STATISTICAL ANALYSIS PLAN

PART A

DOSE ESCALATION (MONOTHERAPY)

Study: ONC001

Product: UCB6114

A PHASE 1/2 OPEN-LABEL, MULTICENTER STUDY TO ASSESS THE SAFETY, PHARMACOKINETICS, AND ANTITUMOR ACTIVITY OF UCB6114 ADMINISTERED INTRAVENOUSLY TO PARTICIPANTS WITH ADVANCED SOLID TUMORS

SAP/Amendment Number	Date
Amendment 4 Final Version 0.1	12 July 2023

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LIST OF ABBREVIATIONS

AE	adverse event
AESI	adverse event of special interest
ADA	anti-drug (UCB6114) antibody
ADaM	Analysis Data Model
ALP	alkaline phosphatase
ALQ	above limit of quantification
ALT	alanine aminotransferase
AST	aspartate aminotransferase
BLQ	below limit of quantification
BMI	body mass index
BOR	best overall response
CA	cancer
CDISC	Clinical Data Interchange Standards Consortium
CDMS	clinical data management system
cGremlin-1	circulating gremlin-1
CI	confidence interval
COVID-19	coronavirus disease 2019
CPPC	CDMS postproduction change
CR	complete response
CSR	clinical study report
ctDNA	circulating tumor deoxyribonucleic acid
CTMS	Clinical trial management system
CV	coefficient of variation
DCR	disease control rate
DEM	data evaluation meeting
DES	DLT evaluable set
DLT	dose limiting toxicity
DOR	duration of response
ECG	electrocardiogram
ECOG	Eastern Cooperative Oncology Group
eCRF	electronic case report form
EMA	European Medicines Agency
ES	enrolled set
EudraCT	European Union Drug Regulating Authorities Clinical Trials
FAP	fibroblast activation protein
FDA	Food and Drug Administration
geoCV	geometric coefficient of variation
geoMean	geometric mean
H & E	hematoxylin & eosin
hh:mm	hours:minutes
HLT	high level term
ICH	International Council for Harmonization
IHC	immunohistochemistry
IM	invasive margin

iv	intravenous
IPD	important protocol deviations
LLOQ	lower limit of quantification
LLT	low level term
LVEF	left ventricular ejection fraction
MedDRA	Medical Dictionary for Regulatory Activities
n	number of study participants
NCA	noncompartmental analysis
NCI CTCAE	National Cancer Institute Common Terminology Criteria for AEs
Nest	not estimable
ORR	objective tumor response rate
OS	overall survival
PCS	potentially clinically significant
PD	pharmacodynamic(s)
PDILI	potential drug-induced liver injury
PDS	pharmacodynamic set
PK	pharmacokinetic(s)
PKS	pharmacokinetic set
PFS	progression-free survival
PPS	per-protocol set
PR	partial response
PT	preferred term
PTEN	phosphatase and tensin homolog
Q2W	every 2 weeks
QTcF	QT interval corrected for heart rate using Fridericia's formula
RECIST	Response Evaluation Criteria in Solid Tumors
RP2D-M	recommended Phase 2 dose – monotherapy
SAE	serious adverse event
SAP	statistical analysis plan
SD	stable disease
SFU	safety follow-up
SI	International System of Units
SMAD4	mothers against decapentaplegic homolog 4
SMC	Safety Monitoring Committee
SOC	system organ class
SoC	standard of care
SS	safety analysis set
TEAE	treatment-emergent adverse event
TEMA	treatment-emergent markedly abnormal
TFL	Table, Figure and Listing
TNM	TNM Classification of Malignant Tumors
TPS	tumor proportion score
UK	United Kingdom
ULN	upper limit of normal
US	United States
WHODD	World Health Organization Drug Dictionary

1 INTRODUCTION

The purpose of this statistical analysis plan (SAP) is to provide all information that is necessary to perform the required statistical analysis of the dose escalation (monotherapy) module (Part A) of study ONC001. It also describes the summary tables, figures and listings (TFLs) to be generated for Part A according to:

Protocol amendment 5, dated 14 January 2022;

Electronic case report form (eCRF) (Clinical Data Management System [CDMS] postproduction change [CPPC] #14, version 23.0, dated 14 April 2023);

UCB's standards for TFL shells version 2023Q1;

Part A TFL shells, final version 2.3, dated 13 March 2023;

UCB's Derivation of Efficacy Endpoints document, version 0.6, dated 21 January 2022.

Unless specified in the sections below, Part A of the study will be analyzed as described in the most recent version of the protocol. If a future protocol amendment necessitates a substantial change to the analysis of the Part A study data, this SAP will be amended accordingly. In addition, if the methodology for the analysis of key study endpoints must be modified or updated prior to the final database lock for Part A of this study, a SAP amendment will be required. Protocol amendments that do not affect the statistical analysis will not necessitate an amendment to the SAP. If, after database lock, additional analyses are required to supplement the planned analyses described in this SAP, these changes will be described in the clinical study report (CSR) together with the associated rationale.

Note that there may be a number of data cut-offs defined prior to the final database lock for Part A due to the regulatory safety reporting requirements for this study.

The content of this SAP is compatible with the International Council for Harmonization (ICH)/Food and Drug Administration (FDA) E9 Guidance (ICH-E9) (Phillips et al, 2003).

UCB is the Sponsor and ICON PLC is the contract research organization (CRO) for this study.

2 PROTOCOL SUMMARY

2.1 Study objectives

2.1.1 Primary objective

The primary objective of Part A (dose escalation module) of this study is to characterize the safety profile of UCB6114 administered as monotherapy in study participants with recurrent or metastatic advanced solid tumors.

2.1.2 Secondary objective

The secondary objective of Part A of this study is to characterize the pharmacokinetics (PK) of UCB6114 administered as monotherapy in study participants with recurrent or metastatic advanced solid tumors.

2.1.3 Exploratory/Tertiary objectives

The exploratory/tertiary objectives of Part A of this study are:

- To document any antitumor activity observed with UCB6114 according to relevant Response Evaluation Criteria in Solid Tumors (RECIST) criteria;
- To explore pharmacodynamics (PD) biomarkers of UCB6114;
- To evaluate the incidence, emergence, and impact of anti-drug (UCB6114) antibody (ADA) activity.

2.2 Study endpoints

2.2.1 Safety endpoints

2.2.1.1 Primary safety endpoints

The primary safety endpoints for Part A of this study are the incidence and severity of treatment-emergent adverse events (TEAEs) (including serious adverse events [SAEs]) from the first dose of study treatment on Day 1 of Cycle 1 to the Safety Follow-up (SFU) visit, and the incidence of dose limiting toxicities (DLTs) from the first dose of study treatment on Day 1 of Cycle 1 to the end of the DLT Observation Period (Day 28 of Cycle 1).

2.2.1.2 Other safety endpoints

The following other safety data will be assessed during Part A of the study to further support the characterization of the safety profile of UCB6114 administered as monotherapy:

- Clinical laboratory data (hematology, serum chemistry, coagulation and urinalysis);
- Vital signs (systolic and diastolic blood pressure, pulse rate, respiratory rate, and body temperature);
- 12-lead electrocardiogram (ECG);
- Echocardiogram (left ventricular ejection fraction [LVEF]);
- Eastern Cooperative Oncology Group (ECOG) performance status;
- Physical examination.

2.2.2 Pharmacokinetic and pharmacodynamic endpoints

2.2.2.1 Secondary pharmacokinetic endpoint

The secondary PK endpoint in Part A is the UCB6114 concentration by scheduled assessment for each UCB6114 dose.

2.2.2.2 Exploratory pharmacokinetic endpoints

The following key and other PK parameters will be calculated, where possible:

[redacted]

2.2.2.3 Exploratory pharmacodynamic endpoints

The following PD endpoints will be assessed in Part A and reported separately outside of the CSR:

- Change in transcriptional and protein marker levels in blood and tumor tissue (where biopsies are available) by scheduled assessment and dose level;
- Change in circulating tumor deoxyribonucleic acid (ctDNA) levels in blood by scheduled assessment and dose level.

2.2.2.4 Exploratory immunogenicity endpoints

Immunogenicity in Part A will be explored using ADA sample status and participant classification, and changes in titer over time. Potential relationships between ADA and PK, PD, anti-tumor activity and safety may also be explored but these analyses will be reported separately outside of the CSR.

2.2.3 Efficacy endpoints

2.2.3.1 Exploratory antitumor activity endpoints

Antitumor activity in Part A will be explored using the following endpoints:

- Objective tumor response rate (ORR);
- Disease control rate (DCR);
- Duration of antitumor response (DOR);
- Progression-free survival (PFS);
- Overall survival (OS).

2.2.3.2 Other exploratory efficacy endpoint

To further explore efficacy in Part A of the study, changes from Baseline in the ECOG performance status scale will be assessed.

2.3 Study design and conduct

Study ONC001 is a multicenter, nonrandomized, open-label, Phase 1/2 study evaluating the safety, PK, efficacy (as assessed by antitumor activity), PD, biomarkers, and immunogenicity (ADA activity) of intravenous (iv) UCB6114 as monotherapy and in combination with selected standard of care (SoC) regimens in study participants with advanced solid tumors.

The study has a modular design including up to 3 dose escalation modules (Parts A, B, and C), 1 dose adaptation module (Part A1), and up to 4 dose expansion modules (Parts D, E, F, and G). Depending on emerging data, not all modules may open. This SAP is focused only on the first dose escalation module of the study (Part A).

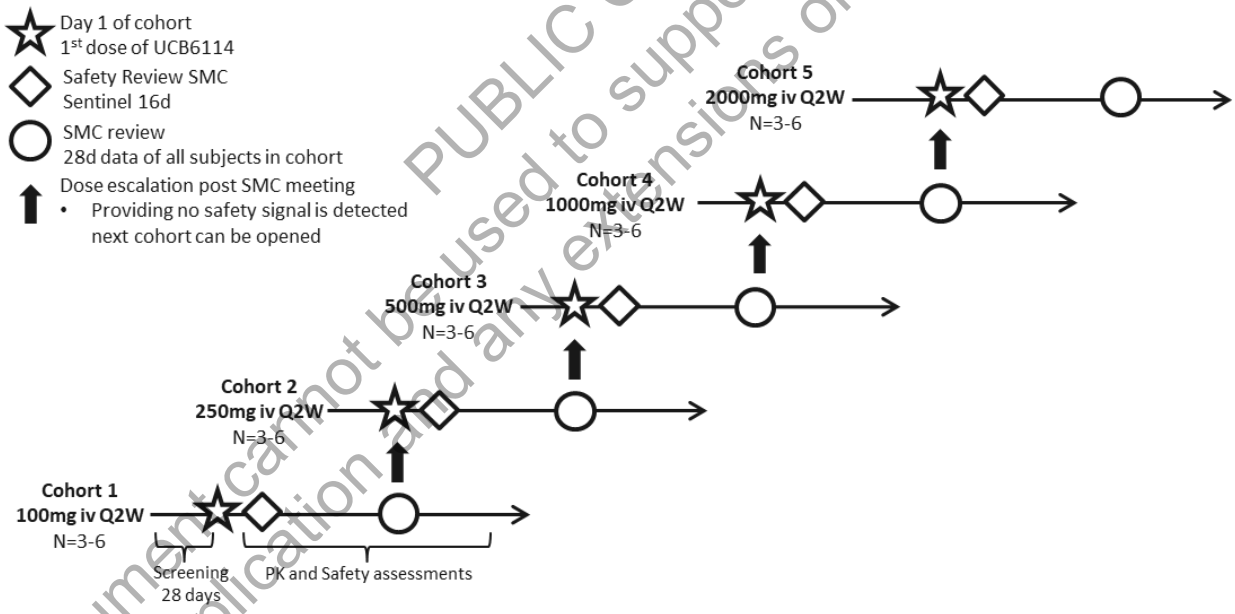
Part A consists of a Screening Period (28 days), a Treatment Period (consisting of 28-day cycles), an SFU visit (approximately 30 days after the last dose of study treatment) and a Final Visit (approximately 3 months after the last dose of study treatment). The planned duration of study treatment is 2 cycles. Participants may remain on study for additional cycles if they are receiving therapeutic benefit or until they fulfill one of the criteria for study discontinuation.

During the Treatment Period, UCB6114 will be administered as monotherapy by iv infusion on Days 1 and 15 of each cycle, until the occurrence of progressive disease, unacceptable toxicity, or participant withdrawal. Dosing levels will be escalated (or de-escalated) stepwise in successive cohorts of 3 to 6 evaluable participants using a modified rolling-6 design until the recommended Phase 2 dose for monotherapy (RP2D-M) is determined. The rolling-6 design is an algorithm-based design in which a total of 6 participants can be enrolled at the same dose level. The modification requires that each dose level incorporates a sentinel participant. The enrollment of a sentinel participant in each cohort has been included as an additional risk mitigation measure to monitor infusion-related reactions and other early onset study treatment-related AEs. Each sentinel participant will be assessed for at least 24 hours following the second treatment administration on Day 15 of Cycle 1 before further participants within the dose cohort can be enrolled. In the absence of a DLT observation in the sentinel participant after 16 days, the remaining 5 participants may be enrolled concurrently (see Figure 4-1 in the protocol). Should the sentinel participant experience a DLT, then participants 2 and 3 will be enrolled and observed for 16 days (see Figure 4-2 in the protocol).

Part A of the study is planned to be conducted at 6 study sites in the United Kingdom (UK).

A schematic diagram of Part A of the study is provided in Figure 2-1.

Figure 2-1: Study Schematic for Part A



d=days; iv=intravenous; Q2W=every 2 weeks; SMC=safety monitoring committee.

Dose escalation to the next cohort can be performed when 3/3, 4/4, 5/5, 5/6, or 6/6 participants have completed the DLT observation period and have not experienced a DLT. When a single DLT has been observed in a given dose level, participants will be included at the same dose level, up to a total of 6 participants. De-escalation will occur when 2 or more participants experience a DLT at a dose level and when less than 6 participants have been evaluated at the dose level below the level at which 2 DLTs occurred. Dose escalation requires at least 3

participants to be treated and observed for at least 28 days after the first dose (assuming UCB6114 is dosed every 2 weeks [Q2W]). If dosing is less frequent (due to missed or delayed doses or due to a planned change in schedule), at least 3 participants should be treated and observed for a minimum of 28 days (i.e. 1 cycle), before dose escalation is considered.

The final decision for dose escalation in the next cohort will be made by a Safety Monitoring Committee (SMC) taking into account all the observed safety and tolerability data, and the PK and PD and ADA profile (where available) of the dose in that cohort and also of the doses in all previous cohorts, as relevant (for further details on the SMC, please refer to Section 4.5).

Eligible participants who withdraw from the study before receiving study treatment will be replaced. Participants who fail to receive the second planned dose of UCB6114 within 7 days of the scheduled dose administration day, during the DLT observation period, for reasons not related to toxicity, will also be replaced for the purpose of DLT assessment. Safety data for replaced participants will be included in the data listings and in the summary tables, as applicable.

2.4 Determination of sample size

No formal statistical sample size calculation has been performed for the dose escalation modules in study ONC001.

The number of participants likely to be enrolled in Part A depends on how many dose levels are needed to define the RP2D-M. Each cohort will be conducted with a minimum of 3 treated participants using a modified rolling-6 design for the evaluation of DLTs. The number of participants assumes all (5) planned dose levels are evaluated in Part A, and that 1 dose level is added due to emerging data, to establish the RP2D-M. It also assumes that, on average, there will be an additional participant required due to drop-out/replacement and/or the modified rolling-6 design.

Based on these assumptions, Part A will include up to 42 eligible participants.

3 DATA ANALYSIS CONSIDERATIONS

3.1 General presentation of summaries and analyses

All TFLs will be produced by ICON PLC using SAS® Version 9.4 or higher (SAS Institute, Cary, North Carolina, USA). ICON PLC will also produce the analysis datasets which will adhere to the Clinical Data Interchange Standards Consortium (CDISC) guidance documents for Analysis Data Model (ADaM) and follow the UCB interpretation. General statistical and reporting conventions will follow the current UCB Global Conventions Document Version 1.1.

Data will be summarized by cohort/dose level (treatment group), visit and timepoint, as applicable. All relevant reported and derived data will be listed and will be presented by treatment group, study participant and visit, as applicable.

Categorical variables will be summarized using frequency counts and percentages. Unless otherwise stated, the denominator for the percentages will be based on the number of participants in the respective analysis set, treatment group, visit and timepoint (as applicable) with non-missing data.

When reporting frequency counts and percentages, the following rules apply:

- For categories where all participants fulfill certain criteria, the percentage value will be displayed as 100;
- For categories where zero participants fulfill certain criteria, there will be no percentage displayed;
- All other percentage displays will use 1 decimal place.

Summary statistics will be presented for continuous variables including number of participants (n), arithmetic mean, standard deviation, median, minimum and maximum. 95% confidence intervals (CIs) for the arithmetic mean may also be included depending on the variable and where stated in the SAP. Geometric mean (geoMean), geometric coefficient of variation (geoCV) and 95% confidence interval (CI) for the geoMean will also be presented in the summaries of UCB6114 concentration data. In all relevant outputs the 95% confidence limits will be restricted to the possible values that the variable can take.

When reporting descriptive statistics for data other than UCB6114 concentration data, the following rules will apply:

- n will be an integer;
- Mean (arithmetic and geometric), standard deviation, median and quartiles will use 1 decimal place more, or 1 significant figure more – depending on the reporting format of the original data – than the original data. Original data may be data as reported directly onto the eCRF or summary data based on data reported onto the eCRF (e.g. mean of triplicates or percentage change from Baseline);
- Confidence intervals will be presented to the same number of decimal places as the value around which the confidence interval is constructed;
- Minimum and maximum will be reported using the same number of decimal places or significant figures as the original value;
- A minimum of 3 values are required to calculate summary statistics. If only 2 values are available, then these should be presented as the minimum and maximum with other summary statistics reported as missing ("- ");
- If no participants have data at a given timepoint, then only n=0 will be presented;
- Percentage change from Baseline values will be calculated and displayed to 1 decimal place in the listings. In the summaries, where applicable, the arithmetic mean, standard deviation and median percentage change from Baseline values will be presented to 2 decimal places and the minimum and maximum values presented to 1 decimal place.

When reporting individual UCB6114 concentration data in listings and figures, and presenting summary statistics in tables, the following rules will apply:

- UCB6114 concentration data should be reported in the listings to the same level of precision as received from the bioanalytical laboratory;
- Missing data should be reported as 'NV' (no value) in the listings;
- Concentrations below the lower limit of quantification (LLOQ) should be reported as BLQ (below the limit of quantification) in the listings;

- BLQ values prior to C_{max} should be set to 0 for purposes of plotting a figure (to capture lag-time);
- Actual sampling times will be used in the spaghetti plots of individual PK concentrations over time, and nominal sampling times will be used in the summaries of geoMean concentrations over time;
- UCB6114 concentration data should be plotted on both linear and semi-logarithmic scales;
- To calculate summary statistics, BLQ values should be set to half the LLOQ value and missing values should be excluded;
- When the total number of BLQ and missing values exceeds one third of the total then only minimum and maximum should be reported for this timepoint. Other summary statistics should be reported as missing ("-"). The minimum should be reported as BLQ;
- When the mean value includes one or more replaced BLQ values then a footnote should be included to say "contains one or more BLQ values replaced by half the LLOQ value";
- A minimum of 3 values are required to calculate summary statistics. If only 2 values are available, then these should be presented as the minimum and maximum with other summary statistics reported as missing ("- ");
- If no participants have data at a given timepoint, then only n=0 will be presented;
- Summary statistics for UCB6114 concentration data will be reported to the same level of precision as the individual data for the minimum and maximum, and to 1 additional decimal place or 1 additional significant figure – depending on the reporting format of the original data with a maximum of 3 significant figures - for the mean (arithmetic and geometric), median and standard deviation. The 95% CI for the geoMean will use the same number of decimal places or significant figures as the geoMean. It will be left blank if the geoCV is 0;
- Geometric coefficient of variation will be reported as a percentage to 1 decimal place. The geoCV will be calculated using the following formula where SD is the standard deviation from the log-transformed data:

$$GeoCV\ (\%) = sqrt[(exp\ (SD^2) - 1)] \times 100$$

When reporting PK parameters in listings and figures, and presenting summary statistics in tables, the following rules will apply:

[redacted]

3.2 General study level definitions

3.2.1 Relative day and time

For each participant, the relative day of an event or assessment will be derived using the date of their first dose of study treatment as reference.

Relative days for an event or assessment occurring before the date of first dose are calculated as follows:

Relative Day = Event/Assessment Date - Date of First Dose

The relative day for an event or assessment occurring on the date of first dose is 1. The relative day for an event or assessment occurring on or after the first dose to the date of the last dose of study treatment will be calculated as follows:

Relative Day = (Event/Assessment Date - Date of First Dose) + 1

For events or assessments occurring after the date of the last dose, relative day will be prefixed with '+' in the data listings and will be calculated as follows:

Relative Day = Event/Assessment Date – Date of Last Dose

There is no relative Day 0. Relative day will not be calculated in cases where dates are partial and should be presented as "--" in the relevant data listing.

Relative time of TEAEs recorded on the day of infusion (Days 1 and 15 of each cycle) will be derived in minutes as follows using the infusion start time as reference:

Relative Time of TEAE = Onset Time of TEAE – Start Time of Infusion

Relative times of PK and PD sampling will be derived in hours using the end of infusion times on the day of dosing as reference, i.e. on Days 1 and 15 of each cycle:

Relative Sampling Time = Sampling Time – End of Infusion Time

3.2.2 Study periods

Part A of the study will consist of the following study periods:

- Screening Period – up to 28 days;

- Treatment Period – Successive 28-day cycles of study treatment (Q2W dosing on Day 1 and Day 15 of each cycle continuing until disease progression, unmanageable toxicity, or participant withdrawal). Within the first cycle of the Treatment Period, a 28-day DLT Observation Period is defined to determine safety events for dose escalation decisions. If a study participant is a sentinel participant in the cohort, there is an initial DLT Observation Period of 16 days, after which the cohort may be opened for further enrollment;
- Safety Follow-up Period – up to 30 days after the last dose of study treatment.

There will be a further extended follow-up period, up to 3 months after the last dose of study treatment, at which time the Final Visit will be performed.

For each participant, the end of the Treatment Period is defined by the date of their last dose of study treatment.

The end of Part A of the study is defined by the date of the Final Visit for the last participant (3 months after the last participant's last dose of study treatment), or the date of the SFU visit, if they discontinue prior to attending the Final Visit, or their last contact date if they discontinue early from the study without attending the SFU visit.

3.2.3 Visits

Unless otherwise specified, in the TFLs, visits will be labelled as follows (as applicable):

Screening
Baseline
Cycle 1, Day X
Cycle 2, Day X
Cycle 3, Day X
Cycle 4, Day X
Cycle X, Day X
Etc.
SFU
Final Visit

3.3 Definition of Baseline values

Baseline in Part A will be the last available value prior to the first dose of study treatment. Both scheduled and unscheduled values, as well as any repeated values, should be used when defining Baseline.

Measurement-specific Baseline definitions are presented in Table 3-1.

Table 3-1: Definition of Baseline

Measurement	Definition of Baseline
Echocardiogram (LVEF) PD biomarkers from tissue (optional tumor biopsies) Tumor assessments (antitumor activity)	Screening value
12-lead ECG Physical examination and weight Vital signs Clinical laboratory data ECOG performance status	Predose value obtained on Cycle 1, Day 1, or, if missing, Screening value
Serum and urinary markers of bone turnover Circulating Gremlin-1 (cGremlin-1) Immunogenicity (ADA)	Predose sample value obtained on Cycle 1, Day 1

ADA=anti-drug (UCB6114) antibody; ECG=electrocardiogram; ECOG=Eastern Cooperative Oncology Group; LVEF=left ventricular ejection fraction; PD=pharmacodynamic.

3.4 Protocol deviations

Per ICH definition, important protocol deviations (IPDs) are a subset of protocol deviations that may significantly impact the completeness, accuracy, and/or reliability of the study data or that may significantly affect a participant's rights, safety, or well-being. The criteria for identifying potentially important protocol deviations will be defined within the IPD specifications document.

For Part A of this study, IPDs will be categorized as follows:

- Inclusion/exclusion criteria deviations
- Incorrect treatment or dose administered
- Procedural non-compliance
- Prohibited concomitant medication use (see Section 6.5.2 of the protocol)
- Withdrawal criteria deviation

All protocol deviations will be reviewed as part of the ongoing data cleaning process and Data Evaluation Meetings (DEMs), and decisions made on whether they should be considered important or not, and whether they warrant a participant's exclusion from an analysis set, or partial exclusion from an analysis due to being an IPD (e.g. prohibited concomitant medication use). Multiple DEMs will be scheduled prior to the final database lock for Part A, in line with regulatory safety reporting requirements, with the final one held after all data have been verified/coded/entered into the database.

More specifically, participants who have IPDs relating to dosing of study treatment (e.g. interrupted, discontinued and missed infusion, incomplete/incorrect dose administered, additional dose received, or infusions administered outside of the defined visit window) will be

reviewed at the DEM for potential exclusion of UCB6114 concentration data from the by-visit summaries at an individual visit or from the visit at which the dosing deviation was observed onwards.

Any protocol deviations that are considered related to coronavirus disease 2019 (COVID-19) will be reviewed on an ongoing basis in case they collectively or individually give reason to consider a protocol amendment (e.g. study design changes or changes to primary analysis methods etc.). To facilitate this ongoing review, protocol deviations will be categorized as 'related to COVID-19' within the Clinical Trial Management System (CTMS). The COVID-19-related IPDs will then be listed separately for review and discussion at the DEMs.

3.5 Analysis sets

3.5.1 Enrolled Set (ES)

The Enrolled Set (ES) consists of all study participants who sign the Informed Consent Form.

This analysis set includes screening failures and will be used for the summary of disposition of study participants and for selected data listings (which will include all available data for the screening failures).

3.5.2 Safety Analysis Set (SS)

The Safety Analysis Set (SS) consists of all study participants who receive at least 1 full or partial dose of study treatment.

This analysis set will be used for the reporting of demographic, Baseline, safety and immunogenicity data. All summaries of the exploratory antitumor activity endpoints will be repeated for the SS as a sensitivity analysis.

3.5.3 Per-protocol Set (PPS)

The Per-protocol Set (PPS) consists of all study participants in the SS who do not have IPDs that may substantially affect antitumor activity. Potential exclusions will be reviewed at the DEMs and a final determination of the composition of this analysis set will be made prior to the final database lock for Part A.

The PPS will be the primary analysis set for the analysis of the exploratory antitumor activity endpoints.

3.5.4 Pharmacokinetic Set (PKS)

The Pharmacokinetic Set (PKS) consists of all study participants in the SS who have at least 1 evaluable postdose UCB6114 concentration sample (i.e. a sample which is above the lower limit of quantitation and for which the date and time of the sample and prior date and time of dosing are known). Additional participants or specific samples may be excluded from the PKS at the discretion of the Advanced Modeling and Simulation scientist/Quantitative Clinical Pharmacologist at UCB.

Pharmacokinetic analysis will be performed for the PKS.

3.5.5 Anti-drug Antibody Set (ADAS)

The Anti-drug Antibody Set (ADAS) consists of all study participants in the SS who have at least 1 evaluable ADA assessment.

Immunogenicity analyses will be performed for the ADAS.

3.5.6 Pharmacodynamic Set (PDS)

The Pharmacodynamic Set (PDS) consists of all study participants in the SS who have at least 1 evaluable PD assessment (where appropriate, the sample should be above the lower limit of quantitation and the date and time of the sample should be known).

Pharmacodynamic analysis will be performed for the PDS.

3.5.7 DLT Evaluable Set (DES)

The DLT Evaluable Set (DES) will include all study participants who, during the 28-day DLT Observation Period, receive the planned dose of UCB6114.

The DES will be used only for evaluations by the SMC for dose-escalation decisions.

3.6 Treatment assignment and treatment groups

In Part A, it is planned that study participants will be dosed Q2W at ascending dose levels in 5 cohorts. Treatment groups will be defined by each cohort/dose level and will be presented in ascending order and labelled in the TFLs as illustrated in Table 3-2.

Table 3-2: Treatment Group Labels

Cohort/Dose Level	Planned Treatment Group Label
Cohort 1 (Dose Level 1)	UCB6114 100mg
Cohort 2 (Dose Level 2)	UCB6114 250mg
Cohort 3 (Dose Level 3)	UCB6114 500mg
Cohort 4 (Dose Level 4)	UCB6114 1000mg
Cohort 5 (Dose Level 5)	UCB6114 2000mg

Note that the actual dose levels and treatment group labels may change depending on whether dose escalation criteria are met. Further, additional cohorts/dose levels may be included based on emerging data.

Cohort/dose level will be referred to as ‘treatment group’ from this point onwards in the SAP and in the TFLs.

3.7 Center pooling strategy

Each study site will contribute to the summaries of data from Part A according to the number of evaluable participants recruited; no separate summaries for each site will be presented.

3.8 Coding dictionaries

Adverse events and medical history will be coded by UCB, using the latest available version of the Medical Dictionary for Regulatory Activities (MedDRA®) (Version 25.1 or higher). The National Cancer Institute Common Terminology Criteria for AEs (Version 5.0) (NCI CTCAE) dictionary will also be used by the investigator to assign CTCAE severity grades to each AE and will be merged with the clinical database to define a CTCAE code and term to be used in the summaries of TEAEs by maximum CTCAE severity grade.

Medications (including prior anti-cancer systemic therapies) will be coded according to the World Health Organization Drug Dictionary (WHODD) (Version SEP/2020). Medical procedures will not be coded.

The versions of the coding dictionaries used will be displayed in the relevant TFLs.

3.9 Changes to protocol-defined analyses

The following changes to the protocol have been incorporated into the SAP:

- Other safety data have not been defined as safety endpoints in the protocol, e.g. clinical laboratory data, vital signs, ECG, echocardiogram, ECOG performance status and physical examination. These have been listed in Section 2.2.1 of the SAP as 'other safety endpoints' to support the characterization of the safety profile of UCB6114 and to provide supporting evidence of any measurements that are deemed abnormal and clinically significant and reported as an AE.
- ECOG performance status is defined as an efficacy assessment in Section 8.6.2 of the protocol, however, it will also be assessed from a safety perspective in Part A. The SAP therefore includes ECOG performance status as both a safety endpoint (Section 2.2.1) and an exploratory efficacy endpoint (changes from Baseline during Part A in Section 2.2.3).
- Section 9.4.2.1 of the protocol does not explicitly define the analysis set to be used for the antitumor activity endpoints but defines the denominator as the number of treated participants, which matches the protocol definition for the SS in Section 9.1 of the protocol. The SAP has been written to clarify that the PPS will be the primary analysis set for the analysis of the antitumor activity endpoints (Section 3.5.3) and that the SS will be used for the sensitivity analysis (Section 3.5.2).

4 STATISTICAL/ANALYTICAL ISSUES

4.1 Adjustments for covariates

Not applicable.

4.2 Handling of dropouts or missing data

There will be no imputation of missing data unless otherwise stated in the sections below.

4.2.1 Pharmacokinetics and pharmacodynamics

The reporting and handling of missing values and values that are BLQ in the TFLs is described in Section 3.1. Zero values will be assumed at the predose timepoint on Day 1 of Cycle 1.

4.2.2 Safety laboratory data

The rules for handling values that are BLQ in the safety laboratory data will be the same as those described for PK data in Section 3.1. Any values above the limit of quantification (ALQ) will be assigned as the value of upper limit of quantification.

4.2.3 Dates and times

Partial dates may be imputed for the following reasons:

- Classification of adverse events (AEs) as treatment-emergent;
- Classification of medications recorded on the concomitant medications log as prior or concomitant;
- Calculation of time since initial diagnosis, time since completion of most recent line of prior anti-cancer systemic therapy and time since progression/relapse on most recent line of prior anti-cancer systemic therapy.

Imputed dates will not be shown in the listings; all dates will be displayed as reported in the database.

The following rules will be applied for partial onset/start dates:

- If only the month and year are specified and the month and year of the first dose of study treatment is not the same as the month and year of the start date then the 1st of the month will be used, or the date of the Screening visit if this is later (if the latter imputation results in an end date that is earlier than the start date, then the 1st of the month will be used);
- If only the month and year are specified and the month and year of the first dose of study treatment is the same as the month and year of the start date, then the date of the first dose of study treatment will be used. If this results in an imputed start date that is after the specified end date, then the 1st of the month will be used, or the date of Screening if this is later (if the latter imputation results in an end date that is earlier than the start date, then the 1st of the month will be used). If the imputed date is the same date as the date of the first dose of study treatment then, for AEs, the event will be regarded as treatment-emergent. For medications, the medication will be classified as concomitant;
- If only the year is specified, and the year of the first dose of study treatment is not the same as the year of the start date then January 01 will be used;
- If only the year is specified, and the year of the first dose of study treatment is the same as the year of the start date, then the date of the first dose of study treatment will be used. If this results in an imputed start date that is after the specified end date, then January 01, or the date of the Screening visit if this is later will be used (if the latter imputation results in an end date that is earlier than the start date, then January 01 will be used). If the imputed date is the date of the first dose of study treatment then, for AEs, the event will

be regarded as treatment-emergent. For medications, the medication will be classified as concomitant.

- If the onset/start date is completely missing then the onset/start date will be imputed to the date of first dose of study treatment and therefore, for AEs, the event will be regarded as treatment-emergent and, for medications, the medication will be classified as concomitant.

The following rules will be applied to partial end/stop dates:

- If only the month and year are specified, then the last day of the month will be used;
- If only the year is specified, then December 31 of the known year will be used;
- If the stop date is completely unknown, the stop date will not be imputed.

Note that the start date or stop date of a prior medication (partial or otherwise) should not be imputed past the Screening date - 1.

In addition to onset and stop dates, the onset and end times of AEs occurring on the day of infusion will be collected on the eCRF. Onset and end times may also be recorded for other AEs that do not occur on the same day as the infusion. The duration of AEs with onset and end times will be calculated in days and hours:minutes (hh:mm) as:

Duration of AE = End Date and Time – Onset date and time

In cases where only the onset and stop dates are recorded for an AE, the duration of an AE will be calculated in days as:

Duration of AE = (Stop Date – Onset Date) + 1

Note that for participants who have an AE which starts and stops on the same day, but with only a start time or only a stop time recorded, it will be assumed that their AE started from 00:00 (if no start time is recorded) and ended at 23:59 (if no stop time is recorded) on that day.

If the date of a participant's initial diagnosis is incomplete, it will be imputed to the most recent feasible date for the calculation of time since initial diagnosis as follows:

- If only the day is missing, it will be imputed to the last day of the known month;
- If the day and month are missing, it will be imputed to December 31 in the known year;
- If the date of initial diagnosis is completely missing, then time since initial diagnosis will not be calculated.

The above date imputation rules will be applied to partially missing stop dates of a participant's last prior anti-cancer systemic therapy as well as partially and completely missing dates of progression/relapse on last prior anti-cancer systemic therapy.

In cases where the stop date of a participant's last prior anti-cancer systemic therapy and/or a participant's date of progression on last line of prior anti-cancer systemic therapy is completely missing, the participant's Screening date - 1 will be used in the calculation of the time since completion of most recent line of prior anti-cancer systemic therapy and the time since progression/relapse on most recent line of prior anti-cancer systemic therapy, respectively.

Note that partial dates will not be imputed as a participant's first dose of study treatment in the calculation of time since initial diagnosis, time since completion of most recent line of prior anti-cancer systemic therapy and time since progression/relapse on most recent line of prior anti-cancer systemic therapy.

4.2.4 Impact of COVID-19

The FDA and European Medicines Agency (EMA) have provided guidance (see references listed in Section 12) to help assure the safety of all trial participants, maintaining compliance with good clinical practice (GCP), and minimizing risks to trial integrity during the COVID-19 pandemic. At the time of writing this SAP, the impact of the pandemic is still evolving and regulators continue to clarify their position, and how to handle missing or delayed assessments resulting from the pandemic is part of the risk assessment of the impact of COVID-19 on trial integrity. For this purpose, the impact at a visit level will be assessed by data collected on a specific COVID-19 impact eCRF form and protocol deviations related to COVID-19. Due to the timing of the start-up of recruitment of participants into this study, the consequences for Part A are not expected to be significant and, as a result, no details on strategies for handling missing data are included in this version of the SAP. However, should the ongoing review of COVID-19-related protocol deviations suggest that the impact is more significant than expected, e.g. in the case of a second wave, the SAP may be updated to include further details of handling missing data and/or any sensitivity analyses required. Note that there are no guidelines regarding how much missing data is too much, and there is no proportion of missing data under which valid results and preservation of study power can be guaranteed. In accordance with the EMA guidance, an independent Data Monitoring Committee (DMC) may be convened to make an assessment regarding the scientific integrity of the study.

4.3 Handling of repeated and unscheduled measurements

All repeated and unscheduled measurements will be presented in the data listings, where applicable. Repeated measurements are defined as more than 1 measurement at the same timepoint. For example, the same laboratory parameters assessed twice using the same batch of blood samples due to issues with the first assessment. The following general rules will apply to all repeated and unscheduled measurements:

- Unscheduled and repeated measurements prior to the first dose of study treatment will be used in the determination of Baseline and hence in the calculation of summary statistics at Baseline;
- Unscheduled and repeated measurements performed after the first dose of study treatment will not be included in the calculation of change from Baseline, summary measures such as minimum, maximum, average and last post-Baseline value calculated for the summaries of laboratory data (see Section 8.3), vital signs (see Section 8.4.1) and 12-lead ECG (see Section 8.4.2), or summary statistics, i.e. only the scheduled measurements will be used and summarized. Similarly, only scheduled visits will be used in the summaries of shifts from Baseline to the worst post-Baseline CTCAE severity grade for laboratory data (see Section 8.3).
- For the summaries of the investigator's overall tumor response assessment, protocol-defined windows will be applied to all post-Baseline tumor assessments (scheduled or

unscheduled, but excluding tumor assessments performed at the SFU visit), as detailed in Section 10.1.2. Those tumor assessments which fall outside of the window will be considered as unscheduled assessments and not included in the summaries.

- Best overall response, DOR and PFS derivations will use data from all scheduled and unscheduled tumor assessments.
- All data from unscheduled visits will, however, be included on the relevant data listings.

4.4 Handling of measurements obtained for early withdrawals

Participants who withdraw early from the study for any reason will be asked to return to the clinic to complete the SFU visit. The SFU procedures performed at this visit are as shown in the Schedule of Activities in the protocol and will be summarized together with all other SFU visit data in the tables.

4.5 Interim analyses and data monitoring

No formal interim analyses are planned during Part A of this study.

The SMC will be established which will comprise key UCB personnel and investigators from participating sites. The SMC will meet after the sentinel participant in each cohort has completed the 16-day DLT Observation Period during Cycle 1 of study treatment. They will review primarily all safety data for this participant, including the individual DLTs (as applicable). Once the last participant in a given cohort has completed the required 28-day DLT Observation Period, a further SMC meeting will be convened to review all safety data (including DLTs) and any available PK, ADA and PD data from all participants in that cohort (and participants in previous cohorts, if applicable). PK, ADA and PD data reported at each SMC will always be based on the previous cohort due to availability and processing time required for these data. The SMC will then decide whether to halt dose escalation, further expand the cohort to gain additional safety data, or determine the next dose level to be evaluated. Further details are included in the SMC Charter and specifications for the data presentations will be included in a separate output specifications document for the SMC reviews.

All data presented to the SMC will be cumulative in order that the members can review and discuss the data in its totality at the end of all completed cohorts, i.e. all safety information beyond Cycle 1 for all previous cohorts will be presented cumulatively for review during each subsequent SMC meeting.

In addition to the planned SMC data review meetings, UCB and the SMC will have the ability to hold/request *ad hoc* meetings should they be deemed necessary (e.g. if safety concerns arise during Part A of the study and/or during other ongoing nonclinical and clinical studies).

4.6 Multicenter studies

Part A of this study is planned to be conducted at 6 study sites in the UK. With the exception of participant disposition, no summaries will be presented by site.

4.7 Multiple comparisons/multiplicity

Not applicable.

4.8 Use of an efficacy subset of participants

The PPS will be used as the primary analysis set for the summaries of the exploratory antitumor activity endpoints in Part A.

4.9 Active-control studies intended to show equivalence

Not applicable.

4.10 Examination of subgroups

Not applicable.

5 STUDY POPULATION CHARACTERISTICS

5.1 Study participant disposition

The number of study participants who were screened for Part A of this study, the number and percentage of screen failures and the primary reasons for screen failure will be summarized for the ES. A listing of participants who did not meet the eligibility criteria for Part A will also be presented for the ES. In addition, the disposition of study participants screened and who received study treatment will be summarized by site. This table will include, for each site and overall, site number, principal investigator name, the dates of the first participant in and the last participant out, the number of participants screened (ES), the number of screen failures, the number of participants who were treated (SS) and included in the PPS, PKS, ADAS and PDS. Disposition in each analysis set across all study sites will be summarized by treatment group.

The number of study participants who received study treatment and the primary reason for discontinuation of study treatment during Part A will be summarized by treatment group, together with the number and percentage of participants who continued participation in the study after discontinuation of study treatment (at subsequent scheduled visits and/or SFU visit and Final Visit). This summary will be based on the SS.

The number of study participants enrolled into Part A, who were screen failures as well as the number of eligible participants who were assigned to a study cohort but not treated will be presented for the ES. For those participants who did not receive study treatment, the reasons for early discontinuation from the study will be summarized.

Of those participants who received study treatment, the number and percentage of participants who completed the study (i.e. participants who received at least 2 complete cycles of study treatment and attended the SFU visit), who received at least 2 complete cycles of study treatment but who did not attend the SFU visit and who discontinued early from Part A, together with the primary reasons for study discontinuation will be presented for all participants.

The number and percentage of participants who discontinued due to AEs will be summarized separately for all participants, based on the SS. This will be used for European Union Drug Regulating Authorities Clinical Trials (EudraCT) reporting.

Visits impacted by COVID-19 will be listed for the ES. This listing will include, visit, visit date, relative day, impact category (e.g. visit performed out of window, visit performed by telephone, visit not done, missed study drug administration/dispensation, termination of study

participation), relationship to COVID-19 (confirmed COVID-19 infection, suspected COVID-19 infection, general circumstances around COVID-19 or other) and a narrative for the event. The number and percentage of participants with visits impacted by COVID-19 will be presented by treatment group and by impact category. This summary will be presented for the different relationships to COVID-19. The denominator for the percentage calculations will be the number of participants in the SS.

In addition, the following listings will be presented:

- Study participant disposition (ES);
- Study treatment discontinuation (SS);
- Study discontinuation (ES);
- Visit dates (ES);
- Participant analysis sets and exclusions from analysis sets (ES)*.

* DES is not included in this listing as it is only relevant for the SMC, and not required for the reporting of data in the CSR.

The listing of study participant disposition will include the date of informed consent, date and time of first and last dose of study treatment, date of early study discontinuation (if applicable) and primary reason for discontinuation. The listing of study treatment discontinuation will include date and time of first and last dose of study treatment, date of decision to discontinue study treatment and primary reason for discontinuation of study treatment, date of clinical progression (if applicable), number of doses of study treatment received (based on 2 doses per cycle), total dose of study treatment received across all cycles, number of complete cycles of study treatment received, and whether or not the participant had continued participation in the study (at subsequent visits, the SFU visit or the Final Visit).

Note that a participant is deemed to have completed a full cycle of study treatment if they received a dose of study treatment on Days 1 and 15 of the cycle and a decision was not made to discontinue their study treatment up to and including Day 28 relative to Day 1 of the cycle. This will be derived based on a participant's last dose of study treatment and whether or not the participant attended the visit at which they were scheduled to receive their next dose of study treatment. For example, if a participant received study treatment on Day 15 of Cycle 1, they attended the clinic on Day 1 of Cycle 2 for their next dose of study treatment then the participant will be counted as having completed Cycle 1. If the participant did not attend Day 1 of a subsequent cycle, then it is likely that a decision was made to discontinue their treatment and/or the study. Therefore, the date that the decision was made to discontinue study treatment will be used to determine whether the participant completed a cycle of study treatment. If a decision was made to discontinue study treatment on >Day 28 relative to Day 1 of the particular cycle then the participant will be counted as having completed the cycle. For any interim deliveries at a data cut-off, if the participant did not attend Day 1 of their next cycle and there was no decision to discontinue study treatment, then the latest date available for that participant should be used to determine whether they have completed a 28-day cycle.

Whether or not a participant has completed the study is defined as having received at least 2 complete cycles of study treatment and attended the SFU visit. The investigator will record a

study participant's disposition status at study termination according to this definition of a 'completed' participant, however, a study completion flag will also be programmatically derived based on the relevant data on the database and the above rules for defining completion of a full cycle of study treatment.

The listing of study discontinuation will include the primary reason for early study discontinuation, the number of cycles of study treatment received, and the total number of days on study treatment.

The total number of days on study treatment will be calculated as follows:

$$Total\ Number\ of\ Days\ on\ Study\ Treatment = (Date\ of\ Last\ Dose\ Received - Date\ of\ First\ Dose\ Received) + 1$$

5.2 Protocol deviations

Important protocol deviations will be identified and classified by the deviation types defined in the IPD specification document, as per Section 3.4.

A listing of all IPDs identified at the DEM will be presented for all study participants based on the SS and will include the deviation type and description. In addition, a listing of all protocol deviations related to COVID-19 (whether considered important or not) will be presented for the SS. The number and percentage of participants in the SS with IPDs will be summarized by treatment group and for all participants for each deviation type. The number and percentage of participants who were excluded from the PPS will also be presented. The denominator for the percentage calculations will be the number of participants in the SS. A summary will also be presented for all protocol deviations related to COVID-19, all IPDs related to COVID-19 and all IPDs related to COVID-19 leading to exclusion from the PPS.

6 DEMOGRAPHICS AND OTHER BASELINE CHARACTERISTICS

6.1 Demographics

A by-participant listing of demographics will be presented based on the ES. This will include the year of birth, age (as entered by investigator in the eCRF in years), sex, race, ethnicity, height (in cm), weight (in kg) and body mass index (BMI, in kg/m^2). Height will be the measurement obtained at the Screening visit and weight will be the last non-missing value prior to the first dose of study treatment.

The BMI will be derived in the database using the height and weight measurements recorded at the Screening visit and will be automatically reported to 1 decimal place on the eCRF.

All demographic characteristics (except for date of birth) will be summarized by treatment group and for all study participants based on the SS. The summary of age will include descriptive statistics and categorical summaries, the latter based on requirements for EudraCT and clinicaltrials.gov reporting.

For the EudraCT reporting, the categories will include:

- 18 to <65 years;

- 65 to <85 years.

For clinicaltrials.gov reporting, the categories will include:

- ≤18 years;
- 19 to <65 years;
- ≥65 years.

Childbearing potential and method of birth control will be listed for the ES.

6.2 Cancer history

All cancer history data for Part A participants will be listed for the ES. This listing will include date of initial diagnosis, tumor type, TNM Classification of Malignant Tumors (TNM) classifications and stage, Duke's score and Gleason score (if relevant to the tumor type), histological and cytological diagnosis details (as relevant), whether the participant had any metastases and associated anatomical location, and whether the participant had received any prior anti-cancer therapies (including the number of lines of any prior systemic therapies, prior radiation therapies and prior anti-cancer surgeries).

Time since initial diagnosis (calculated in months using date of Screening visit and date of initial diagnosis and multiplying the duration in days by 12/365.25), tumor type, T, N, M classifications and TNM stage, Duke's score, Gleason score, presence of metastases and anatomical location of metastases will be summarized by treatment group and for all study participants based on the SS. In the summaries of categorical variables, percentages will be calculated based on the number of study participants with non-missing data. Further, for the cM0(i+) M classification, Duke's score and Gleason score, the denominator for the percentage calculation will be the number of study participants for which these assessments are applicable (since they only apply to certain tumor types).

6.3 Prior anti-cancer therapy

Details recorded for each line of prior anti-cancer systemic therapy received by a study participant will be listed for the ES. This listing will include the line and type of systemic therapy, intent, drug name and dose, formulation, indication (current/ultimate), start and end dates, number of cycles received and the number of days per cycle, the participant's best response and the date of that best response, reason for discontinuation and whether the participant had disease progression prior to the next line of systemic therapy. If there was progression, then the date of progression will also be listed. In addition, time from completion of the last prior anti-cancer systemic therapy to the start of study treatment, whether the participant had progression after the last line of systemic therapy and, if so, the time from progression to the start of study treatment will be derived and listed.

For those participants in the ES who received prior radiotherapy, the following data will be listed: treatment site, type of radiotherapy, intent, settings (concurrent with other anti-cancer systemic therapy or stand-alone radiation therapy), and, if concurrent radiotherapy, the anti-cancer systemic therapy line that the radiotherapy was given with and the drug name. In addition, the start and stop dates, total cumulative dose (if known), number of fractions (if known), the

participant's best response to radiotherapy and whether the tumor at the treatment site had progressed since radiotherapy will be included in this listing.

A further listing of prior anti-cancer radiotherapy with systemic therapy regimens will be presented for participants in the ES who had concurrent prior systemic therapy and radiotherapy as their prior anti-cancer therapy. This listing will include the relevant data described above together with the participant's best response to that regimen.

Date of surgery/procedure, anatomical location, description of the surgical procedure and whether the tumor was completely removed will be listed for those study participants in the ES who had prior anti-cancer surgeries or procedures.

