STATISTICAL ANALYSIS PLAN

CTX-471-001

A PHASE 1, OPEN-LABEL, MULTIPLE-ASCENDING DOSE STUDY OF THE SAFETY AND TOLERABILITY OF CTX-471 ADMINISTERED EITHER AS A MONOTHERAPY OR IN COMBINATION WITH PEMBROLIZUMABIN PATIENTS WITH INADEQUATE RESPONSES TO PD-1/PD-L1 CHECKPOINT INHIBITORS IN METASTATIC OR LOCALLY ADVANCED MALIGNANCIES

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STATISTICAL ANALYSIS PLAN SIGNATURE PAGE

Statistical Analysis Plan V2.0 (Dated20Feb2025) for Protocol CTX-471-001.

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2.0	16Feb2022	Melissa Hays	Updated to cover both parts 1 and 2 Updated for Protocol version 8.0, based on protocol amendment 7.0 which includes combination therapy Updated based on sponsor review comments

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1. INTRODUCTION

This document describes the rules and conventions to be used in the presentation and analysis of safety and tolerability, pharmacokinetics (PK), pharmacodynamic (PD), immunogenicity, and clinical activity data for Protocol CTX-471-001. It describes the data to be summarized and analyzed, including specifics of the statistical analyses to be performed. This statistical analysis plan (SAP) is based on protocol version 8, based on protocol amendment 7.0 dated 09Nov2023.

2. STUDY OBJECTIVES

2.1. Primary Objectives

2.1.1. Monotherapy Arm 1 (CTX-471 alone)

2.1.1.1. PART 1:

Evaluate the safety and tolerability of escalating doses of CTX-471.

Determine the dose(s) of CTX-471 to be examined in Part 2 and the recommended Phase 2 dose(s).

2.1.1.2. PART 2

Evaluate the safety and tolerability of the CTX-471 dose(s) selected from Part 1.

2.1.2. Combination Therapy Arm 2 (CTX-471+Pembrolizumab)

2.1.2.1. PART 1:

Evaluate the safety and tolerability of escalating doses of CTX-471 in combination with pembrolizumab.

Determine the dose(s) of CTX-471 in combination with pembrolizumab to be examined in Part 2 and the recommended Phase 2 dose(s).

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2.1.2.2. Part 2:

Evaluate the safety and tolerability of the CTX-471 dose(s) selected from Part 1 in combination with pembrolizumab.

2.2. Secondary Objectives

2.2.1. All Parts

Evaluate the PK of CTX-471 in combination with pembrolizumab

Evaluate the immunogenicity of CTX-471 in combination with pembrolizumab

Evaluate the clinical activity of CTX-471 in combination with pembrolizumab

2.3. Exploratory Objectives (All Parts)

Characterize pharmacodynamic markers related to CTX-471 exposure.

3. STUDY DESIGN

3.1. General Description

This study is divided into 2 arms; Monotherapy Arm 1 will investigate CTX-471 as a monotherapy; Combination Arm 2 will investigate CTX-471 in combination with pembrolizumab (Keytruda®). Each Arm will have two Parts: a dose escalation cohort and a dose expansion cohort, referred to as Part 1 and Part 2, respectively, for each of the two Arms.

Monotherapy (Arm 1) Part 1 – Dose Escalation

Part 1 of Arm1 will use a 3+3 design to evaluate escalating doses of CTX-471 monotherapy. Approximately 36 patients are anticipated for enrollment. A total of 19 patients were treated in Part 1 Dose Escalation, defining the NTD of 1.2 mg/kg and MTD of 0.6 mg/kg.

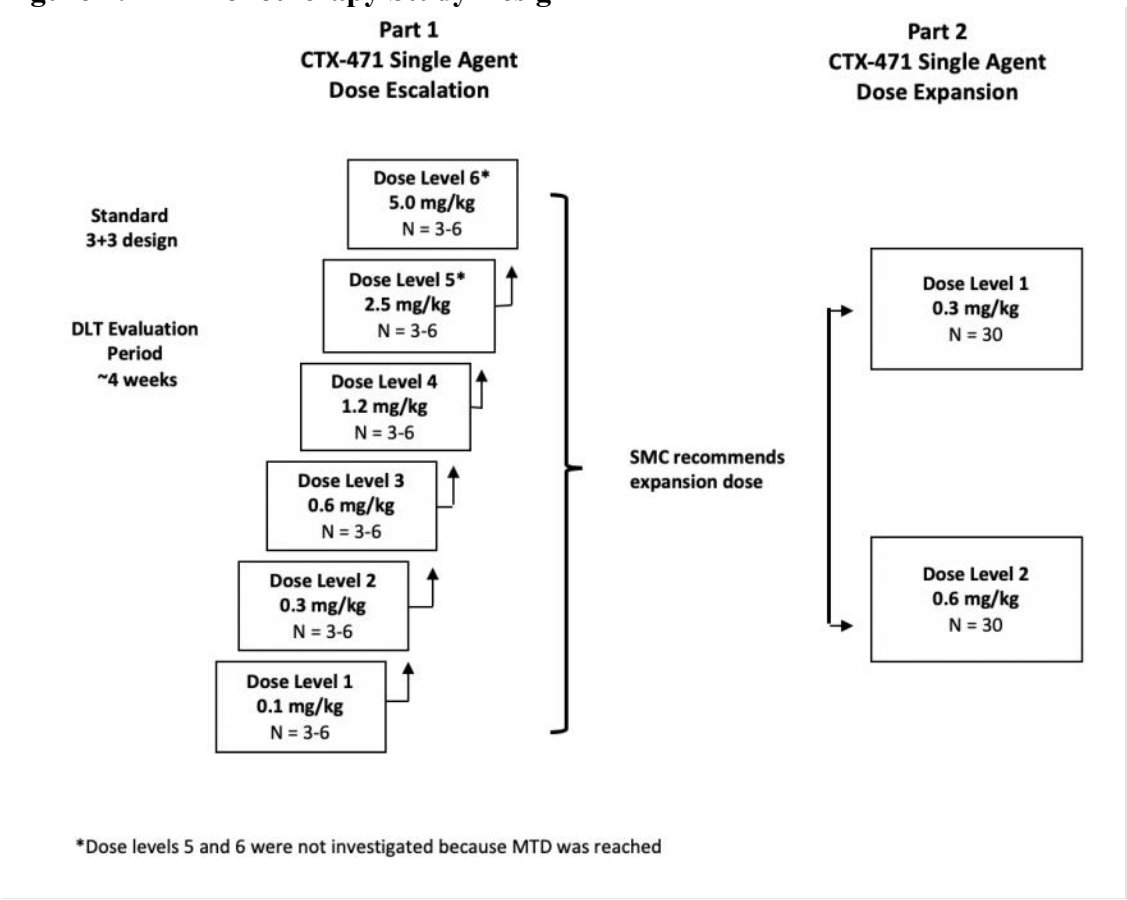
Monotherapy (Arm 1), Part 2 – Dose Expansion

