Official Protocol Title:	A Phase 1b Study of ARQ 751 as a Single Agent or in Combination with Other Anti-cancer Agents in Adult Subjects with Advanced Solid Tumors with PIK3CA/AKT/ PTEN Mutations
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STATISTICAL ANALYSIS PLAN

PROTOCOL MK-4440-001/ARQ 751-101

A Phase 1b Study of ARQ 751 as a Single Agent or in Combination with Other Anti-cancer Agents in Adult Subjects with Advanced Solid Tumors with PIK3CA/AKT/PTEN Mutations

Protocol Number: MK-4440-001/ARQ 751-101

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Name of Testing Drug: MK-4440/ARQ 751

Phase: Phase 1b

Methodology: Open-Label, Multi-Arm, Dose Escalation, Dose Expansion

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Analysis Plan Date: 10 March 2021

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APPROVAL SIGNATURE PAGE

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Document Date / Version: 10 March 2021 / Version 1.0

Veristat, Inc. Author:

Approval Signature	Job Title
DocuSigned by: PPD Signer Name: PPD Signing Reason: I am the author of this document Signing Time: 11-Mar-2021 | 11:45:56 AM EST D6289431A2DE47DCBD24B50D311E09BA	Senior Biostatistician

Sponsor Approval

By signing this document, I acknowledge that I have read the document and approve of the planned statistical analyses described herein. I agree that the planned statistical analyses are appropriate for this study, are in accordance with the study objectives, and are consistent with the statistical methodology described in the protocol, clinical development plan, and all applicable regulatory guidances and guidelines.

I have discussed any questions I have regarding the contents of this document with the biostatistical author.

I also understand that any subsequent changes to the planned statistical analyses, as described herein, may have a regulatory impact and/or result in timeline adjustments. All changes to the planned analyses will be described in the clinical study report.

Sponsor Signatory:

Approval Signature	Job Title
	Senior Scientist, Biostatistics
	Study Director

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LIST OF ABBREVIATIONS AND DEFINITION OF TERMS

Abbreviation	Definition
AE	Adverse event
AKT	v-Akt murine thymoma viral oncogene homolog
ALT (SGPT)	Alanine aminotransferase (serum glutamic pyruvic transaminase)
ASaT	All-Subjects-as-Treated
AST (SGOT)	Aspartate aminotransferase (serum glutamic oxaloacetic transaminase)
BOR	Best overall response
CI	Confidence interval
CR	Complete response
CRF	Case report form
CSR	Clinical study report
CTCAE	Common Terminology Criteria for Adverse Events
DCR	Disease control rate
DLT	Dose-limiting toxicity
ECOG	Eastern Cooperative Oncology Group
ECG	Electrocardiogram
EE	Efficacy-evaluable
ER	Estrogen receptor
IM	Intramuscular
IV	Intravenous
MedDRA	Medical Dictionary for Regulatory Activities
MTD	Maximum tolerated dose
mTOR	Mammalian target of rapamycin
MUGA	Multiple gated acquisition
NCI	National Cancer Institute
ORR	Objective response rate
PD	Pharmacodynamic
PI3K	Phosphatidylinositol 3-kinase
PIK3CA	phosphatidylinositol-4,5-bisphosphate 3-kinase catalytic subunit alpha
PK	Pharmacokinetic
PR	Partial response
PT	Preferred term
PTEN	Phosphatase and tensin homolog deleted on chromosome ten
QD	Daily
QOD	Every other day
QW	Weekly

Abbreviation	Definition
RECIST	Response evaluation Criteria in Solid Tumors
RP2D	Recommended phase 2 dose
SAE	Serious adverse event
SAP	Statistical analysis plan
SD	Stable disease
SOC	System organ class
TEAE	Treatment-emergent adverse event
ULN	Upper limit of normal
WHO	World Health Organization

1. INFORMATION FROM THE STUDY PROTOCOL

1.1. Introduction and Objectives

1.1.1. Introduction

The phosphatidylino-3-kinase (PI3K) / v-Akt murine thymoma viral oncogene homolog (AKT) / mammalian target of rapamycin (mTOR) signaling pathway (PI3K pathway) plays a major role in physiological processes regulating cellular growth, proliferation, angiogenesis, survival, and metabolism [1, 2, 4]. The PI3K pathway is frequently altered in solid malignancies, promoting tumor growth, proliferation and survival. The pathway's three critical nodes, PI3K, AKT and mTOR, have been recognized as important therapeutic targets.

MK-4440 (ARQ 751) is a potent allosteric pan-AKT inhibitor with biochemical IC_{50} values of 0.55, 0.81, and 1.31 nM against AKT1, AKT2, and AKT3, respectively and is highly selective among the kinome. Out of 245 kinases screened, MK-4440 did not inhibit any kinase other than AKT1 by more than 50% at a concentration of 5 μM.

The anti-tumor *in vivo* activity of MK-4440 was tested in an athymic mouse xenograft model explanted with the AN3CA cells. Tumor growth inhibition (TGI) of MK-4440 after ten days oral treatment at 120 mg/kg daily to 5 mg/kg ranged from 92% to 29%. Furthermore, combination of MK-4440 at defined concentrations with estrogen receptor (ER) antagonist, fulvestrant (10 μM), or aromatase inhibitor, anastrozole (200 μ M), showed significant enhancement in anti-proliferative activity in MFE-280 (ER+, PIK3CAH1047R), HEC-1B (ER+, PIK3CAG1049R), and Ishkawa (ER+, PIK3R1T319fs*1&V290fs*1), compared to single agents (data on file). These studies suggest MK-4440 is a promising anticancer agent by itself and/or in combination with other anti-cancer agents.

This study (MK-4440-001/ARQ 751-101) was initiated in August 2016 as an open-label, phase 1, first-in-human, dose escalation study, and has been amended to a phase 1b trial exploring two treatment routes for MK-4440:

Part 1: MK-4440 as a single agent (dose escalation and expansion)

Part 2: MK-4440 in combination with paclitaxel and with fulvestrant (dose escalation and expansion)

As of November 2018 the dose escalation study of MK-4440 as a single agent was completed. Seven dose levels of MK-4440 (from 5 mg daily [QD] to 100 mg QD) were evaluated and the recommended phase 2 dose (RP2D) was determined to be 75 mg QD. As of August 2020, enrollment for the study (both Part 1 expansion and Part 2) has been discontinued.

1.1.2. Study Objectives

The primary objectives of this study are:

Part 1 – MK-4440 as single agent:

To assess the safety and tolerability of MK-4440 in subjects with advanced solid tumors with AKT1, 2, 3 genetic alterations, activating PI3K mutations, phosphatase and tensin homolog deleted on chromosome ten (PTEN)-null, or other known actionable PTEN mutations.

Part 2 – MK-4440 in combination with other anti-cancer agents:

To assess the safety and tolerability of MK-4440 in combination with paclitaxel or fulvestrant in subjects with advanced, inoperable, metastatic and/or recurrent solid tumors with phosphatidylinositol-4,5-bisphosphate 3-kinase catalytic subunit alpha (PIK3CA) / PTEN actionable mutations and/or AKT genetic alterations.

The secondary objectives of this study are:

Part 1 – MK-4440 as single agent:

- To assess the pharmacokinetic (PK) profile of MK-4440
- To assess the pharmacodynamic (PD) activity of MK-4440 in blood specimens obtained from subjects with advanced solid tumors with AKT1, 2, 3 genetic alterations, activating PI3K mutations, PTEN-null, or other known actionable PTEN mutations
- To determine the maximum tolerated dose (MTD) and/or RP2D of MK-4440 as single agent
- To generate preliminary evidence of anti-tumor activity

Part 2 – MK-4440 in combination with other anti-cancer agents:

- To determine MTD/RP2D dose of MK-4440 in combination with paclitaxel or fulvestrant
- To assess the PK profile of MK-4440 in combination with paclitaxel or fulvestrant
- To generate preliminary evidence of anti-tumor activity of MK-4440 in combination with paclitaxel or fulvestrant in subjects with advanced, inoperable, metastatic and/or recurrent solid tumors with PIK3CA/PTEN actionable mutations and/or AKT genetic alterations

1.1.3. Purpose of this Document

This statistical analysis plan (SAP) is designed to outline the methods to be used in the analysis of study data in order to answer the study objectives. Populations for analysis, data handling rules, statistical methods, and formats for data presentation are provided. The statistical analyses and summary tabulations described in this SAP will provide the basis for the results sections of the clinical study report (CSR) for this trial.

This SAP will also outline any differences in the currently planned analytical objectives relative to those planned in the study protocol.

1.2. Study Design

1.2.1. Synopsis of Study Design

MK-4440-001 is a Phase 1b, multi-center, open label study of a second-generation pan-AKT inhibitor MK-4440 administered orally as a single agent or in combination with paclitaxel or fulvestrant in subjects with advanced, inoperable, metastatic and/or recurrent solid tumors with PIK3CA/AKT/PTEN mutations.

The study has two parts and explores 3 treatment arms (Arm A, Arm B, Arm C) according to combination of anti-tumor agents as summarized in Section 1.2.1.4, Table 1. Part 1, MK-4440 as a single agent which includes a dose escalation portion and an expansion portion (Arm A). Part 2, MK-4440 in combination with other anti-cancer agents (Arm B and Arm C), with each arm having a dose escalation and dose expansion portion.

