial infarction
MRI	magnetic resonance imaging
MTD	maximum tolerated dose

mTOR	mammalian target of rapamycin
mTORC2	mammalian target of rapamycin complex 2
NCI	National Cancer Institute
NHGRI	National Human Genome Research Institute
NIH	National Institutes of Health
NYHA	New York Heart Association
pAKT	phosphorylated AKT
PD	pharmacodynamic(s)
PDK1	phosphoinositide-dependent kinase 1
PE	pulmonary embolism
P-gp	P-glycoprotein 1
PH	pleckstrin homology
PI3K	phosphatidylinositol 3-kinase
PIK3CA	phosphatidylinositol-4,5-bisphosphate 3-kinase, catalytic subunit alpha
PIP3	phosphatidylinositol 3,4,5-triphosphate
PK	pharmacokinetic(s)
PND	postnatal day
pPRAS40	phospho-PRAS40
PR	partial response
PRAS40	proline-rich AKT substrate of 40 kilodaltons
PROS	PIK3CA-related Overgrowth Spectrum
PS	Proteus Syndrome
PT	prothrombin time
PTEN	phosphatase and tensin on chromosome 10
PTT	partial thromboplastin time
qd	once daily
qd-qow	one dose every other week (Q2W)
qod	every other day
QoL	quality of life
qow	every other week
qw	once per week

SAE	serious adverse event
SAP	statistical analysis plan
SAR	serious adverse reaction
SCC	single cell clone
Ser473	serine 473
SUSAR	suspected unexpected serious adverse reaction
TEAE	treatment-emergent adverse event
Thr308	threonine 308
T_{max}	time to maximum plasma drug concentration
ULN	upper limit of normal
US	ultrasound
VA	vascular anomalies
VM	vascular malformations
WMA	World Medical Association

1 INTRODUCTION

The PI3K/AKT/mTOR signaling pathway plays a major role in the physiological processes regulating cellular growth, proliferation, angiogenesis, survival, and metabolism [Brazil DP, Yang ZZ, Hemmings BA 2004] [Bellacosa, A., et al 2005] [Engelman JA, Luo J, Cantley LC 2006]. In the last 2 decades, the PI3K/AKT/mTOR signaling pathway has been extensively studied in cancer due to its critical role in tumor growth, survival, metabolism, and the development of metastases [Khan, K. H., et al 2013]. In addition, somatic activating mutations in PI3K and AKT1 (serine-threonine protein kinase) have been shown to cause abnormal segmental overgrowth phenotypes [Lindhurst, M. J., et al 2011] [Keppler-Noreuil KM, Rios JJ, Parker VE, Semple RK, Lindhurst MJ 2015]. The umbrella term of "phosphatidylinositol-4,5-biphosphate 3-kinase, catalytic subunit alpha (PIK3CA)-Related Overgrowth Spectrum (PROS)" is intended to encompass both the known conditions, including macrodactyly, FAO, HHML, CLOVES and related megalencephaly conditions, and the emerging clinical entities associated with somatic PIK3CA mutations [Keppler-Noreuil KM, Rios JJ, Parker VE, Semple RK, Lindhurst MJ 2015]. A consensus on diagnostic criteria, testing eligibility and evaluation of patients with PIK3CA-associated somatic overgrowth disorders was reached at a NIH workshop and reported by Keppler-Noreuil, et al in 2015 [Keppler-Noreuil KM, Rios JJ, Parker VE, Semple RK, Lindhurst MJ 2015].

Proteus Syndrome is another rare segmental overgrowth disorder caused by a somatic gain of function mutation in the oncogene AKT1 (AKT1-E17K). AKT serves a range of cellular functions with effects on metabolism and cell survival, and through indirect activation of mTOR controls cell proliferation, protein translation, and autophagy [Keppler-Noreuil, K. M., et al 2016]. Tissues and cell lines from patients with PS harbor admixtures of mutant alleles that ranged from <1% to approximately 50%. This mutation causes constitutive activation of AKT1, through Ser473 and Thr308 phosphorylation [Lindhurst, M. J., et al 2011] [Keppler-Noreuil KM, Rios JJ, Parker VE, Semple RK, Lindhurst MJ 2015] [Biesecker LG, Lindhurst MJ, Yourick MR, Dransfield DT 2014].

In contrast to cancer, which is characterized by multiple genetic aberrations, a single activating mutation has been identified in both PROS and PS. In general, clinical presentation is characterized by a mosaic distribution, sporadic occurrence, progressive course of the overgrowth lesions that can affect any tissue or organ in the human body (connective tissue or bone hyperplasia, vascular malformation, etc.). Onset usually occurs at birth or early in life (the first 6-18 months of life). Affected areas generally keep growing throughout the life, but at a slower pace after the patient reaches their third decade of life [Keppler-Noreuil KM, Rios JJ, Parker VE, Semple RK, Lindhurst MJ 2015] [Martinez-Lopez, A., et al 2017] [Biesecker, L. G. 2019]. Currently there is no drug therapy for PROS or PS; the treatment consists of symptom management, mainly surgical management of overgrowth lesions, that ultimately leads to severe physical disabilities with unsatisfactory QoL. The potential to modify and control disease progression is greatest during the rapid disease progression stage which occurs in early childhood. Later treatment may be beneficial, but it will likely have a limited effect.

Miransertib is a novel, potent, and selective allosteric pan-AKT inhibitor with activity against both the active and inactive forms of AKT. AKT1, 2, and 3 are inhibited with IC_{50} values of 5.0, 4.5, and 16 nM, respectively. Biochemical and cellular analysis showed that miransertib inhibited AKT activation not only by dephosphorylating the membrane associated active form of AKT but also by preventing the inactive form from localizing into the plasma membrane [Yu Y, Savage RE, Eathiraj S, Meade J, Wick MJ, et al. 2015].

1.1 Nonclinical Effects of Miransertib on Overgrowth Syndromes In Vitro

Antiproliferative activity of miransertib was assessed in 6 fibroblast cell lines derived from PROS patients with HHML (PIK3CA H1047R), CLOVES (PIK3CA H1047R), Macrodactyly (PIK3CA H1047R), and MCAP (PIK3CA H1047R, or PIK3CA E81K). These PROS fibroblast cell lines showed elevated AKT activity. Miransertib very potently inhibited proliferation of PROS fibroblasts in a dose- and time-dependent manner with less cytotoxicity as compared with rapamycin (mTOR inhibitor) and wortmannin (PI3K inhibitor). Treatment with miransertib markedly suppressed AKT and its downstream targets [Ranieri, C., et al 2018]. In addition, fibroblasts from the skin of a patient with FAO (PIK3CA H1047R) were evaluated and the results showed that miransertib inhibited both pAKT and pPRAS40 in a dose-dependent manner [Biesecker LG, Lindhurst MJ, Yourick MR, Dransfield DT 2014].

Miransertib was further evaluated in skin fibroblasts isolated from several patients with PS harboring the activating mutant of AKT1, AKT1 E17K mutation [Lindhurst, M. J., et al 2015]. pAKT levels were 7- to 29-fold higher and pPRAS40 levels were 9- to 20-fold higher in the mutation-positive SCC compared with mutation-negative SCC. Phosphorylation of AKT1 and its substrate PRAS40 and other AKT downstream targets was markedly reduced on treatment of miransertib for 24 hours at the concentration range of 31 to 500 nM. With as little as 30 nM of miransertib, pAKT levels were reduced to approximately half compared with the levels in untreated fibroblasts. At 500 nM of miransertib, all pAKT levels were nearly zero.

In an ex vivo study, pAKT levels were assessed in skin biopsies from 2 affected toes of one patient that were incubated in a culture medium for 96 hours at 37°C with or without serum in the presence or absence of miransertib at 125 nM [Lindhurst, M. J., et al 2015]. Phosphorylation of AKT was reduced from 4- to 7-fold for tissues incubated with serum and 9- to 27-fold for those in serum-free medium when miransertib was added. pPRAS40 levels were also reduced, though not as dramatically as pAKT.

In vitro antiproliferative activity of miransertib was also conducted in skin fibroblast cells from patients with PS (AKT1-E17K) and unaffected cells with wild type AKT1 were used as comparison [Lindhurst, M. J., et al 2015]. In both high (10%) and low (0.5%) serum, the mutation-positive cells were more sensitive to increased levels of miransertib than mutation-negative cells.

In summary, the PI3K/AKT pathway, which is dysregulated in overgrowth diseases such as PROS and PS, is frequently activated through mutations in PIK3CA or *AKT*. AKT1 mutation-positive cells and PROS cells treated with 625 nM of miransertib had 25% to 40%

reduction in cell viability (measured by AKT phosphorylation) compared with untreated cells, whereas in mutation-negative cells the reduction was 0% to 20% [Lindhurst, M. J., et al 2011]. A similar effect on PIK3CA-mutant cells was observed at miransertib concentrations of 1000 nM or below. The target tissue concentration required for adequate (50%-75%) inhibition of AKT phosphorylation is between 500 and 1000 nM; when concentrations were above 2500 nM, no additional effect on cellular proliferation was noted [Loconte DC, Grossi V, Bozzao C, Forte G, Bagnulo R 2015]. Thus, inhibition of AKT by miransertib is a rational approach for the therapeutic intervention in such diseases.

1.2 Toxicology of Miransertib in Animals

Miransertib was generally well tolerated in rats and monkeys up to doses of about 10 mg/kg/day. The toxicity profile in juvenile rats was not different from that of adult rats and there was no effect on male or female fertility in the juvenile toxicology study.

Based on the 4-week rat study, the STD_{10} of miransertib was determined to be 15 mg/kg/day when given daily via oral gavage. This correlates to a human equivalent dose of 90 mg/m^2/day. Based on the 4-week monkey study, the HNSTD of miransertib was determined to be 10 mg/kg/day when given via oral gavage daily. This correlates to a human equivalent dose of 120 mg/m^2/day. Hence, based on the ICH S9 guidance document, the Phase 1 starting dose was thus calculated to be 9 mg/m^2/day or 13.5 mg/day. The initial starting dose of miransertib in humans was suggested to be 10 mg/day. The actual starting dose in the first-in-human study, ARQ 092-101, was 10 mg qod.

Dosing in the juvenile toxicity study in rats started on PND 21, correlating with a 2-year old child. Therefore, the results support the safe use of miransertib in pediatric patients down to 2 years of age. The weight of evidence indicates that miransertib is not mutagenic or aneugeic but is weakly clastogenic. Additional details can be found in the IB.

1.3 Effects of Miransertib in Humans

1.3.1 EFFECTS OF MIRANSERTIB IN ONCOLOGY

Safety, tolerability and preliminary efficacy of miransertib have been tested in more than 150 adult participants with advanced solid tumors and recurrent malignant lymphoma (ARQ 092-101 [NCT# 01473095] and ARQ 092-102 [NCT# 02476955]).

1.3.1.1 ARQ 092-101

ARQ 092-101, A Phase 1 Dose Escalation Study of Miransertib in Adult Subjects with Advanced Solid Tumors and Recurrent Malignant Lymphoma, was an open-label, first-in-human of miransertib. A total of 120 participants were treated with miransertib monotherapy. miransertib was initially administered at 10 mg qod and dose escalated from 10 mg qd to 350 mg bid qw. Fifteen dose levels and 3 dosing schedules (continuous [up to 80 mg qd], intermittent [up to 270 mg qd one week on and one week off], and weekly [up to 350 mg bid qw]) were explored in this study. The MTD in adult cancer patients was determined to be 60 mg qd (approximately 30 mg/m^2).

The most common reason for treatment discontinuation was radiological disease progression (76/120, 63.3%). Safety and PK details for the 28 participants who received continuous, daily dosing of miransertib are summarized below. This subset of ARQ 092-101 participants' data are the most relevant for Study ARQ 092-103. Additional details can be found in the IB.

The drug-related TEAEs at continuous dosing are shown in Table 1.

Table 1 ARQ 092-101 Drug-Related TEAE Reported by More Than 1 Participant With QOD/QD Dosing

Preferred Term	10 mg QOD (n=4)	10 mg QD (n=3)	20 mg QD (n=3)	40 mg QD (n=4)	60 mg QD (n=7)	80 mg QD (n=7)	Total (n=28)
Diarrhoea		1 (33.3)	1 (33.3)	1 (25.0)	1 (14.3)	2 (28.6)	6 (21.4)
Dry Mouth	1 (25.0)	1 (33.3)			1 (14.3)		3 (10.7)
Nausea		2 (66.7)		1 (25.0)	2 (28.6)	4 (57.1)	9 (32.1)
Stomatitis					1 (14.3)	1 (14.3)	2 (7.1)
Fatigue	1 (25.0)			1 (25.0)	1 (14.3)	1 (14.3)	4 (14.3)
Decreased Appetite				1 (25.0)		2 (28.6)	3 (10.7)
Hyperglycaemia					1 (14.3)	4 (57.1)	5 (17.9)
Dermatitis Acneiform						2 (28.6)	2 (7.1)
Dry Skin					1 (14.3)	2 (28.6)	3 (10.7)
Palmar-Plantar Erythrodysaesthesia Syndrome					1 (14.3)	1 (14.3)	2 (7.1)
Pruritus		1 (33.3)			2 (28.6)	2 (28.6)	5 (17.9)
Rash Maculo-Papular					2 (28.6)	3 (42.9)	5 (17.9)

ALT=alanine aminotransferase; AST=aspartate aminotransferase; QD=once daily; QOD=every other day
Final study data; 07 Aug 2017

In Cohort 5, 80 mg qd, one of the first 3 participants experienced 2 DLTs (Grade 3 cardiac failure congestive and Grade 4 cardiomyopathy) and the Cohort was expanded to enroll 3 additional participants. After 2 more DLTs (Grade 3 maculopapular rash and Grade 3 hyperglycemia) were experienced by 2 other participants, qd dosing was reduced to 60 mg for Cohort 6. In Cohort 6, one of the first 3 participants experienced a DLT (Grade 3 increased AST) and the Cohort was expanded with no additional DLTs reported. The MTD was declared as 60 mg qd for the continuous dosing schedule.

