ADU-CL-11

A PHASE 1/2, OPEN-LABEL SAFETY AND EFFICACY EVALUATION OF CRS-207 IN COMBINATION WITH EPACADOSTAT IN ADULTS WITH PLATINUM-RESISTANT OVARIAN, FALLOPIAN, OR PERITONEAL CANCER

Abbreviated Statistical Analysis Plan (ASAP)

ASAP VERSION 1.0
DATE OF PLAN:

03MAY2018

STUDY DRUG:

CRS-207, epacadostat, and pembrolizumab

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Protocol Number: ADU-CL-11
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07MAY2018
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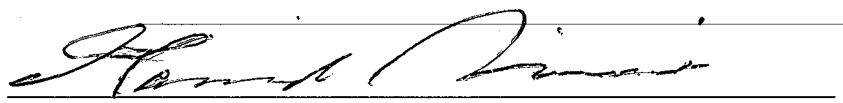

07MAY 2018

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Contents

ABBREVIATIONS

AE	Adverse event
AESI	Adverse event of special interest
ALT	Alanine aminotransferase
ANC	Absolute neutrophil count
AST	Aspartate aminotransferase
ATC	Anatomic Therapeutic Class
CA-125	Cancer antigen-125
CTCAE	Common Terminology Criteria for Adverse Events
CFU	Colony-forming units
CR	Complete Response
CSR	Clinical study report
ECG	Electrocardiogram
ECOG	Eastern Cooperative Oncology Group
EOT	End of treatment
FAS	Full analysis set
GCIG	Gynecological Cancer Intergroup
IDO	Epacadostat
LLN	Lower limit of normal
MedDRA	Medical Dictionary for Medical Affairs
mRECIST	Modified Response Evaluation Criteria in Solid Tumors
ORR	Objective response rate
OS	Overall survival
PBMC	Peripheral blood mononuclear cell(s)
Pembro	Pembrolizumab
PR	Partial response
PPS	Per protocol set
PD	Progressive disease or Pharmacodynamics
PT	Preferred Term
PFS	Progression-free survival
RBC	Red blood cell
RECIST	Response Evaluation Criteria in Solid Tumors
RP2D	Recommended phase 2 dose
SAE	Serious adverse events
SAP	Statistical analysis plan
SD	Stable disease or Standard deviation
SOC	System Organ Class
SRT	Safety review team
T_{reg}	Regulatory T Cells
ULN	Upper limit of normal
WBC	White blood cell
WHO	World Health Organization

1. INTRODUCTION

This is an abbreviated statistical analysis plan (ASAP) designed to outline the planned analysis required to satisfy the Clinical Study Report (CSR) synopsis of study number ADU-CL-11: A Phase 1/2, Open-Label Safety and Efficacy Evaluation of CRS-207 in Combination with Epacadostat in Adults with Platinum-Resistant Ovarian, Fallopian, or Peritoneal Cancer. The derivation and analysis of selected immunological/ biomarker endpoints and PK parameters will be discussed in another standalone document(s). The statistical analyses and summary tabulations described in this ASAP will provide the basis for the CSR synopsis reporting of the final analysis results from this trial. Population, data handling rules, statistical methods, changes from the study protocol, and formats for data presentation are provided. The content of this SAP is based on the protocol Amendment 3 18FEB2017. Protocol revision history appears as follows:

V1.0	28OCT2015	Original
V2.0	22APR2016	Amendment 1
V3.0	15NOV2016	Amendment 2
V4.0	18FEB2017	Amendment 3

2. STUDY OBJECTIVES AND ENDPOINTS

Phase 1: Dose Evaluation, Assigned Arms:

Objectives	**Endpoints**
Primary	
• Determine the RP2D of epacadostat administered with CRS-207 in subjects with platinum-resistant ovarian, fallopian or peritoneal cancer • Assess safety and tolerability of CRS-207 alone and CRS-207 in combination with epacadostat in subjects with platinum-resistant ovarian, fallopian or peritoneal cancer	• Hematologic and non-hematologic DLTs; • Adverse events by CTCAE grade; vital signs, physical exam findings, changes in ECG readings and changes in chemistry and hematology and coagulation parameters
Secondary	
• *Characterize the PK of epacadostat • Evaluate the preliminary anti-tumor activity of each study drug regimen • *Characterize pharmacological effects on immune biomarkers in peripheral blood and tumor tissue	• Plasma concentration of epacadostat and derived PK parameters; • ORR, defined as CR or PR as determined by mRECIST, RECIST v1.1, and GCIG CA-125 criteria; • PFS, defined as the time from the date of first dose to PD or death due to any cause.

• *Characterize shedding and clearance of CRS-207 when given alone or with epacadostat	PFS is measured through the last tumor assessment or commencement of a new systemic therapy. PD is determined by mRECIST, RECIST v1.1 and GCIG CA-125 criteria; • Disease control rate, defined as CR+PR+SD as determined by mRECIST, RECIST v1.1, and GCIG CA-125 criteria; • Duration of response, defined as the time from first CR or PR until PD as determined by mRECIST, RECIST v1.1, and GCIG CA-125 criteria; • OS, defined as the time from first dose until date of death due to any cause; • Ratio of tumor infiltrating lymphocytes CD8/Treg (FoxP3); • Plasma kynurenine/tryptophan ratio; • Other immunological and tumor biomarker endpoints: o Cytokine/chemokine responses o Antibody responses o Modulation of immune cell populations and functions in PBMCs and tumor, and o CA-125, mesothelin, IDO-1, PD-L1 and additional tumor biomarkers; and • Detection of CRS-207 in urine, saliva, feces, and blood

Phase 2: Randomized, 2-stage:

Objectives	**Endpoints**
Primary	
• Assess safety of CRS-207/pembrolizumab administered with or without epacadostat • Assess tumor response and PFS	• Adverse events, vital signs, physical exam findings, changes in ECG readings, and changes in chemistry, hematology, and coagulation parameters • ORR, defined as CR or PR as determined by mRECIST • PFS, defined as the time from the date of first dose to PD or death due to any cause. PFS is measured through the last tumor assessment or commencement of a new systemic therapy. PD is determined by

	mRECIST.
Secondary	
• Assess disease control rate and duration of response • Assess OS	• Disease control rate, defined as CR+PR+SD as determined by mRECIST, RECIST v1.1, and GCIG CA-125 criteria • Duration of response, defined as the time from first CR or PR until PD as determined by mRECIST, RECIST v1.1, and GCIG CA-125 criteria • ORR as determined by RECIST v1.1 and GCIG CA-125 criteria • OS, defined as the time from first dose until date of death due to any cause • PFS where PD is determined by RECIST v1.1 and GCIG CA-125 criteria
Additional	
• *Assess the association of clinical efficacy (ORR, PFS, and OS) with immunologic and tumor biomarkers • *Characterize the PK of epacadostat • *Characterize shedding and clearance of CRS-207/pembrolizumab administered with or without epacadostat	Immunological and tumor biomarker endpoints: • Cytokine/chemokine and antibody responses • Modulation of immune cell populations and functions in PBMCs and tumor • Mesothelin, IDO-1 and PD-L1 expression • CA-125 and additional candidate tumor biomarkers Pharmacokinetic endpoints: • Plasma concentration of epacadostat and derived PK parameters • Detection of CRS-207 in urine, saliva, feces, and blood

This ASAP provided derivation and listing of the efficacy endpoint, however no summary tables will be produced for these endpoints. The derivation and analysis of selected immunological/ biomarker endpoints and PK parameters will be discussed in another standalone document(s).