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During Dose Expansion, the safety, tolerability, and preliminary efficacy of CTX-471 will be evaluated in two dose levels: 0.3 mg/kg and 0.6 mg/kg

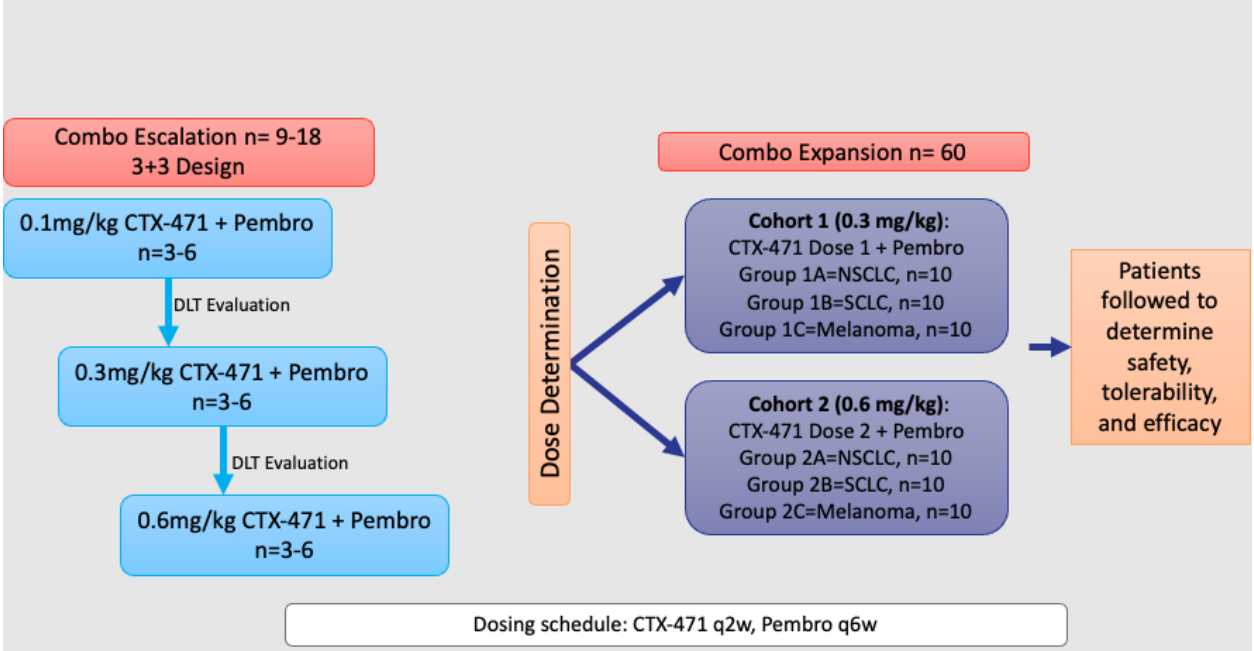
The monotherapy study design is presented in Figure 1, and combination therapy design in Figure 2.

Figure 1: Monotherapy Study Design



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Figure 2: Combination Arm Study Design



Combination Therapy (Arm 2) Part 1 – Dose Escalation

The starting dose of CTX-471 in Arm 2 will be 0.1 mg/kg, based on the findings from monotherapy Arm 1 of the study.

Part 1 will use a 3+3 design to evaluate escalating doses of CTX-471 in combination with pembrolizumab. Approximately 9-18 patients are anticipated for enrollment.

Dose escalation will continue until one of the following occurs:

- Confirmation that the CTX-471 doses used in the Monotherapy Arm 1 Part 2 do not result in a DLT in the Combination Arm
- Recommendation by the SMC to halt dose escalation based on comprehensive review of all applicable data

Combination Therapy (Arm 2) Part 2 – Dose Expansion

During Dose Expansion, the safety, tolerability, and preliminary efficacy of CTX-471 in combination with pembrolizumab will be further evaluated in two CTX-471 dose level cohorts (0.3 mg/kg and 0.6 mg/kg) and in three tumor type subgroups (NSCLC, SCLC, and melanoma). Approximately 60 patients will be enrolled (30 per cohort) with approximately 10 response evaluable patients per tumor type subgroup.

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Both CTX-471 dose levels will enroll simultaneously, and dose level assignments will be alternating based on each tumor type group.

3.2. Schedule of Events/Assessments

Schedule of events/assessments can be found in Table 1 of the protocol.

4. ANALYSIS SETS

Agreement and authorization of subjects included/excluded from each analysis set will be conducted prior to database lock for the study per the definitions provided below.

4.1. DLT-Evaluable Analysis Set

All patients in Part 1 (Dose Escalation) who received at least 1 dose of CTX-471 and 1 dose of pembrolizumab (Combination Arm 2 Only) and either completed the DLT evaluation period or experienced a DLT during this period. This analysis set will be used to assess the tolerability of CTX-471 in the dose-escalation phase. Over the entire dose escalation phase, patients will be grouped based on the highest dose level each patient received.

4.2. All-Treated Analysis Set (ATAS)

All patients who received any amount of CTX-471 or pembrolizumab (Combination Arm 2 Only) with treatment group based on the highest dose level received. This analysis set will be the primary analysis set for all safety endpoints, excluding DLT evaluation. This analysis set will also be used for analysis of efficacy endpoints for Combination Arm 2.

4.3. Response-Evaluable Analysis Set (REAS)

All patients with measurable disease at Baseline who received any amount of CTX-471 or pembrolizumab (Combination Arm 2 Only) and had at least 1 post-Baseline response assessment or discontinued treatment due to disease progression (including death caused by disease progression) within 8 weeks (± 5 days window) of the first dose of study treatment.

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This analysis set will be the primary analysis set for efficacy endpoints for Monotherapy Arm 1.

