STATISTICAL ANALYSIS PLAN

A Phase 2, Single Arm, Two Period Study of Sodium Cridanimod in Conjunction with Progestin Therapy in Patients with Endometrial Carcinoma

Sponsor: XENETIC BIOSCIENCES, INC.

Protocol Number: VX-EC-2-02

NCT Number: 03077698

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Date: 05 May 2020

Version: Final 1.0 - Abbreviated

SMC

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Contents

Abbreviation	Definition
AE	Adverse Event
ALT	Alanine Aminotransferase
AST	Aspartate Aminotransferase
ß-hCG	Beta-human Chorionic Gonadotropin
BMI	Body Mass Index
BUN	Blood Urea Nitrogen
cGFR	Calculated Glomerular Filtration Rate
CI	Confidence Interval
CKD-EPI	Chronic Kidney Disease Epidemiology Collaboration.
CR	Complete Response
CSR	Clinical Study Report
CT	Computed Tomography
CTCAE	Common Terminology Criteria for Adverse Events
DSMB	Data and Safety Monitoring Board
ECG	Electrocardiogram
eCRF	Electronic Case Report Form
ENT	Ears, Nose and Throat
FAS	Full Analysis Set
FDA	Food and Drug Administration
GOG	Gynecologic Oncology Group
ICH	International Conference on Harmonisation
IEC	Independent Ethics Committee
IHC	Immunohistochemistry
i.m.	Intramuscularly
IRB	Institutional Review Board
LDH	Lactate Dehydrogenase
MA	Megestrol Acetate
MCHC	Mean Corpuscular Hemoglobin Concentration
MCV	Mean Corpuscular Volume
MedDRA®	Medical Dictionary for Regulatory Activities
MRI	Magnetic Resonance Imaging
NCI	National Cancer Institute
NE	Not Evaluable
ODCR	Overall Disease Control Rate
ORR	Overall Response Rate
OS	Overall Survival
PD	Progressive Disease
PDF	Portable Document Format
PFS	Progression-Free Survival
PK	Pharmacokinetic
p.o.	Per Os (per mouth)

PPS	Per Protocol Set
PR	Partial Response
PrR	Progesterone Receptor
PT	Preferred Term
QTcB	QT ECG Interval Corrected for Heart Rate using Bazett's Formula
QTcF	QT ECG Interval Corrected for Heart Rate using Fridericia's formula
RECIST	Response Evaluation Criteria In Solid Tumors
RTF	Rich Text Format
SAE	Serious Adverse Event
SAP	Statistical Analysis Plan
SD	Stable Disease
SDC	Statistics and Data Corporation, Incorporated
SGOT	Serum Glutamic Oxaloacetic Transaminase
SGPT	Serum Glutamic Pyruvic Transaminase
SOC	System Organ Class
TEAE	Treatment-Emergent Adverse Event

1. Introduction

The purpose of this statistical analysis plan (SAP) is to describe the planned abbreviated analyses and reporting for protocol VX-EC-2-02, version 6.0 dated 02January 2018. The study described in the protocol is ending early and thus the scope of the final analysis is abbreviated. Most data will be presented only in listing format.

This SAP is being written with due consideration of the recommendations outlined in the most recent International Conference on Harmonisation (ICH) E9 Guideline entitled Guidance for Industry: Statistical Principles for Clinical Trials and the most recent ICH E3 Guideline, entitled Guidance for Industry: Structure and Content of Clinical Study Reports (CSR).

This SAP describes the data that will be analyzed and the subject characteristics, efficacy, and safety assessments that will be evaluated. This SAP provides details of the specific statistical methods that will be used. The statistical analysis methods presented in this document will supersede the statistical analysis methods described in the clinical protocol. If additional analyses are required to supplement the planned analyses described in this SAP they may be completed and will be identified in the CSR.

2. Study Objectives

Since the study is closing early, none of the protocol objectives will be analyzed. Existing data will be presented in listings.

2.1 Primary Objective

To assess the antitumor activity of Sodium Cridanimod in conjunction with progestin therapy as measured by Overall Disease Control Rate (ODCR) in women with recurrent or persistent endometrial carcinoma not amenable to surgical treatment or radiotherapy who have either failed progestin monotherapy or who have been identified as progesterone receptor (PrR) negative.

2.2 Secondary Objectives

1. Efficacy: To assess Objective Response Rate (ORR), including partial response (PR) and complete response (CR), Progression-Free Survival (PFS), Duration of Stable Disease (SD) and Overall Survival (OS) for subjects receiving Sodium Cridanimod, possibly in conjunction with progestin therapy.
2. Safety: To evaluate the safety and tolerability of Sodium Cridanimod, possibly in conjunction with progestin therapy, as measured by adverse events (AE), laboratory safety parameters, and cardiac safety assessments (including QT prolongation potential).

2.3 Translational Objective

To assess pharmacokinetic (PK) data of Sodium Cridanimod (SC) and Megestrol Acetate (MA) after a single dose and multiple dose administration and possible pharmaceutical interaction between SC and MA.

3. Study Variables

3.1 Efficacy Variables

The efficacy variables include the following:

- ODCR
- ORR
- Duration of SD
- PFS
- OS

Since the study is closing early, no summaries of overall disease control rate, or overall response rate will be calculated as part of the final analysis. However, best overall response, duration of SD (where applicable), PFS and OS for each subject will be listed.

3.2 Safety Variables

The safety variables include the following:

- AEs
- Physical Examinations
- Vital Signs
- Gynecologic Oncology Group (GOG) Performance Status
- Cardiac Monitoring via 12-Lead Electrocardiograms (ECG) assessments (including QT prolongation potential).
- Clinical Laboratory Tests

Since the study is closing early, safety data will only be presented in listings.

3.3 Pharmacokinetic Variables

Though one subject signed informed consent for PK samples to be taken, no samples were obtained from any subject. No PK data is presented in the abbreviated analysis.

3.4 Other Variables

In addition to the variables above, concomitant medications, concomitant procedures and pregnancy testing will also be recorded.

All subjects will also have endometrial cancer PrR status determined from an archival sample at Screening at a central laboratory by immunohistochemistry (IHC) testing. All subjects determined to be PrR positive (and otherwise eligible) may enroll in Treatment Period 1 (Progestin Monotherapy). Subjects determined to be PrR negative (and otherwise eligible) will proceed to Treatment Period 2 (Combination Treatment). Subjects who do not have an archived tumor tissue sample available for testing of PrR status by the central lab will be excluded from study participation.

3.5 Statistical Hypotheses

As this is a Phase 2, single-arm open-label study, no formal hypothesis testing is planned. The abbreviated analyses will consist of listings and one electrocardiogram (ECG) table with descriptive statistics.

4. Study Design and Procedures

4.1 General Study Design

This is an open-label, multi-center, single-arm, two-period Phase 2 study. The study will investigate the efficacy of Sodium Cridanimod in conjunction with progestin therapy in a population of subjects with endometrial cancer, who have failed progestin monotherapy or who been identified as PrR negative. All subjects must have endometrial cancer PrR status determined from an archival sample at Screening. The PrR status (positive or negative) will be determined by central laboratory by IHC testing. The tumor is considered to be PrR negative if the number of PrR positive cells is less than 1% determined by use of IHC. Conversely, the tumor is considered to be PrR positive if the number of PrR positive cells is 1% or greater as determined by IHC. There are two treatment periods and a follow-up period within the study.