3. STUDY DESIGN

3.1. Study Design and Population

The study is designed to assess the safety and efficacy of the following investigational treatment regimens in adult females with epithelial ovarian, fallopian, or primary peritoneal cancer that is platinum-resistant (i.e. has progressed within 6 months after completing platinum-based chemotherapy):

- CRS-207/epacadostat/pembrolizumab (CRS-207/IDO/pembro)
- CRS-207/pembrolizumab (CRS-207/pembro)

The study will be conducted in 2 phases as depicted in **Figure 1**. Phase 1 seeks to evaluate safety and tolerability and is aimed at determining the recommended Phase 2 dose (RP2D) of epacadostat administered with CRS-207 for further evaluation in Phase 2. The randomized Phase 2 portion of the study will begin with a safety-run in to evaluate the addition of pembrolizumab, followed by a 2-stage design to evaluate safety and efficacy in subjects who have received no more than 3 prior chemotherapy regimens for locally advanced or metastatic disease.

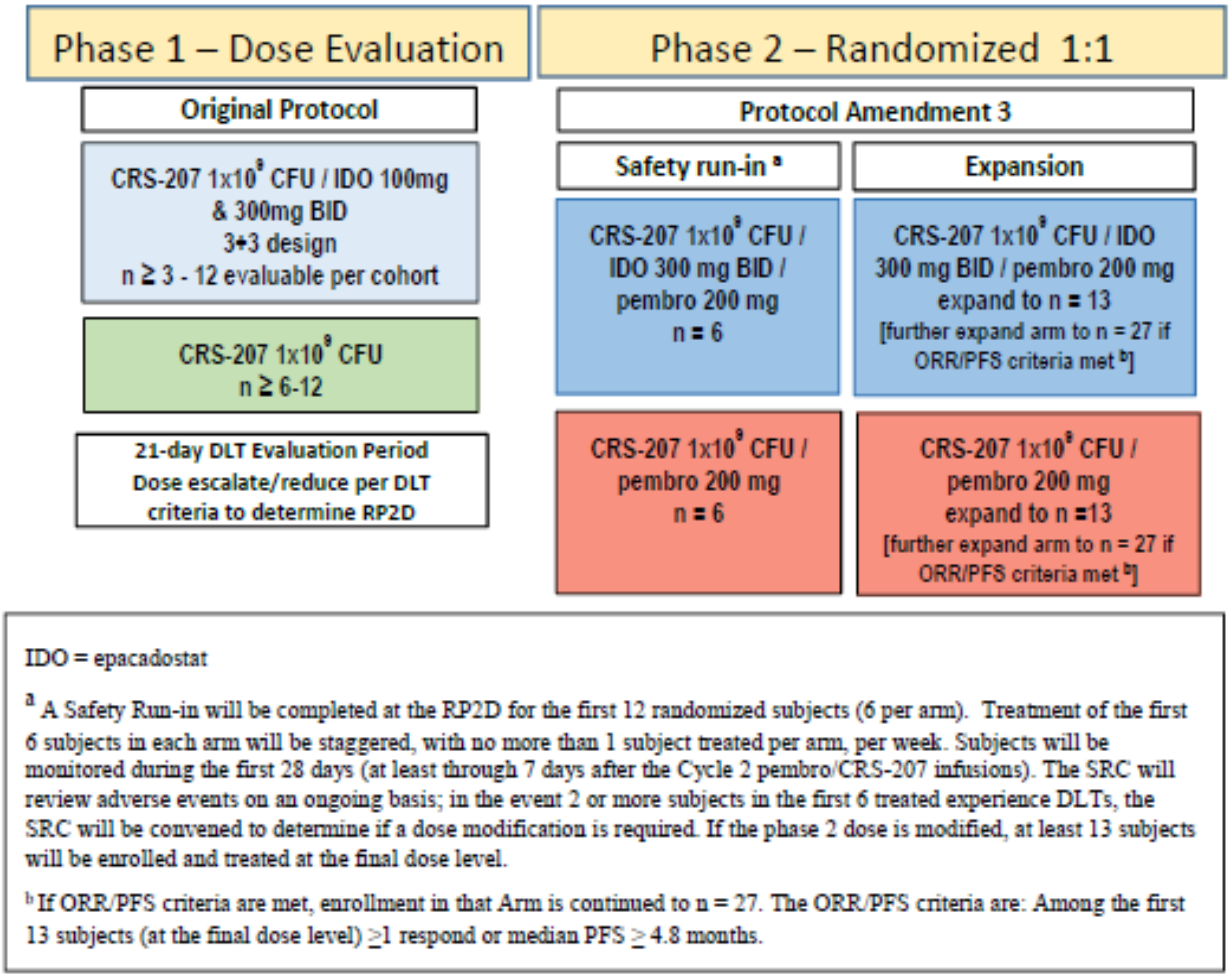

Figure 1: Study Schematic

In Phase 1, the epacadostat dose will be evaluated based on a 3+3 design utilizing protocol defined DLT criteria as follows in **Table 1**.

Table 1: Dose-limiting Toxicity Criteria

Cohort[3]	0/3 subjects have DLT[1]	1/3 subjects have DLT[1]	<2/6 subjects have DLT[1]	≥2 in a cohort have DLT[1,2]
Dose Cohort 1 [4] CRS-207 + 100 mg BID IDO	Escalate to Dose Cohort 2	Expand Dose Cohort 1 to 6 subjects	Escalate to Dose Cohort 2	De-escalate to Dose Cohort -1 (CRS-207 + 50 mg BID IDO)[3]
Dose Cohort 2 CRS-207 + 300 mg BID IDO	Expand cohort to 12 subjects with paired biopsies	Expand Dose Cohort 2 to 6 subjects	Expand cohort to 12 subjects with paired biopsies	Dose expand with 100 mg BID IDO

1. DLT period is 21 days after first dose of CRS-207.
2. In the case that a cohort is closed to enrollment, subjects who are ongoing at that dose level without DLTs may continue treatment at the assigned dose level at the discretion of the Investigator.
3. Evaluation of Dose Cohort -1 will enable the same 3+3 rules for dose cohort expansion or de-escalation to 25 mg (Dose Cohort -2). Evaluation of Dose Cohort -2 will enable the same 3+3 rules for dose cohort expansion. If Dose Cohort -2 is not tolerated, the Arm will be terminated.
4. As an added safety measure, Dose Cohort 1 will have a staggered enrollment of no more than 1 new subject treated per week during the dose escalation phase. Thereafter, a decision to further stagger combination enrollment will be made by the Safety Review Committee (SRC) and will be based on emergent safety data.