4.4. PK Analysis Set (PKAS)

All enrolled patients who received at least one dose of CTX-471 or pembrolizumab (Combination Arm 2 Only) and have at least one post dose measurement of one analyte without protocol deviations or events affecting the validity of the PK results. This analysis set will be used for the analysis of PK parameters as further defined in the protocol. Pharmacokinetic-response correlations may be performed. The PK exposure-response analysis will include patients who have both valid PK and valid response data. Changes to the procedures or events, which may impact the quality of the PK data, will be considered important protocol deviations and will be described within the clinical study report. These changes or events will include any circumstances that will alter the evaluation of the PK. Examples include, but may not be limited to, sample processing errors that lead to inaccurate bioanalytical results, and/or inaccurate dosing on the day of PK. In the case of an important protocol deviation or event, PK data collected during the affected treatment period will be listed but excluded from the PK results. Other changes to the procedures or events which do not impact the quality of the PK data will not be considered significant. Common examples of a non-significant protocol deviation are a missed blood sample or deviations from blood collection times.

This analysis set will be used for the analysis of immunogenicity endpoints as further defined in the protocol.

5. GENERAL CONSIDERATIONS

5.1. Reference Start Date and Study Day

Study Day will be calculated from the reference start date and will be used to show start/ stop day of assessments and events. Reference start date is defined as the day of the first dose of study medication, (Day 1 is the day of the first dose of study medication) and will appear in every listing where an assessment date or event date appears.

- If the date of the event is on or after the reference date then:

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STUDY DAY = (DATE OF EVENT – REFERENCE DATE) + 1.

- If the date of the event is prior to the reference date then:

STUDY DAY = (DATE OF EVENT – REFERENCE DATE).

In the situation where the event date is partial or missing, the date will appear partial or missing in the listings, and Study Day, and any corresponding durations will be presented based on the imputations specified in Appendix 1; Partial Date Conventions.

5.2. Baseline

Unless otherwise specified, baseline is defined as the last non-missing measurement taken prior to reference start date (including unscheduled assessments). In the case where the last non-missing measurement and the reference start date coincide, that measurement will be considered pre-baseline, but Adverse Events (AEs) and medications commencing on the reference start date will be considered post-baseline.

5.3. Retests, Unscheduled Visits and Early Termination Data

In general, for by-visit summaries, data recorded at the nominal visit will be presented. Unscheduled measurements will not be included in by-visit summaries. If the retest measurement occurs prior to the dosing of the investigational product, the retest measurement will be used in the summary statistics if it is the last measurement taken prior to the dose. In the case of a post-dose retest (same visit number assigned), the earliest available measurement for that visit will be used in summary statistics for post dose measurements.

Early termination data will be mapped to the next available visit number for by-visit summaries.

Listings will include scheduled, unscheduled, retest and early discontinuation data.

5.4. Windowing Conventions

No visit windowing will be performed for this study. Only scheduled visits will be presented in summary tables. Listings will include all visits.

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5.5. Statistical Tests

As the intent of this study is exploratory and descriptive, no statistical testing is planned.

5.6. Common Calculations

Height, unit conversion: height in centimeters = height in inches x 2.54.

Weight, unit conversion: weight in kilograms = weight in pounds x 0.4536.

Body mass index: BMI (kg/ m^2) = weight (kg)/ height $(m)^2$.

For quantitative measurements, change from baseline will be calculated as:

- Test Value at Visit X – Baseline Value
- Age (years) = age = floor((intck('month', birthday, Date of informed consent) – (day(date of informed consent) < day(birthday))) / 12)

5.7. Software Version

All tables, listings, and figures will be generated using SAS® Version 9.4 or higher (SAS Institute, Inc., Cary, North Carolina).

Pharmacokinetic parameters for serum will be derived using noncompartmental methods with Phoenix® WinNonlin® Version 8.3, or higher, (Certara L.P., Princeton, New Jersey, United States). All PK statistics will be performed using SAS® Version 9.4 or higher (SAS Institute, Inc., Cary, North Carolina, United States). Graphical presentations of PK data will be prepared with SAS Version 9.4, or higher.

6. STATISTICAL CONSIDERATIONS

6.1. Multicenter Studies

There will be no adjustment for study centers.

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6.2. Missing data

Missing safety data will not be imputed. All data will be evaluated as observed. No imputation method for missing values will be used. A subject who withdraws prior to the end of planned observation in a trial period will be included in the analyses up to the time of withdrawal.

6.3. Multiple Comparisons/ Multiplicity

Statistical methods will be primarily descriptive in nature. No hypothesis will be formally tested. Therefore, no adjustment for multiplicity will be performed.

6.4. Examination of Subgroups

Analyses will be conducted by dose group. No other subgroup analyses are planned.

7. OUTPUT PRESENTATIONS

The format and content of the summary tables, listings, and figures will be provided in a separate template document. Parts 1 and 2 will be presented in separate tables and figures. All subjects will be presented in a single listing but will identify whether subjects are from Part 1 or Part 2.

8. DISPOSITION AND WITHDRAWALS

The number and percentage of patients in each disposition category (e.g., enrolled, included in each Analysis Set, discontinuing treatment, and discontinuing study, with a breakdown of the reasons for discontinuation) will be summarized by dose level and cohort.

Listing and summary of subject disposition will be provided by dose level. This summary will include the number of enrolled subjects in each of the categories listed below:

DLT-Evaluable Analysis Set (for escalation parts only)

All-Treated Analysis Set

Response-Evaluable Analysis Set

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PK Analysis Set

Treatment and discontinuation reason for discontinuation

Study and discontinuation reason for discontinuation

The All Treated Analysis Set will be used as the basis for percentages, except for enrolled.

Summary of inclusion and exclusion by dose level will be provided for all screened subjects.

Listing and summary of protocol deviation by dose level will be provided for All Treated Analysis Set.

9. DEMOGRAPHIC AND OTHER BASELINE CHARACTERISTICS

Demographics will be summarized by dose level for the All-Treated Analysis Set. Characteristics to be summarized include:

- Sex
- Race
- Ethnicity
- Age

The following baseline characteristics will be summarized:

- Medical History, including type of cancer and tumor stage (tumor-node-metastases) at diagnosis and study entry
- Prior Surgical History
- Prior Cancer Therapy, including prior PD-1/PD-L1 therapy

No statistical testing will be carried out for demographic or baseline characteristics. Listings of these characteristics will be provided as well. Medical history information will be coded using MedDRA, Version 22.0 or higher. Medical History conditions are defined as those conditions which stop prior to or at Screening.