1.2.1.1. Part 1 – MK-4440 as Single Agent

Part 1 of this study was open to subjects with advanced solid tumors with AKT1, 2, 3 genetic alterations, activating PI3K mutations, PTEN-null, or other known actionable PTEN mutations. Eligibility for Part 1 subjects enrolled under Amendment 5 includes adult subjects with any of the above mutations whose cancer has progressed following standard therapy, or for whom standard therapy is not available or is not tolerable.

1.2.1.1.1. Dose Escalation

The dose escalation followed a 3 + 3 dose escalation design with the initial dose of 5 mg QD and the highest dose of 100 mg QD, continuously.

Treatment dosing was administered orally in 28-day treatment cycles. The dose limiting toxicity (DLT) evaluation period was 1 cycle of treatment (i.e., 28 days). See Section 1.2.1.3 for the definition of a DLT. Enrollment at the next dose level and/or additional subjects into the ongoing cohort occurred according to the following:

- If 0 of 3 initially treated subjects experience a treatment-related DLT by Day 29, then dose escalation to the next dose level will occur.
- If 1 of 3 initially treated subjects experience a treatment-related DLT by Day 29, then an additional 3 subjects will be enrolled for a total of 6 subjects treated at the same dose level. Escalation will occur if no additional DLTs are seen in that cohort (DLT in 1 of 6 subjects).
- If 2 or more treated subjects at a dose level experience a treatment-related DLT by Day 29 of continuous dosing, dose escalation will stop and the prior dose level and/or a less frequent drug administration schedule will be considered the MTD for that schedule. If the first dose level results in DLTs in 2 or more subjects, subsequent subjects will be enrolled at a less frequent drug administration schedule (e.g., 5 mg every other day [QOD])

Dose escalation continued until the MTD and/or RP2D and dosing schedule was reached. The MTD is defined as the dose level at which no more than 1 out of 6 subjects have an observable DLT.

Additional details on dose escalation included the following:

- If a subject withdraws from the study treatment for any reason other than a DLT during the first cycle (28 days), that subject is replaced.
- During the dose escalation period, intra-subject dose escalation is only permitted if the following criteria are met:
    - The next higher dose for this regimen has demonstrated to be safe by at least 3 subjects and the last subject completed one cycle without exceeding a DLT.
    - The subject in question has not experienced a DLT.
- Once MTD is determined, intra-subject dose escalation to the MTD can be considered for subjects enrolled at lower dose levels.

As of November 2018, 34 subjects are enrolled in the Part 1 dose escalation portion.

1.2.1.1.2. Dose Expansion

To further evaluate safety and tolerability, and to assess preliminary efficacy of MK-4440 as a single agent, up to 30 subjects will be enrolled and treated with MK-4440 at the RP2D in expansion cohort (Arm A). It is planned to enroll up to 15 subjects with solid tumors with PIK3CA or PTEN actionable mutations and up to 15 subjects with AKT genetic alterations. Subjects enrolled in Arm A will receive MK-4440 at 75 mg QD, continuously.

1.2.1.2. Part 2 – MK-4440 in Combination with Other Anti-Cancer Agents

Part 2 of this study is open to subjects with advanced, inoperable, metastatic, and/or recurrent solid tumors with PIK3CA/PTEN actionable mutations and/or AKT genetic alterations. Subjects may be assigned to one of the combination treatment arms (Arm B: MK-4440 + paclitaxel or Arm C: MK-4440 + fulvestrant) based on Investigator discretion, if such therapy choice is deemed appropriate for the subject's disease.

1.2.1.2.1. Dose Escalation

Dose escalation follows the standard 3 + 3 escalation design with two MK-4440 dose levels of 50 mg QD and 75 mg QD (RP2D of MK-4440 as a single agent). The dose levels for paclitaxel (Arm B) and fulvestrant (Arm C) will not change in dose escalation phase (Table 1):

- Arm B: paclitaxel 80 mg/m^2 weekly (QW) (intravenous [IV]) on days 1, 8, 15 followed by a week of rest.
- Arm C: fulvestrant 500 mg (intramuscular [IM]) on days 1 and 15 of Cycle 1, and on day 1 of all subsequent cycles.

Dose escalation criteria for MK-4440 enrollment at the next dose level and/or additional subjects into the ongoing cohort is the same as Part 1 as described in Section 1.2.1.1.1, with the exception of dose modification in case the initial dose of 50 mg MK-4440 results in 2 or more subjects experiencing a DLT:

- If the first dose level of study treatment (50 mg QD) results in 2 or more subjects experiencing a DLT, subsequent subjects will be enrolled at 25 mg QD (Cohort -1 in Table 1)

DLT for dose escalation portion in Part 2 will be determined during the first cycle (28 days) of combination therapy. DLT is defined identically to Part 1 as described in Section 1.2.1.3 with an additional criterium below:

- The Investigator is to assess alanine aminotransferase (ALT) and aspartate aminotransferase (AST) changes to determine if these changes may be a DLT:
  - ≥ Grade 3 ALT or AST elevation for subjects with ALT/AST ≤ 3x upper limit of normal (ULN) at baseline
  - ALT/AST levels for subjects with known liver metastases and ALT/AST ≤ 5x ULN at baseline
  - Grade 2 ALT/AST elevation accompanied by ≥ Grade 2 elevation in bilirubin

1.2.1.2.2. Dose Expansion

Following the determination of the RP2D in dose escalation phase, 6 – 9 subjects will be enrolled in each of the combination therapy arms for the dose expansion portion:

- Arm B: MK-4440 at RP2D and paclitaxel 80 mg/m^2 QW (IV) on days 1, 8, 15 followed by a week of rest.
- Arm C: MK-4440 at RP2D and fulvestrant 500 mg (IM) on days 1 and 15 of Cycle 1, and on day 1 of all subsequent cycles.

1.2.1.3. Dose Limiting Toxicity

A DLT is defined by the occurrence of any of the following toxicities related, probably related, or possibly related to MK-4440, when administered either as a single agent (Part 1) or in combination with another anti-cancer agent (Part 2), within the first cycle (28 days) of treatment and graded by Common Terminology Criteria for Adverse Events (CTCAE) version 4.03:

- Grade 4 anemia
- Grade 4 neutropenia
- Grade 4 thrombocytopenia
- Grade 3 neutropenia lasting longer than 7 days despite optimal treatment
- Grade 3 thrombocytopenia in the presence of bleeding

- ≥ Grade 3 hyperglycemia (fasting blood glucose > 250 mg/dL or non-fasting > 500 mg/dL) requiring insulin (uncontrolled with oral hypoglycemic agents)
- ≥ Grade 3 non-hematological toxicity of any duration, except for the following:
    - Nausea, vomiting, or diarrhea responding to optimal medical management within 48 hours
    - Alopecia
- Any other toxicity that in the view of the Investigator represents a clinically significant hazard to the subject

1.2.1.4. Dosing Details

The investigational drug MK-4440 is supplied as capsules for oral administration. MK-4440 is packaged in strength of 25 mg and is supplied to the pharmacy at the clinical site. MK-4440 should be administered by mouth under fasted condition (one hour prior to or two hours after the meal) and should be taken at approximately the same time each day. Paclitaxel and fulvestrant will be obtained by the subject from commercial sources, and administration of them should follow the Food and Drug Administration (FDA) approved label, National Comprehensive Cancer Network (NCCN) guidelines, or institutional practice. The dosing scheme is described in Table 1.

For an individual subject, treatment with MK-4440 as a single agent or in combination with paclitaxel or fulvestrant will continue until unacceptable toxicity, documented disease progression (clinical or radiological), or another discontinuation criterion is met. It is expected that most subjects will receive between one (4 weeks) and six cycles (24 weeks) of treatment with MK-4440 as a single agent or in combination with other anti-cancer agents. A treatment cycle is defined as 28 days.

Based on review of the preliminary safety, PD and anti-tumor data from 34 subjects enrolled in the dose escalation portion of Part 1 of this study, the RP2D was selected as 75 mg QD and all subjects enrolled in Part 1 expansion cohort were dosed with MK-4440 at 75 mg QD.

When a MK-4440-related toxicity (any toxicity considered to be related, probably related, or possibly related to MK-4440) is observed, dose delays and/or reductions in MK-4440 administration are allowed. If dose reduction is indicated, the subject should be assigned to the previous (lower) cohort dose and schedule (dose re-escalation is not permitted) or to a dose and schedule agreed upon by the Sponsor and the Investigator. In the event of a dose modification, the dose change(s) must be captured in the electronic data capture (EDC) system. In general, once the dose of MK-4440 has been modified for a subject, all subsequent doses should be administered to that subject at the modified dose level and dose administration schedule.

In case of non-MK-4440-related toxicity and if treatment with paclitaxel or fulvestrant is interrupted, the subject may continue taking MK-4440 upon agreement between the Investigator and the Sponsor's Medical Monitor. In case of MK-4440-related toxicity that required MK-4440-treatment interruption, the subject may continue treatment with paclitaxel or fulvestrant upon agreement between the Investigator and the Sponsor's Medical Monitor.

Table 1 Dosing Scheme for Dose Escalation and Dose Expansion for MK-4440-001

Study Part	Study Cohorts		MK-4440	Anti-tumor Agents to be Combined with MK-4440	Number of Subjects
Part 1	Dose Escalation	1	5 mg QD	None	34 enrolled
		2	10 mg QD		
		3	25 mg QOD		
		4	25 mg QD		
		5	50 mg QD		
		6	100 mg QD		
		7*	75 mg QD		
	Expansion (Arm A)	Expansion (MTD/RP2D)	75 mg QD		30 planned
Part 2 (Arm B)	Dose Escalation	-1	25 mg QD	Paclitaxel 80 mg/m^2 (IV) on days 1, 8, 15 followed by a week of rest	6 – 9 planned
		1	50 mg QD		
		2	75 mg QD		
	Expansion	Expansion (MTD/RP2D)	RP2D		6 – 9 planned
Part 2 (Arm C)	Dose Escalation	-1	25 mg QD	Fulvestrant 500 mg (IM) on days 1 and 15 of Cycle 1, and day 1 of all subsequent cycles	6 – 9 planned
		1	50 mg QD		
		2	75 mg QD		
	Expansion	Expansion (MTD/RP2D)	RP2D		6 – 9 planned

Abbreviations: IM = intramuscularly; IV = intravenously; MTD = maximum tolerated dose; QD = once daily; RP2D = recommended phase 2 dose.