The following summaries of prior anti-cancer therapy regimens and surgeries will be presented by treatment group and for all participants for the SS:

- Number of prior anti-cancer therapy regimens (0, 1, 2, 3, >3) (including all anti-cancer systemic therapy lines given alone and concurrently with radiotherapy)
- Best response to the most recent prior anti-cancer therapy regimen
- Number of prior anti-cancer systemic therapy + radiotherapy regimens (0, 1, 2, 3, >3)
- Best response to the most recent anti-cancer systemic therapy + radiotherapy regimen
- Reasons for discontinuation of the most recent line[a]
- Time from completion of most recent line[a] to the start of study treatment (<1 month, 1-<3 months, 3-6 months, >6 months)[b]
- For participants that progressed after their most recent line[a], the time from progression to the start of study treatment (<1 month, 1-<3 months, 3-6 months, >6 months)[b]
- Number of prior anti-cancer radiotherapies (including radiotherapies given alone and concurrently with anti-cancer systemic therapy) (0, 1, 2, >2)
- Number of prior anti-cancer surgeries and procedures (0, 1, 2, >2)

[a] Most recent line is the last prior anti-cancer therapy regimen received which may be a prior anti-cancer systemic therapy given alone or concurrently with radiotherapy.
[b] 1 month = 30 days.

Time from completion and time from progression relative to the last line of anti-cancer systemic therapy will also be summarized using frequency counts and percentages as well as summary statistics.

The number and percentage of participants with any prior anti-cancer systemic therapy, and any prior anti-cancer systemic therapy given concurrently with radiotherapy will be summarized for the SS by treatment group and for all participants, and by WHODD Anatomical Main Group [Level 1 term text], Pharmacological Subgroup [Level 3 term text] and PT.

6.4 Cancer status at Screening

The current cancer status of study participants at entry into Part A of this study will be assessed at the Screening visit and listed for the ES. This listing will include tumor type, T, N and M classifications and TNM stage, Duke's score and Gleason score (if relevant to the tumor type),

histological and cytological diagnosis details (as relevant), whether the participant has any metastases and associated anatomical location, whether the tumor is recurrent and whether the participant had relapsed from their last line of anti-cancer therapy.

Tumor type, TNM classifications and stage, Duke's score, Gleason score, presence of metastases and anatomical location of metastases, and time since relapse on last line of therapy (calculated in days using the date of the Screening visit and date of relapse) will be summarized by treatment group and for all study participants based on the SS. In the summaries of categorical variables, percentages will be calculated based on the number of study participants with non-missing data. Further, for the cM0(i+) M classification, Duke's score and Gleason score, the denominator for the percentage calculation will be the number of study participants for which these assessments are applicable (since they only apply to certain tumor types).

6.5 Medical history and concomitant diseases

Medical history will be listed for the ES and summarized by MedDRA system organ class (SOC) and preferred term (PT) by treatment group and for all study participants for the SS. The reported term will be included in the listing. Previous medical history (any previous medical conditions with a stop date prior to the start of study treatment) and ongoing medical history (any ongoing medical conditions with a missing stop date but recorded as ongoing on the eCRF) will be summarized separately. These summaries will include the number and percentage of study participants and will be sorted alphabetically by SOC and by descending incidence of PT within each SOC, based on the incidence in all study participants.

Non-anti-cancer procedure history will be listed for the ES and concomitant medical procedures performed during the study will be listed for the SS.

6.6 Prior and concomitant medications

Prior medications will include any medications that started prior to the date of the first dose of study treatment. This will include medications that started prior to the first dose and continued after.

Concomitant medications will include medications with a start date on or after the first dose of study treatment and prior to the date of the last dose of study treatment + 30 days, and whose stop date is either missing, or on or after the date of the first dose of study treatment. Any medications with a start date prior to the first dose of study treatment and a stop date after, or continued to be ongoing during the study, will also be classified as concomitant medications. Medications with a start date > 30 days after the last dose of study treatment will be considered as post-study medications and will not be included in the summaries of concomitant medication.

Any medication that started prior to, and stopped after the first dose of study treatment, or continued to be ongoing during the study, will be classified as both prior and concomitant.

Any medications with missing start dates will be classified as both prior and concomitant provided that a stop date is not present or a stop date is present and it is prior to the first dose of UCB6114.

Any medications with partially missing dates will be handled as described in Section 4.2.3 to classify them as prior or concomitant.

All medications (prior, concomitant and post-study) will be listed for the ES. Any prohibited concomitant medications, rescue medications or steroid use will be identified via a medical review and flagged in this listing.

Prior and concomitant medications (per the definitions above) will be summarized for the SS by treatment group and by WHODD Anatomical Main Group [Level 1 term text], Pharmacological Subgroup [Level 3 term text] and PT. The reported term will be included in the listing. Separate summaries will be presented for prior medications and concomitant medications. As per the definitions above, prior medications which continued into the Treatment Period will also be classified as concomitant and will be included in both summaries.

All tabulations will be sorted alphabetically by Level 1 term, alphabetical Level 3 term within Level 1 and decreasing frequency of PT in all study participants.

A glossary of all prior and concomitant medications will be presented for the SS including the Anatomical Main Group (Level 1), Pharmacological Subgroup (Level 3), PT and reported term.

7 MEASUREMENTS OF TREATMENT COMPLIANCE

During Part A of this study, administration of study treatment will be performed via iv infusion at the study site under the supervision of the designated site personnel and in compliance with the Guideline for First in Human clinical studies (EMEA/CHMP/SWP/28367/07Rev. 1). Compliance will be monitored at the site through a review of accountability logs which will be used to record study treatment dispensing and return information to ensure that each study participant received the correct dose level.

Any dosing deviations will be reviewed as IPDs at the DEMs and assessed for possible impact on the PPS. If considered important, these deviations will be included in the summary and listing of IPDs.

8 SAFETY ANALYSES

All safety summaries and listings will be presented by treatment group based on the SS, unless otherwise stated.

8.1 Extent of exposure

Details on study treatment administration on Day 1 and Day 15 of each cycle of study treatment will be listed. This listing will be split into two parts. The first part will include the start and stop dates and times of infusion, duration of infusion, infusion rate, whether the infusion was temporarily stopped/interrupted, whether the infusion was permanently discontinued and, if this was the case, whether the interruption or permanent discontinuation was due to an AE or other reason. The second part of this listing will include, for each visit, infusion site, total volume delivered, volume infused, planned total dose and total dose actually administered at infusion. In addition, the percentage of planned dose received, total dose administered across all cycles, the number of complete cycles of study treatment received and the total number of doses of study treatment received will be listed.

The percentage of planned dose received will be calculated for each study participant at each dosing visit within each cycle as follows:

$$Percentage\ of\ Planned\ Dose\ Received = 100 \times \frac{Total\ Dose\ Administered}{Planned\ Total\ Dose}$$

Actual duration of infusion will be calculated in minutes only for those study participants who did not have any temporary interruption(s) of their infusion using the infusion start and stop times and included on this listing. Length of interruption(s) will be calculated for those study participants who had temporary interruption(s) of their infusion.

Extent or duration of exposure will be calculated and summarized. Frequency counts and percentages for the number of complete cycles of study treatment received (1, 2, 3, 4, >4) and summary statistics for the total dose of study treatment received across all cycles, the total number of doses of study treatment received and the duration of exposure to study treatment will be presented.

Duration of exposure will be calculated in days as follows:

$$Duration\ of\ Exposure = (Date\ of\ Last\ Dose - Date\ of\ First\ Dose) + 30$$

Note that 30 days is added to this calculation to account for a participant's continued exposure to UCB6114 following their last dose of study treatment.

Note that a participant is deemed to have completed a full cycle of study treatment if they receive a dose of study treatment on Day 1 and Day 15 of the cycle and a decision was not made to discontinue study treatment up to and including Day 28 relative to Day 1 of a cycle.

8.2 Adverse events

The primary safety endpoints for Part A of this study are the incidence and severity of TEAEs (including SAEs) from the first dose of study treatment on Day 1 of Cycle 1 until the end of the SFU Period (up to 30 days following the last dose of study treatment), and the incidence of DLTs from the first dose of study treatment on Day 1 of Cycle 1 until the end of the DLT Observation Period (Day 28 of Cycle 1).

All AEs in Part A of the study will be coded using MedDRA® and classified as pre-treatment and treatment-emergent relative to the first dose of study treatment. Adverse events with a start date prior to the first dose of study treatment will be defined as pre-treatment AEs. A TEAE is defined as any AE with a start date on or after the first dose of study treatment up until the last dose of study treatment + 30 days. A pre-treatment AE which increases in severity on or after the first dose of study treatment will also be counted as a TEAE. Note that in this case, the pre-existing AE will have a stop date and an outcome of 'worsened' and a new AE (with the same verbatim) will be entered with the same start date and the increased severity recorded on the eCRF. Any AE (including SAEs) with an onset date later than the last dose of study treatment + 30 days will not be considered as treatment-emergent and therefore will not be included in the tabulations of TEAEs. These AEs will be considered as post-study AEs and will be listed only. Where onset dates are missing or partially missing, AEs will be assumed to be treatment-emergent, unless there is clear evidence to suggest that the AE started prior to the first dose of study treatment and it has not increased in severity. Missing or partially missing dates for AEs

will be handled as described in Section 4.2.3. All AEs for a participant will be recorded in the eCRF from the time of informed consent until completion or early discontinuation of Part A of this study. Serious adverse events are to be reported up to 30 days after the Final Visit (i.e. up to 150 days after the last dose of study treatment).

Adverse events will be assigned an NCI CTCAE severity grade (Grade 1/Grade 2/Grade 3/Grade 4/Grade 5), where possible. If a CTCAE toxicity grading is not possible, then the intensity of the AE (mild/moderate/severe) will be recorded on the eCRF. If the AE is not gradable, is serious, and is considered as life threatening, then the intensity for this AE will be missing and one of the reasons for seriousness will be recorded as life threatening.

Adverse events will also be categorized according to their relationship to study treatment (related/not related), and whether the event is a DLT, as judged by the investigator. A DLT is defined as a TEAE related to study treatment that occurs during Cycle 1 and fulfills any of the criteria listed in Section 4.1.1.4 of the protocol. The investigator is expected to record whether an AE is a DLT on the eCRF.

An overview of the number and percentage of participants who experience TEAEs will be presented. This summary will include the number and percentage of participants with any TEAEs, serious TEAEs, related TEAEs, discontinuations from study treatment due to TEAE(s), discontinuations from the study due to TEAE(s), CTCAE Grade ≥ 3 TEAEs, CTCAE Grade ≥3 related TEAEs, DLTs, AEs leading to death and TEAEs leading to death; event counts will also be included against each of these categories.

In addition, the following summaries will be presented by SOC, high level term (HLT) and PT:

- Incidence of TEAEs;
- Incidence of serious TEAEs;
- Incidence of non-serious TEAEs;
- Incidence of TEAEs leading to a temporary interruption and/or reduction in dose of study treatment;
- Incidence of TEAEs leading to discontinuation of study treatment;
- Incidence of TEAEs leading to discontinuation of study;
- Incidence of DLTs;
- Incidence of adverse events of special interest (AESIs) (Hy's Law – see Section 8.2.1 below);
- Incidence of infusion-related reactions (defined as hypersensitivity reactions, anaphylactic reactions and cytokine release syndrome – See Section 8.2.2);
- Incidence of TEAEs by maximum CTCAE severity grade;
- Incidence of TEAEs by maximum relationship;
- Incidence of TEAEs by relationship;
- Incidence of serious TEAEs by relationship;

- Incidence of non-serious TEAEs by relationship;
- Incidence of fatal TEAEs by relationship;
- Incidence and event rate of TEAEs by treatment-emergent ADA positivity.

The following summaries will be presented by SOC and PT for EudraCT reporting:

- Incidence of non-serious TEAEs above the threshold of 5% of participants in any treatment group;
- Incidence of non-serious TEAEs above the threshold of 5% of participants in any treatment group by relationship.

The above summaries of TEAEs will be ordered alphabetically by SOC, alphabetically by HLT within SOC and decreasing incidence of PT events within SOC/HLT in all study participants. For tables including only the number and percentage of participants, summaries will be ordered alphabetically by SOC, alphabetically by HLT within SOC and decreasing incidence of participants with each PT within SOC/HLT in all study participants.

The incidence of TEAEs by maximum CTCAE severity grade will be presented by CTCAE term. CTCAE term will be obtained from the NCI CTCAE Version 5.0 via a mapping of MedDRA lower level terms. This summary will be ordered by decreasing incidence of participants with each CTCAE term in all study participants.

Summary tables will contain frequency counts and percentages, and the number of events, where applicable. A study participant who experiences the same event multiple times will be counted only once in the frequency counts for the PT, but all events will be included.

In the summaries of TEAEs by relationship, participants will be counted in "Not related" and "Related" categories (or "Missing" in the case where an event has a missing relationship). A study participant who experiences the same event multiple times will be included in the most related category for the summaries by maximum relationship.

In the overview summary of TEAEs, participants will be counted as having at least one TEAE with CTCAE severity grade ≥3, and in the summary of TEAEs by maximum CTCAE severity grade, participants will be counted as having at least one TEAE in the following categories: 'Grade 1', 'Grade 2', 'Grade 3', 'Grade 4', 'Grade 3 or 4', 'Grade 5', 'Grade ≥3'. Events for which no CTCAE severity grade is recorded by the investigator but an intensity is recorded instead, the intensity of this event will be assigned to a CTCAE severity grade for the purpose of these summaries, i.e. 'Mild' will be included as 'Grade 1', 'Moderate' will be included as 'Grade 2', 'Severe' will be included as 'Grade 3', 'Life Threatening' will be included as 'Grade 4' and, if the participant dies due to the event, it will be included as 'Grade 5'. The determination of whether the event is life threatening or results in death will be based on the reason for seriousness recorded as life-threatening or death on the eCRF, or on the event having a fatal outcome. Otherwise, if both the CTCAE severity grade and intensity is missing then the CTCAE severity grade in these summaries will be missing. A study participant who experiences the same event multiple times will be included in the highest severity grade category in the summary of TEAEs by maximum CTCAE severity grade.

A glossary of all AEs will be presented including the MedDRA SOC, HLT, PT, reported term and low level term (LLT).

A listing of all AEs will be presented by study participant for the ES. The listing will include the onset date and stop date of the event (including relative days) and also the onset times and stop times of events where available. Period of onset of AEs will also be presented on this listing.

Period of onset of AEs will be defined as follows for the purpose of the listing:

- If the AE has an onset date prior to the date of the Screening visit, then Period=Pre-study;
- If the AE has an onset date on or after the date of the Screening visit and has an onset date and time prior to the start time of study treatment (i.e. prior to the start time of the infusion on Day 1 of Cycle 1) then Period=Screening;
- If the AE has an onset date and time on or after the start time of study treatment (i.e. on or after the start time of the infusion on Day 1 of Cycle 1) and up to the date and time of the start of Cycle 2 (i.e. prior to the start time of the infusion on Day 1 of Cycle 2) then Period=Cycle 1;
- If the AE has an onset date and time on or after the start time of study treatment (i.e. on or after the start time of the infusion on Day 1 of Cycle 2) and up to the date and time of the start of Cycle 3 (i.e. prior to the start time of the infusion on Day 1 of Cycle 3) then Period=Cycle 2;
- Same as above for subsequent cycles (Cycle 3 etc.);
- If the AE has an onset date after the last dose of study treatment up to and including 30 days after the last dose of study treatment, then Period=SFU;
- If the event has an onset date after the 30-day period following the last dose of study treatment, then Period=Post-study.

The listing of all AEs will also include the AE duration (derived in days, hh:mm for AEs with onset and stop times recorded and derived in days for all other AEs with only onset dates and times recorded, days/time since infusion (time if an onset time is recorded, days otherwise), seriousness and reason for seriousness, CTCAE severity grade, intensity (where a CTCAE severity grade is not recorded), pattern of event, relationship to study treatment and action taken with study treatment (including other action taken), whether an autopsy was performed and cause of death. In addition, the listing will flag AEs that led to discontinuation from the study, TEAEs, AESIs, SAEs, infusion-related reactions, and DLTs. Whether an AE is related to a concomitant medication (which will include the COVID-19 vaccination), the names of any co-suspect medications and the outcome (sequelae, date and time) of the AE will also be listed.

Separate listings of all SAEs, TEAEs leading to discontinuation of study treatment and TEAEs leading to discontinuation of the study will also be presented.

All deaths that occur on study (defined as during study treatment or within 30 days of study treatment discontinuation) will be listed separately. This listing will include the primary cause of death and the number of days between the date of the last dose of study treatment and death.

8.2.1 Adverse events of special interest

An AESI is any AE that a regulatory authority has mandated be reported on an expedited basis, regardless of the seriousness, expectedness, or relatedness of the AE to the administration of a UCB product/compound.

For ONC001, potential Hy's Law is used to identify AESIs and is defined using the laboratory data and the following potential drug-induced liver injury (PDILI) criteria:

- ≥3x upper limit of normal (ULN) alanine aminotransferase (ALT) *or* aspartate aminotransferase (AST) with coexisting ≥2xULN total bilirubin in the absence of ≥2xULN alkaline phosphatase (ALP), with no alternative explanation for the biochemical abnormality;
- Study participants who have evidence of liver metastases may be considered to have an alternate etiology for the described laboratory abnormalities.

All AESIs will be flagged on the listing of AEs.

8.2.2 Infusion-related reactions

Infusion-related reactions are defined as hypersensitivity reactions, anaphylactic reactions and cytokine release syndrome with onset within 24 hours after the start of the UCB6114 infusion.

All potential infusion-related reactions will be identified programmatically and will then undergo medical review for confirmation based on participant characteristics and other signs and symptoms. The final assessment from the medical review will be used in the programming to ensure that all infusion-related reactions are flagged correctly in the listings and included in the relevant summaries.

Hypersensitivity reactions will be programmatically identified as any TEAE with a PT from both a narrow and broad scope search of category A terms of the 'Hypersensitivity' Standardized MedDRA Query (SMQ).

Anaphylactic reactions will be programmatically identified using an algorithmic approach based on the 'Anaphylactic Reaction' SMQ. Further details on this algorithm are given in Section 13.1. Note that if the MedDRA version is increased from 25.1 during the study, any changes to the terms included in the 'Anaphylactic Reaction' SMQ should be applied.

Cytokine release syndrome will be programmatically identified as any TEAE with a PT of 'Cytokine release syndrome' from the broad scope search of category A terms of the 'Hypersensitivity' SMQ. Since this disorder is characterized by fever, headache, tachycardia, hypotension, rash, tachypnoea and/or hypoxia, a further medical review of participants with these events occurring within 24 hours after infusion of study treatment will be performed to confirm any further infusion-related reactions.

Note that any other AEs (i.e. not identified as infusion-related reactions using the rules above) which result in a temporary interruption or permanent discontinuation of an infusion will not be considered as an infusion-related reaction.

8.3 Clinical laboratory evaluations

The use of multiple local laboratories (1 per site in the UK) in Part A of this study has meant that results have been recorded in different units and with reference to different normal ranges, and

further, for some laboratory tests, different normal ranges have been applied to males and females and age groups. As a first step to ensure comparability of laboratory results, results and normal ranges will be converted to the same International System of Units (SI) units using UCB's standard conversion factors. This will be programmed at the Study Data Tabulation Model (SDTM) level. Note though that the simple conversion to SI units does not represent a full homogenization of results from different local laboratories using different methods. To ensure full comparability, the observed laboratory results will be normalized to a unique set of standard reference ranges using the location-scale normalization formula (Chuang-Stein, 1992) which normalizes all results in relation to a standard set of reference ranges (for hematology, clinical chemistry and coagulation parameters):

$$s = L_S + (x - L_X)\frac{(U_S - L_S)}{(U_X - L_X)}$$

where:

s = normalized observed value
x = original observed value in SI units
L_S = Lower Limit of the reference range chosen to be the standard reference range
U_S = Upper Limit of the reference range chosen to be the standard reference range
L_X = Lower Limit of the reference range associated with the original observed value in SI units (local laboratory reference range)
U_X = Upper Limit of the reference range associated with the original observed value in SI units (local laboratory reference range)

This transformation preserves the distance of the original laboratory result from the lower limit of normal as a multiple of the specified standard reference range.

Note that the choice of the standard reference range is arbitrary, however, the most recent reference ranges used by ICON Central Laboratories (including the age and gender specific reference ranges for parameters, where available) will be used to normalize the results in this study.

Normalization of the laboratory results will be performed in the ADaM programming by ICON.

All laboratory data (hematology, serum chemistry and coagulation) and changes from Baseline for numeric variables will be listed for participants who have at least one value outside of the reference range. All urinalysis data will be listed for all participants. Data will be listed by study participant, laboratory panel, laboratory parameter and visit within each treatment group. Any laboratory measurements that are BLQ or ALQ will be handled as described in Section 4.2.2. For the relevant numeric laboratory parameters, the reference ranges supplied by the local analytical laboratory will be used to flag values outside the reference range as low or high in this listing. For the parameters for which the local laboratory cannot supply the reference ranges, the reference ranges provided by ICON Central Laboratories will be used instead. A listing of all laboratory results outside of the reference range will also be presented. The reference ranges will also be reported in the listings.

In addition, for the relevant laboratory tests, CTCAE severity grades (Grade 1, Grade 2, Grade 3, Grade 4) will be applied (where possible) in the ADaM programming according to NCI CTCAE Version 5.0, and these grades will also be listed for the relevant laboratory parameters. Note that Grade 0 will be applied in cases where a result is normal for the relevant laboratory test and Grade 5 is not applicable in the grading of laboratory data.

Observed values and changes from Baseline in the hematology, serum chemistry and coagulation parameters presented below in Table 8-1 will be summarized at each visit. In addition, for each of these parameters, the Baseline value, the minimum, maximum, average and last post-Baseline value for each participant will be summarized by cycle using descriptive statistics. These post-Baseline summary measures will be calculated based on all available scheduled postdose values within each cycle, i.e. from Day 8 of the current cycle up to Day 1 (predose) of the subsequent cycle. The last value in a cycle will be the predose value of the subsequent cycle where a subsequent cycle occurs, otherwise it will be the value at the last scheduled assessment. If only 1 value is available then the average will not be calculated and presented but this value will be used for the minimum, maximum and last post-Baseline summary measures. These summary measures for each cycle will also be listed.

For those laboratory parameters with a CTCAE toxicity assigned, shift tables for the change from Baseline in CTCAE severity grade at each visit and to the worst post-Baseline CTCAE severity grade during the Treatment Period will be presented.

Table 8-1: Clinical Laboratory Assessments

Laboratory Assessment	Laboratory Parameters
Hematology	Platelet Count, RBC Count, Hemoglobin, Hematocrit, RBC Indices (MCV, MCH, MCHC), WBC Count with Differential (Absolute Neutrophils, Absolute Lymphocytes, Absolute Monocytes, Absolute Eosinophils, Absolute Basophils)
Clinical Chemistry	ALT, AST, ALP (including liver-specific ALP for use in assessing participants with bone metastases at Screening), Bicarbonate, Sodium, Potassium, Magnesium, Chloride, Calcium, Total Bilirubin, BUN or Urea, Serum Creatinine, Glucose (non-fasted), Phosphorus or Phosphate, Albumin, Total Protein, Uric Acid, Amylase, GGT, Cholesterol, Creatine Kinase, CRP, LDH, Lipase, Triglycerides
Coagulation	aPTT and either PT or INR
Routine Urinalysis	Specific Gravity, pH, Glucose, Protein, Blood, Ketones, Bilirubin, Urobilinogen, Nitrite, Leukocyte Esterase by Dipstick Microscopic Examination (if blood or protein is abnormal, including crystals)
Screening Tests	Pregnancy tests: FSH and estradiol (for women of non-childbearing potential only); serum or urine hCG pregnancy test (for women of childbearing potential) Bone turnover markers: blood BAP, blood CTx, urinary NTx and urinary CTxII Tumor markers: PSA, CA125, CA19-9

ALP=alkaline phosphatase; ALT=alanine aminotransferase; aPPT=activated partial thromboplastin time; AST=aspartate aminotransferase; BAP=bone alkaline phosphatase; BUN=blood urea nitrogen; CA=cancer antigen; CRP=C-reactive protein; CTx=C-terminal telopeptide; FSH=follicle-stimulating hormone; GGT=gamma glutamyl transferase; hCG=human chorionic gonadotropin; INR=international normalized ratio; LDH=lactate dehydrogenase; MCH=mean corpuscular hemoglobin; MCHC=mean corpuscular hemoglobin concentration; MCV=mean corpuscular volume; NTx=N-terminal telopeptide; PSA=prostate specific antigen; PT=prothrombin time; RBC=red blood cell; WBC=white blood cell.

The screening laboratory tests included above in Table 8-1 will be listed only.

Liver function abnormalities will be defined using the following criteria:

- ALT or AST ≥2xULN
- ALT or AST ≥3xULN
- Total bilirubin ≥2xULN
- Total bilirubin ≥3xULN
- ALT or AST ≥5xULN
- ALT or AST ≥8xULN
- ALT or AST ≥3xULN AND total bilirubin ≥2xULN (>35% direct bilirubin)

For the subgroups of participants with liver metastases and without liver metastases at Baseline, the number and percentage of participants in each liver function abnormality category will be summarized at each visit.

In addition, participants with potential drug induced liver injury (PDILI) criteria are those that fulfill the following laboratory data (based on liver function tests) criteria at a visit:

- AST or ALT and total bilirubin within the normal range at Baseline and AST or ALT ≥3xULN concurrent with total bilirubin ≥2xULN;
- AST, ALT or total bilirubin above ULN at Baseline and AST or ALT ≥2 times Baseline values AND AST or ALT ≥3xULN (participants without liver metastases at Baseline)/AST or ALT ≥8xULN (participants with liver metastases at Baseline) concurrent with total bilirubin above ULN at Baseline and total bilirubin ≥2 times Baseline value or ≥3xULN (whichever is lower).

All relevant laboratory data collected for participants with a PDILI event (i.e. liver function tests) will be listed at the visits at which at least one of the above criteria was fulfilled.

The number and percentage of participants meeting different combinations of the ALT, AST and total bilirubin criteria defined above will be summarized by treatment group. This summary will be presented for all participants as well as for the subgroups of participants who had liver metastases at Baseline and participants without liver metastases at Baseline.

A separate listing will also be produced containing DILI-relevant family medical history, lifestyle data (alcohol consumption or drug abuse in the previous 6 months), hepatic event supplemental medical history and any hepato-toxic medications taken for participants in the SS with a PDILI event.

8.4 Vital signs, physical findings, and other observations related to safety

8.4.1 Vital signs

Vital signs will be measured in a semi-supine position after 5 minutes rest and will include:

- Systolic and diastolic blood pressure;
- Pulse rate;
- Oral body temperature;
- Respiratory rate.

On dosing visits (Days 1 and 15 of each cycle), vital signs on treatment days (i.e. on Days 1 and 15 of each cycle) will be assessed at multiple timepoints: predose, 10 minutes (±5 minutes) and 30 minutes (±10 minutes) after the start of the infusion, at the end of the infusion (+15 minutes); and at 1 hour (+15 minutes) after the end of the infusion. In addition, on Cycle 1 Day 1, vital signs will also be assessed at 2 hours (+1 hour) and 8 hours (+2 hours) after the end of the infusion, to correspond with PK sampling timepoints; vital signs measurements will be performed prior to the collection of PK samples.

At Screening and on non-treatment days (Days 2, 8, 16 and 22 of Cycle 1 and Day 8 of Cycle 2 and the SFU visit), vital signs will be measured once prior to collection of PK samples.

Observed vital sign measurements and changes from Baseline will be listed by visit and timepoint and summarized using descriptive statistics. In addition, for each of the vital signs, the Baseline value, the minimum, maximum, average and last post-Baseline value for each participant will be calculated based on all available scheduled postdose values during each cycle up to the predose value on Day 1 of the subsequent cycle and will be summarized by cycle using descriptive statistics. The last value in a cycle will be the predose value of the subsequent cycle where a subsequent cycle occurs, otherwise it will be the value at the last scheduled assessment. If only 1 value is available then the average will not be calculated and presented but this value will be used for the minimum, maximum and last post-Baseline summary measures. These summary measures for each cycle will also be listed.

For the multiple vital signs measurements on treatment days (i.e. on Days 1 and 15 of each cycle), changes from the predose value will be calculated at each postdose timepoint and summarized using descriptive statistics.

For each vital signs parameter, the mean (±standard deviation) change from Baseline value will be plotted over scheduled visit and timepoint with treatment group overlaid on the same plot.

The incidence of treatment-emergent markedly abnormal (TEMA)/potentially clinically significant (PCS) vital signs based on blood pressure and pulse rate measurements will be summarized by visit and timepoint using frequency counts and percentages. The criteria for identifying a TEMA/PCS are included in Table 8-2.

Table 8-2: TEMA/PCS Criteria for Vital Signs

Variable (unit)	Low[a]	High[a]
Systolic Blood Pressure (mmHg)	Value <90 and ≥20 decrease from Baseline	Value >140 and ≥20 increase from Baseline
Diastolic Blood Pressure (mmHg)	Value <50 and ≥15 decrease from Baseline	Value >90 and ≥15 increase from Baseline
Pulse Rate (bpm)	Value <45 and ≥15 decrease from Baseline	Value >90 and ≥15 increase from Baseline

bpm=beats per minute; PCS=potentially clinically significant; mmHg=millimeter of mercury; TEMA=treatment-emergent markedly abnormal.
[a] Both conditions must be satisfied for a measurement to be considered PCS.

8.4.2 12-Lead Electrocardiograms

Electrocardiograms will be performed at each visit and timepoint in triplicate with the participant in a supine position after a minimum of 5 minutes rest.

On Days 1 and 15 of Cycle 1, ECGs will be performed in triplicate at multiple timepoints relative to the dose of study treatment (predose, end of infusion, and 8 hours after the end of infusion prior to PK sampling). On all other treatment days (Days 1 and 15 of all subsequent cycles of study treatment), ECGs will be performed in triplicate predose. At Screening and on non-treatment days, ECGs will be performed once in triplicate prior to PK sampling.

All ECGs will be evaluated for any clinically relevant changes by the investigator.

Electrocardiograms will also be collected for central reading, the data from which will be analyzed separately.

All summaries and listings of ECG data will be based on the local (site) 12-lead ECG measurements.

The following ECG parameters will be reported:

- PR interval;
- QT interval;
- QRS interval;
- QTcF interval (QT corrected for heart rate using Fridericia's formula [QTcF]);
- Heart rate.

Observed values and changes from Baseline in these ECG parameters will be listed and summarized by visit using descriptive statistics. The mean of the triplicate measurements taken for each parameter will be used in the summary at each visit and timepoint. If less than 3 of the triplicate measurements are taken then the mean of the available measurements will be used (if only 1 of the 3 triplicate measurements is available then this value will be used in the summaries). The Baseline value will be the mean of the last scheduled or unscheduled triplicate measurements taken prior to first dose of study treatment on Day 1 of Cycle 1. If no predose triplicate measurements are taken then the mean of the triplicate measurements taken at Screening will be used. The mean of only the scheduled triplicate measurements at each Post-Baseline visit and timepoint will be included in the summary. In addition, for each of the ECG parameters, the minimum, maximum, average and last post-Baseline value for each participant will be calculated based on the mean of the triplicate of all available scheduled postdose measurements during each cycle up to the predose value on Day 1 of the subsequent cycle, and will be summarized by cycle using descriptive statistics. The last value in a cycle will be the predose mean triplicate value of the subsequent cycle where a subsequent cycle occurs, otherwise it will be the mean triplicate value at the last scheduled assessment. If only 1 mean triplicate value is available then the average will not be calculated and presented but this value will be used for the minimum, maximum and last post-Baseline value summary measures. These summary measures for each cycle will also be listed.

For the multiple ECGs performed on Days 1 and 15 of Cycle 1, changes from the predose value will be calculated at each postdose timepoint and summarized using descriptive statistics.

Mean (±standard deviation) change from Baseline in QTcF will be plotted over scheduled visit with treatment groups overlaid on the same plot. Individual observed values of QTcF will be presented over actual time in a spaghetti plot.

The following cut-points in QTcF will be applied for observed data and changes from Baseline:

For observed QTcF data:

- <450 msec;
- ≥450 to <480 msec;
- ≥480 to <500 msec;

- ≥500 msec.

For changes from Baseline in QTcF:

- <30 msec;
- ≥30 to <60 msec;
- ≥60 msec.

The incidence of participants in each of these categories will be summarized using frequency counts and percentages by visit.

A listing of 12-lead ECG abnormal findings will be presented.

Electrocardiograms will also be collected for central reading; however, these data will be reported in an addendum to the CSR.

8.4.3 Echocardiogram

Echocardiograms will be performed at the Screening visit, on Day 1 of Cycles 2 and 3, and then on Day 1 of even cycles from Cycle 3 onwards.

All details on the echocardiogram assessments performed at each visit will be listed including the observed LVEF measurements and changes from Baseline, as well as information on whether the result was normal, abnormal NCS or abnormal CS.

Observed values and changes from Baseline in LVEF will be summarized by visit using descriptive statistics. In addition, shift tables for the change from Baseline in normal, abnormal NCS, abnormal CS LVEF results will be summarized by visit.

Mean (±standard deviation) change from Baseline in LVEF will be plotted over scheduled visit with treatment groups overlaid on the same plot. Individual observed LVEF results will be presented over actual time in a spaghetti plot.

8.4.4 ECOG performance status

ECOG performance status will be listed by participant and visit and will be summarized using frequency counts and percentages. A shift table summarizing the changes from Baseline to each post-Baseline visit will also be presented. Further detail on the ECOG performance scale, the listings and summaries are included in Section 10.2.

8.4.5 Physical examination

Physical examination abnormalities from the complete physical examination performed at Screening and predose on Day 1 of Cycle 1, and from the symptom-directed physical examinations performed at other visits (predose on dosing visits), will be listed.

9 PHARMACOKINETICS AND PHARMACODYNAMICS

9.1 Pharmacokinetics

9.1.1 Secondary pharmacokinetic endpoint

The secondary PK endpoint for Part A of the study is the UCB6114 concentration in blood by time and dose.

UCB6114 concentrations will be listed for the SS and summarized using descriptive statistics by dose level (treatment group) and nominal (scheduled) sampling timepoints for the PKS (n, arithmetic mean, standard deviation, median, minimum, maximum, geoMean, geoCV and 95% CI for the geoMean [assuming lognormally distributed data]).

Listings of the UCB6114 concentration data will include the actual and nominal (scheduled) sampling times and any deviations between them. Deviations will be calculated relative to the start of the iv infusion. Any samples that are obtained outside the tolerance window permitted at the specified timepoint will be discussed at the DEM and any possible exclusion from the summaries will be documented accordingly.

Individual study participant UCB6114 concentration-time profiles and spaghetti plots of the individual concentration-time profiles for UCB6114 will be displayed graphically on the linear and semi-logarithmic scale. Geometric mean profiles of UCB6114 concentrations over nominal (scheduled) time will be presented with treatment group overlaid on the same plot, on both the linear and semi-logarithmic scale. The 95% CIs for the geoMean will be displayed on the linear scale plot only and the LLOQ will be included on all semi-logarithmic scale plots of UCB6114 concentrations.

Depending on the data, the UCB6114 concentration-time data may be subject to a population PK analysis using non-linear mixed effects modelling to characterize the disposition characteristics of UCB6114 in the current study. The influence of important variables such as body weight and ADA status on the population PK parameter estimates may be evaluated. These analyses will be described in a separate data analysis plan and reported separately.

9.1.2 Exploratory pharmacokinetic endpoints

Where possible, key and other PK parameters will be derived by ICON PLC using noncompartmental analysis (NCA) performed using Phoenix WinNonlin® v8.0.0.3716 or higher (Certara L.P., Princeton, NJ, USA) and according to UCB's Guideline on Performing NCA Analysis version 1.0 dated 15 Nov 2017. An assessment of dose-proportionality will also be performed.

Key and other derived PK parameters are defined in Table 9-1.

Table 9-1: Pharmacokinetic Parameters

[redacted]

[redacted]

9.2 Pharmacodynamics

The following exploratory PD and biomarker endpoints will be obtained from blood and urine samples which will be analyzed at a number of external laboratory vendors:

- Serum markers of bone turnover;
- Urinary markers of bone turnover;
- cGremlin-1;
- Serum protein/proteomic analysis;
- Transcriptomic analysis;
- Genetic analysis;
- CtDNA.

The impact of UCB6114 on bone turnover will be explored using the serum and urinary markers provided by the analytical laboratory. These markers will be listed for the SS and summarized descriptively over time for the PDS by dose level (treatment group), as described for the clinical laboratory parameters in Section 8.3. For each marker of bone turnover, the mean (±standard deviation) value and the mean (±standard deviation) change from Baseline value will be plotted over scheduled visit with treatment group overlaid on the same plot.

cGremlin-1 will be reported as concentration in blood by nominal (scheduled) assessment and dose level. Concentrations of cGremlin-1 will be listed for the SS and summarized for the PDS

using descriptive statistics by dose level (treatment group) and nominal (scheduled) sampling timepoints (n, arithmetic mean, standard deviation, median, minimum, maximum, geoMean, geoCV and 95% CI for the geoMean [assuming lognormally distributed data]). Changes from Baseline will also be summarized. Individual study participant cGremlin-1 concentration-time profiles will be displayed graphically in spaghetti plots and geoMean cGremlin-1 concentration and 95% CI will be plotted at each nominal (scheduled) timepoint with treatment group overlaid on the same plot.

Serum protein/proteomic analysis, transcriptomic analysis, genetic analysis and the analysis of the test results from the blood samples taken for ctDNA will be performed and reported separately outside of the CSR.

Hematoxylin and eosin (H & E) staining and immunohistochemistry (IHC) will be used to analyze any available historical tissue biopsy samples obtained prior to a participant's entry into the study (e.g. at the time of diagnosis).

Test results from the H & E staining and for target genes, phosphatase and tensin homolog (PTEN), Ki67 (cellular marker for proliferation in tumors), Gremlin-1, mothers against decapentaplegic homolog 4 (SMAD4) and fibroblast activation protein (FAP) will be listed by variable and sample analyzed (multiple tissue samples from a tumor biopsy may have been analyzed for a participant) for the SS. No summaries of these data will be generated due to the expected small numbers of historical biopsy samples analyzed for each dose level (treatment group).

The following key/component variables will be derived based on H & E staining, PTEN, Ki67, Gremlin-1 and FAP test results. No derived variables will be generated for SMAD4; only raw test results will be listed. Note that multiple tissue samples from a tumor biopsy may have been analyzed for a participant and therefore multiple test results will be presented in the listings.

H & E: Tissue Integrity (Percentage of Necrosis in Tumor Area)

In order to assess tissue integrity, percentage of necrosis in the tumor area will be categorized as '<20%' and '>=20%'. If percentage of necrosis data are missing but other H & E staining and IHC data are available for a participant (i.e. the participant had historical tumor biopsy sample(s) analyzed), then the result will be categorized as 'Not Done'.

This categorical variable will be listed together with all other H & E test results.

PTEN: Tissue Sample Quality Control

The presence of staining of intrinsic control elements on the slides together with the level of staining intensity will be used to determine the tissue sample quality control.

If staining of intrinsic control elements on stained slides='YES' and staining intensity of intrinsic control elements on stained slides is 1, 2 or 3 then the tissue sample quality control is 'Good', otherwise if the staining intensity of intrinsic control elements=0 then the tissue sample quality

control is 'Questionable'. If staining of intrinsic control elements on stained slides='NOT PRESENT' then the tissue sample quality control is 'No staining present'. If both variables are missing but other IHC results are available (i.e. the participant had historical tumor biopsy sample(s) analyzed), then the result will be categorized as 'Not done'.

This categorical variable will be listed together with the presence/absence of staining of intrinsic control elements on the slides, the level of staining intensity, staining pattern, staining artifacts and any assay-specific comments. Since the percent of tumor cells with staining intensity 0/1/2/3 and the H-score (test results for which will be provided by the laboratory) are less relevant to assessing the quality control of the tissue sample, these raw test results will not be listed.

Ki67 – Proliferative Activity of the Tumor

In order to assess the proliferative activity of the tumor mass, cellular proliferation reflected by the number of Ki67-positive cell objects in the tumor region divided by the total number of cell objects in the tumor region will be categorized as '<=10%' or '>10%' with the latter category indicating an actively/moderately proliferating tumor. If the test result is 'NOT EVALUABLE' or missing but IHC results are available (i.e. the participant had historical tumor biopsy sample(s) analyzed), then the result will be categorized as 'Not done'.

This categorical variable will be listed together with all other Ki67 raw test results.

Gremlin-1: Cytoplasmic Histoscore

The cytoplasmic histoscore will be calculated as a weighted score based on the percentage of tumor cells with Gremlin-1 cytoplasmic staining intensity 1, 2 or 3 as follows:

(1 x percent tumor cells with Gremlin-1 cytoplasmic staining intensity 1) + (2 x percent tumor cells with Gremlin-1 cytoplasmic staining intensity 2) + (3 x percent tumor cells with Gremlin-1 cytoplasmic staining intensity 3).

The cytoplasmic histoscore will be missing if the participant had a historical biopsy tumor sample analyzed but there are no test results for percent tumor cells with Gremlin-1 cytoplasmic staining intensity 1, 2 or 3.

The cytoplasmic histoscore will be listed together with all other Gremlin-1 raw test results.

FAP

From the image analysis of FAP-stained slides, the tumor will be classified into 2 regions: the cancer (CN) tumor region and the invasive margin (IM) region using a pre-established digital automated algorithm. The IM region is usually a small proportion of the whole tumor and, per standard procedures at the analytical laboratory, will be identified first. As a result, there is a risk that some parts of the CN tumor region may be inaccurately classified as part of the IM region, particularly in cases when the tumor is small. Therefore, instead of using the results for the

percentage of high, medium and low intensity FAP provided by the laboratory, a decision was made to back-calculate the areas of the CN tumor region and the IM region and add these together in order to re-calculate the percentage of high, medium and low intensity FAP in the whole tumor.

These back-calculated results and derived variables based on FAP test results are defined in Table 9-2.

Table 9-2: FAP Derived Variables

Variable No.	FAP Derived Variable	Description and Calculation
1[a]	Total Analyzed Tumor Area (um^2)	This is the total tumor area (um^2) across the CN tumor region and the IM region and will be calculated as the sum of the areas of the CN tumor region (um^2) and the IM region (um^2) where a non-missing numeric test result is available for both the area of the CN tumor region and the area of the IM region. Note that, in cases where no IM region is defined, the area of the IM region will be recorded as 0 or 'NOT APPLICABLE', or may be missing. If the area of the IM region is recorded as 'NOT APPLICABLE' or is missing, then 0 will be assumed in this calculation and the total analyzed tumor area will be equal to the area of the CN tumor region. This variable will be missing if both the areas of the CN tumor region and IM region are missing, or if one or both are 'NOT EVALUABLE' or 'NOT DIAGNOSTIC'.
2	Measured Area of Weakly Stained FAP in the CN Tumor Region (um^2)	This is the back-calculated area of weakly stained FAP in the CN tumor region (weak positive) and will be calculated by multiplying the area of the CN tumor region (um^2) and the relative area of weakly stained FAP in the CN tumor region (%) where a non-missing numeric test result is available for both the area of the CN tumor region and the relative area of weakly stained FAP in the CN tumor region. This variable will be set to 0 if one or both are missing, 'NOT EVALUABLE' or 'NOT DIAGNOSTIC'.
3	Measured Area of Moderately Stained FAP in the CN Tumor Region (um^2)	This is the back-calculated area of moderately stained FAP in the CN tumor region (moderate positive) and will be calculated by multiplying the area of the CN tumor region (um^2) and the relative area of moderately stained FAP in the CN tumor region (%) where a non-missing numeric test result is available for both the area of the CN tumor region and the relative area of moderately stained FAP in the CN tumor region.

Variable No.	FAP Derived Variable	Description and Calculation
		This variable will be set to 0 if one or both are missing, 'NOT EVALUABLE' or 'NOT DIAGNOSTIC'.
4	Measured Area of Strongly Stained FAP in the CN Tumor Region (um^2)	This is the back-calculated area of strongly stained FAP in the CN tumor region (strong positive) and will be calculated by multiplying the area of the CN tumor region (um^2) and the relative area of strongly stained FAP in the CN tumor region (%) where a non-missing numeric test result is available for both the area of the CN tumor region and the relative area of strongly stained FAP in the CN tumor region. This variable will be set to 0 if one or both are missing, 'NOT EVALUABLE' or 'NOT DIAGNOSTIC'.
5	Measured Area of Weakly Stained FAP in the IM Region (um^2)	This is the back-calculated area of weakly stained FAP in the IM region (weak FAP-positive) and will be calculated by multiplying the area of the IM region (um^2) and the relative area of weakly stained FAP in the IM region (%) where a non-missing numeric test result is available for both the area of the IM region and the relative area of weakly stained FAP in the IM region. This variable will be set to 0 if one or both are missing, 'NOT EVALUABLE' or 'NOT DIAGNOSTIC'.
6	Measured Area of Moderately Stained FAP in the IM Region (um^2)	This is the back-calculated area of moderately stained FAP in the IM region (moderate FAP-positive) and will be calculated by multiplying the area of the IM region (um^2) and the relative area of moderately stained FAP in the IM region (%) where a non-missing numeric test result is available for both the area of the IM region and the relative area of moderately stained FAP in the IM region. This variable will be set to 0 if one or both are 'NOT EVALUABLE' or 'NOT DIAGNOSTIC'.
7[a]	Measured Area of Strongly Stained FAP in the IM Region (um^2)	This is the back-calculated area of strongly stained FAP in the IM region (strong FAP-positive) and will be calculated by multiplying the area of the IM region (um^2) and the relative area of strongly stained FAP in the IM region (%) where a non-missing numeric test result is available for both the area of the IM region and the relative area of strongly stained FAP in the IM region. This variable will be set to 0 if one or both are missing, 'NOT EVALUABLE' or 'NOT DIAGNOSTIC'.

Variable No.	FAP Derived Variable	Description and Calculation
8[a]	Total FAP-Positive Tumor Area (um^2)	This is the total FAP-positive area across the CN tumor region and the IM region (whole tumor) and will be calculated as the sum of component derived variables 2-7. If all 6 component variables are 0 then this derived variable will be missing.
9[a]	Total Measured Area of Weakly Stained FAP (um^2)	This is the total weak FAP-positive area across the CN tumor region and the IM region (whole tumor) and will be calculated as the sum of component FAP derived variables 2 and 5.
10[a]	Total Measured Area of Moderately Stained FAP (um^2)	This is the total moderate FAP-positive area across the CN tumor region and the IM region (whole tumor) and will be calculated as the sum of component FAP derived variables 3 and 6.
11[a]	Total Measured Area of Strongly Stained FAP (um^2)	This is the total strong FAP-positive area across the CN tumor region and the IM region (whole tumor) and will be calculated as the sum of component FAP derived variables 4 and 7.
12[a]	Total Relative Area of Weakly Stained FAP (%)	This is the percentage of weak FAP expression across the CN tumor region and IM region (whole tumor) and will be calculated using component FAP derived variables 1 and 9 as (Total Measured Area Of Weakly Stained FAP / Total Analyzed Tumor Area) x 100 If the total analyzed tumor area is missing then this variable cannot be calculated and will be missing.
13[a]	Total Relative Area of Moderately Stained FAP (%)	This is the percentage of moderate FAP expression across the CN tumor region and IM region (whole tumor) and will be calculated using component FAP derived variables 1 and 10 as (Total Measured Area Of Moderately Stained FAP / Total Analyzed Tumor Area) x 100 If the total analyzed tumor area is missing then this variable cannot be calculated and will be missing.
14[a]	Total Relative Area of Strongly Stained FAP (%)	This is the percentage of strong FAP expression across the CN tumor region and IM region (whole tumor) and will be calculated using component FAP derived variables 1 and 11 as

Variable No.	FAP Derived Variable	Description and Calculation
		(Total Measured Area Of Strongly Stained FAP / Total Analyzed Tumor Area) x 100 If the total analyzed tumor area is missing then this variable cannot be calculated and will be missing.
15[a]	Total Relative FAP-Positive Tumor Area (TPS) (%)	This is the total proportion score which is the percentage of FAP-positive area across the CN tumor region and the IM region (whole tumor) and will be calculated using component derived variables 1 and 8 as (Total FAP-Positive Tumor Area / Total Analyzed Tumor Area) x 100 If the total analyzed tumor area is missing then this variable cannot be calculated and will be missing.
16[a]	Total FAP Histoscore	This is a histoscore for the combined CN tumor region and IM region (whole tumor) and will be calculated as a weighted score based on component derived variables 12, 13 and 14 as (1 x Total Relative Area of Weakly Stained FAP) + (2 x Total Relative Area of Moderately Stained FAP) + (3 x Total Relative Area of Strongly Stained FAP)

CN=cancer; FAP=fibroblast activation protein, IM=invasive margin, TPS=total proportion score.
[a] Included in the listing of FAP test results.

The derived variables containing the [a] flag in Table 9-2 above will be listed together with information on staining artifacts and any assay-specific comments provided by the laboratory.

Further informal analyses may be performed to explore the relationship between the PD and biomarker endpoints with antitumor activity, ADA status, and also with key PK parameters. The PK-PD effects of UCB6114 may be assessed using a population analysis approach. These analyses will also be performed separately outside of the CSR and the details of analysis methods will be included in a separate analysis plan.