BID = twice daily; DLT = dose-limiting toxicity

A Safety Review Committee (SRC) will be convened for the study, consisting of the Investigators who enrolled subjects in the study, the Lead Investigator, Study Medical Monitor, and Sponsor representatives. Adverse events, DLTs and safety data for all subjects will be reviewed on an ongoing basis by the SRC. Dose escalation and reduction decisions, determination of the recommended dose for expansion, and R2PD will be made by the SRC.

Additionally, up to 12 subjects will be enrolled in in the CRS-207 alone arm to assess the safety and tolerability of CRS-207 in subjects with platinum-resistant ovarian, fallopian or peritoneal cancer.

Phase 2 will begin by assessing safety of the addition of pembrolizumab to CRS-207 and CRS-207/epacadostat; pembrolizumab will be administered at the 200 mg fixed dose level (as approved in other cancer indications). Phase 2 will initiate after the RP2D of CRS-207/epacadostat is determined in Phase 1 and approximately 12 subjects with paired biopsies have been dosed at that level.

A Safety Run-in will be completed since there are no precedent data on the addition of pembrolizumab to the planned drug combinations. Treatment of the first 6 randomized subjects in each treatment arm will be staggered, with no more than 1 subject treated per week, per arm. Subjects will be monitored during the Safety Run-in Period [the first 21 days] using the protocol defined DLT criteria. In the event ≥2 subjects in up to 6 (per arm) experience DLTs, the SRC will convene to determine if subsequent subjects enrolled will require a different dose level (per **Table 2**), or if additional subjects should be enrolled at a specified dose level to further assess safety and tolerability. In the event >2 subjects in the next 6 subjects (per arm) treated experience DLTs, the SRC will reconvene to determine if the dose will be further modified for the remaining subjects to be enrolled. The SRC may convene at any time during the Safety Run-in Period to review and evaluate available safety data as warranted by emerging safety data.

Table 2: Safety Run-in Dose Levels and Dose Reduction Table

Dose level	pembrolizumab	epacadostat	CRS-207
1	200 mg	300 mg BID	1×10^9 CFU
-1	200 mg	100 mg BID	1×10^9 CFU
-2	Further dose reductions will be discussed and confirmed by the SRC based on emergent safety data.		

Phase 2 will utilize a 2-stage design. Subjects will be randomized 1:1 into 2 treatment arms. In the first stage, once the final dose is confirmed in the Safety Run-in, a total of 13 subjects will be randomized into each arm (total 26 subjects). If the phase 2 dose is modified, at least 13 subjects will be enrolled and treated at the final dose level in each arm. If the pre-specified objective response-rate (ORR) and progression-free survival (PFS) criteria for advancement in the 2-stage design are met (≥1 response or median PFS ≥ 4.8 months) for an arm, an additional 14 subjects will be enrolled in that arm, for a potential total of 27 subjects per arm (up to 54 subjects total if both arms advance to stage 2).

In the event that during the safety run in there are 2 DLTs in 6 patients in the CRS-207/pembrolizumab arm but the CRS-207/pembrolizumab/epacadostat has 0 or 1 DLTs in 6 patients using the same dose levels as in the 2 arm combination, the SRC will review the data and may allow enrollment of another 3 subjects in each run-in to better define the toxicities.

The Schedules of Events for Phases 1 and 2 are provided in Protocol Appendix F and Table 1, respectively. The study consists of a 28-day screening period, followed by administration of study drug(s) in 3-week cycles. Treatment will continue for as long as there is adequate safety and potential for clinical benefit with the exception that pembrolizumab may be given for up to 24 months to subjects without disease progression. After 6 cycles, CRS-207 will be administered every 6 weeks (Q6W); all other assigned treatments remain the same.

Archived tumor tissue and paired tumor biopsies (collected at Screening and Cycle 2 Day 15) will be used to explore the association of programmed death receptor ligand-1 (PD-L1) expression, mesothelin expression, and tumor-infiltrating lymphocyte (TIL) characteristics with clinical responses. Tumor evaluation by radiographic imaging will be performed within 28 days blood will be collected to assess immune responses directed against L. monocytogenes, mesothelin, and other tumor-associated antigens. Circulating levels of Cancer antigen 125 (CA-125) will be assessed at Screening and on Day 1 of each 3 week cycle while on treatment, and every 9 weeks thereafter until disease progression is confirmed. CRS-207 shedding and clearance will be assessed during Phase 1 and during the Safety Run-in of Phase 2 at US sites only. Urine, rectal swab, oral swab, and whole blood will be collected from subjects treated with CRS-207. Additional assessments will be performed if results are positive for CRS-207 at the Day 8 time point.

An End-of-Treatment (EOT) Visit will be scheduled once treatment has been discontinued. Blood will be collected at EOT to assess clearance of CRS-207 and at [redacted]

[redacted]. To eliminate any potentially residual CRS-207, subjects will be administered antibiotics at the EOT Visit; the antibiotic regimen should be completed prior to receiving any subsequent cancer-related therapy. An additional Safety Follow-up Visit will occur 30 days after the last dose of study drug. If the subject begins another anticancer therapy before the end of the 30-day period, the subject should complete all of the Safety Follow-up Visit assessments prior to commencing the new therapy.

After the Safety Follow-up Visit, subjects will return to the clinic every 9 weeks for tumor evaluation and CA-125 until radiographic disease progression is confirmed, at which time subjects will be followed every 12 weeks by phone/email (if no recent medical charting available) to collect data on survival and any subsequent anti-cancer treatment that may have been administered. Follow-up will continue until death, withdrawal of consent, or the end of the study, whichever occurs first. At the conclusion of the study, all remaining subjects who have received at least 1 dose of study treatment will be offered enrollment in a long-term follow-up study and continue to be followed for survival.

3.2. Randomization and Blinding

In Phase 2 of the study, subjects will be randomized into dose levels identified in **Figure 1** in a 1:1 ratio. The study is open-label and knowledge of treatment assignments is not restricted.

3.3. Sample Size Considerations

During Phase 1, dose escalation will be based on traditional escalation guidelines (3+3) to determine the RP2D and evaluate safety data (including DLTs and adverse events) of each planned treatment.