4.2 Treatment Period 1 (Progestin Monotherapy)

During Treatment Period 1, all eligible subjects determined to be PrR positive will receive progestin monotherapy (MA 160 mg p.o. [per os {per mouth}] / day) for up to 14 weeks. Subjects will have a magnetic resonance imagery (MRI) or computed tomography (CT) scan after 12 weeks of progestin monotherapy, with response to treatment being assessed in accordance with Response Evaluation Criteria in Solid Tumors (RECIST) 1.1 criteria and will return for safety evaluations and the results of the eligibility scans. Subjects experiencing progressive disease at this time will enter Treatment Period 2. All other subjects will continue MA treatment for an additional 12 weeks. After 24 weeks of progestin monotherapy (at Visit TP1-EXT), scans will be performed again. Subjects experiencing progressive disease will enter Treatment Period 2. All subjects who achieve disease control (CR, PR or SD) or whose disease status in not evaluable (NE), as determined by this tumor assessment will be ineligible to enter Treatment Period 2. (Confirmation

of CR or PR by additional scans is not required.) These subjects will return 2 weeks following the TP1-EXT Visit for the End of Study-TP1 Visit. Subjects will be treated in accordance with local standards and clinical practice (which may include continuation of progestin therapy

A subject may be discontinued from Treatment Period 1 at any time if the subject experiences a change in symptoms and/or if disease progression is suspected by the Investigator. Where disease progression is suspected an MRI or CT scan will be performed. If the scan indicates disease control the subject is ineligible to enter Treatment Period 2. If the scan indicates PD, the subject may enter Treatment Period 2 if the subject completed at least 4 weeks of MA treatment in Treatment Period 1. Subjects who discontinue Treatment Period 1 prematurely (receiving < 4 weeks of progestin monotherapy) for any reason will be excluded from the remainder of the study. If a subject discontinues from Treatment Period 1 after at least 4 weeks of progestin monotherapy due to reasons other than suspected progression, a scan will not be performed and the subject will not be allowed to enter Treatment Period 2. In either case, subjects discontinuing from Treatment Period 1 prior to 12 weeks will receive safety assessments approximately 2 weeks days after last progestin dose as part of discontinuation from Treatment Period 1 (End of Study-TP1).

Subjects determined to be PrR negative at Screening will not enroll into Treatment Period 1. These subjects will enroll directly into Treatment Period 2.

4.3 Treatment Period 2 (Combination Treatment)

All subjects determined to be PrR negative at Screening or who received at least 4 weeks of progestin monotherapy and experienced disease progression during Treatment Period 1 will enter Treatment Period 2 of the study (Visit 1, Day 0-TP2). During Treatment Period 2, subjects will receive Sodium Cridanimod (500 mg, 2 times / week, intramuscularly [i.m.]) in combination with continued progestin treatment (MA 160 mg p.o. / day). For those subjects who participated in Treatment Period 1, there should be no interruption of progestin therapy between Treatment Period 1 and Treatment Period 2. Subjects will receive treatment until disease progression as defined by RECIST 1.1 criteria, with response assessments performed at 12-week intervals. Confirmation of objective responses will be performed at least 4 weeks after the criteria for response are first met.

4.4 Follow-Up Period

Once subjects progress during Treatment Period 2, they will return for a Safety Follow-Up TP2 Visit four (4) weeks following the last treatment, and then continue to be followed for an additional 12-month period for overall survival. No additional visits are required after the Safety Follow-up TP2 Visit. Study staff will confirm survival status via telephone, personal contact or through clinic records, once, at the end of the 12-month period. This outcome will be recorded in the eCRF.

4.5 Subject Population

Subjects are required to meet all inclusion and none of the exclusion criteria as presented in the protocol in order to be enrolled. A total of 72 women with recurrent or persistent endometrial cancer will be enrolled in the study.

At the time of study closing, a total of 25 women were enrolled in the study (36 screened).

4.6 Schedules of Visits and Assessments

4.6.1 Screening Assessments

Screening	
Study Calendar (Weeks)	-18 to -15
Procedures and Assessments	
Informed consent	X
Eligibility Criteria	X
Demographics	X
Medical History	X
Concomitant Medication	X
Physical Exam	X
Vital Signs	X
Height	X
Weight	X
Performance Status	X
CBC w/ diff, platelets	X
Serum chemistry[A]	X
eGFR	X
Urinalysis	X
Serum Pregnancy Test (B-hCG)[B]	X
ECG	X
Assessment of Adverse Events	X
PrR status of archived tumor tissue determined by central lab	X

Imaging (CT/MRI) [E]	X
Tumor Assessment (using RECIST criteria) [E]	X

Footnotes
A - Phosphate, sodium, potassium, chloride, calcium, bicarbonate, creatinine, creatine kinase, glucose, blood urea nitrogen (BUN), total proteins, albumin, total bilirubin, alkaline phosphatase, LDH, SGOT/AST, SGPT/ALT.
B - For women of childbearing potential.
E - Screening tumor assessments must be performed <10 days before Visit -3.

4.6.2 TREATMENT PERIOD 1 ASSESSMENTS

	Treatment Period 1 (PrR Positive Patients Only)				**Subjects Ineligible to enter TP2 or who Withdraw Early**
Study Visits	**-3**	**-2**	**-1**	**TP1-EXT**	**End of Study (EOS)**
Study Calendar (Weeks)	-14	-8	-2	+12 wks	+ 2 weeks
Treatments					
Progestin therapy (Megestrol acetate) Dispensing/Return [F]	D	R/D	R/D	R/D	R
Procedures and Assessments					
Eligibility Criteria	X				
Concomitant Medication	X	X	X	X	X
Physical Exam	X[C]	X	X	X	X
Vital Signs	X	X	X	X	X
Weight	X[C]	X	X	X	X
Performance Status	X[C]	X	X	X	X
CBC w/ diff, platelets	X[C]	X	X	X	X
Serum chemistry [A]	X[C]	X	X	X	X
eGFR	X[C]	X	X	X	X

Urinalysis					X
Urine Pregnancy Test[B]					X
ECG	X[H]	X[H]	X[H]	X[H]	X
Blood Draw (for PK sub-study)[G]	X[G]				
Assessment of Adverse Events	X	X	X	X	X
Imaging (CT/MRI)			X	X[D]	
Tumor Assessment (using RECIST criteria)			X	X[D]	
Patient Diary Issue/Collection[F]	I	I/C	I/C	I/C	C
Subject Compliance		X	X	X	X

Footnotes
A - Phosphate, sodium, potassium, chloride, calcium, bicarbonate, creatinine, creatine kinase, glucose, blood urea nitrogen (BUN), total proteins, albumin, total bilirubin, alkaline phosphatase, LDH, SGOT/AST, SGPT/ALT.
B - For women of childbearing potential.
C - These assessments on Visit -3 are only performed if more than 7 days have passed since the previous evaluation at Screening.
D - The tumor assessments near the conclusion of Treatment Period 1 are scheduled to take place within 2 weeks prior to TP1 EOS Visit or TP2 Visit 1 (Day 0) so as to allow adequate time to obtain tumor measurements prior to Treatment Period 2. This 2 week window can be shortened (and Visit 1 may occur) as soon as these tumor measurements are available.
F - D = Dispense, R = Return, I = Issue, C = Collect
G - For subjects who consent to participate in the PK sub-study, blood samples are taken before administration of megestrol acetate as well as 1, 2, 3, 4, 6, 24, 48, 72 and 96 hours after first administration of megestrol acetate during Visit -3.
H – ECGs to be performed prior to study drug administration whenever possible. Exception: ECG performed at End of Study Visit.