The incidence of available historical tumor biopsies will be summarized by treatment group. The incidence of PD samples taken from blood and urine will be summarized by cycle and treatment group.

9.3 Immunogenicity

Anti-drug (UCB6114) antibody status and classification, changes from Baseline in titer over time and the incidence of treatment-emergent ADA positivity are exploratory immunogenicity endpoints in Part A of this study. Potential relationships between ADA and PK, PD, antitumor activity and safety will also be explored but this will be reported separately outside of the CSR.

Serum samples will be collected from all study participants for the measurement of ADA and the evaluation of immunogenicity according to the Schedule of Activities in the protocol.

All listings of ADA will be presented for the SS and summaries of the ADA data will be presented by treatment group for the ADAS.

Anti-drug (UCB6114) antibodies will be measured using a three-tiered assay approach: Screening assay, confirmatory assay and titration assay.

Samples will first be evaluated in the Screening assay using a false positivity rate of 5% (reported as 'negative screen' or 'positive screen'), followed by analysis of screened positive samples in the confirmatory assay (which is a drug depletion assay) to confirm the positivity of the samples (reported as 'negative immunodepletion' or 'positive immunodepletion'). Samples that are confirmed as positive in the confirmatory assay will be evaluated in a titration assay to assess the ADA level and this will be reported as titer (reciprocal dilution factor including minimum required dilution).

Anti-drug (UCB6114) antibody sample status will be determined as follows from the pre-treatment sample taken on Day 1 of Cycle 1 (Baseline) and all post-treatment (post-Baseline) samples.

- Sample values that are either 'negative screen' or 'positive screen' and 'negative immunodepletion' will be defined as **ADA negative**
- Sample values that are 'positive screen' and 'positive immunodepletion' will be defined as **ADA positive**

Anti-drug (UCB6114) antibody sample status will be listed for each participant at each visit by treatment group. This listing will include sampling dates and times, the Screening assay result, the confirmatory assay result and the derived ADA sample status. In addition, the titer from the titration assay (if applicable) will be listed together with the change from Baseline in titer. The number and percentage of participants with a positive or negative sample at each visit will be summarized by treatment group. Percentages will be calculated based on the number of participants with a non-missing/sufficient sample at the visit.

Based on the ADA status of the samples, study participants will be categorized according to the following 6 ADA classifications in Table 9-3:

Table 9-3: ADA Classifications

Classification	Classification Label	Definition
1	Pre-ADA negative – treatment induced ADA negative	Includes participants who have an ADA negative status at Baseline, or missing/insufficient Baseline sample, and an ADA negative status at all sampling timepoints post-Baseline (including SFU). Participants with missing post-Baseline samples are included as long as the missing samples do not result in an unmonitored period greater than 16 weeks.
2	Pre-ADA negative – treatment induced ADA positive	Includes participants who have an ADA negative status at Baseline, or missing/insufficient Baseline sample, and an ADA positive status at any sampling timepoint post-Baseline (including SFU).
3	Pre-ADA positive – treatment reduced ADA	Includes participants who have an ADA positive status at Baseline and an ADA negative status at all sampling timepoints post-Baseline (including SFU)
4	Pre-ADA positive – treatment unaffected ADA	Includes participants who have an ADA positive status at Baseline and an ADA positive status at any sampling timepoint post-Baseline (including SFU) with titer values of the same magnitude as Baseline (≤1.80-fold difference from the Baseline value) or with decreased titer values compared to Baseline (>1.80-fold decrease from the Baseline value).
5	Pre-ADA positive – treatment boosted ADA positive	Includes participants who have an ADA positive status at Baseline and an ADA positive status at any sampling timepoint post-Baseline (including SFU) with increased titer values compared to Baseline (>1.80-fold increase from the Baseline value.
6	Inconclusive	Includes participants who do not satisfy the criteria for classifications 1-5

ADA=anti-drug (UCB6114) antibody; SFU=Safety Follow-up.
Note: The terminology 'treatment unaffected' is ambiguous as the criteria refers to ADA responses that are not increased upon dosing compared to Baseline level whereas titers may reduce.

A study participant will be classified as having **treatment-emergent ADA positivity** if they satisfy one of the following criteria:

- The Baseline result is ADA negative and at least one post-Baseline result is ADA positive (pre-ADA negative – treatment induced ADA positive) – ADA classification 2 in Table 9-3;
- The Baseline result is ADA positive and at least one post-Baseline result shows a pre-defined fold increase in titer from the Baseline value (the fold increase from Baseline required to meet this criterion will be defined with the development of the assay and will be included in the TFLs) (pre-ADA positive – treatment boosted ADA positive) – ADA classification 5 in Table 9-3.

Total anti-drug (UCB6114) antibody **incidence** will be determined by the number and percentage of participants with treatment-emergent ADA positivity (as defined above). The denominator for the percentage calculation will be the number of participants with at least one available/reported post-Baseline result.

Total **prevalence** of pre-anti-drug (UCB6114) antibody will be determined by the number and percentage of participants who are pre-ADA positive (i.e. participants who have a positive ADA status at Baseline). The denominator for the percentage calculation will be the number of participants with an available/reported Baseline sample result.

Total anti-drug (UCB6114) antibody **prevalence** will be determined by the number and percentage of participants with ADA classifications 2, 4 and 5 in Table 9-3 (i.e. an ADA positive status at any post-Baseline sampling timepoint. The denominator for the percentage calculation will be the number of participants with at least one available/reported sample result (either at Baseline and/or post-Baseline).

The ADA classification for each participant will be listed by treatment group. This listing will also include whether or not the participant achieved treatment-emergent ADA positivity (ADA incidence), whether the participant was pre-ADA positive (pre-ADA prevalence) and whether the participant had an ADA positive status at any post-Baseline sampling timepoint (ADA prevalence). In addition, the visit at which the participant first achieved treatment-emergent ADA positivity will be included.

The number and percentage of participants in each of the 6 ADA classifications defined above in Table 9-3 will be presented by treatment group. Also, in this tabulation, ADA incidence and prevalence (as defined above) will be summarized.

The first occurrence of treatment-emergent ADA positivity (based on the criteria above) will be summarized using frequency counts and percentages at each post-Baseline visit by treatment group. This tabulation will include a count of the number of participants at each post-Baseline visit who fulfill at least one of the above defined criteria for treatment-emergent ADA positivity; participants will be counted in the numerator based on the earliest visit at which one of these criteria is fulfilled. At other visits, participants will be counted in the denominator (assuming an assessment of treatment-emergent positivity is available) and this will be used in the percentage calculations.

Individual study participant ADA titer profiles over actual time will be presented graphically on the linear and the semi-logarithmic scale. The linear scale plots will be repeated for the subset of participants who achieve treatment-emergent ADA positivity during Part A.

Mean (±standard deviation) C_{min} will be plotted by ADA sample status over scheduled time with treatment groups overlaid on the same plot.

10 EFFICACY ANALYSES

10.1 Antitumor activity

The analysis of antitumor activity is exploratory in Part A of this study.

10.1.1 Definitions of the antitumor activity endpoints

The following endpoints are defined based on RECIST (Version 1.1) which standardizes solid tumor measurements and provides guidelines for the objective assessment of changes in tumor size during anti-cancer treatment.

Appendix 9 (Section 11.9) of the protocol contains the RECIST 1.1 guidelines to be used in this study, adapted from Eisenhauer (2009), and includes the definitions of target and non-target lesions, the definitions of target and non-target lesion responses at each tumor assessment, the criteria for determining overall tumor response at each tumor assessment based on target lesion response, non-target lesion response and the presence/absence of new lesions, and a participant's best overall response (BOR).

At each post-Baseline tumor assessment, the investigator will record responses for target lesions and non-target lesions, whether or not there has been an appearance of any new lesions, and the participant's overall tumor response based on their target lesion response, non-target lesion response and the presence/absence of new lesions. Note that target lesion response and non-target lesion response assessments will be based on the changes in the pre-existing lesions at Baseline and the appearance of new lesions will only factor in the determination of an overall tumor response of PD at that tumor assessment visit (i.e. per Tables A and B in Section 11.9.2 of Appendix 9 of the protocol).

Objective response rate (ORR) is defined as the percentage of participants with a BOR of complete response (CR) or partial response (PR) during Part A.

Disease Control Rate (DCR) is defined as the percentage of participants with a BOR of CR, PR, or stable disease (SD) during Part A.

Best overall response (BOR) is defined for each study participant as the best overall tumor response from each tumor assessment (scheduled and unscheduled assessments performed between Days 21 and 28 of every even cycle of study treatment) according to the RECIST criteria for changes in target and non-target lesions and the appearance of new lesions. Best overall response is determined from the start of study treatment until documented objective disease progression or the date of subsequent anti-cancer therapy (systemic therapy, surgery or radiotherapy for cancer), whichever occurs first. If anti-cancer therapy is started on the same day as a tumor assessment, then the overall response from that assessment will be used in the derivation of BOR. For a BOR of SD, a participant's tumor measurements must have met the SD criteria at least once after the start of study treatment at a minimum interval of no less than 6–8 weeks (42-56 days).

For Part A of this study, BOR determination requires confirmation of CR or PR responses at a subsequent assessment ≥4 weeks (28 days) after the criteria for CR or PR responses are first met. In addition, Table C in Appendix 10.9 of the protocol provides the derivation of BOR when confirmation of CR and PR responses are required. Confirmed BOR and unconfirmed BOR will be derived programmatically based on the overall tumor assessment data recorded on the eCRF

by the investigator and using the detailed guidance included in the Derivation of Efficacy Endpoints document Version 0.6 (dated 21 January 2022).

Duration of response (DOR) will be calculated for participants with a confirmed BOR of CR or PR as the time in days from the start date of the confirmed CR or PR to the first date that recurrent or progressive disease is objectively documented (i.e. according to the RECIST guidelines). This will be referred to as the duration of confirmed response and the following calculation will be performed:

$$\begin{aligned} &Duration\ of\ Confirmed\ Response \\ &\quad = (Date\ of\ First\ Objective\ Disease\ Progression \\ &\quad - \ Start\ Date\ of\ Confirmed\ CR\ or\ PR\ Response) + 1 \end{aligned}$$

Duration of response will also be calculated for participants with an unconfirmed BOR of CR or PR (which may either be confirmed at a later tumor assessment or unconfirmed) as the time in days from the start date of the CR or PR to the date of the first documented objective disease progression (i.e. according to the RECIST guidelines). The following calculation will be performed:

$$\begin{aligned} &Duration\ of\ Unconfirmed\ Response \\ &\quad = (Date\ of\ First\ Objective\ Disease\ Progression \\ &\quad - \ Start\ Date\ of\ CR\ or\ PR\ Response) + 1 \end{aligned}$$

For the purpose of a sensitivity analysis of both duration of confirmed response and duration of unconfirmed response, the above calculations will take into consideration the occurrence of both objective disease progression (per RECIST 1.1) and clinical disease progression (as described in Appendix 11.9 of the protocol and as determined by the investigator and recorded as a reason for study treatment discontinuation on the eCRF), whichever occurs first. If clinical disease progression occurs on the same date that a participant's objective disease progression is determined, then the participant will be included in the sensitivity analyses as having objective disease progression.

The following calculations will therefore be performed for the sensitivity analyses:

$$\begin{aligned} &Duration\ of\ Confirmed\ Response \\ &\quad = (Date\ of\ First\ Objective\ or\ Clinical\ Disease\ Progression \\ &\quad - \ Start\ Date\ of\ Confirmed\ CR\ or\ PR\ Response) + 1 \end{aligned}$$

$$\begin{aligned} &Duration\ of\ Unconfirmed\ Response \\ &\quad = (Date\ of\ First\ Objective\ or\ Clinical\ Disease\ Progression \\ &\quad - \ Start\ Date\ of\ CR\ or\ PR\ Response) + 1 \end{aligned}$$

For participants who die without objective disease progression, duration of confirmed response and duration of unconfirmed response will be censored on the date of death, regardless of cause. For a participant who discontinues early from Part A of the study with no objective disease progression, duration of confirmed response and duration of unconfirmed response will be censored on the date of their last available (scheduled or unscheduled) tumor assessment at which a lack of objective disease progression was determined. Participants who discontinue study treatment but who do not have documented objective disease progression (i.e. according to the RECIST guidelines), duration of confirmed response and duration of unconfirmed response will be censored at the date of their last available (scheduled or unscheduled) tumor assessment

at which a lack of objective disease progression was determined. Such participants might include those that are ongoing in Part A at the time of any defined data cut-off.

In the sensitivity analyses of duration of confirmed response and duration of unconfirmed response, the same censoring rules will apply except that the date of last contact will be used for the censoring of participants who discontinue early from Part A, complete Part A of the study or are ongoing in the study at a data cut-off for Part A without objective disease progression, clinical disease progression or death.

Date of last contact will be the latest of the dates of premature study termination and of last contact recorded on Study Termination eCRF page, the date of death, the date of last dose of study treatment, the dates of all visits, AE start and end dates (with partial dates imputed as earliest possible) and the date of contact recorded on the Survival Safety Follow-up and Survival Final Follow-up eCRF forms.

Further details on the derivation of duration of confirmed response and duration of unconfirmed response are included in the Derivation of Efficacy Endpoints document Version 0.6 (dated 21 January 2022).

Progression-free survival (PFS) will be calculated as the time in days from the first dose of study treatment to the date of the first documented objective disease progression (i.e. according to the RECIST guidelines), or death due to any cause, whichever occurs first. The following calculation will be performed:

$$PFS = (Date\ of\ Objective\ Progressive\ Disease/Death - Date\ of\ First\ Dose) + 1$$

Participants who die due to any cause without a documented objective disease progression will be considered to have progressed on the date of their death. Participants who do not have any post-Baseline tumor assessments will be censored on the date of their first dose of study treatment. Participants who discontinue early from Part A or discontinue study treatment without documented objective disease progression or death, will be censored on the date of their last available (scheduled or unscheduled) tumor assessment at which a lack of objective disease progression was determined. Participants who start anti-cancer therapy during Part A without a prior documented objective disease progression will be censored on the date of their last available (scheduled or unscheduled) tumor assessment prior to the initiation of the subsequent anti-cancer therapy. If anti-cancer therapy starts on the same date as the participant's tumor assessment and determination of objective disease progression, or the participant's death (due to any cause), then the participant will not be censored and the participant will be included as having an uncensored event on this date. This censoring rule will also be applied to participants who are ongoing at any data cut-off for an analysis of Part A data who have no documented objective disease progression. The use of anti-cancer therapy during Part A will be identified via ongoing medical review of the concomitant medications together with the start dates of further anti-cancer therapy information recorded on the survival follow-up pages of the eCRF.

As a sensitivity analysis, PFS will also be calculated as the time in days from the first dose of study treatment to the date of the first documented objective disease progression (per RECIST 1.1), the date of clinical disease progression, as determined by the investigator, or the date of death due to any cause, whichever occurs first. Last contact date (as defined above for DOR) will be used for the censoring of participants still alive with no reported disease progression

(objective or clinical). The same rules described above for the censoring of participants who start anti-cancer therapy will be applied in this sensitivity analysis.

Further details on the derivation of PFS are included in the Derivation of Efficacy Endpoints document Version 0.6 (dated 21 January 2022).

Overall survival (OS) will be calculated as the time in days from the date of first dose of study treatment to the date of death from any cause. Participants will be followed up to ascertain their survival status at the SFU visit (within 30 days after their last dose of study treatment) and at the Final Visit (3 months after their last dose of study treatment); they will not be followed up beyond this timepoint.

The following calculation will be performed:

$$OS = (Date\ of\ Death - Date\ of\ First\ Dose\ of\ Study\ Treatment) + 1$$

For participants who discontinue early from Part A of the study or who discontinue study treatment due to disease progression but continue in the study, who complete the Part A, or who are ongoing in the study at a data cut-off for Part A, but are not known to have died, OS will be censored on the date of their last contact.

10.1.2 Analysis of the antitumor activity endpoints

The analyses of the antitumor activity endpoints in Part A will be performed for the PPS. As a sensitivity analysis, all analyses will be repeated for the SS. All listings will be presented for the SS. Summaries and listings will be presented by treatment group.

All lesion assessment data recorded at Baseline and during the Treatment Period (during every even cycle of study treatment) will be listed separately for target lesions, non-target lesions and new lesions. These listings will include lesion number and lesion type (nodal/non-nodal), location, method of assessment, dimension (or an indication that the lesion is too small to measure, for target lesions only) and lesion response evaluation (for non-target lesions at post-Baseline assessments). The listing for target lesions will also include the derived eCRF component data used for the determination of the overall target lesion response at each post-Baseline assessment (e.g. sum of all dimensions across target lesions and percentage change from Baseline in the sum). In addition, the overall response assessment for target lesions and non-target lesions, as determined by the investigator, will be listed together with the presence of new lesions and the investigator's overall tumor response assessment.

The investigator's overall tumor response assessment will be summarized using frequency counts and percentages by visit (tumor assessment). For the purpose of this summary, post-Baseline tumor assessments (scheduled or unscheduled but excluding tumor assessments performed at the SFU visit) will be assigned to the targeted Day 22 visit of each even cycle of study treatment using the protocol-defined window of Day 21 to 28 (±2 days). For participants who receive 2 or more cycles of study treatment, post-Baseline tumor assessments that were performed on Day 19 to Day 30 relative to Day 1 of each even cycle will be included as Cycle 2/4/6/8 etc. Day 22 assessments. For participants who discontinue study treatment prior to the start of Cycle 2, post-Baseline tumor assessments that were performed on Day 47 to 58 relative to Day 1 of Cycle 1 will be included as a Cycle 2 Day 22 assessment. Otherwise, the tumor assessment will be classified as an unscheduled assessment and not included in the summary of overall tumor response.

Bar charts will also be produced for overall tumor response rate by treatment group for each visit. In addition, waterfall plots of participants' percentage change from Baseline in the sum of dimensions for all target lesions will be presented by treatment group and visit. The individual participants' bars will be colored by overall tumor response at the visit.

Confirmed BOR and unconfirmed BOR for each participant will be derived programmatically using the investigator's overall tumor response assessments (scheduled and unscheduled) performed between Days 21 and 28 of Cycle 2 and each subsequent even cycle of study treatment and the RECIST criteria. Whether a BOR of CR or PR is confirmed or unconfirmed will be indicated on this listing. Using a participant's confirmed BOR and unconfirmed BOR, whether the participant achieves an objective tumor response (i.e. a BOR of CR or PR) and/or disease control (i.e. a BOR of CR, PR or SD) during study treatment will be determined based on both confirmed BOR and unconfirmed BOR. These derived data will be listed for the SS.

Confirmed BOR and unconfirmed BOR will be summarized using frequency counts and percentages. Bar charts will also be produced for confirmed BOR and unconfirmed BOR by treatment group.

The number and percentage of participants achieving objective tumor response and disease control (ORR and DCR) based on confirmed BOR and unconfirmed BOR will be presented and, if data allow, exact 95% confidence intervals for binomial proportions will be calculated using the Clopper-Pearson method and presented for the response rates. In the calculation of ORR and DCR, the denominator will include all participants in the analysis set. Objective response rate and DCR (based on confirmed BOR and unconfirmed BOR) will also be summarized in bar charts by treatment group overall and by tumor type and ECOG performance status at Baseline.

In addition, waterfall plots of each participant's best percentage change from Baseline in the sum of the dimensions for all target lesions will be presented by treatment group overall and by tumor type and ECOG performance status at Baseline with the individual participants' bars colored by confirmed BOR and unconfirmed BOR.

The summaries and analyses of DOR, PFS and OS will be carried out as described below, if the data allow.

Duration of confirmed response, duration of unconfirmed response and PFS will be listed and summarized descriptively using Kaplan-Meier estimation. These summaries will be repeated for the sensitivity analyses of these endpoints (defined in Section 10.1.1 above) and will include the number and percentage of participants with the event, the number and percentage of participants censored, minimum and maximum values and Kaplan-Meier estimates of the 25th percentile, median, 75th percentile and corresponding 95% CIs calculated using Greenwood's formula. In addition, DOR and PFS rates at specific timepoints (3 months, 6 months, 9 months) will be derived from the Kaplan-Meier estimation and presented together with associated 95% CIs.

Kaplan-Meier curves will be presented for duration of confirmed response, duration of unconfirmed response and PFS, and for the associated sensitivity analyses. Treatment groups will be overlaid on each plot.

Survival status collected on the eCRF at the SFU visit and at the Final Visit will be listed for each participant by treatment group. This listing will include the participant's survival status,

date and cause of death, whether an autopsy was performed and date of autopsy, whether the participant had received any further antitumor treatment after the last dose of study treatment and the type of treatment, and whether the participant's disease had been assessed since the end of study treatment including method of assessment and the overall response.

Overall survival times will be listed and summarized descriptively using Kaplan-Meier estimation. Note that since participants are only followed up for survival until the Final Visit in Part A of the study, a summary of OS may not be meaningful (i.e. if no participants die then OS cannot be assessed).

Additional exploratory analyses of selected antitumor activity endpoints may be performed based on subgroups of participants in the SS.

Additionally, the relationship of the antitumor activity variables with key PK parameters may be explored but this will be reported separately.

10.2 ECOG performance status

ECOG performance status is an additional efficacy assessment performed in Part A of this study and is defined in Table 10-1.

Table 10-1: ECOG Performance Status Scale

Grade	ECOG performance status scale
0	Fully active, able to carry on all pre-disease performance without restriction
1	Restricted in physically strenuous activity but ambulatory and able to carry out work of a light or sedentary nature (e.g. light housework, office work)
2	Ambulatory and capable of all self-care but unable to carry out any work activities. Up and about more than 50% of waking hours
3	Capable of only limited self-care, confined to bed or chair for more than 50% of waking hours
4	Completely disabled. Cannot carry out any self-care. Totally confined to bed or chair
5	Dead

ECOG=Eastern Cooperative Oncology Group.

ECOG performance status will be listed by treatment group at each visit together with changes from Baseline for the SS.

ECOG performance status will be summarized as an ordinal categorical variable using frequency counts and percentages. Shift tables for the change from Baseline in each grade will be summarized by visit.

11 OTHER ANALYSES

Not applicable.

12 REFERENCES

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13 APPENDICES

13.1 SMQ algorithm for identification of anaphylactic reactions

Based on MedDRA Version 25.1, the SMQ='Anaphylactic reaction' consists of 3 parts:

1) A **narrow search** containing PTs that represent core anaphylactic reaction terms:

Category A

Anaphylactic reaction

Anaphylactic shock

Anaphylactic transfusion reaction

Anaphylactoid reaction

Anaphylactoid shock

Circulatory collapse

Dialysis membrane reaction

Kounis syndrome

Procedural shock

Shock

Shock symptom

Type I hypersensitivity

2) A **broad search**:

Category B

Acute respiratory failure

Asthma

Bronchial oedema

Bronchospasm

Cardio-respiratory distress

Chest discomfort

Choking

Choking sensation

Circumoral oedema

Cough

Cough variant asthma

Cyanosis

Dyspnoea

Hyperventilation

Irregular breathing

Laryngeal dyspnoea

Laryngeal oedema

Laryngospasm

Laryngotracheal oedema

Mouth swelling

Nasal obstruction

Oedema mouth

Oropharyngeal oedema

Oropharyngeal spasm

Oropharyngeal swelling

Pharyngeal oedema

Pharyngeal swelling

Respiratory arrest

Respiratory distress

Respiratory failure

Reversible airways obstruction

Sensation of foreign body

Sneezing

Stridor

Swollen tongue

Tachypnoea

Throat tightness

Tongue oedema

Tracheal obstruction

Tracheal oedema

Upper airway obstruction

Vaccine associated enhanced respiratory disease

Wheezing

Category C

Allergic oedema

Angioedema

Circumoral swelling

Erythema

Eye oedema

Eye pruritis

Eye swelling

Eyelid oedema

Face oedema

Flushing

Injection site urticaria

Lip oedema

Lip swelling

Nodular rash

Ocular hyperaemia

Oedema

Oedema blister

Periorbital oedema

Periorbital swelling

Pruritis

Pruritis allergic

Rash

Rash erythematous

Rash pruritic

Skin swelling

Swelling

Swelling face

Swelling of eyelid

Urticaria

Urticaria papular

Category D

Blood pressure decreased

Blood pressure diastolic decreased

Blood pressure systolic decreased

Cardiac arrest

Cardio-respiratory arrest

Cardiovascular insufficiency

Diastolic hypotension

Hypotension

Hypotensive crisis

Post procedural hypotension

Note that if the MedDRA version is increased from 25.1 during the study, any changes to the terms in the above categories should be applied.

The following **algorithmic approach** will be applied: A or (B and C) or [D and (B or C)], i.e.

If a participant has a TEAE which codes to a PT included in Category A, then the event will be flagged as an anaphylactic reaction. Note that participants with a TEAE coded to a PT=’Type 1 hypersensitivity’ will also be flagged as having a hypersensitivity reaction as this PT is also included in the Category A narrow search for the ‘Hypersensitivity’ SMQ.

OR

If a participant has a TEAE which codes to a PT included in Category B **AND** has a TEAE which codes to a PT included in Category C**, and both TEAEs have the same start date**, then both events will be flagged as anaphylactic reactions.

OR

If a participant has a TEAE which codes to a PT included in Category D **AND** has (either a TEAE which codes to a PT included in Category B **OR** a TEAE which codes to a PT included in Category C), **and both TEAEs have the same start date**, then both events will be flagged as anaphylactic reactions.

13.2 SAP Amendment 4 changes

The main rationale for SAP Amendment 4 is to include details on the additional key derived and component exploratory variables required based on the results from the analyses of historical tumor biopsy samples in Part A. It was decided that these additional variables were needed to improve the interpretability of the test results received from the laboratory. Note that there have not been any tumor biopsies performed at Screening or at Cycle 1 Day 22 in Part A. Per protocol, these tumor biopsies are optional in Part A and only samples available from historical tumor biopsies have been sent to the laboratory and analyzed to date. This SAP amendment also provides some clarifications relating to the handling of data for the purpose of summarizing safety and exploratory anti-tumor activity endpoints.

The key changes are summarized in the table below (note that additional minor corrections and clarifications were also applied in this amendment but are not included in this table).

Section	Description of Change
1	The versions and dates of supporting study documentation were updated.
3.5.7	The definition of the DLT Evaluable Set (DES) was included in this section consistent with the latest version of the protocol.
5.1	An update was made to the example illustrating the definition of a complete cycle of UCB6114.
8.1	The additional summary of the total number of doses of study treatment received was included.
8.2	Rules for handling missing relationship to study treatment for an adverse event were updated.
8.4.2	Clarification on the handling of triplicate ECG measurements was included.
9.2	Details on the analysis of the historical tumor biopsy samples was included together with rules for defining key and component derived variables based on the test results received from the laboratory. These variables were considered important for clearer interpretation of these results from data listings.
9.3	A predefined fold-increase of 1.80 was included.

Section	Description of Change
10.1.2	Rules for applying the protocol-defined window around the post-Baseline tumor assessments (scheduled and unscheduled) for the purpose of summarizing the investigator's overall tumor response assessment were included.
General	MedDRA® version number was updated to the latest version (25.1) throughout the document.

STATISTICAL ANALYSIS PLAN SIGNATURE PAGE

This document has been reviewed and approved per the Review and Approval of Clinical Documents Standard Operating Procedures. Signatures indicate that the final version of the Statistical Analysis Plan (SAP) or amended SAP is released for execution.

STATISTICAL ANALYSIS PLAN

PART A1

DOSE OPTIMIZATION (MONOTHERAPY)

Study: ONC001

Product: UCB6114

A PHASE 1/2 OPEN-LABEL, MULTICENTER STUDY TO ASSESS THE SAFETY, PHARMACOKINETICS, AND ANTITUMOR ACTIVITY OF UCB6114 ADMINISTERED INTRAVENOUSLY TO PARTICIPANTS WITH ADVANCED SOLID TUMORS

SAP/Amendment Number	Date
Amendment 1	25 July 2023

Confidentiality Statement

TABLE OF CONTENTS

LIST OF ABBREVIATIONS

AE	adverse event
AESI	adverse event of special interest
ADA	anti-drug (UCB6114) antibody
ADaM	Analysis Data Model
ADAS	anti-drug antibody set
ALP	alkaline phosphatase
ALQ	above limit of quantification
ALT	alanine aminotransferase
AST	aspartate aminotransferase
BLQ	below limit of quantification
BMI	body mass index
BOR	best overall response
CA	cancer
CDISC	Clinical Data Interchange Standards Consortium
CDMS	clinical data management system
cGremlin-1	circulating gremlin-1
CI	confidence interval
COVID-19	coronavirus disease 2019
CPPC	CDMS postproduction change
CR	complete response
CS	clinically significant
CRC	colorectal adenocarcinoma
CRO	contract research organization
CSR	clinical study report
ctDNA	circulating tumor deoxyribonucleic acid
CTMS	clinical trial management system

DCR	disease control rate
DEM	data evaluation meeting
DES	DLT evaluable set
DLT	dose limiting toxicity
DOR	duration of response
ECG	electrocardiogram
ECOG	Eastern Cooperative Oncology Group
eCRF	electronic case report form
EMA	European Medicines Agency
ES	enrolled set
EudraCT	European Union Drug Regulating Authorities Clinical Trials
FAP	fibroblast activation protein
FDA	Food and Drug Administration
GCP	good clinical practice
GEJ	gastroesophageal junction
geoCV	geometric coefficient of variation
geoMean	geometric mean
H & E	hematoxylin and eosin
hh:mm	hours:minutes
HLT	high level term
ICH	International Council for Harmonization
IHC	immunohistochemistry
IM	invasive margin
iv	intravenous
IPD	important protocol deviations
LLOQ	lower limit of quantification
LLT	lowest level term
LoT	list of TFLs

LVEF	left ventricular ejection fraction
MedDRA®	Medical Dictionary for Regulatory Activities
MRD	minimum required dilution
n	number of study participants
NCI CTCAE	National Cancer Institute Common Terminology Criteria for AEs
NC	not calculable
NCS	not clinically significant
NEst	not estimable
NV	no value
ORR	objective tumor response rate
OS	overall survival
PCS	potentially clinically significant
PD	pharmacodynamic(s)
PDILI	potential drug-induced liver injury
PDS	pharmacodynamic set
PK	pharmacokinetic(s)
PKS	pharmacokinetic set
PFS	progression-free survival
PPS	per-protocol set
pSMAD1/5/8	phosphorylated mothers against decapentaplegic homolog 1/5/8
PR	partial response
PT	preferred term
PTEN	phosphatase and tensin homolog
Q2W	every 2 weeks
Q3W	every 3 weeks
Q4W	every 4 weeks
QTcF	QT interval corrected for heart rate using Fridericia's formula
RECIST	Response Evaluation Criteria in Solid Tumors

SAE	serious adverse event
SAP	statistical analysis plan
SD	stable disease
SDTM	Study Data Tabulation Model
SFU	safety follow-up
SI	International System of Units
SMAD4	mothers against decapentaplegic homolog 4
SMC	Safety Monitoring Committee
SoC	standard of care
SOC	system organ class
SS	safety analysis set
TEAE	treatment-emergent adverse event
TEMA	treatment-emergent markedly abnormal
TFL	Table, Figure and Listing
TNM	TNM Classification of Malignant Tumors
TPS	tumor proportion score
UK	United Kingdom
ULN	upper limit of normal
US	United States
WHODD	World Health Organization Drug Dictionary

1 INTRODUCTION

The purpose of this statistical analysis plan (SAP) is to provide all information that is necessary to perform the required statistical analysis of the dose optimization module (Part A1) of study ONC001. Separate SAPs are available for the other parts of the study. This SAP also describes the summary tables, figures and listings (TFLs) to be generated for Part A1 according to

Protocol amendment 6, dated 26 JUN 2023,

Electronic case report form (eCRF) (Clinical Data Management System [CDMS] postproduction change [CPPC] #14, Version 23.0, dated 14 APR 2023),

UCB's standards for TFL shells Version 2023Q1,

Part A TFL shells Final Version 2.4, dated 4 JUL 2023,

Part A1 TFL shells Final Version 2.0, dated 25 JUL 2023,

Part A, A1, B, C List of TFLs (LoT) Draft Version 1.1, dated 13 MAR 2023,

ONC001 Derivation of Efficacy Endpoints Version 0.6, dated 21 JAN 2022.

Unless specified in the sections below, Part A1 of the study will be analyzed as described in the most recent version of the protocol. If a future protocol amendment necessitates a substantial change to the analysis of the Part A1 study data, this SAP will be amended accordingly. In addition, if the methodology for the analysis of key study endpoints must be modified or updated prior to the final database lock for Part A1 of this study, a SAP amendment will be required. Protocol amendments that do not affect the statistical analysis will not necessitate an amendment to the SAP. If, after database lock, additional analyses are required to supplement the planned analyses described in this SAP, these changes will be described in the clinical study report (CSR) together with the associated rationale.

Note that there may be a number of data cut-offs defined prior to the final database lock for Part A1 due to the regulatory safety reporting requirements for this study.

The content of this SAP is compatible with the International Council for Harmonization (ICH)/Food and Drug Administration (FDA) E9 Guidance.

UCB is the Sponsor and ICON PLC is the contract research organization (CRO) for this study.

2 PROTOCOL SUMMARY

2.1 Study objectives

2.1.1 Primary objective

The primary objective of Part A1 (dose optimization module) of this study is to characterize the safety profile of UCB6114 administered as monotherapy in study participants with unresectable locally advanced or metastatic colorectal adenocarcinoma, gastric adenocarcinoma, adenocarcinoma of the gastroesophageal junction, or pancreatic adenocarcinoma.

2.1.2 Secondary objective

The secondary objective of Part A1 of this study is to characterize the pharmacokinetics (PK) of UCB6114 administered as monotherapy in study participants with unresectable locally advanced or metastatic colorectal adenocarcinoma, gastric adenocarcinoma, adenocarcinoma of the gastroesophageal junction, or pancreatic adenocarcinoma.

2.1.3 Exploratory/Tertiary objectives

The exploratory/tertiary objectives of Part A1 of this study are:

- To document any antitumor activity observed with UCB6114 administered according to relevant Response Evaluation Criteria in Solid Tumors (RECIST) criteria;
- To explore pharmacodynamics (PD) biomarkers of UCB6114;
- To evaluate the incidence, emergence, and impact of anti-drug (UCB6114) antibody (ADA) activity.

2.2 Study endpoints

2.2.1 Safety endpoints

2.2.1.1 Primary safety endpoints

The primary endpoints for Part A1 of this study are for safety, specifically the incidence and severity of treatment-emergent adverse events (TEAEs) (including serious adverse events [SAEs]) from the first dose of UCB6114 on Day 1 of Cycle 1 to the Safety Follow-up (SFU) visit, and the incidence of dose limiting toxicities (DLTs) from the first dose of UCB6114 on Day 1 of Cycle 1 to the end of the 28-day DLT Observation Period for all cohorts.

2.2.1.2 Other safety endpoints

The following other safety data will be assessed during Part A1 of the study to further support the characterization of the safety profile of UCB6114 administered as monotherapy:

- Clinical laboratory data (hematology, serum chemistry, coagulation and urinalysis);
- Vital signs (systolic and diastolic blood pressure, pulse rate, respiratory rate, and body temperature);
- 12-lead electrocardiogram (ECG);
- Echocardiogram (left ventricular ejection fraction [LVEF]);
- Eastern Cooperative Oncology Group (ECOG) performance status;
- Physical examination.

2.2.2 Pharmacokinetic and pharmacodynamic endpoints

2.2.2.1 Secondary pharmacokinetic endpoint

The secondary endpoint in Part A1 of this study is for PK, specifically UCB6114 concentration by scheduled assessment for each UCB6114 dose schedule cohort.

2.2.2.2 Exploratory pharmacokinetic endpoints

[redacted] will be exploratory PK endpoints in Part A1.

2.2.2.3 Exploratory pharmacodynamic endpoints

The following exploratory PD endpoints will be assessed in Part A1 and reported separately outside of the CSR:

- Change in transcriptional and protein marker levels in blood and tumor tissue by scheduled assessment/timepoint and for each UCB6114 dose schedule cohort.
- Change in circulating tumor deoxyribonucleic acid (ctDNA) levels in blood by scheduled assessment and for each UCB6114 dose schedule cohort.

2.2.2.4 Exploratory immunogenicity endpoints

Immunogenicity in Part A1 will be explored using ADA sample status and participant classification, and changes in titer over time. Potential relationships between ADA and PK, PD, anti-tumor activity and safety may also be explored but these analyses will be reported separately outside of the CSR.

2.2.3 Efficacy endpoints

2.2.3.1 Exploratory antitumor activity endpoints

Antitumor activity in Part A1 will be explored using the following endpoints:

- Objective tumor response rate (ORR);
- Disease control rate (DCR);
- Duration of antitumor response (DOR);
- Progression-free survival (PFS);
- Overall survival (OS).

2.2.3.2 Other exploratory efficacy endpoint

To further explore efficacy in Part A1 of the study, changes from Baseline in the ECOG performance status scale will be assessed.

2.3 Study design and conduct

Study ONC001 is a multicenter, nonrandomized, open-label, Phase 1/2 study evaluating the safety, PK, efficacy (as assessed by antitumor activity), PD, biomarkers, and immunogenicity (ADA activity) of intravenous (iv) UCB6114 as monotherapy and in combination with selected standard of care (SoC) regimens in study participants with advanced solid tumors.

The study has a modular design including up to 3 dose escalation modules (Parts A, B, and C), 1 dose optimization module (Part A1), and up to 4 dose expansion modules (Parts D, E, F, and G). Depending on emerging data, not all modules may open. This SAP is focused only on the dose optimization module of the study to evaluate alternative dosing schedules for UCB6114 administered as monotherapy in participants with unresectable locally advanced or metastatic colorectal adenocarcinoma, gastric adenocarcinoma, adenocarcinoma of the gastroesophageal junction, or pancreatic adenocarcinoma.

Part A1 consists of a Screening Period, Treatment Period (consisting of 28-day cycles for Cohorts 1, 2, and 4, and of 21-day cycles for Cohort 3), a SFU visit and a Final Visit. During the Treatment Period, UCB6114 will be administered as iv infusion as per the defined dosing

schedules in Table 6-6 of the protocol until the occurrence of progressive disease, unacceptable toxicity, or withdrawal of consent.

Part A1 will be initiated after Cohort 5 of Part A (2000mg every 2 weeks [Q2W]) has been determined to be safe (i.e. DLT incidence <33%, see Section 4.1.2.4 of the protocol). Eligible participants with unresectable locally advanced or metastatic colorectal adenocarcinoma, gastric adenocarcinoma, adenocarcinoma of the gastroesophageal junction, or pancreatic adenocarcinoma will receive iv infusion of UCB6114 as monotherapy.

The planned dose optimization scheme for Part A1 will assess the safety and tolerability of the new drug formulation and will explore shortening of the infusion time and less frequent dosing as follows:

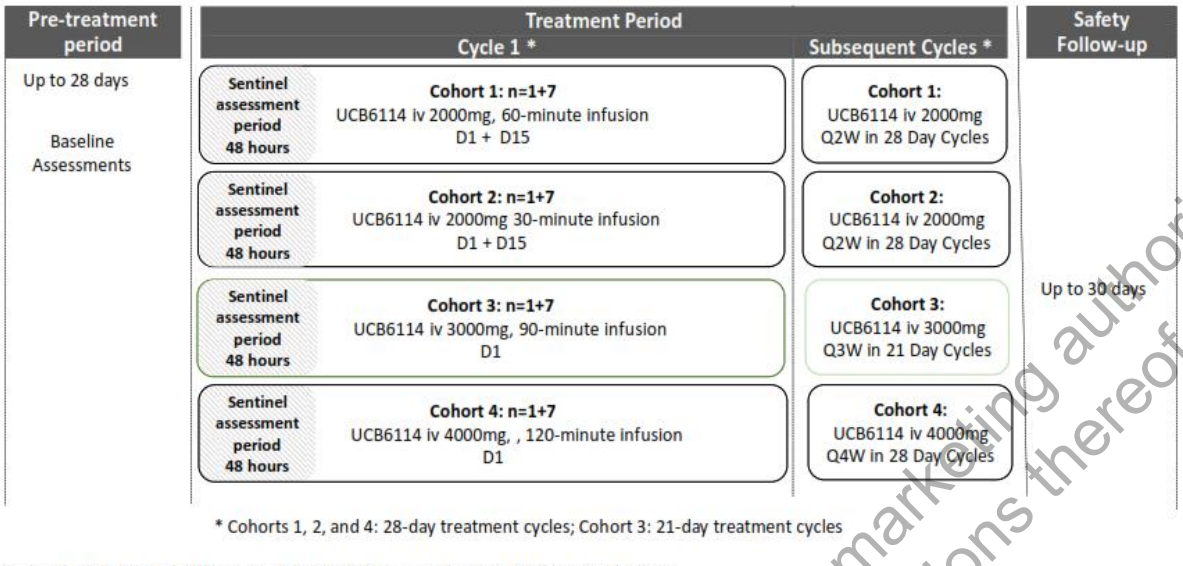
- Cohort 1: 2000mg Q2W (60-minute iv infusion), 28-day treatment cycle
- Cohort 2: 2000mg Q2W (30-minute iv infusion), 28-day treatment cycle
- Cohort 3: 3000mg every 3 weeks (Q3W) (90-minute iv infusion), 21-day treatment cycle
- Cohort 4: 4000mg every 4 weeks (Q4W) (120-minute iv infusion), 28-day treatment cycle

Up to 32 participants will be allocated 1:1:1:1 to one of the 4 cohorts, with each cohort enrolling up to 8 study participants including 1 sentinel participant with an observation period of 48 hours. The enrollment of a sentinel participant in each cohort has been included as an additional risk mitigation measure to monitor infusion related reactions and other early onset treatment-related AEs.

The planned duration of study treatment is 2 cycles. Participants may, however, remain in the study for additional cycles if they are receiving therapeutic benefit (stable disease [SD], partial response [PR], or complete response [CR]) or until they fulfill one of the criteria for study treatment discontinuation. Participants will continue study treatment until disease progression, unmanageable toxicity, or withdrawal of consent. Upon discontinuation from study treatment, participants will be referred to appropriate follow-up care per the investigator's judgment.

A schematic diagram of Part A1 of the study is provided in Figure 2-1.

Figure 2-1: Study Schematic for Part A1



A Safety Monitoring Committee (SMC) will convene after each sentinel participant is assessed for at least 48 hours following the first administration of UCB6114 in the first cycle of a cohort to determine whether further participants within the cohort can be enrolled. The SMC will also convene after 25%, 50% and 100% of study participants in Part A1 have completed the required 28-day DLT Observation Period. If deemed necessary, an additional SMC meeting can convene after 75% of the participants have completed the required 28-day DLT Observation Period. If 1 or more DLTs are reported for a cohort then an *ad hoc* SMC will convene to determine if the dosing schedule and study module can continue as planned.

After consultation, the SMC will provide recommendations which could include an expansion of enrollment in a particular cohort to gain additional safety data, continuation of Part A1 with modifications or a temporary suspension of enrollment in a particular cohort. Details are described in the Part A1 SMC Charter.

2.4 Determination of sample size

In Part A1, up to 32 eligible participants will be enrolled across 4 alternative dosing schedules; 8 participants per cohort is considered sufficient to protect against an unacceptable level of toxicity. The probability of declaring a dose schedule (cohort) too toxic, given a toxicity rate greater than the maximum tolerable toxicity rate (33%) is approximately 90%. However, the probability is reduced to 80% when the dose optimization module is considered independent of Part A. An administrative decision to stop enrolling into Part A1 may be made by the Sponsor at any time.

3 DATA ANALYSIS CONSIDERATIONS

3.1 General presentation of summaries and analyses

All TFLs will be produced by ICON PLC using SAS® Version 9.4 or higher (SAS Institute, Cary, North Carolina, USA). ICON PLC will also produce the analysis datasets which will adhere to the Clinical Data Interchange Standards Consortium (CDISC) guidance documents for Analysis Data Model (ADaM) and follow UCB's interpretation. General statistical and reporting conventions will follow the current UCB Global Conventions Document Version 1.1.

Data will be summarized by UCB6114 dose schedule cohort (treatment group), visit and timepoint, as applicable. All relevant reported and derived data will be listed and will be presented by treatment group, study participant and visit, as applicable.

Categorical variables will be summarized using frequency counts and percentages. Unless otherwise stated, the denominator for the percentages will be based on the number of participants in the respective analysis set, treatment group, visit and timepoint (as applicable) with non-missing data.

When reporting frequency counts and percentages, the following rules apply:

- For categories where all participants fulfill certain criteria, the percentage value will be displayed as 100;
- For categories where zero participants fulfill certain criteria, there will be no percentage displayed;
- All other percentage displays will use 1 decimal place.

Summary statistics will be presented for continuous variables including number of participants (n), arithmetic mean, standard deviation, median, minimum and maximum. 95% confidence intervals (CIs) for the arithmetic mean may also be included depending on the variable and where stated in the SAP. Geometric mean (geoMean), geometric coefficient of variation (geoCV) and 95% CI for the geoMean will also be presented in the summaries of UCB6114 concentration data. In all relevant outputs the 95% confidence limits will be restricted to the possible values that the variable can take.

When reporting descriptive statistics for data other than UCB6114 concentration data, the following rules will apply:

- n will be an integer;
- Mean (arithmetic and geometric), standard deviation, median and quartiles will use 1 decimal place more, or 1 significant figure more – depending on the reporting format of the original data – than the original data. Original data may be data as reported directly onto the eCRF or summary data based on data reported onto the eCRF (e.g. mean of triplicates or percentage change from Baseline);
- Confidence intervals will be presented to the same number of decimal places as the value around which the CI is constructed;
- Minimum and maximum will be reported using the same number of decimal places or significant figures as the original value;

- A minimum of 3 values are required to calculate summary statistics. If only 2 values are available, then these should be presented as the minimum and maximum with other summary statistics reported as missing ("- "); if no participants have data at a given timepoint, then only n=0 will be presented;
- Percentage change from Baseline values will be calculated and displayed to 1 decimal place in the listings. In the summaries, where applicable, the mean, standard deviation and median percentage change from Baseline values will be presented to 2 decimal places and the minimum and maximum values presented to 1 decimal place.

When reporting individual UCB6114 concentration data in listings and figures, and presenting summary statistics in tables, the following rules will apply:

- UCB6114 concentration data should be reported in the listings to the same level of precision as received from the bioanalytical laboratory;
- Missing data should be reported as 'NV' (no value) in the listings;
- Concentrations below the lower limit of quantification (LLOQ) should be reported as BLQ (below the limit of quantification) in the listings;
- BLQ values prior to C_{max} should be set to 0 for purposes of plotting a figure (to capture lag-time);
- Actual sampling times will be used in the spaghetti plots of individual PK concentrations over time, and nominal sampling times will be used in the summaries of geoMean concentrations over time;
- UCB6114 concentration data should be plotted on both linear and semi-logarithmic scales;
- To calculate summary statistics, BLQ values should be set to half the LLOQ value and missing values should be excluded;
- When the total number of BLQ and missing values exceeds one third of the total then only minimum and maximum should be reported for this timepoint. Other summary statistics should be reported as missing ("-"). The minimum should be reported as BLQ;
- When the mean value includes one or more replaced BLQ values then a footnote should be included to say "contains one or more BLQ values replaced by half the LLOQ value";
- A minimum of 3 values are required to calculate summary statistics. If only 2 values are available, then these should be presented as the minimum and maximum with other summary statistics reported as missing ("- "); if no participants have data at a given timepoint, then only n=0 will be presented;
- Summary statistics for UCB6114 concentration data will be reported to the same level of precision as the individual data for the minimum and maximum, and to 1 additional decimal place or 1 additional significant figure – depending on the reporting format of the original data with a maximum of 3 significant figures - for the mean (arithmetic and geometric), median and standard deviation. The 95% CI for the geoMean will use the same number of decimal places or significant figures as the geoMean. It will be left blank if the geoCV is 0;

- Geometric coefficient of variation will be reported as a percentage to 1 decimal place. The geoCV will be calculated using the following formula where SD is the standard deviation from the log-transformed data:

$$GeoCV(\%) = \sqrt{\exp SD^2 - 1} \times 100$$

When reporting PK parameters in listings and figures, and presenting summary statistics in tables, the following rules will apply:

[redacted]

3.2 General study level definitions

3.2.1 Relative day and time

For each participant, the relative day of an event or assessment will be derived using the earliest date of their first dose of UCB6114 as reference.

Relative days for an event or assessment occurring before the date of the first dose are calculated as follows:

Relative Day = Event/Assessment Date - Date of First Dose of UCB6114

The relative day for an event or assessment occurring on the date of first dose is 1. The relative day for an event or assessment occurring on or after the first dose to the date of the last dose of UCB6114 will be calculated as follows:

Relative Day = (Event/Assessment Date - Date of First Dose of UCB6114) + 1

For events or assessments occurring after the date of the last dose of UCB6114, relative day will be prefixed with '+' in the data listings and will be calculated as follows:

Relative Day = Event/Assessment Date – Date of Last Dose of UCB6114

There is no relative Day 0. Relative day will not be calculated in cases where dates are partial and should be presented as "--" in the relevant data listing.