* Based on drug-related AEs observed in cohort 6 of Part 1 dose escalation (100 mg QD), the intermediate dose of 75 mg QD was introduced

1.2.2. Randomization Methodology

Randomization is not applicable for this Phase 1b, open-label study, as all subjects will receive active treatment with MK-4440. Concurrent enrollment into expansion Arms A, B, or C will be based on Investigator assessment.

1.2.3. Stopping Rules and Unblinding

Unblinding is not applicable to this open-label study.

Subjects will be removed from the **treatment** at any time if they meet any of the following criteria:

- Documented radiographic or clinical progression of disease – subjects may remain on study treatment if, in the opinion of the Investigator and with the agreement of the Sponsor's Medical Monitor, they continue to derive benefit from MK-4440
- Clinically unacceptable toxicities despite optimal treatment or dose reduction.
- Noncompliance with any part of the study, as evaluated by the Investigator and Medical Monitor.
- Withdrawal of consent.
- Investigator decision (in agreement with the Sponsor/Medical Monitor or designee).
- Death

Subjects will be removed from the **study** at any time if they meet any of the following criteria:

- Safety follow-up visit is completed per the protocol and drug-related adverse events (AEs) have resolved to baseline, National Cancer Insttitute (NCI) CTCAE (Common Terminology Criteria for Adverse Events) Grade 1, stabilized, or are deemed irreversible.
- Withdrawal of consent.
- Lost to follow-up.
- Death.

1.2.4. Study Procedures

The schedule of assessment, as outlined in the study protocol, is provided in Table 2 and Table 3. Study visits will consist of a Screening Visit, during which the subject's eligibility for the study and baseline disease state will be evaluated, weekly visits for the first 3 weeks of each cycle of treatment during which the subject will be evaluated throughout the treatment period, the End of Treatment Visit, and a 30-Day Safety Follow-up. Study visits for Arm B and Arm C are presented in Table 4 and Table 5 to show paclitaxel and fulvestrant administration visits. Imaging scans will be performed during screening, every cycle throughout the treatment period, and during End of Treatment Visit.

Table 2 Schedule of Assessment for MK-4440-001

Tests & Procedures	**Screening**	**Treatment Visits**								**End of Treatment**	**30-day Safety Follow-**
Cycle	**Baseline**	**Cycle 1**				**Cycle 2+**				Within 7 days of decision to permanently discontinue	30+ days after the last dose of MK-4440
Day	**0**	**1**	**2**	**8[1]**	**15**	**1**	**2**	**8[1]**	**15[2]**		
Window (in days)	-14 - 0	-1	0	±2	±3[3]	±3[3]	0	±2	±3[3]		
Written Informed Consent[4]	X										
Medical History	X										
Physical Examination (including skin)	X	X		X	X	X		X	X	X	
ECOG PS	X	X		X	X	X		X	X	X	
Vital Signs[5]	X	X		X	X	X		X	X	X	
Fasting Clinical Blood Tests[6]	X	X		X	X	X		X	X	X	
Urinalysis	X									X	
Serum Pregnancy Test (if applicable)	X									X	
CYP2D6 Sample		X									
ctDNA Sample		X									
Glucose Metabolism Blood Samples[7]		X	X		X	X	X				
PK Blood Samples[7]		X	X		X	X	X				
Home Blood Glucose Monitoring[8]			X	X	X						
Blood Tumor Markers (if applicable)[9]	X	X	X	X	X	X	X	X	X	X	
12-Lead ECG[10]	X	X			X	X				X	
Bone Scan	X										
Electrocardiography/MUGA (if applicable)	X										
Tumor Assessment and Re-staging[12]	X					X				X	
Concomitant Medications	X	X		X	X	X		X	X	X	X
Adverse Events Assessment		X		X	X	X		X	X	X	X
MK-4440 Dispensation		X				X					

1 Day 8 visits are only required for Arm B (MK-4440+paclitaxel)

2 Cycle 2 Day 15 visit is only required for Arm B (MK-4440+paclitaxel) and Arm C (MK-4440+fulvestrant). Day 15 visits in Cycle 3 are higher are required only for Arm B (MK-4440+paclitaxel)

3 Window of ±3 days is allowed for Arms A (MK-4440 single agent) and Arm C (MK-4440+fulvestrant), but window of ±2 days is required for Arm B (MK-4440+paclitaxel).

4 ICF can be signed greater than 14 days prior to first dose.

5 Temperature, BP, HR and RR at every visit. Height only at Screening. Weight at Screening, Day 1 of each cycle and at End of Treatment visit.

6 Refer to Protocol Section 5.4 for detailed description of clinical laboratory tests

7 Refer to Protocol Section 5.5 and Appendix 3 of the study protocol for details on PK and glucose metabolism (insulin and glucose) timepoints.

8 Refer to Protocol Section 5.6. Home blood glucose monitoring should be performed by the subjects at least once per day (before breakfast) for the first 4 weeks. Not necessary on days where glucose will be tested at the study site. After the first four weeks of treatment, the Investigator will determine if a subject should continue home glucose testing and the testing frequency.

9 Tumor markers testing (if applicable) will be done at the study site. Tumor markers will be tested at Screening and frequency of testing while on treatment will be as per FDA/NCCN guidelines, or institutional standards.

10 Refer to Protocol Section 5.3. Single 12-lead ECG to be performed at Screening and at End of Treatment visit. Repeat triplicate ECGs to be performed at C1D1, C1D15, C2D1, C3D1 and C4D1. See Appendix 3 for details for scheduled visits. Additional ECGs may be conducted if clinically indicated.

11 Echo/MUGA only required for subjects who received prior therapy with anthracyclines

12 Refer to Protocol Section 5.7. Tumor assessment (CT and/or MRI) at Screening can be done up to 28 days prior to the 1st dose of MK-4440). Post treatment, tumor assessment must be done at the beginning of every other cycle, starting at Cycle 3 Day 1. Tumor assessment required at the End of Treatment (EOT) visit unless disease progression was seen on the prior scan.

Table 3 Schedule of Assessment for Part 1 Subjects Enrolled under Amendment 5 for MK-4440-001

Tests & Procedures	Pre-Study	Treatment Visits								End of Treatment	30-day Safety Follow-up
Cycle	**Baseline**	**Cycle 1**						**Cycle 2+**		7 days after the last dose of MK-4440	30 days after the last dose of MK-4440
Week		**1**		**2**	**3**	**4**		**1**	**3**		
Day	**0**	**1**	**2**	**8**	**15**	**22**	**23**	**1**	**15**		
Window (in days)	-14 - 0	-1	0	±3			0	±3		±3	±3
Written Informed Consent	X										
Medical History	X										
Physical Examination (including skin)	X	X		X	X	X		X	X	X	
ECOG PS	X	X		X	X	X		X	X	X	
Vital Signs (T°, BP, RR, HR)	X	X	X	X	X	X	X	X	X	X	
• **Height**	X										
• **Weight**	X	X						X		X	
Fasting Clinical Blood Tests	X	X		X	X	X		X	X	X	
Urinalysis	X	X		X	X	X		X		X	
Serum Pregnancy Test (if applicable)	X									X	
CYP2D6 Sample		X									
Glucose Metabolism Blood Samples[7]		X	X	X	X	X	X	X	X		
PK Blood Samples[7]		X						X		X	
Home Blood Glucose Monitoring[8]		X	X	X	X	X		X	X		
Tumor Markers Blood Sample, if applicable[9]	X	X						X		X	
12-Lead ECG[10]	X	X						X		X	
• **In triplicate, pre- and post-dose**		X						X			
Electrocardiography/MUGA (if applicable)[10]	X							X		X	

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Tests & Procedures	Pre-Study	Treatment Visits								End of Treatment	30-day Safety Follow-up
Cycle	**Baseline**	**Cycle 1**						**Cycle 2+**		7 days after the last dose of MK-4440	30 days after the last dose of MK-4440
Week		**1**		**2**	**3**	**4**		**1**	**3**		
Day	**0**	**1**	**2**	**8**	**15**	**22**	**23**	**1**	**15**		
Window (in days)	-14 - 0	-1	0	±3			0	±3		±3	±3
Archival and/pr Fresh Tumor Biopsy[7]	X				X						
Tumor Assessment and Re-staging[11]	X							X		X	
Concomitant Medications	X	X	X	X	X	X	X	X	X	X	X
Adverse Events Assessment[9]		X	X	X	X	X	X	X	X	X	X
MK-4440 Dispensation		X	X	X	X	X	X	X	X		

1 Detailed description of clinical laboratory tests recorded in Protocol Section 5.4

2 Refer to Annex 1 of the study protocol for timepoints. Day 22 and Day 23 PK and glucose metabolism blood samples should be collected on Day 21 and Day 22 for subjects receiving MK-4440 QOD.