1.3.1.2 ARQ 092-101 Pharmacokinetics

Miransertib PK data for this study are available for all 28 participants treated with the continuous dosing. The mean C_{max} of miransertib ranged from 11 nM (10 mg qod dose) to 166 nM (60 mg qd dose) on Day 1 and from 29 nM (10 mg qod dose) to 787 nM (80 mg qd dose) on Day 15. The mean AUC_{0-24} of miransertib ranged from 163 h*nM (10 mg qod dose) to 2217 h*nM (60 mg qd dose) on Day 1 and from 489 h*nM (10 mg qod dose) to 15212 h*nM (80 mg qd dose) on Day 15. Miransertib accumulates with accumulation ratios ranging

from 2.9 (10 mg qd dose) to 7.2 (80 mg qd dose) for C_{max}, and from 3.0 (10 mg qd dose) to 8.6 (80 mg qd dose) for AUC_{0-24}. Due to the long elimination phase, the half-life of miransertib could not be accurately determined; however, it is estimated that the half-life of miransertib is in the range of 40 to 60 hours. Additional details can be found in the IB.

1.3.1.3 ARQ 092-102

ARQ 092-102 is an open-label, Phase 1b study of miransertib in combination with carboplatin plus paclitaxel, paclitaxel alone, or anastrozole for the treatment of selected solid tumors. As of the data cutoff date, 34 participants have been treated with miransertib. The most common miransertib-related TEAEs (≥20%) seen were diarrhea (35.3%), nausea (32.4%), fatigue (26.5%), maculopapular rash (26.5%), and decreased appetite (20.6%). Additional details can be found in the IB.

1.3.2 Effects of Miransertib in Overgrowth Diseases

1.3.2.1 A Phase 1 Dose-Finding Study of Miransertib in Children and Adults With Proteus Syndrome

Study 16-HG-0014 is an investigator sponsored study conducted under NIH IND 126197 [NCT02594215]). The primary endpoint of the study was to determine the biological effect of miransertib as measured by changes in pAKT levels in the affected tissue. Results from the study have been reported and are summarized below [Keppler-Noreuil, K. M., et al 2019].

In 5 of 6 participants, a reduction of 50% or greater of tissue pAKT levels was reported, and the primary endpoint of the study was met. The clinical efficacy measurements showed significant reduction in size of the CCTN in 2 participants at Cycle 12 by quantitative standardized photography. Three participants reported an improvement in pain as assessed by a standardized pain scale.

Overall, the drug was well tolerated with most AEs considered mild or moderate in severity. The most common drug-related AEs (observed in ≥3 participants) were headache (66.7%) increase bone formation (66.7%), exostosis (66.7%), and pain in extremity (66.7%). Detailed summary of the safety data as reported by NHGRI Investigators' can be found in the IB.

1.4 Conclusion

Based on the nonclinical data and observed activity in patients with PS treated with miransertib, this Phase 1/2 study was initiated to further explore the single agent activity of miransertib in patients with PROS and PS with known PI3KCA and AKT1 somatic activating mutations.

2 INVESTIGATIONAL PLAN

PROS and PS are characterized by overlapping clinical features, but caused by different somatic activating mutations, PIK3CA and AKT1, respectively. The overgrowth can affect any organ and cause multiple disabling complications. The significant morbidity and mortality associated with these progressive disorders, together with their unique, single genetic mutations, make them good candidates for AKT/PIK3CA targeted therapies that were initially developed for oncology indications [Keppler-Noreuil KM, Rios JJ, Parker VE, Semple RK, Lindhurst MJ 2015] [Keppler-Noreuil, K. M., et al 2016].

As of 31-JAN-2019, a total of 15 PROS and PS patients with PIK3CA or AKT1 mutations have been enrolled and treated in Study 092 103.

The study includes 2 parts:

Part A: All participants enrolled before Amendment 6. Part A was designed to enroll 25 to 40 participants with PROS and PS.

Part B: All participants enrolled under Amendment 6 or higher. Cohort 1 will enroll PROS patients; Cohort 2 will enroll PS patients; Cohort 3 will enroll either PROS or PS patients who do not meet the eligibility criteria for Cohorts 1 or 2; and Cohort 4 will enroll patients previously treated with miransertib or currently receiving miransertib under Compassionate Use/Expanded Access.

Cohorts 1 and 2 were originally designed to determine the response rate of miransertib in a selected participant population, as measured by a change in target lesion size from baseline, using blinded independent central imaging review: volumetric MRI in PROS or cerebriform CCTN photography in PS.

2.1 Study Objectives

Under this amendment, the primary study objective for both Part A and Part B is to describe the safety and tolerability of miransertib in patients with PROS and PS, and further efficacy assessments have been removed. Part A was closed to enrollment after the approval of Amendment 6.

Amendment 7 will complete the final enrollment into the MOSAIC study and Compassionate Use/Expanded Access Program. In the future, patients will be transitioned to new miransertib programs.

2.2 Overall Study Design

This is an open-label, multicenter Phase 1/2 study of oral miransertib administered daily to patients with PROS and PS. The study will be conducted at up to 20 sites globally.

Part B will enroll approximately 65 participants with clinical diagnosis of PROS or PS with documented somatic PIK3CA or AKT1 mutations. Part B will be comprised of 4 Cohorts: Cohort 1 will enroll 20 participants with PROS with a measurable lesion by the study-

standardized volumetric MRI. Cohort 2 will enroll 10 participants with PS with measurable CCTN and pre-CCTN lesional area by the study-standardized photography. Cohort 3 will enroll approximately 25 PROS or PS patients who do not meet the eligibility criteria for enrollment in Cohort 1 or Cohort 2. Cohort 4 will enroll participants previously treated with miransertib or currently receiving miransertib Compassionate Use/Expanded Access.

In Part B (except Cohort 4), participants will receive miransertib at the 15 mg/m^2 qd dose level during the first 3 cycles, (a cycle of therapy is considered to 28 days). The dose will be increased to 25 mg/m^2 qd provided no clinically significant drug-related toxicity is observed. Participants who experienced miransertib-related toxicity or are unable to tolerate study medication during the first 3 cycles may be treated at lower doses.

Participants enrolled in Cohort 4 will continue treatment at the dose they were on at the time of enrollment, but their dose should not exceed the 25 mg/m^2.

For all participants, actual dose will be calculated using BSA, per the DuBois formula.

Participants will stay on treatment for up to 48 cycles.

To better understand the natural history of the disease of each individual participant, all participants will be asked to provide a detailed history of their disease, including prenatal and postnatal evaluations, and surgical operations, results of any functional tests performed before the study enrollment, and, when possible, imaging scans (eg, CT, MRI, US), photographs, and/or video recordings collected before study enrollment.

PIK3CA or AKT1 somatic mutations must be documented before enrollment. If the status is unknown, an archival or fresh tissue biopsy must be collected and tested for PIK3CA or AKT1 somatic mutations. For all enrolled participants, archival or fresh tissue biopsy should be collected and sent to the Sponsor or designee.

For Part B Cohort 1, 2, and 3, safety (eg, physical examination, vital sign measurements, clinical laboratory tests, use of concomitant medications, and collection of AE information) assessments will be performed at baseline, twice during the first cycle, and at each study visit thereafter. All clinical assessments and laboratory tests will be performed per the Schedule of Events [Table 3]

For Cohort 4, safety (eg, physical examination, vital sign measurements, clinical laboratory tests, use of concomitant medications, and collection of AE information) assessments will be performed every 3 months (Table 4). If clinically indicated, unscheduled laboratory tests and any clinical assessments or evaluations may be performed per the discretion of the investigator.

A single blood sample will be collected for CYP2D6 genotyping. The final clinical safety follow-up will be performed 30 days after the last dose of miransertib.

Miransertib is supplied as 5- and 10-mg capsules and should be swallowed whole (1 hour before or 2 hours after a meal). When medically necessary, the capsules can be opened and

sprinkled onto a small amount of sweetened semiliquid food (eg, apple sauce, chocolate syrup, or ice cream).

The study data and endpoints were reviewed by the Sponsor in 2020. It was concluded that the current data from this study would not be sufficient to establish efficacy for either the PROS or PS patients. As a consequence, Amendment 7 was written to remove all efficacy assessments, including the volumetric MRIs for the PROS patients, the CCTN photography for the PS patients, as well as to remove the functional assessments, among others.

2.3 Study Endpoints

Under this amendment, the endpoints for Part A and Part B have been combined to assess the safety and tolerability of miransertib in participants with PROS and PS based on the frequency, duration, and severity of AEs from the first dose of the drug through 90 days after the last dose of the drug.

3 SELECTION OF STUDY POPULATION

Participants with PROS or PS with a documented PIK3CA or AKT1 somatic mutation will be enrolled in this study. It is expected that the study will be conducted at up to 10 sites globally. Part A is closed to enrollment. Part B will enroll approximately 65 participants. Participant accrual will occur over a period of approximately 24 months.

Participants must meet ALL of the inclusion criteria and NONE of the exclusion criteria to be enrolled.

3.1 Inclusion Criteria

Part A is closed to enrollment after the approval of Amendment 6. See Annex 1 for inclusion/exclusion criteria for Part A.

3.1.1 Part B:

1. Signed informed consent, and when applicable, signed assent

2. **Cohort 1 (PROS) specific criteria**

   - Male or female participants ≥2 years and ≤30 years of age with BSA of ≥0.33 m^2. Participants should meet the age criterion by/on the date of the first dose Cycle 1 Day 1.

   - Have clinical diagnosis of PROS per Diagnostic Criteria for PROS (Appendix 1) and documented somatic PIK3CA variant.

   - Have at least one lesion that can be accurately measured by study-standardized volumetric MRI (eligibility to be confirmed by blinded central imaging review).

3. **Cohort 2 (PS) specific criteria**

   - Male or female participants ≥2 years and ≤18 years of age with BSA of ≥0.33 m^2. Participants should meet the age criterion by/on the date of the first dose Cycle 1 Day 1.

   - Have clinical diagnosis of PS per Diagnostic Criteria for PS (Appendix 1) and documented somatic AKT1 variant.

   - Have at least one plantar CCTN and pre-CCTN lesion that can accurately be measured by standardized photography. The CCTN is defined as a nevus with at least 2 gyri and 3 sulci and should affect between 10% and 70% of the total surface area of the foot (eligibility to be confirmed by blinded independent central photo review).

4. **Cohort 3 specific criteria**

   - Male or female PROS or PS patients ≥2 years old with BSA of ≥0.33 m^2 and who fail to meet the eligibility criteria for Cohorts 1 or 2. Participants should meet the age criterion by/on the date of the first dose Cycle 1 Day 1.