Relative time of TEAEs recorded on, but not limited to, the day of UCB6114 infusion, will be derived in minutes as follows using the infusion start time as reference:

Relative Time of TEAE = Onset Time of TEAE – Start Time of UCB6114 Infusion

Relative times of PK and PD sampling will be derived in hours using the end of infusion times on the day of UCB6114 dosing as reference:

Relative Sampling Time = Sampling Time – End Time of UCB6114 Infusion

3.2.2 Study periods

Part A1 of the study will consist of the following study periods:

- Screening Period – up to 28 days;
- Treatment Period – Successive 28-day cycles for Cohorts 1, 2, and 4, and 21-day cycles for Cohort 3. UCB6114 is administered as iv infusion as per defined dosing schedules until the occurrence of progressive disease, unacceptable toxicity, or withdrawal of consent;
- Safety Follow-up Period – up to 30 days after the last dose of UCB6114.

There will be a further extended follow-up period, up to 3 months after the last dose of UCB6114, at which time the Final Visit will be performed.

For each participant, the end of the Treatment Period is defined by the date of their last dose of UCB6114.

The end of Part A1 of the study is defined by the date of the Final Visit for the last participant (3 months after the last participant's last dose of UCB6114), or the date of the SFU visit, if they discontinue prior to attending the Final Visit, or their last contact date if they discontinue early from the study without attending the SFU visit.

3.2.3 Visits

Unless otherwise specified, in the TFLs, visits will be labelled as follows (as applicable) using timepoints as recorded in the database:

Screening
Baseline
Cycle 1, Day X
Cycle 2, Day X
Cycle 3, Day X
Cycle 4, Day X
Cycle X, Day X
Etc.
SFU
Final Visit

3.3 Definition of Baseline values

Baseline in Part A1 will be the last available value prior to the first dose of UCB6114. Both scheduled and unscheduled values, as well as any repeated values, should be used when defining Baseline.

Measurement-specific Baseline definitions are presented in Table 3-1 below.

Table 3-1: Definition of Baseline

Measurement	Definition of Baseline
Echocardiogram (LVEF) Tumor assessments (antitumor activity) Tumor biopsy (Ki67, SMAD4, FAP, pSMAD1/5/8)	Screening value
12-lead ECG Physical examination and weight Vital signs Clinical laboratory data ECOG performance status	Predose value obtained on Cycle 1, Day 1, or, if missing, Screening value
Circulating gremlin-1 (cGremlin-1) Immunogenicity (ADA)	Predose sample value obtained on Cycle 1, Day 1

ADA=anti-drug (UCB6114) antibody; ECG=electrocardiogram; ECOG=Eastern Cooperative Oncology Group; LVEF=left ventricular ejection fraction.

3.4 Protocol deviations

Per ICH definition, important protocol deviations (IPDs) are a subset of protocol deviations that may significantly impact the completeness, accuracy, and/or reliability of the study data or that may significantly affect a participant's rights, safety, or well-being. The criteria for identifying potentially important protocol deviations will be defined within the IPD specifications document.

For Part A1 of this study, IPDs will be categorized as follows:

- Inclusion/exclusion criteria deviations;
- Incorrect treatment or dose administered;
- Procedural non-compliance;
- Prohibited concomitant medication use (see Section 6.5.6 of the protocol);
- Withdrawal criteria deviation.

All protocol deviations will be reviewed as part of the ongoing data cleaning process and Data Evaluation Meetings (DEMs), and decisions made on whether they should be considered important or not, and whether they warrant a participant's exclusion from an analysis set, or partial exclusion from an analysis due to being an IPD (e.g. prohibited concomitant medication use). Multiple DEMs will be scheduled prior to the final database lock for Part A1, in line with

regulatory safety reporting requirements, with the final one held after all data have been verified/coded/entered into the database.

More specifically, participants who have IPDs relating to dosing of UCB6114 (e.g. interrupted, discontinued and missed infusion, incomplete/incorrect dose administered, additional dose received, or infusions administered outside of the defined visit window) will be reviewed at the DEM for potential exclusion of UCB6114 concentration data from the by-visit summaries at an individual visit or from the visit at which the dosing deviation was observed onwards.

Any protocol deviations that are considered related to coronavirus disease 2019 (COVID-19) will be reviewed on an ongoing basis in case they collectively or individually give reason to consider a protocol amendment (e.g. study design changes or changes to primary analysis methods etc.). To facilitate this ongoing review, protocol deviations will be categorized as 'related to COVID-19' within the Clinical Trial Management System (CTMS) (ICOTrial). The COVID-19-related IPDs will then be listed separately for review and discussion at the DEMs.

3.5 Analysis sets

Study participants will be analyzed according to the dose, frequency of dosing and duration of infusion they actually received regardless of which treatment group they were assigned to.

3.5.1 Enrolled Set (ES)

The Enrolled Set (ES) consists of all study participants who sign the Informed Consent Form.

This analysis set includes screening failures and will be used for the summary of disposition of study participants and for selected data listings (which will include all available data for the screening failures).

3.5.2 Safety Analysis Set (SS)

The Safety Analysis Set (SS) consists of all study participants who receive at least 1 full or partial dose of UCB6114.

This analysis set will be used for the reporting of demographic, baseline characteristics, safety and immunogenicity data. All summaries of the exploratory antitumor activity endpoints will be repeated for the SS as a sensitivity analysis.

3.5.3 Per-protocol Set (PPS)

The Per-protocol Set (PPS) consists of all study participants in the SS who do not have IPDs that may substantially affect antitumor activity. Potential exclusions will be reviewed at the DEMs and a final determination of the composition of this analysis set will be made prior to the final database lock for Part A1.

The PPS will be the primary analysis set for the analysis of the exploratory antitumor activity endpoints.

3.5.4 Pharmacokinetic Set (PKS)

The Pharmacokinetic Set (PKS) consists of all study participants in the SS who have at least 1 evaluable postdose UCB6114 concentration sample (i.e. a sample which is above the lower limit of quantitation and for which the date and time of the sample and prior date and time of dosing are known). Additional participants or specific samples may be excluded from the PKS at

the discretion of the Advanced Modeling and Simulation scientist/Quantitative Clinical Pharmacologist at UCB.

Pharmacokinetic analysis will be performed for the PKS.

3.5.5 Anti-drug Antibody Set (ADAS)

The Anti-drug Antibody Set (ADAS) consists of all study participants in the SS who have at least 1 evaluable ADA assessment (i.e. a sample that has a reported result [is not missing or inconclusive]).

Immunogenicity analyses will be performed for the ADAS.

3.5.6 Pharmacodynamic Set (PDS)

The Pharmacodynamic Set (PDS) consists of all study participants in the SS who have at least 1 evaluable PD assessment (where appropriate, the sample should be above the lower limit of quantitation and the date and time of the sample should be known).

Pharmacodynamic analyses will be performed for the PDS.

3.5.7 DLT Evaluable Set (DES)

The DLT Evaluable Set (DES) will include all study participants who, during the 28-day DLT Observation Period, receive the planned dose of UCB6114.

The DES will be used only for evaluations by the SMC to determine if a dosing schedule and Part A1 can continue as planned.

3.6 Treatment assignment and treatment groups

In Part A1, it is planned that study participants will be dosed with UCB6114 to evaluate a new dose formulation, different frequencies of dosing (e.g. Q3W, Q4W), and different durations of infusion. Treatment groups will be defined by each UCB6114 dose schedule cohort and will be presented in ascending cohort number order and labelled in the TFLs as illustrated in Table 3-2.

Table 3-2: Treatment Group Labels

UCB6114 Dose Schedule Cohort	Planned Treatment Group Label
Cohort 1	UCB6114 2000mg Q2W (60-min), 28D
Cohort 2	UCB6114 2000mg Q2W (30-min), 28D
Cohort 3	UCB6114 3000mg Q3W (90-min), 21D
Cohort 4	UCB6114 4000mg Q4W (120-min), 28D

min=minutes; Q2W=every 2 weeks; Q3W=every 3 weeks; Q4W=every 4 weeks; 21D=21-day cycle; 28D=28-day cycle.

UCB6114 dose schedule cohort will be referred to as ‘treatment group’ from this point onwards in the SAP and in the TFLs.

3.7 Center pooling strategy

Each study site will contribute to the summaries of data from Part A1 according to the number of evaluable participants recruited; no separate summaries for each site will be presented.

3.8 Coding dictionaries

Adverse events (AEs) and medical history will be coded by UCB, using the latest available version of the Medical Dictionary for Regulatory Activities (MedDRA®) (Version 25.1 or higher). The National Cancer Institute Common Terminology Criteria for AEs (Version 5.0) (NCI CTCAE) dictionary will also be used by the investigator to assign CTCAE severity grades to each adverse event (AE) and will be merged with the clinical database to define a CTCAE code and term to be used in the summaries of TEAEs by maximum CTCAE severity grade.

Medications (including prior anti-cancer systemic therapies) will be coded according to the World Health Organization Drug Dictionary (WHODD) (Version SEP/2020). Medical procedures will not be coded.

The versions of the coding dictionaries used will be displayed in the relevant TFLs.

3.9 Changes to protocol-defined analyses

The following changes to the protocol have been incorporated into the SAP:

- Other safety data have not been defined as safety endpoints in the protocol, e.g. clinical laboratory data, vital signs, ECG, echocardiogram, ECOG performance status and physical examination. These have been listed in Section 2.2.1 of the SAP as 'other safety endpoints' to support the characterization of the safety profile of UCB6114 and to provide supporting evidence of any measurements that are deemed abnormal and clinically significant and reported as an AE.
- ECOG performance status is defined as an efficacy assessment in Section 9.6.2 of the protocol, however, it will also be assessed from a safety perspective in Part A1. The SAP therefore includes ECOG performance status as both a safety endpoint (Section 2.2.1) and an exploratory efficacy endpoint (changes from Baseline during Part A1 in Section 2.2.3).

4 STATISTICAL/ANALYTICAL ISSUES

4.1 Adjustments for covariates

Not applicable.

4.2 Handling of dropouts or missing data

There will be no imputation of missing data unless otherwise stated in the sections below.

4.3 Pharmacokinetics and pharmacodynamics

The reporting and handling of missing values and values that are BLQ in the TFLs is described in Section 3.1. Zero values will be assumed at the predose timepoint on Day 1 of Cycle 1.

4.4 Safety laboratory data

The rules for handling values that are BLQ in the safety laboratory data will be the same as those described for PK data in Section 3.1. Any values above the limit of quantification (ALQ) will be assigned as the value of upper limit of quantification.

4.4.1 Dates and times

Partial dates may be imputed for the following reasons:

- Classification of AEs as treatment-emergent;
- Classification of medications recorded on the concomitant medications log as prior or concomitant;
- Calculation of time since initial diagnosis, time since completion of most recent line of prior anti-cancer systemic therapy and time since progression/relapse on most recent line of prior anti-cancer systemic therapy.

Imputed dates will not be shown in the listings; all dates will be displayed as reported in the database.

The following rules will be applied for partial onset/start dates:

- If only the month and year are specified and the month and year of the first dose of UCB6114 is not the same as the month and year of the start date then the 1st of the month will be used, or the date of the Screening visit if this is later (if the latter imputation results in an end date that is earlier than the start date, then the 1st of the month will be used);
- If only the month and year are specified and the month and year of the first dose of UCB6114 is the same as the month and year of the start date, then the date of the first dose of UCB6114 will be used. If this results in an imputed start date that is after the specified end date, then the 1st of the month will be used, or the date of the Screening visit if this is later (if the latter imputation results in an end date that is earlier than the start date, then the 1st of the month will be used). If the imputed date is the same date as the date of the first dose of UCB6114 then, for AEs, the event will be regarded as treatment-emergent. For medications, the medication will be classified as concomitant;
- If only the year is specified, and the year of the first dose of UCB6114 is not the same as the year of the start date then January 01 will be used;
- If only the year is specified, and the year of the first dose of UCB6114 is the same as the year of the start date, then the date of the first dose of UCB6114 will be used. If this results in an imputed start date that is after the specified end date, then January 01, or the date of the Screening visit if this is later will be used (if the latter imputation results in an end date that is earlier than the start date, then January 01 will be used). If the imputed date is the date of the first dose of UCB6114 then, for AEs, the event will be regarded as treatment-emergent. For medications, the medication will be classified as concomitant.
- If the onset/start date is completely missing then the onset/start date will be imputed to the date of first dose of UCB6114 and therefore, for AEs, the event will be regarded as

treatment-emergent and, for medications, the medication will be classified as concomitant.

The following rules will be applied to partial end/stop dates:

- If only the month and year are specified, then the last day of the month will be used;
- If only the year is specified, then December 31 of the known year will be used;
- If the stop date is completely unknown, the stop date will not be imputed.

Note that the start date or stop date of a prior medication (partial or otherwise) should not be imputed past the Screening visit date - 1.

In addition to onset and stop dates, the onset and end times of AEs occurring on the day of UCB6114 infusion will be collected on the eCRF. Onset and end times may also be recorded for other AEs that do not occur on the same day as the UCB6114 infusion. The duration of AEs with onset and end times will be calculated in days and hours:minutes (hh:mm) as:

Duration of AE = End Date and Time – Onset Date and Time

In cases where only the onset and stop dates are recorded for an AE, the duration of an AE will be calculated in days as:

Duration of AE = (Stop Date – Onset Date) + 1

Note that for participants who have an AE which starts and stops on the same day, but with only a start time or only a stop time recorded, it will be assumed that their AE started from 00:00 (if no start time is recorded) and ended at 23:59 (if no stop time is recorded) on that day.

If the date of a participant's initial diagnosis is incomplete, it will be imputed to the most recent feasible date for the calculation of time since initial diagnosis as follows:

- If only the day is missing, it will be imputed to the last day of the known month;
- If the day and month are missing, it will be imputed to December 31 in the known year;
- If the date of initial diagnosis is completely missing, then time since initial diagnosis will not be calculated.

The above date imputation rules will be applied to partially missing stop dates of a participant's last prior anti-cancer systemic therapy as well as partially and completely missing dates of progression/relapse on last prior anti-cancer systemic therapy.

In cases where the stop date of a participant's last prior anti-cancer systemic therapy and/or a participant's date of progression on last line of prior anti-cancer systemic therapy is completely missing, the participant's Screening date -1 will be used in the calculation of the time since completion of most recent line of prior anti-cancer systemic therapy and the time since progression/relapse on most recent line of prior anti-cancer systemic therapy, respectively.

Note that partial dates will not be imputed as a participant's first dose of UCB6114 in the calculation of time since initial diagnosis, time since completion of most recent line of prior anti-

cancer systemic therapy and time since progression/relapse on most recent line of prior anti-cancer systemic therapy.

4.4.2 Impact of COVID-19

The FDA and European Medicines Agency (EMA) have provided guidance (see references listed in Section 12) to help assure the safety of all trial participants, maintaining compliance with good clinical practice (GCP), and minimizing risks to trial integrity during the COVID-19 pandemic. At the time of writing this SAP, the impact of the pandemic is still evolving, and regulators continue to clarify their position, and how to handle missing or delayed assessments resulting from the pandemic is part of the risk assessment of the impact of COVID-19 on trial integrity. For this purpose, the impact at a visit level will be assessed by data collected on a specific COVID-19 impact eCRF form and protocol deviations related to COVID-19. Due to the timing of the start-up of recruitment of participants into this study, the consequences for Part A1 are not expected to be significant and, as a result, no details on strategies for handling missing data are included in this version of the SAP. However, should the ongoing review of COVID-19-related protocol deviations suggest that the impact is more significant than expected, e.g. in the case of a new wave, the SAP may be updated to include further details of handling missing data and/or any sensitivity analyses required. Note that there are no guidelines regarding how much missing data is too much, and there is no proportion of missing data under which valid results and preservation of study power can be guaranteed.

4.5 Handling of repeated and unscheduled measurements

All repeated and unscheduled measurements will be presented in the data listings, where applicable. Repeated measurements are defined as more than 1 measurement at the same timepoint. For example, the same laboratory parameters assessed twice using the same batch of blood samples due to issues with the first assessment. The following general rules will apply to all repeated and unscheduled measurements:

- Unscheduled and repeated measurements prior to the first dose of UCB6114 will be used in the determination of Baseline and hence in the calculation of summary statistics at Baseline.
- Unscheduled and repeated measurements performed after the first dose of UCB6114 will not be included in the calculation of change from Baseline or summary statistics, i.e. only the scheduled measurements will be used and summarized. Similarly, only scheduled visits will be used in the summaries of shifts from Baseline to the worst post-Baseline CTCAE severity grade for laboratory data (see Section 8.3).
- For the summaries of the investigator's overall tumor response assessment, protocol-defined windows will be applied to all post-Baseline tumor assessments (scheduled or unscheduled, but excluding tumor assessments performed at the SFU visit), as detailed in Section 10.1.2. Those tumor assessments which fall outside of the window will be considered as unscheduled assessments and not included in the summaries.
- Best overall response, DOR and PFS derivations will use all scheduled and unscheduled tumor assessments.

- Blood samples for PK and/or cGremlin-1 analysis collected on the day of the On-Treatment biopsy when these blood samples are not scheduled will be documented on unscheduled eCRF pages; these data will be included in the summaries.
- All data from unscheduled visits will, however, be included on the relevant data listings.

4.6 Handling of measurements obtained for early withdrawals

Participants who withdraw early from the study for any reason will be asked to return to the clinic to complete the SFU visit. The SFU procedures performed at this visit are as shown in the Schedule of Activities in the protocol and will be summarized together with all other SFU visit data in the tables.

4.7 Interim analyses and data monitoring

No formal interim analyses are planned during Part A1 of this study.

In Part A1, the SMC will review all the safety and tolerability data for the sentinel participant in each UCB6114 dose schedule cohort (48 hours following first UCB6114 administration). The SMC will also review available safety, tolerability, and PK data as well as any available biomarker and ADA data once 25%, 50% and 100% study participants in Part A1 have completed the required 28-day DLT Observation Period. If deemed necessary, an additional SMC meeting can convene after 75% of the participants have completed the required 28-Day DLT Observation Period. If 1 or more DLTs (refer to Protocol Section 4.1.2.4 for the definition of DLTs) are reported for a cohort then, an *ad hoc* SMC will convene to determine if the dosing schedule and Part A1 can continue as planned.

The SMC established for Part A is comprised of key Sponsor personnel and investigators from participating sites. Investigators joined the SMC from new sites added in Parts B and C. The SMC for Part A1 will include the cumulative members, who are still actively enrolling study participants into the study.

In addition to the planned SMC data review meetings, the Sponsor and the SMC will have the ability to hold/request *ad hoc* meetings should they be deemed necessary (e.g. if safety concerns arise during Part A1 of the study and/or during other ongoing nonclinical and clinical studies).

4.8 Multicenter studies

Part A1 of this study is planned to be conducted at study sites in the UK and US. With the exception of participant disposition, no summaries will be presented by site or country.

4.9 Multiple comparisons/multiplicity

Not applicable.

4.10 Use of an efficacy subset of participants

The PPS will be used as the primary analysis set for the summaries of the exploratory antitumor activity endpoints in Part A1.

4.11 Active-control studies intended to show equivalence

Not applicable.

4.12 Examination of subgroups

Not applicable.

5 STUDY POPULATION CHARACTERISTICS

5.1 Study participant disposition

The number of study participants who were screened for Part A1 of this study, the number and percentage of screen failures and the primary reasons for screen failure will be summarized for the ES. A listing of participants who did not meet the eligibility criteria for Part A1 will also be presented for the ES. In addition, the disposition of study participants screened and who received study treatment will be summarized by country and site. This table will include, for each site in the UK and US and overall, site number, principal investigator name, the dates of the first participant in and the last participant out, the number of participants screened (ES), the number of screen failures, the number of participants who were treated (SS) and included in the PPS, PKS, ADAS and PDS. Disposition in each analysis set across all study sites will be summarized by treatment group.

The number of study participants who received study treatment and the primary reason for discontinuation of study treatment during Part A1 will be summarized by treatment group, together with the number and percentage of participants who continued participation in the study after discontinuation of study treatment (at subsequent scheduled visits and/or SFU visit and Final Visit). This summary will be based on the SS.

The number of study participants enrolled into Part A1, who were screen failures as well as the number of eligible participants who were assigned to a study cohort but not treated will be presented for the ES. For those participants who did not receive study treatment, the reasons for early discontinuation from the study will be summarized.

Of those participants who received study treatment, the number and percentage of participants who completed the study (i.e. participants who received at least 2 complete cycles of UCB6114 and attended the SFU visit), who received at least 2 complete cycles of study treatment but who did not attend the SFU visit and who discontinued early from Part A1, together with the primary reasons for study discontinuation will be presented for all participants.

The number and percentage of participants who discontinued due to AEs will be summarized separately for all participants, based on the SS. This will be used for European Union Drug Regulating Authorities Clinical Trials (EudraCT) reporting.

The following study disposition tables will also be presented by tumor type (colorectal adenocarcinoma [CRC], gastric adenocarcinoma and adenocarcinoma of the gastroesophageal junction combined [Gastric/GEJ-Cancer] and Pancreatic Adenocarcinoma), depending on the number of participants with specific tumor types.

- Disposition and Reasons for Discontinuation of Study Treatment
- Disposition and Reasons for Discontinuation of Study
- Discontinuation of the Study Due to AEs

Visits impacted by COVID-19 will be listed for the ES. This listing will include, visit, visit date, relative day, impact category (e.g. visit performed out of window, visit performed by telephone, visit not done, missed study drug administration/dispensation, termination of study participation), relationship to COVID-19 (confirmed COVID-19 infection, suspected COVID-19 infection, general circumstances around COVID-19 or other) and a narrative for the event. The number and percentage of participants with visits impacted by COVID-19 will be presented by treatment group and by impact category. This summary will be presented for the different relationships to COVID-19. The denominator for the percentage calculations will be the number of participants in the SS.

In addition, the following listings will be presented:

- Study participant disposition (ES);
- Study treatment discontinuation (SS);
- Study discontinuation (ES);
- Visit dates (ES);
- Participant analysis sets and exclusions from analysis sets (ES)*.

*DES is not included in this listing as it is only relevant for the SMC, and not required for the CSR.

The listing of study participant disposition will include the date of informed consent, date and time of first and last dose of UCB6114, date of early study discontinuation (if applicable) and primary reason for discontinuation.

The listing of study treatment discontinuation will include date and time of first and last dose of UCB6114, date of decision to discontinue UCB6114 and primary reason for discontinuation of UCB6114, date of clinical progression (if applicable), number of doses of UCB6114 received (based on doses per cycle), total dose of UCB6114 received across all cycles, number of complete cycles of UCB6114 received, and whether or not the participant had continued participation in the study (at subsequent visits, the SFU visit or the Final Visit).

A participant in Cohort 1 or 2 is deemed to have completed a full cycle of UCB6114 if they receive a dose of UCB6114 on Day 1 and Day 15 of the cycle and a decision was not made to discontinue study treatment up to and including Day 28 relative to Day 1 of the cycle.

A participant in Cohort 3 is deemed to have completed a full cycle of UCB6114 if they receive a dose of UCB6114 on Day 1 of the cycle and a decision was not made to discontinue study treatment up to and including Day 21 relative to Day 1 of the cycle.

A participant in Cohort 4 is deemed to have completed a full cycle of UCB6114 if they receive a dose of UCB6114 on Day 1 of the cycle and a decision was not made to discontinue study treatment up to and including Day 28 relative to Day 1 of the cycle.

Whether or not a participant has completed a full cycle of UCB6114 will be derived based on the participant's last dose of UCB6114 and whether or not the participant attended the visit at which they were scheduled to receive their next dose of UCB6114. For example, in Cohorts 1 and 2, if a participant received UCB6114 on Day 1 and Day 15 of Cycle 1 and attended the clinic for their

UCB6114 infusion on Day 1 of Cycle 2 then the participant will be counted as having completed Cycle 1. If the participant in Cohort 1 or 2 did not attend Day 1 of a subsequent cycle, then it is likely that a decision was made to discontinue their UCB6114 treatment and/or the study. Therefore, the date that the decision was made to discontinue UCB6114 will be used to determine whether the participant completed a cycle of study treatment. If a decision was made to discontinue UCB6114 on >Day 28 relative to Day 1 of the particular cycle then the participant will be counted as having completed the cycle. Similar derivations will be programmed for Cohort 3 based on a 21-day cycle, and for both Cohorts 3 and 4 based on Day 1 dosing only.

For any interim deliveries at a data cut-off, if a participant did not attend Day 1 of their next cycle and there was no decision to discontinue UCB6114, then the latest date available for that participant should be used to determine whether they have completed a full cycle of UCB6114.

Whether or not a participant has completed the study is defined as having received at least 2 complete cycles of study treatment and attended the SFU visit. The investigator will record a study participant's disposition status at study termination according to this definition of a 'completed' participant, however, a study completion flag will also be programmatically derived based on the relevant data on the database and the above rules for defining completion of a full cycle of study treatment.

The listing of study discontinuation will include the primary reason for early study discontinuation, the number of cycles of study treatments received, and the total number of days on study treatment.

5.2 Protocol deviations

Important protocol deviations will be identified and classified by the deviation types defined in the IPD specification document, as per Section 3.4.

A listing of all IPDs identified at the DEM will be presented for all study participants based on the SS and will include the deviation type and description. In addition, a listing of all protocol deviations related to COVID-19 (whether considered important or not) will be presented for the SS. The number and percentage of participants in the SS with IPDs will be summarized by treatment group and for all participants for each deviation type. The number and percentage of participants who were excluded from the PPS will also be presented. The denominator for the percentage calculations will be the number of participants in the SS. A summary will also be presented for all protocol deviations related to COVID-19, all IPDs related to COVID-19 and all IPDs-related to COVID-19 leading to exclusion from the PPS.

6 DEMOGRAPHICS AND OTHER BASELINE CHARACTERISTICS

6.1 Demographics

A by-participant listing of demographics will be presented based on the ES. This will include the year of birth, age (as entered by investigator in the eCRF in years), sex, race, ethnicity, height (in cm), weight (in kg) and body mass index (BMI, in kg/m^2). Height will be the measurement obtained at the Screening visit and weight will be the last non-missing value prior to the first dose of study treatment.

The BMI will be derived in the database using the height and weight measurements recorded at the Screening visit and will be automatically reported to 1 decimal place on the eCRF.

All demographic characteristics (except for date of birth) will be summarized by treatment group and for all study participants based on the SS. The summary of age will include descriptive statistics and categorical summaries, the latter based on requirements for EudraCT and clinicaltrials.gov reporting. In addition, summaries will be programmed by tumor type (CRC, Gastric/GEJ-Cancer and Pancreatic Adenocarcinoma) depending on the number of participants with specific tumor types and may be presented in the CSR.

For the EudraCT reporting, the categories will include:

- 18 to <65 years;
- 65 to <85 years.

For clinicaltrials.gov reporting, the categories will include:

- ≤18 years;
- 19 to <65 years;
- ≥65 years.

Childbearing potential and method of birth control will be listed for the ES.

6.2 Cancer history

All cancer history data for Part A1 participants will be listed for the ES. This listing will include date of initial diagnosis, tumor type, TNM Classification of Malignant Tumors (TNM) classifications and stage, Duke's score (participants with CRC only), histological and cytological diagnosis details (as relevant), whether the participant had any metastases and associated anatomical location, and whether the participant had received any prior anti-cancer systemic therapies (including the number of lines of any prior anti-cancer systemic therapies, prior radiation therapies and prior anti-cancer surgeries).

Time since initial diagnosis (calculated in months using date of Screening visit and date of initial diagnosis and multiplying the duration in days by 12/365.25), tumor type, T, N, and M classifications and TNM stage, Duke's score (participants with CRC only), presence of metastases and anatomical location of metastases will be summarized by treatment group and for all study participants based on the SS. In the summaries of categorical variables, percentages will be calculated based on the number of study participants with non-missing data. Further, for the Duke's score, the denominator for the percentage calculation will be the number of participants with CRC.

Cancer history will be programmed by tumor type (CRC, Gastric/GEJ-Cancer and Pancreatic Adenocarcinoma) depending on the number of participants with specific tumor types and may be presented in the CSR.

6.3 Prior anti-cancer therapy

Details recorded for each line of prior anti-cancer systemic therapy received by a study participant will be listed for the ES. This listing will include the line and type of systemic

therapy, intent, drug name and dose, formulation, indication (current/ultimate), start and end dates, number of cycles received and the number of days per cycle, the participant's best response and the date of that best response, reason for discontinuation and whether the participant had disease progression prior to the next line of systemic therapy. If there was progression, then the date of progression will also be listed. In addition, time from completion of the last prior anti-cancer systemic therapy to the start of UCB6114, whether the participant had progression after the last line of anti-cancer systemic therapy and, if so, the time from progression to the start of UCB6114 will be derived and listed.

For those participants in the ES who received prior radiotherapy, the following data will be listed: treatment site, type of radiotherapy, intent, settings (concurrent with other anti-cancer systemic therapy or stand-alone radiation therapy), and, if concurrent radiotherapy, the anti-cancer systemic therapy line that the radiotherapy was given with and the drug name. In addition, the start and stop dates, total cumulative dose (if known), number of fractions (if known), the participant's best response to radiotherapy and whether the tumor at the treatment site had progressed since radiotherapy will be included in this listing.

A further listing of prior anti-cancer radiotherapy with systemic therapy regimens will be presented for participants in the ES who had concurrent prior anti-cancer systemic therapy and radiotherapy as their prior anti-cancer therapy. This listing will include radiotherapy treatment site, start and stop dates of radiotherapy and systemic therapy together with the participant's best response to that regimen.

Date of surgery/procedure, anatomical location, description of the surgical procedure and whether the tumor was completely removed will be listed for those study participants in the ES who had prior anti-cancer surgeries or procedures.

The following summaries of prior anti-cancer therapy regimens and surgeries will be presented by treatment group and for all participants for the SS:

- Number of prior anti-cancer therapy regimens (0, 1, 2, 3, >3) (including all anti-cancer systemic therapy lines given alone and concurrently with radiotherapy)
- Best response to the most recent prior anti-cancer therapy regimen
- Number of prior anti-cancer systemic therapy + radiotherapy regimens (0, 1, 2, 3, >3)
- Best response to the most recent anti-cancer systemic therapy + radiotherapy regimen
- Reasons for discontinuation of the most recent line[a]
- Time from completion of most recent line[a] to the start of UCB6114 (<1 month, 1-<3 months, 3-6 months, >6 months)[b]
- For participants that progressed after their most recent line[a], the time from progression to the start of UCB6114 (<1 month, 1-<3 months, 3-6 months, >6 months)[b]
- Number of prior anti-cancer radiotherapies (including radiotherapies given alone and concurrently with anti-cancer systemic therapy) (0, 1, 2, >2)
- Number of prior anti-cancer surgeries and procedures (0, 1, 2, >2)

[a] Most recent line is the last prior anti-cancer therapy regimen received which may be a prior anti-cancer systemic therapy given alone or concurrently with radiotherapy.

[b] 1 month = 30 days.

Time from completion and time from progression relative to the last line of anti-cancer systemic therapy will also be summarized using frequency counts and percentages as well as summary statistics.

The number and percentage of participants with any prior anti-cancer systemic therapy, and any prior anti-cancer systemic therapy given concurrently with radiotherapy will be summarized for the SS by treatment group and for all participants, and by WHODD Anatomical Main Group [Level 1 term text], Pharmacological Subgroup [Level 3 term text] and PT.

Prior anti-cancer therapy summaries will be programmed by tumor type (CRC, Gastric/GEJ-Cancer and Pancreatic Adenocarcinoma) depending on the number of participants with specific tumor types and may be presented in the CSR.

6.4 Cancer status at Screening

The current cancer status of study participants at entry into Part A1 of this study will be assessed at the Screening visit and listed for the ES. This listing will include tumor type, T, N and M classifications and TNM stage, Duke's score (participants with CRC only), histological and cytological diagnosis details (as relevant), whether the participant has any metastases and associated anatomical location, whether the tumor is recurrent and whether the participant had relapsed from their last line of anti-cancer systemic therapy.

Tumor type, T, N, and M classifications and TMN stage, Duke's score (participants with CRC only), presence of metastases and anatomical location of metastases, and time since relapse on last line of therapy (calculated in days using the date of the Screening visit and date of relapse) will be summarized by treatment group and for all study participants based on the SS. In the summaries of categorical variables, percentages will be calculated based on the number of study participants with non-missing data. Further, for the Duke's score, the denominator for the percentage calculation will be the number of study participants with CRC.

Cancer status will be programmed by tumor type (CRC, Gastric/GEJ-Cancer and Pancreatic Adenocarcinoma) depending on the number of participants with specific tumor types and may be presented in the CSR.

6.5 Medical history and concomitant diseases

Medical history will be listed for the ES and summarized by MedDRA® system organ class (SOC) and preferred term (PT) by treatment group and for all study participants for the SS. The reported term will be included in the listing. Previous medical history (any previous medical conditions with a stop date prior to the start of UCB6114) and ongoing medical history (any ongoing medical conditions with a missing stop date but recorded as ongoing on the eCRF) will be summarized separately. These summaries will include the number and percentage of study participants and will be sorted alphabetically by SOC and by descending incidence of PT within each SOC, based on the incidence in all study participants.

Non-anti-cancer procedure history will be listed for the ES and concomitant medical procedures performed during the study will be listed for the SS.

Medical history and concomitant disease may be presented by tumor type (CRC, Gastric/GEJ-Cancer and Pancreatic Adenocarcinoma) depending on the number of participants with specific tumor types.

6.6 Prior and concomitant medications

Prior medications will include any medications that started prior to the date of the first dose of UCB6114. This will include medications that started prior to the first dose of UCB6114 and continued after.

Concomitant medications will include medications with a start date on or after the first dose of UCB6114 and prior to the date of the last dose of UCB6114 + 30 days, and whose stop date is either missing, or on or after the date of the first dose of UCB6114. Any medications with a start date prior to the first dose of UCB6114 and a stop date after, or continued to be ongoing during the study, will also be classified as concomitant medications. Medications with a start date > 30 days after the last dose of UCB6114 will be considered as post-study medications and will not be included in the summaries of concomitant medication.

Any medication that started prior to and stopped after the first dose of UCB6114 or continued to be ongoing during the study, will be classified as both prior and concomitant.

Any medications with completely missing start dates will be classified as both prior and concomitant provided that a stop date is not present or a stop date is present but is prior to the first dose of UCB6114.

Any medications with partially missing dates will be handled as described in Section 4.4.1 to classify them as prior or concomitant.

All medications (prior, concomitant and post-study) will be listed for the ES. Any prohibited concomitant medications, rescue medications or steroid use will be identified via a medical review and flagged in this listing.

Prior and concomitant medications (per the definitions above) will be summarized for the SS by treatment group and by WHODD Anatomical Main Group [Level 1 term text], Pharmacological Subgroup [Level 3 term text] and PT. The reported term will be included in the listing. Separate summaries will be presented for prior medications and concomitant medications.

All tabulations will be sorted alphabetically by Level 1 term, alphabetical Level 3 term within Level 1 and decreasing frequency of PT in all study participants.

A glossary of all prior and concomitant medications will be presented for the SS including the Anatomical Main Group (Level 1), Pharmacological Subgroup (Level 3), PT and reported term.

Prior and concomitant medications will be programmed by tumor type (CRC, Gastric/GEJ-Cancer and Pancreatic Adenocarcinoma) depending on the number of participants with specific tumor types and may be presented in the CSR.

7 MEASUREMENTS OF TREATMENT COMPLIANCE

During Part A1 of this study, administration of study treatment will be performed via iv infusion at the study site under the supervision of the designated site personnel and in compliance with the Guideline for First in Human clinical studies (EMEA/CHMP/SWP/28367/07Rev. 1). Compliance will be monitored at the site through a review of accountability logs which will be used to record study treatment dispensing and return information to ensure that each study participant received the correct dose level and frequencies of dosing (e.g. Q3W, Q4W).

Any dosing deviations will be reviewed as IPDs at the DEMs and assessed for possible impact on the PPS and PKS. If considered important, these deviations will be included in the summary and listing of IPDs.

8 SAFETY ANALYSES

All safety summaries and listings will be presented by treatment group based on the SS, unless otherwise stated.

All safety summaries will be programmed by tumor type (CRC, Gastric/GEJ-Cancer and Pancreatic Adenocarcinoma) depending on the number of participants with specific tumor types and may be presented in the CSR.

8.1 Extent of exposure

Details on UCB6114 administration on Day 1 (all cohorts) and Day 15 (Cohort 1 and 2 only) of each cycle will be listed. This listing will be split into two parts. The first part will include the start and stop dates and times of infusion, duration of infusion, infusion rate, whether the infusion was temporarily stopped/interrupted, whether the infusion was permanently discontinued and, if this was the case, whether the interruption or permanent discontinuation was due to an AE or other reason. The second part of this listing will include, for each visit, infusion site, total volume delivered, volume infused, planned total dose and total dose actually administered at infusion. In addition, the percentage of planned dose received, total dose administered across all cycles, the number of complete cycles of UCB6114 received and the total number of doses of UCB6114 received will be listed.

The percentage of planned dose received will be calculated for UCB6114 for each study participant at each dosing visit within each cycle as follows:

$$Percentage\ of\ Planned\ Dose\ Received = 100 \times \frac{Total\ Dose\ Administered}{Planned\ Total\ Dose}$$

Actual duration of infusion will be calculated in minutes only for those study participants who did not have any temporary interruption(s) of their infusion using the infusion start and stop times and included on this listing. Length of interruption(s) will be calculated in minutes for those study participants who had temporary interruption(s) of their infusion.

Extent or duration of exposure will be calculated and summarized. Frequency counts and percentages for the number of complete cycles of UCB6114 received (0, 1, 2, 3, 4, >4) and summary statistics for the total dose of UCB6114 received across all cycles, the total number of doses of UCB6114 received and the duration of exposure to UCB6114 will be presented.

Total duration of exposure will be calculated in days as follows:

$$Total\ Duration\ of\ Exposure = (Date\ of\ Last\ Dose - Date\ of\ First\ Dose) + 30$$

Note that 30 days is added to this calculation to account for a participant's continued exposure to UCB6114 following their last dose of study treatment.

Note that the definition of a participant deemed to have completed a full cycle of UCB6114 is given in Section 5.1.

8.2 Adverse events

The primary safety endpoints for Part A1 of this study are the incidence and severity of TEAEs (including SAEs) from the first dose of UCB6114 treatment on Day 1 of Cycle 1 until the end of the SFU Period (up to 30 days following the last dose of UCB6114), and the incidence of DLTs from the first dose of UCB6114 on Day 1 of Cycle 1 until the end of the DLT Observation Period (Day 28 of Cycle 1).

All AEs for a participant will be recorded in the eCRF from the time of informed consent until completion or early discontinuation of Part A1 of this study. Serious adverse events are to be reported up to 30 days after the Final Visit (i.e. up to 150 days after the last dose of UCB6114). All AEs in Part A1 of the study will be coded using MedDRA® and classified as pre-treatment and treatment-emergent relative to the first infusion of UCB6114.

Adverse events with a start date prior to the first dose of UCB6114 will be defined as pre-treatment AEs. A TEAE is defined as any AE with a start date on or after the first dose of UCB6114 up until the last dose of UCB6114 + 30 days. A pre-treatment AE which increases in severity on or after the first dose of UCB6114 will also be counted as a TEAE. Note that in this case, the pre-existing AE will have a stop date and an outcome of 'worsened' and a new AE (with the same verbatim) will be entered with the same start date and the increased severity recorded on the eCRF. Any AE (including SAEs) with an onset date later than the last dose of UCB6114 + 30 days will not be considered as treatment-emergent and therefore will not be included in the tabulations of TEAEs. These AEs will be considered as post-study AEs and will be listed only. Where onset dates are missing or partially missing, AEs will be assumed to be treatment-emergent, unless there is clear evidence to suggest that the AE started prior to the first dose of UCB6114 and did not increase in severity. Missing or partially missing dates for AEs will be handled as described in Section 4.4.1.

Adverse events will be assigned an NCI CTCAE severity grade (Grade 1/Grade 2/Grade 3/Grade 4/Grade 5), where possible. If a CTCAE toxicity grading is not possible, then the intensity of the AE (mild/moderate/severe) will be recorded on the eCRF. If the AE is not gradable, is serious, and is considered as life threatening, then the intensity for this AE will be missing and one of the reasons for seriousness will be recorded as life threatening.

Adverse events will also be categorized according to their relationship to UCB6114 (related/not related), and whether the event is a DLT, as judged by the investigator. A DLT is defined as a TEAE at least possibly related to UCB6114 that occurs during Cycle 1 and fulfills any of the criteria listed in Section 4.1.2.4 of the protocol. The investigator is expected to record whether an AE is a DLT on the eCRF.

An overview of the number and percentage of participants who experience TEAEs will be presented. This summary will include the number and percentage of participants with any TEAEs, serious TEAEs, related TEAEs (related to UCB6114), discontinuations from study treatment (UCB6114) due to TEAE(s), discontinuations from the study due to TEAE(s), CTCAE Grade ≥ 3 TEAEs, CTCAE Grade ≥3 related TEAEs, DLTs, AEs leading to death and TEAEs leading to death; event counts will also be included against each of these categories. The overview of TEAEs may be presented by tumor type (CRC, Gastric/GEJ-Cancer and Pancreatic Adenocarcinoma) depending on the number of participants with specific tumor types.

In addition, the following summaries will be presented by SOC, high level term (HLT) and PT, and, where indicated, also by tumor type (CRC, Gastric/GEJ-Cancer and Pancreatic Adenocarcinoma) depending on the number of participants with specific tumor types:

- Incidence of TEAEs (overall and by tumor type);
- Incidence of serious TEAEs (overall and by tumor type);
- Incidence of non-serious TEAEs (overall and by tumor type);
- Incidence of TEAEs leading to a temporary interruption of study treatment infusion and/or dose reduction (overall and by tumor type);
- Incidence of TEAEs leading to discontinuation of study treatment (overall and by tumor type);
- Incidence of TEAEs leading to discontinuation of study (overall and by tumor type);
- Incidence of DLTs (overall and by tumor type);
- Incidence of adverse events of special interest (AESIs) (Potential Hy's Law – see Section 8.2.1 below) (overall and by tumor type);
- Incidence of UCB6114 infusion-related reactions (defined as hypersensitivity reactions, anaphylactic reactions and cytokine release syndrome – see Section 8.2.2) (overall and by tumor type);
- Incidence of TEAEs by maximum CTCAE severity grade (overall and by tumor type);
- Incidence of TEAEs by maximum relationship to UCB6114 (overall and by tumor type);
- Incidence of TEAEs by relationship;
- Incidence of serious TEAEs by relationship;
- Incidence of non-serious TEAEs by relationship;
- Incidence of fatal TEAEs by relationship;
- Incidence and event rate of TEAEs by treatment-emergent ADA positivity.

The following summaries will be presented by SOC and PT for EudraCT reporting:

- Incidence of non-serious TEAEs above the threshold of 5% of participants in any treatment group;

- Incidence of non-serious TEAEs above the threshold of 5% of participants in any treatment group by relationship;

The above summaries of TEAEs will be ordered alphabetically by SOC, alphabetically by HLT within SOC and decreasing incidence of PT events within SOC /HLT in all study participants. For tables including only the number and percentage of participants, summaries will be ordered alphabetically by SOC, alphabetically by HLT within SOC and decreasing incidence of participants with each PT within SOC /HLT in all study participants.

The incidence of TEAEs by maximum CTCAE severity grade will be presented by CTCAE term. CTCAE term will be obtained from the NCI CTCAE Version 5.0 via a mapping of MedDRA® lowest level terms (LLTs). This summary will be ordered by decreasing incidence of participants with each CTCAE term in all study participants.

Summary tables will contain frequency counts and percentages, and the number of events, where applicable. A study participant who experiences the same event multiple times will be counted only once in the frequency counts for the PT, but all events will be included.

In the summaries of TEAEs by relationship, participants will be counted in "Not related" and "Related" categories (or "Missing" in the case where an event has a missing relationship). A study participant who experiences the same event multiple times will be included in the most related category for the summaries by maximum relationship.

In the overview summary of TEAEs, participants will be counted as having at least one TEAE with CTCAE severity grade ≥3, and in the summary of TEAEs by maximum CTCAE severity grade, participants will be counted as having at least one TEAE in the following categories: 'Grade 1', 'Grade 2', 'Grade 3', 'Grade 4', 'Grade 3 or 4', 'Grade 5', and 'Grade ≥3'. Events for which no CTCAE severity grade is recorded by the investigator but an intensity is recorded instead, the intensity of this event will be assigned to a CTCAE severity grade for the purpose of these summaries, i.e. 'Mild' will be included as 'Grade 1', 'Moderate' will be included as 'Grade 2', 'Severe' will be included as 'Grade 3' and 'Life Threatening' will be included as 'Grade 4' and, if the participant dies due to the event, it will be included as 'Grade 5'. The determination of whether the event is life threatening or results in death will be based on the reason for seriousness recorded as life-threatening or death on the eCRF, or on the event having a fatal outcome. Otherwise, if both the CTCAE severity grade and intensity is missing then the CTCAE severity grade in these summaries will be missing. A study participant who experiences the same event multiple times will be included in the highest severity grade category in the summary of TEAEs by maximum CTCAE severity grade.

A glossary of all AEs will be presented including the MedDRA® SOC, HLT, PT, reported term and LLT.

A listing of all AEs will be presented by study participant for the ES. The listing will include the onset date and stop date of the event (including relative days) and also the onset times and stop times of events where available. The period of onset of AEs will also be presented on this listing.

Period of onset of AEs will be defined as follows for the purpose of the listing:

- If the AE has an onset date prior to the date of the Screening visit, then Period=Pre-study;

- If the AE has an onset date on or after the date of the Screening visit and has an onset date and time prior to the start time of UCB6114 infusion on Day 1 of Cycle 1 then Period=Screening;

- If the AE has an onset date and time on or after the start time of UCB6114 infusion on Day 1 of Cycle 1 and up to the date and time of the start of Cycle 2 (i.e. prior to the start time of the UCB6114 infusion on Day 1 of Cycle 2) then Period=Cycle 1;

- If the AE has an onset date and time on or after the start time of UCB6114 infusion on Day 1 of Cycle 2 and up to the date and time of the start of Cycle 3 (i.e. prior to the start time of the UCB6114 infusion on Day 1 of Cycle 3) then Period=Cycle 2;

- Same as above for subsequent cycles (Cycle 3 etc.);

- If the AE has an onset date after the last dose of UCB6114 up to and including 30 days after the last dose of UCB6114, then Period=SFU;

- If the event has an onset date after the 30-day period following the last dose of UCB6114, then Period=Post-study.

The listing of all AEs will also include the AE duration (derived in days, hh:mm for AEs with onset and stop times recorded and derived in days for all other AEs with only onset and stop dates recorded), days since start of UCB6114 infusion (time if an onset time is recorded, days otherwise), seriousness and reason for seriousness, CTCAE severity grade, intensity (where a CTCAE severity grade is not recorded), pattern of event, relationship to UCB6114 and action taken with UCB6114 (including other action taken), the outcome of the AE, whether an autopsy was performed and cause of death. In addition, the listing will flag AEs that led to discontinuation from the study, TEAEs, AESIs, SAEs, infusion-related reactions, and DLTs. Whether an AE is related to a concomitant medication (which will include the COVID-19 vaccination) and the names of any co-suspect medications will also be listed.

Separate listings of all SAEs, TEAEs leading to discontinuation of UCB6114 and TEAEs leading to discontinuation of the study will also be presented.

All deaths that occur on study (defined as during study treatment or within 30 days of the latest dose of UCB6114) will be listed separately. This listing will include the primary cause of death and the number of days between the date of the last dose of UCB6114 and death, defined as

$$Days\ since\ last\ dose = (Date\ of\ death - Date\ of\ last\ dose\ of\ UCB6114) + 1$$

8.2.1 Adverse events of special interest

An AESI is any AE that a regulatory authority has mandated be reported on an expedited basis, regardless of the seriousness, expectedness, or relatedness of the AE to the administration of a UCB product/compound.

For ONC001, potential Hy's Law is used to identify AESIs and is defined using the laboratory data and the following potential drug-induced liver injury (PDILI) criteria:

- ≥3x upper limit of normal (ULN) alanine aminotransferase (ALT) *or* aspartate aminotransferase (AST) with coexisting ≥2xULN total bilirubin on the same day, in the absence of ≥2xULN alkaline phosphatase (ALP), with no alternative explanation for the biochemical abnormality;
- Study participants who have evidence of liver metastases may be considered to have an alternate etiology for the described laboratory abnormalities.

All AESIs will be flagged on the listing of AEs.

8.2.2 Infusion-related reactions

Infusion-related reactions are defined as hypersensitivity reactions, anaphylactic reactions and cytokine release syndrome with onset within 24 hours after the start of the UCB6114 infusion.

All potential infusion-related reactions will be identified programmatically and will then undergo medical review for confirmation based on participant characteristics and other signs and symptoms. The final assessment from the medical review will be used in the programming to ensure that all infusion-related reactions are flagged correctly in the listings and included in the relevant summaries.

Hypersensitivity reactions will be programmatically identified as any TEAE with a PT from both a narrow and broad scope search of category A terms of the 'Hypersensitivity' SMQ.

Anaphylactic reactions will be programmatically identified using an algorithmic approach based on the 'Anaphylactic Reaction' SMQ. Further details on this algorithm are given in Section 13.1. Note that if the MedDRA® version is increased from 25.1 during the study, any changes to the terms included in the 'Anaphylactic Reaction' SMQ should be applied.