3 PD blood samples should be collected on Day 1 of Cycle 1, 2, 3 and End of treatment visit.

4 Refer to Annex 1 of the study protocol for timepoints. Home blood glucose monitoring should be performed at least once per day (before breakfast) for the first 4 weeks except for PK days (Cycle 1 Days 1, 2, 8, 15, 22 [Day 21 for subjects receiving MK-4440 QOD], and 23 [Day 22 for subjects receiving MK-4440 QOD]). After the first four weeks of treatment, the Investigator will determine if a subject should continue home glucose testing and the testing frequency.

5 Tumor markers testing will be done at the study site

6 12-lead ECG should be performed at Baseline and on Day 1 of the first six cycles; and in triplicate pre- and post-dose on Day 1 of Cycle 1 and Cycle 2. If applicable (previous treatment with anthracyclines), echocardiography or MUGA scan should be done at Baseline, every eight weeks for the first 24 weeks (six cycles) of treatment and every 12 weeks thereafter.

7 Archival tumor samples should be collected for all enrolled subjects; paired, pre- and post-treatment biopsy is optional for subjects enrolled in the Dose Escalation and Food-effect cohorts and mandatory for subjects enrolled in the Expanded cohort. Post-treatment biopsy can be performed Day 15 of Cycle 1 and Day 1 of Cycle 2.

8 Tumor assessment should be done at Baseline (if done within 28 days prior to the 1st dose of MK-4440), every eight weeks during treatment, and at End of Treatment (EOT) unless it was done within 28 days prior to the EOT visit.

9 Only AEs that occurred after the administration of the first dose of MK-4440 and within 30 days of the Safety Follow-up period should be reported as an AE, any AE that occurred prior to the administration of the first dose of MK-4440 should be reported as Medical history.

10 These tests and procedures must be performed on C1D1. MK-4440 must be dispensed on C1D1.

Table 4 Study Visits for Arm B (MK-4440 + Paclitaxel)

Screening	Cycle 1		Cycle 2+	Cycle 2+	EOT	30-day Safety Follow up
(-14 to -1 days)	**Day 1** (-1 to 0 days)	**Day 8 and Day 15** (±2 days)	**Day 1** (±2 days)	**Day 8 and Day 15** (±2 days)	(within 7 days of decision to permanently discontinue)	(30 days+ after last dose)
☐ Signed ICF ☐ Medical history ☐ Physical exam, incl. skin ☐ Vital signs (temperature, blood pressure, respiration rate, pulse) & height, weight ☐ ECOG PS ☐ Fasting clinical blood tests ☐ Tumor markers[5] ☐ Urinalysis ☐ 12-lead ECG[2] ☐ Record concomitant medications (conmeds) ☐ Tumor measurement and staging ☐ Echocardiogram or MUGA scan to assess LVEF[3] ☐ Bone scan ☐ Serum pregnancy test ☐ Collect redacted copy of tumor gene sequencing report	☐ Physical exam, incl. skin ☐ Vital signs (temperature, blood pressure, respiration rate, pulse) & weight ☐ ECOG PS ☐ Fasting clinical blood tests[1] ☐ Tumor markers[5] ☐ Blood samples for PK[4] ☐ Triplicate 12-lead ECG[2] ☐ Administer ARQ 751 ☐ Administer paclitaxel ☐ Dispense ARQ 751 ☐ Record conmeds ☐ Assess AEs ☐ Blood sample for CYP2D6 ☐ Blood sample for ctDNA	☐ Physical exam, incl. skin ☐ Vital signs (temperature, blood pressure, respiration rate, a pulse) & weight ☐ ECOG PS ☐ Fasting clinical blood tests[1] ☐ Tumor markers[5] ☐ Blood samples for PK[4] (Day 15 ONLY) ☐ Triplicate 12-lead ECG[2] (Day 15 ONLY) ☐ Administer ARQ 751 ☐ Administer paclitaxel ☐ Record conmeds ☐ Assess AEs	☐ Physical exam, incl. skin ☐ Vital signs (temperature, blood pressure, respiration rate, a pulse) & weight ☐ ECOG PS ☐ Fasting clinical blood tests[1] ☐ Tumor markers[5] ☐ Blood samples for PK[4] (ONLY at Cycles 2, 3 and 4) ☐ Triplicate 12-lead ECG[2] (ONLY at Cycles 2, 3 and 4 and if clinically indicated) ☐ Radiographic tumor assessment (per Section 5.8) ☐ Administer ARQ 751 ☐ Administer paclitaxel ☐ Dispense ARQ 751 ☐ Record conmeds ☐ Assess AEs	☐ Physical exam, incl. skin ☐ Vital signs (temperature, blood pressure, respiration rate, pulse) & weight ☐ ECOG PS ☐ Fasting clinical blood tests[1] ☐ Tumor markers[5] ☐ Administer ARQ 751 ☐ Administer paclitaxel ☐ Record conmeds ☐ Assess AEs	☐ Physical exam, incl. skin ☐ Vital signs (temperature, blood pressure, respiration rate, pulse) & weight ☐ ECOG PS ☐ Fasting clinical blood tests[1] ☐ Tumor markers[5] ☐ Urinalysis ☐ Serum pregnancy test ☐ 12-lead ECG[2] ☐ Radiographic tumor assessment (if PD not seen on prior scan) ☐ Record conmeds ☐ Assess AEs	☐ Record conmeds ☐ Record AEs

1 Fasting clinical blood tests (see Section 5.4) may be obtained within 24 hours of the visit (except for timepoints where insulin and glucose samples that are collected serially– see Appendix 3)
2 Collect redacted copies of all ECG tracings. See Appendix 3 for details on ECG timepoints.
3 Only for subjects who received prior therapy with anthracyclines
4 See Appendix 3 for details on PK timepoints
5 Tumor markers (if applicable) - at Screening and frequency of testing while on treatment as per FDA/NCCN guidelines, or institutional standards

Table 5 Study Visits for Arm C (MK-4440 + Fulvestrant)

Screening	**Cycle 1**		**Cycle 2+**	**Cycle 2 (only)**	**EOT**	**30-day Safety Follow up**
(-14 to -1 days)	**Day 1** (-1 to 0 days)	**Day 15** (±3 days)	**Day 1** (±3 days)	**Day 15** (±3 days)	(within 7 days of decision to permanently discontinue)	(30 days+ after last dose)
☐ Signed ICF ☐ Medical history ☐ Physical exam, incl. skin ☐ Vital signs (temperature, blood pressure, respiration rate, pulse) & height, weight ☐ ECOG PS ☐ Fasting clinical blood tests ☐ Tumor markers[5] ☐ Urinalysis ☐ 12-lead ECG[2] ☐ Record concomitant medications (conmeds) ☐ Tumor measurement and staging ☐ Echocardiogram or MUGA scan to assess LVEF[3] ☐ Bone scan ☐ Serum pregnancy test ☐ Collect redacted copy of tumor gene sequencing report	☐ Physical exam, incl. skin ☐ Vital signs (temperature, blood pressure, respiration rate, pulse) & weight ☐ ECOG PS ☐ Fasting clinical blood tests[1] ☐ Tumor markers[5] ☐ Blood samples for PK[4] ☐ Triplicate 12-lead ECG[2] ☐ Administer ARQ 751 ☐ Administer fulvestrant ☐ Dispense ARQ 751 ☐ Record conmeds ☐ Assess AEs ☐ Blood sample for CYP2D6 ☐ Blood sample for ctDNA	☐ Physical exam, incl. skin ☐ Vital signs (temperature, blood pressure, respiration rate, pulse) ☐ ECOG PS ☐ Fasting clinical blood tests[1] ☐ Tumor markers[5] ☐ Blood samples for PK[4] ☐ Triplicate 12-lead ECG[2] ☐ Administer ARQ 751 ☐ Administer fulvestrant ☐ Record conmeds ☐ Assess AEs	☐ Physical exam, incl. skin ☐ Vital signs (temperature, blood pressure, respiration rate, pulse) & weight ☐ ECOG PS ☐ Fasting clinical blood tests[1] ☐ Tumor markers[5] ☐ Blood samples for PK[4] (ONLY at Cycles 2, 3 and 4) ☐ Triplicate 12-lead ECG[2] (ONLY at Cycles 2, 3 and 4 and if clinically indicated) ☐ Radiographic tumor assessment (per Section 5.8 ☐ Administer ARQ 751 ☐ Administer fulvestrant ☐ Dispense ARQ 751 ☐ Record conmeds ☐ Assess AEs	☐ Physical exam, incl. skin ☐ Vital signs (temperature, blood pressure, respiration rate, pulse) ☐ ECOG PS ☐ Fasting clinical blood tests[1] ☐ Tumor markers[5] ☐ Administer ARQ 751 ☐ Record conmeds ☐ Assess AEs	☐ Physical exam, incl. skin ☐ Vital signs (temperature, blood pressure, respiration rate, pulse) & weight ☐ ECOG PS ☐ Fasting clinical blood tests[1] ☐ Tumor markers[5] ☐ Urinalysis ☐ Serum pregnancy test ☐ 12-lead ECG[2] ☐ Radiographic tumor assessment (if PD not seen on prior scan) ☐ Record conmeds ☐ Assess AEs	☐ Record conmeds ☐ Record AEs

1 Fasting clinical blood tests (see Section 5.4) may be obtained within 24 hours of the visit (except for timepoints where insulin and glucose samples that are collected serially– see Appendix 3)
2 Collect redacted copies of all ECG tracings. See Appendix 3 for details on ECG timepoints.
3 Only for subjects who received prior therapy with anthracyclines
4 See Appendix 3 for details on PK timepoints
5 Tumor markers (if applicable) - at Screening and frequency of testing while on treatment as per FDA/NCCN guidelines, or institutional standards

1.2.5. Safety, Efficacy, Pharmacokinetic, and Pharmacodynamic Parameters

1.2.5.1. Safety Parameters

The safety profile of MK-4440 is one of the primary endpoints of the study. Safety parameters include AEs, vital signs, Eastern Cooperative Oncology Group (ECOG) performance status, electrocardiogram (ECG), echocardiograms/Multiple gated acquisition (MUGA) scan, physical examination, and clinical laboratory tests including hematology, coagulation, chemistry, and urinalysis.