5. **Cohort 4 (PROS or PS) specific criteria**

   - Participants previously treated with miransertib or currently receiving miransertib under Compassionate Use/Expanded Access

6. Archival or fresh overgrowth tissue sample available to be shipped to Sponsor or designee

7. Except for Cohort 4, clinically progressive or worsening disease defined as an increase in number or size of the overgrowth lesion(s) in the last 6 months as assessed by the investigator

8. Adequate organ function as indicated by the following laboratory values:

   a. Hematological

      1. Hgb depending on age:

         - 2 to 5 years male and female: ≥10.0 g/dL
         - 6 to 9 years male and female: ≥11.5 g/dL
         - 10 to 17 years female: ≥11.0 g/dL
         - 10 to 17 years male: ≥11.5 g/dL
         - ≥18 years male and female: ≥10.0 g/dL

      2. HbA1c: ≤8% (≤64 mmol/mol)

3. ANC: ≥1.5 x 10^9/L
4. Platelet count ≥150 10^9/L

b. Hepatic

1. Total bilirubin ≤1.5 x ULN
2. AST and ALT ≤3 x ULN

c. Renal

1. Serum creatinine depending on age:
   - 2 to 5 years male and female: maximum 0.80 mg/dL
   - 6 to 10 years male and female: maximum 1.0 mg/dL
   - 11 to 15 years male and female: maximum 1.2 mg/dL
   - >15 years male and female: maximum 1.5 mg/dL
2. Estimated glomerular filtration rate (eGFR) ≥60 mL/min/1.73 m^2

d. Metabolic (lipids)

1. Cholesterol: ≤400 mg/dL (≤10.34 mmol/L)
2. Triglyceride: ≤500 mg/dL (≤5.7 mmol/L)

9. Male or female participants of child-producing potential must agree to use double-barrier contraceptive measures, oral contraception, or avoidance of intercourse during the study and for 90 days after the last dose of miransertib

10. Ability to complete the study questionnaires by the participant or his/her caregiver

3.2 Exclusion Criteria – Part B

1. History of Type 1 diabetes mellitus or Type 2 uncontrolled diabetes mellitus requiring regular medication (other than metformin or other oral hypoglycemic agents) or fasting glucose ≥160 mg/dL (>12 years old) and ≥180 mg/dL (if ≤12 years old) at the Screening Visit

2. History of significant cardiac disorders

3. MI or congestive heart failure defined as Class II to IV per the NYHA classification within 6 months of the first dose of miransertib (MI occurring >6 months of the first dose of miransertib will be permitted)

4. Grade 2 (per current version of NCI CTCAE) or worse conduction defect (eg, right or left bundle branch block)

5. Major surgical procedures or locoregional therapy within 4 weeks of the first dose of miransertib

6. Any experimental systemic therapy for the purposes of treating PROS or PS (eg, sirolimus, everolimus, high dose steroids) within 2 weeks of the first dose of miransertib

7. Intolerance of or severe toxicity attributed to AKT inhibitors (eg, miransertib, uprosertib, afuresertib, ipatasertib)

8. Concurrent severe uncontrolled illness not related to PROS or PS, including:

    - Ongoing or active infection
    - Known HIV infection
    - Malabsorption syndrome
    - Psychiatric illness/substance abuse/social situation that would limit compliance with study requirements

9. Pregnant or breastfeeding

10. Inability to comply with study evaluations or to follow drug administration guidelines

4 STUDY VISITS

Before the start of any study required procedures, the investigator or designee must obtain a signed written ICF and, when applicable, signed assent for the study from each prospective participant or his/her parent or legal guardian.

For Part A, all ongoing participants will continue treatment and will follow the Schedule of Events in Annex 1.

For Part B Cohorts 1, 2 and 3, study visits will consist of a Screening Visit, (during which the participant's eligibility for the study and baseline disease state will be evaluated), 2 visits during the first and fourth cycles, one visit per cycle for Cycles 2 and 3, and 5, then once every 2 cycles for Visits 7, 9, 11, and 13, and then one visit per every 3 cycles until EOT, during which the participant's clinical status will be evaluated, and a 30-Day Safety Follow-up (Table 3).

For participants enrolled in Cohort 4, study visits will consist of a Screening Visit, (during which the participant's eligibility for the study and baseline disease state will be evaluated), Cycle 1 Day 1 visit and then one visit per every 3 cycles (eg, Cycle 4 Day 1, Cycle 7 Day 1,

Cycle 10 Day 1, Cycle 13 Day 1, etc.) until EOT, during which the participant's clinical status will be evaluated, and a 30-Day Safety Follow-up (Table 4).

After the Screening Visit and a determination by the investigator and with Sponsor approval that the participant meets all inclusion criteria and none of the exclusion criteria, the participant will be considered entered into the study.

Participants enrolled in Part B, Cohorts 1 and 2, must also meet eligibility requirements according to applicable central imaging criteria.

4.1 Informed Consent

A sample ICF and Assent Form with core information will be provided to each study site. Before study initiation at a given study site, each site/investigator must obtain a written approval/favorable opinion from its respective IRB/IEC for the ICF, assent form, and any other written information to be provided to participants. All ICFs and assent forms must be compliant with the ICH GCP guidelines and local regulations and must be approved by the Sponsor before submission to the IRB/IEC. The written approval of the IRB/IEC, together with the approved participant information, ICF, and assent forms, must be maintained in the study master files.

Written informed consent and/or assent must be obtained from a prospective participant and his/her parent/legal guardian before any study-specific procedures are performed on that individual. Participants who agree to participate in the study will sign the most recently approved ICF and/or Assent Form and will be provided with a copy of the fully executed document(s). The original, executed ICF and Assent Form will be maintained in the respective participant's clinical study file.

The ICF can be signed greater than 45 days before dosing and does not need to be re-signed before dosing unless specific reasons or local regulations apply (eg, a new consent version has been issued and approved by the IRB/IEC).

All screening imaging assessments must be performed within 21 days of C1D1, unless rescan by MRI or repeat photography is required.

4.2 Participant Discontinuation

Participants in the study will be removed from treatment or the study at any time if they meet any of the following criteria:

4.2.1 Discontinuation From Treatment

- Participant experiences, in the opinion of the investigator, an acceleration of the overgrowth disease.
- Miransertib-related clinically significant toxicities that do not recover despite optimal treatment or dose reduction.
- Participant needs to take or elects to take another investigational agent.

- Development of any concurrent medical condition that might preclude or contraindicate the further administration of miransertib.
- Serious protocol violations such as noncompliance with treatment or required follow-up and evaluation as determined by the investigator.
- Investigator's decision (in agreement with the Sponsor's Medical Monitor or designee).
- Participant, or guardian, refusal of further treatment/withdrawal of consent. Reasons for refusal of further treatment/withdrawal of consent should be noted in that participant's medical record.
- Death.

4.2.2 Discontinuation From the Study

- Participant and/or guardian refusal of further examinations (follow-up visits) and/or communications with the site/withdrawal of consent. Reasons for refusal/withdrawal of consent should be noted in that participant's medical record.
- Lost to follow-up.
- Death.

4.3 Study Discontinuation

The Sponsor reserves the right to temporarily or permanently discontinue the study at any investigative site and at any time. Reasons for study discontinuation may include, but are not limited to, the following:

- Safety concerns
- Poor enrollment
- Investigator noncompliance with the protocol, GCP guidelines, or other regulatory requirements
- Request to discontinue the study by a regulatory or health authority
- Discontinuation of product development
- Manufacturing difficulties/concerns

The Sponsor and/or designee will promptly inform all Investigators and the appropriate regulatory authorities if the study is suspended or terminated for safety reasons. In the case of such termination, the investigator will notify their IRB/IEC.

5 STUDY PROCEDURES

5.1 Medical History

Medical history will include but not be limited to the following:

- Demography: date of birth, sex, race and ethnicity
- Clinically significant prior diagnoses and surgical operations (not related to PROS or PS)
- Medications used within 45 days before the first dose of miransertib and throughout the treatment period should be reported
- Natural history of the disease (up to the study enrollment):
    - Perinatal history; prenatal and postnatal evaluations; family history; intellectual and psychomotor developmental milestones; disease-related manifestations (anatomical location, severity, frequency); management of the disease, including prophylactic and symptomatic therapies, hospitalizations, surgical operations; results of the clinical function assessments
- Genetic testing results: AKT1 or PIK3CA mutation status in the affected tissue must be confirmed before dosing. The AKT1 or PIK3CA mutation (dependent on clinical diagnosis) results will be captured in the EDC database and copies of the genetic report will be forwarded to the Sponsor or designee. If mutational status is unknown, archival or fresh tissue biopsy must be collected and tested for mutation status to confirm eligibility for the study.
    - An archival tissue sample is to be sent to the Sponsor or designee for central confirmation of mutation analysis, if required.
- When possible, imaging scans (eg, MRI, CT, US), photography, video recordings, and/or other assessments of size such as linear and/or circumference measurements performed before study enrollment will be collected and forwarded to the Sponsor or designee.

5.2 12-Lead Electrocardiogram

A 12-lead ECG will be conducted at specific timepoints (see Table 3 and Table 4). Additional ECGs may be conducted if clinically indicated or required per standard of care (triplicate if possible). The ECG parameters will be captured in the EDC database and copies of ECG tracings will be collected and forwarded for future analyses by the Sponsor or its designee.

5.3 Clinical Laboratory Tests

Safety laboratory determinations will include hematology, blood chemistry, and urinalysis. Refer to the Schedule of Events (Table 3 and Table 4) of the protocol for testing frequency. All laboratory tests required for scheduled visits during the study must be obtained at the local laboratory at the investigational site. If laboratory tests need to be performed to assess an AE in between scheduled study visits, these tests can be performed at a laboratory close to the participant's home after agreement with the Sponsor.

Chemistry samples should be taken in a fasting state (fasting for at least 4 hours for children <6 years of age and at least 8 hours for children ≥6 years of age). If, in error, the participant has eaten ahead of testing, this should be documented as a fed rather than a fasting sample on the eCRF.

- Hematology: CBC including Hgb, hematocrit, white blood cell count with 5-part differential, red blood cell, platelet, and reticulocyte count
- HbA1c (**screening only**)
- Coagulation tests (**screening only**): PT, PTT, and INR, D-dimer and fibrinogen
- Blood chemistry: alkaline phosphatase, bicarbonate, calcium, phosphorus, magnesium, albumin, glucose, serum creatinine, and insulin
- Liver function tests: AST, ALT, LDH, alkaline phosphatase, total and direct bilirubin, uric acid, total protein, and BUN
- Electrolytes: sodium, potassium, and chloride
- Lipids: cholesterol, HDL, LDL, and triglycerides
- Routine urinalysis: dipstick and microscopy including protein, specific gravity, glucose and blood
- Serum pregnancy test for female participants of child-bearing potential, if applicable
- Clinical laboratory tests can be collected within 24 hours of CXDX clinic visit for all visits except C1D1.

5.4 Pharmacokinetic Assessments

With Amendment 7, PK analyses will be limited to data already collected, as additional PK samples will not be collected.

PK variables measured will include C_{max}, T_{max}, and AUC.

For Part A, blood samples for PK analysis will be collected during Cycle 1 on Day 1 and Day 15 and on Cycle 2 Day 1 (Annex 1). Blood samples for PK analysis will also be collected during Cycles 4 and 7. If the dose did not increase during Cycle 4 or Cycle 7, a

single PK sample will be collected on Day 1 of these cycles. If the dose did increase during Cycle 4 or Cycle 7, blood samples for PK analysis will be collected on Day 1 and Day 15, and a single PK sample will be collected on Cycle 5 Day 1 and Cycle 8 Day 1. The blood sampling date and time and the time of dosing of miransertib administration on the days of PK collection must be recorded on the eCRF.

For Part B (Cohorts 1, 2, and 3), blood samples for PK analysis will be collected during Cycles 1 and 4 according to the schedule in Table 2. The blood sampling date and time and the time of dosing of miransertib administration on the days of PK collection must be recorded on the eCRF.

Table 2 Part B: PK Sampling Schedule (Cohorts 1, 2, and 3)

Day	Procedure	Collection Timepoint	Permitted Window for blood draw
CYCLE 1 and CYCLE 4 Day 1			
1	Draw blood sample	0 hour (before the first dose of miransertib)	NA
1	Draw blood sample	3 hours	(± 15 minutes)
1	Draw blood sample	8 hours	(± 1 hour)
CYCLE 1 and CYCLE 4 Day 15			
1	Draw blood sample	0 hour (before dosing)	NA
1	Draw blood sample	4 hours	(± 15 minutes)
1	Draw blood sample	6 hours	(± 1 hour)

NA=not applicable

Detailed instructions for collection and shipment of plasma PK samples will be provided in the Laboratory Manual. Samples for PK assessments will be labeled by personnel from the institution with the participants' study ID; the participants' identity will not be made known to employees from the Sponsor, additional collaborators, or other Investigators. Samples will only be used for the purposes of the protocol and will only be used by the Sponsor's personnel or by an external laboratory chosen by the Sponsor to outsource the analyses according to internal guidelines. Samples will be kept until all protocol-related analyses are completed, for a period not exceeding 10 years or as required by local law.

5.5 Other Assessments

A single blood sample will be collected from all participants for detecting polymorphism of CYP2D6. The goal will be to explore the impact of these variants on study endpoints as well as on PK. This may only be explored for participants enrolled before Amendment 7.

5.6 Additional Tests

No longer applicable with the adoption of Amendment 7.

5.7 Home Blood Glucose Monitoring

At home, fasting glucose measurements may be performed as necessary in case of symptoms or as determined by the investigator.

5.8 Schedule of Events

5.8.1 Cohorts 1, 2, and 3

Table 3 is intended as a list of visits and associated assessments. Please refer to relevant protocol sections for detailed information.