10. CONCOMITANT MEDICATIONS AND CONCOMITANT PROCEDURES

Concomitant medications and concomitant procedures will be summarized by dose level for the All-

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Treated Analysis Set. Medication will be coded using the most current World Health Organization Drug Dictionary (WHO-DD). Summary will be presented by Anatomical-Therapeutic-Chemical Second Level (ATC2) and preferred term.

A listing will be provided for prior and concomitant medications and procedures.

See Appendix 1 for handling of partial dates for medications, in the case where it is not possible to define a medication as prior or concomitant, the medication will be classified by the worst case; (i.e., concomitant).

- 'Prior' medications are medications which started and stopped prior to the first dose of study medication.
- 'Concomitant' medications and procedures:
    - Started prior to, on or after the first dose of study medication and started no later than date of the safety follow-up visit,

  AND

    - Ended on or after the date of first dose of study medication or were ongoing at the date of the safety follow-up visit.

11. STUDY MEDICATION AND PEMBROLIZUMAB EXPOSURE

For both CTX-471 and, for the combination subjects, Pembrolizumab, the summary statistics of exposure will be tabulated by dose level. In the summary, the following will be included:

- dose modification (interruptions and delays, including those outside of the protocol window)
- use of supportive medications (i.e. pre-medications)
- the cumulative number of days of exposure
- the number of doses completed,
- total dose received, and
- the relative dose intensity

All variables are predefined:

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- The cumulative number of days of exposure for each patient equals to the date of the last day of exposure minus the date of the first day of exposure plus 1.
- The number of doses is equal to the number received/completed. For the number of doses completed, if a patient has any record of starting administration number "X," the patient will be counted as completed administration X-1.
- The relative dose intensity is defined as the percentage of the planned treatments completed. It is the ratio of the cumulative actual dose (mg) and cumulative planned dose (mg) times 100. In this definition,
- the cumulative actual dose (mg) is the sum of the actual doses (mg) that the patient receives during the study
- the cumulative planned dose (mg) is the cumulative number of days of exposure times the planned dose level (mg)

All analyses within this section will be based on the All-Treated Set unless otherwise specified.

12. SAFETY OUTCOMES

The All-Treated Analysis Set will be used to evaluate all safety endpoints except for the DLT evaluation endpoints.

For Monotherapy and Combination therapy Parts 1 the number and type of DLTs experienced by patients will be summarized for each dose level, accompanied by a by-patient listing of DLT events. The listing will include the description, severity, and relationship of the events to CTX-471 and pembrolizumab (Combination Arm 2 only).

For all Part 1 and Part 2, safety data, including vital signs, ECGs, laboratory test results, PEs, and AEs will be summarized by dose and assessment time points, as appropriate. Cumulative data from both parts will be separated by study arm, unless otherwise noted.

There will be no statistical comparisons for safety data. Continuous variables will be summarized using descriptive statistics (n, mean, SD, median, minimum, and maximum). Categorical variables will be summarized by presenting the number (frequency) and percentage in each category.

Data summaries will be presented by dose level, and scheduled visit as appropriate. Cumulative data from both parts will be separated by study arm, unless otherwise noted.

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12.1. Adverse Events

AEs will be coded using the Medical Dictionary for Regulatory Activities (MedDRA) version 21.0 or higher and will be graded according to the NCI-CTCAE version 5.0 or higher (see Appendix 3 in protocol).

Summaries of AEs will include TEAEs. A TEAE is an AE that emerges or worsens in the period from the first dose of study treatment to the Safety Follow-Up Visit after the last dose of CTX-471. TEAEs will be summarized by dose level, and by the frequency within MedDRA system organ class (SOC) and preferred term (PT). Separate tabulations will also be provided for TEAEs related to CTX-471 and/or pembrolizumab, TEAEs that led to treatment discontinuation, TEAEs that led to death, and TEAEs ≥ Grade 3 in severity. Treatment-emergent SAEs and SAEs related to CTX-471 and pembrolizumab will also be tabulated.

Detailed information of AEs will be included in a listing, TEAEs that led to treatment discontinuation, TEAEs that led to death, and TEAEs ≥ Grade 3 in severity. Treatment-emergent SAEs and SAEs related to CTX-471 will also be tabulated

See Appendix 1 for handling of partial dates for AEs. In the case where it is not possible to define an AE as treatment emergent or not, the AE will be classified by the worst case, i.e. treatment emergent. Incidence of TEAEs will be presented by System Organ Class (SOC), severity by National Cancer Institute Common Terminology Criteria for Adverse Events (NCI-CTCAE) grades, and Preferred Term (PT).

12.1.1. Severity

AE severity will be assessed using NCI-CTCAE version 5.0 or higher:

- **Grade 1** Mild; asymptomatic or mild symptoms; clinical or diagnostic observations only; intervention not indicated.
- **Grade 2** Moderate; minimal, local or noninvasive intervention indicated; limiting age-appropriate instrumental ADL.
- **Grade 3** Severe or medically significant but not immediately life-threatening; hospitalization or prolongation of hospitalization indicated; disabling; limiting selfcare ADL.
- **Grade 4** Life-threatening consequences; urgent intervention indicated.

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- **Grade 5** Death related to AE.

Not all Grades are appropriate for all AEs. Therefore, some AEs are listed with fewer than five options for Grade selection. Grade 5 (Death) is not appropriate for some AEs and therefore is not an option.

AEs with a missing severity but identified as a life-threatening serious adverse event (SAE) or one requiring inpatient hospitalization or prolongation of existing hospitalization will be classified as Grade 4 (Potentially Life-threatening), otherwise missing severity will be classified as Grade 3 (severe). If a subject reports an AE more than once within that SOC/PT, the AE with the worst-case severity will be used in the corresponding severity summaries.

12.1.2. Relationship to Study Medication

The relatedness categories of an AE to CTX-471 and pembrolizumab (Combination Arm 2 Only) are unknown, unrelated, unlikely to be related, possibly related, probably related, and related. The TEAEs with the relationships of possibly related, probably related and related will be combined for the tabulations of adverse events related to study medication. AE with missing relationship will be treated as “Drug Related”. If a subject reports the same AE more than once within that SOC/ PT, the AE with the worst-case relationship to study medication will be used in the corresponding relationship summaries.

12.1.3. TEAEs Leading to Discontinuation of Study Medication

TEAEs leading to discontinuation of the study medication will be identified by the response to the AE action question “Study drug discontinued” on the AE page of the eCRF.

TEAEs leading to discontinuation of study medication will be summarized and listed separately.