4.6.3 Treatment Period 2 Assessments

Treatment Period 2															
Study Visits	**1**	**2**	**3**	**4**	**5**	**6**	**7**	**8**	**9**	**10**	**11**	**12**	**13 - ?**	**Safety Follow-up Visit[G]**	**Follow Up Period- OS**
Study Calendar (Weeks)	0	4	8	12	16	20	24	28	32	36	40	44	48, 60 etc.[F]		
Treatments															
Sodium Cridanimod	Sodium Cridanimod is administered twice a week on either Mondays and Thursdays or Tuesdays and Fridays for the duration of Treatment Period 2.														
Progestin therapy (Megestrol acetate) Dispensing/Return[J]	R/D	R/D	R/D	R/D	R/D	R/D	R/D	R/D	R/D	R/D	R/D	R/D	R/D[H]	R	
Procedures and Assessments															
Eligibility Criteria	X														
Concomitant Medication	X	X	X	X	X	X	X	X	X	X	X	X	X	X	
Physical Exam	X		X		X		X		X		X		X	X	
Vital Signs	X	X	X	X	X	X	X	X	X	X	X	X	X	X	
Weight	X		X		X		X		X		X		X	X	
Performance Status	X		X		X		X		X		X		X	X	
CBC w/ diff, platelets	X	X	X	X	X	X	X	X	X	X	X	X	X	X	
Serum chemistry[A]	X	X	X	X	X	X	X	X	X	X	X	X	X	X	
eGFR	X	X	X	X	X	X	X	X	X	X	X	X	X	X	
Urinalysis							X						X	X	
Urine Pregnancy Test[C]							X							X	
ECG	X[E]	X	X[E]	X	X	X	X	X	X	X	X	X	X	X	

Blood Draw (for PK sub-study)	X[D]		X[D]	X[D]											
Assessment of Adverse Events	X	X	X	X	X	X	X	X	X	X	X	X	X	X	
Imaging (CT/MRI)				X			X			X			X	X[B]	
Tumor Assessments (using RECIST criteria)	Tumor assessments and radiologic imaging are repeated every 12 weeks during Treatment Period 2. In subjects with an objective response, an additional tumor assessment is performed 4 weeks later to confirm the presence of an objective response. Documentation (CT or MRI) must be provided for subjects removed from study for progressive disease.													X[B]	
Patient Diary Issue/Collection[J]	I/C	I/C	I/C	I/C	I/C	I/C	I/C	I/C	I/C	I/C	I/C	I/C	I/C[H]	C	
Subject Compliance	X	X	X	X	X	X	X	X	X	X	X	X	X		
Phone or other contact to determine survival															X[I]

Footnotes

A - Phosphate, sodium, potassium, chloride, calcium, bicarbonate, creatinine, creatine kinase, glucose, blood urea nitrogen (BUN), total proteins, albumin, total bilirubin, alkaline phosphatase, LDH, SGOT/AST, SGPT/ALT.

B - Only performed on subjects discontinued for reasons other than disease progression (if not obtained within 4 weeks of withdrawal)

C - For women of childbearing potential.

D - For the subjects who consented to participate in the PK sub-study, blood samples are taken before administration of Sodium Cridanimod and megestrol acetate as well as 15 min, 30 min, 45 min, 60 min, 90 min, 2, 3, 4 and 6 hours (all times +/- 2 minutes) after administration at Visit 1. Blood samples are also taken on Days 3, 7, 10, 56 (Visit 3) and 84 (Visit 4), before Sodium Cridanimod and megestrol acetate administration.

E - ECG will be performed 5 times at Visits 1 and 3: before Sodium Cridanimod administration, 15, 60, 120 and 360 (±5) minutes after administration. At all other visits, ECG is only performed before administration. Exception: ECG performed at Safety Follow-up Visit.

F - Subjects with disease control (non-PD) after one year of treatment in Period 2 (Visit 13) will continue treatment and will switch to study visits every 12 weeks, until discontinuation of treatment.

G - Safety Follow-up Visit occurs four weeks following the discontinuation of treatment.

H - At the visit where treatment is discontinued, study drug will not be dispensed, and a new patient diary will not be issued. The remaining drug will be returned and the final patient diary will be collected.

I – After subjects discontinue treatment and undergo the Safety Follow-up Visit, they will be followed for overall survival for an additional 12 months (from the date of treatment discontinuation) by phone call or other personal contact.

J - D = Dispense, R = Return, I = Issue, C = Collect

4.7 Data Safety Monitoring Committee

A Data and Safety Monitoring Board (DSMB) will be used to evaluate safety as needed during the trial and to review results of interim efficacy and safety analyses. The DSMB will consist of at least two clinicians (who are not Investigators for this trial) and one biostatistician with expertise in oncology trials. The DSMB will make recommendations to the Sponsor regarding the conduct of the study, including possible early discontinuation of the study for excessive toxicity or extreme efficacy. A separate DSMB Charter document will specify the procedures governing the conduct of the DSMB. Qualified individuals not affiliated with the Sponsor, including a statistician, will be responsible for preparing reports for the DSMB.

4.8 Duration of Treatment and Follow-Up

Considering the estimated accrual rate of 4-6 subjects per month, the total duration of the study after the first visit of the first subject is about 36 months.

At the time of study closing, the duration will be approximately 34 months.

5. Study Treatments

5.1 Method of Assigning Subjects to Treatment Groups

All enrolled subjects will receive the same course of study drug(s) in the respective Treatment Periods. Following providing informed consent, potential subjects will be assigned a subject identification number and undergo screening procedures to determine eligibility for the study.

Subjects satisfying all inclusion/exclusion criteria who are PrR positive will be enrolled in Treatment Period 1 and receive MA only. MA will be taken p.o. in a total daily dose of 160 mg. MA is a synthetic derivative of the naturally occurring steroid hormone progesterone and is Food and Drug Administration (FDA) approved for the treatment of advanced endometrial cancer.

Subjects determined to be PrR negative at Screening will not enroll in Treatment Period 1. These subjects will enroll directly into Treatment Period 2. All subjects who achieve disease control (CR, PR, or SD) as indicated by tumor assessment after Treatment Period 1, will be ineligible to enter Treatment Period 2. Additionally, subjects who discontinue Treatment Period 1 prematurely (receiving < 4 weeks of progestin monotherapy) for any reason will also be excluded from the remainder of the study. All other subjects may enroll in Treatment Period 2. During Treatment Period 2, subjects will receive MA in combination with Sodium Cridanimod. Sodium Cridanimod is a synthetic interferon inducer that was developed for use against viral infections. Sodium Cridanimod has been shown to increase endometrial cancer expression of PrR and increase the efficacy of progestin therapy in some hormone resistant recurrent or persistent endometrial cancer subjects. During Treatment Period 2:

- MA is to be taken p.o. in a total daily dose of 160 mg. Subjects will be provided a diary and instructed to record all doses of MA. At Study Visits when both SC and MA are to be administered, the dose of MA should be administered prior to SC. Whenever possible, the a.m. or p.m. dose of megestrol acetate should be taken in the clinic during the Study Visit.
- SC (500 mg / 4 mL) is to be diluted with 1 mL of 2% lidocaine hydrochloride (5 mL total) and administered twice a week i.m. in accordance with either Schedule 1 (Mondays and Thursdays) or Schedule 2 (Tuesdays and Fridays). For SC doses that do not correspond to a Study Visit, the drug may be administered either at the clinical site or at home by a medical service provider.

5.2 Blinding and Unblinding

This is an open-label, single-arm study; therefore, no randomization or blinding procedures will be performed.

5.3 Dose Modifications

There will be no allowed modifications to the dosage, including dose reduction, of either MA or SC during the trial.

If an injection of SC is not administered on the scheduled dosing date, this can be done during the next two days but no later than 1 day before the next scheduled dose. The subsequent injection of SC should be given in accordance with the study drug administration schedule. If a subject misses a dose of MA, the next dose should be taken at the regularly scheduled time.

SC and MA combination therapy should be discontinued if an AE of Grade 3 or higher (in accordance with NCI-CTCAE [National Cancer Institute-Common Terminology Criteria for Adverse Events] Version 4.03 criteria) is observed and determined to be potentially related to either medication**.** When combination treatment is discontinued, both SC and MA are to be discontinued. Monotherapy in Treatment Period 2 is not permitted. The treatment will not be re-started and the subject will be withdrawn from Treatment Period 2 and enter the Follow-Up Period.