Table 3 Schedule of Events Part B Cohorts 1, 2 and 3

Phase	**Screening**	**Treatment (Year 1) [1]**					**Treatment (Years 2-4)**	**Follow-Up**	
Tests & Procedures / Visit Name	**Screening**	**C1D1**	**C1D15 C4D15**	**C2, C3, C5, C9, C11,**	**C4D1**	**C7, C13**	**C16, C19, C22, C25, C28, C31, C34, C37, C40, C43, C46**	**EOT (C48)**	**30-day Safety Follow-up**
Window (days)	**-14 to 0**	**-1 to 0**	**± 3**	**± 5**		**± 5**	**± 5**	**Within 7 days**	**30+ Days**
Written informed consent	X								
Medical history	X								
Physical examination	X	X	X	X	X	X	X	X	X
Vital signs	X	X	X	X	X	X	X	X	X
Calculate BSA / dose		X		X	X	X	X		
Dose increase to 25 mg/m^2					X				
12-lead ECG		X	X		X			X	X
Fasting clinical blood tests	X			X	X	X	X	X	X
Insulin/glucose blood tests	X					X	X (C19, C25, C37)	X	
Urinalysis	X			X	X	X	X	X	X
Serum pregnancy test (if applicable)	X							X	X
Dispense study medication [2]		X		X	X	X	X		
Collect and count returned miransertib capsules				X	X	X	X	X	
Concomitant medications	X	X	X	X	X	X	X	X	X
Adverse events		X	X	X	X	X	X	X	X

BSA=body surface area; C=cycle; D=day; ECG=electrocardiogram; EOT=end of treatment.

1 The following CXDX visit assessments may be performed within a 24-hour window of dosing (Physical Examination, ECG)

2 Dispense monthly allotments at C1, C2, C3, C4; 2-month allotments at C5, C7, C9, C11; 3-month allotments at C13, C16, C19, C22, C25, C28, C31, C34, C37, C40, C43; 2-month allotment at C46

5.8.2 Cohort 4

Table 4 is intended as a list of visits and associated assessments. Please refer to relevant protocol sections for detailed information.

Table 4 Schedule of Events Part B Cohort 4

Phase	**Screening**	**Treatment (year 1)**			**Treatment (years 2-4)**		**Follow-Up**
Tests & Procedures / Visit Name	**Screening**	**C1**	**C4**	**C7, C10, C13**	**C16, C19, C22, C25, C28, C31, C34, C37, C40, C43, C46**	**EOT (C48)**	**30-day Safety Follow-up**
Window (days)	**-14 to 0**	**-1 to 0**	**± 5**	**± 5**	**± 5**	**Within 7 days**	**30+ Days**
Written informed consent	X						
Medical history	X						
Physical examination	X	X	X	X	X	X	X
Vital Signs	X	X	X	X	X	X	X
Calculate BSA / dose		X	X	X	X		
12-Lead ECG		X	X			X	X
Fasting clinical blood tests	X		X	X	X	X	X
Insulin/glucose blood tests	X			X	X (C19, C25, C37)	X	
Urinalysis	X		X	X	X	X	X
Serum pregnancy test (if applicable)	X					X	X
Tissue biopsy	X						
Blood for CYP2D6		X					
Lesion measurement by imaging (e.g. DXA)	X						
Dispense miransertib[1]		X	X	X	X		
Collect and count returned miransertib capsules			X	X	X	X	
Concomitant medications	X	X	X	X	X	X	X
Adverse events		X	X	X	X	X	X

BSA=body surface area; C=cycle; DXA=dual-energy X-ray absorptiometry ECG=electrocardiogram; EOT=end of treatment.

[1] Dispense 3-month allotments from C1 through C43; dispense 2-month allotment at C46.

6 TREATMENT

6.1 Miransertib

Miransertib capsules will be supplied to the pharmacy at the clinical site in bottles containing 30 capsules each. Study medication will be labeled as an investigational agent, limited by federal and other applicable laws, as required. The appropriate number of bottles will be dispensed to the participant to ensure that they have sufficient drug at the prescribed dose level until their next drug dispensing visit. Miransertib should be stored according to the instructions provided on the bottle label.

6.2 Miransertib Accountability

The Sponsor will provide all study medication required for completion of this study. The recipient will acknowledge receipt of the drug indicating shipment content and condition. Damaged supplies will be replaced. Until dispensed to the participants, the study medication will be stored in a secure locked area, accessible to authorized personnel only. Drug accountability records will be maintained. The clinical site's pharmacy records should record quantities of study medication received and quantities dispensed to participants, including the lot number, date received and dispensed, participant identifier number, participant initials (when applicable), protocol number, dose, quantity returned, balance remaining, and the initials of the person dispensing the drug. Accurate records of all study medication dispensed from and returned to the clinical site are to be maintained. The clinical site must supply a copy of their drug destruction policy to the Sponsor before authorization for destruction will be granted. Product accountability will be monitored throughout the study. On completion or termination of the study, and after inventory by the Sponsor's monitor or designee, all unopened drug is to be returned to the Sponsor or designee in the original containers.

6.3 Miransertib Administration

In Part A, the first 6 participants (all with PROS) were enrolled in the dose escalation cohort and treated at 15 mg/m^2 qd for 3 cycles, with a cycle defined as 28 days. They were allowed to have 2 dose escalations (25 mg/m^2, 35 mg/m^2 qd). Only the first participant had the dose increased to 35 mg/m^2. Subsequently, based on nonclinical and clinical data from the NHGRI, and data from the 6 participants in this study, 15 mg/m^2 qd for at least 3 cycles with an option to dose increase to 25 mg/m^2 was determined to be safe. All subsequently enrolled participants received miransertib at 15 mg/m^2, with a dose increase to 25 mg/m^2 permitted after either 3 or 6 cycles of therapy.

For Part B (Cohorts 1, 2, and 3), participants will receive miransertib at the starting dose of 15 mg/m^2 qd for the first 3 cycles, (a cycle of therapy is 28 days), and then the dose will be increased to 25 mg/m^2 qd, provided no clinically significant drug-related toxicity is observed.

Participants in Cohort 4 receiving miransertib at the time of enrollment under Compassionate Use/Expanded Access will continue with their current dose, but their dose should not exceed 25 mg/m^2. Participants who previously received miransertib but were not on the study medication at the time of enrollment, will receive miransertib at the starting dose of

15 mg/m^2 qd for the first 3 cycles with a potential dose increase to 25 mg/m^2 qd, provided no clinically significant drug-related toxicity is observed. Actual dose will be calculated using BSA, per the DuBois formula.

Miransertib will be supplied as 5 and 10-mg capsules, which should be taken either 1 hour before or 2 hours after a meal. Capsules should be swallowed whole. The preferred beverage for administration is water. However, in cases where there is a medical problem affecting the participant's ability to swallow (eg, the participant has an enlarged tongue), the capsules can be opened, and the powder contents sprinkled onto a small amount of sweetened semiliquid food (eg, apple sauce, chocolate syrup, or ice cream) and administered in its entirety to the participant. The same type of semiliquid food should be used, if possible, for the duration of the study. Refer to the Pharmacy Manual for specific instructions on opening the capsules. To maximize safety and avoid unnecessary exposure to the drug by caregivers, it is recommended that gloves and a facemask be worn by the caregiver when handling opened capsules and that the gloves and facemask are discarded along with the empty capsule shells after use. Pregnant women should not open the capsules.

Miransertib will be administered once daily. Dose will be calculated based on BSA, and actual dose level will be rounded to the nearest 5 mg using a dosing nomogram (Appendix 2). Miransertib will be capped at a BSA >1.77 m^2. During site visits, miransertib dosing will be adjusted for changes in BSA according to the dosing nomogram.

Participants and/or their guardians must use the diary card provided to keep a record of daily intake of each dose of miransertib and the method of administration (capsules swallowed whole or opened and swallowed with semiliquid).

6.4 Missed or Vomited Doses

A missed or vomited dose should not be replaced. The participant will be instructed to take the next scheduled dose at the regularly scheduled time.

6.5 Dose Modifications

When a drug-related toxicity is observed, dose interruptions and/or reductions in miransertib administration are allowed. In general, once the dose of miransertib has been modified for a participant, all subsequent doses should be administered to that participant at the modified dose level. A drug-related toxicity is any toxicity considered related, probably related, or possibly related to miransertib.

Dose reduction should occur according to Table 5. Guidelines for dose interruptions for drug-related toxicities and hyperglycemia are detailed in Table 6 and Table 7, respectively.

Table 5 Miransertib Dose Reduction Schedule

Administered Dose	Dose Reduction
25 mg/m^2 qd:	15 mg/m^2 qd
	10 mg/m^2 qd
	5 mg/m^2 qd
15 mg/m^2 qd (during first 3 cycles)	10 mg/m^2 qd
	5 mg/m^2 qd

qd=once per day

Dose reduction is allowed and should be performed per Table 5. If the dose reduction is indicated, the participant should be assigned to the lower dose and it should be agreed on by the investigator and the Sponsor. Dose re-escalation will not be permitted.

Treatment will be permanently discontinued in case of Grade 2 drug-related toxicity that does not recover within 21 days after holding miransertib, or Grade 3 drug-related toxicity at the lowest dose (5 mg/m^2), or if another discontinuation criterion listed in the protocol is met.

Table 6 Dose Interruptions/Reductions for Drug-Related Toxicity Except Hyperglycemia

Event Grade (CTCAE)	Action
Grade 1	Continue current dose level.
Grade 2	Withhold miransertib until recovery to Grade 1 or baseline. If recovery occurs within 21 days of holding miransertib, restart miransertib at the same dose level, unless further dose reduction is required. If a participant experienced a Grade 2 drug-related toxicity that does not recover within 21 days of holding miransertib at a higher dose level (25 mg/m^2 or 15 mg/m^2), they will be allowed to reduce the dose to the next lower level once the event has recovered to Grade 1 or baseline.
Grade 3-4	Withhold miransertib until recovery to Grade 1 or baseline. If recovery occurs within 21 days of holding miransertib, restart miransertib at the next lower dose level for subsequent doses, unless further dose reduction is required. If recovery occurs after more than 21 days on drug hold, permanently discontinue miransertib.

Table 7 Dose Modification for Drug-Related Hyperglycemia and Suggested Clinical Treatment and Management of Hyperglycemia

Event Grade (CTCAE)	Miransertib Dose Modification	Suggested Clinical Treatment and Management of Hyperglycemia
Grade 1	Continue treatment with the current dose level and schedule.	Start once per day home glucose monitoring (alternate between before breakfast and dinner, preferably fasting). No treatment needed.
Grade 2	Withhold miransertib until recovery to Grade 1 or baseline. If recovery occurs within 21 days of holding miransertib, restart miransertib at the next lower dose level for subsequent doses, unless further dose reduction is required. If recovery does not occur within 21 days of drug hold at the lowest dose permanently discontinue miransertib.	Start home glucose monitoring twice per day (before breakfast and dinner, preferably fasting). Treat hyperglycemia per the institutional standard of care.
Grade 3 or 4	Withhold miransertib until recovery to Grade 1 or baseline. If recovery occurs within 21 days of holding miransertib, restart miransertib at the next lower dose level for subsequent doses, unless further dose reduction is required. If recovery does not occur within 21 days of drug hold, permanently discontinue miransertib.	Treat hyperglycemia per the institutional standard of care.

6.6 Treatment Compliance

A participant is considered compliant with the study protocol when study medication is administered at a compliance level of ≥80% (excluding dose holds for surgical operations or drug-related AEs).

Compliance will be calculated using the following equation:

([Number of capsules ingested] / [Number of capsules that should have been ingested]) *100%

6.7 Blinding

This is an open-label study. Neither the participant nor the investigator or site staff will be blinded to the treatment administered.

6.8 Concomitant Medication and Procedures

6.8.1 Permitted Treatment

The following treatments are permitted while on study:

- Standard therapies, including sclerotherapy, for concurrent medical conditions
- Oral hypoglycemic treatment or insulin for elevated blood glucose
- Topical or low dose systemic steroid treatment
- High dose steroid treatment is permitted when used intermittently for acute exacerbation of disease
- Factor Xa inhibitors (fondaparinux, rivaroxaban, apixaban, and edoxaban) are preferred to warfarin if anticoagulation therapy is needed
- Surgical procedures are allowed, provided that in the opinion of the investigator, the participant does not meet criteria for treatment discontinuation
    - A minor surgical operation or procedure generally does not require extensive resection (eg, biopsy, tooth extraction, etc.) and hospitalization (eg, day surgical operation), presents low risk of complications, and may not require treatment interruption. If drug hold is required, the investigator and the Sponsor should discuss the duration of drug hold before and after the surgical operation.
    - A major surgical operation requires a more extensive resection (eg, appendectomy, tumor excision), prolonged hospitalization with higher risk of complications, and treatment interruption for at least 2 weeks before and 1 week after the surgical operation. If a surgery is required, the investigator and the Sponsor should discuss the duration of drug hold before and after the surgical operation.

6.8.2 Prohibited Treatment

The following treatments are prohibited while on study:

- Other investigational agents
- Inhibitors of the mTOR pathway (eg, sirolimus, everolimus)
- Immunosuppressive therapies

- Continuous high dose steroids

6.8.3 Medications to be Avoided While on Study

Miransertib is metabolized by CYP2D6, CYP2C9, and CYP3A4. Additionally, miransertib has been shown to inhibit CYP2C19, CYP2C9, and CYP2D6 with IC_{50} values of 4.0, 3.0, and 10.2 µM, respectively.