Cytokine release syndrome will be programmatically identified as any TEAE with a PT of 'Cytokine release syndrome' from the broad scope search of category A terms of the 'Hypersensitivity' SMQ. Since this disorder is characterized by fever, headache, tachycardia, hypotension, rash, tachypnoea and/or hypoxia, a further medical review of participants with these events occurring within 24 hours after the start of the infusion of UCB6114 will be performed to confirm any further infusion-related reactions.

Note that any other AEs (i.e. not identified as infusion-related reactions using the rules above) which result in a temporary interruption or permanent discontinuation of a UCB6114 infusion will not be considered as an infusion-related reaction.

8.3 Clinical laboratory evaluations

Laboratory tests will be performed at the Screening visit, predose on UCB6114 dosing visits (Days 1 and 15 of each cycle for participants in Cohorts 1 and 2 and on Day 1 of each cycle for participants in Cohorts 3 and 4) and at the SFU visit. In addition, participants in Cohort 4 will have laboratory tests performed on non-dosing Day 15 of Cycle 1 and 2 only.

Due to the use of multiple local laboratories (1 per site in the UK and US) in Part A1 of this study, results will potentially be recorded in different units and with reference to different normal ranges. Further, for some laboratory tests, different normal ranges will be applied to males and females and age groups. As a first step to ensure comparability of laboratory results, results and

normal ranges will be converted to the same International System of Units (SI) units using UCB's standard conversion factors. This will be programmed at the Study Data Tabulation Model (SDTM) level. Note though that the simple conversion to SI units does not represent a full homogenization of results from different local laboratories using different methods. To ensure full comparability, the observed laboratory results will be normalized to a unique set of standard reference ranges (for hematology, clinical chemistry and coagulation parameters) using the location-scale normalization formula (Chuang-Stein, 1992).

$$s = L_S + (x - L_X)\frac{(U_S - L_S)}{(U_X - L_X)}$$

and when the standard lower limit is 0: $s = x\frac{U_S}{U_X}$ where:

s = normalized observed value
x = original observed value in SI units
LS = Lower Limit of the reference range chosen to be the standard reference range
US = Upper Limit of the reference range chosen to be the standard reference range
LX = Lower Limit of the reference range associated with the original observed value in SI units (local laboratory reference range)
UX = Upper Limit of the reference range associated with the original observed value in SI units (local laboratory reference range)

This transformation preserves the distance of the original laboratory result from the lower limit of normal as a multiple of the specified standard reference range.

Note that the choice of the standard reference range is arbitrary, however, the most recent reference ranges used by ICON Central Laboratories (including the age and gender specific reference ranges for parameters, where available) will be used to normalize the results in this study.

Normalization of the laboratory results will be performed in the ADaM programming by ICON.

All laboratory data (hematology, serum chemistry and coagulation) and changes from Baseline for numeric variables will be listed for participants who have at least one value outside of the reference range. All urinalysis data will be listed for all participants. Data will be listed by study participant, laboratory panel, laboratory parameter and visit within each treatment group. Any laboratory measurements that are BLQ or ALQ will be handled as described in Section 4.4. For the relevant numeric laboratory parameters, the reference ranges supplied by the local analytical laboratory will be used to flag values outside the reference range as low or high in this listing. For the parameters for which the local laboratory cannot supply the reference ranges, the reference ranges provided by ICON Central Laboratories will be used instead. A listing of all laboratory results outside of the reference range will also be presented. The reference ranges will also be reported in the listings.

In addition, for the relevant hematology, clinical chemistry and coagulation laboratory tests, CTCAE severity grades (Grade 1, Grade 2, Grade 3, Grade 4) will be applied (where possible) in the ADaM programming according to NCI CTCAE Version 5.0, and these grades will also be listed for the relevant laboratory parameters. Note that Grade 0 will be applied in cases where a

result is normal for the relevant laboratory test and Grade 5 is not applicable in the grading of laboratory data.

Observed values and changes from Baseline in the hematology, serum chemistry and coagulation parameters presented below in Table 8-1 will be summarized at each visit.

The summaries of normalized hematology, serum chemistry and coagulation values and changes from Baseline may be presented by tumor type (CRC, Gastric/GEJ-Cancer and Pancreatic Adenocarcinoma) depending on the number of participants with specific tumor types.

For those laboratory parameters with a CTCAE toxicity assigned, shift tables for the change from Baseline in CTCAE severity grade at each visit will be presented.

Table 8-1: Clinical Laboratory Assessments

Laboratory Assessment	Laboratory Parameters
Hematology	Platelet Count, RBC Count, Hemoglobin, Hematocrit, RBC Indices (MCV, MCH, MCHC), WBC Count with Differential (Absolute Neutrophils, Absolute Lymphocytes, Absolute Monocytes, Absolute Eosinophils, Absolute Basophils)
Clinical Chemistry	ALT, AST, ALP[a] , Bicarbonate, Sodium, Potassium, Magnesium, Chloride, Calcium, Total Bilirubin, BUN or Urea, Serum Creatinine, Glucose (non-fasted), Phosphorus or Phosphate, Albumin, Total Protein, Uric Acid, Amylase, GGT, Cholesterol, Creatine Kinase, CRP, LDH, Lipase, Triglycerides
Coagulation	aPTT and either prothrombin time or INR
Routine Urinalysis	Specific Gravity, pH, Glucose, Protein, Blood, Ketones, Bilirubin, Urobilinogen, Nitrite, Leukocyte Esterase by Dipstick Microscopic Examination (if blood or protein is abnormal, including crystals)
Screening Tests	Pregnancy tests: FSH and estradiol (for women of non-childbearing potential only); serum or urine hCG pregnancy test (for women of childbearing potential) Bone turnover markers: blood BAP, blood CTx, urinary NTx and urinary CTxII Tumor markers: e.g. PSA, CA125, CA19-9

ALP=alkaline phosphatase; ALT=alanine aminotransferase; aPTT=activated partial thromboplastin time; AST=aspartate aminotransferase; BAP=bone alkaline phosphatase; BUN=blood urea nitrogen; CA=cancer antigen; CRP=C-reactive protein; CTx=C-terminal telopeptide; FSH=follicle-stimulating hormone; GGT=gamma glutamyl transferase; hCG=human chorionic gonadotropin; INR=international normalized ratio; LDH=lactate dehydrogenase; MCH=mean corpuscular hemoglobin; MCHC=mean corpuscular hemoglobin concentration; MCV=mean corpuscular volume; NTx=N-terminal telopeptide; PSA=prostate specific antigen; RBC=red blood cell; WBC=white blood cell.
[a] including liver-specific ALP for use in assessing participants with bone metastases at Screening. In the case of bone metastases liver function abnormalities considered potential Hy's law cases, the liver-specific ALP must be separated from the total in participants with bone metastases and used to assess the liver function instead of the total ALP.

The screening laboratory tests included above in Table 8-1 (as available for Part A1) will be listed only.

Liver function abnormalities will be defined using the following criteria:

- ALT or AST ≥2xULN

- ALT or AST ≥3xULN
- Total bilirubin ≥2xULN
- Total bilirubin ≥3xULN
- ALT or AST ≥5xULN
- ALT or AST ≥8xULN
- ALT or AST ≥3xULN AND total bilirubin ≥2xULN (>35% direct bilirubin)

For the subgroups of participants with liver metastases and without liver metastases at Baseline, the number and percentage of participants in each liver function abnormality category will be summarized at each visit.

In addition, participants with PDILI criteria are those that fulfill the following laboratory data (based on liver function tests) criteria at a visit:

- AST or ALT and total bilirubin within the normal range at Baseline and AST or ALT ≥3xULN concurrent with total bilirubin ≥2xULN;
- AST, ALT or total bilirubin above ULN at Baseline and AST or ALT ≥2 times Baseline values AND AST or ALT ≥3xULN (participants without liver metastases at Baseline)/AST or ALT ≥8xULN (participants with liver metastases at Baseline) concurrent with total bilirubin above ULN at Baseline and total bilirubin ≥2 times Baseline value or ≥3xULN (whichever is lower).

All relevant laboratory data collected for participants with a PDILI event (i.e. liver function tests) will be listed at the visits at which at least one of the above criteria was fulfilled.

The number and percentage of participants meeting different combinations of the ALT, AST and total bilirubin criteria defined above will be summarized by treatment group. This summary will be presented for all participants as well as for the subgroups of participants who had liver metastases at Baseline and participants without liver metastases at Baseline.

A separate listing will also be produced containing drug-induced liver injury relevant family medical history, lifestyle data (alcohol consumption or drug abuse in the previous 6 months), hepatic event supplemental medical history and any hepato-toxic medications taken for participants in the SS with a PDILI event.

8.4 Vital signs, physical findings, and other observations related to safety

8.4.1 Vital signs

Vital signs will be measured in a semi-supine position after 5 minutes rest and will include:

- Systolic and diastolic blood pressure;
- Pulse rate;
- Oral body temperature;
- Respiratory rate.

Vital signs will be measured at the Screening visit, on UCB6114 dosing visits (Days 1 and 15 of each cycle for participants in Cohorts 1 and 2 and on Day 1 of each cycle for participants in Cohorts 3 and 4) and at the SFU visit. In addition, participants in Cohort 4 will have vital signs measured on non-dosing Day 15 of Cycle 1 and 2 only.

On UCB6114 dosing visits, vital signs will be measured at multiple timepoints relative to the UCB6114 infusion: predose, 10 minutes (±5 minutes) and 30 minutes (±10 minutes), after the start of the infusion, at the end of the infusion (+15 minutes) and at 2 hours (+15 minutes) after the end of the infusion.

In addition, on Cycle 1 Day 1, vital signs will also be assessed at 5 hours (+2 hours) after the end of the infusion. All vital signs measurements on UCB6114 dosing visits and at the SFU visit will be performed prior to the collection of PK samples.

Observed vital sign measurements and changes from Baseline will be listed by visit and timepoint and summarized using descriptive statistics.

For the multiple vital signs measurements on UCB6114 dosing visits (i.e. on Days 1 and 15 of each cycle for participants in Cohorts 1 and 2 and on Day 1 of each cycle for participants in Cohorts 3 and 4), changes from the predose value will be calculated at each postdose timepoint and summarized using descriptive statistics.

For each vital signs parameter, the mean (±standard deviation) change from Baseline value will be plotted over scheduled visit and timepoint with treatment group overlaid on the same plot. Vital signs may be presented by tumor type (CRC, Gastric/GEJ-Cancer and Pancreatic Adenocarcinoma) depending on the number of participants with specific tumor types.

The incidence of treatment-emergent markedly abnormal (TEMA)/potentially clinically significant (PCS) vital signs based on blood pressure and pulse rate measurements will be summarized by visit and timepoint using frequency counts and percentages. The criteria for identifying a TEMA/PCS are included in Table 8-2.

Table 8-2: TEMA/PCS Criteria for Vital Signs

Variable (unit)	Low[a]	High[a]
Systolic Blood Pressure (mmHg)	Value <90 and ≥20 decrease from Baseline	Value >140 and ≥20 increase from Baseline
Diastolic Blood Pressure (mmHg)	Value <50 and ≥15 decrease from Baseline	Value >90 and ≥15 increase from Baseline
Pulse Rate (bpm)	Value <45 and ≥15 decrease from Baseline	Value >90 and ≥15 increase from Baseline

bpm=beats per minute; PCS=potentially clinically significant; mmHg=millimeter of mercury; TEMA=treatment-emergent markedly abnormal.
a Both conditions must be satisfied for a measurement to be considered PCS.

8.4.2 12-Lead Electrocardiograms

ECGs will be performed at the Screening visit, on Day 1 of each cycle and at the SFU visit. On

Day 1 of Cycle 1, ECGs will be performed prior to dosing, at the end of the infusion and at 2 hours after the end of the infusion. ECGs at each scheduled timepoint will be performed in triplicate with the participant in a supine position after a minimum of 5 minutes rest. When an ECG assessment coincides with PK (and PD) sampling, the ECG should be performed first.

All ECGs will be evaluated for any clinically relevant changes by the investigator.

Electrocardiograms will also be collected for central reading, the data from which will be analyzed separately and reported in an addendum to the CSR.

All summaries and listings of ECG data will be based on the local (site) 12-lead ECG measurements.

The following ECG parameters will be reported:

- PR interval;
- QT interval;
- QRS interval;
- QTcF interval (QT corrected for heart rate using Fridericia's formula [QTcF]);
- Heart rate.

Observed values and changes from Baseline in these ECG parameters will be listed and summarized by visit using descriptive statistics. The mean of the triplicate measurements taken for each parameter will be used in the summary at each visit and timepoint. If less than 3 of the triplicate measurements are taken then the mean of the available measurements will be used (if only 1 of the 3 triplicate measurements is available, then this value will be used in the summaries). The Baseline value will be the mean of the last scheduled or unscheduled triplicate measurements taken prior to the first dose of study treatment on Day 1 of Cycle 1. If no predose triplicate measurements are taken then the mean of the triplicate measurements taken at Screening will be used. The mean of only the scheduled triplicate measurements at each Post-Baseline visit and timepoint will be included in the summary.

For the multiple ECGs performed, changes from the predose value will be calculated at each postdose timepoint and summarized using descriptive statistics.

Mean (±standard deviation) change from Baseline in QTcF will be plotted over scheduled visit with treatment groups overlaid on the same plot. Individual observed values of QTcF will be presented over actual time in a spaghetti plot. Plots may be presented by tumor type (CRC, Gastric/GEJ-Cancer and Pancreatic Adenocarcinoma) depending on the number of participants with specific tumor types.

The following cut-points in QTcF will be applied for observed data and changes from Baseline:

For observed QTcF data:

- <450 msec;
- ≥450 to <480 msec;
- ≥480 to <500 msec;
- ≥500 msec.

For changes from Baseline in QTcF:

- <30 msec;
- ≥30 to <60 msec;
- ≥60 msec.

The incidence of participants in each of these categories will be summarized using frequency counts and percentages by visit.

A listing of 12-lead ECG abnormal findings will be presented.

8.4.3 Echocardiogram

Echocardiograms will be performed at the Screening visit, on Day 1 of Cycle 3 (+/- 7 days), as clinically indicated afterwards, and at the SFU visit.

All details on the echocardiogram assessments performed at each visit will be listed including the observed LVEF measurements and changes from Baseline, as well as information on whether the result was normal, abnormal not clinically significant (NCS) or abnormal clinically significant (CS).

Observed values and changes from Baseline in LVEF will be summarized by visit using descriptive statistics. In addition, shift tables for the change from Baseline in normal, abnormal NCS, abnormal CS LVEF results will be summarized by visit.

Mean (±standard deviation) change from Baseline in LVEF will be plotted over scheduled visit with treatment groups overlaid on the same plot. Individual observed LVEF results will be presented over actual time in a spaghetti plot. Plots may be presented by tumor type (CRC, Gastric/GEJ-Cancer and Pancreatic Adenocarcinoma) depending on the number of participants with specific tumor types.

8.4.4 ECOG performance status

ECOG performance status will be assessed at the Screening visit, on Day 1 of each cycle and at the SFU visit. ECOG performance status will be listed by participant and visit and will be summarized using frequency counts and percentages. A shift table summarizing the changes from Baseline to each post-Baseline visit will also be presented. Further details on the ECOG performance scale, the listings and summaries are included in Section 10.2.

8.4.5 Physical examination

Physical examination will be undertaken at the Screening visit and on Cycle 1 Day 1 prior to dosing with UCB6114. Symptom-directed physical examinations will be performed prior to dosing with UCB6114 (Days 1 and 15 of each cycle for participants in Cohorts 1 and 2 and on Day 1 of each cycle for participants in Cohorts 3 and 4) and at the SFU visit. In addition, participants in Cohort 4 may have symptom-directed physical examinations performed on non-dosing Day 15 in Cycle 1 and 2 only.

All physical examination data will be listed.

9 PHARMACOKINETICS AND PHARMACODYNAMICS

9.1 Pharmacokinetics

9.1.1 Secondary pharmacokinetic endpoint

[redacted]

9.1.2 Exploratory pharmacokinetic endpoints

[redacted]

[redacted]

9.2 Pharmacodynamics

The following exploratory PD and biomarker endpoints/analyses will be obtained/performed from blood samples which will be analyzed at a number of external laboratory vendors:

- cGremlin-1;
- Serum protein/proteomic analysis;
- Transcriptomic analysis;
- Genetic analysis;
- ctDNA.

For all cohorts, blood samples for cGremlin-1 analysis will be collected on Day 1 of Cycle 1 at the following timepoints relative to the UCB6114 infusion: predose (within 30 minutes prior to the infusion), end of the infusion (+15 minutes) and 4 hours (+1 hour) postinfusion. For Cohorts 1, 2 and 4, a blood sample will be collected predose (within 30 minutes prior to the infusion) on Day 15 or on the day of the Day 15 visit if this is not a dosing day (Cohort 4). For Cohort 3, a blood sample will be taken on Day 15. In all subsequent cycles for all cohorts, blood samples will be collected at predose (within 30 minutes prior to the infusion) on Day 1 and at the SFU visit. For Cycle 3 only, an additional sample will be taken on Day 1. An additional sample should also be collected on the day of the On-Treatment biopsy (only if taking place on a day where no samples for cGremlin-1 are scheduled).

cGremlin-1 will be reported as concentration in blood by nominal (scheduled) assessment and treatment group. Concentrations of cGremlin-1 will be listed for the SS and summarized for the PDS using descriptive statistics by treatment group and nominal (scheduled) sampling timepoints (n, arithmetic mean, median, standard deviation, minimum, maximum, geoMean, geoCV and 95% CI for the geoMean [assuming lognormally distributed data]). Changes from Baseline will also be summarized. Individual study participant cGremlin-1 concentration-time profiles will be displayed graphically in spaghetti plots and geoMean cGremlin-1 concentration and 95% CI will be plotted at each nominal (scheduled) timepoint with treatment group overlaid on the same plot.

Serum protein/proteomic analysis, transcriptomic analysis, genetic analysis and the analysis of the test results from the blood samples taken for ctDNA will be performed and reported separately outside of the CSR.

Hematoxylin and eosin (H & E) staining and immunohistochemistry (IHC) will be used to analyze tissue samples obtained from any available historical tumor biopsies taken prior to participants' entry into the study (e.g. at the time of diagnosis), from the tumor biopsy performed

at Baseline [between Day -28 and Day -1 during the Screening Period] and from the On-Treatment tumor biopsy performed within 2 weeks post Cycle 1 Day 15 [i.e. between Cycle 1 Day 15 and Cycle 2 Day 1] for Cohorts 1, 2 and 4, and within 2 weeks post Cycle 2 Day 1 [i.e. between Cycle 2 Day 1 and Cycle 2 Day 15] for Cohort 3).

Test results from the H & E staining and for target genes, phosphatase and tensin homolog (PTEN), Ki67 (cellular marker for proliferation in tumors), Gremlin-1, mothers against decapentaplegic homolog 4 (SMAD4), fibroblast activation protein (FAP) and phosphorylated mothers against decapentaplegic homolog 1/5/8 (pSMAD1/5/8) will be listed by variable, timepoint and sample analyzed (multiple tissue samples from a tumor biopsy may have been analyzed for a participant).

The following key/component variables will be derived based on H & E staining, PTEN, Ki67, Gremlin-1, FAP and pSMAD1/5/8 test results. Selected raw test results and key variables will be listed and summarized as described below. No derived variables will be generated for SMAD4; only raw test results and changes from Baseline (where relevant) will be listed and summarized. Listings will be generated for the SS and summaries will be based on the PDS.

Changes from Baseline will be calculated for selected raw test results and key variables. Since a participant may have multiple tissue samples analyzed from the Baseline tumor biopsy, the mean of the test results at Baseline will be used in the calculation of the change from Baseline for each On-Treatment sample result.

Summaries of the selected key derived variables and raw test results (observed values and changes from Baseline) will be generated on a tissue sample level basis, i.e. results for all samples analyzed for all participants at each timepoint will be included.

H & E: Tissue Integrity (Percentage of Necrosis in Tumor Area)

All H & E raw test results will be listed.

In order to assess tissue integrity, percentage of necrosis in the tumor area will be categorized as '<20%' and '>=20%'. If percentage of necrosis data are missing but other H & E staining and IHC data are available for tumor biopsy samples analyzed, then results will be categorized as 'Not done'.

This categorical variable will be listed and summarized using frequency counts and percentages at each timepoint (i.e. historical, Baseline and On-Treatment) by treatment group.

PTEN: Tissue Sample Quality Control

The presence/absence of staining of intrinsic control elements on the slides and the level of staining intensity will be listed together with the staining pattern, staining artifacts and any assay-specific comments. Since the percent of tumor cells with staining intensity 0/1/2/3 and the H-score (test results for which will be provided by the laboratory) are less relevant to assessing the quality control of the tissue sample, these raw test results will not be listed.

The presence of staining of intrinsic control elements on the slides together with the level of staining intensity will be used to determine the tissue sample quality control.

If staining of intrinsic control elements on stained slides='YES' and staining intensity of intrinsic control elements on stained slides is 1, 2 or 3 then the tissue sample quality control is 'Good', otherwise, if the staining intensity of intrinsic control elements=0 then the tissue sample quality control is 'Questionable'. If staining of intrinsic control elements on stained slides='NOT PRESENT' then the tissue sample quality control is 'No staining present'. If both variables are missing but other IHC results are available for tumor biopsy samples analyzed, then results will be categorized as 'Not done'.

This categorical variable will be listed and summarized using frequency counts and percentages at each timepoint (i.e. historical, Baseline and On-Treatment) by treatment group.

Ki67 – Proliferative Activity of the Tumor

All Ki67 raw test results will be listed together with changes from Baseline in the number of Ki67-positive cell objects in the tumor region divided by the total number of cell objects in the tumor region, and the number of Ki67-positive cell objects in the tumor region divided by the area of the tumor region for each On-Treatment test result.

In order to assess the proliferative activity of the tumor mass, cellular proliferation reflected by the number of Ki67-positive cell objects in the tumor region divided by the total number of cell objects in the tumor region will be categorized as '<=10%' or '>10%' with the latter category indicating an actively/moderately proliferating tumor. If the test result is 'NOT EVALUABLE' or missing but IHC results are available for tumor biopsy samples analyzed, then results will be categorized as 'Not done'.

This categorical variable will be listed and summarized using frequency counts and percentages at each timepoint (i.e. Historical, Baseline and On-Treatment) by treatment group. The number of Ki67-positive cell objects in the tumor region divided by the total number of cell objects in the tumor region will also be summarized at each timepoint together with the change from Baseline at the On-Treatment timepoint using descriptive statistics (n, arithmetic mean, standard deviation, median, minimum and maximum) by treatment group.

Gremlin-1: Cytoplasmic Histoscore

Tissue sample results will be available for Gremlin-1 from historical tumor biopsies and biopsies performed at Baseline (during the Screening period prior to the first dose of UCB6114), where available.

All Gremlin-1 raw test results will be listed.

The cytoplasmic histoscore will be calculated as a weighted score based on the percentage of tumor cells with Gremlin-1 cytoplasmic staining intensity 1, 2 or 3 as follows:

(1 x percent tumor cells with Gremlin-1 cytoplasmic staining intensity 1) + (2 x percent tumor cells with Gremlin-1 cytoplasmic staining intensity 2) + (3 x percent tumor cells with Gremlin-1 cytoplasmic staining intensity 3).

The histoscore will be missing if the participant had tumor biopsy samples analyzed but there are no test results for percent tumor cells with Gremlin-1 cytoplasmic staining intensity 1, 2 or 3.

Summary statistics (n, arithmetic mean, standard deviation, median, minimum and maximum) will be presented at each timepoint (Historical and Baseline) by treatment group for the cytoplasmic histoscore and the tumor proportion score. The cytoplasmic histoscore will be listed together with the Gremlin-1 raw test results.

SMAD4

All SMAD4 raw test results will be listed together with the changes from Baseline in percent SMAD4 protein expression loss for each On-Treatment test result.

Observed values of percent SMAD4 protein expression loss will be summarized using descriptive statistics (n, arithmetic mean, standard deviation, median, minimum and maximum) at each timepoint (Historical, Baseline and On-Treatment) by treatment group. In addition, changes from Baseline at the On-Treatment timepoint will be summarized by treatment group.

FAP

During the image analyses of FAP-stained slides from tumor biopsies at each timepoint, the tumor will be classified into 2 regions: the cancer (CN) tumor region and the invasive margin (IM) region using a pre-established digital automated algorithm. The IM region is usually a small proportion of the whole tumor and, per standard procedures at the analytical laboratory, will be identified first. As a result, there is a risk that some parts of the CN tumor region may be inaccurately classified as part of the IM region, particularly in cases when the tumor is small. Therefore, instead of using the results for the percentage of high, medium and low intensity FAP provided by the laboratory, a decision was made to back-calculate the areas of the CN tumor region and the IM region and add these together in order to re-calculate the percentage of high, medium and low intensity FAP in the whole tumor.

These back-calculated results and derived variables based on FAP test results at each timepoint are defined in Table 9-1.

Table 9-1: FAP Derived Variables

Variable No.	FAP Derived Variable	Description and Calculation
1[a]	Total Analyzed Tumor Area (um^2)	This is the total tumor area (um^2) across the CN tumor region and the IM region and will be calculated as the sum of the areas of the CN tumor region (um^2) and the IM region (um^2) where a

Variable No.	FAP Derived Variable	Description and Calculation
		non-missing numeric test result is available for both the area of the CN tumor region and the area of the IM region. Note that, in cases where no IM region is defined, the area of the IM region will be recorded as 0 or 'NOT APPLICABLE', or may be missing. If the area of the IM region is recorded as 'NOT APPLICABLE' or is missing, then 0 will be assumed in this calculation and the total analyzed tumor area will be equal to the area of the CN tumor region. This variable will be missing if both the areas of the CN tumor region and IM region are missing, or if one or both are 'NOT EVALUABLE' or 'NOT DIAGNOSTIC'.
2	Measured Area of Weakly Stained FAP in the CN Tumor Region (um^2)	This is the back-calculated area of weakly stained FAP in the CN tumor region (weak positive) and will be calculated by multiplying the area of the CN tumor region (um^2) and the relative area of weakly stained FAP in the CN tumor region (%) where a non-missing numeric test result is available for both the area of the CN tumor region and the relative area of weakly stained FAP in the CN tumor region. This variable will be set to 0 if one or both are missing, 'NOT EVALUABLE' or 'NOT DIAGNOSTIC'.
3	Measured Area of Moderately Stained FAP in the CN Tumor Region (um^2)	This is the back-calculated area of moderately stained FAP in the CN tumor region (moderate positive) and will be calculated by multiplying the area of the CN tumor region (um^2) and the relative area of moderately stained FAP in the CN tumor region (%) where a non-missing numeric test result is available for both the area of the CN tumor region and the relative area of moderately stained FAP in the CN tumor region. This variable will be set to 0 if one or both are missing, 'NOT EVALUABLE' or 'NOT DIAGNOSTIC'.
4	Measured Area of Strongly Stained FAP in the CN Tumor Region (um^2)	This is the back-calculated area of strongly stained FAP in the CN tumor region (strong positive) and will be calculated by multiplying the area of the CN tumor region (um^2) and the relative area of strongly stained FAP in the CN tumor region (%) where a non-missing numeric test result is available for both the area of the CN tumor region and the relative area of strongly stained FAP in the CN tumor region. This variable will be set to 0 if one or both are missing, 'NOT EVALUABLE' or 'NOT DIAGNOSTIC'.

Variable No.	FAP Derived Variable	Description and Calculation
5	Measured Area of Weakly Stained FAP in the IM Region (um^2)	This is the back-calculated area of weakly stained FAP in the IM region (weak FAP-positive) and will be calculated by multiplying the area of the IM region (um^2) and the relative area of weakly stained FAP in the IM region (%) where a non-missing numeric test result is available for both the area of the IM region and the relative area of weakly stained FAP in the IM region. This variable will be set to 0 if one or both are missing, 'NOT EVALUABLE' or 'NOT DIAGNOSTIC'.
6	Measured Area of Moderately Stained FAP in the IM Region (um^2)	This is the back-calculated area of moderately stained FAP in the IM region (moderate FAP-positive) and will be calculated by multiplying the area of the IM region (um^2) and the relative area of moderately stained FAP in the IM region (%) where a non-missing numeric test result is available for both the area of the IM region and the relative area of moderately stained FAP in the IM region. This variable will be set to 0 if one or both are 'NOT EVALUABLE' or 'NOT DIAGNOSTIC'.
7	Measured Area of Strongly Stained FAP in the IM Region (um^2)	This is the back-calculated area of strongly stained FAP in the IM region (strong FAP-positive) and will be calculated by multiplying the area of the IM region (um^2) and the relative area of strongly stained FAP in the IM region (%) where a non-missing numeric test result is available for both the area of the IM region and the relative area of strongly stained FAP in the IM region. This variable will be set to 0 if one or both are missing, 'NOT EVALUABLE' or 'NOT DIAGNOSTIC'.
8[a]	Total FAP-Positive Tumor Area (um^2)	This is the total FAP-positive area across the CN tumor region and the IM region (whole tumor) and will be calculated as the sum of component derived variables 2-7. If all 6 component variables are 0 then this derived variable will be missing.
9[a]	Total Measured Area of Weakly Stained FAP (um^2)	This is the total weak FAP-positive area across the CN tumor region and the IM region (whole tumor) and will be calculated as the sum of component FAP derived variables 2 and 5.
10[a]	Total Measured Area of Moderately Stained FAP (um^2)	This is the total moderate FAP-positive area across the CN tumor region and the IM region (whole tumor) and will be

Variable No.	FAP Derived Variable	Description and Calculation
		calculated as the sum of component FAP derived variables 3 and 6.
11[a]	Total Measured Area of Strongly Stained FAP (um^2)	This is the total strong FAP-positive area across the CN tumor region and the IM region (whole tumor) and will be calculated as the sum of component FAP derived variables 4 and 7.
12[a]	Total Relative Area of Weakly Stained FAP (%)	This is the percentage of weak FAP expression across the CN tumor region and IM region (whole tumor) and will be calculated using component FAP derived variables 1 and 9 as (Total Measured Area Of Weakly Stained FAP / Total Analyzed Tumor Area) x 100 If the total analyzed tumor area is missing then this variable cannot be calculated and will be missing.
13[a]	Total Relative Area of Moderately Stained FAP (%)	This is the percentage of moderate FAP expression across the CN tumor region and IM region (whole tumor) and will be calculated using component FAP derived variables 1 and 10 as (Total Measured Area Of Moderately Stained FAP / Total Analyzed Tumor Area) x 100 If the total analyzed tumor area is missing then this variable cannot be calculated and will be missing.
14[a]	Total Relative Area of Strongly Stained FAP (%)	This is the percentage of strong FAP expression across the CN tumor region and IM region (whole tumor) and will be calculated using component FAP derived variables 1 and 11 as (Total Measured Area Of Strongly Stained FAP / Total Analyzed Tumor Area) x 100 If the total analyzed tumor area is missing then this variable cannot be calculated and will be missing.
15[a]	Total Relative FAP-Positive Tumor Area (TPS) (%)	This is the total proportion score which is the percentage of FAP-positive area across the CN tumor region and the IM region (whole tumor) and will be calculated using component derived variables 1 and 8 as (Total FAP-Positive Tumor Area / Total Analyzed Tumor Area) x 100 If the total analyzed tumor area is missing then this variable cannot be calculated and will be missing.

Variable No.	FAP Derived Variable	Description and Calculation
16[a]	Total FAP Histoscore	This is a histoscore for the combined CN tumor region and IM region (whole tumor) and will be calculated as a weighted score based on component derived variables 12, 13 and 14 as (1 x Total Relative Area of Weakly Stained FAP) + (2 x Total Relative Area of Moderately Stained FAP) + (3 x Total Relative Area of Strongly Stained FAP)

CN=cancer; FAP=fibroblast activation protein, IM=invasive margin, TPS=total proportion score.
[a] Included in the listing of FAP test results.

The derived variables containing the [a] flag in Table 9-1 above will be listed together with information on staining artifacts and any assay-specific comments provided by the laboratory.

Observed values for total relative FAP-positive tumor area (TPS) and total FAP histoscore will be summarized using descriptive statistics (n, arithmetic mean, standard deviation, median, minimum and maximum) at each timepoint (Historical, Baseline and On-Treatment) by treatment group. In addition, changes from Baseline in TPS and total FAP histoscore at the On-Treatment timepoint will be listed and summarized by treatment group.

pSMAD1/5/8: Nuclear Histoscore

All pSMAD1/5/8 raw test results will be listed.

The nuclear histoscore will be calculated as a weighted score based on the percentage of tumor cells with pSMAD1/5/8 nuclear staining intensity 1+, 2+ or 3+ as follows:

(1 x percent tumor cells with pSMAD1/5/8 nuclear staining intensity 1+) + (2 x percent tumor cells with pSMAD1/5/8 nuclear staining intensity 2+) + (3 x percent tumor cells with pSMAD1/5/8 nuclear staining intensity 3+).

The histoscore will be missing if the participant had tumor biopsy samples analyzed but there are no test results for percent tumor cells with pSMAD1/5/8 nuclear staining intensity 1+, 2+ or 3+.

Summary statistics (n, arithmetic mean, standard deviation, median, minimum and maximum) will be presented at each timepoint (Historical, Baseline and On-Treatment) by treatment group the nuclear histoscore and the tumor proportion score.

Further informal analyses may be performed to explore the relationship between the PD and biomarker endpoints with antitumor activity and ADA status. The PK-PD effects of UCB6114 may be assessed using a population analysis approach. These analyses will also be performed separately outside of the CSR and the details of analysis methods will be included in a separate analysis plan.

The incidence of PD samples taken from the blood and tumor biopsies will be summarized by visit/timepoint and treatment group.

9.3 Immunogenicity

Anti-drug (UCB6114) antibody status and classification, changes from Baseline in titer over time and the incidence of treatment-emergent ADA positivity are exploratory immunogenicity endpoints in Part A1 of this study. Potential relationships between ADA and PK, PD, antitumor activity and safety will also be explored but this will be reported separately outside of the CSR.

Serum samples will be collected from all study participants for the measurement of ADA and the evaluation of immunogenicity according to the Schedule of Activities in the protocol.

All listings of ADA will be presented for the SS and summaries of the ADA data will be summarized by treatment group for the ADAS.

Anti-drug (UCB6114) antibodies will be measured using a three-tiered assay approach: Screening assay, confirmatory assay and titration assay.

Samples will first be evaluated in the Screening assay (reported as 'negative screen' or 'positive screen'), followed by analysis of screened positive samples in the confirmatory assay to confirm the positivity of the samples (reported as 'negative immunodepletion' or 'positive immunodepletion'). Samples that are confirmed as positive in the confirmatory assay will be evaluated in a titration assay to assess the ADA level and this will be reported as titer (reciprocal dilution factor including minimum required dilution [MRD]).

The ADA sample status will be determined as follows from the pre-treatment sample taken on Day 1 of Cycle 1 (Baseline) and all post-treatment (post-Baseline) samples.

- Sample values that are either 'negative screen' or 'positive screen' and 'negative immunodepletion' will be defined as **ADA negative**
- Sample values that are 'positive screen' and 'positive immunodepletion' will be defined as **ADA positive**

Anti-drug (UCB6114) antibody sample status will be listed for each participant at each visit by treatment group. This listing will include sampling dates and times, the Screening assay result, the confirmatory assay result and the derived ADA sample status. In addition, the titer from the titration assay (if applicable) will be listed together with the change from Baseline in titer. The number and percentage of participants with a positive or negative sample at each visit will be summarized by treatment group. Percentages will be calculated based on the number of participants with a non-missing/sufficient sample at the visit.

Based on the ADA status of the samples, study participants will be categorized according to the following 6 ADA classifications in Table 9-2:

Table 9-2: ADA Classifications

Classification	Classification Label	Definition
1	Pre-ADA negative – treatment induced ADA negative	Includes participants who have an ADA negative status at Baseline, or missing/insufficient Baseline sample, and an ADA negative status at all sampling timepoints post-Baseline (including SFU). Participants with missing post-Baseline samples are included as long as the missing samples do not result in an unmonitored period greater than 16 weeks.
2	Pre-ADA negative – treatment induced ADA positive	Includes participants who have an ADA negative status at Baseline, or missing/insufficient Baseline sample, and an ADA positive status at any sampling timepoint post-Baseline (including SFU).
3	Pre-ADA positive – treatment reduced ADA	Includes participants who have an ADA positive status at Baseline and an ADA negative status at all sampling timepoints post-Baseline (including SFU)
4	Pre-ADA positive – treatment unaffected ADA	Includes participants who have an ADA positive status at Baseline and an ADA positive status at any sampling timepoint post-Baseline (including SFU) with titer values of the same magnitude as Baseline (≤1.80-fold difference from the Baseline value) or with decreased titer values compared to Baseline (>1.80-fold decrease from the Baseline value).
5	Pre-ADA positive – treatment boosted ADA positive	Includes participants who have an ADA positive status at Baseline and an ADA positive status at any sampling timepoint post-Baseline (including SFU) with increased titer values compared to Baseline (>1.80-fold increase from the Baseline value.
6	Inconclusive	Includes participants who do not satisfy the criteria for classifications 1-5

ADA=anti-drug (UCB6114) antibody; SFU=Safety Follow-up.
Note: The terminology 'treatment unaffected' is ambiguous as the criteria refers to ADA responses that are not increased upon dosing compared to Baseline level whereas titers may reduce.

A study participant will be classified as having **treatment-emergent ADA positivity** if they satisfy one of the following criteria:

- The Baseline result is ADA negative and at least one post-Baseline result is ADA positive (pre-ADA negative – treatment induced ADA positive) – ADA classification 2 in Table 9-2;
- The Baseline result is ADA positive and at least one post-Baseline result shows a pre-defined fold increase in titer from the Baseline value (the fold increase from Baseline required to meet this criterion will be defined with the development of the assay and will be included in the TFLs) (pre-ADA positive – treatment boosted ADA positive) – ADA classification 5 in Table 9-2.

Total anti-drug (UCB6114) antibody **incidence** will be determined by the number and percentage of participants with treatment-emergent ADA positivity (as defined above). The denominator for the percentage calculation will be the number of participants with at least one available/reported post-Baseline result.

Total **prevalence** of pre-ADA will be determined by the number and percentage of participants who are pre-ADA positive (i.e. participants who have a positive ADA sample status at Baseline). The denominator for the percentage calculation will be the number of participants with an available/reported Baseline sample result.

Total anti-drug (UCB6114) antibody **prevalence** will be determined by the number and percentage of participants with ADA classifications 2, 4 and 5 in Table 9-2 (i.e. an ADA positive status at any post-Baseline sampling timepoint. The denominator for the percentage calculation will be the number of participants with at least one available/reported sample result (either at Baseline and/or post-Baseline).

The ADA classification for each participant will be listed by treatment group. This listing will also include whether or not the participant achieved treatment-emergent ADA positivity (ADA incidence), whether the participant was pre-ADA positive (pre-ADA prevalence) and whether the participant had an ADA positive status at any post-Baseline sampling timepoint (ADA prevalence). In addition, the visit at which the participant first achieved treatment-emergent ADA positivity will be included.

The number and percentage of participants in each of the 6 ADA classifications defined above in Table 9-2 will be presented by treatment group. The denominator for the percentage calculations will be the number of participants who have a non-missing ADA classification. Also, in this tabulation, ADA incidence and prevalence (as defined above) will be summarized.

The first occurrence of treatment-emergent ADA positivity (based on the criteria above) will be summarized using frequency counts and percentages at each post-Baseline visit by treatment group. This tabulation will include a count of the number of participants at each post-Baseline visit who fulfill at least one of the above defined criteria for treatment-emergent ADA positivity; participants will be counted in the numerator based on the earliest visit at which one of these criteria is fulfilled. At other visits, participants will be counted in the denominator (assuming an assessment of treatment-emergent positivity is available) and this will be used in the percentage calculations.

Individual study participant ADA titer profiles over actual time will be presented graphically on the linear and the semi-logarithmic scale. The linear scale plots will be repeated for the subset of participants who achieve treatment-emergent ADA positivity during Part A1.

Mean (±standard deviation) C_{min} will be plotted by ADA sample status over scheduled time with treatment groups overlaid on the same plot.

10 EFFICACY ANALYSES

10.1 Antitumor activity

The analysis of antitumor activity is exploratory in Part A1 of this study.

Tumor assessments will be performed at the Screening visit, every 8 weeks from Day 1 of Cycle 1, and at the SFU visit.

10.1.1 Definitions of the antitumor activity endpoints

The following endpoints are defined based on RECIST (Version 1.1) which standardizes solid tumor measurements and provides guidelines for the objective assessment of changes in tumor size during anti-cancer treatment.

Appendix 9 (Section 11.9) of the protocol contains the RECIST 1.1 guidelines to be used in this study, adapted from Eisenhauer (2009), and includes the definitions of target and non-target lesions, the definitions of target and non-target lesion responses at each tumor assessment, the criteria for determining overall tumor response at each tumor assessment based on target lesion response, non-target lesion response and the presence/absence of new lesions, and a participant's best overall response (BOR). Further details on the rules to apply in the derivation of BOR are included in the Derivation of Efficacy Endpoints document Version 0.6 (dated 21 JAN 2022) which has been developed to support this SAP.

At each post-Baseline tumor assessment, the investigator will record responses for target lesions and non-target lesions, whether or not there has been an appearance of any new lesions, and the participant's overall tumor response based on their target lesion response, non-target lesion response and the presence/absence of new lesions. Note that target lesion response and non-target lesion response assessments will be based on the changes in the pre-existing lesions at Baseline and the appearance of new lesions will only factor in the determination of an overall tumor response of PD at that tumor assessment visit (i.e. per Tables A and B in Section 11.9.2 of Appendix 9 of the protocol).

Objective response rate (ORR) is defined as the percentage of participants with a BOR of complete response (CR) or partial response (PR) during Part A1.

Disease Control Rate (DCR) is defined as the percentage of participants with a BOR of CR, PR, or stable disease (SD) during Part A1.

Best overall response (BOR) is defined for each study participant as the best overall tumor response from each tumor assessment (scheduled and unscheduled assessments performed every 8 weeks from Day 1 of Cycle 1 (±7 days)) according to the RECIST criteria for changes in target and non-target lesions and the appearance of new lesions. Best overall response is determined from the start of study treatment (first dose of UCB6114) until documented objective disease progression or the date of subsequent anti-cancer therapy (systemic therapy, surgery or radiotherapy for cancer), whichever occurs first. If anti-cancer therapy is started on the same day as a tumor assessment, then the overall tumor response from that assessment will be used in the derivation of BOR. If a participant does not have objective disease progression and does not start a subsequent anti-cancer therapy, then all tumor assessments (scheduled and unscheduled) up to the SFU visit will be included in the derivation of BOR. For a BOR of SD, a participant's tumor measurements must have met the SD criteria at least once after the start of study treatment at a minimum interval of no less than 49 days.

For Part A1, BOR determination requires confirmation of CR or PR responses at a subsequent assessment ≥4 weeks (28 days) after the criteria for CR or PR responses are first met, however, an unconfirmed BOR will also be derived for each participant for the purpose of reporting (as

described below in Section 10.1.2). Table C in Appendix 11.9 of the protocol and Table 1 and subsequent text in the Derivation of Efficacy Endpoints document provides detail on the derivation of BOR when confirmation of CR and PR responses is required. The definition of an unconfirmed BOR is also included in this document. Although the derivation of unconfirmed BOR does not include the requirement for a CR or PR response to be confirmed ≥4 weeks (28 days) after the initial response, a participant's CR or PR response may, in fact, be confirmed at a subsequent assessment ≥4 weeks (28 days) after the criteria for the CR or PR response are first met.

Confirmed BOR and unconfirmed BOR will be derived programmatically based on the overall tumor assessment data recorded on the eCRF by the investigator.

Duration of response (DOR) will be calculated for participants with a confirmed BOR of CR or PR as the time in days from the start date of the confirmed CR or PR (i.e. the date of the first overall tumor response of CR or PR, which is at least 4 weeks before a second overall tumor response of CR or PR) to the first date that recurrent or progressive disease is objectively documented (i.e. according to the RECIST guidelines). This will be referred to as the duration of confirmed response and the following calculation will be performed:

$$Duration\ of\ Confirmed\ Response = (Date\ of\ First\ Objective\ Disease\ Progression - Start\ Date\ of\ Confirmed\ CR\ or\ PR\ Response) + 1$$

Duration of response will also be calculated for participants with an unconfirmed BOR of CR or PR (which may either be confirmed at a later tumor assessment or unconfirmed) as the time in days from the start date of the CR or PR to the date of the first documented objective disease progression (i.e. according to the RECIST guidelines). The following calculation will be performed:

$$Duration\ of\ Unconfirmed\ Response = (Date\ of\ First\ Objective\ Disease\ Progression - Start\ Date\ of\ CR\ or\ PR\ Response) + 1$$

For the purpose of a sensitivity analysis of both duration of confirmed response and duration of unconfirmed response, the above calculations will take into consideration the occurrence of both objective disease progression (per RECIST 1.1) and clinical disease progression (as described in Appendix 11.9 of the protocol and as determined by the investigator and recorded as a reason for study treatment discontinuation on the eCRF), whichever occurs first. If clinical disease progression occurs on the same date that a participant's objective disease progression is determined, then the participant will be included in the sensitivity analyses as having objective disease progression.

The following calculations will therefore be performed for the sensitivity analyses:

$$Duration\ of\ Confirmed\ Response = (Date\ of\ First\ Objective\ or\ Clinical\ Disease\ Progression - Start\ Date\ of\ Confirmed\ CR\ or\ PR\ Response) + 1$$

$$Duration\ of\ Unconfirmed\ Response = (Date\ of\ First\ Objective\ or\ Clinical\ Disease\ Progression - Start\ Date\ of\ CR\ or\ PR\ Response) + 1$$

For participants who die without objective disease progression, duration of confirmed response and duration of unconfirmed response will be censored on the date of death, regardless of cause. For a participant who discontinues early from Part A1 of the study with no objective disease progression, DOR will be censored on the date of their last available (scheduled or unscheduled) tumor assessment at which a lack of objective disease progression was determined. Participants who discontinue study treatment but who do not have documented objective disease progression (i.e. according to the RECIST guidelines), duration of confirmed response and duration of unconfirmed response will be censored at the date of their last available (scheduled or unscheduled) tumor assessment at which a lack of objective disease progression was determined. Such participants might include those that are ongoing in Part A1 at the time of any defined data cut-off. Likewise, participants who have not discontinued early and do not have documented objective disease progression after a confirmed or unconfirmed response, duration of confirmed response and duration of unconfirmed response will be censored at the date of their last available (scheduled or unscheduled) tumor assessment.

In the sensitivity analyses of duration of confirmed response and duration of unconfirmed response, the same censoring rules will apply except that the date of last contact will be used for the censoring of participants who discontinue early from Part A1 without objective disease progression, clinical disease progression or death.

Date of last contact will be the latest of the dates of premature study termination and of last contact recorded on Study Termination eCRF page, the date of death, the date of last dose of study treatment, the dates of all visits, AE start and end dates (with partial dates imputed as earliest possible) and the date of contact recorded on the Survival Safety Follow-up and Survival Final Follow-up eCRF forms.

Further details on the rules to apply in the derivation of duration of confirmed response and duration of unconfirmed response are included in the Derivation of Efficacy Endpoints document Version 0.6 (dated 21 JAN 2022) which has been developed to support this SAP.

Progression-free survival (PFS) will be calculated as the time in days from the first dose of study treatment to the date of the first documented objective disease progression (i.e. according to the RECIST guidelines), or death due to any cause, whichever occurs first. The following calculation will be performed:

$$PFS = (Date\ of\ Objective\ Progressive\ Disease/Death - Date\ of\ First\ Dose) + 1$$

Participants who die due to any cause without a documented objective disease progression will be considered to have progressed on the date of their death. Participants who do not have any post-Baseline tumor assessments will be censored on the date of their first dose of study treatment. Participants who discontinue early from Part A1 or discontinue study treatment without documented objective disease progression or death, will be censored on the date of their

last available (scheduled or unscheduled) tumor assessment at which a lack of objective disease progression was determined. Participants who start anti-cancer therapy during Part A1 without a prior documented objective disease progression will be censored on the date of their last available (scheduled or unscheduled) tumor assessment prior to the initiation of the subsequent anti-cancer therapy. If anti-cancer therapy starts on the same date as the participant's tumor assessment and determination of objective disease progression, or the participant's death (due to any cause), then the participant will not be censored and the participant will be included as having an uncensored event on this date. This censoring rule will also be applied to participants who are ongoing at any data cut-off for an analysis of Part A1 data who have no documented objective disease progression. The use of anti-cancer therapy during Part A1 will be identified via ongoing medical review of the concomitant medications together with the start dates of further anti-cancer therapy information recorded on the survival follow-up pages of the eCRF.

As a sensitivity analysis, PFS will also be calculated as the time in days from the first dose of study treatment to the date of the first documented objective disease progression (per RECIST 1.1), the date of clinical disease progression, as determined by the investigator, or the date of death due to any cause, whichever occurs first. Last contact date (as defined above for DOR) will be used for the censoring of participants still alive with no reported disease progression (objective or clinical). The same rules described above for the censoring of participants who start anti-cancer therapy will be applied in this sensitivity analysis.

Further details on the rules to apply in the derivation of PFS are included in the Derivation of Efficacy Endpoints document Version 0.6 (dated 21 JAN 2022) which has been developed to support this SAP.