12.1.4. Serious Adverse Events

Serious adverse events (SAEs) are those events recorded as ”Serious” on the Adverse Events page of the (e)CRF. A summary of serious TEAEs by SOC and PT will be prepared.

12.1.5. Adverse Events Leading to Death

TEAEs leading to Death are those events which are recorded CTCAE grading as ”Fatal”, an

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outcome of 'Fatal', or an SAE criteria of 'Death' on the Adverse Events page of the (e)CRF.

12.2. Laboratory Evaluations

All statistical analyses of laboratory values will be performed using International System units. All statistical analyses will be by cohort and by dose level within cohort if applicable.

Quantitative laboratory measurements reported as "< X", i.e. below the lower limit of quantification (BLQ) or "> X", i.e., above the upper limit of quantification (ULQ), will be converted to X for the purpose of quantitative summaries, but will be presented as recorded, i.e. as "< X" or "> X" in the listings.

The following clinical laboratory tests will be summarized:

- Thyroid stimulating hormone (TSH)
- Hematology laboratory parameters
- Blood chemistry laboratory parameters
- Coagulation laboratory parameters.

Refer to section 6.1.9 of the protocol for laboratory test details. Laboratory results will be listed and summarized by dose level and visit.

The following summaries will be provided for laboratory data:

- Actual and change from baseline results will be summarized by scheduled visit and dose level.
- Abnormality of laboratory data will be summarized and tabulated by number and percentage of patients with ≥ Grade 3 in severity by scheduled visit and dose level.
- Shifts in Grade from baseline to the worst post-baseline (including unscheduled) result (i.e. low, normal, high), where worst is determined as the largest absolute departure from the normal range, will be summarized by number and percentage of patients within each category.

- Listings of individual patient results of the above summaries will be presented. As well as the following listings:

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- Hematology, serum chemistry, and coagulation values outside the reference ranges will be provided. This listing will include data from scheduled and unscheduled time points.
- Serum and urine pregnancy test results.
- Complete urinalysis with qualitative analysis for protein (dipstick).

Hepatitis serologies and HIV assessments (Screening only). A listing of individual patient hematology, serum chemistry, and coagulation values outside the reference ranges will be provided. This listing will include data from scheduled and unscheduled time points.

12.2.1. Laboratory Reference Ranges and Markedly Abnormal Criteria

Quantitative laboratory measurements will be compared with the relevant laboratory reference ranges in SI units and categorized as:

- Low: Below the lower limit of the laboratory reference range.
- Normal: Within the laboratory reference range (upper and lower limit included).
- High: Above the upper limit of the laboratory reference range.

12.3. ECG Evaluations

Results from standard 12-lead Electrocardiogram (ECG) will be included in the reporting of this study.

The following ECG parameters will be reported for this study:

- PR Interval (msec)
- QRS Interval (msec)
- QT Interval (msec)
- QTcF Interval (msec) [derived]
- HR (bpm)

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- Overall assessment of ECG (Investigator's judgment):
  - Normal
  - Abnormal, Not Clinically Significant (ANCS)
  - Abnormal, Clinically Significant (ACS)

Actual and change from baseline results and subjects with markedly abnormal criteria will be summarized by scheduled visit and dose level.

A listing of the ECG results of subjects meeting at least one markedly abnormal criteria will also be provided.

12.3.1. ECG Specific Derivations

- Fridericia's Correction (msec)
  - $QTcF$ (msec) $= \frac{QT\ (ms)}{\sqrt[3]{RR\ (ms)/1000}}$

12.4. Vital Signs

The following vital signs will be collected.

- Systolic Blood Pressure (mm Hg)
- Diastolic Blood Pressure (mm Hg)
- Heart Rate (bpm)
- Respiratory Rate (resp/min)
- Temperature (^{0}C)
- O2 oximetry
- Weight (kg)

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- Height (cm)
- BMI (kg/m^2).

On days of infusion, vital signs are to be measured prior to CTX-471, every 15 min (+/- 3 min) during infusion, then hourly (+/- 10 min) during the post-infusion observation period.

The following summaries of vital signs data will be provided:

- Actual and change from baseline results will be summarized by visit and dose level.
- Incidence of markedly abnormal values.

A listing of vital signs data by subject will be provided.

12.4.1. Vital Signs Markedly Abnormal Criteria

Markedly abnormal quantitative Vital Signs measurements will be identified in accordance with the following predefined markedly abnormal criteria:

Variable	Unit	Low	High
SBP	mmHg	≤ 90 mmHg AND change from baseline ≤ -20 mmHg	≥ 180 mmHg AND change from baseline ≥ 20 mmHg
DBP	mmHg	≤ 50 mmHg AND change from ≤ -15 mmHg	≥ 105 mmHg AND change from baseline ≥ 15 mmHg
Heart rate	Bpm	≤ 50 bpm AND change from baseline ≤ -15 bpm	≥ 120 bpm AND change from baseline ≥ 15 bpm
Body temperature	˚C	NA	≥ 38.3 ˚C AND change from baseline ≥ 1.1 ˚C

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Variable	Unit	Low	High
Weight	Kg	percentage change from baseline ≤ -7.0 %	percentage change from baseline ≥ 7.0 %

12.5. Physical Examination

A full physical examination (PE) and symptom-directed PE will be performed at the time points specified in the Schedule of Assessments (Table 1) in the protocol. Physical exams will also be conducted as clinically indicated.

The PE will include an assessment of general appearance, skin, head, neck, throat, lymph nodes, cardiovascular, neurological, thyroid, musculoskeletal/extremities, respiratory, abdomen, height, and weight.

The number and percentage of subjects with the results (normal/abnormal) will be presented by body system, visit and dose level. A by subject listing of these results will be provided.

13. PHARMACOKINETIC ANALYSIS

Analysis of the PK of CTX-471 will be the responsibility of the clinical pharmacokineticist at IQVIA. The PK summaries, data listings, figures, and the statistical analysis of the PK parameter and concentration data will be the responsibility of the biostatistician at IQVIA.

Quantitative variables will be summarized using descriptive statistics, including n, mean, standard deviation (SD), CV%, median, minimum, maximum, and in addition for PK parameters, geometric mean (Geo mean), and geometric CV% (GCV%). For t_{max}, only n, median, minimum, and maximum will be provided.