A preliminary assessment of the effect of CYP450 inhibitors on miransertib exposure was performed using available data from the ARQ 092-101 clinical study. A subset of 32 participants with normal CYP2D6 expression who received doses of miransertib ranging from 10 mg qd to 270 mg qd-qow were evaluated. The majority of these participants (28/32) were taking one or more known CYP450 inhibitors (2D6, 3A4, 2C19, 2C9) concurrently with miransertib. The average AUC_{0-24} divided by dose for participants taking CYP inhibitors (17/32 2D6, 21/32 3A4, 13/32 2C19, and 12/32 2C9) was within 30% of the AUC_{0-24} of all participants regardless of inhibitor combination, with the lowest average AUC_{0-24} observed in participants taking no known inhibitors (4/32). Moreover, AEs known to be associated with miransertib such as hyperglycemia and rash were not observed more frequently in any subgroup. However, this analysis was conducted on a limited sample of participants, and to date, no formal DDI studies have been performed for miransertib.

Therefore, the following strong CYP inhibitors, inducers, and substrates are not permitted during the study:

- Strong CYP2D6 inhibitors and inducers
- Strong CYP3A4 inhibitors and inducers
- Strong CYP2C9 inhibitors and inducers
- Strong CYP2C19 substrates and inducers
- Grapefruit juice

See Appendix 3 for details.

6.8.4 Potential of Drug-Drug Interaction When Miransertib and Warfarin Are Coadministered

Warfarin is the standard treatment for participants at risk for developing DVT or PE. To date, no formal clinical studies have been conducted to assess the potential for DDI of miransertib with warfarin. Hence, the following assessment is based on in vitro CYP450 studies with miransertib, clinical experience of miransertib (monotherapy) in Phase 1 oncology studies, and literature data available for warfarin.

Miransertib is metabolized by CYP2D6, CYP2C9, and CYP3A4. Additionally, miransertib has been shown to inhibit CYP2C19, CYP2C9, and CYP2D6 with IC_{50} values of 4.0, 3.0,

and 10.2 µM, respectively. Warfarin is also metabolized by CYP2C9, CYP3A4, and CYP1A2.

Because both agents are metabolized by CYP2C9 and CYP3A4, and miransertib is a moderate to strong inhibitor of CYP2C9, the continued use of warfarin for participants taking miransertib is not recommended. Also, sensitive substrates for CYP2C19 should be avoided or used with caution. See Appendix 3 for details.

For participants who show a clinical need for an antithrombolic agent, there are alternative therapies that do not have a high DDI risk based on CYP metabolism. Possible options include thrombin inhibitors such as argatroban that is minimally involved in CYP3A4/5 metabolism (in vitro) or dabigatran (not metabolized by any CYP450 enzymes). Dabigatran is a P-glycoprotein 1 (P-gp) substrate/inhibitor (Appendix 4); it should be noted that while miransertib is not a P-gp substrate, it has not been tested in P-gp inhibition studies.

6.9 Potential Risks

Based on data from oncology and nononcology clinical studies, participants should be monitored for signs and symptoms of hyperglycemia, skin toxicities (rash maculopapular, rash, pruritus, dermatitis, etc.), stomatitis/mucosal inflammation, transaminase (ALT and AST) elevation, and diarrhea. These potential risks are generally consistent with the PI3K/AKT/mTOR pathway inhibitor class. The current safety information for miransertib can be found in the IB.

Also, based on nonclinical data it has been suggested that miransertib may cause a phototoxic reaction in some participants exposed to the drug and sunlight. The amount of miransertib that may be required to cause such reaction is unknown. All participants should be instructed to avoid exposure to sunlight, to use sunscreen to protect exposed areas of the body (eg, forehead, nose, lips, and hands), and to report symptoms that may be associated with phototoxic reaction (eg, redness, pruritus, swelling, blister formation).

There can be other drug-related risks factors that have not yet been reported.

7 SAFETY ASSESSMENTS

Adverse events will be assessed throughout study and categorized by the current version of CTCAE. Participants will be evaluated according to the Schedule of Events in Table 3 and Table 4. If clinically indicated, unscheduled laboratory tests and any clinical assessments or evaluations may be performed per the discretion of the investigator.

7.1 Definitions

7.1.1 Adverse Event

AE means any untoward medical occurrence associated with the use of a drug in humans, whether considered drug related. An AE can therefore be any unfavorable and unintended sign (including an abnormal laboratory finding, for example), symptom, or disease temporally associated with the use of a medicinal product and does not imply any judgment about causality.

7.1.2 Adverse Reaction

An adverse reaction is defined as any event for which there is a reasonable possibility that the drug caused the event.

7.1.3 Suspect Adverse Reaction

A suspected adverse reaction is defined as any AE for which there is a reasonable possibility that the drug caused the AE. Reasonable possibility means that there is evidence to suggest a causal relationship between the drug and the AE. Suspected adverse reaction implies a lesser degree of certainty about causality than adverse reaction, which means any AE caused by a drug.

7.1.4 Unexpected

An AE or SAR is considered "unexpected" if it is not listed in the IB or is not listed at the specificity or severity that has been observed. "Unexpected" also refers to AEs or SARs that are mentioned in the IB as occurring with a class of drugs or as anticipated from the pharmacological properties of the drug but are not specifically mentioned as occurring with the particular drug under investigation.

7.1.5 Serious

An AE or SAR is considered "serious" (an SAE) if, in the view of either the investigator or Sponsor, it results in any of the following outcomes: death, a life-threatening AE, in-patient hospitalization or prolongation of existing hospitalization, a persistent or significant incapacity or substantial disruption of the ability to conduct normal life functions, or a congenital anomaly/birth defect. Important medical events that may not result in death, be life-threatening, or require hospitalization may be considered serious when, based on appropriate medical judgment, they may jeopardize the participant and may require medical or surgical intervention to prevent one of the outcomes listed. An AE or SAR is considered "life-threatening" if, in the view of either the investigator or Sponsor, its occurrence places the participant at immediate risk of death.

7.1.6 Suspected Unexpected Serious Adverse Reaction (SUSAR)

All AEs that are determined by the investigator or by the Sponsor as having a reasonable suspected causal relationship (possibly, probably, or definitely related) to a study medication including placebo and that are both unexpected and serious are considered to be SUSAR and are subject to expedited regulatory reporting.

7.1.7 Hospitalization

Hospitalization is defined as a hospital admission that lasts more than 24 hours.

7.1.8 Study Medication-related Adverse Event or Serious Adverse Event

Study medication-related AE or SAE is defined as an AE or SAE that is related to the treatment with miransertib. A related AE or SAE is any AE or SAE considered related, probably related, or possibly related to miransertib.

7.1.9 Further Adverse Event and Serious Adverse Event Defining

Wherever possible, a specific disease or syndrome rather than individual associated signs and symptoms should be identified. However, if an observed or reported sign or symptom is not considered a component of a specific disease or syndrome by the investigator, it should be recorded as a separate AE.

Laboratory data are to be collected as stipulated in this protocol. Clinical syndromes associated with laboratory abnormalities are to be recorded as appropriate (eg, diabetes mellitus instead of hyperglycemia).

Scheduled hospitalizations or elective surgical procedures will not be considered as AEs or SAEs. Prolongation of a scheduled hospitalization can be considered an SAE.

Complications associated with scheduled procedures are considered AEs or SAEs.

Treatment-emergent AEs, including SAEs are events with the onset or the worsening of the severity that occurred at or any time after administration of the first dose and through 90 days after the administration of the last dose of the study medication.

Any AEs, including SAEs which are observed before administration of the study medication should be reported as medical history.

7.2 Responsibilities and Procedures

The responsibility for the safety of an individual participant lies in all cases with the investigator. This includes the timely review of all safety data obtained during the course of the study.

An investigator must instruct his/her participants to report any AE and SAEs they experience. Investigators must capture, evaluate, and document all AEs and SAEs occurring during a

participant's participation in the study, commencing with the first day of treatment and including the protocol-defined 30-day post-treatment follow-up period as source documents and on designated eCRF pages. These AEs/SAEs must be recorded in the EDC system of this study.

Investigators should assess AEs at each scheduled and nonscheduled visit, by the use of open-ended questioning, physical examination, and review of laboratory results. It is important to record all AEs and SAEs that result in temporary and permanent discontinuation of study medication, regardless of severity.

Investigators must report all SAEs, whether they are considered study medication related, to the Sponsor or designee within 24 hours from knowledge of the event (see Section 8.4).

In cases of SUSARs, Investigators are responsible for reporting to their local IRB/IEC as required by regulation; and the Sponsor or designee is responsible for notifying regulatory authorities and all relevant Investigators of SUSARs.

7.3 Adverse Event and Serious Adverse Event Criteria

AEs and SAEs are evaluated and graded using current NCI CTCAE guidelines.

7.4 Serious Adverse Event Reporting

In the event of any new SAE occurring during the study, the investigator must notify the Sponsor or designee within 24 hours of becoming aware of the event by telephone, or by email. When an event is reported by telephone, a written report must be sent immediately thereafter by email. For names, addresses, telephone numbers for SAE reporting, see information included on the SAE Report Form. All written reports should be transmitted using the SAE Report Form, which must be completed by the investigator after specific completion instructions. The AE section of the eCRF must be completed. Relevant pages from the eCRF may be provided in parallel. Additional documents may be provided by the investigator, if available (for ex; laboratory results, hospital report, autopsy report). In all cases, the information provided on the SAE Report Form must be consistent with the data on the event that is recorded in the corresponding sections of the eCRF. The investigator must respond to any request for follow-up information or to any question the Sponsor or designee may have on the AE within the same timelines as described for initial reports.

The information provided on the SAE Report Form should be as complete as possible but contain a minimum of:

- A short description of the AE (diagnosis) and the reason why the AE was categorized as serious
- Participant identification and treatment (if applicable)
- Investigator's name and phone number (if applicable)
- Name of the suspect medicinal product and dates of administration

- Assessment of causality

If all information about the SAE is not yet known, the investigator will be required to report any additional information within 24 hours as it becomes available.

All SAEs will be evaluated by the Sponsor's Medical Monitor or designee. The Sponsor will make an assessment of the expectedness of an SAE based on the criteria outlined in Section 8.1.4. In the case of a SUSAR, once all of the relevant information is compiled on the event, the Sponsor or designee will report the event to all pertinent regulatory authorities having jurisdiction over ongoing miransertib studies in an expedited manner (within 7 days or 15 days of knowledge) and to all Investigators involved in miransertib clinical studies.

The Investigators must in turn notify their governing IRB/IEC as required by regulation.

7.5 Posttreatment Safety Follow-up

In this study, the posttreatment safety follow-up period is defined as 30 days after the last dose of miransertib. All AEs occurring during the study period from the time of the first dose to the last day of the 30-day posttreatment follow-up period will be captured.

All participants will be followed for a minimum of 30 days after discontinuation of miransertib. All participants should be instructed to report AEs or SAEs occurring during the 30-day posttreatment safety follow-up period.

Unresolved study medication-related (see Section 8.1.8 for definition) AEs and SAEs at the time of treatment discontinuation or new study medication-related AEs and SAEs that occur during the 30-day safety follow-up period will be followed until they have, in opinion of the Investigator, resolved to baseline, have stabilized, or are deemed to be irreversible.

7.6 Grading of Severity

Each AE or SAE will be graded for severity according to the current NCI CTCAE version. The criteria can be found at http://ctep.cancer.gov/reporting/ctc.html.

For AEs not listed in the NCI CTCAE, a similar grading system should be used as follows:

- Grade 1 Mild AE
- Grade 2 Moderate AE
- Grade 3 Severe AE
- Grade 4 Life-threatening or disabling AE
- Grade 5 Death related to AE

For AEs that can be described by the NCI CTCAE guidelines, the current NCI CTCAE version Grade 4 (life-threatening or disabling AE) is assessed based on unique clinical descriptions of severity for each AE and these criteria may be different from those used for

the assessment of AE seriousness. An AE assessed as Grade 4 based on the NCI CTCAE Grades may or may not be assessed as serious based on the seriousness criteria.

7.7 Assessment of Causality

The relationship between an AE and miransertib will be determined by the investigator by his/her clinical judgment and the following definitions:

7.7.1 Related

- The AE follows a reasonable temporal sequence from study medication administration and cannot be reasonably explained by the participant's clinical state or other factors (eg, disease under study, concomitant diseases, concomitant medications).
- The AE follows a reasonable temporal sequence from study medication administration and is a known reaction to the drug under study or its chemical group or is predicted by known pharmacology as a known reaction to agent or chemical group or predicted by known pharmacology.
- A related AE is any AE considered related, probably related, or possibly related to miransertib.

7.7.2 Not Related

- The AE does not follow a reasonable sequence from study product administration or can be reasonably explained by the participant's clinical state or other factors (eg, disease under study, concurrent diseases, and concomitant medications).

8 ASSESSMENT OF RESPONSE

Efficacy assessments are no longer being conducted in this protocol with the adoption of Amendment 7. Analyses of previously collected responses may be performed by the Sponsor.

8.1 Measurable Disease

No longer applicable with the adoption of Amendment 7.

8.2 Response Evaluation

No longer applicable with the adoption of Amendment 7.

9 PLANNED STATISTICAL METHODS

9.1 General Considerations

Details of the statistical analyses presented below will be provided in the study's SAP. The SAP will be finalized before database lock. Any changes to the methods described in the plan will be described and justified in the final clinical study report.