6. Sample Size and Power Considerations

The primary objective of the study is to evaluate the efficacy of the study drug by the frequency of subjects with overall disease control (CR, PR and SD). The null hypothesis assumes an historical disease control rate of < 5%, given that these subjects have already failed progestin therapy. A clinically significant difference is predefined as a 15% increase (i.e. disease control rate of 20%). Using A'Hern's update of Fleming's single stage procedure (in which a predetermined number of subjects is recruited to the study and a decision about activity is obtained from the number of responses [including CR, PR] and SD amongst these subjects) with the probabilities of type I and type II errors of 5% (one-sided) and 10%, respectively, approximately 40 subjects are needed to contribute to the primary analysis in

Treatment Period 2. It is estimated that approximately 20-25% of all enrolled subjects will be classified as PrR negative and go directly into Treatment Period 2. This group will represent 14-16 of the Treatment Period 2 subjects. The rate of subjects who will have PD following treatment with MA in Treatment Period 1 and then move on to Treatment Period 2 is estimated at 55-60%. These subjects will represent 30-32 of the Treatment Period 2 subjects (estimating that approximately 24-25 subjects treated in Treatment Period 1 will not exhibit PD and will not move into Treatment Period 2.) Estimating the rate of subjects who will be unavailable for disease assessment for various reasons at 10-15%, it is planned to enroll 72 total subjects. An estimated 20% screen failure rate will require up to 90 screened subjects to allow for enrollment of 72 subjects.

Since the study is closing early, no summaries of overall disease control rate, or overall response rate will be calculated as part of the final analysis. Thus, the sample size calculations are no longer applicable.

7. Data Preparation

All reported study data will be recorded on the electronic Case Report Forms (eCRF) supplied by Statistics and Data Corporation, Inc. (SDC) using iMedNet, v1.164.1 or higher. Only the Principal Investigator and authorized study staff in accordance with the Delegation of Responsibilities log are entitled to make entries in the eCRF.

- After data are entered in the clinical study database, electronic edit checks and data review will be performed. All data validation specifications and procedures are detailed in the Data Validation Manual as a separate document. When the database has been declared to be complete and accurate, the database will be locked. Any changes to the database after data have been locked can only be made with the approval of the Sponsor in consultation with SDC.

All analyses outlined in this document will be carried out after the following have occurred:

- All data management requirements are met in accordance with SDC standard operating procedures, including data entry, performance of edit and validation checks, documentation and resolution of data queries, and database lock with written authorization provided by appropriate SDC and Sponsor personnel
- Protocol deviations have been identified and status defined (major/minor deviations)
- Analysis populations have been determined

8. Analysis Populations

All subjects who sign the informed consent, satisfy all eligibility requirements and are assigned a subject number (CCC-SS-XX), which consists of a 3-digit country code (CCC), a 2-digit site number (SS)

followed by 2-digit consecutive enrollment number (XX) will be considered enrolled subjects. This will be the population used in the disposition listings. Subjects who do not satisfy the criteria as enrolled subjects are considered screen failures. The following subsets of the enrolled subjects will be used for all other analyses.

8.1 Safety Population

1. The Safety Population will consist of all subjects who receive at least one full or partial dose of either study treatment. For subjects treated solely in Treatment Period 1 this will include all subjects treated with at least one full or partial dose of MA. For all other subjects, the Safety Population will include all subjects treated with at least one full or partial dose of either MA or SC. Safety data will be reported separately for subjects in Treatment Period 1 who do not go on to Treatment Period 2, and for those subjects in Treatment Period 1 who are treated in both periods.

8.2 Full Analysis Set

The Full Analysis Set (FAS) will consist of all Safety Population subjects treated in Treatment Period 2 who either undergo a tumor assessment at Visit 4, Week 12 (i.e. they have not discontinued Treatment Period 2 prior to Visit 4, Week 12) or those who have discontinued Treatment Period 2 prior to Visit 4, Week 12 solely due to documented disease progression since Treatment Period 2 dosing started. This population will be used for efficacy evaluation.

8.3 Per Protocol Set

The Per Protocol Set (PPS) will consist of all FAS subjects, excluding those for whom major protocol deviations have been identified. This population will be used for supportive analysis of the response rate and other efficacy parameters.

Since the study is closing early, the PPS is no longer applicable.

8.4 Pharmacokinetic Population

All subjects who receive at least one full or partial dose of either study treatment (i.e. are included in the Safety Population) with at least one analyzable blood sample will be included in the pharmacokinetic population.

9. General Statistical Considerations

9.1 Unit of Analysis

The unit of analysis in this study will be the subject for all efficacy and safety summaries.

9.2 Missing Data and Adjustments for Multiplicity

This is a phase 2, exploratory study. Missing values will not be estimated. All data will be included in safety analysis. Censoring rules for time to event analyses are described in Section 14. Since no

statistical testing will be performed, there will be no adjustments for multiplicity. Fleming's procedure is based on a one sample hypothesis test for a proportion. Because there is a single primary hypothesis, treatment corrections for multiplicity are not required.

9.3 Definition of Baseline

Baseline is defined as the last measurement prior to the first dose of study medication. In Treatment Period 1 this will be the last measurement prior to the first dispensing of MA (Visit -3). In Treatment Period 2 this will be the last measurement prior to the first in-clinic administration of MA and SC (Visit 1,Day 0-TP2). For subjects treated in both Treatment Period 1 and Treatment Period 2, baseline resets at the start of Treatment Period 2. Change from baseline will be calculated as the value at the time point of interest minus the baseline value.

9.4 Data Analysis Conventions

All data analysis will be performed by SDC after the study is completed and the database has been locked. Statistical programming and analyses will be performed using SAS® Version 9.4 or higher. Output will be provided in portable document format (PDF) and Excel. All study data will be listed by subject and visit (as applicable) based on all enrolled subjects unless otherwise specified.

Summaries for continuous and ordinal variables will include the number of observations (n), arithmetic mean, standard deviation, median, minimum, and maximum). Minima and maxima will be reported with the same precision as the raw values; means and medians will be presented to one additional decimal place than reported in the raw values. Standard deviations will be presented to two additional decimal places than reported in the raw values. Summaries for discrete variables will include frequency counts and percentages. All percentages will be rounded to one decimal place (i.e., XX.X%). The baseline measure will be defined as the last non-missing measure prior to initiation of investigational treatment.

9.5 Visit Windows

Each Study Visit has an acceptable window for when it must occur (Protocol Section 5.4). Any visit that falls outside of the acceptable window must be clearly documented as a protocol deviation.

9.6 Analysis Conventions

Disposition, safety and PK data will be reported for: Subjects in Treatment Period 1 only, Subjects in Treatment Period 2 only, Subjects in Treatment Period 1 Followed by Treatment Period 2, All Treatment Period 1 Subjects, All Treatment Period 2 Subjects, and All Subjects. Efficacy data will be reported for: Subjects in Treatment Period 2 only, Subjects in Treatment Period 1 Followed by Treatment Period 2, All Treatment Period 2 Subjects, and All Subjects.

10. Disposition of Subjects

10.1 Disposition and Discontinuation

Subject disposition including which subjects were enrolled in, completed or discontinued from each Treatment Period participated in Follow-Up and, if applicable, time in Follow-Up will be presented in a listing. Screen failure subjects will be also presented in a listing, including the reasons for screen failure. The possible reasons for screen failure are:

- Eligibility Criteria Not Met
- Physician Decision
- Withdrawal of Consent
- Adverse Event
- Other

The reasons for discontinuation from Treatment Period 1 (prior to Week 12) are:

- Disease Progression
- AE
- Withdrawal of Consent
- Pregnancy
- Non-Compliance
- Death
- Lost to Follow-Up
- Concurrent Illness
- Physician's Decision
- Protocol Deviations
- Sponsor Termination of Study
- Other

Some Treatment Period 1 subjects will proceed to Treatment Period 2 and others will not proceed. Reasons for not proceeding to Treatment Period 2 are:

- Disease Control (CR, PR, or SD)

- AE
- Withdrawal of consent
- Pregnancy
- Non-Compliance
- Death
- Lost to Follow-Up
- Concurrent Illness
- Physician's Decision
- Protocol Deviations
- Sponsor Termination of Subject
- Subject Did Not Receive at Least 4 Weeks of Treatment in Treatment Period 1
- Other

The reasons for Sodium Cridanimod treatment discontinuation (in Treatment Period 2) are:

- Disease Progression
- AE
- Withdrawal of consent
- Pregnancy
- Non-Compliance
- Death
- Lost to Follow-Up
- Concurrent illness
- Other

The reasons for not completing Safety Follow-Up are:

- AE
- Lost to Follow-Up

- Physician's Decision
- Protocol Deviations
- Sponsor Termination of Study
- Withdrawal of Consent
- Other

A subject listing of informed consent date(s) and applicable protocol amendment versions will also be provided.