Pharmacokinetic parameters will be rounded for reporting purposes both in the summary tables and by-subject listings. For the calculation of descriptive statistics and the statistical analysis, unrounded values will be used. All data will be reported and analyzed with the same precision as the source data regardless of how many significant figures or decimals the data carry. For most derived PK parameters, 3 significant digits will be used as the standard rounding procedure, with the following exceptions:

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- Parameters directly derived from source data (e.g., C_{max}) will be reported and analyzed with the same precision as the source data.

- Parameters derived from actual elapsed sample collection times (e.g., t_{max}) will be reported in hours with 2 decimal places.

- Apparent terminal rate constant (λz) will be reported with 4 decimal places.

Reporting of mean (arithmetic and geometric), SD, minimum, median, maximum, and bounds of all CIs will follow the rounding convention of the individual PK data and, in inferential analysis tables, mean ratios and associated CIs for treatment comparisons will be reported as percentages (%) to 2 decimal places. Coefficient of variation will always be reported to 1 decimal place.

Extra measurements (such as unscheduled or repeat assessments) will not be included in the descriptive statistics but will be included in subject listings. Pharmacokinetic summaries will be presented for all subjects in the PK population. Data from subjects excluded from an analysis population will be included in the data listings, but not in the summaries.

In general, serum PK data (concentrations and parameters) will be presented by study arm, CTX-471 dose group and study week/day and nominal time as applicable. For the monotherapy study arm, Part 1 and Part 2 will be combined for all presentations while for the combination study arm, Part1 and Part 2 will be presented separately.

In the case of a major protocol deviation or event, affected PK data collected will be excluded from the summaries and statistical analyses, but will be reported in the PK listings.

13.1. Serum Concentrations

Concentrations of CTX-471 in serum will be summarized descriptively by study arm, part (combination arm only), dose and study week/day and nominal time as applicable.

Any serum CTX-471 concentrations or summary statistics below the limit of quantification will be represented as “BLQ” in tables and listings. If the calculated mean concentration is below the limit of quantitation (BLQ), the mean shall be reported as BLQ and the SD, CV%, Geo mean, and GCV% shall be reported as ND (not determined). Minimum, median, and maximum may be reported and, if any are BLQ, they shall be reported as such and indicated as BLQ.

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Graphical displays of individual subject and mean serum CTX-471 concentrations will be presented by study arm, part (combination arm only), dose and study week/day and nominal time as applicable on both linear and semi-logarithmic scales by time point including pre-dose. CTX-471 trough concentrations will be summarized in tabular and graphical presentations. Listings of PK blood sample collection times as well as derived sampling time deviations will be provided.

13.2. Serum Pharmacokinetic Parameters

For the calculation of single-dose serum PK parameters, predose samples that are BLQ or missing will be assigned a numerical value of zero. Any anomalous concentration values observed at predose on Week 1, Day 1 will be identified in the study report and used for the computation of PK parameters. If the anomalous concentration is greater than 5% of C_{max}, the PK parameters for the given subject will be calculated and reported in the listing and will be evaluated on a case-by-case basis whether exclusion from statistical summaries and analyses is warranted. For the calculation of multiple-dose serum PK parameters on Week 9, Day 1, predose samples that are BLQ will be assigned a numerical value of zero and missing predose samples will be set to missing for analysis.

Any other BLQ concentrations will be assigned a value of zero if they precede quantifiable samples in the initial portion of the profile. A BLQ value that occurs between quantifiable data points, especially prior to C_{max}, will be evaluated to determine if an assigned concentration of zero makes sense, or if exclusion of the data is warranted. Following C_{max}, BLQ values embedded between 2 quantifiable data points will be treated as missing when calculating PK parameters. If a BLQ value occurs at the end of the collection interval (after the last quantifiable concentration), it will be set to zero. If consecutive BLQ concentrations are followed by quantifiable concentrations in the terminal portion of the concentration curve, these quantified values will be excluded from the PK analysis by setting them to missing, unless otherwise warranted by the concentration-time profile. A minimum of 3 quantifiable post-dose serum concentrations is required for the calculation of serum PK parameters.

If missing, Phoenix® WinNonlin® does not estimate a concentration at the end of infusion (C_{eof}). In subjects where C_{eof} is missing or not collected, C_{eof} will be estimated using the Phoenix® WinNonlin® IV bolus model in order to more accurately compute AUC. The original concentration-time data will be augmented by inserting the estimated C_{eof} (C0 from the IV bolus model) concentration. The inserted C_{eof} value will be identified in the analysis file so that the value is clearly distinguished from the source bioanalytical data, and it will not be included in any

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concentration summaries.

For Part 1 of both study arms, the following single-dose serum PK parameters (Week 1 through Week 3) will be estimated by noncompartmental methods for CTX-471 using actual elapsed time from start of infusion:

C_{max}	Maximum observed serum concentration
t_{max}	Time of maximum observed serum concentration
AUC_{0-24}	Area under the serum concentration-time curve from time zero to 24 hours, calculated by linear up log down trapezoidal summation.
AUC_{0-336}	Area under the serum concentration-time curve from time zero to 336 hours, calculated by linear up log down trapezoidal summation. (Note: if majority of subjects have concentrations <LLOQ before 336 hours, AUC_{0-last} will be reported rather than $AUC_{0-336.}$
AUC_{0-inf}	Area under the serum concentration-time curve from time zero extrapolated to infinity, calculated by linear up log down trapezoidal summation.
$t_{1/2}$	Terminal elimination half-life
λ_z	Elimination rate constant (1/h), determined by linear regression of the terminal points of the log-linear concentration-time curve.
CL	Systemic clearance (L/h), determined by Dose/AUC_{0-inf}
V_z	Volume of distribution (L), determined as Dose/ (λ_z* AUC_{0-inf})

In addition, the following single-dose serum PK parameters will be calculated for diagnostic purposes and listed only:

$t_{½}$, Interval	The time interval (h) of the log-linear regression to determine $t_{½}$.
$t_{½}$, N	Number of data points included in the log-linear regression analysis.

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Rsq (adj)	Coefficient of determination (goodness of fit statistic for calculation of λ_z). If value is less than 0.800, then $t_{½}$ and λ_z will be listed but not included in summary presentations or statistical analyses.
$\%AUC_{ex}$	The percentage of $AUC_{0\text{-}inf}$ obtained by extrapolation, will be calculated as $[(C_{last}/\lambda_z)/AUC_{0\text{-}inf}\times 100]$. If the $\%AUC_{ex}$ is greater than 20.0%, values for $AUC_{0\text{-}inf}$, CL, and V_z will be listed but excluded from summary presentations and analyses.