All data listings, summaries, figures and statistical analyses will be generated using SAS version 9.4 or higher. Summaries will be presented by Part (A/B), Cohort (and by dose within, Cohort for AEs), and overall. Continuous variables will be summarized by the number of nonmissing observations, mean, median, standard deviation, minimum and maximum. Categorical variables will be summarized by presenting the frequency and percent. Percentages will be based on the number of nonmissing observations or the participant population unless otherwise specified. For each variable, all categories will be shown. Zero frequencies (but not the percent) within a category will be presented.

9.2 Analysis Populations

Safety Population: all patients who have received a dose of study medication.

9.3 Study Endpoints

Under this amendment, the endpoints for Part A and Part B have been combined to assess the safety and tolerability of miransertib in participants with PROS and PS based on the frequency, duration, and severity of AEs from the first dose of the drug through 90 days after the last dose of the drug.

9.3.1 Determination of Sample Size

Part B of this study is designed to determine the efficacy in PROS and PS patients treated with a daily dose of miransertib. The primary endpoint for Cohort 1 and Cohort 2 is response rate as assessed by blinded reviewers (with adjudication) using protocol response criteria. Sample size is justified based on the precision of a 95% confidence interval on the response rate. To exclude a clinically irrelevant response rate of 5%, the lower limit of the 95% confidence interval should be higher than 5%.

- Cohort 1, PROS: A sample size of n=20 participants will provide a two-sided exact Clopper-Pearson 95% confidence interval of (6%, 44%) on an observed response rate of 30%.

- Cohort 2, PS: A sample size of n=10 participants will provide a two-sided exact Clopper-Pearson 95% confidence interval of (7%, 65%) on an observed response rate of 30%.

9.3.2 Data Handling Rules for Efficacy Endpoint Analyses

With Amendment 7, efficacy assessments will no longer be collected, and the primary objective is the evaluation of safety and tolerability of miransertib. Therefore, data handling rules for efficacy endpoint analyses are no longer applicable with the adoption of Amendment 7.

9.4 Safety Analysis

All participants who receive at least one dose of study treatment will be evaluated for safety. The incidence rates of TEAEs, treatment-related adverse events, and serious adverse events (SAEs will be described, as identified with preferred terms and MedDRA system organ class.

The frequency of occurrence of overall toxicity, categorized by the maximum toxicity grades (severity), will also be described. Listings of laboratory test results and CTCAE grades will be generated, and descriptive statistics summarizing the changes in laboratory tests over time will be presented.

The safety analyses will be presented by dose and overall using the Safety Population. Safety assessments include AEs, 12-lead ECGs, physical examination, clinical laboratory, and home fasting glucose measurements.

Adverse events will be graded according to the current version of CTCAE.

Exploratory analyses will also be performed on other safety parameters, as deemed appropriate, and within subgroups defined by age, sex, race, mutation status, prior therapies, medical history, and other prognostic factors. Exploratory analyses may also be performed on previously collected laboratory analytes, including PK samples.

Exposure to study treatment over time will be summarized with time on treatment, total amount of administered treatment, dose intensity and relative dose intensity.

9.5 Pharmacokinetic Analysis

Summary statistics for steady-state trough (predose) levels may be computed from previously collected samples. PK data may be used in an exposure-response analysis for safety and efficacy. Details will be provided in the SAP.

9.6 Data Monitoring Committee

The DMC will monitor patients' safety by reviewing and evaluating study data, reviewing study conduct and progress, and making recommendations concerning the continuation, modification, or termination of the study. DMC meetings will take place at least 2 times per year. There will be a formal charter outlining DMC membership and responsibilities.

10 COMPLIANCE WITH GOOD CLINICAL PRACTICE AND ETHICAL CONSIDERATIONS

10.1 Institutional Review Board or Independent Ethics Committee Approval

The protocol, any protocol modifications, the ICF, and, if applicable, permission to use private health information must be approved by the investigator's IRB/IEC before study initiation. Documentation of this approval must be provided to the Sponsor or designee and made available during an inspection by the FDA or other regulatory agency inspectors. The investigator will also provide the Sponsor with the General Assurance Number documenting that the IRB/IEC is duly constituted, as well as a list of the names, occupations, and affiliations of the members of the IRB/IEC when available.

Before initiating a study, the investigator/Institution should have written and dated approval/favorable opinion from the IRB/IEC and where applicable, competent authorities/regulatory bodies for the protocol/amendment(s), written ICF, participant

recruitment procedures (eg, advertisements), and written information to be provided to participants.

10.2 Compliance With Good Clinical Practice and Ethical Considerations

This study must be conducted in compliance with IRB/IEC informed consent regulation and the ICH GCP guidelines. In addition, all local regulatory requirements will be adhered to, in particular those affording greater protection to the safety of the study participants.

This study will also be conducted according to the current revision and all subsequent revisions of the WMA Declaration of Helsinki – Ethical Principles for Medical Research Involving Human Subjects and with local laws and regulations relevant to the use of new therapeutic agents in the country of conduct.

Changes to the protocol will require written IRB/IEC and, where applicable, competent authorities/regulatory bodies approval/favorable opinion before implementation, except when the modification is needed to eliminate an immediate hazard(s) to participants.

10.3 Participant Information and Consent/Assent

The investigator, or designee, is responsible for the content of the ICF and Assent Form, but the original and any updated versions must be approved by the Sponsor before submission to the IRB/IEC. The ICF and Assent Form should also include any additional information required by local laws relating to institutional review.

Before the start of any study-related procedures are undertaken, the investigator or designee must obtain written, informed consent and/or assent from each study participant (or his/her legal guardian) in accordance with the ICH document "Guidance for Industry – E6 Good Clinical Practice: Consolidated Guidance" and country specific regulations (eg, 21 CFR Part 50). Informed consent/assent will be obtained by discussing with the participant and his/her legal guardian the purpose of the study, the risks and benefits, the study procedures, and any other information relevant to the participant.

The investigator or designee must explain to the participant and his/her legal guardian that for purposes of evaluating the study results, the participant's private health information obtained during the study may be shared with the study Sponsor, regulatory agencies, and IRBs/IECs, before enrolling that participant into the study. It is the investigator's (or designee's) responsibility to obtain permission to use private health information per HIPAA or GDPR and/or other applicable laws from each participant or, if appropriate, the participant's legal guardian.

The participant or his/her legal guardian will document his/her informed consent/assent by signing the current version of the written, IRB/IEC-approved ICF and/or Assent Form. The person who conducted the informed consent/assent discussion with the participant and/or participant's legal guardian must also sign the ICF and Assent Form. The participant or his/her legal guardian is given a fully executed copy of the ICF and/or Assent Form bearing all appropriate signatures; the original(s) must be maintained in the clinical master files at the site.

All active participants participating on the protocol must be reconsented each time the ICF/Assent Form is updated and re-approved by the IRB/IEC.

11 STUDY MANAGEMENT AND MATERIALS

11.1 Monitoring, Verification of Data, Audit, and Inspection

A Sponsor monitor or designee will periodically visit each clinical study site to discuss the progress of the clinical study and to review eCRFs and source documents for accuracy of data recording, study medication accountability, and correspondence. When requested, the investigator must be available to the study monitor for personal, one-to-one consultation.

Periodically, some or all of the facilities used in the study may be reviewed or inspected by the IRB/IEC and/or regulatory authorities. An audit or inspection may include, for example, a review of all source documents, drug records, and original clinical medical notes.

The investigator is to ensure that the study participants are aware of and consent to the review of personal information during the data verification process, as part of the monitoring/auditing process conducted by properly authorized agents of the Sponsor or be subject to inspection by regulatory authorities. In addition, participation and personal information is treated as strictly confidential to the extent of applicable law and is not publicly available.

11.2 Data Recording and Retention of Study Data

In compliance with GCP, the medical records/medical notes, and other study-related materials should be clearly marked and permit easy identification of participation by an individual in a specified clinical study.

The investigator is to record all data with respect to protocol procedures, drug administration, laboratory data, safety, and efficacy on the eCRFs.

If the investigator relocates or retires, or otherwise withdraws his/her responsibility for maintenance and retention of the master clinical study records, the Sponsor must be notified in writing so that adequate provision can be made concerning the study documents.

Study documents should be retained for at least 2 years after the approval of a marketing application in an ICH region and until there are no pending or planned marketing applications in an ICH region, or until at least 2 years have elapsed since the formal discontinuation of clinical development of miransertib by the Sponsor. The documents should be retained for a longer period, however, if required by the applicable regulatory requirements or by an agreement with the Sponsor that it will inform the investigator, in writing, as to when the retention of these documents is no longer necessary.

11.3 Electronic Case Report Forms

An EDC system will be used to collect the data in this study. The EDC system provides functionality for the clinical sites to enter the data directly into the eCRFs and respond to data discrepancies. Once the data are entered, the information is encrypted and transmitted over the Internet to a clinical study server where it is electronically reviewed. Any resulting data queries are immediately sent back to the site for resolution. The system automatically keeps a full audit trail of all data changes that occur. The clinical team will undertake additional manual review of the data, but all resulting data queries or clarifications will be entered into the EDC system for resolution. All eCRFs will be completed according to instructions provided in the eCRF Completion Guidelines and ICH/GCP guidelines.

11.4 Confidentiality, Publication, and Disclosure Policy

The investigator understands that the Sponsor will use the information developed in the clinical study in connection with the development of miransertib. This information may be disclosed to other clinical Investigators, the FDA, and other government agencies, including publication on public websites, such as www.clinicaltrials.gov.

All information disclosed to the investigator by the Sponsor for the purpose of having the investigator conduct the clinical study described in this protocol, or information generated by the investigator as results in the clinical study shall be treated by the investigator as strictly confidential. The investigator shall not use such information other than for the purpose of conducting the clinical study and may not disclose such information to others, except when such disclosure is made to colleagues and/or employees who reasonably require the information to assist in carrying out the clinical study and who are bound by like-obligations of confidentiality. Notwithstanding, the investigator may use or disclose to others any information which: (i) was known to the investigator before the date of its disclosure; (ii) is now, or becomes in the future, publicly available; or (iii) is lawfully disclosed to the investigator on a nonconfidential basis by a third party who is not obligated to the Sponsor or any other party to retain such information in confidence.

The Sponsor acknowledges that the investigator has certain professional responsibilities to report to the scientific community on findings made in the clinical investigations they conduct. The investigator shall have the right to publish the results of research performed under this protocol, provided that such publication does not disclose any Confidential Information or trade secrets of the Sponsor (other than the data). If the study is conducted as part of a multicenter protocol, the investigator agrees not to independently publish the findings except as part of an overall multicenter publication, unless specifically approved in writing by the Sponsor or unless more than 12 months have elapsed since the last participant in the study has completed his/her study designed treatment.

12 REFERENCE LIST

[Bellacosa, A., et al 2005]	Bellacosa A, Kumar CC, Di Cristofano A, Testa JR. Activation of AKT kinases in cancer: implications for therapeutic targeting. Adv Cancer Res. 2005:29-86.	[05MQLQ]
[Biesecker LG, Lindhurst MJ, Yourick MR, Dransfield DT 2014]	Biesecker LG, Lindhurst MJ, Yourick MR, Dransfield DT. Inhibition of AKT signaling in Proteus and PROS cells: A simple model for cancer therapeutics targeting the AKT/PI3K pathway. Poster presented at: The American Society of Human Genetics Annual Meeting; 2014 October 18-22; San Diego, CA USA.	[05GMDH]
[Biesecker, L. 2006]	Biesecker L. The challenges of Proteus syndrome: diagnosis and management. Eur J Hum Genet. 2006;14:1151-7.	[05NZK2]
[Biesecker, L. G. 2019]	Biesecker LG, Sapp JC. GeneReviews [Internet]. Adam MP, Ardinger HH, Pagon RA, et al., editors. Seattle (WA): University of Washington; c1993-2020. Proteus syndrome; 2012 Aug 9 [updated 2019 Jan 10; cited 2020 Dec 18]; 15 p. Available from: https://www.ncbi.nlm.nih.gov/books/NBK99495/.	[05NZM7]
[Brazil DP, Yang ZZ, Hemmings BA 2004]	Brazil DP, Yang ZZ, Hemmings BA. Advances in protein kinase B signalling: AKTion on multiple fronts. Trends Biochem Sci. 2004 May;29(5):233-42.	[05FPFQ]
[Engelman JA, Luo J, Cantley LC 2006]	Engelman JA, Luo J, Cantley LC. The evolution of phosphatidylinositol 3-kinases as regulators of growth and metabolism. Nat Rev Genet. 2006 Aug;7(8):606-19.	[05FPFW]
[Keppler-Noreuil KM, Rios JJ, Parker VE, Semple RK, Lindhurst MJ 2015]	Keppler-Noreuil KM, Rios JJ, Parker VE, Semple RK, Lindhurst MJ, Sapp JC, et al. PIK3CA-related overgrowth spectrum (PROS): diagnostic and testing eligibility criteria, differential diagnosis, and evaluation. Am J Med Genet A. 2015 Feb;167A(2):287-95.	[05FPFZ]