10.2 Analysis Populations

A subject listing of analysis populations and treatment periods will be provided including reasons for exclusion.

10.3 Visit Dates

A subject listing of all visit dates for each will be presented.

10.4 Protocol Deviations

Protocol deviations will be collected and monitored by the site monitors and transferred to SDC as an Excel spreadsheet. Protocol deviations are collected for the following categories:

- Assessment Not Done
- Assessment Out of Window
- Inclusion/Exclusion Criteria
- Safety Related
- Visit Not Done

Prior to database lock, deviations will be reviewed to determine major/minor status. Any violations of the inclusion or exclusion criteria or subject compliance in study drug administration outside of the 80-120% acceptable range will be considered major protocol deviations. A subject listing will be provided including the date of the deviation, the deviation category and description and the classification of whether the deviation was judged to be major or minor.

11. Demographic and Pretreatment Variables

11.1 Demographic Variables

The following demographic and baseline characteristics of subjects will be provided in a listing.

- Age

- Sex
- Race
- Ethnicity
- Screening GOG Performance Status
- Screening Height
- Screening Weight

Age will be reported in years and calculated using the following formula:

Age = floor ((informed consent date – date of birth) + 1) / 365.25

11.2 Pretreatment Variables

Listings of subjects receiving prior cancer therapies (chemotherapies, hormonal therapies, radiation therapy and surgery) will be provided. Number of cycles, and best response will be presented for prior chemotherapies. Listings of these data will also include indication (as text field for prior chemotherapies) and indication plus localization (as text fields for prior radiotherapies)

11.3 Cancer Disease History and PrR Status

Subject cancer history including histology (serous adenocarcinoma or endometrioid carcinoma), date of histology assessment, TNM stage, and PrR status, intensity, percent of nuclei staining, date of tumor sample and date of central lab results will be presented in a listing.

11.4 Medical History

Listings of medical history data using the Medical Dictionary for Regulatory Activities (MedDRA®) dictionary, version 20.0, by System Organ Class (SOC) and Preferred Term (PT) will be generated, including the applied coding terms.

11.5 Pregnancy Testing

Pregnancy tests are applicable to all subjects of childbearing potential (i.e. excluding those who are anatomically sterile or are post-menopausal). A serum pregnancy test (measuring *-human chorionic gonadotropin [ß-hCG]) will be performed at the Screening Visit, and a urine pregnancy test will be performed at the End of Study-TP1 Visit, at Visit 7, Visit 13**,** and the Safety Follow-Up TP2 Visit. Results of pregnancy testing will be reported in a subject listing.

12 Concomitant Medications

Concomitant medication is defined as any medication, other than the investigational medicinal product (SC) and MA, taken at any point in the duration from the Screening Visit until the End of Study-TP1 Visit

or the Safety Follow-Up TP2 Visit. This includes all prescription medications, over-the-counter medications, and herbal remedies. All concomitant medications will be recorded. A subject listing of concomitant medications will be provided. Medications administered prior to first dose of study drugs will be distinguished from those administered once study drug dosing has begun.

13. Dosing Compliance and Treatment Exposure

13.1 Dosing Compliance

Treatment compliance will be monitored by the review of study drug accountability, inventory records by study personnel, and subject diaries. Treatment compliance (for each study drug individually) lower than 80% or higher than 120% will be considered a major protocol deviation. In the case of poor compliance, the reason for the discrepancy will be documented in the eCRF and the Investigator, together with the Sponsor, will decide on a clinical basis as to whether the subject may remain in the study. For SC, all doses are administered at the clinic or by qualified personnel at the subject's home and are recorded on the Study Drug Administration eCRF. For MA, at all visits following the Screening Visit, the subject will be provided with a Patient Diary and asked to record the administration of their daily doses of megestrol acetate (including those taken in clinic during a study visit). In addition, subjects are to record any AEs and concomitant medications in the diary. Diaries will be completed by the subjects until they exit the study at the End of Study-TP1 Visit or the Safety Follow-up TP2 Visit. Subjects will be instructed to return their completed diary at each Study Visit and a new diary will be provided to the subject.

13.2 Treatment Exposure

Subject listings of all exposure/dosing variables will be provided, including dosing days and times, lot number for SC, dose delays for SC and number of tablets per dose and other diary data for MA. Additionally, a listing of MC accountability data will be provided, including number of dispensed and returned tablets and bottles, number of tablets taken since previous visit and lot number will be produced.

14. Efficacy Analyses

The efficacy variables include the following:

- ODCR
- ORR
- Duration of SD
- PFS
- OS

Note that since the study is closing early, no summaries of overall disease control rate, or overall response rate will be calculated as part of the final analysis. However, best overall response, duration of SD (where applicable), PFS and OS for each subject in Treatment Period 2 will be listed.

Tumor response will be determined in accordance with RECIST 1.1 criteria using objective measurements of target lesions, assessments of non-target lesions and identification of new lesions. Disease response utilizes the categories: CR, PR, SD, Progressive Disease (PD), and Not Evaluable (NE).

A disease or tumor assessment will be performed by clinical examination for palpable or visual tumor lesions as well as by CT or MRI. Tumor assessments will be performed at Screening, during Treatment Period 1 following 12 weeks of treatment (at Visit -1) of Treatment Period 1, and, if disease control is achieved at that time, after an additional 12 weeks of treatment (at Visit TP1-EXT), and continuing during Treatment Period 2 every 12 weeks (± 7 day window) until disease progression is documented. CT scan or MRI of chest, abdomen, and pelvis are appropriate, but all scans for an individual subject must use the same procedure as was performed at baseline. Conventional CT and MRI should be performed with contiguous cuts of 10mm or less in slice thickness. Spiral CT should be performed by use of a 5 mm contiguous reconstruction algorithm. Ultrasound should not be used for measurement. Clinically detected lesions will only be considered measurable if they are superficial (e.g. skin nodules and palpable lymph nodes). For skin lesions, documentation by color photography, including a tool to estimate size of the lesion, is recommended.

For evaluating subject responses during Treatment Period 2, the tumor assessments for determining progression in Treatment Period 1 will be used as the new baseline measurements. For subjects entering Treatment Period 2 directly, the tumor assessments from Screening will be used as the baseline measurements. From this point forward any objective responses (CR, PR) must be confirmed at least 4 weeks after the criteria for response are first met. Once subjects progress during Treatment Period 2, they will return for a Safety Follow-Up TP2 Visit four (4) weeks following the last treatment, and then continue to be followed for an additional 12-month period for survival. If a subject discontinues Treatment Period 2 for any reason other than disease progression (i.e. intolerable AE), every reasonable effort should be taken to encourage subjects to continue receiving regular tumor assessments until disease progression is documented, with the date of disease progression still recorded in the eCRF.

If at any point during either Treatment Period, the Investigator feels that the subject's clinical status warrants radiographic assessment an unscheduled scan may be performed. If disease progression is observed at an unscheduled scan during TP1, the subject is eligible to enter TP2 if she has received > 4 weeks of treatment, otherwise the subject must return for an End of Study-TP1 Visit and be discontinued from the trial. If disease progression is observed at an unscheduled scan during TP2, the

subject must be withdrawn from treatment, enter the Follow-up Period and return for the Safety Follow-up TP2 Visit. An Unscheduled scan eCRF is to be completed.
Subjects with a global deterioration of health status requiring discontinuation of treatment in Treatment Period 2 without objective evidence of disease progression at that time should be classified as having symptomatic deterioration. Reasonable efforts should be taken to obtain radiographic evidence to confirm disease progression. Subjects experiencing symptomatic deterioration during Treatment Period 1 without objective evidence of disease progression are ineligible to enter Treatment Period 2 (as they do not meet the inclusion criteria requiring radiographic evidence of progression).