Phase 2 will be an open-label, randomized study design conducted in 2 stages to achieve up to 27 treated subjects per Arm. After 13 subjects in an Arm are randomized at the confirmed dose following the Safety Run-in (Stage 1), an additional 14 subjects will be enrolled in that Arm (Stage 2) if 1 or more subjects respond or if the median PFS is at least 4.8 months. If the criteria for either ORR or PFS are not met, the preliminary anti-tumor activity in the Arm will be rejected and no further subjects will be randomized to the Arm. If the Arm goes on to stage 2, a total of 27 treated subjects will be studied in that Arm. The Arm will be considered successful if 4 or more subjects respond or the median PFS is at least 4.8 months. If the criteria for either ORR or PFS are not met, the Arm will be rejected. This design is applied to each Arm independently. There are no formal comparisons planned between Arms.

This is an exploratory study of each Arm where the sample size and ORR and PFS criteria for each stage are based on clinical judgement; each Arm is assumed to be evaluated separately. Type 1 error will not be controlled over both Arms. The ORR criteria and number of subjects for each stage within Arm are based on a Simon minimax 2-stage design (null hypothesis that ORR ≤ 0.05 versus the alternative that ORR≥ 0.20 with alpha = 0.05 and power = 0.80). The PFS criteria are based on the lower limit of the 95% CI determined based on meta-analysis in the 3rd

relapse patient population where the median PFS is 5.6 months, (95% CI: 4.8 to 6.2 months) (Hanker, 2012). The one-sided test for PFS (i.e. observing median PFS≥ 4.8 months) has a Type I error rate of 0.0744 when the null hypothesis is that the median PFS=3.6 months, PFS is exponentially distributed, accrual is uniform, and total study duration is 30 months for 27 subjects enrolled over 24 months. For a one-sided test of observing PFS≥ 4.8 months, there is approximately 77% power to detect a median PFS of 5.6 months and 50% power to detect a median PFS of 4.8 months.

Assuming a non-negative correlation between the one-sided tests for ORR and PFS, the overall Type I error for either test criteria being met is at most 0.1203. There is at least 70% power to meet at least one of the test criteria if ORR=0.25 and median PFS=4.8 and at least 79% power if ORR=0.25 and median PFS=5.6.

3.4. Interim Analysis

Safety data will be reviewed on an ongoing basis by the SRC.

For Phase 2 of the study, after 13 subjects have been treated with the CRS-207 dose identified at the end of the Safety run-in period within an Arm (Stage 1), an additional 14 treated subjects will be enrolled in the Arm (Stage 2) if 1 or more subjects respond (objective disease response of CR or PR) or if the median PFS is at least 4.8 months. Objective response rate and PFS are based on mRECIST. If neither of the criteria for response and PFS is met, preliminary antitumor activity in the Arm has not been identified and no further subjects will be randomized to the Arm.

3.5. Timing of Analyses

On 12 December 2017, Aduro decided to cease development activities of CRS-207 and close out ongoing studies. As of 12 January 2018 every subject had completed their end of treatment visit except for 2 subjects who will have the option to continue treatment based on agreement between the Investigator and patient. All data through 12 January 2018 will be cleaned and soft-locked for CSR synopsis reporting. Additional data collection will be ongoing for these 2 subjects through to the date of database soft-lock. Additional data following database lock will be captured in an amendment to the final CSR synopsis once the 2 subjects have completed their end of study follow-up. This ASAP details the analysis plans for the CSR synopsis.

4. DATA ANALYSIS CONSIDERATIONS

All analyses will be conducted based on SAS 9.3 or higher.

All data in the database will be presented in by-subject data listings.

Unless otherwise stated, all listings will be sorted by subject number and assessment date (and time, if available).

Unless stated otherwise, continuous data will be summarized by Arm and overall within each Phase based on n, mean, median, standard deviation (SD), first quartile (Q1), third quartile (Q3), minimum value, and maximum value.

Unless stated otherwise, categorical data will be summarized by treatment group using n and percentage based on the number of nonmissing values.

- The number of missing values will be presented as a separate category with no percentage, but only if one or more subjects are missing data.
- Counts of zero will be presented without percentages.

Precision

- Mean, Median, Q1, and Q3: one additional decimal place to that reported for Minimum and Maximum
- SD: two additional decimal places than the Minimum and Maximum
- Percentages: reported to one decimal place

No statistical significance test will be performed.

With the exception of missing data handling noted in Section 5.6, data will not be imputed for analysis purposes.

4.1. Stratification and Covariates

Not Applicable.

4.2. Evaluation of Subgroups

No subgroup analyses are planned.

4.3. Multiple Comparisons and Multiplicity

Not applicable.

5. GENERAL DATA HANDLING CONVENTIONS

5.1. Assigned and Actual Treatment

All subjects enrolled in the study are assigned to a therapy Arm based on the information in **Table 3**:

Table 3: ADU-CL-11 Treatment Cycles by Arm

Phase	Arm	Dose [1] / Route	Treatment Cycle
1	CRS-207/ IDO	CRS-207: 1×10^9 CFU by IV infusion over ~ 1 hour IDO: 100 mg or 300 mg BID Oral	CRS-207: Day 1 of each cycle (Cycles 1-6); Q6W thereafter IDO: BID starting Cycle 1 Day 2
	CRS-207	CRS-207: 1×10^9 CFU by IV infusion over ~ 1 hour	CRS-207: Day 1 of each cycle (Cycles 1-6); Q6W thereafter
2	CRS-207/ Pembro/ IDO	Pembro: 200 mg by IV infusion over 30 min CRS-207: 1×10^9 CFU by IV infusion over ~ 1 hour IDO: 300 mg Oral BID [1]	Pembro: Day 1 of each cycle CRS-207: Day 2 of each cycle (Cycles 1-6); Q6W thereafter IDO: BID starting Cycle 1 Day 3
	CRS-207/ Pembro	Pembro: 200 mg by IV infusion over 30 min CRS-207: 1×10^9 CFU by IV infusion over ~ 1 hour	Pembro: Day 1 of each cycle CRS-207: Day 2 of each cycle (Cycles 1-6); Q6W thereafter

BID = twice daily; CFU = colony-forming units; IDO = epacadostat; IV = intravenous; pembro = pembrolizumab; Q6W = once every 6 weeks
[1] RP2D of epacadostat based on Phase 1 dose-evaluation parameters and determined by the SRC; the phase 2 dose may be further adjusted during Phase 2 Safety Run-in

Phase 2 is a randomized assignment.

Subject data will appear in the column representing the treatment they were assigned during enrollment/randomization, regardless of the treatment actually received.

5.2. Reference Dates

- Age and time from diagnosis uses the enrollment date as its reference date.
- Safety data, such as AEs and laboratory assessments will use the first treatment date as a reference date.
- Efficacy data will use the first date of study treatment as a reference date.
- Study day will be based on the date of first study treatment as a reference date.