[Keppler-Noreuil, K. M., et al 2016]	Keppler-Noreuil KM, Parker VER, Darling TN, Martinez-Agosto JA. Somatic overgrowth disorders of the PI3K/AKT/mTOR pathway & therapeutic strategies. Am J Med Genet C Semin Med Genet. 2016;172C:402-21.	[05MQQG]
[Keppler-Noreuil, K. M., et al 2019]	Keppler-Noreuil KM, Sapp JC, Lindhurst MJ, Darling TN, Burton-Akright J, Bagheri M, et al. Pharmacodynamic study of miransertib in individuals with Proteus syndrome. Am J Hum Genet. 2019 Mar 7;104:484-91.	[05MQP3]
[Khan, K. H., et al 2013]	Khan KH, Yap TA, Yan L, Cunningham D. Targeting the PI3K-AKT-mTOR signaling network in cancer. Chin J Cancer. 2013;32(5):253-65.	[05MQQH]
[Lindhurst, M. J., et al 2011]	Lindhurst MJ, Sapp JC, Teer JK, Johnston JJ, Finn EM, Peters K, et al. A mosaic activating mutation in AKT1 associated with the Proteus syndrome. N Engl J Med. 2011 Aug 18;365(7):611-9.	[05MYY8]
[Lindhurst, M. J., et al 2015]	Lindhurst MJ, Yourick MR, Yu Y, Savage RE, Ferrari D, Biesecker LG. Repression of AKT signaling by ARQ 092 in cells and tissues from patients with Proteus syndrome. Sci Rep. 2015 Dec 11;5:17162.	[05MQQJ]
[Loconte DC, Grossi V, Bozzao C, Forte G, Bagnulo R 2015]	Loconte DC, Grossi V, Bozzao C, Forte G, Bagnulo R, Stella A, et al. Molecular and Functional Characterization of Three Different Postzygotic Mutations in PIK3CA-Related Overgrowth Spectrum (PROS) Patients: Effects on PI3K/AKT/mTOR Signaling and Sensitivity to PIK3 Inhibitors. PLoS One. 2015 Apr 27;10(4):e0123092.	[05FPG5]
[Martinez-Lopez, A., et al 2017]	Martinez-Lopez A, Blasco-Morente G, Perez-Lopez I, Herrera-Garcia JD, Luque-Valenzuela M, Sanchez-Cano D, et al. CLOVES syndrome: review of a PIK3CA-related overgrowth spectrum (PROS). Clin Genet. 2017;91:14-21.	[05NZMM]

[Ranieri, C., et al 2018]	Ranieri C, Di Tommaso S, Loconte DC, Grossi V, Sanese P, Bagnulo R, et al. In vitro efficacy of ARQ 092, an allosteric AKT inhibitor, on primary fibroblast cells derived from patients with PIK3CA-related overgrowth spectrum (PROS). Neurogenetics. 2018;19:77-91.	[05MQQR]
[Yu Y, Savage RE, Eathiraj S, Meade J, Wick MJ, et al. 2015]	Yu Y, Savage RE, Eathiraj S, Meade J, Wick MJ, et al. Targeting AKT1-E17K and the PI3K/AKT Pathway with an Allosteric AKT Inhibitor, ARQ 092. PLoS One. 2015 Oct 15;10(10):e0140479.	[05FQ5Q]

APPENDIX 1 CLINICAL DIAGNOSTIC CRITERIA CLINICAL DIAGNOSTIC CRITERIA FOR PROS

Required:	Congenital or Early Childhood Onset Overgrowth Sporadic and Mosaic (Other terms: Patchy, Irregular) Presence of PIK3CA mutation in overgrowth lesion Features described in either A or B
A. Spectrum (2 or more)	Overgrowth: Adipose, Muscle, Nerve, Skeletal Vascular Malformations: Capillary Venous, Arteriovenous Malformation, Lymphatic Epidermal Nevus
B. Isolated Features	Large Isolated Lymphatic Malformation Isolated Macrodactyly OR Overgrown Splayed Feet/Hands, Overgrown Limbs Truncal Adipose Overgrowth Hemimegalencephaly Epidermal Nevus Seborrheic Keratoses Benign Lichenoid Keratoses

Keppler-Noreuil KM, et al. Am J Med Genet A. 2015 Feb;167A(2):287-95 [Keppler-Noreuil KM, Rios JJ, Parker VE, Semple RK, Lindhurst MJ 2015]

Clinical Diagnostic Criteria for Proteus Syndrome

To make a diagnosis of PS, one must have all the general criteria, and various specific criteria	
General Criteria	**Specific Criteria**
All the following:	**Either**
Mosaic distribution of lesions	Category A or,
Sporadic occurrence	Two from category B or,
Progressive course	Three from category C
Specific criteria categories	Plus AKT1 mutation in overgrowth lesion
Category A.	**Category C**
Cerebriform connective tissue nevus	1. Dysregulated adipose tissue
Category B.	Either one:
1. Linear epidermal nevus	a) Lipomas
2. Asymmetric, disproportionate overgrowth	b) Regional lipohypoplasia
One or more:	2. Vascular malformations
a) Limbs	One or more:
b) Hyperostosis of the skull	a) Capillary malformation
c) Hyperostosis of the external auditory canal	b) Venous malformation
d) Megaspondylodysplasia	c) Lymphatic malformation
e) Viscera:	3. Lung cysts
f) Spleen/thymus	4. Facial phenotype (all of the following)
3. Specific tumors before 2nd decade	a) Dolichocephaly
One of the following:	b) Long face
a) Bilateral ovarian cystadenoma	c) Down slanting palpebral fissures and/or minor ptosis
b) Parotid monomorphic adenoma	d) Low nasal bridge
	e) Wide or anteverted nares
	f) Open mouth at rest

Biesecker L. Eur J Hum Genet. 2006 Nov;14(11):1151-7 [Biesecker, L. 2006].

Definition of the Total Cerebriform Connective Tissue Nevus (CCTN) Lesional Area:

- The plantar surface of the foot is defined as CCTN, pre-CCTN and nonaffected area. The percentage of the affected area (total CCTN lesional area) is calculated based on the size of the sole, excluding toes

- Total lesional area is defined as the space encompassing CCTN and noncerebriform affected area

- The CCTN is defined as a nevus with at least 2 gyri and 3 sulci and should affect between 10% and 70% of the total surface area of the sole.

The pre-CCTN is defined as an area characterized by a confluent growth with visible papules and nodules but without typical nevus growths

APPENDIX 2 DOSING NOMOGRAM

15 mg/m^2 Dose Level									
BSA range (m^2)	0.33-0.49	0.5-0.82	0.83-1.16	1.17-1.49	1.50-1.83	1.84-2.16	2.17-2.49	2.50-2.83	≥2.84
Target range (mg/day)	4.95-7.35	7.5-12.3	12.45-17.40	17.55-22.35	22.50-27.45	27.60-32.40	32.55-37.35	37.50-42.45	≥42.60
Actual Dose (mg qd)	5	10	15	20	25	30	35	40	45
25 mg/m^2 Dose Level									
BSA range (m^2)	0.33-0.49	0.5-0.69		0.70-0.89	0.90-1.09	1.1-1.29	1.30-1.49	1.50-1.69	≥1.70
Target range (mg/day)	8.25-12.25	12.5-17.25		17.5-22.25	22.5-27.25	27.5-32.25	32.5-37.25	37.5-42.25	≥42.5
Actual Dose (mg qd)	10	15		20	25	30	35	40	45

Target mg/day range = Desired dose level (eg, 15 mg/m^2 or 25 mg/m^2) x BSA range(m^2)

Actual mg/m^2 dose range = Actual dose (mg) / BSA range(m^2)

Generally, a child of BSA 0.5 m^2 (the average BSA for a 2-year-old child) should receive 1/4 to 1/3 the dose in mg of that of an adult of BSA ~ 1.7 m^2. Hence, if the adult gets a 40-mg dose, the child should get a 10-mg dose.

APPENDIX 3 EXAMPLES OF IN VIVO SUBSTRATES, INHIBITORS, AND INDUCERS FOR SPECIFIC ENZYMES

CYP	Substrate (sensitive)	Inhibitor (strong)	Inducer (strong)
2D6	atomoxetine, desipramine, dextromethorphan, eliglustat, nortriptyline, tolterodine, nebivolol, perphenazine, venlafaxine	bupropion, fluoxetine, paroxetine, quinidine, terbinafine	none identified
3A4/ 3A5	remifentanil, avanafil, buspirone, conivaptan, darifenacin, darunavir, ebastine, everolimus, ibrutinib, lomitapide, lovastatin, midazolam, naloxegol, nisoldipine, saquinavir, simvastatin, sirolimus, tacrolimus, tipranavir, triazolam, vardenafil	boceprevir, cobicistat, conivaptan, grapefruit juice, itraconazole, ketoconazole, ritonavir, clarithromycin, diltiazem, idelalisib, nefazodone, nelfinavir	carbamazepine, enzalutamide, mitotane, phenytoin, rifampin, St. John's wort
2C9	celecoxib	none identified	none identified
2C19	S-mephenytoin, omeprazole	fluconazole, fluoxetine, fluvoxamine, ticlopidine	rifampin, ritonavir
2C8	repaglinide	clopidogrel, gemfibrozil	none identified

Source: https://www fda.gov/Drugs/DevelopmentApprovalProcess/DevelopmentResources/ucm093664.htm

(accessed 5 March 2019)

Note: This is not an exhaustive list.

Sensitive substrates are drugs that show an increase in AUC of ≥5-fold with strong index inhibitors of a given metabolic pathway in clinical DDI studies.

Strong, moderate, and weak inhibitors are drugs that increase the AUC of sensitive index substrates of a given metabolic pathway ≥5-fold.

Strong inducers are drugs that decreases the AUC of sensitive index substrates of a given metabolic pathway by ≥80%.

APPENDIX 4 EXAMPLES OF IN VIVO SUBSTRATES, INHIBITORS, AND INDUCERS OF P-GLYCOPROTEIN

Transporter	Clinical Substrates	Clinical Inhibitors
P-gp (Gene *ABCB1*)	dabigatran, digoxin, fexofenadine	amiodarone, carvedilol, clarithromycin, dronedarone, itraconazole, lapatinib, propafenone, quinidine, ranolazine, ritonavir, telaprevir, verapamil

Source: Guidance for Industry: Drug Interaction Studies – Study Design, Data Analysis, Implications for Dosing, and Labeling Recommendations. (http://www fda.gov/downloads/Drugs/GuidanceComplianceRegulatoryInformation/Guidances/UCM292362.pdf) Not an exhaustive list. For an updated list, see the following link: http://www fda.gov/Drugs/DevelopmentApprovalProcess/DevelopmentResources/DrugInteractionsLabeling/ucm080499 htm.

Criteria for selecting clinical substrates for P-gp are those which (1) result in AUC fold-increase ≥2 with verapamil or quinidine coadministration and (2) in vitro transport by P-gp expression systems, but not extensively metabolized.

Criteria for selecting in vivo inhibitors for P-gp are those which (1) AUC fold-increase of digoxin ≥2 with coadministration and (2) in vitro inhibitor.

ANNEX 1

PART A: ELIGIBILITY

Patients (≥2 years old) with PROS or PS with documented PIK3CA or AKT1 somatic mutation will be enrolled in this study.

Patient accrual will occur over a period of approximately 30 months.

Patients must meet ALL of the inclusion criteria and NONE of the exclusion criteria to be enrolled.

INCLUSION CRITERIA

1. Signed informed consent, and when applicable, signed assent
2. Male or female patients ≥2 years old with BSA of ≥0.33 m^2
3. Have a clinical diagnosis of PROS or PS with documented somatic PIK3CA or AKT1 mutations
4. Archival or fresh overgrowth tissue sample available to be shipped to Sponsor or designee
5. Have poor prognosis, significant morbidity, and/or progressive disease (eg, worsening of the disease/increase in number or size of the overgrowth lesions in the last 12 months)
6. Have measurable disease (at least one overgrowth lesion that can be accurately measured in size by imaging and/or linear or circumference measure)
7. Adequate organ function as indicated by the following laboratory values:
    a. Hematological
        1. Hgb depending on age:
            - 2-5 years male and female: ≥10.0 g/dL
            - 6-9 years male and female: ≥11.5 g/dL
            - 10-17 years female: ≥11.0 g/dL
            - 10-17 years male: ≥11.5 g/dL
            - >17 years male and female: ≥10.0 g/dL
        2. HbA1c: ≤8% (≤64 mmol/mol)
        3. ANC: ≥1.5 x 10^9/L

4. Platelet count ≥150 x 10^9/L

b. Hepatic

1. Total bilirubin ≤1.5 x ULN

2. AST and ALT ≤3 x ULN

c. Renal

3. Serum creatinine depending on age:

- 2-5 years male and female: maximum 0.50 mg/dL
- 6-10 years male and female: maximum 0.59 mg/dL
- 11-15 years male and female: maximum 1.2 mg/dL
- >15 years male and female: maximum 1.5 mg/dL

d. Metabolic (lipids)

1. Cholesterol: ≤400 mg/dL (≤10.34 mmol/L)

2. Triglyceride: ≤500 mg/dL (≤5.7 mmol/L)

8. If a female is of child-bearing potential, documentation of a negative pregnancy test is required before enrollment. Sexually active patients (male and female) must agree to use double-barrier contraceptive measures, oral contraception, or avoidance of intercourse while on study and for up to 90 days after ending treatment

9. Ability to complete the QoL questionnaires by the patient or his/her caregiver

EXCLUSION CRITERIA

1. History of Type 1 or 2 uncontrolled diabetes mellitus requiring regular medication (other than metformin or other oral hypoglycemic agents) or fasting glucose ≥160 mg/dL (if >12 years old) and ≥180 mg/dL (if ≤12 years old) at the Screening Visit

2. History of significant cardiac disorders:

- Myocardial infarction or congestive heart failure defined as Class II to IV per the NYHA classification within 6 months of the first dose of miransertib (MI occurring >6 months of the first dose of miransertib will be permitted)
- Grade 2 (per the current version of the NCI CTCAE) or worse conduction defect (eg, right or left bundle branch block).