A listing of target lesions will present lesion site, description, measurement (in mm), type (nodal vs extranodal), whether the lesion is visible or palpable, was the lesion area previously irradiated, number of lesions assessed, method of assessment, CT/MRI slice thickness and whether contrast median was used. A second listing will summarize target lesion sums of diameters, percentage change from baseline, the investigator-determined overall time point target lesion assessment, sites of new lesions and method of evaluation of new lesions. This listing will also include percentage change from nadir, and which visits were used for baseline and nadir measurements for treatment period 2. Additionally, a listing of non-target lesions sites, description, status, investigator-determined overall time point non-target lesion assessment and number of non-target lesions assessed will be provided (including which visits were used for baseline assessments for subjects participating in Treatment Period 2).

14.1 Determination of Response

At each disease assessment time point Investigators assign a disease response category based on RECIST 1.1. Inclusion criteria for this trial include the presence of measurable disease with at least one target lesion to use for all disease assessments. All measurable lesions up to a maximum of 2 lesions per organ and 5 lesions in total, representative of all involved organs, should be identified as target lesions and recorded and measured at baseline. All other lesions (or sites of disease) including any measurable lesions over and above the 5 target lesions should be identified as non-target lesions and should also be recorded at baseline. Measurements of these lesions are not required, but the presence or absence of each should be noted throughout the study. If a subject misses a disease assessment, or the Investigator declines to assign a response category at an assessment, response for this assessment will be designated NE.

The following table summarizes the determination of overall disease assessment for a given time point.

Evaluation of Time Point Response: Subjects with target (+/– non-target) disease*

Target Lesions	Non Target Lesions	New Lesions	Overall Response	Confirmation Scan (Treatment Period 2 only)
CR	CR	No	CR	Yes
CR	Non CR/Non PD	No	PR	Yes
CR	Not Evaluated	No	PR	Yes
PR	Non CR/Non PD/Not Evaluated	No	PR	Yes
SD	Non CR/Non PD	No	SD	No
PD	Any	Yes or No	PD	No
Any	PD	Yes or No	PD	No
Any	Any	Yes	PD	No

Derived from New Response Evaluation Criteria in Solid Tumours: Revised RECIST guideline (version 1.1),* ***Table 1*

14.2 Minimum Criteria for Stable Disease Determination

For SD to be assigned, the criteria for SD must be met at least once after a minimum of 6 weeks following first dose of study drug (in Treatment Period 1 following first dose of MA, in Treatment Period 2 following the first doses of SC and MA).

14.3 Determination of Best Overall Response

At the conclusion of study drug treatment in Treatment Period 2, the best overall response for each subject who participates in Treatment Period 2 will be determined. Best overall response is defined as the best overall RECIST response recorded from the start of the Treatment Period 2 until the end of this treatment period, ordering response categories from best to worst: CR, PR, SD, PD, and NE. The subject's best response assignment will depend on the achievement of both measurement and confirmation criteria. If a timepoint response of 'NE' follows a response of "CR" or "PR," the next evaluable timepoint response will be used for confirmation.

A swimmer's plot which includes the duration of exposure for each Treatment Period, response over time, duration of follow-up, and best overall response for each subject in the Safety population who participates in Treatment Period 2 will be presented.

Best overall response when confirmation of CR and PR required*

Overall Response First Time Point	Overall Response Subsequent Time Point	Best Overall Response
CR	CR	CR
CR	PR	SD, PD or PR[a]

CR	SD	SD provided minimum criteria for SD duration met, otherwise, PD[a]
CR	PD	SD provided minimum criteria for SD duration met, otherwise, PD[a]

[a]If a CR is truly met at first time point, then any disease seen at a subsequent time point, even disease meeting PR criteria relative to baseline, makes the disease PD at that point (since disease must have reappeared after CR). Best response would depend on whether minimum duration for SD was met. However, sometimes 'CR' may be claimed when subsequent scans suggest small lesions were likely still present and in fact the patient had PR, not CR at the first time point. Under these circumstances, the original CR should be changed to PR and the best response is PR.

**Derived from New Response Evaluation Criteria in Solid Tumours: Revised RECIST guideline (version 1.1), Table 3*

14.4 Overall Disease Control Rate

The ODCR will be determined as the proportion of subjects who achieved CR, PR or SD as their best overall response during Treatment Period 2 in accordance with RECIST 1.1 criteria, relative to the efficacy population. The ODCR will be summarized by number and percentage of subjects meeting the definition of ODCR along with the corresponding exact 2-sided 95% confidence interval (CI). ODCR will not be calculated or presented for Treatment Period 1.

Since the study is closing early, no calculation of ODCR will be made.

14.5 Overall Response Rate

The ORR is defined as the proportion of subjects who achieved CR or PR as their best overall response during Treatment Period 2 in accordance with RECIST 1.1 criteria, relative to the efficacy population. Subjects who do not have an on-study assessment due to safety issues will be included as non-responders. The ORR will be summarized by number and percentage of subjects meeting the definition of ORR along with the corresponding exact 2-sided 95% CI. The ORR will not be calculated or presented for Treatment Period 1.

Since the study is closing early, no calculation of ORR will be made.

14.6 Duration of Stable Disease

Duration of SD is defined for all subjects whose best overall response is SD as the number of days from the date of the first doses of combination therapy on Study Visit 1, Day 0-TP2 in Treatment Period 2 to the first date of disease progression or death due to disease under study (date of progression or death due to disease under study – date of first dose of combination therapy). For subjects who die from causes other than disease under study, duration of SD will be censored at the date of death. For those subjects who discontinue from the study for reasons other than disease progression or death, duration of SD will be censored at the date of the last disease assessment prior to study discontinuation.

Duration of SD will not be calculated or presented for Treatment Period 1. Duration of SD will be listed for individual subjects in Treatment Period 2, but no median duration of SD will be calculated.

14.7 Progression-Free Survival

PFS is defined as the number of days between the date of the first doses of combination therapy on Study Visit 1, Day 0-TP2 in Treatment Period 2 and the first date of disease progression or death from any cause (date of progression or death – date of first dose of study drug + 1). For those subjects who discontinue from the study for reasons other than disease progression or death, including subjects for whom best overall response cannot be determined, PFS will be censored at the date of the last Treatment Period 2 disease assessment prior to study discontinuation (EOS).

PFS will not be calculated or presented for Treatment Period 1. PFS will be listed for individual subjects in Treatment Period 2, but no median PFS will be calculated.

14.8 Overall Survival

OS is defined as the number days between the date of the first doses of combination therapy on Study Visit 1, Day –TP2 in Treatment Period 2 and the date of death from any cause. For those subjects who discontinue from the study for reasons other than death, OS will be censored at the date of last contact.

PFS, Duration of SD, and OS will be analyzed by Kaplan-Meier methods. The estimated survival and probabilities will be presented via Kaplan-Meier curves and median survival/duration including exact 2-sided 95% CI will be reported using both the FAS and the PPS.

OS will not be calculated or presented for Treatment Period 1. OS will be listed for individual subjects in Treatment Period 2, but no median OS will be calculated.

15. Safety Analyses

15.1 Adverse Events

An AE is any untoward medical occurrence in a subject or clinical investigation subject administered a pharmaceutical product that does not necessarily have a causal relationship with this treatment. An AE can therefore be any unfavorable and unintended sign (including a clinically significant abnormal laboratory finding), symptom or disease temporally associated with the use of a pharmaceutical product, whether or not considered related to the pharmaceutical product. AEs may include the onset of new illness and the exacerbation of pre-existing conditions.

For the purposes of this protocol, an AE is any undesirable sign(s), symptom(s) or worsening of pre-existing condition(s) occurring after the signing of the informed consent through the final study visit, even if the event is not considered to be related to the study drug. No AEs information will be collected following the Safety Follow-Up Visit. The nature of each AE, date of onset, outcome, severity, actions taken with respect to dosage, and relationship to study drug will be assessed and recorded.