1.2.5.2. Efficacy Parameters

Efficacy is a secondary objective in Protocol Amendment 7 of the study. The efficacy endpoint is preliminary evidence of anti-tumor activity of MK-4440 as a single agent and in combination with other anti-cancer agents as assessed by Response Evaluation Criteria in Solid Tumor (RECIST) version 1.1 [3].

The efficacy parameters are as follows:

- Best overall response (BOR), defined as the best response recorded from the start of the study treatment until the end of treatment: complete response (CR), partial response (PR), stable disease (SD), or progressive disease.
- Objective response rate (ORR), defined as the proportion of subjects with a best overall response of CR or PR.
- Disease control rate (DCR), defined as the proportion of subjects with a best overall response of CR, PR, or SD; when SD is believed to be the best response, it must also meet the protocol specified minimum time from start of treatment of 8 weeks for inclusion in DCR.

1.2.5.3. Pharmacokinetic and Pharmacodynamic Parameters

Pharmacodynamic activity will be evaluated by changes in serum glucose and insulin levels, and by changes in cell-free circulating tumor deoxyribonucleic acid (ctDNA).

Pharmacokinetic parameters include measurement of maximum plasma drug concentration (C_{max}), area under the curve (AUC), and when possible, elimination half-life ($t_{1/2}$).

PD and PK analysis will be performed independently from this SAP. A separate report will be generated.

2. SUBJECT POPULATION

2.1. Population Definitions

The following subject populations will be evaluated and used for presentation and analysis of the data:

- All-Subjects-as-Treated (ASaT) Population: All subjects who received at least 1 dose of study drug.
- Efficacy-Evaluable (EE) Population: All subjects who have received at least one cycle of MK-4440 and have had at least one disease assessment following the initiation of therapy.

The ASaT population is the primary population for the analysis of efficacy and safety endpoints. Efficacy parameters will also be evaluated for the EE population (see Section 4.4).

2.2. Protocol Deviations

Major protocol deviations will be determined by a review of the data. The Sponsor or designee will be responsible for producing the final determination in collaboration with Veristat, prior to hard database lock.

All protocol violations will be presented in a data listing.

Relevant Output

Table 14.1.7A	Important Protocol Deviations Summary – Part 1 (MK-4440) (All Subjects Enrolled)
Table 14.1.7B	Important Protocol Deviations Summary – Part 2 (Combination Therapy) (All Subjects Enrolled)
Listing 16.2.2.2	Protocol Deviations (ASaT Population)

3. GENERAL STATISTICAL METHODS

3.1. Sample Size Justification

It is expected that approximately 94 subjects will be enrolled in this study; 64 subjects in Part 1 (dose escalation cohorts and Arm A) and 30 subjects in Part 2.

The exact number of subjects estimated for the dose escalation portion in both Part 1 and Part 2 is dependent on the number of subject cohorts investigated based on the toxicity encountered. A standard 3+3 design is used. As of November 2018, the dose escalation portion of Part 1 was completed and 34 subjects were enrolled in this portion of the study.

The dose expansion portion in both Part 1 and Part 2 is designed to examine preliminary evidence of anti-tumor activity of MK-4440, not as a formal efficacy study. The sample sizes were determined to be clinically reasonable to evaluate the study objectives, and consistent with standard sample sizes used in early phase, exploratory studies.

In Part 1, it is planned that up to 30 subjects with advanced, inoperable, metastatic, or recurrent solid tumors will be enrolled in expansion Arm A, up to 15 subjects with PIK3CA/PTEN activating mutations and up to 15 subjects with AKT genetic alterations. In Part 2, approximately 15 subjects (6 – 9 in escalation and 6 – 9 in expansion) will be enrolled in each combination therapy arm (Arm B, MK-4440+paclitaxel and Arm C, MK-4440+fulvestrant).

3.2. General Methods

All data listings that contain an evaluation date will contain a relative study day (Rel Day). Pre-treatment and on-treatment study days are numbered relative to the day of the first dose of study medication which is designated as Day 1. The preceding day is Day -1, the day before that is Day -2, etc.

All output will be incorporated into Microsoft Word or Excel files, or Adobe Acrobat PDF files, sorted and labeled according to the International Council for Harmonisation of Technical Requirements for Pharmaceuticals for Human Use (ICH) recommendations, and formatted to the appropriate page size(s).

Tabulations will be produced for appropriate demographic, baseline, efficacy, and safety parameters. For categorical variables, summary tabulations of the number and percentage of subjects within each category (with a category for missing data) of the parameter will be presented. For continuous variables, the number of subjects, mean, median, standard deviation, minimum, and maximum values will be presented.

The study is primarily descriptive in nature; therefore, no formal statistical hypothesis tests are planned. Data will be presented by subject and summarized by treatment arm and dose level. Evaluation of the data will consist primarily of summary displays (e.g., descriptive statistics and graphs). All tabulation of dose levels will be based on initial dose level received.

3.3. Computing Environment

All descriptive statistical analyses will be performed using SAS statistical software Version 9.4, unless otherwise noted. Medical history and adverse events will be coded using the Medical Dictionary for Regulatory Activities (MedDRA) Version 22.0 and CTCAE Version 4.03 will be used for the description of AE terms and toxicity grade. Concomitant medications will be coded using the World Health Organization (WHO) Drug Dictionary Global B3 March 2019.

3.4. Baseline Definitions

For all analyses, baseline will be defined as the most recent measurement prior to the first administration of study drug (MK-4440).

3.5. Methods of Pooling Data

Data will be pooled across sites within each arm/cohort. No additional pooling of data is planned.

3.6. Adjustments for Covariates

No formal statistical analyses that adjust for possible covariate effects are planned.

3.7. Multiple Comparisons/Multiplicity

Multiplicity is not of concern for this study with a descriptive interpretation and a primary objective to assess safety and tolerability.

3.8. Subpopulations

A subgroup analysis will be performed on efficacy endpoints based on mutation types.

3.9. Withdrawals, Dropouts, Loss to Follow-up

In the dose escalation portion of the study, if a subject withdraws from the study treatment for any reason other than a DLT during the first cycle (28 days), that subject will be replaced.

3.10. Missing, Unused, and Spurious Data

In general, there will be no substitutions made to accommodate missing data points, other than as described in this section for the determination of treatment-emergence in AE and the determination of concomitancy (vs. prior) in concomitant medication. All data recorded on the case report form (CRF) will be included in data listings that will accompany the CSR.

When tabulating adverse event data, partial dates will be handled as follows. If the day of the month is missing, the onset day will be set to the first day of the month unless it is the same month and year as study treatment. In this case, in order to conservatively report the event as treatment-emergent, the onset date will be assumed to be the date of treatment. If the onset day and month are both missing, the day and month will be assumed to be January 1, unless the

event occurred in the same year as the study treatment. In this case, the event onset will be coded to the day of treatment in order to conservatively report the event as treatment-emergent. A missing onset date will be coded as the day of treatment. If an imputed start date is after a reported end date, the start date will be coded to the end date. Partial dates are imputed only to determine treatment emergence; by-subject listings will display the partial date as recorded.

When tabulating concomitant medication data, if an end date is missing or the medication is ongoing, the medication will be included as a concomitant medication.

3.11. Visit Windows

It is expected that all visits should occur according to the protocol schedule. All data will be tabulated per the evaluation visit as recorded on the CRF even if the assessment is outside of the visit window. In data listings, the relative day of all dates will be presented.

3.12. Interim Analyses

No interim analyses are planned for this study.

4. STUDY ANALYSES

4.1. Subject Disposition

Subject disposition will be tabulated, including number of subjects screened and enrolled, the number of subjects treated in each treatment arm, dose level, and study portion, and the number and percentage of subjects in each analysis population. The number and percentage of subjects who prematurely withdrew from the treatment or from the study, along with the primary reasons for withdrawal, will also be summarized.

A by-subject data listing of study completion information including the reason for premature study withdrawal, if applicable, will be presented.

Relevant Output

Table 14.1.1A	Subject Disposition by Treatment and Initial Dose Level – Part 1 (MK-4440)
Table 14.1.1B	Subject Disposition by Treatment and Initial Dose Level – Part 2 (Combination Therapy)
Listing 16.2.1.1	Treatment Completion
Listing 16.2.1.2	Study Completion
Listing 16.2.1.3	Informed Consent and Re-Consent
Listing 16.2.2.1	Inclusion/Exclusion Criteria Not Met
Listing 16.2.3.1	Study Populations

4.2. Demographics, Baseline Characteristics and Medical History

All demographic and baseline characteristics will be descriptively summarized for the ASaT Population. Categorical variables will be summarized by the number and percentage of subjects in each category. Continuous variables will be summarized by mean, standard deviation, median, minimum, and maximum.

Demographic characteristics include age, gender, race, ethnicity, baseline characteristics include ECOG performance status, height, weight, and body mass index (BMI).