Also, for Part 1 of the monotherapy arm of the study, the following multiple-dose serum PK parameters on Week 9, Day 1 will be estimated by noncompartmental methods for CTX-471 using actual elapsed time from start of infusion:

$C_{max,ss}$	Maximum concentration in serum (ng/mL) during the dosing interval, obtained directly from the observed concentration versus time data.
$t_{max,ss}$	Time of maximum concentration (h) during the dosing interval, obtained directly from the observed concentration versus time data.
$AUC_{0\text{-}24,ss}$	Area under the concentration-time curve in serum from time zero to 24 hours following multiple dosing (ng·h/mL), calculated by linear up log down trapezoidal summation.
RC_{max}	Accumulation ratio based on C_{max}, determined as $C_{max,ss}$ (Week 9, Day 1)/ C_{max} (Week 1, Day 1)
RAUC	Accumulation ratio based on AUC, determined as $AUC_{0\text{-}24,ss}$ (Week 9, Day 1)/ $AUC_{0\text{-}24}$ (Week 1, Day 1)

Scatter plots of individual and geometric mean single-dose $AUC_{0\text{-}24}$, $AUC_{0\text{-}336}$, and C_{max} and multiple dose $AUC_{0\text{-}24,ss}$ and $C_{max,ss}$ versus dose will be presented. Additional graphical presentations of PK data may be added at the discretion of the PK scientist if further illustration of the PK results is deemed appropriate.

The dose proportionality of the log-transformed PK parameters [single-dose (both study arms): AUC0-336, AUC0-24, and Cmax; multiple-dose (monotherapy arm only): AUC0-24,ss, and Cmax,ss], over the administered dose range will be investigated as exploratory analysis using the

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following power model $PK\ Parameter = \alpha . Dose^{\beta}$, with the log transformation yielding the simple linear regression model as below:

Log (PK Parameter) = a + b * Log (Dose)

where 'a' is the intercept and 'b' is the slope.

The power model parameters (slope and intercept) along with the corresponding 90% CIs will be estimated using least-squares regression or an equivalent method. For a given parameter, a minimum of 3 dose levels with a minimum of 3 values per dose level must be available for that dose level to be included in the dose proportionality analysis.

As the study sample size was not statistically powered to perform these statistical assessments, the analyses performed are purely exploratory and no meaningful inferences or conclusions can be drawn from the results of the analyses.

13.1. Immunogenecity

A listing will be provided of all available immunogenicity data. Additionally, a listing of immunogenicity data from those patients with at least 1 positive ADA at any timepoint will be provided by dose level. The summary of frequency of subjects with at least 1 positive ADA assessment, and frequency of subjects who develop ADA after a negative baseline assessment will be provided by dose level.

14. EFFICACY OUTCOMES

All efficacy analyses will be based on the Response Evaluation Analysis Set for Monotherapy Arm 1, unless otherwise specified. Efficacy analysis for Combination Arm 2 will be based on All-Treated Analysis Set. Percent change from baseline in sum of target lesions will be summarized.

Response will be assessed according to RECIST 1.1 (see Appendix 4 in protocol) and will be reported with response category (CR, PR, SD, or PD) counts. For each scheduled efficacy assessment visit, the number and percentage of responses will be tabulated by category for each cohort (and dose level).

For each patient, the ORR (Overall Response Rate) is defined via the best overall response across all efficacy assessments. For each dose level and each cohort, the ORR will be summarized by response

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category determined by the Investigator. The Clopper-Pearson 95% confidence interval will also be included in the summaries for cohorts (and dose levels) in the dose expansion phase.

Time to event efficacy endpoints will be analyzed using Kaplan-Meier (KM) methods:

- DOR (Duration of Response) will be calculated for those patients with a CR, or PR from the time of first response (of CR or PR) to date of PD or death due to any cause(or censoring), whichever occurs first.

Table 1. Censoring Rule for DOR and PFS

Situation	Date of Event or Censoring	Outcome
Subjects with inadequate baseline disease assessment	Date of randomization	Censored
Subjects with no post-baseline assessments and no death reported	Date of randomization	Censored
Subjects last known 1) to be alive, 2) not to have started new (non-protocol) anti-cancer treatment and 3) to be progression-free, and who have a baseline and at least one post-baseline assessment	Date of last measurable radiological assessment	Censored
Subjects last known 1) to be alive, 2) to have started new (non-protocol) anti-cancer treatment and 3) to be progression-free, and who have a baseline and at least one post-baseline assessment	Date of the last objective disease assessment documenting no progression prior to the start of the new treatment	Censored
No post baseline response assessment but death reported following randomization	Date of death	Event
Subjects who progressed after the first dose treatment	Date of the assessment reporting progression	Event

- Progression-Free Survival (PFS) will be assessed from time of first treatment to PD (or censoring) as determined by the Investigator, or death. Censoring rule is the same as DOR censoring rule as in table 1.

- Overall Survival (OS) will be assessed from time of first CTX-471 and/or pembrolizumab treatment to end of study (or censoring). In the absence of confirmation of death, survival time will be censored at the last date the subject is known to be alive.

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KM plots will be provided as appropriate for relevant endpoints.

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REFERENCES

APPENDIX 1. PARTIAL DATE CONVENTIONS

Imputed dates will NOT be presented in the listings.

Algorithm for Treatment Emergence of Adverse Events:

START DATE	STOP DATE	ACTION
Known	NA	If start date < study med start date or start date > date of Safety Follow-Up Visit after the last dose, then not TEAE If start date >= study med start date and start date <= date of Safety Follow-Up Visit after the last dose, then TEAE
Partial, but known components show that it cannot be on or after study med start date	NA	Not TEAE
Partial, could be on or after study med start date	Known	Impute start date as earliest possible date, (i.e. first day of month if day unknown or 1st January if day

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START DATE	STOP DATE	ACTION
		and month are unknown), except if only day is missing and month and year of start date are the same as for study med start date or if day and month are missing and year of start date is the same as for study med start date. In the later cases, the study med start date will be used for the imputation. If stop date < study med start date or start date > date of Safety Follow-Up Visit after the last dose, then not TEAE If stop date >= study med start date, then TEAE
	Partial	Impute stop date as latest possible date (i.e. last day of month if day unknown or 31st December if day and month are unknown), if not resulting in a date later than the date of subject's death. In the later case the date of death will be used for imputation, then: If stop date < study med start date, then not TEAE