Overall survival (OS) will be calculated as the time in days from the date of first dose of UCB6114 to the date of death from any cause. Participants will be followed up to ascertain their survival status at the SFU visit (within 30 days after their last dose of UCB6114) and at the Final Visit (3 months after their last dose of UCB6114); they will not be followed up beyond this timepoint.

The following calculation will be performed:

$$OS = (Date\ of\ Death - Date\ of\ First\ Dose\ of\ UCB6114) + 1$$

For participants who discontinue early from Part A1 of the study or who discontinue study treatment due to disease progression but continue in the study, who complete Part A1, or who are ongoing in the study at a data cut-off for Part A1, but are not known to have died, OS will be censored on the date of their last contact.

Further details on the rules to apply in the derivation of OS are included in the Derivation of Efficacy Endpoints document Version 0.6 (dated 21 JAN 2022) which has been developed to support this SAP.

10.1.2 Analysis of the antitumor activity endpoints

The analyses of the antitumor activity endpoints in Part A1 will be performed for the PPS. As a sensitivity analysis, all analyses will be repeated for the SS. All listings will be presented for the SS. Summaries and listings will be presented by treatment group.

All lesion assessment data recorded at Baseline (Screening) and during the Treatment Period (every 8 weeks from Day 1 of Cycle 1 [±7 days]) will be listed separately for target lesions, non-

target lesions and new lesions. Each post-Baseline tumor assessment will be labelled as 'Tumor Assessment 1, Tumor Assessment 2 etc. – see further details below). These listings will include lesion number and lesion type (nodal/non-nodal), location, method of assessment, dimension (or an indication that the lesion is too small to measure, for target lesions only) and lesion response evaluation (for non-target lesions at post-Baseline assessments). The listing for target lesions will also include the derived eCRF component data used for the determination of the overall target lesion response at each post-Baseline assessment (e.g. sum of all dimensions across target lesions and percentage change from Baseline in the sum). In addition, the overall response assessment for target lesions and non-target lesions, as determined by the investigator, will be listed for each post-Baseline tumor assessment (Tumor Assessment 1, Tumor Assessment 2 etc.) together with the presence of new lesions and the investigator's overall tumor response assessment.

The investigator's overall tumor response assessment will be summarized using frequency counts and percentages over time (tumor assessment). Post-Baseline tumor assessments are scheduled to be performed per protocol every 8 weeks from Day 1 (±7 days). For the purpose of this summary, the first post-Baseline tumor assessment (scheduled or unscheduled) will be assigned to 'Tumor Assessment 1' using the protocol-defined window of Day 50 to 64 (Day 57 ± 7 days) relative to Day 1 (first dose of UCB6114). For all subsequent post-Baseline tumor assessments (scheduled or unscheduled, but excluding tumor assessments performed at the SFU visit), these will be assigned to 'Tumor Assessment 2', 'Tumor Assessment 3' etc. using the protocol-defined window of Day 50-64 relative to the previous post-Baseline tumor assessment. If a post-Baseline tumor assessment is missed, then the scheduled day of the missed assessment will be used to window the next tumor assessment. In cases where a scheduled and unscheduled tumor assessment occurs in the same window, the investigator's overall tumor response at both assessments will be considered. If the overall tumor response is NE at one of the assessments, then the overall tumor response from the other assessment will be included in the summary table. If the overall tumor response is not NE at both assessments, then the tumor assessment that is closest to the target day of the tumor assessment will be included in the summary table. In the event that the two tumor assessments are equidistant from the target day of the tumor assessment and neither have an overall tumor response of NE, then the worst case overall tumor response will be included in the summary table. Otherwise, if the post-Baseline tumor assessment falls outside of the protocol-defined window, it will be classified as an unscheduled assessment and not included in the summary of overall tumor response.

Bar charts will also be produced for overall tumor response rate by treatment group over time (tumor assessment). In addition, waterfall plots of participants' percentage change from Baseline in the sum of dimensions for all target lesions will be presented by treatment group over time (tumor assessment). The individual participants' bars will be colored by overall tumor response at each timepoint.

Confirmed and unconfirmed BOR for each participant will be derived programmatically using the investigator's overall tumor response assessments (scheduled and unscheduled) performed every 8 weeks from Day 1 of Cycle 1 and the RECIST criteria. Whether a BOR of CR or PR is confirmed or unconfirmed will be indicated on this listing. Using a participant's confirmed BOR and unconfirmed BOR, whether the participant achieves an objective tumor response (i.e. a BOR of CR or PR) and/or disease control (i.e. a BOR of CR, PR or SD) during study treatment will be determined. These derived data will be listed for the SS.

Confirmed BOR and unconfirmed BOR will be summarized using frequency counts and percentages. Bar charts will be produced for confirmed BOR and unconfirmed BOR by treatment group.

The number and percentage of participants achieving objective tumor response and disease control (ORR and DCR) based on confirmed BOR and unconfirmed BOR will be presented and, if data allow, exact 95% CIs for binomial proportions will be calculated using the Clopper-Pearson method and presented for the response rates. In the calculation of ORR and DCR, the denominator will include all participants in the analysis set. Objective response rate and DCR (based on confirmed BOR and unconfirmed BOR) will also be summarized in bar charts by treatment group overall and by tumor type and ECOG performance status at Baseline.

In addition, waterfall plots of each participant's best percentage change from Baseline in the sum of the dimensions for all target lesions will be presented by treatment group overall and by tumor type and ECOG performance status at Baseline with the individual participants' bars colored by confirmed BOR and unconfirmed BOR.

The summaries and analyses of DOR, PFS and OS will be carried out as described below, if the data allow.

Duration of confirmed response, duration of unconfirmed response and PFS will be listed and summarized descriptively using Kaplan-Meier estimation. These summaries will be repeated for the sensitivity analyses of these endpoints (defined in Section 10.1.1 above) and will include the number and percentage of participants with the event, the number and percentage of participants censored, minimum and maximum values and Kaplan-Meier estimates of the 25th percentile, median, 75th percentile and corresponding 95% CIs calculated using Greenwood's formula. In addition, DOR and PFS rates at 3 months, 6 months and 9 months will be derived from the Kaplan-Meier estimation and presented together with associated 95% CIs.

Kaplan-Meier curves will be presented for duration of confirmed response and duration of unconfirmed response and PFS, and for the associated sensitivity analyses. Treatment groups will be overlaid on each plot.

Survival status collected on the eCRF at the SFU visit and at the Final Visit will be listed for each participant by treatment group. This listing will include the participant's survival status, date and cause of death, whether an autopsy was performed and date of autopsy, whether the participant had received any further antitumor treatment after the last dose of study treatment and the type of treatment, and whether the participant's disease had been assessed since the end of study treatment including method of assessment and the overall response.

Overall survival times will be listed and summarized descriptively using Kaplan-Meier estimation. Note that since participants are only followed up for survival until the Final Visit in Part A1 of the study, a summary of OS may not be meaningful (i.e. if no participants die then OS cannot be assessed).

Additional exploratory analyses of selected antitumor activity endpoints may be performed based on subgroups of participants in the SS.

Additionally, the relationship of the antitumor activity variables with key PK parameters may be explored but this will be reported separately.

10.2 ECOG performance status

ECOG performance status is an additional efficacy assessment performed in Part A1 of this study and is defined in Table 10-1.

Table 10-1: ECOG Performance Status Scale

Grade	ECOG performance status scale
0	Fully active, able to carry on all pre-disease performance without restriction
1	Restricted in physically strenuous activity but ambulatory and able to carry out work of a light or sedentary nature (e.g. light housework, office work)
2	Ambulatory and capable of all self-care but unable to carry out any work activities. Up and about more than 50% of waking hours
3	Capable of only limited self-care, confined to bed or chair for more than 50% of waking hours
4	Completely disabled. Cannot carry out any self-care. Totally confined to bed or chair
5	Dead

ECOG=Eastern Cooperative Oncology Group.

ECOG performance status will be listed by treatment group at each visit for the SS.

ECOG performance status will be summarized as an ordinal categorical variable using frequency counts and percentages. Shift tables for the change from Baseline in each grade will be summarized by visit.

11 OTHER ANALYSES

Not applicable.

12 REFERENCES

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International Council for Harmonization/Food and Drug Administration E9 Guidance (ICH-E9) (Phillips et al, 2003).

US Food and Drug Administration FDA Guidance on Conduct of Clinical Trials of Medical Products During COVID-19 Public Health Emergency Guidance for Industry, Investigators and Institutional Review Boards, accessed 29-March-2020.

(https://www.fda.gov/media/136238/download)

13 APPENDICES

13.1 SMQ algorithm for identification of anaphylactic reactions

Based on MedDRA® Version 25.1 or higher, the SMQ='Anaphylactic reaction' consists of 3 parts:

1) A **narrow search** containing PTs that represent core anaphylactic reaction terms:

Category A

Anaphylactic reaction
Anaphylactic shock
Anaphylactic transfusion reaction
Anaphylactoid reaction
Anaphylactoid shock
Circulatory collapse
Dialysis membrane reaction
Kounis syndrome
Procedural shock
Shock
Shock symptom
Type I hypersensitivity

2) A **broad search**:

Category B

Acute respiratory failure
Asthma
Bronchial oedema
Bronchospasm
Cardio-respiratory distress
Chest discomfort
Choking
Choking sensation
Circumoral oedema
Cough
Cough variant asthma
Cyanosis
Dyspnoea
Hyperventilation
Irregular breathing
Laryngeal dyspnoea
Laryngeal oedema
Laryngospasm
Laryngotracheal oedema
Mouth swelling
Nasal obstruction
Oedema mouth
Oropharyngeal oedema
Oropharyngeal spasm
Oropharyngeal swelling
Pharyngeal oedema
Pharyngeal swelling
Respiratory arrest

Respiratory distress	Throat tightness
Respiratory failure	Tongue oedema
Reversible airways obstruction	Tracheal obstruction
Sensation of foreign body	Tracheal oedema
Sneezing	Upper airway obstruction
Stridor	Vaccine associated enhanced respiratory disease
Swollen tongue	Wheezing
Tachypnoea	
Category C	
Allergic oedema	Oedema
Angioedema	Oedema blister
Circumoral swelling	Periorbital oedema
Erythema	Periorbital swelling
Eye oedema	Pruritus
Eye pruritus	Pruritus allergic
Eye swelling	Rash
Eyelid oedema	Rash erythematous
Face oedema	Rash pruritic
Flushing	Skin swelling
Injection site urticaria	Swelling
Lip oedema	Swelling face
Lip swelling	Swelling of eyelid
Nodular rash	Urticaria
Ocular hyperaemia	Urticaria papular
Category D	
Blood pressure decreased	Cardiovascular insufficiency
Blood pressure diastolic decreased	Diastolic hypotension
Blood pressure systolic decreased	Hypotension
Cardiac arrest	Hypotensive crisis
Cardio-respiratory arrest	Post procedural hypotension

Note that if the MedDRA® version is increased from 25.1 during the study, any changes to the terms in the above categories should be applied.

The following **algorithmic approach** will be applied: A or (B and C) or [D and (B or C)], i.e.

If a participant has a TEAE which codes to a PT included in Category A, then the event will be flagged as an anaphylactic reaction. Note that participants with a TEAE coded to a PT='Type 1 hypersensitivity' will also be flagged as having a hypersensitivity reaction as this PT is also included in the Category A narrow search for the 'Hypersensitivity' SMQ.

OR

If a participant has a TEAE which codes to a PT included in Category B **AND** has a TEAE which codes to a PT included in Category C**, and both TEAEs have the same start date**, then both events will be flagged as anaphylactic reactions.

OR

If a participant has a TEAE which codes to a PT included in Category D **AND** has (either a TEAE which codes to a PT included in Category B **OR** a TEAE which codes to a PT included in Category C), **and both TEAEs have the same start date**, then both events will be flagged as anaphylactic reactions.

13.2 SAP Amendment 1 changes

The main rationale for SAP Amendment 1 is to include details on the additional key derived and component exploratory variables required based on the results from the analyses of historical tumor biopsy samples and tumor biopsy samples taken during the Screening period and, wherever possible, during study treatment (within 2 weeks post Cycle 1 Day 15 for cohorts 1, 2 and 4, and within 2 weeks post Cycle 2 for cohort 4) in Part A1. It was decided that these additional variables were needed to improve the interpretability of the test results received from the laboratory.

This SAP amendment also provides some clarifications relating to the handling of data for the purpose of summarizing safety and exploratory anti-tumor activity endpoints.

The key changes are summarized in the table below (note that additional minor corrections and clarifications were also applied in this amendment but are not included in this table).

Section	Description of Change
1	The versions and dates of supporting study documentation were updated.
5.1	An update was made to the example illustrating the definition of a complete cycle of UCB6114.
8.1	The additional summary of the total number of doses of study treatment received was included.
8.2	Rules for handling missing relationship to study treatment for an adverse event were updated.
8.4.2	Clarification on the handling of triplicate ECG measurements was included.

Section	Description of Change
9.2	Details on the analysis of the historical, Baseline and On-Treatment tumor biopsy samples was included together with rules for defining key and component derived variables based on the test results received from the laboratory. A description of the raw test results to be listed for each target gene and the required summary tables was also included.
9.3	A predefined fold-increase of 1.80 was included.
10.1.2	Rules for applying the protocol-defined window around the post-Baseline tumor assessments (scheduled and unscheduled) for the purpose of summarizing the investigator's overall tumor response assessment were included.
General	MedDRA® version number was updated to 25.1 (latest version) throughout the document.

STATISTICAL ANALYSIS PLAN SIGNATURE PAGE

This document has been reviewed and approved per the Review and Approval of Clinical Documents Standard Operating Procedures. Signatures indicate that the final version of the Statistical Analysis Plan (SAP) or amended SAP is released for execution.

STATISTICAL ANALYSIS PLAN

PART B

DOSE ESCALATION (COMBINATION THERAPY)

Study: ONC001

Product: UCB6114

A PHASE 1/2 OPEN-LABEL, MULTICENTER STUDY TO ASSESS THE SAFETY, PHARMACOKINETICS, AND ANTITUMOR ACTIVITY OF UCB6114 ADMINISTERED INTRAVENOUSLY TO PARTICIPANTS WITH ADVANCED SOLID TUMORS

SAP/Amendment Number	Date
Version 1.0	24 August 2021
Amendment 1 Version 1.0	13 October 2023

Confidentiality Statement

TABLE OF CONTENTS

LIST OF ABBREVIATIONS

AE	adverse event
AESI	adverse event of special interest
ADA	anti-drug (UCB6114) antibody
ADaM	Analysis Data Model
ALP	alkaline phosphatase
ALQ	above limit of quantification
ALT	alanine aminotransferase
AST	aspartate aminotransferase
bid	twice daily
BLQ	below limit of quantification
BMI	body mass index
BOR	best overall response
BSA	body surface area
CA	cancer
CDISC	Clinical Data Interchange Standards Consortium
CDMS	clinical data management system
cGremlin-1	circulating gremlin-1
CI	confidence interval
COVID-19	coronavirus disease 2019
CPPC	CDMS postproduction change
CR	complete response
CS	clinically significant
CRC	colorectal adenocarcinoma
CSR	clinical study report
ctDNA	circulating tumor DNA
CTMS	clinical trial management system
DCR	disease control rate
DEM	data evaluation meeting
DES	DLT evaluable set
DLT	dose limiting toxicity
DMC	Data Monitoring Committee
DOR	duration of response
ECG	electrocardiogram
ECOG	Eastern Cooperative Oncology Group
eCRF	electronic case report form
EMA	European Medicines Agency
ES	enrolled set
EudraCT	European Union Drug Regulating Authorities Clinical Trials
FAP	fibroblast activation protein
FDA	Food and Drug Administration

Gastric cancer	gastric adenocarcinoma
GEJ cancer	adenocarcinoma of the gastroesophageal junction
geoCV	geometric coefficient of variation
geoMean	geometric mean
hh:mm	hours:minutes
H & E	hematoxylin and eosin
HLT	high level term
IHC	immunohistochemistry
ICH	International Council for Harmonization
IM	invasive margin
iv	intravenous
IPD	important protocol deviations
LLOQ	lower limit of quantification
LLT	low level term
LVEF	left ventricular ejection fraction
MedDRA®	Medical Dictionary for Regulatory Activities
MTD	maximum tolerated dose
mTPI	modified toxicity probability interval
n	number of study participants
NCI CTCAE	National Cancer Institute Common Terminology Criteria for AEs
NC	not calculable
NCS	not clinically significant
NEst	not estimable
NV	no value
ORR	objective tumor response rate
OS	overall survival
PCS	potentially clinically significant
PD	pharmacodynamic(s)
PDILI	potential drug-induced liver injury
PDS	pharmacodynamic set
PK	pharmacokinetic(s)
PKS	pharmacokinetic set
PFS	progression-free survival
PPS	per-protocol set
PR	partial response
PT	preferred term
PTEN	phosphatase and tensin homolog
Q2W	every 2 weeks
QTcF	QT interval corrected for heart rate using Fridericia's formula
RECIST	Response Evaluation Criteria in Solid Tumors
RP2D-T	recommended Phase 2 dose of UCB6114 when used in combination with TFD/TPI
SAE	serious adverse event

SAP	statistical analysis plan
SD	stable disease
SDTM	Study Data Tabulation Model
SFU	safety follow-up
SI	International System of Units
SMAD4	mothers against decapentaplegic homolog 4
SMC	Safety Monitoring Committee
SoC	standard of care
SOC	system organ class
SS	safety analysis set
SSC	Study Steering Committee
TEAE	treatment-emergent adverse event
TEMA	treatment-emergent markedly abnormal
TFD/TPI	trifluridine/tipiracil
TFL	Table, Figure and Listing
TNM	TNM Classification of Malignant Tumors
TPS	tumor proportion score
UK	United Kingdom
ULN	upper limit of normal
US	United States
WHODD	World Health Organization Drug Dictionary

1. INTRODUCTION

The purpose of this statistical analysis plan (SAP) is to provide all information that is necessary to perform the required statistical analysis of the dose escalation (combination therapy) module (Part B) of study ONC001. It also describes the summary tables, figures and listings (TFLs) to be generated for Part B according to:

Protocol amendment 6, dated 26 June 2023;

Electronic case report form (eCRF) (Clinical Data Management System [CDMS] postproduction change [CPPC] #14, version 23.0, dated 14 April 2023);

UCB's standards for TFL shells version 2023Q1;

Part A TFL shells, final version 2.4, dated 04 July 2023;

Part B and C Mocks draft version 1.4, dated 4 September 2023 (under development);

Part A, B and C List of TFLs (LoT) draft version 1.2, dated 04 July 2023 (under development);

UCB's Derivation of Efficacy Endpoints document, version 0.6, dated 21 January 2022.

Unless specified in the sections below, Part B of the study will be analyzed as described in the most recent version of the protocol. If a future protocol amendment necessitates a substantial change to the analysis of the Part B study data, this SAP will be amended accordingly. In addition, if the methodology for the analysis of key study endpoints must be modified or updated prior to the final database lock for Part B of this study, a SAP amendment will be required. Protocol amendments that do not affect the statistical analysis will not necessitate an amendment to the SAP. If, after database lock, additional analyses are required to supplement the planned analyses described in this SAP, these changes will be described in the clinical study report (CSR) together with the associated rationale.

Note that there may be a number of data cut-offs defined prior to the final database lock for Part B due to the regulatory safety reporting requirements for this study.

The content of this SAP is compatible with the International Council for Harmonization (ICH)/Food and Drug Administration (FDA) E9 Guidance (ICH-E9).

UCB is the Sponsor and ICON PLC is the contract research organization (CRO) for this study.

2. PROTOCOL SUMMARY

2.1 Study objectives

2.1.1 Primary objective

The primary objective of Part B (dose escalation module) of this study is to characterize the safety profile of UCB6114 administered in combination with a trifluridine/tipiracil (TFD/TPI) standard of care (SoC) regimen in participants with locally advanced or metastatic colorectal adenocarcinoma, gastric adenocarcinoma, or adenocarcinoma of the gastroesophageal junction.

2.1.2 Secondary objective

The secondary objective of Part B of this study is to characterize the pharmacokinetics (PK) of UCB6114 administered in combination with a TFD/TPI SoC regimen in participants with locally advanced or metastatic colorectal adenocarcinoma, gastric adenocarcinoma, or adenocarcinoma of the gastroesophageal junction.

2.1.3 Exploratory/Tertiary objectives

The exploratory/tertiary objectives of Part B of this study are:

- To document any antitumor activity observed with UCB6114 administered in combination with a TFD/TPI SoC regimen according to relevant Response Evaluation Criteria in Solid Tumors (RECIST) criteria;
- To explore pharmacodynamics (PD) biomarkers of UCB6114 administered in combination with a TFD/TPI SoC regimen;
- To evaluate the immunogenicity of UCB6114 administered in combination with a TFD/TPI SoC regimen.

2.2 Study endpoints

2.2.1 Safety endpoints

2.2.1.1 Primary safety endpoints

The primary safety endpoints for Part B of this study are the incidence and severity of treatment-emergent adverse events (TEAEs) (including serious adverse events [SAEs]) from the first dose of UCB6114 on Day 1 of Cycle 1 to the Safety Follow-up (SFU) visit, and the incidence of dose limiting toxicities (DLTs) from the first dose of UCB6114 on Day 1 of Cycle 1 to the end of the DLT Observation Period (Day 28 of Cycle 1).

2.2.1.2 Other safety endpoints

The following other safety data will be assessed during Part B of the study to further support the characterization of the safety profile of UCB6114 administered in combination with a TFD/TPI SoC regimen.

- Clinical laboratory data (hematology, serum chemistry, coagulation and urinalysis);
- Vital signs (systolic and diastolic blood pressure, pulse rate, respiratory rate, and body temperature);
- 12-lead electrocardiogram (ECG);
- Echocardiogram (left ventricular ejection fraction [LVEF]);
- Eastern Cooperative Oncology Group (ECOG) performance status;
- Physical examination.

2.2.2 Pharmacokinetic and pharmacodynamic endpoints

2.2.2.1 Secondary pharmacokinetic endpoint

The secondary PK endpoint in Part B is the UCB6114 concentration by scheduled assessment for each UCB6114 dose level.

2.2.2.2 Exploratory pharmacokinetic endpoints

[redacted] will be exploratory PK endpoints in Part B.

2.2.2.3 Exploratory pharmacodynamic endpoints

The following PD endpoints will be assessed in Part B and reported separately outside of the CSR:

- Change in protein marker levels in blood by scheduled assessment and UCB6114 dose level;
- Change in circulating tumor deoxyribonucleic acid (ctDNA) levels in blood by scheduled assessment and UCB6114 dose level.

2.2.2.4 Exploratory immunogenicity endpoints

Immunogenicity in Part B will be explored using anti-drug (UCB6114) antibody (ADA) sample status and participant classification, and changes in titer over time. Potential relationships between ADA and PK, PD, anti-tumor activity and safety may also be explored but these analyses will be reported separately outside of the CSR.

2.2.3 Efficacy endpoints

2.2.3.1 Exploratory antitumor activity endpoints

Antitumor activity in Part B will be explored using the following endpoints:

- Objective tumor response rate (ORR);
- Disease control rate (DCR);
- Duration of antitumor response (DOR);
- Progression-free survival (PFS);
- Overall survival (OS).

2.2.3.2 Other exploratory efficacy endpoint

To further explore efficacy in Part B of the study, changes from Baseline in the ECOG performance status scale will be assessed.

2.3 Study design and conduct

Study ONC001 is a multicenter, nonrandomized, open-label, Phase 1/2 study evaluating the safety, PK, efficacy (as assessed by antitumor activity), PD, biomarkers, and immunogenicity (ADA activity) of intravenous (iv) UCB6114 as monotherapy and in combination with selected SoC regimens in study participants with advanced solid tumors.

The study has a modular design including up to 3 dose escalation modules (Parts A, B, and C), 1 dose adaptation module (Part A1), and up to 4 dose expansion modules (Parts D, E, F, and G). Depending on emerging data, not all modules may open. This SAP is focused only on the

ascending dose escalation module of the study evaluating UCB6114 in combination with a TFD/TPI SoC regimen (Part B).

Part B consists of a Screening Period (28 days), a Treatment Period (consisting of 28-day cycles), a SFU visit (approximately 30 days after the last dose of study treatment), and a Final Visit (approximately 3 months after the last dose of study treatment).

In Part B, eligible participants with unresectable locally advanced or metastatic colorectal adenocarcinoma, gastric adenocarcinoma, or adenocarcinoma of the gastroesophageal junction will receive UCB6114 as an iv infusion in combination with orally administered TFD/TPI. The starting dose and schedule of UCB6114 will depend on the dose level evaluated in Cohort 3 of Part A (anticipated to be 500mg every 2 weeks [Q2W] iv), the emerging safety profile of UCB6114 monotherapy, and any predicted overlapping toxicities with TFD/TPI. Up to 3 UCB6114 dose levels (anticipated to be 500mg, 1000mg, and 2000mg administered Q2W iv) will be explored and up to 27 participants may be enrolled. Dose escalation decisions in this module will be guided by a model-based estimation of the probability of DLT in Cycle 1.

Part B will be undertaken using the modified toxicity probability interval (mTPI) method. The mTPI design uses a Bayesian decision framework to inform dose-escalation and dose de-escalation decisions. A target DLT rate of 25% with an equivalence interval (20% to 30%) will be used to estimate the maximum tolerated dose (MTD) of the combination regimen during dose escalation. For all UCB6114 dose levels, enrolled participants will be treated in cohorts of 2 to 4 participants (target of 3), who can be treated in parallel. Each UCB6114 dose level may have more than one cohort and will have a minimum of 3 and a maximum of 9 evaluable participants. For further detail on the mTPI method, the calculated model-based dose-escalation/dose de-escalation decisions to help inform the Safety Monitoring Committee (SMC)'s decision, and the determination of the MTD, please refer to Section 4.1.3.2.2 of the protocol. Detail on the operating characteristics for the mTPI design is included in Section 2.4 below.

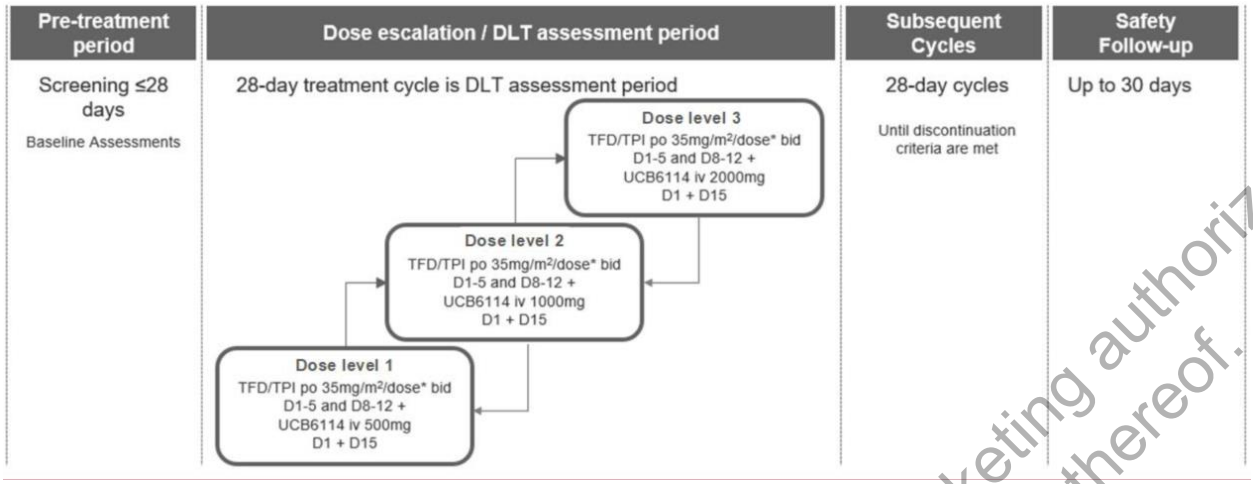
The planned duration of study treatment during Part B is 2 cycles. Participants may remain on study for additional cycles if they are receiving therapeutic benefit or until they fulfill one of the criteria for study discontinuation. Participants will continue treatment until disease progression, unmanageable toxicity, or withdrawal of consent. Upon discontinuation of treatment, participants will be referred to appropriate follow-up care per the investigator's judgment.

From Part B, a recommended Phase 2 dose for UCB6114 in combination with TFD/TPI (RP2D-T) will be determined based upon the totality of information, including the safety profile, PK data, PD biomarker data, and available antitumor activity.

Part B of the study is planned to be conducted at study sites in the United Kingdom (UK) and United States (US).

A schematic diagram of Part B of the study is provided in Figure 2-1.

Figure 2-1: Study Schematic for Part B



bid=twice daily; D=Day; DLT=dose-limiting toxicity; iv=intravenous; mTPI= modified toxicity probability interval; po=oral; TFD/TPI=trifluridine/tipiracil
*Dose must not exceed 80mg/dose
Notes: A dose may be given in more than 1 cohort
Escalation to the next dose level or de-escalation to the previous dose level will be guided by the mTPI algorithm.

A Study Steering Committee (SSC) will be implemented prior to the start of Part B. In consultation with the SMC, the SSC will recommend to the Sponsor the dose and dosing regimen to be taken forward for Part B. Part B of ONC001 is planned to be initiated after Cohort 3 of Part A has completed the 28-day DLT assessment period, after consultation with the SMC, and when the SCC has provided a recommendation to dose escalate to the next protocol-defined level in Part A of the study. The SSC members will include the coordinating investigator, supporting co-investigators, and clinical experts not involved in the study. The medical, scientific, and clinical study expertise of the SSC will assist the Sponsor in identifying and resolving any study related issues, such as study design, study implementation and conduct, and data analysis and reporting.

During the Treatment Period, UCB6114 will be administered as an iv infusion Q2W, while TFD/TPI will be administered orally twice daily (bid) within 1 hour of completion of morning and evening meals at home on Days 1 to 5 and Days 8 to 12 of each 28-day cycle. For the convenience of the participants, TFD/TPI can be administered at home to allow for the 12-hour interval between TFD/TPI doses associated with meals. The starting dose of TFD/TPI in adults is 35mg/m2 administered orally bid (total daily dose of 70mg/m2) with dosage calculated for each participant according to body surface area (BSA) (see Table 4-4 of the protocol). The dosage must not exceed 80mg/m2 (based on the trifluridine component).

It is expected that up to 3 dose levels of UCB6114 will be explored in combination with the standard TFD/TPI dosing regimen. However, additional dose levels may be added based on emerging data and recommendations of the SMC. Dose escalation steps are currently planned at a maximum of 2-fold. Escalating dose levels in Part B will not exceed a dose level tested and considered safe by the SMC to allow dose escalation in monotherapy (Part A).

Eligible participants who withdraw from the study before receiving study treatment will be replaced. Participants who fail to receive the second planned dose of UCB6114 within 7 days of

the scheduled administration day during the 28-day DLT Observation Period for reasons not related to toxicity will be replaced by a new participant in that cohort. Safety data for replaced participants will be included in the data listings and in the summary tables, as applicable.

2.4 Determination of sample size

No formal statistical sample size calculation has been performed for the dose escalation modules in study ONC001.

The number of participants likely to be enrolled in Part B depends on how many dose levels are needed to define the RP2D-T for combination therapy. In Part B, up to 27 eligible participants will be enrolled. It is expected that up to 3 dose levels of UCB6114 will be explored in combination with the TFD/TPI dosing regimen, respectively. However, additional dose levels may be added based on emerging data and recommendations of the SMC.

Between 3 and 9 participants are expected to be enrolled at each dose level of UCB6114 depending on the observed toxicity/observation of DLTs. An administrative decision to stop enrolling into Part B may be made by the Sponsor at any time. "Dose level" refers to a particular UCB6114 dose, that can be given to one or more cohorts, not necessarily consecutively.

The operating characteristics of the mTPI design were evaluated using a simulation approach under four scenarios (see Table 2-1) and based on no DLTs observed in the first 2 cohorts in Part A monotherapy treatment (UCB6114 100mg and 250mg). The results of this evaluation can be seen in Table 2-2.

Table 2–1: Scenarios used for evaluating the operating characteristics of the mTPI design. Orange cells indicate the correct decision assuming a maximum tolerated toxicity of 25% (equivalence limits 20%, 30%)

	Probability of a DLT			
UCB6114 Dose	**Scenario 1**	**Scenario 2**	**Scenario 3**	**Scenario 4**
Dose 1 (500 mg)	0.05	0.05	0.15	0.25
Dose 2 (1000 mg)	0.05	0.15	0.25	0.35
Dose 3 (2000 mg)	0.05	0.25	0.35	0.50

Table 2–2: Evaluation of the operating characteristics of the mTPI design with a target maximum tolerated toxicity of 25%, using 5000 simulated trials for each scenario. Orange cells indicate the correct decision.

Final UCB6114 Dose Selected	Scenario 1	Scenario 2	Scenario 3	Scenario 4
	% of Simulations (Number of Simulations)			
Dose 1 (500 mg)	3.9% (196)	5.2% (262)	31.6% (1580)	53.3% (2666)
Dose 2 (1000 mg)	3.9% (195)	35.1% (1755)	40% (1999)	26.7% (1337)
Dose 3 (2000 mg)	91.4% (4571)	58.9% (2947)	21.6% (1080)	3.8% (191)
Overly Toxic at First Cohort	0.8% (38)	0.7% (36)	6.7% (336)	15.2% (758)
Overly Toxic after First Cohort	0	0	0.1% (5)	1% (48)

3. DATA ANALYSIS CONSIDERATIONS

3.1 General presentation of summaries and analyses

All TFLs will be produced by ICON PLC using SAS® Version 9.4 or higher (SAS Institute, Cary, North Carolina, USA). ICON PLC will also produce the analysis datasets which will adhere to the Clinical Data Interchange Standards Consortium (CDISC) guidance documents for Analysis Data Model (ADaM) and follow the Sponsor's interpretation. General statistical and reporting conventions will follow the current UCB Global Conventions Document Version 1.1.

Data will be summarized by UCB6114 dose level (treatment group), visit and timepoint, as applicable. All relevant reported and derived data will be listed and will be presented by treatment group, study participant and visit, as applicable.

Categorical variables will be summarized using frequency counts and percentages. Unless otherwise stated, the denominator for the percentages will be based on the number of participants in the respective analysis set, treatment group, visit and timepoint (as applicable) with non-missing data.

When reporting frequency counts and percentages, the following rules apply:

- For categories where all participants fulfill certain criteria, the percentage value will be displayed as 100;
- For categories where zero participants fulfill certain criteria, there will be no percentage displayed;
- All other percentage displays will use 1 decimal place.

Summary statistics will be presented for continuous variables including number of participants (n), arithmetic mean, standard deviation, median, minimum and maximum. 95% confidence

intervals (CIs) for the arithmetic mean may also be included depending on the variable and where stated in the SAP. Geometric mean (geoMean), geometric coefficient of variation (geoCV) and 95% CI for the geoMean will also be presented in the summaries of UCB6114 concentration data. In all relevant outputs the 95% confidence limits will be restricted to the possible values that the variable can take.

When reporting descriptive statistics for data other than UCB6114 concentration data, the following rules will apply:

- n will be an integer;
- Mean (arithmetic and geometric), standard deviation, median and quartiles will use 1 decimal place more, or 1 significant figure more – depending on the reporting format of the original data – than the original data. Original data may be data as reported directly onto the eCRF or summary data based on data reported onto the eCRF (e.g. mean of triplicates or percentage change from Baseline);
- Confidence intervals will be presented to the same number of decimal places as the value around which the CI is constructed;
- Minimum and maximum will be reported using the same number of decimal places or significant figures as the original value;
- A minimum of 3 values are required to calculate summary statistics. If only 2 values are available, then these should be presented as the minimum and maximum with other summary statistics reported as missing ("- ");
- If no participants have data at a given timepoint, then only n=0 will be presented;
- Percentage change from Baseline values will be calculated and displayed to 1 decimal place in the listings. In the summaries, where applicable, the mean, standard deviation and median percentage change from Baseline values will be presented to 2 decimal places and the minimum and maximum values presented to 1 decimal place.

When reporting individual UCB6114 concentration data in listings and figures, and presenting summary statistics in tables, the following rules will apply:

- UCB6114 concentration data should be reported in the listings to the same level of precision as received from the bioanalytical laboratory;
- Missing data should be reported as 'NV' (no value) in the listings;
- Concentrations below the lower limit of quantification (LLOQ) should be reported as BLQ (below the limit of quantification) in the listings;
- BLQ values prior to C_{max} should be set to 0 for purposes of plotting a figure (to capture lag-time);
- Actual sampling times will be used in the spaghetti plots of individual PK concentrations over time, and nominal sampling times will be used in the summaries of geoMean concentrations over time;
- UCB6114 concentration data should be plotted on both linear and semi-logarithmic scales;

- To calculate summary statistics, BLQ values should be set to half the LLOQ value and missing values should be excluded;
- When the total number of BLQ and missing values exceeds one third of the total then only minimum and maximum should be reported for this timepoint. Other summary statistics should be reported as missing ("-"). The minimum should be reported as BLQ;
- When the mean value includes one or more replaced BLQ values then a footnote should be included to say "contains one or more BLQ values replaced by half the LLOQ value";
- A minimum of 3 values are required to calculate summary statistics. If only 2 values are available, then these should be presented as the minimum and maximum with other summary statistics reported as missing ("- ");
- If no participants have data at a given timepoint, then only n=0 will be presented;
- Summary statistics for UCB6114 concentration data will be reported to the same level of precision as the individual data for the minimum and maximum, and to 1 additional decimal place or 1 additional significant figure – depending on the reporting format of the original data with a maximum of 3 significant figures - for the mean (arithmetic and geometric), median and standard deviation. The 95% CI for the geoMean will use the same number of decimal places or significant figures as the geoMean. It will be left blank if the geoCV is 0;
- Geometric coefficient of variation will be reported as a percentage to 1 decimal place. The geoCV will be calculated using the following formula where SD is the standard deviation from the log-transformed data:

$$GeoCV(\%) = \sqrt{\exp SD^2 - 1} \times 100$$

When reporting PK parameters in listings and figures, and presenting summary statistics in tables, the following rules will apply:

[redacted]

[redacted]

3.2 General study level definitions

3.2.1 First and last dose of study treatment

For each participant the start of study treatment is defined as the date and time of the first dose of UCB6114. This will be considered as the starting point of the combination therapy.

Note that TFD/TPI is taken by the participant at home prior to attending the clinic for the infusion of UCB6114 on C1D1.

Similarly, for each participant, the last dose of study treatment will be the date of the last dose of UCB6114.

3.2.2 Relative day and time

For each participant, the relative day of an event or assessment will be derived using the date of their first dose of UCB6114 as reference.

Relative days for an event or assessment occurring before the date of first dose of UCB6114 are calculated as follows:

Relative Day = Event/Assessment Date - Date of First Dose of UCB6114

The relative day for an event or assessment occurring on the date of first dose of UCB6114 is 1. The relative day for an event or assessment occurring on or after the first dose of UCB6114 to the date of the last dose of UCB6114 will be calculated as follows:

Relative Day = (Event/Assessment Date – Date of First Dose of UCB6114) + 1

For events or assessments occurring after the date of the last dose of UCB6114, relative day will be prefixed with '+' in the data listings and will be calculated as follows:

Relative Day = Event/Assessment Date – Date of Last Dose of UCB6114

There is no relative Day 0. Relative day will not be calculated in cases where dates are partial and should be presented as "--" in the relevant data listing.

Relative time of TEAEs recorded on, but not limited to, the day of UCB6114 infusion (Days 1 and 15 of each cycle) will be derived in minutes as follows using the infusion start time as reference:

Relative Time of TEAE = Onset Time of TEAE – Start Time of UCB6114 Infusion

Relative times of PK and PD sampling will be derived in hours using the end of UCB6114 infusion time on the day of dosing as reference, i.e. on Days 1 and 15 of each cycle:

Relative Sampling Time = Sampling Time – End Time of UCB6114 Infusion

3.2.3 Study periods

Part B of the study will consist of the following study periods:

- Screening Period – up to 28 days;
- Treatment Period – Successive 28-day cycles of study treatment (UCB6114 will be administered as an iv Q2W dose on Day 1 and Day 15 of each cycle and TFD/TPI will be

administered [bid] within 1 hour of completion of morning and evening meals at home on Days 1 to 5 and Days 8 to 12, continuing until disease progression, unmanageable toxicity, or participant withdrawal). Within the first cycle of the Treatment Period, a 28-day DLT Observation Period is defined to determine safety events for dose escalation decisions using mTPI;

- Safety Follow-up Period – up to 30 days after the last dose of UCB6114.

There will be a further extended follow-up period, up to 3 months after the last dose of UCB6114, at which time the Final Visit will be performed.

For each participant, the end of the Treatment Period is defined by the date of their last dose of UCB6114.

The end of Part B of the study is defined by the date of the Final Visit for the last participant (3 months after the last participant's last dose of UCB6114), or the date of the SFU visit, if they discontinue prior to attending the Final Visit, or their last contact date if they discontinue early from the study without attending the SFU visit.

3.2.4 Visits

Unless otherwise specified, in the TFLs, visits will be labelled as follows (as applicable) using timepoints as recorded in the database:

Screening
Baseline
Cycle 1, Day X
Cycle 2, Day X
Cycle 3, Day X
Cycle 4, Day X
Cycle X, Day X
Etc.
SFU
Final Visit

3.3 Definition of Baseline values

Baseline in Part B will be the last available value prior to the first dose of UCB6114. Both scheduled and unscheduled values, as well as any repeated values, should be used when defining Baseline.

Measurement-specific Baseline definitions are presented in Table 3-1.

Table 3-1: Definition of Baseline

Measurement	Definition of Baseline
Echocardiogram (LVEF) Tumor assessments (antitumor activity)	Screening value
12-lead ECG Physical examination and weight Vital signs Clinical laboratory data ECOG performance status	Predose value obtained on Cycle 1, Day 1, or, if missing, Screening value
Serum and urinary markers of bone turnover Circulating gremlin-1 (cGremlin-1) Immunogenicity (ADA)	Predose sample value obtained on Cycle 1, Day 1

ADA=anti-drug (UCB6114) antibody; ECG=electrocardiogram; ECOG=Eastern Cooperative Oncology Group; LVEF=left ventricular ejection fraction.

3.4 Protocol deviations

Per ICH definition, important protocol deviations (IPDs) are a subset of protocol deviations that may significantly impact the completeness, accuracy, and/or reliability of the study data or that may significantly affect a participant's rights, safety, or well-being. The criteria for identifying potentially important protocol deviations will be defined within the IPD specifications document.

For Part B of this study, IPDs will be categorized as follows:

- Inclusion/exclusion criteria deviations
- Incorrect treatment or dose administered
- Procedural non-compliance
- Prohibited concomitant medication use (see Section 6.5.5 of the protocol)
- Withdrawal criteria deviation

All protocol deviations will be reviewed as part of the ongoing data cleaning process and Data Evaluation Meetings (DEMs), and decisions made on whether they should be considered important or not, and whether they warrant a participant's exclusion from an analysis set, or partial exclusion from an analysis due to being an IPD (e.g. prohibited concomitant medication use). Multiple DEMs will be scheduled prior to the final database lock for Part B, in line with regulatory safety reporting requirements, with the final one held after all data have been verified/coded/entered into the database.

More specifically, participants who have IPDs relating to dosing of study treatment (e.g. interrupted, discontinued and missed infusion, incomplete/incorrect dose administered, additional dose received, or infusions administered outside of the defined visit window) will be reviewed at the DEM for potential exclusion of UCB6114 concentration data from the by-visit summaries at an individual visit or from the visit at which the dosing deviation was observed onwards.

Any protocol deviations that are considered related to coronavirus disease 2019 (COVID-19) will be reviewed on an ongoing basis in case they collectively or individually give reason to consider a protocol amendment (e.g. study design changes or changes to primary analysis methods etc.). To facilitate this ongoing review, protocol deviations will be categorized as 'related to COVID-19' within the Clinical Trial Management System (CTMS) (ICOTrial). The COVID-19-related IPDs will then be listed separately for review and discussion at the DEMs.

3.5 Analysis sets

3.5.1 Enrolled Set (ES)

The Enrolled Set (ES) consists of all study participants who sign the Informed Consent Form.

This analysis set includes screening failures and will be used for the summary of disposition of study participants and for selected data listings (which will include all available data for the screening failures).

3.5.2 Safety Analysis Set (SS)

The Safety Analysis Set (SS) consists of all study participants who receive at least 1 full or partial dose of UCB6114.

This analysis set will be used for the reporting of demographic, baseline characteristics, safety and immunogenicity data. All summaries of the exploratory antitumor activity endpoints will be repeated for the SS as a sensitivity analysis.

3.5.3 Per-protocol Set (PPS)

The Per-protocol Set (PPS) consists of all study participants in the SS who do not have IPDs that may substantially affect antitumor activity. Potential exclusions will be reviewed at the DEMs and a final determination of the composition of this analysis set will be made prior to the final database lock for Part B.

The PPS will be the primary analysis set for the analysis of the exploratory antitumor activity endpoints.

3.5.4 Pharmacokinetic Set (PKS)

The Pharmacokinetic Set (PKS) consists of all study participants in the SS who have at least 1 evaluable postdose UCB6114 concentration sample (i.e. a sample which is above the lower limit of quantitation and for which the date and time of the sample and prior date and time of dosing are known). Additional participants or specific samples may be excluded from the PKS at the discretion of the Advanced Modeling and Simulation scientist/Quantitative Clinical Pharmacologist at UCB.

Pharmacokinetic analysis will be performed for the PKS.

3.5.5 Anti-drug Antibody Set (ADAS)

The Anti-drug Antibody Set (ADAS) consists of all study participants in the SS who have at least 1 evaluable ADA assessment.

Immunogenicity analyses will be performed for the ADAS.

3.5.6 Pharmacodynamic Set (PDS)

The Pharmacodynamic Set (PDS) consists of all study participants in the SS who have at least 1 evaluable PD assessment (where appropriate, the sample should be above the lower limit of quantitation and the date and time of the sample should be known).

Pharmacodynamic analysis will be performed for the PDS.

3.5.7 DLT Evaluable Set (DES)

The DLT Evaluable Set (DES) will include all study participants who, during the 28-day DLT assessment period receive the planned dose of UCB6114 and at least 80% of the planned dose of TFD/TPI or stopped treatment due to DLT.

The DES will be used by the SMC for all dose escalation/de-escalation decision making.

3.6 Treatment assignment and treatment groups

In Part B, it is planned that study participants will be dosed with UCB6114 Q2W at ascending dose levels and TFD/TPI will be administered orally bid. Treatment groups will be defined by each UCB6114 dose level and will be presented in ascending order and labelled in the TFLs as illustrated in Table 3-2.

Table 3-2: Treatment Group Labels

UCB6114 Dose Level	Planned Treatment Group Label
Dose Level 1 (any cohort)	UCB6114 500mg + TFD/TPI SoC
Dose Level 2 (any cohort)	UCB6114 1000mg + TFD/TPI SoC
Dose Level 3 (any cohort)	UCB6114 2000mg + TFD/TPI SoC

UCB6114 dose level will be referred to as 'treatment group' from this point onwards in the SAP and in the TFLs.

3.7 Center pooling strategy

Each study site will contribute to the summaries of data from Part B according to the number of evaluable participants recruited; no separate summaries for each site will be presented.

3.8 Coding dictionaries

Adverse events and medical history will be coded by UCB, using the latest available version of the Medical Dictionary for Regulatory Activities (MedDRA®) (Version 25.1 or higher). The National Cancer Institute Common Terminology Criteria for AEs (Version 5.0) (NCI CTCAE) dictionary will also be used by the investigator to assign CTCAE severity grades to each adverse event (AE) and will be merged with the clinical database to define a CTCAE code and term to be used in the summaries of TEAEs by maximum CTCAE severity grade.

Medications (including prior anti-cancer systemic therapies) will be coded according to the World Health Organization Drug Dictionary (WHODD) (Version SEP/2020). Medical procedures will not be coded.

The versions of the coding dictionaries used will be displayed in the relevant TFLs.

3.9 Changes to protocol-defined analyses

The following changes to the protocol have been incorporated into the SAP:

- Other safety data have not been defined as safety endpoints in the protocol, e.g. clinical laboratory data, vital signs, ECG, echocardiogram, ECOG performance status and physical examination. These have been listed in Section 2.2.1 of the SAP as 'other safety endpoints' to support the characterization of the safety profile of UCB6114 and to provide supporting evidence of any measurements that are deemed abnormal and clinically significant and reported as an AE.
- ECOG performance status is defined as an efficacy assessment in Section 9.6.2 of the protocol, however, it will also be assessed from a safety perspective in Part B. The SAP therefore includes ECOG performance status as both a safety endpoint (Section 2.2.1) and an exploratory efficacy endpoint (changes from Baseline during Part B in Section 2.2.3).
- Section 9.4.2.1 of the protocol does not explicitly define the analysis set to be used for the antitumor activity endpoints but defines the denominator as the number of treated participants, which matches the protocol definition for the SS in Section 9.1 of the protocol. The SAP has been written to clarify that the PPS will be the primary analysis set for the analysis of the antitumor activity endpoints (Section 3.5.3) and that the SS will be used for the sensitivity analysis (Section 3.5.2).

4. STATISTICAL/ANALYTICAL ISSUES

4.1 Adjustments for covariates

Not applicable.

4.2 Handling of dropouts or missing data

There will be no imputation of missing data unless otherwise stated in the sections below.