Baseline disease characteristics including current cancer type, tumor grade and staging at initial diagnosis, grade and staging at study entry, histology, ER (estrogen receptor), progesterone receptor, and human epidermal growth factor receptor 2 (HER2) status, gene mutation, and specific PTEN gene mutation will be presented. Frequency and percentage of subjects with any prior radiotherapy, surgery, and systemic cancer therapy will be summarized by therapy type.

Medical history will be tabulated by system organ class (SOC) and preferred term (PT). Baseline concomitant medication will also be summarized.

Demographic, baseline characteristic, disease history, prior surgeries, cancer therapies and medical history data for each subject will be provided in data listings.

Relevant Output

Table 14.1.2A	Demographics and Baseline Characteristics by Treatment and Initial Dose Level – Part 1 (MK-4440) (ASaT Population)
Table 14.1.2B	Demographics and Baseline Characteristics by Treatment and Initial Dose Level – Part 2 (Combination Therapy) (ASaT Population)
Table 14.1.3A	Baseline Disease Characteristics by Treatment and Initial Dose Level – Part 1 (MK-4440) (ASaT Population)
Table 14.1.3B	Baseline Disease Characteristics by Treatment and Initial Dose Level – Part 2 (Combination Therapy) (ASaT Population)
Table 14.1.4A	Prior Therapy by Treatment Arm and Initial Dose Level – Part 1 (MK-4440) (ASaT Population)
Table 14.1.4B	Prior Therapy by Treatment Arm and Initial Dose Level – Part 2 (Combination Therapy) (ASaT Population)
Table 14.1.5A	Medical History by Treatment Arm and Initial Dose Level – Part 1 (MK-4440) (ASaT Population)
Table 14.1.5B	Medical History by Treatment Arm and Initial Dose Level – Part 2 (Combination Therapy) (ASaT Population)
Table 14.1.6A	Prior Medications by Treatment Arm and Initial Dose Level – Part 1 (MK-4440) (ASaT Population)
Table 14.1.6B	Prior Medications by Treatment Arm and Initial Dose Level – Part 2 (Combination Therapy) (ASaT Population)
Listing 16.2.4.1	Demographics and Baseline Characteristics
Listing 16.2.4.2	Medical History
Listing 16.2.4.3.1	Current Cancer History: Histology
Listing 16.2.4.3.2	Current Cancer History: Initial Diagnosis and Study Entry
Listing 16.2.4.3.3	Current Cancer History: Receptor Status
Listing 16.2.4.3.4	Current Cancer History: Molecular Profile
Listing 16.2.4.3.5	Current Cancer History: Mutation
Listing 16.2.4.4	Current Cancer Radiotherapy History
Listing 16.2.4.5	Current Cancer Surgical History
Listing 16.2.4.6	Current Cancer Systemic Therapy History
Listing 16.2.4.7	Bone Scan

4.3. Safety Analyses

The safety analyses will be based on the ASaT Population.

4.3.1. Study Drug Exposure

Study drug exposure will be summarized for MK-4440, including number of treatment cycles and duration of exposure (days). Cumulative dose (mg), dose intensity (mg/day), and overall treatment compliance (%) for MK-4440 will be summarized.

Duration of exposure is defined as the total number of days of study drug administration, ignoring any temporary drug discontinuation. If the date of last administration is unknown, the

date until which the dispensed drug would have lasted without counting the extra drug provided will be used. Duration of exposure will be calculated by the formula:

Duration of exposure (days) = (date of last dose) – (date of first dose) + 1

Cumulative dose (mg) is defined as the total number of milligrams of MK-4440 that have been ingested. Cumulative dose (mg) is calculated as below:

*Cumulative dose (mg) = (Number of tablets*mg concentration dispensed) – (Number of tablets*mg concentration returned)*

Dose intensity (mg/day) is defined as the dose administered per unit time. Dose intensity is calculated as:

Dose intensity = Cumulative dose / Duration of exposure

Overall treatment compliance by subjects with study drug MK-4440 will be summarized and calculated as:

$$Percent\ Compliance = \frac{(Number\ of\ tablets\ dispensed - Number\ of\ tablets\ returned)}{(Number\ of\ tablets\ dispensed)} \times 100$$

Treatment exposure and subject compliance with study drug will be presented in a data listing, including exposure data for combination therapies (paclitaxel and fulvestrant).

Relevant Output

Table 14.3.5.1.1	MK-4440 Study Drug Exposure in Part 1 by Initial Dose Level (ASaT Population)
Table 14.3.5.1.2	MK-4440 Study Drug Exposure in Part 2 by Initial Dose Level (ASaT Population)
Listing 16.2.5.1.1	MK-4440 Administration
Listing 16.2.5.1.2	Paclitaxel Administration (Arm B)
Listing 16.2.5.1.3	Fulvestrant Administration (Arm C)
Listing 16.2.5.1.4	Study Drug Accountability
Listing 16.2.5.2.1	MK-4440 Overall Study Drug Exposure
Listing 16.2.5.2.2	Combination Drug Overall Study Drug Exposure

4.3.2. Adverse Events

All AEs will be coded using the MedDRA coding system and displayed in tables and data listings using SOC and PT.

Analyses of adverse events will be performed on those events that are considered treatment-emergent, where treatment-emergent is defined as any adverse event with onset after the administration of study treatment through the end of the study (30 days after the last dose), or any event that was present at baseline but worsened in intensity or was subsequently considered

drug-related to MK-4440 (for Part 1) or drug-related to MK-4440 or combination drug (for Part 2) by the Investigator through the end of the study.

A Summary of treatment-emergent AEs (TEAEs) will be presented by initial dose level received and include the number of and percentage of subjects with any of the following:

- All TEAEs
- TEAEs related to MK-4440 (for Part 1)
- TEAEs related to MK-4440 or combination drugs (for Part 2)
- Severe and treatment related severe TEAEs (Grade 3 or higher)
- Serious and treatment related serious Adverse Events (SAEs)
- TEAEs and treatment related TEAEs leading to treatment discontinuation
- TEAEs and treatment related TEAEs leading to dose interruption or reduction
- TEAEs and treatment related TEAEs resulting in death
- TEAEs listed according to maximum severity
- Dose limiting toxicity TEAEs
- Common (> 10% in one or more treatment group) TEAE

In addition to the overall summary, separate summaries of each of the above categories will also be presented by SOC and PT. In these tabulations, each subject will contribute only once to the count for a given adverse event (SOC or PT), regardless of the number of episodes (i.e., adverse events are summarized by subject incidence rates).

For tabulations that include classification by maximum severity grade or TEAE >= Grade 3 (Severe TEAE), AEs with missing severity will be included in a missing severity category, and each participant will contribute only once (e.g., the most intense occurrence) to each of the incidence rates in the descriptive analysis, regardless of the number of episodes. For tabulations that include classification by relationship to study treatment, AEs with missing relationship will be considered related to treatment drug.

In addition to the summary tabulations, the following by-subject data listings will be provided:

- All AEs, with a flag indicating TEAEs
- All SAEs
- All AEs leading to Death
- All TEAEs characterized as a DLT (if any)
- All AEs leading to discontinuation of study treatment

Relevant Output

Table 14.3.1.1.1 Treatment-Emergent Adverse Events Summary by Initial Dose Level – Part 1 (MK-4440) (ASaT Population)

Table 14.3.1.1.2	Treatment-Emergent Adverse Events Summary by Treatment Arm and Initial Dose Level – Part 2 (Combination Therapy) (ASaT Population)
Table 14.3.1.2.1A	Treatment-Emergent Adverse Events by MedDRA System Organ Class, Preferred Term, Treatment Arm and Initial Dose Level – Part 1 (MK-4440) (ASaT Population)
Table 14.3.1.2.1B	Treatment-Emergent Adverse Events by MedDRA System Organ Class, Preferred Term, Treatment Arm and Initial Dose Level – Part 2 (Combination Therapy) (ASaT Population)
Table 14.3.1.2.2A	MK-4440 Related Treatment-Emergent Adverse Events by MedDRA System Organ Class, Preferred Term, Treatment Arm and Initial Dose Level – Part 1 (MK-4440) (ASaT Population)
Table 14.3.1.2.2B	MK-4440 or Combination Drug Related Treatment-Emergent Adverse Events by MedDRA System Organ Class, Preferred Term, Treatment Arm and Initial Dose Level – Part 2 (Combination Therapy) (ASaT Population)
Table 14.3.1.2.3A	MK-4440 Related Treatment-Emergent Adverse Events by Decreasing Incidence, MedDRA Preferred Term, Treatment Arm and Initial Dose Level – Part 1 (MK-4440) (ASaT Population)
Table 14.3.1.2.3B	MK-4440 or Combination Drug Related Treatment-Emergent Adverse Events by Decreasing Incidence, MedDRA Preferred Term, Treatment Arm and Initial Dose Level – Part 2 Arm B (MK-4440 + Paclitaxel) (ASaT Population)
Table 14.3.1.2.3C	MK-4440 or Combination Drug Related Treatment-Emergent Adverse Events by Decreasing Incidence, MedDRA Preferred Term, Treatment Arm and Initial Dose Level – Part 2 Arm C (MK-4440 + Fulvestrant) (ASaT Population)
Table 14.3.1.3.1A	Treatment-Emergent Adverse Events with CTCAE Grade >= 3 by MedDRA System Organ Class, Preferred Term, Treatment Arm and Initial Dose Level – Part 1 (MK-4440) (ASaT Population)
Table 14.3.1.3.1B	Treatment-Emergent Adverse Events with CTCAE Grade >= 3 by MedDRA System Organ Class, Preferred Term, Treatment Arm and Initial Dose Level – Part 2 (Combination Therapy) (ASaT Population)
Table 14.3.1.3.2A	MK-4440 Related Treatment-Emergent Adverse Events with CTCAE Grade >= 3 by MedDRA System Organ Class, Preferred Term, Treatment Arm and Initial Dose Level – Part 1 (MK-4440) (ASaT Population)
Table 14.3.1.3.2B	MK-4440 or Combination Drug Related Treatment-Emergent Adverse Events with CTCAE Grade >= 3 by MedDRA System Organ Class, Preferred Term, Treatment Arm and Initial Dose Level – Part 2 (Combination Therapy) (ASaT Population)
Table 14.3.1.3.3A	Treatment-Emergent Adverse Events with CTCAE Grade >= 3 by Decreasing Incidence, MedDRA Preferred Term, Treatment Arm and Initial Dose Level – Part 1 (MK-4440) (ASaT Population)
Table 14.3.1.3.3B	Treatment-Emergent Adverse Events with CTCAE Grade >= 3 by Decreasing Incidence, MedDRA Preferred Term, Treatment Arm and Initial Dose Level – Part 2 Arm B (MK-4440 + Paclitaxel) (ASaT Population)
Table 14.3.1.3.3C	Treatment-Emergent Adverse Events with CTCAE Grade >= 3 by Decreasing Incidence, MedDRA Preferred Term, Treatment Arm and