The date of first study treatment will be based on the first date on which any therapy component was taken.

5.3. Study Day and Duration Variables

Reference date calculations will be defined as the following:

- date of interest – reference date + 1 when the date of interest >= reference date;
- otherwise, date of interest – reference date.

For instance, study day will be based on the date of first study treatment as the reference would either have a negative value if collected before dosing or a positive value if collected after drug dosing; there will be no study day zero.

Duration of time is dependent on reference dates and will be calculated in a manner similar to that of the reference date calculation, assuming that dates of interest will strictly follow reference dates (e.g. no negative values). For example, duration on study treatment is defined as the end of study date – first dose date + 1. Duration of treatment is defined as the last date of treatment – first dose date + 1. Duration of the safety observation period is defined as (the last date of treatment + 30 days) – first dose date + 1. Subjects still receiving ongoing treatment or participating in study follow up at the time of analysis will use imputed treatment end and end of study dates as described in Section **5.6**.

Survival, or time-to-event, endpoints such as progression-free survival (PFS) or overall survival (OS) are followed until first event or censoring. As a result, survival time will be calculated as: event or censoring date – reference date + 1. These are further described in Section 7.

When reporting survival or duration outcomes, the results (in days) above will be converted to an appropriate unit. When reporting in months it will be divided by 30.4375; for reporting in weeks it will be divided by 7; and for reporting in years it will be divided by 365.25.

5.4. Study Time Periods

Safety reporting will be classified by the following study periods for analysis:

Pre-therapy is defined as the period prior to a subject's first dose of study treatment.

On therapy is defined as the period between first dose of study treatment and within 30 days following the last dose of study treatment.

Post-therapy is defined as the period of time following the on therapy period.

5.5. Baseline, Post-Baseline Changes, and Endpoint

Baseline will be based on the last nonmissing value collected prior to or on the date [and time, if applicable] of first study treatment. Post-baseline values will be those collected after first dose of study drug.

Change from baseline is defined as: value – baseline value.

Percentage change from baseline is defined as: (value – baseline value)/baseline value X 100%.

Most extreme change: The maximum most extreme change will be the maximum post-baseline value; the minimum most extreme change will be the smallest post-baseline value. This calculation will consider all assessments collected within the on therapy period, scheduled or unscheduled.

5.6. Imputation of Partial Dates

Adverse Events and Concomitant Medications

- If the AE start date is completely missing, no imputation will be conducted.
- If the AE start date is missing day and month, do the following:
    - If the treatment start date is missing or the AE year does not fall in the same as that of first treatment or if the AE contains information to indicate that the event ended before the date of first study treatment (e.g. AE end date month and year are earlier than the treatment start date or the full date is known and occurs earlier than the date of first treatment), then set the start month and day to January 1st
    - Otherwise, set the start date to the date of first study treatment
- If only the day is missing, do the following:
    - If the study treatment start date is missing or the month and year does not fall in the same as that of first treatment or if the AE contains information to indicate that the event ended before the date of first study treatment, then set the start month and day to the 1st of the stated month
    - Otherwise, set the start date to the date of first study treatment
- End dates will not be imputed

Subsequent Anticancer Therapy, Radiotherapy or Anticancer Surgical Procedures

Partial dates for subsequent therapies will not typically be imputed, but may be needed to support efficacy outcome derivations (e.g. PFS censoring dates). In this case, the following will be applied for imputation of new anti-cancer therapies taken after first study treatment:

- If the start date is completely missing, no imputation will be conducted
- If the start date is missing day and month, do the following:
    - If progressive disease (PD) has been identified in the year noted, new anti-cancer therapy date will be assigned to begin one day after the date of PD.
    - Otherwise the new anti-cancer therapy date will be assigned to January 1st.
- If only the day is missing, do the following:

- If PD has been identified in the year noted, new anti-cancer therapy date will be assigned to begin one day after the date of PD.
- Otherwise the new anti-cancer therapy date will be assigned to the 1st of the stated month.

Overall Response Date

For each visit-specific disease assessment, the date of overall response will need to be established. For complete response (CR) and partial response (PR), set the date of overall response to the latest of all tumor assessments for the specified visit. Otherwise, set to the earliest date of all assessments made during the specified visit.

Treatment End Date

Missing treatment end dates will not necessarily be imputed at the end of the study. However, due to ongoing reporting needs, treatment end date will be imputed as the earliest of the data cutoff date, date of death, or date of treatment study withdrawal.

End of Study Date

Missing study end dates will not necessarily be imputed at the end of the study. However, due to ongoing reporting needs, end of study dates will be imputed as the earliest of the data cutoff date or date of death.

5.7. Lost to Follow Up or Lapse of Adequate Assessments

If a subject has missed two or more scheduled disease assessments, a censoring date will be required in support of relevant survival endpoint derivations. For example, PFS will be censored at the last adequate disease assessment prior to the lost to follow up window. However, this survival outcome would be considered censored after an extended amount of time without additional assessment (after two have been missed). Based on a protocol specified disease assessment schedule of every 9 weeks, a window of 140 days [18 weeks + 14 days] would be used as the censoring date (assuming a protocol window period of 7 days for each assessment).

6. STUDY SUBJECT DATA

6.1. Analysis Populations/Sets

The Safety Analysis Set (SAF) includes all randomized subjects who received at least 1 dose of any study drug. The SAF will be conducted on the basis of the treatment assigned and is the basis of analysis summary tables unless otherwise indicated.

6.2. Subject Disposition

Summaries of analysis population membership; final study status (ongoing or terminated), including reasons for study termination; treatment status (ongoing or discontinued), including reasons for treatment discontinuation will be produced based on all subjects enrolled in the study. Time on study and duration of treatment will also be summarized.

Screen failures and final subject disposition status will be listed.

6.3. Protocol Deviations

Protocol deviations will be identified and classified as major (violations) before the database is locked. Major protocol deviations may include but are not limited to:

- Violation of Inclusion/Exclusion Criteria
- Dose not properly administered, including
    - Administrations in which protocol-required pre-medication were not administered
- Use of prohibited medications

Protocol deviations will be listed.

6.4. Demographic and Baseline Characteristics

Subject demographics will be summarized for age (years), sex, ethnicity, race, baseline height (cm), baseline weight (kg), BMI (kg/m^2), and BSA (m^2). Age will also be categorized as a categorical variable (age < 65, ≥ 65 years) for reporting.