4.2.1 Pharmacokinetics and pharmacodynamics

The reporting and handling of missing values and values that are BLQ in the TFLs is described in Section 3.1. Zero values will be assumed at the predose timepoint on Day 1 of Cycle 1.

4.2.2 Safety laboratory data

The rules for handling values that are BLQ in the safety laboratory data will be the same as those described for PK data in Section 3.1. Any values above the limit of quantification (ALQ) will be assigned as the value of upper limit of quantification.

4.2.3 Dates and times

Partial dates may be imputed for the following reasons:

- Classification of adverse events (AEs) as treatment-emergent;

- Classification of medications recorded on the concomitant medications log as prior or concomitant;
- Calculation of time since initial diagnosis, time since completion of most recent line of anti-cancer therapy and time since progression/relapse on most recent line of anti-cancer therapy.

Imputed dates will not be shown in the listings; all dates will be displayed as reported in the database.

The following rules will be applied for partial onset/start dates:

- If only the month and year are specified and the month and year of the first dose of UCB6114 is not the same as the month and year of the start date then the 1st of the month will be used, or the date of the Screening visit if this is later (if the latter imputation results in an end date that is earlier than the start date, then the 1st of the month will be used);
- If only the month and year are specified and the month and year of the first dose of UCB6114 is the same as the month and year of the start date, then the date of the first dose of UCB6114 will be used. If this results in an imputed start date that is after the specified end date, then the 1st of the month will be used, or the date of Screening if this is later (if the latter imputation results in an end date that is earlier than the start date, then the 1st of the month will be used). If the imputed date is the same date as the date of the first dose of UCB6114 then, for AEs, the event will be regarded as treatment-emergent. For medications, the medication will be classified as concomitant;
- If only the year is specified, and the year of the first dose of UCB6114 is not the same as the year of the start date then January 01 will be used;
- If only the year is specified, and the year of the first dose of UCB6114 is the same as the year of the start date, then the date of the first dose of UCB6114 will be used. If this results in an imputed start date that is after the specified end date, then January 01, or the date of the Screening visit if this is later will be used (if the latter imputation results in an end date that is earlier than the start date, then January 01 will be used). If the imputed date is the date of the first dose of UCB6114 then, for AEs, the event will be regarded as treatment-emergent. For medications, the medication will be classified as concomitant;
- If the onset/start date is completely missing then the onset/start date will be imputed to the date of first dose of UCB6114 and therefore, for AEs, the event will be regarded as treatment-emergent and, for medications, the medication will be classified as concomitant.

The following rules will be applied to partial end/stop dates:

- If only the month and year are specified, then the last day of the month will be used;
- If only the year is specified, then December 31 of the known year will be used;
- If the stop date is completely unknown, the stop date will not be imputed.

Note that the start date or stop date of a prior medication (partial or otherwise) should not be imputed past the Screening date - 1.

In addition to onset and stop dates, the onset and end times of AEs occurring on the day of UCB6114 infusion will be collected on the eCRF. Onset and end times may also be recorded for other AEs that do not occur on the same day as the UCB6114 infusion. The duration of AEs with onset and end times will be calculated in days and hours:minutes (hh:mm) as:

Duration of AE = End Date and Time – Onset Date and Time

In cases where only the onset and stop dates are recorded for an AE, the duration of an AE will be calculated in days as:

Duration of AE = (Stop Date – Onset Date) + 1

Note that for participants who have an AE which starts and stops on the same day, but with only a start time or only a stop time recorded, it will be assumed that their AE started from 00:00 (if no start time is recorded) and ended at 23:59 (if no stop time is recorded) on that day.

If the date of a participant's initial diagnosis is incomplete, it will be imputed to the most recent feasible date for the calculation of time since initial diagnosis as follows:

- If only the day is missing, it will be imputed to the last day of the known month;
- If the day and month are missing, it will be imputed to December 31 in the known year;
- If the date of initial diagnosis is completely missing, then time since initial diagnosis will not be calculated.

The above date imputation rules will be applied to partially missing stop dates of a participant's last prior anti-cancer systemic therapy as well as partially and completely missing dates of progression/relapse on last prior anti-cancer systemic therapy.

In cases where the stop date of a participant's last prior anti-cancer systemic therapy and/or a participant's date of progression on last line of prior anti-cancer systemic therapy is completely missing, the participant's Screening date - 1 will be used in the calculation of the time since completion of most recent line of prior anti-cancer systemic therapy and the time since progression/relapse on most recent line of prior anti-cancer systemic therapy, respectively.

Note that partial dates will not be imputed as a participant's first dose of UCB6114 in the calculation of time since initial diagnosis, time since completion of most recent line of prior anti-cancer systemic therapy and time since progression/relapse on most recent line of prior anti-cancer systemic therapy.

4.2.4 Impact of COVID-19

The FDA and European Medicines Agency (EMA) have provided guidance (see references listed in Section 12) to help assure the safety of all trial participants, maintaining compliance with good clinical practice (GCP), and minimizing risks to trial integrity during the COVID-19 pandemic. At the time of writing this SAP, the impact of the pandemic is still evolving and regulators continue to clarify their position, and how to handle missing or delayed assessments resulting from the pandemic is part of the risk assessment of the impact of COVID-19 on trial integrity. For this purpose, the impact at a visit level will be assessed by data collected on a specific COVID-19 impact eCRF form and protocol deviations related to COVID-19. Due to the timing

of the start-up of recruitment of participants into this study, the consequences for Part B are not expected to be significant and, as a result, no details on strategies for handling missing data are included in this version of the SAP. However, should the ongoing review of COVID-19-related protocol deviations suggest that the impact is more significant than expected, e.g. in the case of a new wave, the SAP may be updated to include further details of handling missing data and/or any sensitivity analyses required. Note that there are no guidelines regarding how much missing data is too much, and there is no proportion of missing data under which valid results and preservation of study power can be guaranteed. In accordance with the EMA guidance, an independent Data Monitoring Committee (DMC) may be convened to make an assessment regarding the scientific integrity of the study.

4.3 Handling of repeated and unscheduled measurements

All repeated and unscheduled measurements will be presented in the data listings, where applicable. Repeated measurements are defined as more than 1 measurement at the same timepoint. For example, the same laboratory parameters assessed twice using the same batch of blood samples due to issues with the first assessment. The following general rules will apply to all repeated and unscheduled measurements:

- Unscheduled and repeated measurements prior to the first dose of UCB6114 will be used in the determination of Baseline and hence in the calculation of summary statistics at Baseline;
- Unscheduled and repeated measurements performed after the first dose of UCB6114 will not be included in the calculation of change from Baseline, summary measures such as minimum, maximum, average and last post-Baseline value calculated for the summaries of laboratory data (see Section 8.3), vital signs (see Section 8.4.1) and 12-lead ECG (see Section 8.4.2), or summary statistics, i.e. only the scheduled measurements will be used and summarized. Similarly, only scheduled visits will be used in the summaries of shifts from Baseline to the worst post-Baseline CTCAE severity grade for laboratory data (see Section 8.3);
- For the summaries of the investigator's overall tumor response assessment, protocol-defined windows will be applied to all post-Baseline tumor assessments (scheduled or unscheduled, but excluding tumor assessments performed at the SFU visit), as detailed in Section 10.1.2. Those tumor assessments which fall outside of the window will be considered as unscheduled assessments and not included in the summaries;
- Best overall response, DOR and PFS derivations will use data from all scheduled and unscheduled tumor assessments.;
- All data from unscheduled visits will, however, be included on the relevant data listings.

4.4 Handling of measurements obtained for early withdrawals

Participants who withdraw early from the study for any reason will be asked to return to the clinic to complete the SFU visit. The SFU procedures performed at this visit are as shown in the Schedule of Activities for Part B in the protocol and will be summarized together with all other SFU visit data in the tables.

4.5 Interim analyses and data monitoring

No formal interim analyses are planned during Part B of this study.

A SSC will be implemented prior to the start of Part B. In consultation with the SMC, the SSC will recommend to the Sponsor the dose and dosing regimen to be taken forward for Part B. The SSC members will include the coordinating investigator, supporting co-investigators, and clinical experts not involved in the study. The medical, scientific, and clinical study expertise of the SSC will assist the Sponsor in identifying and resolving any study related issues, such as study design, study implementation and conduct, and data analysis and reporting.

The SMC already established for Part A of the study, comprising investigators from UK sites participating in Part A and key Sponsor personnel, will continue as the SMC for Part B as long as they are actively enrolling study participants into the study. In addition, investigators from US sites who are actively enrolling study participants into Part B of the study will also become members of the SMC for Part B.

Responsibilities of the SMC for Part B include:

- Review of safety data for study participants including review and provision of adjudication of individual DLTs, if needed;
- Review of available PK and PD biomarker data;
- Make dose escalation recommendations;
- Determination of the MTD, if applicable.

The SMC will convene after the last participant in a given cohort has completed the required 28-day DLT Observation Period. The SMC will decide whether to halt dose escalation, further expand the dose level to gain additional safety data, or determine the next dose level to be tested.

All data presented to the SMC will be cumulative in order that the members can review and discuss the data in its totality at the end of all completed cohorts, i.e. all safety information beyond Cycle 1 for all previous cohorts will be presented cumulatively for review during each subsequent SMC meeting.

In addition to the planned SMC data review meetings, the Sponsor and the SMC will have the ability to hold/request *ad hoc* meetings should they be deemed necessary (e.g. if safety concerns arise during Part B of the study and/or during other ongoing nonclinical and clinical studies).

4.6 Multicenter studies

Part B of this study is planned to be conducted at study sites in the UK and US. With the exception of participant disposition, no summaries will be presented by site.

4.7 Multiple comparisons/multiplicity

Not applicable.

4.8 Use of an efficacy subset of participants

The PPS will be used as the primary analysis set for the summaries of the exploratory antitumor activity endpoints in Part B.

4.9 Active-control studies intended to show equivalence

Not applicable.

4.10 Examination of subgroups

Not applicable.

5. STUDY POPULATION CHARACTERISTICS

5.1 Study participant disposition

The number of study participants who were screened for Part B of this study, the number and percentage of screen failures and the primary reasons for screen failure will be summarized for the ES. A listing of participants who did not meet the eligibility criteria for Part B will also be presented for the ES. In addition, the disposition of study participants screened and who received study treatment will be summarized by country and site. This table will include, for each site and overall, site number, principal investigator name, the dates of the first participant in and the last participant out, the number of participants screened (ES), the number of screen failures, the number of participants who were treated (SS) and included in the PPS, PKS, ADAS and PDS. Disposition in each analysis set across all study sites will be summarized by treatment group.

The number of study participants who received study treatment and the primary reason for discontinuation of UCB6114 and TFD/TPI study treatment during Part B will be summarized by treatment group, together with the number and percentage of participants who continued participation in the study after discontinuation of study treatment (at subsequent scheduled visits and/or SFU visit and Final Visit). This summary will be based on the SS.

The number of study participants enrolled into Part B, who were screen failures as well as the number of eligible participants who were not treated will be presented for the ES. For those participants who did not receive study treatment, the reasons for early discontinuation from the study will be summarized.

Of those participants who received UCB6114, the number and percentage of participants who completed the study (i.e. participants who received at least 2 complete cycles of UCB6114 and attended the SFU visit), who received at least 2 complete cycles of UCB6114 but who did not attend the SFU visit and who discontinued early from Part B, together with the primary reasons for study discontinuation will be presented for all participants.

The number and percentage of participants who discontinued due to AEs will be summarized separately for all participants, based on the SS. This will be used for European Union Drug Regulating Authorities Clinical Trials (EudraCT) reporting.

The following study disposition tables will also be presented by gastric adenocarcinoma, adenocarcinoma of the gastroesophageal junction (Gastric/GEJ-Cancer) and colorectal

adenocarcinoma (CRC) tumor type depending on the number of participants with specific tumor types.

- Disposition and Reasons for Discontinuation of Study Treatment;
- Disposition and Study Discontinuation Reasons;
- Discontinuation of the Study Due to AEs.

Visits impacted by COVID-19 will be listed for the ES. This listing will include, visit, visit date, relative day, impact category (e.g. visit performed out of window, visit performed by telephone, visit not done, missed study drug administration/dispensation, termination of study participation), relationship to COVID-19 (confirmed COVID-19 infection, suspected COVID-19 infection, general circumstances around COVID-19 or other) and a narrative for the event. The number and percentage of participants with visits impacted by COVID-19 will be presented by treatment group and by impact category. This summary will be presented for the different relationships to COVID-19. The denominator for the percentage calculations will be the number of participants in the SS.

In addition, the following listings will be presented:

- Study participant disposition (ES);
- Study treatment discontinuation (SS);
- Study discontinuation (ES);
- Visit dates (ES);
- Participant analysis sets and exclusions from analysis sets (ES)*.

*DES is not included in this listing as it is only relevant for the SMC, and not required for the CSR.

The listing of study participant disposition will include the date of informed consent, date and time of first and last dose of study treatments (UCB6114 and TFD/TPI), date of early study discontinuation (if applicable) and primary reason for discontinuation.

Separate listings of UCB6114 and TFD/TPI study treatment discontinuation will include date and time of first and last dose of study treatments, date of decision to discontinue study treatment and primary reason for discontinuation of study treatments, date of clinical progression (if applicable), number of doses of study treatments received (based on 2 doses per cycle for UCB6114), total dose of study treatment received across all cycles, number of complete cycles of study treatment received, and whether or not the participant had continued participation in the study (at subsequent visits, the SFU visit or the Final Visit).

Note that a participant is deemed to have completed a full cycle of study treatment if they received the planned dose of UCB6114 on Days 1 and 15 of the cycle (i.e. the infusion was not permanently discontinued due to an AE or other reason such that less than the planned dose was received) and a decision was not made to discontinue UCB6114 up to and including Day 28 relative to Day 1 of the cycle. This will be derived based on a participant's last dose of UCB6114 and whether or not the participant attended the visit at which they were scheduled to receive their next dose of UCB6114. For example, if a participant received UCB6114 on Day 1 and Day 15 of

Cycle 1 and attended the clinic for their UCB6114 infusion on Day 1 of Cycle 2 then the participant will be counted as having completed Cycle 1. If the participant did not attend Day 1 of a subsequent cycle, then it is likely that a decision was made to discontinue their UCB6114 treatment and/or the study. Therefore, the date that the decision was made to discontinue UCB6114 will be used to determine whether the participant completed a cycle of study treatment. If a decision was made to discontinue UCB6114 on >Day 28 relative to Day 1 of the particular cycle then the participant will be counted as having completed the cycle. For any interim deliveries at a data cut-off, if the participant did not attend Day 1 of their next cycle and there was no decision to discontinue UCB6114, then the latest date available for that participant should be used to determine whether they have completed a 28-day cycle.

Whether or not a participant has completed the study is defined as having received at least 2 complete cycles of UCB6114 and attended the SFU visit. The investigator will record a study participant's disposition status at study termination according to this definition of a 'completed' participant, however, a study completion flag will also be programmatically derived based on the relevant data on the database and the above rules for defining completion of a full cycle of UCB6114.

The listing of study discontinuation will include the primary reason for early study discontinuation, the number of cycles of UCB6114 received, and the total number of days on UCB6114.

5.2 Protocol deviations

Important protocol deviations will be identified and classified by the deviation types defined in the IPD specification document, as per Section 3.4.

A listing of all IPDs identified at the DEM will be presented for all study participants based on the SS and will include the deviation type and description. In addition, a listing of all protocol deviations related to COVID-19 (whether considered important or not) will be presented for the SS. The number and percentage of participants in the SS with IPDs will be summarized by treatment group and for all participants for each deviation type. The number and percentage of participants who were excluded from the PPS will also be presented. The denominator for the percentage calculations will be the number of participants in the SS. A summary will also be presented for all protocol deviations related to COVID-19, all IPDs related to COVID-19 and all IPDs related to COVID-19 leading to exclusion from the PPS.

6. DEMOGRAPHICS AND OTHER BASELINE CHARACTERISTICS

6.1 Demographics

A by-participant listing of demographics will be presented based on the ES. This will include the year of birth, age (as entered by investigator in the eCRF in years), sex, race, ethnicity, height (in cm), weight (in kg) and body mass index (BMI, in kg/m^2). Height will be the measurement obtained at the Screening visit and weight will be the last non-missing value prior to the first dose of UCB6114.

The BMI will be derived in the database using the height and weight measurements recorded at the Screening visit and will be automatically reported to 1 decimal place on the eCRF.

All demographic characteristics (except for date of birth) will be summarized by treatment group and for all study participants based on the SS. The summary of age will include descriptive statistics and categorical summaries, the latter based on requirements for EudraCT and clinicaltrials.gov reporting. In addition, the summary of demographic characteristics will be presented by Gastric/GEJ-Cancer and CRC tumor type depending on the number of participants with each specific tumor type.

For the EudraCT reporting, the categories will include:

- 18 to <65 years;
- 65 to <85 years.

For clinicaltrials.gov reporting, the categories will include:

- ≤18 years;
- 19 to <65 years;
- ≥65 years.

Childbearing potential and method of birth control will be listed for the ES.

6.2 Cancer history

All cancer history data for Part B participants will be listed for the ES. This listing will include date of initial diagnosis, tumor type, TNM Classification of Malignant Tumors (TNM) classifications and stage, Duke's score (participants with colorectal adenocarcinoma only), histological and cytological diagnosis details (as relevant), whether the participant had any metastases and associated anatomical location, and whether the participant had received any prior anti-cancer therapies (including the number of lines of any prior systemic therapies, prior radiation therapies and prior anti-cancer surgeries).

Time since initial diagnosis (calculated in months using date of Screening visit and date of initial diagnosis and multiplying the duration in days by 12/365.25), tumor type, T, N, and M classifications and TNM stage, Duke's score (participants with colorectal adenocarcinoma only), presence of metastases and anatomical location of metastases will be summarized by treatment group and for all study participants based on the SS. In the summaries of categorical variables, percentages will be calculated based on the number of study participants with non-missing data. Further, for the Duke's score, the denominator for the percentage calculation will be the number of study participants with colorectal adenocarcinoma.

Cancer history will be presented by Gastric/GEJ-Cancer and CRC tumor type depending on the number of participants with specific tumor types.

6.3 Prior anti-cancer therapy

Details recorded for each line of prior anti-cancer systemic therapy received by a study participant will be listed for the ES. This listing will include the line and type of systemic therapy, intent, drug name and dose, formulation, indication (current/ultimate), start and end dates, number of cycles received and the number of days per cycle, the participant's best

response and the date of that best response, reason for discontinuation and whether the participant had disease progression prior to the next line of systemic therapy. If there was progression, then the date of progression will also be listed. In addition, time from completion of the last prior anti-cancer systemic therapy to the start of UCB6114 , whether the participant had progression after the last line of systemic therapy and, if so, the time from progression to the start of UCB6114 will be derived and listed.

For those participants in the ES who received prior radiotherapy, the following data will be listed: treatment site, type of radiotherapy, intent, settings (concurrent with other anti-cancer systemic therapy or stand-alone radiation therapy), and, if concurrent radiotherapy, the anti-cancer systemic therapy line that the radiotherapy was given with and the drug name. In addition, the start and stop dates, total cumulative dose (if known), number of fractions (if known), the participant's best response to radiotherapy and whether the tumor at the treatment site had progressed since radiotherapy will be included in this listing.

A further listing of prior anti-cancer radiotherapy with systemic therapy regimens will be presented for participants in the ES who had concurrent prior systemic therapy and radiotherapy as their prior anti-cancer therapy. This listing will include the relevant data described above together with the participant's best response to that regimen.

Date of surgery/procedure, anatomical location, description of the surgical procedure and whether the tumor was completely removed will be listed for those study participants in the ES who had prior anti-cancer surgeries or procedures.

The following summaries of prior anti-cancer therapy regimens and surgeries will be presented by treatment group and for all participants for the SS:

- Number of prior anti-cancer therapy regimens (0, 1, 2, 3, >3) (including all anti-cancer systemic therapy lines given alone and concurrently with radiotherapy)
- Best response to the most recent prior anti-cancer therapy regimen
- Number of prior anti-cancer systemic therapy + radiotherapy regimens (0, 1, 2, 3, >3)
- Best response to the most recent anti-cancer systemic therapy + radiotherapy regimen
- Reasons for discontinuation of the most recent line[a]
- Time from completion of most recent line[a] to the start of UCB6114 (<1 month, 1-<3 months, 3-6 months, >6 months)[b]
- For participants that progressed after their most recent line[a], the time from progression to the start of UCB6114 (<1 month, 1-<3 months, 3-6 months, >6 months)[b]
- Number of prior anti-cancer radiotherapies (including radiotherapies given alone and concurrently with anti-cancer systemic therapy) (0, 1, 2, >2)
- Number of prior anti-cancer surgeries and procedures (0, 1, 2, >2)

[a] Most recent line is the last prior anti-cancer therapy regimen received which may be a prior anti-cancer systemic therapy given alone or concurrently with radiotherapy.
[b] 1 month = 30 days.

Time from completion and time from progression relative to the last line of anti-cancer systemic therapy will also be summarized using frequency counts and percentages as well as summary statistics.

The number and percentage of participants with any prior anti-cancer systemic therapy, and any prior anti-cancer systemic therapy given concurrently with radiotherapy will be summarized for the SS by treatment group and for all participants, and by WHODD Anatomical Main Group [Level 1 term text], Pharmacological Subgroup [Level 3 term text] and PT.

Prior anti-cancer therapy will be presented by Gastric/GEJ-Cancer and CRC tumor type depending on the number of participants with specific tumor types.

6.4 Cancer status at Screening

The current cancer status of study participants at entry into Part B of this study will be assessed at the Screening visit and listed for the ES. This listing will include tumor type, T, N and M classifications and TNM stage and Duke's score (participants with colorectal adenocarcinoma only), histological and cytological diagnosis details (as relevant), whether the participant has any metastases and associated anatomical location, whether the tumor is recurrent and whether the participant had relapsed from their last line of anti-cancer therapy.

Tumor type, T, N and M classifications and TNM stage, Duke's score (participants with colorectal adenocarcinoma only), presence of metastases and anatomical location of metastases, and time since relapse on last line of therapy (calculated in days using the date of the Screening visit and date of relapse) will be summarized by treatment group and for all study participants based on the SS. In the summaries of categorical variables, percentages will be calculated based on the number of study participants with non-missing data. Further, for Duke's score, the denominator for the percentage calculation will be the number of study participants with colorectal adenocarcinoma.

Cancer status will be presented by Gastric/GEJ-Cancer and CRC tumor type depending on the number of participants with specific tumor types.

6.5 Medical history and concomitant diseases

Medical history will be listed for the ES and summarized by MedDRA® system organ class (SOC) and preferred term (PT) by treatment group and for all study participants for the SS. The reported term will be included in the listing. Previous medical history (any previous medical conditions with a stop date prior to the start of UCB6114) and ongoing medical history (any ongoing medical conditions with a missing stop date but recorded as ongoing on the eCRF) will be summarized separately. These summaries will include the number and percentage of study participants and will be sorted alphabetically by SOC and by descending incidence of PT within each SOC, based on the incidence in all study participants.

Non-anti-cancer procedure history will be listed for the ES and concomitant medical procedures performed during the study will be listed for the SS.

Medical history and concomitant disease will be presented by Gastric/GEJ-Cancer and CRC tumor type depending on the number of participants with specific tumor types.

6.6 Prior and concomitant medications

Prior medications will include any medications that started prior to the date of the first dose of UCB6114. This will include medications that started prior to the first dose of UCB6114 and continued after.

Concomitant medications will include medications with a start date on or after the first dose of UCB6114 and prior to the date of the last dose of UCB6114 + 30 days, and whose stop date is either missing, or on or after the date of the first dose of UCB6114. Any medications with a start date prior to the first dose of UCB6114 and a stop date after, or continued to be ongoing during the study, will also be classified as concomitant medications. Medications with a start date > 30 days after the last dose of UCB6114 will be considered as post-study medications and will not be included in the summaries of concomitant medication.

Any medication that started prior to, and stopped after the first dose of UCB6114 or continued to be ongoing during the study, will be classified as both prior and concomitant.

Any medications with missing start dates will be classified as both prior and concomitant.

Any medications with partially missing dates will be handled as described in Section 4.2.3 to classify them as prior or concomitant provided that a stop date is not present or a stop date is present but prior to the first dose of UCB6114.

All medications (prior, concomitant and post-study) will be listed for the ES. Any prohibited concomitant medications, rescue medications or steroid use will be identified via a medical review and flagged in this listing.

Prior and concomitant medications (per the definitions above) will be summarized for the SS by treatment group and by WHODD Anatomical Main Group [Level 1 term text], Pharmacological Subgroup [Level 3 term text] and PT. The reported term will be included in the listing. Separate summaries will be presented for prior medications and concomitant medications. As per the definitions above, prior medications which continued into the Treatment Period will also be classified as concomitant and will be included in both summaries.

All tabulations will be sorted alphabetically by Level 1 term, alphabetical Level 3 term within Level 1 and decreasing frequency of PT in all study participants.

A glossary of all prior and concomitant medications will be presented for the SS including the Anatomical Main Group (Level 1), Pharmacological Subgroup (Level 3), PT and reported term.

Prior and concomitant medications will be presented by Gastric/GEJ-Cancer and CRC tumor type depending on the number of participants with specific tumor types.

7. MEASUREMENTS OF TREATMENT COMPLIANCE

During Part B of this study, administration of UCB6114 will be performed via iv infusion at the study site under the supervision of the designated site personnel and in compliance with the Guideline for First in Human clinical studies (EMEA/CHMP/SWP/28367/07Rev. 1). Compliance will be monitored at the site through a review of accountability logs which will be used to record UCB6114 dispensing and return information to ensure that each study participant received the correct UCB6114 dose level.

Study participant compliance with respect to the actual dose of TFD/TPI taken will be evaluated through the use of a participant diary, data from which will be transcribed onto the TFD/TPI study medication administration form in the eCRF which includes the total dose of TFD/TPI taken in the 15mg and 20mg tablets prescribed to a participant on Days 1 to 5 and Days 8 to 12 of each cycle. Percentage compliance will be calculated overall and by cycle as defined below:

Compliance (%) =

$$\frac{\text{(Actual dosage administered)}}{\text{Expected dosage}} x\ 100$$

Where

The actual dosage administered is calculated as the sum of the actual dose administered on Days 1 to 5 and Days 8 to 12 (inclusive) during each cycle and overall.

Expected dosage in a cycle = Prescribed total daily dose (as recorded on the eCRF) × Expected number of dosing days in a cycle.

Expected dosage overall = Prescribed total daily dose (as recorded on the eCRF) × Expected number of dosing days overall.

Expected number of dosing days in a cycle is defined as the sum of Days 1 to 5 and Days 8 to 12 (inclusive) (10 days for participants who complete a cycle or up to the last scheduled dosing day for participants who discontinue TFD/TPI during a cycle).

Expected number of dosing days overall is the number of cycles of TFD/TPI received x 10 for participants who complete dosing in all cycles up to Day 12 or, for participants who discontinue TFD/TPI during a cycle, it is the number of completed cycles of TFD/TPI received x 10 + the number of scheduled dosing days up to the discontinuation of TFD/TPI).

Note that, per protocol, intake of TFD/TPI is twice a day, every 12 hours, and the prescribed number of tablets should be taken within 1 hour of completion of morning and evening meals. In cases where the first intake on Day 1 and/or Day 8 of a cycle is delayed into the afternoon then TFD/TPI dosing in this cycle may extend into Day 6 and/or Day 13. This is acceptable and therefore all dosing days should be taken into account in the compliance calculation.

Any dosing deviations will be reviewed as IPDs at the DEMs and assessed for possible impact on the PPS and the summaries of PK endpoints. If considered important, these deviations will be included in the summary and listing of IPDs.

8. SAFETY ANALYSES

All safety summaries and listings will be presented by Gastric/GEJ-Cancer and CRC treatment group based on the SS, unless otherwise stated.

All safety summaries may be presented by tumor type depending on the number of participants with specific tumor types.

8.1 Extent of exposure

Extent of exposure to UCB6114 and TFD/TPI administered in Part B will be summarized and listed. In addition, a separate summary table and listing of participant compliance, with respect to taking TFD/TPI tablets, will be presented.

8.1.1 UCB6114

Details of UCB6114 treatment administration on Day 1 and Day 15 of each cycle of study treatment will be listed. This listing will be split into two parts. The first part will include the start and stop dates and times of infusion, duration of infusion, infusion rate, whether the infusion was temporarily stopped/interrupted, whether the infusion was permanently discontinued and, if this was the case, whether the interruption or permanent discontinuation was due to an AE or other reason. The second part of this listing will include, for each visit, infusion site, total volume delivered, volume infused, planned total dose and total dose actually administered at infusion. In addition, the percentage of planned dose received, total dose administered across all cycles, the number of complete cycles of UCB6114 received and the total number of doses of UCB6114 received will be listed.

The percentage of planned UCB6114 dose received will be calculated for each study participant at each dosing visit within each cycle as follows:

$$Percentage\ of\ Planned\ Dose\ Received = 100 \times \frac{Total\ Dose\ Administered}{Planned\ Total\ Dose}$$

Actual duration of each UCB6114 infusion will be calculated in minutes only for those study participants who did not have any temporary interruption(s) of their infusion using the infusion start and stop times and included on this listing. Length of interruption(s) will be calculated for those study participants who had temporary interruption(s) of their infusion.

The number of complete cycles of UCB6114 received (0, 1, 2, 3, 4, >4) will be summarized using frequency counts and percentages, and summary statistics will be presented for the total dose of UCB6114 received across all cycles, the total number of doses of UCB6114 received and the total duration of exposure to UCB6114.

Total duration of exposure will be calculated in days as follows:

Total Duration of Exposure = (Date of Last Dose of UCB6114-Date of First Dose of UCB6114) + 30

Note that 30 days is added to this calculation to account for a participant's continued exposure to UCB6114 following their last dose of study treatment.

Note that a participant is deemed to have completed a full cycle of UCB6114 if they receive the planned dose of UCB6114 on Day 1 and Day 15 of the cycle and a decision was not made to discontinue UCB6114 up to and including Day 28 relative to Day 1 of a cycle.

8.1.2 TFD/TPI

Details of TFD/TPI treatment administration on Days 1 to 5 and Days 8 to 12 of each cycle of study treatment will be listed. The listing will include prescribed total daily dose, date of TFD/TPI administration, time of morning dose, number of 15mg and 20mg tablets taken in the morning, time of evening dose, number of 15mg and 20mg tablets taken in the evening and total daily dose administered. A separate listing of compliance to TFD/TPI treatment will be presented. This will include, overall and in each cycle, the total dosage administered, the prescribed total daily dose, expected number of dosing days, expected dosage and the percentage compliance.

Summary statistics will be presented for the total dose of TFD/TPI received across all cycles and for the total duration of exposure to TFD/TPI.

Total duration of exposure will be calculated in days as follows:

Total duration of Exposure = (Date of Last Dose of TFD/TPI -Date of First Dose of TFD/TPI) + 30

Summary statistics will be presented for overall percentage compliance, and by cycle, together with a categorical summary of the number and percentage of participants who were <80%, 80-90%, and >90% compliant with respect to taking the prescribed TFD/TPI dose.

8.2 Adverse events

The primary safety endpoints for Part B of this study are the incidence and severity of TEAEs (including SAEs) from the first dose of UCB6114 treatment on Day 1 of Cycle 1 until the end of the SFU Period (up to 30 days following the last dose of UCB6114 treatment), and the incidence of DLTs from the first dose of UCB6114 on Day 1 of Cycle 1 until the end of the 28-day DLT Observation Period (Day 28 of Cycle 1).

All AEs in Part B of the study will be coded using MedDRA® and classified as pre-treatment and treatment-emergent relative to the first dose of UCB6114 treatment. Adverse events with a start date prior to the first infusion of UCB6114 will be defined as pre-treatment AEs. A TEAE is defined as any AE with a start date on or after the first dose of UCB6114 up until the last dose of UCB6114 + 30 days. A pre-treatment AE which increases in severity on or after the first dose of UCB6114 will also be counted as a TEAE. Note that in this case, the pre-existing AE will have a stop date and an outcome of 'worsened' and a new AE (with the same verbatim) will be entered with the same start date and the increased severity recorded on the eCRF. Any AE (including SAEs) with an onset date later than the last dose of UCB6114 + 30 days will not be considered as treatment-emergent and therefore will not be included in the tabulations of TEAEs. These AEs will be considered as post-study AEs and will be listed only. Where onset dates are missing or partially missing, AEs will be assumed to be treatment-emergent, unless there is clear evidence to suggest that the AE started prior to the first dose of UCB6114 and it has not increased in severity. Missing or partially missing dates for AEs will be handled as described in Section 4.2.3 All AEs for a participant will be recorded in the eCRF from the time of informed consent until completion or early discontinuation of Part B of this study. Serious adverse events are to be reported up to 30 days after the Final Visit (i.e. up to 150 days after the last dose of study treatment).

Adverse events will be assigned an NCI CTCAE severity grade (Grade 1/Grade 2/Grade 3/Grade 4/Grade 5), where possible. If a CTCAE toxicity grading is not possible, then the intensity of the AE (mild/moderate/severe) will be recorded on the eCRF. If the AE is not gradable, is serious, and is considered as life threatening, then the intensity for this AE will be missing and one of the reasons for seriousness will be recorded as life threatening. Adverse events will also be categorized according to their relationship to UCB6114 and/or TPD/TPI treatment (related/not related), and whether the event is a DLT, as judged by the investigator. A DLT is defined as a TEAE at least possibly related to UCB6114 that occurs during Cycle 1 and fulfills any of the criteria listed in Section 4.1.1.4 of the protocol. The investigator is expected to record whether an AE is a DLT on the eCRF.

An overview of the number and percentage of participants who experience TEAEs will be presented. This summary will include the number and percentage of participants with any TEAEs, serious TEAEs, related TEAEs (related to UCB6114 only and related to UCB6114 and/or TFD/TPI), discontinuations from study treatment (UCB6114 and TFD/TPI and TFD/TPI only) due to TEAE(s), discontinuations from the study due to TEAE(s), CTCAE Grade ≥ 3 TEAEs, CTCAE Grade >=3 TEAEs related to UCB6114 only, CTCAE Grade >=3 TEAEs related to UCB6114 and/or TFD/TPI, DLTs, AEs leading to death and TEAEs leading to death; event counts will also be included against each of these categories. The overview of TEAEs will be presented by Gastric/GEJ-Cancer and CRC tumor type depending on the number of participants with specific tumor types.

In addition, the following summaries will be presented by SOC, high level term (HLT) and PT, and where indicated also by Gastric/GEJ-Cancer and CRC tumor type depending on the number of participants with specific tumor types:

- Incidence of TEAEs (overall and by tumor type);
- Incidence of serious TEAEs (overall and by tumor type);
- Incidence of non-serious TEAEs (overall and by tumor type);
- Incidence of TEAEs leading to a temporary interruption of UCB6114 infusion and/or dose reduction (overall and by tumor type);
- Incidence of TEAEs leading to a temporary interruption and/or reduction in dose of TFD/TPI (overall and by tumor type);
- Incidence of TEAEs leading to discontinuation of UCB6114 and TFD/TPI (overall and by tumor type);
- Incidence of TEAEs leading to discontinuation of TFD/TPI only (overall and by tumor type);
- Incidence of TEAEs leading to discontinuation of study (overall and by tumor type);
- Incidence of DLTs (separately for during the 28-day DLT Observation Period and after the 28-day DLT Observation Period) (overall and by tumor type);
- Incidence of adverse events of special interest (AESIs) (Hy's Law – see Section 8.2.1 below) (overall and by tumor type);

- Incidence of UCB6114 infusion-related reactions (defined any TEAE with a PT from both a narrow and broad scope search of category A terms of the 'Hypersensitivity' Standardized MedDRA® Query (SMQ) – see Section 8.2.2) (overall and by tumor type);
- Incidence of TEAEs by maximum CTCAE severity grade (overall and by tumor type);
- Incidence of TEAEs related to UCB6114 only by maximum CTCAE severity grade (overall and by tumor type);
- Incidence of TEAEs related to UCB6114 and/or TFD/TPI by maximum CTCAE severity grade (overall and by tumor type);
- Incidence of TEAEs by maximum relationship to UCB6114 only (overall and by tumor type);
- Incidence of TEAEs by maximum relationship to UCB6114 and/or TFD/TPI (overall and by tumor type);
- Incidence of TEAEs by relationship to UCB6114 only;
- Incidence of TEAEs by relationship to UCB6114 and/or TFD/TPI;
- Incidence of serious TEAEs by relationship to UCB6114 only;
- Incidence of serious TEAEs by relationship to UCB6114 and/or TFD/TPI;
- Incidence of non-serious TEAEs by relationship to UCB6114 only;
- Incidence of non-serious TEAEs by relationship to UCB6114 and/or TFD/TPI;
- Incidence of fatal TEAEs by relationship to UCB6114 only;
- Incidence of fatal TEAEs by relationship to UCB6114 and/or TFD/TPI;
- Incidence and event rate of TEAEs by treatment-emergent ADA positivity.

The following summary will be presented by SOC and PT for EudraCT reporting:

- Incidence of non-serious TEAEs above the threshold of 5% of participants in any treatment group.

The above summaries of TEAEs will be ordered alphabetically by SOC, alphabetically by HLT within SOC and decreasing incidence of PT events within SOC /HLT in all study participants. For tables including only the number and percentage of participants, summaries will be ordered alphabetically by SOC, alphabetically by HLT within SOC and decreasing incidence of participants with each PT within SOC /HLT in all study participants.

The incidence of TEAEs by maximum CTCAE severity grade will be presented by CTCAE term. CTCAE term will be obtained from the NCI CTCAE Version 5.0 via a mapping of MedDRA® lower level terms. This summary will be ordered by decreasing incidence of participants with each CTCAE term in all study participants.

Summary tables will contain frequency counts and percentages, and the number of events, where applicable. A study participant who experiences the same event multiple times will be counted only once in the frequency counts for the PT, but all events will be included.

In the summaries of TEAEs by relationship, participants will be counted in "Not related" and "Related" categories (or "Missing" in the case where an event has a missing relationship). A study participant who experiences the same event multiple times will be included in the most related category for the summaries by maximum relationship.

In the overview summary of TEAEs, participants will be counted as having at least one TEAE with CTCAE severity grade ≥3, and in the summary of TEAEs by maximum CTCAE severity grade, participants will be counted as having at least one TEAE in the following categories: 'Grade 1', 'Grade 2', 'Grade 3', 'Grade 4', 'Grade 5', 'Grade 3 or 4' and 'Grade >=3'. Events for which no CTCAE severity grade is recorded by the investigator but an intensity is recorded instead, the intensity of this event will be assigned to a CTCAE severity grade for the purpose of these summaries, i.e. 'Mild' will be included as 'Grade 1', 'Moderate' will be included as 'Grade 2', 'Severe' will be included as 'Grade 3', 'Life Threatening' will be included as 'Grade 4' and, if the participant dies due to the event, it will be included as 'Grade 5'. The determination of whether the event is life threatening or results in death will be based on the reason for seriousness recorded as life-threatening or death on the eCRF, or on the event having a fatal outcome. Otherwise, if both the CTCAE severity grade and intensity is missing then the CTCAE severity grade in these summaries will be missing. A study participant who experiences the same event multiple times will be included in the highest severity grade category in the summary of TEAEs by maximum CTCAE severity grade.

A glossary of all AEs will be presented including the MedDRA® SOC, HLT, PT, reported term and low level term (LLT).

A listing of all AEs will be presented by study participant for the ES. The listing will include the onset date and stop date of the event (including relative days) and also the onset times and stop times of events where available. Period of onset of AEs will also be presented on this listing.

Period of onset of AEs will be defined as follows for the purpose of the listing:

- If the AE has an onset date prior to the date of the Screening visit, then Period=Pre-study;
- If the AE has an onset date on or after the date of the Screening visit and has an onset date and time prior to the start time of UCB6114 infusion on Day 1 of Cycle 1 then Period=Screening;
- If the AE has an onset date and time on or after the start time of UCB6114 infusion on Day 1 of Cycle 1 and up to the date and time of the start of Cycle 2 (i.e. prior to the start time of the UCB6114 infusion on Day 1 of Cycle 2) then Period=Cycle 1;
- If the AE has an onset date and time on or after the start time of UCB6114 infusion on Day 1 of Cycle 2 and up to the date and time of the start of Cycle 3 (i.e. prior to the start time of the UCB6114 infusion on Day 1 of Cycle 3) then Period=Cycle 2;
- Same as above for subsequent cycles (Cycle 3 etc.);
- If the AE has an onset date after the last dose of UCB6114 up to and including 30 days after the last dose of UCB6114, then Period=SFU;
- If the event has an onset date after the 30-day period following the last dose of UCB6114, then Period=Post-study.

The listing of all AEs will also include the AE duration (derived in days, hh:mm for AEs with onset and stop times recorded and derived in days for all other AEs with only onset and stop dates recorded), days since start of UCB6114 infusion (time if an onset time is recorded, days otherwise), seriousness and reason for seriousness, CTCAE severity grade, intensity (where a CTCAE severity grade is not recorded), pattern of event, relationship to UCB6114 and TFD/TPI and action taken with UCB6114 and TFD/TPI (including other action taken), the outcome of the AE, whether an autopsy was performed and cause of death. In addition, the listing will flag AEs that led to discontinuation from the study, TEAEs, AESIs, SAEs, UCB6114 infusion-related reactions, and DLTs. Whether an AE is related to a concomitant medication, (and separately whether it is related to the COVID-19 vaccination), the names of any co-suspect medications will also be listed.

Separate listings of all SAEs, TEAEs leading to discontinuation of UCB6114 and TFD/TPI, TEAEs leading to discontinuation of TFD/TPI only and TEAEs leading to discontinuation of the study will also be presented.

All deaths that occur on study (defined as during study treatment or within 30 days of the last dose of UCB6114) will be listed separately. This listing will include the primary cause of death and the number of days between the date of the last dose of UCB6114 and death, defined as

$$Days\ since\ last\ dose = (Date\ of\ death - Date\ of\ latest\ dose\ of\ UCB6114\ )$$

8.2.1 Adverse events of special interest

An AESI is any AE that a regulatory authority has mandated be reported on an expedited basis, regardless of the seriousness, expectedness, or relatedness of the AE to the administration of a UCB product/compound.

For ONC001, potential Hy's Law is used to identify AESIs and is defined using the laboratory data and the following potential drug-induced liver injury (PDILI) criteria:

- ≥3x upper limit of normal (ULN) alanine aminotransferase (ALT) *or* aspartate aminotransferase (AST) with coexisting ≥2xULN total bilirubin in the absence of ≥2xULN alkaline phosphatase (ALP), with no alternative explanation for the biochemical abnormality;
- Study participants who have evidence of liver metastases may be considered to have an alternate etiology for the described laboratory abnormalities.

All AESIs will be flagged on the listing of AEs.

8.2.2 Infusion-related reactions

Infusion-related reactions are defined as hypersensitivity reactions, anaphylactic reactions and cytokine release syndrome with onset within 24 hours after the start of an infusion of UCB6114.

All potential infusion-related reactions will be identified programmatically and will then undergo medical review for confirmation based on participant characteristics and other signs and symptoms. The final assessment from the medical review will be used in the programming to ensure that all infusion-related reactions are flagged correctly in the listings and included in the relevant summaries.

Hypersensitivity reactions will be programmatically identified as any TEAE with a PT from both a narrow and broad scope search of category A terms of the 'Hypersensitivity' SMQ.

Anaphylactic reactions will be programmatically identified using an algorithmic approach based on the 'Anaphylactic Reaction' SMQ. Further details on this algorithm are given in Section 11. Note that if the MedDRA® version is increased from 25.1 during the study, any changes to the terms included in the 'Anaphylactic Reaction' SMQ should be applied.

Cytokine release syndrome will be programmatically identified as any TEAE with a PT of 'Cytokine release syndrome' from the broad scope search of category A terms of the 'Hypersensitivity' SMQ. Since this disorder is characterized by fever, headache, tachycardia, hypotension, rash, tachypnoea and/or hypoxia, a further medical review of participants with these events occurring within 24 hours after infusion of UCB6114 will be performed to confirm any further infusion-related reactions.

Note that any other AEs (i.e. not identified as infusion-related reactions using the rules above) which result in a temporary interruption or permanent discontinuation of a UCB6114 infusion will not be considered as an infusion-related reaction.

8.3 Clinical laboratory evaluations

The use of multiple local laboratories (1 per site in the UK and US) in Part B of this study has meant that results have been recorded in different units and with reference to different normal ranges, and further, for some laboratory tests, different normal ranges have been applied to males and females and age groups. As a first step to ensure comparability of laboratory results, results and normal ranges will be converted to the same International System of Units (SI) units using UCB's standard conversion factors. This will be programmed at the Study Data Tabulation Model (SDTM) level. Note though that the simple conversion to SI units does not represent a full homogenization of results from different local laboratories using different methods. To ensure full comparability, the observed laboratory results will be normalized to a unique set of standard reference ranges using the location-scale normalization formula (Chuang-Stein, 1992) which normalizes all results in relation to a standard set of reference ranges (for hematology, clinical chemistry and coagulation parameters):

$$s = L_S + (x - L_X)\frac{(U_S - L_S)}{(U_X - L_X)}$$

and when the standard lower limit is 0: $s = x\frac{U_S}{U_X}$ where:

s = normalized observed value
x = original observed value in SI units
L_S = Lower Limit of the reference range chosen to be the standard reference range
U_S = Upper Limit of the reference range chosen to be the standard reference range
L_X = Lower Limit of the reference range associated with the original observed value in SI units (local laboratory reference range)
U_X = Upper Limit of the reference range associated with the original observed value in SI units (local laboratory reference range)

This transformation preserves the distance of the original laboratory result from the lower limit of normal as a multiple of the specified standard reference range.

Note that the choice of the standard reference range is arbitrary, however, the most recent reference ranges used by ICON Central Laboratories (including the age and gender specific reference ranges for parameters, where available) will be used to normalize the results in this study.

Normalization of the laboratory results will be performed in the ADaM programming by ICON.

All normalized laboratory data (hematology, serum chemistry and coagulation) and changes from Baseline for numeric variables will be listed for participants who have at least one value outside of the reference range. All urinalysis data will be listed for all participants. Data will be listed by study participant, laboratory panel, laboratory parameter and visit within each treatment group. Any laboratory measurements that are BLQ or ALQ will be handled as described in Section 4.2.2. For the relevant numeric laboratory parameters, the reference ranges supplied by the local analytical laboratory will be used to flag values outside the reference range as low or high in this listing. For the parameters for which the local laboratory cannot supply the reference ranges, the reference ranges provided by ICON Central Laboratories will be used instead. A listing of all laboratory results outside of the reference range will also be presented. The reference ranges will also be reported in the listings.

In addition, for the relevant hematology, clinical chemistry and coagulation laboratory tests, CTCAE severity grades (Grade 1, Grade 2, Grade 3, Grade 4) will be applied (where possible) in the ADaM programming according to NCI CTCAE Version 5.0, and these grades will also be listed for the relevant laboratory parameters. Note that Grade 0 will be applied in cases where a result is normal for the relevant laboratory test and Grade 5 is not applicable in the grading of laboratory data.

Observed normalized values and changes from Baseline in the hematology, serum chemistry and coagulation parameters presented below in Table 8-1 will be summarized at each visit. In addition, for each of these parameters, the Baseline value, the minimum, maximum, average and last post-Baseline value for each participant will be summarized by cycle using descriptive statistics. These post-Baseline summary measures will be calculated based on all available scheduled postdose values within each cycle, i.e. from Day 8 of the current cycle up to Day 1 (pre-UCB6114) of the subsequent cycle. The last value in a cycle will be the predose value of the subsequent cycle where a subsequent cycle occurs, otherwise it will be the value at the last scheduled assessment. If only one value is available then the average will not be calculated and presented but this value will be used for the minimum, maximum and last post-Baseline summary measures. These summary measures for each cycle will also be listed.

The summaries of normalized hematology, serum chemistry and coagulation values and changes from Baseline will also be presented by Gastric/GEJ-Cancer and CRC tumor type depending on the number of participants with specific tumor types.

For those laboratory parameters with a CTCAE toxicity assigned, shift tables for the change from Baseline in CTCAE severity grade at each visit and to the worst post-Baseline CTCAE severity grade during the Treatment Period will be presented.