Table 14.3.1.8.1A	Treatment-Emergent Adverse Events Leading to Death by MedDRA System Organ Class, Preferred Term, Treatment Arm and Initial Dose Level – Part 1 (MK-4440) (ASaT Population)
Table 14.3.1.8.1B	Treatment-Emergent Adverse Events Leading to Death by MedDRA System Organ Class, Preferred Term, Treatment Arm and Initial Dose Level – Part 2 (Combination Therapy) (ASaT Population)
Table 14.3.1.8.2A	MK-4440 Related Treatment-Emergent Adverse Events Leading to Death by MedDRA System Organ Class, Preferred Term, Treatment Arm and Initial Dose Level – Part 1 (MK-4440) (ASaT Population)
Table 14.3.1.8.2B	MK-4440 or Combination Drug Related Treatment-Emergent Adverse Events Leading to Death by MedDRA System Organ Class, Preferred Term, Treatment Arm and Initial Dose Level – Part 2 (Combination Therapy) (ASaT Population)
Table 14.3.1.9A	Dose Limiting Toxicity Treatment-Emergent Adverse Events by MedDRA System Organ Class, Preferred Term, Treatment Arm and Initial Dose Level – Part 1 (MK-4440) (ASaT Population)
Table 14.3.1.9B	Dose Limiting Toxicity Treatment-Emergent Adverse Events by MedDRA System Organ Class, Preferred Term, Treatment Arm and Initial Dose Level – Part 2 (Combination Therapy) (ASaT Population)
Table 14.3.1.10.1A	Treatment-Emergent Adverse Events by Maximum CTCAE Grade, MedDRA System Organ Class, Preferred Term, Treatment Arm and Initial Dose Level – Part 1 (MK-4440) (ASaT Population)
Table 14.3.1.10.1B	Treatment-Emergent Adverse Events by Maximum CTCAE Grade, MedDRA System Organ Class, Preferred Term, Treatment Arm and Initial Dose Level – Part 2 (Combination Therapy) (ASaT Population)
Table 14.3.1.10.2A	MK-4440 Related Treatment-Emergent Adverse Events by Maximum CTCAE Grade, MedDRA System Organ Class, Preferred Term, Treatment Arm and Initial Dose Level – Part 1 (MK-4440) (ASaT Population)
Table 14.3.1.10.2B	MK-4440 or Combination Drug Related Treatment-Emergent Adverse Events by Maximum CTCAE Grade, MedDRA System Organ Class, Preferred Term, Treatment Arm and Initial Dose Level – Part 2 (Combination Therapy) (ASaT Population)
Table 14.3.1.11A	Common (>10% in One or More Treatment Group) Treatment-Emergent Adverse Events by Decreasing Incidence, MedDRA Preferred Term, Treatment Arm and Initial Dose Level – Part 1 (MK-4440) (ASaT Population)
Table 14.3.1.11B	Common (>10% in One or More Treatment Group) Treatment-Emergent Adverse Events by Decreasing Incidence, MedDRA Preferred Term, Treatment Arm and Initial Dose Level – Part 2 Arm B (MK-4440 + Paclitaxel) (ASaT Population)
Table 14.3.1.11C	Common (>10% in One or More Treatment Group) Treatment-Emergent Adverse Events by Decreasing Incidence, MedDRA Preferred Term, Treatment Arm and Initial Dose Level – Part 2 Arm B (MK-4440 + Fulvestrant) (ASaT Population)
Table 14.3.2.1A	Listing of Serious Adverse Events by Subject and System Organ Class / Preferred Term – Part 1 (MK-4440) (ASaT Population)

Table 14.3.2.1B	Listing of Serious Adverse Events by Subject and System Organ Class / Preferred Term – Part 2 (Combination Therapy) (ASaT Population)
Table 14.3.2.2A	Listing of Adverse Events Leading to Death by Subject and System Organ Class / Preferred Term – Part 1 (MK-4440) (ASaT Population)
Table 14.3.2.2B	Listing of Adverse Events Leading to Death by Subject and System Organ Class / Preferred Term – Part 2 (Combination Therapy) (ASaT Population)
Table 14.3.2.3A	Listing of Dose Limiting Toxicity Adverse Events by Subject and System Organ Class / Preferred Term – Part 1 (MK-4440) (ASaT Population)
Table 14.3.2.3B	Listing of Dose Limiting Toxicity Adverse Events by Subject and System Organ Class / Preferred Term – Part 2 (Combination Therapy) (ASaT Population)
Table 14.3.2.4A	Listing of Adverse Events Leading to Treatment Discontinuation by Subject and System Organ Class / Preferred Term – Part 1 (MK-4440)
Table 14.3.2.4B	Listing of Adverse Events Leading to Treatment Discontinuation by Subject and System Organ Class / Preferred Term – Part 2 (Combination Therapy)
Listing 16.2.7.1	Listing of Adverse Events by Subject and System Organ Class / Preferred Term – Part 1 (MK-4440)
Listing 16.2.7.2	Listing of Adverse Events by Subject and System Organ Class / Preferred Term – Part 2 (Combination Therapy)
Listing 16.2.9.8	Safety Follow-Up
Listing 16.2.9.9	Death Details

4.3.3. Laboratory Data

Clinical laboratory values will be expressed in International System of Units (SI units).

The actual value and change from baseline to each on-study evaluation will be summarized for each clinical laboratory parameter, including hematology, clinical chemistry, coagulation, liver function tests, electrolytes, and urinalysis. All lab tests for the corresponding category as identified on the CRF will be included in the analysis. In the event of repeat values, the last non-missing value per study day/time will be used.

Toxicities will be graded according to the NCI CTCAE v4.03. Shift table of changes in toxicity grade from baseline to worst value and from baseline to last value on study will be presented for NCI CTCAE specified laboratory tests. Laboratory values collected from both scheduled and unscheduled visits will be included in these summaries.

All laboratory data will be provided in data listings.

Relevant Output

Table 14.3.5.2.1A	Descriptive Statistics and Change from Baseline for Clinical Laboratory Data: Hematology by Treatment Arm and Initial Dose Level – Part 1 (MK-4440) (ASaT Population)

Table 14.3.5.2.1B	Descriptive Statistics and Change from Baseline for Clinical Laboratory Data: Hematology by Treatment Arm and Initial Dose Level – Part 2 (Combination Therapy) (ASaT Population)
Table 14.3.5.2.2A	Descriptive Statistics and Change from Baseline for Clinical Laboratory Data: Chemistry by Treatment Arm and Initial Dose Level – Part 1 (MK-4440) (ASaT Population)
Table 14.3.5.2.2B	Descriptive Statistics and Change from Baseline for Clinical Laboratory Data: Chemistry by Treatment Arm and Initial Dose Level – Part 2 (Combination Therapy) (ASaT Population)
Table 14.3.5.2.3A	Descriptive Statistics and Change from Baseline for Clinical Laboratory Data: Coagulation by Treatment Arm and Initial Dose Level – Part 1 (MK-4440) (ASaT Population)
Table 14.3.5.2.3B	Descriptive Statistics and Change from Baseline for Clinical Laboratory Data: Coagulation by Treatment Arm and Initial Dose Level – Part 2 (Combination Therapy) (ASaT Population)
Table 14.3.5.2.4A	Descriptive Statistics and Change from Baseline for Clinical Laboratory Data: Glucose/Insulin by Treatment Arm and Initial Dose Level – Part 1 (MK-4440) (ASaT Population)
Table 14.3.5.2.4B	Descriptive Statistics and Change from Baseline for Clinical Laboratory Data: Glucose/Insulin by Treatment Arm and Initial Dose Level – Part 2 (Combination Therapy) (ASaT Population)
Table 14.3.5.2.5A	Descriptive Statistics and Change from Baseline for Clinical Laboratory Data: Urinalysis by Treatment Arm and Initial Dose Level – Part 1 (MK-4440) (ASaT Population)
Table 14.3.5.2.5B	Descriptive Statistics and Change from Baseline for Clinical Laboratory Data: Urinalysis by Treatment Arm and Initial Dose Level – Part 2 (Combination Therapy) (ASaT Population)
Table 14.3.5.3.1	Clinical Laboratory Shifts from Baseline to Worst On-Study and Last On-Study Values by CTCAE Grade: Hematology by Treatment Arm and Initial Dose Level (ASaT Population)
Table 14.3.5.3.2	Clinical Laboratory Shifts from Baseline to Worst On-Study and Last On-Study Values by CTCAE Grade: Chemistry by Treatment Arm and Initial Dose Level (ASaT Population)
Table 14.3.5.3.3	Clinical Laboratory Shifts from Baseline to Worst On-Study and Last On-Study Values by CTCAE Grade: Coagulation by Treatment Arm and Initial Dose Level (ASaT Population)
Table 14.3.5.3.4	Clinical Laboratory Shifts from Baseline to Worst On-Study and Last On-Study Values by CTCAE Grade: Glucose/Insulin by Treatment Arm and Initial Dose Level (ASaT Population)
Listing 16.2.8.1	Clinical Laboratory Results: Hematology
Listing 16.2.8.2	Clinical Laboratory Results: Chemistry
Listing 16.2.8.3	Clinical Laboratory Results: Coagulation
Listing 16.2.8.4	Serial Glucose/Insulin
Listing 16.2.8.5	Home Glucose Monitoring
Listing 16.2.8.6	Clinical Laboratory Results: Urinalysis
Listing 16.2.8.7	Tumor Markers
Listing 16.2.8.8	Pregnancy Test Results