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START DATE	STOP DATE	ACTION
		If stop date >= study med start date, then TEAE
	Missing	Assumed TEAE
Missing	Known	If stop date < study med start date, then not TEAE If stop date >= study med start date, then TEAE
	Partial	Impute stop date as latest possible date (i.e. last day of month if day unknown or 31st December if day and month are unknown), if not resulting in a date later than the date of subject's death. In the later case the date of death will be used for imputation. then: If stop date < study med start date, then not TEAE If stop date >= study med start date, then TEAE
	Missing	Assumed TEAE

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Algorithm for Prior / Concomitant Medications:

START DATE	STOP DATE	ACTION
Known	Known	If stop date < study med start date, assign as prior If stop date >= study med start date and start date <= date of Safety Follow-Up Visit after the last dose, assign as concomitant If start date > date of Safety Follow-Up Visit after the last dose, assign as post study
	Partial	Impute stop date as latest possible date (i.e. last day of month if day unknown or 31st December if day and month are unknown), if not resulting in a date later than the date of subject's death. In the latter case the date of death will be used for imputation, then: If stop date < study med start date, assign as prior If stop date >= study med start date and start date <= date of Safety Follow-Up Visit after the last dose, assign as concomitant If start date > date of Safety Follow-Up Visit after the last dose, assign as post treatment

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START DATE	STOP DATE	ACTION
	Missing	If stop date is missing could never be assumed a prior medication If start date <= date of Safety Follow-Up Visit after the last dose, assign as concomitant If start date > date of Safety Follow-Up Visit after the last dose, assign as post treatment
Partial	Known	Impute start date as earliest possible date (i.e. first day of month if day unknown or 1st January if day and month are unknown), then: If stop date < study med start date, assign as prior If stop date >= study med start date and start date <= date of Safety Follow-Up Visit after the last dose, assign as concomitant If stop date >= study med start date and start date > date of Safety Follow-Up Visit after the last dose, assign as post treatment

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START DATE	STOP DATE	ACTION
	Partial	Impute start date as earliest possible date (i.e. first day of month if day unknown or 1st January if day and month are unknown). Impute stop date as latest possible date (i.e. last day of month if day unknown or 31st December if day and month are unknown), if not resulting in a date later than the date of subject's death. In the latter case the date of death will be used for imputation. Then: If stop date < study med start date, assign as prior If stop date >= study med start date and start date <= date of Safety Follow-Up Visit after the last dose, assign as concomitant If stop date >= study med start date and start date > date of Safety Follow-Up Visit after the last dose, assign as post treatment
	Missing	Impute start date as earliest possible date (i.e. first day of month if day unknown or 1st January if day and month are unknown), then: If stop date is missing could never be assumed a prior medication If start date <= date of Safety Follow-Up Visit after the last dose, assign as concomitant If start date > date of Safety Follow-Up Visit after the last dose, assign as post treatment

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START DATE	STOP DATE	ACTION
Missing	Known	If stop date < study med start date, assign as prior If stop date >= study med start date, assign as concomitant Cannot be assigned as 'post treatment'
	Partial	Impute stop date as latest possible date (i.e. last day of month if day unknown or 31st December if day and month are unknown), then: If stop date < study med start date, assign as prior If stop date >= study med start date, assign as concomitant Cannot be assigned as 'post treatment'
	Missing	Assign as concomitant

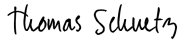
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Signatures: 3
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Thomas Schuetz thomas.schuetz@compasstherapeutics.com CEO Security Level: Email, Account Authentication (Required)	 Signature Adoption: Pre-selected Style Signature ID: EC0BF01E-C831-4C0C-A51B-EFA6AA178EE4 Using IP Address: 38.140.59.197 With Signing Authentication via Docusign password With Signing Reasons (on each tab): I approve this document	Sent: 3/24/2025 8:55:13 AM Viewed: 3/24/2025 9:00:20 AM Signed: 3/24/2025 9:01:08 AM
Electronic Record and Signature Disclosure: Accepted: 10/17/2022 9:13:55 AM ID: 9d424de5-acaf-4f1d-9558-a8fbac1853ee		
Melissa Hays melissa.hays@quintiles.com Security Level: Email, Account Authentication (Required)	 Signature Adoption: Pre-selected Style Signature ID: 58A8D649-97D3-4F58-A784-23233C9317C0 Using IP Address: 162.44.245.32 With Signing Authentication via Docusign password With Signing Reasons (on each tab): I approve this document	Sent: 3/24/2025 9:01:12 AM Resent: 3/24/2025 9:12:48 AM Viewed: 3/24/2025 9:14:19 AM Signed: 3/24/2025 12:30:31 PM
Electronic Record and Signature Disclosure: Accepted: 3/24/2025 9:14:19 AM ID: bbb73567-497e-4f78-aea9-8c61ecb876ae		

Signer Events	Signature	Timestamp
Hal Galbraith hal.galbraith@quintiles.com Security Level: Email, Account Authentication (Required)	 Signature Adoption: Pre-selected Style Signature ID: 9114476D-D4B3-451B-BCCB-878189B8925E Using IP Address: 162.44.245.32 With Signing Authentication via Docusign password With Signing Reasons (on each tab): I approve this document	Sent: 3/24/2025 12:30:34 PM Viewed: 3/24/2025 12:46:08 PM Signed: 3/24/2025 12:46:53 PM
Electronic Record and Signature Disclosure: Accepted: 3/24/2025 12:46:08 PM ID: 681cb08b-ae1b-47a1-87e7-2c1afa6db7e3		

In Person Signer Events	Signature	Timestamp

Editor Delivery Events	Status	Timestamp

Agent Delivery Events	Status	Timestamp

Intermediary Delivery Events	Status	Timestamp

Certified Delivery Events	Status	Timestamp

Carbon Copy Events	Status	Timestamp

Witness Events	Signature	Timestamp

Notary Events	Signature	Timestamp

Envelope Summary Events	Status	Timestamps
Envelope Sent	Hashed/Encrypted	3/24/2025 8:55:13 AM
Envelope Updated	Security Checked	3/24/2025 9:12:48 AM
Envelope Updated	Security Checked	3/24/2025 11:47:00 AM
Certified Delivered	Security Checked	3/24/2025 12:46:08 PM
Signing Complete	Security Checked	3/24/2025 12:46:53 PM
Completed	Security Checked	3/24/2025 12:46:53 PM

Payment Events	Status	Timestamps

Electronic Record and Signature Disclosure

ELECTRONIC RECORD AND SIGNATURE DISCLOSURE

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