3. Major surgical operation, radiotherapy, or immunotherapy within 4 weeks of the first dose of miransertib

4. Any experimental systemic therapy for the purpose of treating PROS or PS (eg, sirolimus, everolimus, high dose steroids) within 2 weeks of the first dose of miransertib, except for patients who were previously or are currently treated with miransertib under a Compassionate Use/Expanded Access program

    - Patients, who were previously treated with or currently are receiving miransertib, will be enrolled and treated according to the Schedule of Events/Study Visits defined in this protocol

5. Intolerance of or severe toxicity attributed to AKT inhibitors (eg, miransertib, uprosertib, afuresertib, ipatasertib)

6. Concurrent severe uncontrolled illness not related to PROS or PS

    - Ongoing or active infection
    - Known HIV infection
    - Malabsorption syndrome
    - Psychiatric illness/substance abuse/social situation that would limit compliance with study requirements

7. Pregnant or breastfeeding

8. Inability to comply with study evaluations or to follow drug administration guidelines

Schedule of Events Part A

This table is intended as a cumulative list of visits and associated assessments.

Phase	Screening	Treatment (Year 1)				Treatment (Years 2-4)		Follow-Up		
Tests & Procedures / Visit Name	**Screening**	**C1D1**	**C1D15 C4D15 C7D15**	**C2, C3, C5, C6, C8, C9, C11, C12 Day 1**	**C4D1 C7D1 C10D1 C13D1**	**C16, C19, C22, C28, C31, C34, C40, C43, C46 Day 1**	**C25D1 C37D1**	**EOT**	**30-day Safety Follow-up**	**3 Month Follow-up**
Window (days)	**-14 to 0**	**-1 to 0**	**± 3**	**± 5**	**± 5**	**± 5**	**± 5**	**Within 7 days**	**30+ days**	**±14 days**
Written informed consent	X									
Medical history	X									
Physical examination	X	X	X	X	X	X	X	X		X
Vital Signs	X	X	X	X	X	X	X	X		X
Calculate BSA / dose		X		X	X	X	X			
12-Lead ECG	X			X	X	X	X	X		X
Fasting clinical blood tests	X			X	X	X	X	X		X
Insulin/glucose blood tests			X							
Urinalysis	X				X	X	X	X		X
Serum pregnancy test (if applicable)	X							X		X
Disease Measurement	X				X					
Dispense miransertib		X		X	X	X	X			
Collect and count returned miransertib				X	X	X	X	X		

Phase	Screening	Treatment (Year 1)				Treatment (Years 2-4)		Follow-Up		
Tests & Procedures / Visit Name	**Screening**	**C1D1**	**C1D15 C4D15 C7D15**	**C2, C3, C5, C6, C8, C9, C11, C12 Day 1**	**C4D1 C7D1 C10D1 C13D1**	**C16, C19, C22, C28, C31, C34, C40, C43, C46 Day 1**	**C25D1 C37D1**	**EOT**	**30-day Safety Follow-up**	**3 Month Follow-up**
Window (days)	**-14 to 0**	**-1 to 0**	**± 3**	**± 5**	**± 5**	**± 5**	**± 5**	**Within 7 days**	**30+ days**	**±14 days**
Concomitant medications	X	X	X	X	X	X	X	X	X	X
Adverse events		X	X	X	X	X	X	X	X	X

[1] C4D15 visit will only occur if the dose (mg/m^2) increases at Cycle 4. C7D15 visit will only occur if the dose (mg/m^2) increases at Cycle 7.

[2] CYP2D6 at C1D15 ONLY. If not collected at C1D15 for previously enrolled participants, it will be collected at the next Cycle visit after reconsenting under the amended protocol.

[3] ECG and PK are tested at C2D1 for all participants and at C5D1 and C8D1 only if the dose was increased at Cycle 4 and Cycle 7, respectively.

[4] Blood for PK ONLY collected at C4D1 and C7D1.

[5] Disease Measurement by US, photography and/or video recording only on C4D1 if no dose increase.

[6] Dispense 3-cycle supply of drug at C13D1 if participant is continuing beyond the first 12 cycles of therapy.

[7] ECGs will only be performed if clinically indicated or if required per standard of care.

Study Visits – Screening Visit, Cycle 1 Day 1, and Cycle 1 Day 15 at 15 mg/m^2 Of Miransertib

Screening visit (-14 – 0 days)	Cycle 1 Day 1 (15 mg/m^2)	Cycle 1 Day 15 (± 3 days) (15 mg/m^2)
• Written Informed consent – can be obtained >14 days before the first dose. • Medical history. • Physical examination, including skin. • Vital signs (height, weight, temperature, blood pressure, respiration rate, and heart rate). • 12-lead ECG. • Fasting Clinical Blood Tests Urinalysis. • Serum pregnancy test, if applicable. • Biopsy of overgrowth tissue to confirm eligibility (if a prior biopsy sample is not available to confirm genetic alteration) or if archival tissue is not available to ship to the Sponsor or designee (for previously enrolled participants, it will be collected after re consenting under the amended protocol). The biopsy can be performed >14 days before the first dose but must meet the requirements for this protocol. • Disease measurement by imaging (eg, MRI, CT, US, photography, video recording) and/or by other circumference measurements within 28 days before the first dose of miransertib. • Record concomitant medication.	• Physical examination, including (If Screening Visit was within 3 days of C1D1, physical examination does not have to be repeated) • Vital signs (height, weight, temperature, blood pressure, respiration rate, and heart rate) • Calculate BSA using the DuBois formula • Blood sample for potential biomarkers, including fibrinogen and D-dimers • Dispense miransertib and administer the first dose after all assessments listed above are completed (other than postdose blood draws) • Record concomitant medication • Assess AEs after the first dose	• Physical examination, including skin • Vital signs (temperature, blood pressure, respiration rate, and heart rate) • Blood sample for insulin/glucose • Record concomitant medication • Assess AEs

Study Visits – Cycle 2 Day 1 to Cycle 13 Day 1

Cycles 2, 3, 5, 6, 8, 9, 11 and 12 - Day 1 (± 5 days) (*when dose did not change either at C4 or at C7 respectively)	**Cycles 4 and 10 - Day 1 (± 5 days) (C4 dose not changed)**	**Cycles 7 and 13 - Day 1 (± 5 days) (C7 dose not changed)**
• Physical examination, including skin • Vital signs (height, weight, temperature, blood pressure, respiration rate, and heart rate) • Calculate BSA using the DuBois formula • 12-lead ECG, predose (ONLY Cycle 2 Day 1) • Fasting Clinical Blood Tests • Where relevant, additional functional test(s) to evaluate individual participant disease status – frequency as per standard of care • Dispense miransertib • Collect and count returned miransertib • Record concomitant medication • Assess AEs	• Physical examination, including skin • Vital signs (height, weight, temperature, blood pressure, respiration rate, and heart rate) • Calculate BSA using the DuBois formula • 12-lead ECG, predose • Fasting Clinical Blood Tests Urinalysis • Fibrinogen and D-dimers • Dispense miransertib • Collect and count returned miransertib • Record concomitant medication • Assess AEs	• Physical examination, including skin • Vital signs (height, weight, temperature, blood pressure, respiration rate, and heart rate) • Calculate BSA using the DuBois formula • 12-lead ECG, predose • Fasting Clinical Blood Tests Urinalysis • Optional lesion biopsy (ONLY Cycle 13) • Fibrinogen and D-dimers • Where relevant, additional functional test(s) to evaluate individual participant disease status – frequency as per standard of care • Dispense miransertib (dispense 3-cycle supply at C13 if participant is continuing beyond first 12 cycles of treatment) • Collect and count returned miransertib • Record concomitant medication • Assess AEs

Study Visits – C4D1, C4D15, C5D1, C7D1, C7D15, and C8D1 When Dose Increased to 25 mg/m^2 of Miransertib

Cycles 4 and 7 - Day 1 (± 5 days) (dose increase to 25 mg/m^2)	Cycles 4 and 7 - Day 15 (± 3 days) (dose increase to 25 mg/m^2 on C4D1 or C7D1 respectively)	Cycles 5 and 8 - Day 1 (± 5 days) (dose increase to 25 mg/m^2 on C4D1 or C7D1 respectively)
• Physical examination, including skin • Vital signs (height, weight, temperature, blood pressure, respiration rate, and heart rate) • Calculate BSA using the DuBois formula • 12-lead ECG, predose • Fasting Clinical Blood Tests • Urinalysis • Fibrinogen and D-dimers • Where relevant, additional functional test(s) to evaluate individual participant disease status – frequency as per standard of care • Dispense miransertib • Collect and count returned miransertib • Record concomitant medication • Assess AEs	• Physical examination, including skin • Vital signs (temperature, blood pressure, respiration rate, and heart rate) • Blood sample for insulin/glucose • Record concomitant medication • Assess AEs	• Physical examination, including skin • Vital signs (height, weight, temperature, blood pressure, respiration rate, and heart rate) • Calculate BSA using the DuBois formula • 12-lead ECG, predose • Fasting Clinical Blood Tests • Blood samples for PK • Where relevant, additional functional test(s) to evaluate individual participant disease status, frequency as per standard of care • Dispense miransertib • Collect and count returned miransertib • Record concomitant medication • Assess AEs

Study Visits – After 12 Cycles of Treatment

Cycles* 16, 19, 22, 28, 31, 34, 40, 43 and 46 - Day 1 (± 5 days)	Cycles* 25 and 37 - Day 1 (± 5 days)
• Physical examination, including skin • Vital signs (height, weight, temperature, blood pressure, respiration rate, and heart rate) • Calculate BSA using the DuBois formula • 12-lead ECG, predose, if clinically indicated or required per standard of care • Fasting Clinical Blood Tests Urinalysis • Urinalysis • Dispense miransertib • Collect and count returned miransertib • Record concomitant medication • Assess AEs	• Physical examination, including skin • Vital signs (height, weight, temperature, blood pressure, respiration rate, and heart rate) • Calculate BSA using the DuBois formula • 12-lead ECG, predose • Fasting Clinical Blood Tests • Urinalysis • Dispense miransertib • Collect and count returned miransertib • Record concomitant medication • Assess AEs

*After the initial 12 months of treatment, the participant may continue receiving treatment and will be seen at the study site once every 3 months per the schedule outlined above.

Study Visits – End of Treatment, 30 Day Safety Follow-Up

End of treatment/EOT* (within 7 days of decision to permanently discontinue)	30-day Safety Follow-up* (30+ days after last dose)
• Physical examination, including skin • Vital signs (height, weight, temperature, blood pressure, respiration rate, and heart rate) • 12-lead ECG • Fasting Clinical Blood Tests Urinalysis • Serum pregnancy test, if applicable • Collect and count returned miransertib • Record concomitant medication • Assess AEs	• Record concomitant medication • Assess AEs

* EOT visit, 30-day safety follow-up and 3-cycle safety follow-up assessments to be performed whenever the participant permanently discontinues miransertib (whether during the first 12 cycles or after the first 12 cycles)

SPONSOR SIGNATURE

Study Title: A Phase 1/2 Study of ARQ 092 (Miransertib) in Subjects with PIK3CA-related Overgrowth Spectrum and Proteus Syndrome

Study Number: ARQ 092-103 / MK-7075-002

This clinical study protocol was subject to critical review and has been approved by the Sponsor. The following personnel contributed to writing and/or approving this protocol:

Signed:_____ Date:_____

PPD

Project Director, Merck & Co.

INVESTIGATOR'S SIGNATURE

Study Title:	A Phase 1/2 Study of ARQ 092 (Miransertib) in Subjects with PIK3CA-related Overgrowth Spectrum and Proteus Syndrome
Study Number:	ARQ 092-103 / MK-7075-002

I have read the protocol described above. I agree to comply with all applicable regulations and to conduct the study as described in the protocol.

Signed by:

Printed Name of Investigator

Signature: Date:

Investigator DD/MMM/YYYY