Listing 16.2.8.9 Pharmacodynamic Archival Tissue Collection

Listing 16.2.8.10 Pharmacodynamic Biopsy Tissue Collection

4.3.4. Vital Signs and Physical Examination

Summary statistics for baseline, each post-baseline measurement, and change from baseline for each post-baseline measurement will be presented for each vital sign parameter including temperature, diastolic/systolic blood pressure, respiration rate, heart rate, and weight.

Vital sign measurements and all physical examination findings will be presented for each subject in data listings.

Relevant Output

Table 14.3.5.4A Descriptive Statistics and Change from Baseline for Vital Signs Data by Treatment Arm and Initial Dose Level – Part 1 (MK-4440) (ASaT Population)

Table 14.3.5.4B Descriptive Statistics and Change from Baseline for Vital Signs Data by Treatment Arm and Initial Dose Level – Part 2 (Combination Therapy) (ASaT Population)

Listing 16.2.9.1 Vital Sign Results

Listing 16.2.9.2 Physical Examination Results

4.3.5. ECOG Performance Status

Number and percentage of subjects within each ECOG performance status level will be presented for baseline and each on-study evaluation. In addition, a summary of shift from baseline status to the worst and last post treatment status will be presented by treatment arm and cohort.

ECOG performance data will be provided in a data listing.

Relevant Output

Table 14.3.5.7.1A ECOG Performance Status Over Time by Treatment Arm and Initial Dose Level – Part 1 (MK-4440) (ASaT Population)

Table 14.3.5.7.1B ECOG Performance Status Over Time by Treatment Arm and Initial Dose Level – Part 2 (Combination Therapy) (ASaT Population)

Table 14.3.5.7.2 ECOG Shifts from Baseline to Worst On-Study and Last On-Study Values by Treatment Arm and Initial Dose Level (ASaT Population)

Listing 16.2.9.3 ECOG Performance Status Results

4.3.6. 12-lead ECG and MUGA/Echocardiogram

Descriptive statistics will be provided for heart rate (HR), PR, QRS, QT and QTcF at baseline and each study visit. Change from baseline will also be summarized. The number and

percentage of subjects within each cardiac rhythm category will be summarized for baseline and each on study visit. Number and percentage of subjects with normal, abnormal, and clinically significant abnormal results at baseline and each study visit for overall ECG interpretation will be provided.

Similarly, descriptive statistics will be summarized for left ventricular ejection fraction (LVEF) from MUGA/echocardiogram performed at Screening. Any post-baseline MUGA/echocardiogram assessments will be included in data listings, but will not be tabulated.

An echocardiogram/MUGA will be conducted at the screening visit only for subjects who received prior therapy with anthracyclines. 12-lead ECGs will be conducted at time points specified in the protocol.

All ECG and MUGA/echocardiogram measurements will be presented in data listings.

Relevant Output

Table 14.3.5.5.1A	Descriptive Statistics and Change from Baseline for Electrocardiogram Data by Treatment Arm and Initial Dose Level – Part 1 (MK-4440) (ASaT Population)
Table 14.3.5.5.1B	Descriptive Statistics and Change from Baseline for Electrocardiogram Data by Treatment Arm and Initial Dose Level – Part 2 (Combination Therapy) (ASaT Population)
Table 14.3.5.5.2A	Electrocardiogram Interpretations Over Time by Initial Dose Level – Part 1 (MK-4440) (ASaT Population)
Table 14.3.5.5.2B	Electrocardiogram Interpretations Over Time by Initial Dose Level – Part 2 (Combination Therapy) (ASaT Population)
Table 14.3.5.6A	Descriptive Statistics for Left Ventricular Ejection Fraction by Treatment Arm and Initial Dose Level – Part 1 (MK-4440) (ASaT Population)
Table 14.3.5.6B	Descriptive Statistics for Left Ventricular Ejection Fraction by Treatment Arm and Initial Dose Level – Part 2 (Combination Therapy) (ASaT Population)
Listing 16.2.9.4	12-Lead Electrocardiogram Results
Listing 16.2.9.5	Echocardiogram/MUGA Results

4.3.7. Concomitant Medications

Concomitant medications will be coded using the WHO Drug Dictionary. Results will be tabulated by anatomic therapeutic class (ATC) level 3 and preferred term per treatment arm and cohort. Any medications that did not end prior to first dose or any medication taken between first and last dose of MK-4440 will be included.

The use of prior and concomitant medications will be included in a by-subject data listing.

Relevant Output

Table 14.3.5.8A	Concomitant Medications by Treatment Arm and Initial Dose Level – Part 1 (MK-4440) (ASaT Population)

Table 14.3.5.8B	Concomitant Medications by Treatment Arm and Initial Dose Level – Part 2 (Combination Therapy) (ASaT Population)
Listing 16.2.9.6	Prior and Concomitant Medications

4.4. Efficacy Evaluation

Efficacy analyses will be performed on the ASaT population and EE population. The efficacy endpoints defined in Section 1.2.5.2 will be summarized overall for dose escalation cohorts, each expansion cohort, and by mutation type. All tumor response assessment will be performed by following RECIST version 1.1.

- BOR will be presented, with a two-sided exact 95% confidence intervals (CIs) for the percentage of subjects in each RECIST response category (i.e., CR, PR, SD, and Progressive Disease).
- ORR, defined as the proportion of subjects with best overall response of CR or PR, will be presented with a two-sided exact 95% CI.
- Disease control rate, defined as the proportion of subjects with an overall response of CR, PR, or SD (for at least 8 weeks), will be presented with a two-sided exact 95% CI.

All efficacy data will be provided in data listings, including scan results and associated parameters for assessment of response.

Relevant Output

Table 14.2.1.1A	Summary of Best Overall Response and Response Rates by Treatment Arm and Initial Dose Level – Part 1 (MK-4440) (ASaT Population)
Table 14.2.1.1B	Summary of Best Overall Response and Response Rates by Treatment Arm and Initial Dose Level – Part 2 (Combination Therapy) (ASaT Population)
Table 14.2.1.2A	Summary of Best Overall Response and Response Rates by Treatment Arm and Initial Dose Level – Part 1 (MK-4440) (Efficacy-Evaluable Population)
Table 14.2.1.2B	Summary of Best Overall Response and Response Rates by Treatment Arm and Initial Dose Level – Part 2 (Combination Therapy) (Efficacy-Evaluable Population)
Table 14.2.1.3A	Summary of Best Overall Response and Response Rates by Treatment Arm and Mutation Type – Part 1 (MK-4440) (ASaT Population)
Table 14.2.1.3B	Summary of Best Overall Response and Response Rates by Treatment Arm and Mutation Type – Part 2 Arm B (MK-4440 + Paclitaxel) (ASaT Population)
Table 14.2.1.3C	Summary of Best Overall Response and Response Rates by Treatment Arm and Mutation Type – Part 2 Arm C (MK-4440 + Fulvestrant) (ASaT Population)

Table 14.2.1.4A	Summary of Best Overall Response and Response Rates by Treatment Arm and Mutation Type – Part 1 (MK-4440) (Efficacy-Evaluable Population)
Table 14.2.1.4B	Summary of Best Overall Response and Response Rates by Treatment Arm and Mutation Type – Part 2 Arm B (MK-4440 + Paclitaxel) (Efficacy-Evaluable Population)
Table 14.2.1.4C	Summary of Best Overall Response and Response Rates by Treatment Arm and Mutation Type – Part 2 Arm C (MK-4440 + Fulvestrant) (Efficacy-Evaluable Population)
Listing 16.2.6.1A	RECIST 1.1 Response Assessment
Listing 16.2.6.1B	Best Overall Response
Listing 16.2.6.2	Target Lesions
Listing 16.2.6.3	Non-Target Lesions
Listing 16.2.6.4	New Lesions

4.5. Pharmacokinetics and Pharmacodynamics Evaluations

All PK and PD analyses will be described in a separate analysis plan.

5. CHANGES TO PLANNED ANALYSES

There are no changes between the protocol-defined statistical analyses and those presented in this SAP. Study drug name is changed from ARQ 751 (per protocol) to MK-4440 per Sponsor request. The Safety Population (per protocol) is renamed to All-Subjects-as-Treated (ASaT) Population per Sponsor's internal standard for early oncology trials.

6. REFERENCES

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