The following conversions and equations will be used as applicable:

- Height (in cm) = height (in inches) * 2.54
- Weight (in kg) = weight (in lbs) * 0.4536
- BMI (kg/m^2) = weight(kg)/[height$(m)^2$]
- BSA(m^2) = $\sqrt{}$[(height(cm)*weight(kg))/3600]

Duration of time from initial diagnosis to screening (in months); cancer type; histology; genetic mutations; TNM staging at diagnosis; TNM staging at study entry; stage at diagnosis; stage at study entry; disease specific genetic mutations; prior systemic therapy, prior radiation and prior surgery (Yes/No); sum of target lesions per RECIST 1.1 at baseline (mm); baseline CA-125 (and response evaluability per GCIG as Yes/No as identified in Section 7); and baseline ECOG will be summarized. Histology and genetic mutations for phase 1 patients will be provided by Aduro outside of the clinical database.

Subject demographics and baseline characteristics, including cancer related surgeries, systemic therapies, and prior radiotherapy, will be listed.

6.5. Medical History

Medical history will be listed.

6.6. Prior and Concomitant Medication

Concomitant medications will be coded to ATC and preferred name based on the WHO Drug Dictionary (WHO-DDE B2, March 2016). Prior medications are those which have been identified to have been discontinued prior to first study treatment (e.g. taken exclusively during the pre-therapy period). Concomitant medications are those which have been identified to have been taken at any point during the on therapy period.

Prior, concomitant, and post-therapy medications will be presented in data listings; medications which do not occur during the on therapy period will be identified.

6.7. Anticancer Therapies

Anticancer therapies will be coded to ATC and preferred name based on the WHO Drug Dictionary (WHO-DDE B2, March 2016). It is assumed that these therapies will be collected on the associated CRF have been taken following study drug discontinuation in compliance with the protocol. Anticancer therapies will be presented in a data listing.

6.8. Study Drug Exposure and Compliance

The number of cycles of administration (of any dose amount) of pembrolizumab and epacadostat will be reported as a continuous and categorical outcome; categories for reporting will include: < 5 Cycles; 5 - 15 Cycles; > 15 to 25 Cycles; and > 25 Cycles.

The number of infusions of CRS-207 will also be reported as both a continuous and categorical outcome; categories for reporting will be < 5 infusions; 5 – 10 infusions; > 10 to 15 infusions; and > 15 infusions.

For CRS-207, the average volume administered for each infusion (or cycle) will be summarized by therapy. This will be calculated for each subject in (mL / infusion or mL / Cycle):

(Sum of Total Volume Administered [mL]) / (Total Number of Administrations)

The average dose intensity for each pembrolizumab cycle will be summarized. This will be calculated for each subject in (mg / Cycle):

(Sum of Total Dose Received [mg]) / (Total Number of Administrations)

The incidence of infusion interruptions, as well as the total number of interruptions will be displayed for CRS-207 and pembrolizumab separately. Reasons for infusion interruption will also be summarized.

The incidence and number of epacadostat dose reductions will be summarized.

For epacadostat, the mean daily dose will be summarized. This will be calculated for each subject in (mg / Day):

(Sum of Total Doses Received [mg]) / (Duration of epacadostat therapy)

Duration of treatment for each drug, based on similar definitions provided in 5.3, will also be summarized.

Epacadostat dosing, CRS-207 and pembrolizumab administrations, infusion interruptions, and dose reduction information, as well as derived drug exposure metrics, will be listed.

7. EFFICACY

All efficacy variables derived from tumor imaging and response assessments will be determined by the local Investigator using modified RECIST 1.1 (mRECIST) guidelines. Based on the study protocol, evaluations of overall response are identified as complete response (CR), partial response (PR), stable disease (SD), progressive disease (PD), or Not Evaluable (NE) by investigators in the CRF based on RECIST 1.1. mRECIST is taken into consideration for cases in which PD have been identified; this is of impact to study discontinuation considerations as noted below.

If radiologic imaging shows initial PD, tumor assessment should be repeated ≥ 4 weeks later in order to confirm PD while continuing study treatment and awaiting radiologic confirmation of progression. If repeat imaging shows a stability or reduction in the tumor burden compared to the initial scan demonstrating PD, treatment may be continued /resumed. If repeat imaging confirms progressive PD, subjects will be discontinued from study therapy and their initial PD evaluation date will be considered as their date of progression. In determining whether or not the tumor burden has increased or decreased, investigators should consider all target lesions as well as non-target lesions.

In subjects who have initial radiological evidence of PD, it is at the discretion of the treating minimum of 4 weeks later. This clinical judgment decision should be based on the subject's overall clinical condition, including performance status, clinical symptoms, and laboratory data. Subjects may receive treatment while waiting for confirmation of PD if they are clinically stable as defined by the following criteria:

- Absence of new or worsening signs and symptoms indicating PD;
- No decline in ECOG performance status;
- Absence of rapid progression of disease; and

- Absence of progressive tumor at critical anatomical sites (e.g. cord compression) requiring urgent alternative medical intervention.

When feasible, subjects should not be discontinued until progression is confirmed. Subjects who are deemed clinically unstable are not required to have repeat imaging for confirmation of PD.

In all other instances, treatment decisions will be made based on investigator review of the clinical and radiographic data.

Progressive serial elevation of serum CA-125 will be used to determine CA-125 response. Guidelines for using CA-125 response have been developed and are based on the Gynecological Cancer Intergroup (GCIG) Definitions for Response and Progression. Subjects should have a pre-treatment CA-125 of at least twice the ULN in order to be considered for CA-125 response assessment. Subjects are not evaluable by CA-125 if they have received mouse antibodies or if there has been medical and/or surgical interference with their peritoneum or pleura during the previous 28 days. In those subjects considered evaluable by CA-125, a CA-125 response would be obtained the moment the CA-125 is reduced by 50% and this should be confirmed with a consecutive CA-125 assessment not earlier than 28 days after the previous one; the date of the first 50% reduction to be the reference date for the CA-125 response.

Progression is conventionally defined according to RECIST 1.1 but can also be based on serum CA-125. In assigning the date of progression, PD by objective change in tumor size should always take precedence over CA-125 should it occur first. If measurable disease is reducing in size during treatment but the CA-125 results suggest progression, the patient should continue to receive protocol treatment. If measurable disease is stable but CA-125 indicates confirmed progression over at least 4 weeks, may advise changing protocol treatment, unless there is the possibility that the therapy could be slowing the rate of rise of CA-125. CA-125 progression is defined as:

- Elevated CA-125 pretreatment and normalisation of CA-125 must show evidence of CA-125 greater than, or equal to, two times the upper normal limit on two occasions at least one week apart or
- Patients with elevated CA-125 pretreatment, which never normalises must show evidence of CA-125 greater than, or equal to, two times the nadir value on two occasions at least one week apart or
- Patients with CA-125 in the normal range pretreatment must show evidence of CA-125 greater than, or equal to, two times the upper normal limit on two occasions at least one week apart.
- Elevated values must be confirmed by two separate measurements obtained at least one week apart. CA 125 progression will be assigned the date of the first measurement that meets the criteria as noted.

A patient may be declared to have progressive disease on the basis of either the objective RECIST criteria or the CA-125 criteria. The date of PD will be the date of the earlier of the two events if both are documented.