An AE is “unexpected” when the nature, severity, specificity, or outcome is not consistent with the term or description used in protocol related documents including the Investigator brochure, product labeling

(e.g. Package Insert or Summary of Product Characteristics), protocol and Independent Ethics Committee (IEC)/ Institutional Review Board (IRB) approved informed consent form. If an Investigator is uncertain whether an AE is expected or unexpected, the AE should be reported as unexpected.

The outcome of each AE should be assessed as follows:

- Fatal: Subject has died due to AE
- Not Recovered/Not Resolved: AE is ongoing
- Recovered/Resolved: AE is no longer present
- Recovered/Resolved with sequelae: AE has resolved but the subject retains a condition that is the consequence of the AE
- Recovered/Resolving: AE is in the process of recovering
- Unknown: Outcome of the AE is not known because the subject did not return for follow-up and attempts to obtain follow-up were unsuccessful

The causality of each AE, with respect to each study drug separately, should be assessed using one of the following terms:

- Related: AE occurring in a plausible time relationship to drug administration, and which cannot be explained by concurrent disease or other drugs or chemicals.
- Possibly Related: AE occurring with a reasonable time sequence to administration of the drug, unlikely to be attributed to concurrent disease or other drugs or chemicals.
- Unlikely Related: AE occurring with a reasonable time sequence to administration of the drug, but which could also be explained by concurrent disease or other drugs or chemicals.
- Not Related: AE with a temporal relationship to drug administration which makes a causal relationship improbable, and in which other drugs, chemicals or underlying disease provide plausible explanations.

For data analysis and Serious Adverse Event (SAE) reporting purposes, any AEs classified as ‘unlikely related” will be regarded as ‘not related’ to study drug. AEs classified as ‘possibly related” will be regarded as ‘related’ to the study drug.

The severity of all AEs should be graded in accordance with the NCI-CTCAE Version 4:

1 – Mild: Does not hamper daily activities

2 – Moderate: Hampers daily activities

3 – Severe: Makes daily activities impossible

4 – Life-Threatening: Imminent risk of death

5 – Death

Disease progression or symptoms related to disease progression will not be considered AEs.

15.2 Serious Adverse Events

An SAE is defined as any untoward medical occurrence that at any dose:

- Results in death;
- Is life-threatening;
- Requires hospitalization or prolongation in existing hospitalization;
- Results in persistent or significant disability or incapacity;
- Is a congenital anomaly or birth defect;
- Is other medically important event.

15.3 Adverse Events Listings

All AEs, SAEs, AEs leading to treatment period discontinuation, and AEs with outcome of death, including the applied coded terms, will be presented in subject listings. Each AE listing will include onset and resolution date, coded term, SOC, PT, relatedness, seriousness, severity, outcome and action taken. Treatment-emergent events will be flagged in these listings.

15.4 Physical Examination

The subject will undergo an evaluation of all major body systems (abdomen, cardiovascular, chest and lungs, ENT [ears, nose and throat], extremities, general appearance, genitourinary, head and neck, lymphatic, musculoskeletal, neuromuscular, skin). Body systems will be classified as Normal or Abnormal, and if abnormal, details will be provided. Physical examinations will be performed at the Screening Visit, at Visits -3, -2, -1, TP1-EXT, End of Study-TP1, 1, 3, 5, 7, 9, 11, 13, at all subsequent quarterly Study Visits, and at the Safety Follow-Up TP2 Visit. A subject listing of the physical examination results at Treatment Period and Visit will be produced.

15.5 Performance Status

A subject will be assigned a GOG Performance Status at the Screening Visit and at Visits -3, -2, -1, TP1-EXT, End of Study-TP1, 1, 3, 5, 7, 9, 11, 13, all subsequent quarterly Study Visits, and at the Safety Follow-Up TP2 Visit, in accordance with the following table:

Gynecologic Oncology Group (GOG) Status Scale	
GOG Score	**Descriptions**
0	Fully active, unrestricted activities of daily living.
1	Ambulatory, but restricted in strenuous activity.
2	Ambulatory, and capable of self care. Unable to work. Out of bed for greater than 50% of waking hours.
3	Limited self care, or confined to bed or chair 50% of waking hours. Needs special assistance.
4	Completely disabled, and no self care.
5	Dead.

Performance Status including change from Treatment Period baseline will be provided in a subject listing.

15.6 Vital Signs

The subject will undergo an assessment of vital signs (diastolic and systolic blood pressure, heart rate and body temperature) after 5 minutes in a supine position at the Screening Visit, at all Study Visits, at the End of Study-TP1 Visit, and at the Safety Follow-Up TP2 Visit.

A subject listing of the vital signs results will be provided.

15.7 Height, Weight and Body Mass Index

Height will be measured once at screening. Weight is measured and Body Mass Index (BMI) calculated at Screening, Visits -3, -2, -1, TP1-EXT, End of Study-TP1, 1, 3, 5, 7, 9, 11, 13, all subsequent quarterly Study Visits, and at the Safety Follow-Up TP2 Visit. BMI will be calculated in accordance with the formula:

$$BMI\ (kg/m^2) = Weight\ (kg) / [Height\ (cm)^2 * 10000]$$

BMI, height, and weight will be provided in a listing.

15.8 Electrocardiogram (ECG)

A 12-lead ECG will be performed to evaluate potential study drug-induced QT prolongation potential at the Screening Visit, at Study Visit -3 prior to the first dose of megestrol acetate, at all remaining Study Visits (prior to administration of megestrol acetate whenever possible), and at the End of Study-TP1 Visit and the Safety Follow-Up TP2 Visit. At Visits 1 and 3 during Treatment Period 2, ECG will be performed 5 times: before administration of both SC and MA, and at 15, 60, 120, and 360 (± 5) minutes after administration of SC. ECGs at all other visits will be performed only once, prior to administration of both SC and MA (in Treatment Period 1 prior to MA dosing). For all ECGs performed after the first dose of SC, any clinically significant changes compared with the ECG recorded at the Screening Visit must be

reported as an AE. All ECG intervals (PR, QRS, QT, QTcB [QT interval corrected for heart rate using Bazett's formula], QTcF [QT interval corrected for heart rate using Fridericia's formula] and RR) will be reported in the eCRF. ECG intervals (PR, QRS, QT, QTcB, QTcB, QTcF and RR), plus Overall results of the ECG (normal; abnormal, not clinically significant; and abnormal, clinically significant) will be presented as listings.

Categorical analysis of QTcB and QTcF relative to the following clinically significant cut-points will be presented in a summary table

- 450 < QTcB/F ≤ 480 msec
- 480 < QTcB/F ≤ 500 msec
- QTcB/F > 500 msec
- QTcB/F Increase of > 30 and ≤ 60 msec from Baseline
- QTcB/F Increase of > 60 msec from Baseline

(For Visit -2, Visit -1, TP1-EXT, and End of Study-TP1 baseline is with respect to Treatment Period 1. For all other visits, baseline is with respect to Treatment Period 2.)

15.9 Routine Clinical Laboratory Data

15.9.1 HEMATOLOGY

Blood samples (5 mL) will be taken at the Screening Visit, at each Study Visit, at the End of Study-TP1Visit, and at the Safety Follow-UpTP2 Visit and used for routine hematology analysis at local laboratories.

Hematology profile will include:

- Differential Leukocyte Count (Basophils, Eosinophils, Lymphocytes, Monocytes, and Neutrophils) (cells x 10^9/L)
- Erythrocytes (cells x 10^{12}/L)
- Hematocrit (L/L)
- Hemoglobin (g/L)
- Leukocytes (cells x 10^9/L)
- Mean Corpuscular Hemoglobin Concentration (MCHC) (mmol/L)
- Mean Corpuscular Volume (MCV) (μm^3)
- Platelets (cells x 10^9/L)

15.9.2 SERUM CHEMISTRY

Blood samples (5 mL) will be taken at the Screening Visit, at each Study Visit, at the End of Study-TP1 Visit, and at the Safety Follow-Up TP2 Visit and used for routine serum chemistry analysis at local laboratories.