The use of GCIG CA-125 in tandem with RECIST 1.1 in the evaluation of overall response at each visit is identified in

Table *4*.

Table 4: Overall Response in Patients with Initial Measurable Disease and Evaluable by CA-125, Combining Both Criteria

Target Lesion	Non-target Lesion	New Lesion	CA-125	Overall Response
CR	CR	No	Normal	CR
CR	Non-CR Non-PD	No	Not PD	PR
CR	CR	No	PR not normal	PR
PR	Non-PD	No	Not PD	PR
NE	Non-PD	No	PR	PR
PD or New > 28 Days from CA-125 PR*			PR	PR
SD	Non-PD	No	PR	PR
SD	Non-PD	No	Not PR or PD	SD
PD or New <= 28 Days from CA-125 PR*			PR	PD
PD	Any	Yes or No	Any	PD
NE	PD	Yes or No	Any	PD
NE	Any	Yes	Any	PD
NE	Any	Yes or No	PD	PD

* patients who have a CA-125 response that occurs more than 28 days from PD according to RECIST are considered a PR according to best response, but PD if the RECIST PD is within 28 days of CA-125 response

For subjects with non-measurable disease, GCIG CA-125 based overall response derivations will be conducted according to **Table 5**.

Table 5: Overall Response in Subjects without Initial Measurable Disease and Evaluable by CA-125

CA-125	Non-target Lesion#	New Lesion	Overall Serological Response
Response and normalized	CR	No	CR
Response	Non-PD	No	PR
Normalized but not response	Non-CR Non-PD	No	SD
Non-PR Non-PD	Non-PD	No	SD
PD	Any	Yes or no	PD
Any	PD*	Yes or no	PD
Any	Any	Yes	PD

#Non-target lesions include ascites and peritoneal thickening, which are not measurable according to RECIST.
*Unequivocal progression in non-target lesions may be accepted as disease progression.

Subjects which do not have measurable disease at study entry will be evaluated based on GCIG criteria and will not be included in mRECIST and RECIST 1.1 analyses; endpoint derivations will be considered not evaluable (NE). Subjects which are not evaluable per GCIG CA-125 criteria will be handled similarly.

7.1. Efficacy Endpoints and Analyses

Refer to Section 2 for further details on Phase 1 and Phase 2 efficacy endpoint hierarchy.

Objective Response Rate

For purposes of mRECIST based derivations, a subject's best overall response (BOR) is determined by the highest qualitative value assessed during the study given a hierarchy of overall response results: CR > PR > SD > PD > NE. In order for a valid value of SD to be assigned, there must be evidence of stable disease for at least 8 weeks. If the minimum time for SD has not been met on the first assessment, the assignment of BOR will depend on subsequent response assessments. Subjects which do not have follow up data after a first assessment of SD prior to the minimum time requirement will be considered as not evaluable. BOR will be based on assessments collected after the first dose of study until confirmed disease progression; assessments collected after the start of new cancer treatment will not be considered.

The objective response rate (ORR) is defined as the number of subjects who exhibit a BOR response of CR or PR divided by the number of evaluable subjects. Subjects who discontinue prior to any evaluation of post-baseline tumor assessments will be considered as non-responders regardless of discontinuation reason. ORR will not be reported in the CSR synopsis.

BOR will be listed for each subject.

Progression-Free Survival

PFS is defined as the number of weeks from the date of first dose of study treatment to the first date of objectively determined progressive disease or death from any cause and is computed as described in Section 5.3. The primary analysis of PFS will include tumor assessments collected after the end of study treatment and will be based on mRECIST criteria for progressive disease confirmation. Tumor assessments taken after switch to another anti-cancer therapy will be excluded from consideration.

The first date of objectively determined progressive disease would be the earliest date of any post-baseline overall response finding of progressive disease is confirmed as part of the tumor lesion assessment data or death, unless a subject is censored at an earlier date. If an assessment occurs over several days, the method described in Section 5.6 will be used. If there are no adequate assessments for a subject, they will be censored on their first dose date unless they died prior to having their first assessment (in which case they will be considered to have had a PFS event of death). If a subject receives subsequent anticancer therapy prior to documentation of

progressive disease, PFS will be censored at the latest adequate assessment prior to therapy initiation.

Subjects who progress or die following an extended period of follow up will also be censored at a latest adequate assessment prior to the end of a predefined lapse window, even if information is available regarding progression or death after this extended period. Should a subject die after the end of this lapse window they will be censored at their first dose date. The lapse window after which PFS events will not be considered is defined in Section 5.7.

If a subject does not receive confirmation of radiologically identified PD, and there are no further assessments prior to censoring, the subject will be considered to have progressed based on their last valid assessment.

Otherwise, if a subject does not have documented progression, the subject will be censored at the latest adequate assessment.

PFS will be listed for each subject.

Disease Control Rate

Disease control rate (DCR) is defined as the number of subjects who exhibit a BOR response of CR, PR or SD divided by the number of evaluable subjects.

The derivation analysis of DCR will be produced based on mRECIST, RECIST 1.1, and GCIG CA-125 criteria. A description of BOR derivations for RECIST 1.1 and GCIG CA-125 can be found in a previous section.

DCR will not be reported in the CSR synopsis. BOR will be listed for each subject.

Duration of Response

Duration of response (DOR) will be computed for subjects who have been identified as a responder (achieved an overall response of CR or PR during the PFS observation period); it will be computed as described in Section 5.3, where the reference date will be the first date where a subject has been documented to have achieved a responder designation. Censoring algorithms similar to those identified for PFS will be used for DOR.

The derivation of DOR will be conducted based on RECIST 1.1 and GCIG CA-125 criteria.

DOR will not be derived if there are no responders on the study.

Objective Response Rate Based on RECIST 1.1 and GCIG CA-125

For purposes of RECIST v1.1 derivation, the BOR will be based on methods described in Section 7.1 but with alternate assumptions around study treatment discontinuation; assessments following an initial, radiologically identified overall response of PD will not be considered regardless of confirmation status.

For purposes of GCIG CA-125 derivation, BOR will be evaluated over the course of the study based on the method described in 7.1, using overall responses as defined in

Table 4 (for subjects with measurable disease at baseline) and **Table 5** (for subjects who did not have measurable disease at baseline).

For both methods, ORR remains defined as the percentage of subjects identified to have responded (CR or PR) for BOR.

The analyses specified in Section 7.1 for ORR will be repeated for ORR based on RECIST v1.1 and GCIG CA-125 criteria.

Overall Survival

Overall survival (OS) is defined as the number of weeks from the date of first dose of study treatment to the date of death from any cause and is computed as described in Section 5.3. Subjects still alive as of the data cut-off date will be censored on the last known alive date from mortality status follow up. For subjects that are lost to follow up, the last visit in the database or last contact date where the subject is documented to be alive will be used to estimate last known date alive.