Chemistry profile will include:

- Albumin (g/L)
- Alkaline Phosphatase (µkat/L)
- Alanine Aminotransferase (ALT)/Serum Glutamic Pyruvic Transaminase (SGPT) (U/L)
- Aspartate Aminotransferase (AST)/Serum Glutamic Oxaloacetic Transaminase (SGOT) (U/L)
- Bicarbonate (mmol/L)
- Blood Urea Nitrogen (BUN) (mmol/L)
- Calcium (mmol/L)
- Chloride (mmol/L)
- Creatine Kinase (nkat/L)
- Creatinine (µmol/L)
- Glucose (mmol/L)
- Lactate Dehydrogenase (LDH) (µkat/L)
- Phosphate (mmol/L)
- Potassium (mmol/L)
- Sodium (mmol/L)
- Total Bilirubin (µmol/L)
- Total Protein (g/L)

Estimated Glomerular Filtration Rate (eGFR, mL/min/1.73 m2) will be calculated based on blood creatinine levels and subject demographics using the CKD Epidemiology Collaboration (CKD-EPI) method:

$$GFR = 141 \times \min(Scr/\kappa, 1)^{\alpha} \times \max(Scr/\kappa, 1)^{-1.209} \times 0.993^{Age} \times 1.018 \text{ [if female]} \times 1.159 \text{ [if black]}$$

where:

Scr is serum creatinine in mg/dL,

κ is 0.7 for females and 0.9 for males,

α is -0.329 for females and -0.411 for males,

min indicates the minimum of Scr/κ or 1, and

max indicates the maximum of Scr/κ or 1

(https://www.niddk.nih.gov/health-information/communication-programs/nkdep/laboratory-evaluation/glomerular-filtration-rate-calculators/ckd-epi-adults-conventional-units).

This formula incorporates normalization to 1.73 m^2 body surface area, which is an accepted average adult surface area. Results are reported in mL/min/1.73 m^2.

15.9.3 URINALYSIS

Urine samples are taken at the Screening Visit, at the End of Study Visit, at Visit 7, at Visit 13, every 12 weeks thereafter until disease progression and at the Safety Follow-Up Visit, and are analyzed at local laboratories.

Urine analysis will include:

- Blood
- Glucose
- Ketones
- pH
- Protein

The local laboratories will provide lab results, normal ranges and units to be entered on the eCRFs. All laboratory data will be converted to standard international units for reporting purposes.

Routine clinical laboratory evaluations (hematology, serum chemistry, and urinalysis) will be listed by subject with values outside of reference ranges marked. The high/low criteria will be determined based on the normal ranges provided by the laboratory.

16. Pharmacokinetic (PK) Analyses

No patients participated in the voluntary PK portion of the study therefore no PK data will be presented in the abbreviated analysis.

17. Pharmacodynamic Analyses

No Pharmacodynamic data will be collected for this study.

18. Quality of Life Analyses

No Quality of Life data will be collected for this study.

19. Interim Analyses

Since the study is closing early no interim analysis will be performed.

20. Changes from Protocol-Stated Analyses

Since the study is closing early, this SAP differs from the protocol-stated analysis in significant respects. With the exception of one ECG table (summarizing QTc categories) all data will only be presented in listings. Two other particular differences are noted:

1. Protocol 7.2.1 states, “The Safety Population will consist of all subjects who receive at least one full or partial dose of study treatment (all treated subjects) in Treatment Period 2. This population will be used for all safety reporting.” This SAP updates this to the following definition: The Safety Population will consist of all subjects who receive at least one full or partial dose of either study treatment. For subjects treated solely in Treatment Period 1 this will include all subjects treated with at least one full or partial dose of MA. For all other subjects, the Safety Population will include all subjects treated with at least one full or partial dose of either MA or SC. Safety data will be reported separately for subjects in Treatment Period 1 who do not go on to Treatment Period 2, and for those subjects in Treatment Period 1 who are treated in both periods.
2. The primary efficacy endpoint ODCR and secondary efficacy endpoint ORR will not be assessed.
3. Protocol 7.7 indicates that protocol deviations will be collected on the eCRFs. Instead, deviations will be collected and monitored by the site monitors and transferred to SDC as an Excel spreadsheet.

Any changes to the planned analyses after database lock and unblinding will be described in the clinical study report.

21. References

R. P. A'Hern. Sample size tables for exact single-stage phase II designs. Statist. Med. 2001; 20:859:866.

Fleming TR. One sample multiple testing procedure for phase II clinical trials. Biometrics 1982; 38:143:151.

22. Revision History

Documentation of revision to the SAP will commence after approval of the Final version 1.0.

23. Tables

14.3.3.7	Electrocardiogram QTcB and QTcF Categories	Safety Population

24. Figures

14.2.1.1	Swimmer's Plot of Treatment and Response Durations	Safety Population Safety Population – Subjects who Participated in Treatment Period 2

25. Listings

Listing Number	Title	Population
16.2.1.1	Subject Disposition	All Enrolled Subjects
16.2.1.2	Screen Failures	All Screened Subjects
16.2.1.3	Informed Consent	All Enrolled Subjects
16.2.1.4	Visit Dates	All Enrolled Subjects
16.2.1.5	Inclusion and Exclusion	All Enrolled Subjects
16.2.2	Protocol Deviations	All Enrolled Subjects
16.2.3	Analysis and Treatment Period Populations	All Enrolled Subjects
16.2.4.1	Demographics and Baseline Characteristics	Safety Population
16.2.4.2	Baseline Disease Characteristics and PrR Status	Safety Population
16.2.4.3	Medical and Surgical History	Safety Population
16.2.4.4	Prior and Concomitant Medications	Safety Population
16.2.4.5.1	Prior Chemotherapy	Safety Population
16.2.4.5.2	Prior Hormonal Therapy	Safety Population
16.2.4.5.3	Prior Radiotherapy	Safety Population
16.2.4.5.4	Prior Cancer Surgery	Safety Population
16.2.4.6	Pregnancy Test Results	Safety Population
16.2.5.1	Sodium Cridanimod Administration	Safety Population

Listing Number	Title	Population
16.2.5.2	Megestrol Acetate Diary	Safety Population
16.2.5.3	Megestrol Acetate Accountability	Safety Population
16.2.6.1	Investigator Target Lesion Assessments by Visit	Full Analysis Set
16.2.6.2	Summary of Investigator Target Lesion Assessments and New Lesions by Visit	Full Analysis Set
16.2.6.3	Investigator Non-Target Lesion Assessments by Visit	Full Analysis Set
16.2.6.4	Best Overall Response	Full Analysis Set
16.2.6.5	Duration of Stable Disease Events	Full Analysis Set – Treatment Period 2 only
16.2.6.6	Progression-Free Survival Events	Full Analysis Set – Treatment Period 2 only
16.2.6.7	Overall Survival Events	Full Analysis Set – Treatment Period 2 only
16.2.7.1	Adverse Events	Safety Population
16.2.7.2	Serious Adverse Events	Safety Population
16.2.7.3	Treatment-Emergent Adverse Events Leading to Discontinuation from Treatment Period 1	Safety Population
16.2.7.4	Treatment-Emergent Adverse Events Leading to Discontinuation from Treatment Period 2	Safety Population
16.2.7.5	Treatment-Emergent Adverse Events as Reason for Not Completing Safety Follow-Up	Safety Population
16.2.7.6	Treatment-Emergent Adverse Events with Outcome of Death	Safety Population
16.2.7.7	Mortality	Safety Population
16.2.8.1	Physical Exam Results	Safety Population
16.2.8.2	Vital Signs Results	Safety Population
16.2.8.3	Height, Weight, and BMI Results	Safety Population
16.2.8.4	GOG Performance Status	Safety Population
16.2.8.5	Electrocardiogram Results	Safety Population
16.2.8.6	Hematology Laboratory Results	Safety Population
16.2.8.7	Serum Chemistry Laboratory Results	Safety Population
16.2.8.8	Urinalysis Laboratory Results	Safety Population