Progression-Free Survival Based on RECIST 1.1 and GCIG CA-125

The analyses specified in Section 7.1 for PFS will be repeated for PFS based on RECIST v1.1 and GCIG CA-125 criteria.

8. SAFETY

All safety analysis reporting will be based on the SAF.

8.1. Adverse Events

Treatment emergent adverse events (TEAEs) are defined as all events that occur from the time of first study drug administration until 30 days following the last dose of study drug or initiation of subsequent cancer-related therapy, whichever occurs first. TEAEs are assessed for severity using the NCI-CTCAE v. 4.0, relationship to each therapy, and seriousness. For Phase 1 data, infusion-related reactions (IRRs) are those which: have an onset date on or one day after the date of a CRS-207 administration; have been identified as related to CRS-207; and are coded to the following specific preferred terms: dyspnoea, chills, decreased appetite, fatigue, headache, hives, hypersensitivity, hypotension, hypoxia, influenza like illness, infusion related reaction, myalgia, nausea, pain, presyncope, pyrexia, rash, and vomiting. Phase 2 IRRs are identified by the investigator using the appropriate eCRF field.

A summary of TEAEs will be produced, including counts and percentages of subjects with any incidences of: TEAEs, CTCAE Grade 3 or higher TEAEs, TEAEs related to any study treatment, CTCAE Grade 3 or higher TEAEs related to any study treatment, serious adverse events (SAEs), SAEs related to any study treatment, TEAEs leading to study drug discontinuation, CRS-207 infusion related reactions, and fatal TEAEs.

A separate summary of AEs identified as CRS-207 IRRs will include the number of infusions received by subjects, the number of subjects having an IRR, total number of IRRs per subject, maximum IRR grade, and dose modifications resulting from IRRs.

Adverse events will be coded based on the Medical Dictionary for Regulatory Affairs (MedDRA) version 18.1 or higher, for reporting by system organ class (SOC) and preferred term (PT) in descending order of overall incidence for the type of event reported. Within these summaries, TEAEs will be sorted for each subject by PT and severity; subjects will be counted once within a PT based on their TEAE having maximum severity.

Summaries of AEs by SOC and PT will include the following types of events:

- TEAEs;
- TEAEs related to any study treatment (Definitely Related, Probably Related, or Possibly Related);
- CTCAE Grade 3 or higher TEAEs;
- CTCAE Grade 3 or higher TEAEs related to any study treatment;
- CRS-207 infusion-related reactions;
- SAEs;
- SAEs related to any study treatment;
- TEAEs that lead to discontinuation of study drug; and
- Fatal TEAEs.

To account for potential differences in the extent of exposure between the treatment categories, a subject-year adjusted rate will also be presented. The rate is calculated as the number of subjects with an event divided by the total subject-years of safety observation, where subject-years of safety observation for each subject is defined as duration of safety observation (defined in Section **5.3**) in days divided by 365.25.

A comprehensive listing of all AEs will be provided in a by-subject data listing; events which do not occur during the on therapy period will be identified. In addition, the following listings will be provided:

- SAEs;
- TEAEs leading to treatment discontinuation; and
- Fatal TEAEs (with identification of those which occur within the on therapy period).
- Dose limiting toxicities (DLTs)
- AEs of special interest (AESIs), as defined in Section 9.1.2 of the study protocol

Deaths

The number and percentage of subjects who died along with primary cause of death will be summarized overall (including the post-study survival surveillance period) and within 30 days of last dose of study drug. All death data will be listed.

8.2. Clinical Laboratory Evaluations

Clinical chemistry and hematology parameters will be reported based on the International System of Units (SI). The following laboratory evaluations will were collected, those with asterisks (*) indicating those that will be graded using NCI-CTCAE v 4.03:

Hematology: hematocrit, hemoglobin*, red blood cell (RBC), platelet count*, white blood cell (WBC)*, absolute neutrophil count*, absolute lymphocyte count*, monocytes, eosinophils, and basophils.

Clinical chemistry: Electrolytes: bicarbonate, calcium*, chloride, magnesium*, phosphorus*, potassium*, sodium*; Hepatic function tests: albumin*, alkaline phosphatase*, bilirubin (total*, direct, indirect), total protein, alanine aminotransferase (ALT)*, aspartate aminotransferase (AST)*; renal function tests: blood urea nitrogen (BUN), creatinine*; Other chemistry tests: glucose*, LDH, amylase*, uric acid*. Note: Uric acid is graded only for Grade 4 as other grades require additional, clinical judgement. It will otherwise be assumed normal (Grade 0).

Coagulation: Activated partial thromboplastin time*, international normalized ratio, D-dimer, and fibrinogen*.

Endocrine testing (for subjects treated with epacadostat): Adrenocorticotropic hormone, serum cortisol, luteinizing hormone, prolactin, thyroid stimulating hormone, T3, FT3, FT4.

Thyroid function testing: Total triiodothyronine (T3), free triiodothyronine (FT3), free thyroxine (FT4), thyroid stimulating hormone.

Shift tables displaying the shift from baseline to the worst value of NCI-CTCAE grades for hematology and clinical chemistry parameters will be presented based on the most extreme change as it relates to the relevant NCI-CTCAE definition. NCI-CTCAE relating to “high/hyper” conditions will depend on the maximum post-baseline value while NCI-CTCAE “low/hypo” will be reported based on the minimum post-baseline value. Shift tables will also include parameters with bi-directional toxicity grading.

All laboratory parameters will be provided in subject data listings. Laboratory evaluations with a CTCAE grade of 3 or higher will also be provided as a separate listing.

8.3. Other Safety Evaluations

Vital Signs

Vital signs include: pulse (bpm); respiratory rate (breaths/min); temperature (ºC); systolic and diastolic blood pressure (mmHg); pulse oximetry (%), and weight (kg).

Vital sign data will be provided in data listings.

Electrocardiogram (ECG)

Electrocardiogram (ECG) parameters include HR (bpm) and the following intervals (ms): PR, QRS, QT, JTc, and QTcF. Observed values for ECG parameters will be listed.

Shifts in investigator-reported ECG interpretation shifts from screening worst case post-baseline will be summarized. Worst case post-baseline will be based on a subject's most abnormal observed investigator-reported ECG interpretation during the on therapy period.

ECG data will be provided in data listings.

ECOG Performance Status

ECOG data will be provided in data listings.

Physical Examinations

Physical examinations will be presented in subject data listings.

9. CHANGES TO THE PLANNED ANALYSIS

All efficacy endpoints will be derived and listed, but will not be summarized.

10. REFERENCES

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11. APPENDICES

11.1. Table of Contents for Tables

11.2. Table of Contents for Listings

11.3. Table of Contents for Figures

No figures planned.