Table 8-1: Clinical Laboratory Assessments

Laboratory Assessment	Laboratory Parameters
Hematology	Platelet Count, RBC Count, Hemoglobin, Hematocrit, RBC Indices (MCV, MCH, MCHC), WBC Count with Differential (Absolute Neutrophils, Absolute Lymphocytes, Absolute Monocytes, Absolute Eosinophils, Absolute Basophils)
Clinical Chemistry	ALT, AST, ALP[a] , Bicarbonate, Sodium, Potassium, Magnesium, Chloride, Calcium, Total Bilirubin, BUN or Urea, Serum Creatinine, Glucose (non-fasted), Phosphorus or Phosphate, Albumin, Total Protein, Uric Acid, Amylase, GGT, Cholesterol, Creatine Kinase, CRP, LDH, Lipase, Triglycerides
Coagulation	aPTT and either prothrombin time or INR
Routine Urinalysis	Specific Gravity, pH, Glucose, Protein, Blood, Ketones, Bilirubin, Urobilinogen, Nitrite, Leukocyte Esterase by Dipstick Microscopic Examination (if blood or protein is abnormal, including crystals)
Screening Tests	Pregnancy tests: FSH and estradiol (for women of non-childbearing potential only); serum or urine hCG pregnancy test (for women of childbearing potential) Bone turnover markers: blood BAP, blood CTx, urinary NTx and urinary CTxII Tumor markers: e.g. PSA, CA125, CA19-9

ALP=alkaline phosphatase; ALT=alanine aminotransferase; aPPT=activated partial thromboplastin time; AST=aspartate aminotransferase; BAP=bone alkaline phosphatase; BUN=blood urea nitrogen; CA=cancer antigen; CRP=C-reactive protein; CTx=C-terminal telopeptide; FSH=follicle-stimulating hormone; GGT=gamma glutamyl transferase; hCG=human chorionic gonadotropin; INR=international normalized ratio; LDH=lactate dehydrogenase; MCH=mean corpuscular hemoglobin; MCHC=mean corpuscular hemoglobin concentration; MCV=mean corpuscular volume; NTx=N-terminal telopeptide; PSA=prostate specific antigen; RBC=red blood cell; WBC=white blood cell.
a including liver-specific ALP for use in assessing participants with bone metastases at Screening. In the case of bone metastases liver function abnormalities considered potential Hy's law cases, the liver-specific ALP must be separated from the total in participants with bone metastases and used to assess the liver function instead of the total ALP

The screening laboratory tests included above in Table 8-1 will be listed only.

Liver function abnormalities will be defined using the following criteria:

- ALT or AST ≥2xULN
- ALT or AST ≥3xULN
- Total bilirubin ≥2xULN
- Total bilirubin ≥3xULN

- ALT or AST ≥5xULN
- ALT or AST ≥8xULN
- ALT or AST ≥3xULN AND total bilirubin ≥2xULN (>35% direct bilirubin)

For the subgroups of participants with liver metastases and without liver metastases at Baseline, the number and percentage of participants in each liver function abnormality category will be summarized at each visit.

In addition, participants with PDILI criteria are those that fulfill the following laboratory data (based on liver function tests) criteria at a visit:

- AST or ALT and total bilirubin within the normal range at Baseline and AST or ALT ≥3xULN concurrent with total bilirubin ≥2xULN;
- AST, ALT or total bilirubin above ULN at Baseline and AST or ALT ≥2 times Baseline values AND AST or ALT ≥3xULN (participants without liver metastases at Baseline)/AST or ALT ≥8xULN (participants with liver metastases at Baseline) concurrent with total bilirubin above ULN at Baseline and total bilirubin ≥2 times Baseline value or ≥3xULN (whichever is lower).

All relevant laboratory data collected for participants with a PDILI event (i.e. liver function tests) will be listed at the visits at which at least one of the above criteria was fulfilled.

The number and percentage of participants meeting different combinations of the ALT, AST and total bilirubin criteria defined above will be summarized by treatment group. This summary will be presented for all participants as well as for the subgroups of participants who had liver metastases at Baseline and participants without liver metastases at Baseline.

A separate listing will also be produced containing drug-induced liver injury -relevant family medical history, lifestyle data (alcohol consumption or drug abuse in the previous 6 months), hepatic event supplemental medical history and any hepato-toxic medications taken for participants in the SS with a PDILI event.

8.4 Vital signs, physical findings, and other observations related to safety

8.4.1 Vital signs

Vital signs will be measured in a semi-supine position after 5 minutes rest and will include:

- Systolic and diastolic blood pressure;
- Pulse rate;
- Oral body temperature;
- Respiratory rate.

On UCB6114 dosing visits (Days 1 and 15 of each cycle), vital signs will be assessed at multiple timepoints: predose, 10 minutes (±5 minutes) and 30 minutes (±10 minutes) after the start of the infusion, at the end of the infusion (+15 minutes); and at 1 hour (+15 minutes) after the end of the infusion. In addition, on Cycle 1 Day 1, vital signs will also be assessed at 2 hours (+1 hour) and 5 hours (+1 hour) after the end of the infusion. Where PK samples are taken on UCB6114

dosing days (predose, at the end of infusion and at 2 hours after the end of infusion on Day 1 of Cycles 1 and 2, and predose on all other UCB6114 dosing days), vital signs will be measured prior to PK sampling.

At all other scheduled visits (Days 8 and 22 of Cycle 1), vital signs will be measured prior to UCB6114 dosing. At the SFU visit, vital signs measurements will be taken prior to PK sampling.

Observed vital sign measurements and changes from Baseline will be listed by visit and timepoint and summarized using descriptive statistics. In addition, for each of the vital signs, the Baseline value, the minimum, maximum, average and last post-Baseline value for each participant will be calculated based on all available scheduled postdose values during each cycle up to the predose value on Day 1 of the subsequent cycle and will be summarized by cycle using descriptive statistics. The last value in a cycle will be the predose value of the subsequent cycle where a subsequent cycle occurs, otherwise it will be the value at the last scheduled assessment. If only 1 value is available then the average will not be calculated and presented but this value will be used for the minimum, maximum and last post-Baseline summary measures. These summary measures for each cycle will also be listed.

For the multiple vital signs measurements on treatment days (i.e. on Days 1 and 15 of each cycle), changes from the predose value will be calculated at each postdose timepoint and summarized using descriptive statistics.

For each vital signs parameter, the mean (±standard deviation) change from Baseline value will be plotted over scheduled visit and timepoint with treatment group overlaid on the same plot.

The incidence of treatment-emergent markedly abnormal (TEMA)/ potentially clinically significant (PCS) vital signs based on blood pressure and pulse rate measurements will be summarized by visit and timepoint using frequency counts and percentages. The criteria for identifying a TEMA/PCS are included in Table 8-2.

Table 8-2: TEMA/PCS Criteria for Vital Signs

Variable (unit)	Low[a]	High[a]
Systolic Blood Pressure (mmHg)	Value <90 and ≥20 decrease from Baseline	Value >140 and ≥20 increase from Baseline
Diastolic Blood Pressure (mmHg)	Value <50 and ≥15 decrease from Baseline	Value >90 and ≥15 increase from Baseline
Pulse Rate (bpm)	Value <45 and ≥15 decrease from Baseline	Value >90 and ≥15 increase from Baseline

bpm=beats per minute; PCS=potentially clinically significant; mmHg=millimeter of mercury; TEMA=treatment-emergent markedly abnormal.
a Both conditions must be satisfied for a measurement to be considered PCS.

8.4.2 12-Lead Electrocardiograms

Electrocardiograms will be performed at each visit and timepoint in triplicate with the participant in a supine position after a minimum of 5 minutes rest.

On Days 1 and 15 of Cycle 1 only, ECGs will be performed in triplicate at multiple timepoints relative to UCB6114 dosing (predose, end of infusion, and 2 hours after the end of infusion). When ECG measurements coincide with blood sampling for PK (and PD), ECG will be performed first. On Days 1 and 15 of Cycle 2 and on Day 1 of all subsequent cycles, ECGs will be performed in triplicate prior to UCB6114 dosing. At the SFU visit, ECGs will be performed once in triplicate prior to PK sampling.

All ECGs will be evaluated for any clinically relevant changes by the investigator.

Electrocardiograms will also be collected for central reading, the data from which will be analyzed separately.

All summaries and listings of ECG data will be based on the local (site) 12-lead ECG measurements.

The following ECG parameters will be reported:

- PR interval;
- QT interval;
- QRS interval;
- QTcF interval (QT corrected for heart rate using Fridericia's formula [QTcF]);
- Heart rate.

Observed values and changes from Baseline in these ECG parameters will be listed and summarized by visit using descriptive statistics. The mean of the triplicate measurements taken for each parameter will be used in the summary at each visit and timepoint. If less than 3 of the triplicate measurements are taken then the mean of the available measurements will be used (if only 1 of the 3 triplicate measurements is available then this value will be used in the summaries). The Baseline value will be the mean of the last scheduled or unscheduled triplicate measurements taken prior to first dose of UCB6114 on Day 1 of Cycle 1. If no predose triplicate measurements are taken then the mean of the triplicate measurements taken at Screening will be used. The mean of only the scheduled triplicate measurements at each Post-Baseline visit and timepoint will be included in the summary. In addition, for each of the ECG parameters, the minimum, maximum, average and last post-Baseline value for each participant will be calculated based on the mean of the triplicate of all available scheduled postdose measurements during each cycle up to the predose value on Day 1 of the subsequent cycle, and will be summarized by cycle using descriptive statistics. The last value in a cycle will be the predose mean triplicate value of the subsequent cycle where a subsequent cycle occurs, otherwise it will be the mean triplicate value at the last scheduled assessment. If only 1 mean triplicate value is available then the average will not be calculated and presented but this value will be used for the minimum, maximum and last post-Baseline value summary measures. These summary measures for each cycle will also be listed.

For the multiple ECGs performed on Days 1 and 15 of Cycle 1, changes from the predose value will be calculated at each postdose timepoint and summarized using descriptive statistics.

Mean (±standard deviation) change from Baseline in QTcF will be plotted over scheduled visit with treatment groups overlaid on the same plot. Individual observed values of QTcF will be presented over actual time in a spaghetti plot.

The following cut-points in QTcF will be applied for observed data and changes from Baseline:

For observed QTcF data:

- <450 msec;
- ≥450 to <480 msec;
- ≥480 to <500 msec;
- ≥500 msec.

For changes from Baseline in QTcF:

- <30 msec;
- ≥30 to <60 msec;
- ≥60 msec.

The incidence of participants in each of these categories will be summarized using frequency counts and percentages by visit.

A listing of 12-lead ECG abnormal findings will be presented.

Electrocardiograms will also be collected for central reading; however, these data will be reported in an addendum to the CSR.

8.4.3 Echocardiogram

Echocardiograms will be performed at the Screening visit, at Cycle 3 Day 1 (+/- 7 days), as clinically indicated afterwards, and at the SFU Visit.

All details on the echocardiogram assessments performed at each visit will be listed including the observed LVEF measurements and changes from Baseline, as well as information on whether the result was normal, abnormal not clinically significant (NCS) or abnormal clinically significant (CS).

Observed values and changes from Baseline in LVEF will be summarized by visit using descriptive statistics. In addition, shift tables for the change from Baseline in normal, abnormal NCS, abnormal CS LVEF results will be summarized by visit.

Mean (±standard deviation) change from Baseline in LVEF will be plotted over scheduled visit with treatment groups overlaid on the same plot. Individual observed LVEF results will be presented over actual time in a spaghetti plot.

8.4.4 ECOG performance status

ECOG performance status will be listed by participant and visit and will be summarized using frequency counts and percentages. A shift table summarizing the changes from Baseline to each post-Baseline visit will also be presented. Further detail on the ECOG performance scale, the listings and summaries are included in Section 10.2.

8.4.5 Physical examination

Physical examination abnormalities from the complete physical examination performed at Screening and predose on Day 1 of Cycle 1, and from the symptom-directed physical examinations performed at other visits (predose on dosing visits), will be listed.

9. PHARMACOKINETICS AND PHARMACODYNAMICS

9.1 Pharmacokinetics

9.1.1 Secondary pharmacokinetic endpoint

[redacted]

9.1.2 Exploratory pharmacokinetic endpoints

[redacted]

[redacted]

9.2 Pharmacodynamics

The following exploratory PD and biomarker endpoints will be obtained from blood and urine samples which will be analyzed at a number of external laboratory vendors:

- Serum markers of bone turnover;
- Urinary markers of bone turnover;
- cGremlin-1;
- Genetic analysis;
- ctDNA.

The impact of UCB6114 on bone turnover will be explored using the serum and urinary markers provided by the analytical laboratory. These markers will be listed for the SS and summarized descriptively over time for the PDS by dose level (treatment group), as described for the clinical laboratory parameters in Section 8.3. For each marker of bone turnover, the mean (±standard deviation) value and the mean (±standard deviation) change from Baseline value will be plotted over scheduled visit with treatment group overlaid on the same plot.

cGremlin-1 will be reported as concentration in blood by nominal (scheduled) assessment and dose level. Concentrations of cGremlin-1 will be listed for the SS and summarized for the PDS using descriptive statistics by dose level (treatment group) and nominal (scheduled) sampling timepoints (n, arithmetic mean, standard deviation, median, minimum, maximum, geoMean, geoCV and 95% CI for the geoMean [assuming lognormally distributed data]). Changes from Baseline will also be summarized. Individual study participant cGremlin-1 concentration-time profiles will be displayed graphically in spaghetti plots and geoMean cGremlin-1 concentration and 95% CI will be plotted at each nominal (scheduled) timepoint with treatment group overlaid on the same plot.

Genetic analysis and the analysis of the test results from the blood samples taken for ctDNA will be performed and reported separately outside of the CSR.

Hematoxylin and eosin (H & E) staining and immunohistochemistry (IHC) will be used to analyze any available historical tissue biopsy samples obtained prior to a participant's entry into the study (e.g. at the time of diagnosis).

Test results from the H & E staining and for target genes, phosphatase and tensin homolog (PTEN), Ki67 (cellular marker for proliferation in tumors), Gremlin-1, mothers against decapentaplegic homolog 4 (SMAD4) and fibroblast activation protein (FAP) will be listed by variable and sample analyzed (multiple tissue samples from a tumor biopsy may have been analyzed for a participant) for the SS. No summaries of these data will be generated due to the

expected small numbers of historical biopsy samples analyzed for each dose level (treatment group).

The following key/component variables will be derived based on H & E staining, PTEN, Ki67, Gremlin-1 and FAP test results. No derived variables will be generated for SMAD4; only raw test results will be listed. Note that multiple tissue samples from a tumor biopsy may have been analyzed for a participant and therefore multiple test results will be presented in the listings.

H & E: Tissue Integrity (Percentage of Necrosis in Tumor Area)

In order to assess tissue integrity, percentage of necrosis in the tumor area will be categorized as '<20%' and '>=20%'. If percentage of necrosis data are missing but other H & E staining and IHC data are available for a participant (i.e. the participant had historical tumor biopsy sample(s) analyzed), then the result will be categorized as 'Not Done'.

This categorical variable will be listed together with all other H & E test results.

PTEN: Tissue Sample Quality Control

The presence of staining of intrinsic control elements on the slides together with the level of staining intensity will be used to determine the tissue sample quality control.

If staining of intrinsic control elements on stained slides='YES' and staining intensity of intrinsic control elements on stained slides is 1, 2 or 3 then the tissue sample quality control is 'Good', otherwise if the staining intensity of intrinsic control elements=0 then the tissue sample quality control is 'Questionable'. If staining of intrinsic control elements on stained slides='NOT PRESENT' then the tissue sample quality control is 'No staining present'. If both variables are missing but other IHC results are available (i.e. the participant had historical tumor biopsy sample(s) analyzed), then the result will be categorized as 'Not done'.

This categorical variable will be listed together with the presence/absence of staining of intrinsic control elements on the slides, the level of staining intensity, staining pattern, staining artifacts and any assay-specific comments. Since the percent of tumor cells with staining intensity 0/1/2/3 and the H-score (test results for which will be provided by the laboratory) are less relevant to assessing the quality control of the tissue sample, these raw test results will not be listed.

Ki67 – Proliferative Activity of the Tumor

In order to assess the proliferative activity of the tumor mass, cellular proliferation reflected by the number of Ki67-positive cell objects in the tumor region divided by the total number of cell objects in the tumor region will be categorized as '<=10%' or '>10%' with the latter category indicating an actively/moderately proliferating tumor. If the test result is 'NOT EVALUABLE' or missing but IHC results are available (i.e. the participant had historical tumor biopsy sample(s) analyzed), then the result will be categorized as 'Not done'.

This categorical variable will be listed together with all other Ki67 raw test results.

Gremlin-1: Cytoplasmic Histoscore

The cytoplasmic histoscore will be calculated as a weighted score based on the percentage of tumor cells with Gremlin-1 cytoplasmic staining intensity 1, 2 or 3 as follows:

(1 x percent tumor cells with Gremlin-1 cytoplasmic staining intensity 1) + (2 x percent tumor cells with Gremlin-1 cytoplasmic staining intensity 2) + (3 x percent tumor cells with Gremlin-1 cytoplasmic staining intensity 3).

The cytoplasmic histoscore will be missing if the participant had a historical biopsy tumor sample analyzed but there are no test results for percent tumor cells with Gremlin-1 cytoplasmic staining intensity 1, 2 or 3.

The cytoplasmic histoscore will be listed together with all other Gremlin-1 raw test results.

FAP

From the image analysis of FAP-stained slides, the tumor will be classified into 2 regions: the cancer (CN) tumor region and the invasive margin (IM) region using a pre-established digital automated algorithm. The IM region is usually a small proportion of the whole tumor and, per standard procedures at the analytical laboratory, will be identified first. As a result, there is a risk that some parts of the CN tumor region may be inaccurately classified as part of the IM region, particularly in cases when the tumor is small. Therefore, instead of using the results for the percentage of high, medium and low intensity FAP provided by the laboratory, a decision was made to back-calculate the areas of the CN tumor region and the IM region and add these together in order to re-calculate the percentage of high, medium and low intensity FAP in the whole tumor.

These back-calculated results and derived variables based on FAP test results are defined in Table 9-1.

Table 9-1: FAP Derived Variables

Variable No.	FAP Derived Variable	Description and Calculation
1[a]	Total Analyzed Tumor Area (um^2)	This is the total tumor area (um^2) across the CN tumor region and the IM region and will be calculated as the sum of the areas of the CN tumor region (um^2) and the IM region (um^2) where a non-missing numeric test result is available for both the area of the CN tumor region and the area of the IM region. Note that, in cases where no IM region is defined, the area of the IM region will be recorded as 0 or 'NOT APPLICABLE', or may be missing. If the area of the IM region is recorded as 'NOT APPLICABLE' or is missing, then 0 will be assumed in this calculation and the total analyzed tumor area will be equal to the area of the CN tumor region.

Variable No.	FAP Derived Variable	Description and Calculation
		This variable will be missing if both the areas of the CN tumor region and IM region are missing, or if one or both are 'NOT EVALUABLE' or 'NOT DIAGNOSTIC'.
2	Measured Area of Weakly Stained FAP in the CN Tumor Region (um^2)	This is the back-calculated area of weakly stained FAP in the CN tumor region (weak positive) and will be calculated by multiplying the area of the CN tumor region (um^2) and the relative area of weakly stained FAP in the CN tumor region (%) where a non-missing numeric test result is available for both the area of the CN tumor region and the relative area of weakly stained FAP in the CN tumor region. This variable will be set to 0 if one or both are missing, 'NOT EVALUABLE' or 'NOT DIAGNOSTIC'.
3	Measured Area of Moderately Stained FAP in the CN Tumor Region (um^2)	This is the back-calculated area of moderately stained FAP in the CN tumor region (moderate positive) and will be calculated by multiplying the area of the CN tumor region (um^2) and the relative area of moderately stained FAP in the CN tumor region (%) where a non-missing numeric test result is available for both the area of the CN tumor region and the relative area of moderately stained FAP in the CN tumor region. This variable will be set to 0 if one or both are missing, 'NOT EVALUABLE' or 'NOT DIAGNOSTIC'.
4	Measured Area of Strongly Stained FAP in the CN Tumor Region (um^2)	This is the back-calculated area of strongly stained FAP in the CN tumor region (strong positive) and will be calculated by multiplying the area of the CN tumor region (um^2) and the relative area of strongly stained FAP in the CN tumor region (%) where a non-missing numeric test result is available for both the area of the CN tumor region and the relative area of strongly stained FAP in the CN tumor region. This variable will be set to 0 if one or both are missing, 'NOT EVALUABLE' or 'NOT DIAGNOSTIC'.
5	Measured Area of Weakly Stained FAP in the IM Region (um^2)	This is the back-calculated area of weakly stained FAP in the IM region (weak FAP-positive) and will be calculated by multiplying the area of the IM region (um^2) and the relative area of weakly stained FAP in the IM region (%) where a non-missing numeric test result is available for both the area of the IM region and the relative area of weakly stained FAP in the IM region. This variable will be set to 0 if one or both are missing, 'NOT EVALUABLE' or 'NOT DIAGNOSTIC'.

Variable No.	FAP Derived Variable	Description and Calculation
6	Measured Area of Moderately Stained FAP in the IM Region (um^2)	This is the back-calculated area of moderately stained FAP in the IM region (moderate FAP-positive) and will be calculated by multiplying the area of the IM region (um^2) and the relative area of moderately stained FAP in the IM region (%) where a non-missing numeric test result is available for both the area of the IM region and the relative area of moderately stained FAP in the IM region. This variable will be set to 0 if one or both are 'NOT EVALUABLE' or 'NOT DIAGNOSTIC'.
7[a]	Measured Area of Strongly Stained FAP in the IM Region (um^2)	This is the back-calculated area of strongly stained FAP in the IM region (strong FAP-positive) and will be calculated by multiplying the area of the IM region (um^2) and the relative area of strongly stained FAP in the IM region (%) where a non-missing numeric test result is available for both the area of the IM region and the relative area of strongly stained FAP in the IM region. This variable will be set to 0 if one or both are missing, 'NOT EVALUABLE' or 'NOT DIAGNOSTIC'.
8[a]	Total FAP-Positive Tumor Area (um^2)	This is the total FAP-positive area across the CN tumor region and the IM region (whole tumor) and will be calculated as the sum of component derived variables 2-7. If all 6 component variables are 0 then this derived variable will be missing.
9[a]	Total Measured Area of Weakly Stained FAP (um^2)	This is the total weak FAP-positive area across the CN tumor region and the IM region (whole tumor) and will be calculated as the sum of component FAP derived variables 2 and 5.
10[a]	Total Measured Area of Moderately Stained FAP (um^2)	This is the total moderate FAP-positive area across the CN tumor region and the IM region (whole tumor) and will be calculated as the sum of component FAP derived variables 3 and 6.
11[a]	Total Measured Area of Strongly Stained FAP (um^2)	This is the total strong FAP-positive area across the CN tumor region and the IM region (whole tumor) and will be calculated as the sum of component FAP derived variables 4 and 7.
12[a]	Total Relative Area of Weakly Stained FAP (%)	This is the percentage of weak FAP expression across the CN tumor region and IM region (whole tumor) and will be calculated using component FAP derived variables 1 and 9 as

Variable No.	FAP Derived Variable	Description and Calculation
		(Total Measured Area Of Weakly Stained FAP / Total Analyzed Tumor Area) x 100 If the total analyzed tumor area is missing then this variable cannot be calculated and will be missing.
13[a]	Total Relative Area of Moderately Stained FAP (%)	This is the percentage of moderate FAP expression across the CN tumor region and IM region (whole tumor) and will be calculated using component FAP derived variables 1 and 10 as (Total Measured Area Of Moderately Stained FAP / Total Analyzed Tumor Area) x 100 If the total analyzed tumor area is missing then this variable cannot be calculated and will be missing.
14[a]	Total Relative Area of Strongly Stained FAP (%)	This is the percentage of strong FAP expression across the CN tumor region and IM region (whole tumor) and will be calculated using component FAP derived variables 1 and 11 as (Total Measured Area Of Strongly Stained FAP / Total Analyzed Tumor Area) x 100 If the total analyzed tumor area is missing then this variable cannot be calculated and will be missing.
15[a]	Total Relative FAP-Positive Tumor Area (TPS) (%)	This is the total proportion score which is the percentage of FAP-positive area across the CN tumor region and the IM region (whole tumor) and will be calculated using component derived variables 1 and 8 as (Total FAP-Positive Tumor Area / Total Analyzed Tumor Area) x 100 If the total analyzed tumor area is missing then this variable cannot be calculated and will be missing.
16[a]	Total FAP Histoscore	This is a histoscore for the combined CN tumor region and IM region (whole tumor) and will be calculated as a weighted score based on component derived variables 12, 13 and 14 as (1 x Total Relative Area of Weakly Stained FAP) + (2 x Total Relative Area of Moderately Stained FAP) + (3 x Total Relative Area of Strongly Stained FAP).

CN=cancer; FAP=fibroblast activation protein, IM=invasive margin, TPS=total proportion score.
[a] Included in the listing of FAP test results.

The derived variables containing the [a] flag in Table 9-1 above will be listed together with information on staining artifacts and any assay-specific comments provided by the laboratory.

Further informal analyses may be performed to explore the relationship between the PD and biomarker endpoints with antitumor activity, ADA status, and also with key PK parameters. The PK-PD effects of UCB6114 may be assessed using a population analysis approach. These analyses will also be performed separately outside of the CSR and the details of analysis methods will be included in a separate analysis plan.

The incidence of available historical tumor biopsies will be summarized by treatment group. The incidence of PD samples taken from blood and urine will be summarized by cycle and treatment group.

9.3 Immunogenicity

Anti-drug (UCB6114) antibody status and classification, changes from Baseline in titer over time (Cycles 1, 2 and even cycles thereafter) and the incidence of treatment-emergent ADA positivity are exploratory immunogenicity endpoints in Part B of this study. Potential relationships between ADA and PK, PD, antitumor activity and safety will also be explored but this will be reported separately outside of the CSR.

Serum samples will be collected from all study participants for the measurement of ADA and the evaluation of immunogenicity according to the Schedule of Activities in the protocol.

All listings of ADA will be presented for the SS and summaries of the ADA data will be presented by treatment group for the ADAS.

Anti-drug (UCB6114) antibodies will be measured using a three-tiered assay approach: Screening assay, confirmatory assay and titration assay.

Samples will first be evaluated in the Screening assay using a false positivity rate of 5% (reported as ‘negative screen’ or ‘positive screen’), followed by analysis of screened positive samples in the confirmatory assay (which is a drug depletion assay) to confirm the positivity of the samples (reported as ‘negative immunodepletion’ or ‘positive immunodepletion’). Samples that are confirmed as positive in the confirmatory assay will be evaluated in a titration assay to assess the ADA level and this will be reported as titer (reciprocal dilution factor including minimum required dilution).

Anti-drug (UCB6114) antibody sample status will be determined as follows from the pre-treatment sample taken on Day 1 of Cycle 1 (Baseline) and all post-treatment (post-Baseline) samples.

- Sample values that are either ‘negative screen’ or ‘positive screen’ and ‘negative immunodepletion’ will be defined as **ADA negative**
- Sample values that are ‘positive screen’ and ‘positive immunodepletion’ will be defined as **ADA positive**

Anti-drug (UCB6114) antibody sample status will be listed for each participant at each visit by treatment group. This listing will include sampling dates and times, the Screening assay result, the confirmatory assay result and the derived ADA sample status. In addition, the titer from the

titration assay (if applicable) will be listed together with the change from Baseline in titer. The number and percentage of participants with a positive or negative sample at each visit will be summarized by treatment group. Percentages will be calculated based on the number of participants with a non-missing/sufficient sample at the visit.

Based on the ADA status of the samples, study participants will be categorized according to the following 6 ADA classifications in Table 9-2:

Table 9-2: ADA Classifications

Classification	Classification Label	Definition
1	Pre-ADA negative – treatment induced ADA negative	Includes participants who have an ADA negative status at Baseline, or missing/insufficient Baseline sample, and an ADA negative status at all sampling timepoints post-Baseline (including SFU). Participants with missing post-Baseline samples are included as long as the missing samples do not result in an unmonitored period greater than 16 weeks.
2	Pre-ADA negative – treatment induced ADA positive	Includes participants who have an ADA negative status at Baseline, or missing/insufficient Baseline sample, and an ADA positive status at any sampling timepoint post-Baseline (including SFU).
3	Pre-ADA positive – treatment reduced ADA	Includes participants who have an ADA positive status at Baseline and an ADA negative status at all sampling timepoints post-Baseline (including SFU)
4	Pre-ADA positive – treatment unaffected ADA	Includes participants who have an ADA positive status at Baseline and an ADA positive status at any sampling timepoint post-Baseline (including SFU) with titer values of the same magnitude as Baseline (≤1.80 fold difference from the Baseline value) or with decreased titer values compared to Baseline (>1.80 fold decrease from the Baseline value).
5	Pre-ADA positive – treatment boosted ADA positive	Includes participants who have an ADA positive status at Baseline and an ADA positive status at any sampling timepoint post-Baseline (including SFU) with increased titer values compared to Baseline (>1.80 fold increase from the Baseline value).
6	Inconclusive	Includes participants who do not satisfy the criteria for classifications 1-5.

ADA=anti-drug (UCB6114) antibody; SFU=Safety Follow-up.
Note: The terminology 'treatment unaffected' is ambiguous as the criteria refers to ADA responses that are not increased upon dosing compared to Baseline level whereas titers may reduce.

A study participant will be classified as having **treatment-emergent ADA positivity** if they satisfy one of the following criteria:

- The Baseline result is ADA negative and at least one post-Baseline result is ADA positive (pre-ADA negative – treatment induced ADA positive) – ADA classification 2 in Table 9-2;
- The Baseline result is ADA positive and at least one post-Baseline result shows a pre-defined fold increase in titer from the Baseline value (the fold increase from Baseline required to meet this criterion will be defined with the development of the assay and will be included in the TFLs) (pre-ADA positive – treatment boosted ADA positive) – ADA classification 5 in Table 9-2.

Total anti-drug (UCB6114) antibody **incidence** will be determined by the number and percentage of participants with treatment-emergent ADA positivity (as defined above). The denominator for the percentage calculation will be the number of participants with at least one available/reported post-Baseline result.

Total **prevalence** of pre-anti-drug (UCB6114) antibody will be determined by the number and percentage of participants who are pre-ADA positive (i.e. participants who have a positive ADA status at Baseline). The denominator for the percentage calculation will be the number of participants with an available/reported Baseline sample result.

Total anti-drug (UCB6114) antibody **prevalence** will be determined by the number and percentage of participants with ADA classifications 2, 3 or 5 in Table 9-2 (i.e. an ADA positive status at any post-Baseline sampling timepoint). The denominator for the percentage calculation will be the number of participants with at least one available/reported sample result (either at Baseline and/or post-Baseline).

The ADA classification for each participant will be listed by treatment group. This listing will also include whether or not the participant achieved treatment-emergent ADA positivity (ADA incidence), whether the participant was pre-ADA positive (pre-ADA prevalence) and whether the participant had an ADA positive status at any post-Baseline sampling timepoint (ADA prevalence). In addition, the visit at which the participant first achieved treatment-emergent ADA positivity will be included.

The number and percentage of participants in each of the 6 ADA classifications defined above in Table 9-2 will be presented by treatment group. Also, in this tabulation, ADA incidence and prevalence (as defined above) will be summarized.

The first occurrence of treatment-emergent ADA positivity (based on the criteria above) will be summarized using frequency counts and percentages at each post-Baseline visit by treatment group. This tabulation will include a count of the number of participants at each post-Baseline visit who fulfill at least one of the above defined criteria for treatment-emergent ADA positivity; participants will be counted in the numerator based on the earliest visit at which one of these criteria is fulfilled. At other visits, participants will be counted in the denominator (assuming an assessment of treatment-emergent positivity is available) and this will be used in the percentage calculations.

Individual study participant ADA titer profiles over actual time will be presented graphically on the linear and the semi-logarithmic scale. The linear scale plots will be repeated for the subset of participants who achieve treatment-emergent ADA positivity during Part B.

Mean (±standard deviation) C_{min} will be plotted by ADA sample status over nominal (scheduled) time with treatment groups overlaid on the same plot. On this plot, mean C_{min} at Cycle 1 Day 15 will be the mean of the derived C_{min} following the first dose of UCB6114 (as described in Section 9.1.2) and, thereafter from Cycle 2 Day 1, mean C_{min} will be the mean of the predose concentrations at the subsequent dosing visits.

10. EFFICACY ANALYSES

10.1 Antitumor activity

The analysis of antitumor activity is exploratory in Part B of this study.

10.1.1 Definitions of the antitumor activity endpoints

The following endpoints are defined based on RECIST (Version 1.1) which standardizes solid tumor measurements and provides guidelines for the objective assessment of changes in tumor size during anti-cancer treatment.

Appendix 9 (Section 11.9) of the protocol contains the RECIST 1.1 guidelines to be used in this study, adapted from Eisenhauer (2009), and includes the definitions of target and non-target lesions, the definitions of target and non-target lesion responses at each tumor assessment, the criteria for determining overall response at each tumor assessment based on target lesion response, non-target lesion response and the presence/absence of new lesions, and a participant's best overall response (BOR). Further details on the rules to apply in the derivation of BOR are included in the Derivation of Efficacy Endpoints document which has been developed to support this SAP.

At each post-Baseline tumor assessment, the investigator will record responses for target lesions and non-target lesions, whether or not there has been an appearance of any new lesions, and the participant's overall response based on their target lesion response, non-target lesion response and the presence/absence of new lesions. Note that target lesion response and non-target lesion response assessments will be based on the changes in the pre-existing lesions at Baseline and the appearance of new lesions will only factor in the determination of an overall response of PD at that tumor assessment visit (i.e. per Tables A and B in Section 11.9.2 of Appendix 9 of the protocol).

Objective response rate (ORR) is defined as the percentage of participants with a BOR of complete response (CR) or partial response (PR) during Part B.

Disease Control Rate (DCR) is defined as the percentage of participants with a BOR of CR, PR, or stable disease (SD) during Part B.

Best overall response (BOR) is defined for each study participant as the best overall tumor response from each tumor assessment performed every 8 weeks from Day 1 of Cycle 1 (±7 days)) according to the RECIST criteria for changes in target and non-target lesions and the appearance of new lesions. Best overall response is determined from the start of study treatment (first dose of UCB6114) until documented objective disease progression or the date of subsequent anti-cancer therapy (systemic therapy, surgery or radiotherapy for cancer), whichever

occurs first. If anti-cancer therapy is started on the same day as a tumor assessment, then the overall response from that assessment will be used in the derivation of BOR. If a participant does not have objective disease progression or does not start a subsequent anti-cancer therapy, then all tumor assessments up to the SFU visit will be included in the derivation of BOR. For a BOR of SD, a participant's tumor measurements must have met the SD criteria at least once after the start of study treatment at a minimum interval of no less than 49 days.

For this study, BOR determination requires confirmation of CR or PR responses at a subsequent assessment ≥4 weeks (28 days) after the criteria for CR or PR responses are first met, however, an unconfirmed BOR will also be derived for each participant for the purpose of reporting (as described below in Section 10.1.2). Table C in Appendix 11.9 of the protocol and Table 1 and subsequent text in the Derivation of Efficacy Endpoints document provides the derivation of BOR when confirmation of CR and PR responses are required. The definition of an unconfirmed BOR is also included in this document. Although the derivation of unconfirmed BOR does not include the requirement for a CR or PR response to be confirmed ≥4 weeks (28 days) after the initial response, a participant's CR or PR response may, in fact, be confirmed at a subsequent assessment ≥4 weeks (28 days) after the criteria for the CR or PR response are first met. Unconfirmed BOR will be referred to as BOR (confirmed or unconfirmed) throughout the rest of this document.

Confirmed BOR and BOR (confirmed or unconfirmed) will be derived programmatically based on the overall tumor assessment data recorded on the eCRF by the investigator.

Duration of response (DOR) will be calculated for participants with a BOR of confirmed CR or PR as the time in days from the start date of the confirmed CR or PR (e.g. the date of the first overall response of CR or PR, which is at least 4 weeks before a second overall response of CR or PR) to the first date that recurrent or progressive disease is objectively documented (i.e. according to the RECIST guidelines). This will be referred to as the duration of confirmed response and the following calculation will be performed:

$$\begin{aligned} &Duration\ of\ Confirmed\ Response \\ &\quad = (Date\ of\ First\ Objective\ Disease\ Progression \\ &\quad - Start\ Date\ of\ Confirmed\ CR\ or\ PR\ Response) + 1 \end{aligned}$$

Duration of response will also be calculated for participants with a BOR of CR or PR which is either confirmed or unconfirmed [DOR (confirmed or unconfirmed)] as the time in days from the start date of the CR or PR to the date of the first documented objective disease progression (i.e. according to the RECIST guidelines). The following calculation will be performed:

$$\begin{aligned} &DOR\ (Confirmed\ or\ Unconfirmed) \\ &\quad = (Date\ of\ First\ Objective\ Disease\ Progression \\ &\quad - Start\ Date\ of\ CR\ or\ PR\ Response) + 1 \end{aligned}$$

For the purpose of a sensitivity analysis of both duration of confirmed response and DOR (confirmed or unconfirmed), the above calculations will take into consideration the occurrence of both objective disease progression (per RECIST 1.1) and clinical disease progression (as described in Appendix 11.9 of the protocol and as determined by the investigator and recorded as a reason for study treatment discontinuation on the eCRF), whichever occurs first. If clinical disease progression occurs on the same date that a participant's objective disease progression is

determined, then the participant will be included in the sensitivity analyses as having objective disease progression.

The following calculations will therefore be performed for the sensitivity analyses:

$$Duration\ of\ Confirmed\ Response = (Date\ of\ First\ Objective\ or\ Clinical\ Disease\ Progression - Start\ Date\ of\ Confirmed\ CR\ or\ PR\ Response) + 1$$

$$DOR\ (Confirmed\ or\ Unconfirmed) = (Date\ of\ First\ Objective\ or\ Clinical\ Disease\ Progression - Start\ Date\ of\ CR\ or\ PR\ Response) + 1$$

For participants who die without objective disease progression, DOR will be censored on the date of death, regardless of cause. For a participant who discontinues early from Part B of the study with no objective disease progression, DOR will be censored on the date of their last available (scheduled or unscheduled) tumor assessment at which a lack of objective disease progression was determined. Participants who discontinue study treatment but who do not have documented objective disease progression (i.e. according to the RECIST guidelines), DOR will be censored at the date of their last available (scheduled or unscheduled) tumor assessment at which a lack of objective disease progression was determined. Such participants might include those that are ongoing in Part B at the time of any defined data cut-off. Likewise, participants who have not discontinued early and do not have disease progression after a confirmed or unconfirmed response, DOR will be censored at the date of their last available (scheduled or unscheduled) tumor assessment.

In the sensitivity analyses of duration of confirmed response and duration of unconfirmed response, the same censoring rules will apply except that the date of last contact will be used for the censoring of participants who discontinue early from Part B or complete Part B without objective disease progression, clinical disease progression or death.

Date of last contact will be the latest of the dates of premature study termination and of last contact recorded on Study Termination eCRF page, the date of death, the date of last dose of study treatment, the dates of all visits, AE start and end dates (with partial dates imputed as earliest possible) and the date of contact recorded on the Survival Safety Follow-up and Survival Final Follow-up eCRF forms.

Further details on the rules to apply in the derivation of DOR are included in the Derivation of Efficacy Endpoints document which has been developed to support this SAP.

Progression-free survival (PFS) will be calculated as the time in days from the first dose of UCB6114 to the date of the first documented objective disease progression (i.e. according to the RECIST guidelines), or death due to any cause, whichever occurs first. The following calculation will be performed:

$$PFS = \left(Date\ of\ Objective\ Progressive\frac{Disease}{Death} - Date\ of\ First\ Dose\ of\ UCB6114\right) + 1$$

Participants who die due to any cause without a documented objective disease progression will be considered to have progressed on the date of their death. Participants who do not have any post-Baseline tumor assessments will be censored on the date of their first dose of UCB6114. Participants who discontinue early from Part B or discontinue study treatment without

documented objective disease progression or death, will be censored on the date of their last available (scheduled or unscheduled) tumor assessment at which a lack of objective disease progression was determined. Participants who start anti-cancer therapy during Part B without a prior documented objective disease progression will be censored on the date of their last available (scheduled or unscheduled) tumor assessment prior to the initiation of the subsequent anti-cancer therapy. If anti-cancer therapy starts on the same date as the participant's tumor assessment and determination of objective disease progression, or the participant's death (due to any cause), then the participant will not be censored and the participant will be included as having an uncensored event on this date. This censoring rule will also be applied to participants who are ongoing at any data cut-off for an analysis of Part B data who have no documented objective disease progression. The use of anti-cancer therapy during Part B will be identified via ongoing medical review of the concomitant medications together with the start dates of further anti-cancer therapy information recorded on the survival follow-up pages of the eCRF.

As a sensitivity analysis, PFS will also be calculated as the time in days from the first dose of UCB6114 to the date of the first documented objective disease progression (per RECIST 1.1), the date of clinical disease progression, as determined by the investigator, or the date of death due to any cause, whichever occurs first. Last contact date will be used for the censoring of participants still alive with no reported disease progression (objective or clinical). The same rules described above for the censoring of participants who start anti-cancer therapy will be applied in this sensitivity analysis.

Further details on the rules to apply in the derivation of PFS are included in the Derivation of Efficacy Endpoints document which has been developed to support this SAP.

Overall survival (OS) will be calculated as the time in days from the date of first dose of UCB6114 to the date of death from any cause. Participants will be followed up to ascertain their survival status at the SFU visit (within 30 days after their last dose of UCB6114) and at the Final Visit (3 months after their last dose of UCB6114); they will not be followed up beyond this timepoint.

The following calculation will be performed:

$$OS = (Date\ of\ Death - Date\ of\ First\ Dose\ of\ UCB6114\ ) + 1$$

OS will be censored on the date of their last contact for participants who discontinue early from Part B of the study or who discontinue study treatment due to disease progression but continue in the study, and are not known to have died.

Further details on the rules to apply in the derivation of OS are included in the Derivation of Efficacy Endpoints document which has been developed to support this SAP.

10.1.2 Analysis of the antitumor activity endpoints

The analyses of the antitumor activity endpoints in Part B will be performed for the PPS. As a sensitivity analysis, all analyses will be repeated for the SS. All listings will be presented for the SS. Summaries and listings will be presented by treatment group.

All lesion assessment data recorded at Baseline (Screening) and during the Treatment Period (every 8 weeks from Day 1 of Cycle 1 [±7 days]) will be listed separately for target lesions, non-

target lesions and new lesions. Each post-Baseline tumor assessment will be labelled as 'Tumor Assessment 1, Tumor Assessment 2 etc. – see further details below). These listings will include lesion number and lesion type (nodal/non-nodal), location, method of assessment, dimension (or an indication that the lesion is too small to measure, for target lesions only) and lesion response evaluation (for non-target lesions at post-Baseline assessments). The listing for target lesions will also include the derived eCRF component data used for the determination of the overall target lesion response at each post-Baseline assessment (e.g. sum of all dimensions across target lesions and percentage change from Baseline in the sum). In addition, the overall response assessment for target lesions and non-target lesions, as determined by the investigator, will be listed for each post-Baseline tumor assessment (Tumor Assessment 1, Tumor Assessment 2 etc.) together with the presence of new lesions and the overall response assessment.

The investigator's overall tumor response assessment will be summarized using frequency counts and percentages over time (tumor assessment). Post-Baseline tumor assessments are scheduled to be performed per protocol every 8 weeks from Day 1 (±7 days). For the purpose of this summary, the first post-Baseline tumor assessment (scheduled or unscheduled) will be assigned to 'Tumor Assessment 1' using the protocol-defined window of Day 50 to 64 (Day 57 ± 7 days) relative to Day 1 (first dose of UCB6114). For all subsequent post-Baseline tumor assessments (scheduled or unscheduled, but excluding tumor assessments performed at the SFU visit), these will be assigned to 'Tumor Assessment 2', 'Tumor Assessment 3' etc. using the protocol-defined window of Day 50-64 relative to the previous post-Baseline tumor assessment. If a post-Baseline tumor assessment is missed, then the scheduled day of the missed assessment will be used to window the next tumor assessment. In cases where a scheduled and unscheduled tumor assessment occurs in the same window, the investigator's overall tumor response at both assessments will be considered. If the overall tumor response is NE at one of the assessments, then the overall tumor response from the other assessment will be included in the summary table. If the overall tumor response is not NE at both assessments, then the tumor assessment that is closest to the target day of the tumor assessment will be included in the summary table. In the event that the two tumor assessments are equidistant from the target day of the tumor assessment and neither have an overall tumor response of NE, then the worst case overall tumor response will be included in the summary table. Otherwise, if the post-Baseline tumor assessment falls outside of the protocol-defined window, it will be classified as an unscheduled assessment and not included in the summary of overall tumor response.

Bar charts will also be produced for overall tumor response rate by treatment group for each visit. In addition, waterfall plots of participants' percentage change from Baseline in the sum of dimensions for all target lesions will be presented by treatment group and visit. The individual participants' bars will be colored by overall tumor response at the visit.

Confirmed and unconfirmed BOR for each participant will be derived programmatically using the investigator's overall tumor response assessments (scheduled and unscheduled) performed every 8 weeks from Day 1 of Cycle 1 (or at unscheduled timepoints) and the RECIST criteria. Whether a BOR of CR or PR is confirmed or unconfirmed will be indicated on this listing. Using a participant's confirmed BOR and unconfirmed BOR, whether the participant achieves an objective tumor response (i.e. a BOR of CR or PR) and/or disease control (i.e. a BOR of CR, PR or SD) during study treatment will be determined. These derived data will be listed for the SS.

Confirmed and unconfirmed BOR will be summarized using frequency counts and percentages. Bar charts will also be produced for confirmed BOR and unconfirmed BOR by treatment group.

The number and percentage of participants achieving objective tumor response and disease control (ORR and DCR) based on confirmed BOR and BOR (confirmed or unconfirmed) will be presented and, if data allow, exact 95% CIs for binomial proportions will be calculated using the Clopper-Pearson method and presented for the response rates. In the calculation of ORR and DCR, the denominator will include all participants in the analysis set. Objective response rate and DCR (based on confirmed BOR and unconfirmed BOR) will also be summarized in bar charts by treatment group overall and by tumor type and ECOG performance status at Baseline.

In addition, waterfall plots of each participant's best percentage change from Baseline in the sum of the dimensions for all target lesions will be presented by treatment group overall and by tumor type and ECOG performance status at Baseline with the individual participants' bars colored by confirmed BOR and unconfirmed BOR.

The summaries and analyses of DOR, PFS and OS will be carried out as described below, if the data allow.

Duration of confirmed response, DOR (confirmed or unconfirmed) and PFS will be listed and summarized descriptively using Kaplan-Meier estimation. These summaries will be repeated for the sensitivity analyses of these endpoints (defined in Section 10.1.1 above) and will include the number and percentage of participants with the event, the number and percentage of participants censored, minimum and maximum values and Kaplan-Meier estimates of the 25th percentile, median, 75th percentile and corresponding 95% CIs calculated using Greenwood's formula. In addition, DOR and PFS rates at 3 months, 6 months and 9 months will be derived from the Kaplan-Meier estimation and presented together with associated 95% CIs.

Kaplan-Meier curves will be presented for duration of confirmed response and DOR (confirmed or unconfirmed) and PFS. Treatment groups will be overlaid on each plot.

Survival status collected on the eCRF at the SFU visit and at the Final Visit will be listed for each participant by treatment group. This listing will include the participant's survival status, date and cause of death, whether an autopsy was performed and date of autopsy, whether the participant had received any further antitumor treatment after the last dose of study treatment and the type of treatment, and whether the participant's disease had been assessed since the end of study treatment including method of assessment and the overall response.

Overall survival times will be listed and summarized descriptively using Kaplan-Meier estimation. Note that since participants are only followed up for survival until the Final Visit in Part B of the study, a summary of OS may not be meaningful (i.e. if no participants die then OS cannot be assessed).

Exploratory analyses of selected antitumor activity endpoints may be performed based on subgroups of participants in the SS. Data permitting, the subgroups will be defined based on participant, disease, and treatment history information (e.g. extent of prior anti-cancer therapy).

Additionally, the relationship of the antitumor activity variables with key PK parameters may be explored but this will be reported separately.

10.2 ECOG performance status

ECOG performance status is an additional efficacy assessment performed in Part B of this study and is defined in Table 10-1.

Table 10-1: ECOG Performance Status Scale

Grade	ECOG performance status scale
0	Fully active, able to carry on all pre-disease performance without restriction
1	Restricted in physically strenuous activity but ambulatory and able to carry out work of a light or sedentary nature (e.g. light housework, office work)
2	Ambulatory and capable of all self-care but unable to carry out any work activities. Up and about more than 50% of waking hours
3	Capable of only limited self-care, confined to bed or chair for more than 50% of waking hours
4	Completely disabled. Cannot carry out any self-care. Totally confined to bed or chair
5	Dead

ECOG=Eastern Cooperative Oncology Group.

ECOG performance status will be listed by treatment group at each visit for the SS.

ECOG performance status will be summarized as an ordinal categorical variable using frequency counts and percentages. Shift tables for the change from Baseline in each grade will be summarized by visit.

11. OTHER ANALYSES

Not applicable.

12. REFERENCES

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Eisenhauer EA, Therasse P, Bogaerts J, et al. New response evaluation criteria in solid tumours: revised RECIST guideline (Version 1.1). Eur J Cancer. 2009 Jan;45(2):228-47.

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International Council for Harmonization/Food and Drug Administration E9 Guidance (ICH-E9).

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(https://www.fda.gov/media/136238/download)

13. APPENDICES

13.1 SMQ algorithm for identification of anaphylactic reactions

Based on MedDRA® Version 25.1, the SMQ='Anaphylactic reaction' consists of 3 parts:

1) A **narrow search** containing PTs that represent core anaphylactic reaction terms:

Category A

Anaphylactic reaction
Anaphylactic shock
Anaphylactic transfusion reaction
Anaphylactoid reaction
Anaphylactoid shock
Circulatory collapse
Dialysis membrane reaction
Kounis syndrome
Procedural shock
Shock
Shock symptom
Type I hypersensitivity

2) A **broad search**:

Category B

Acute respiratory failure
Asthma
Bronchial oedema
Bronchospasm
Cardio-respiratory distress
Chest discomfort
Choking
Choking sensation
Circumoral oedema
Cough
Cough variant asthma
Cyanosis
Dyspnoea
Hyperventilation
Irregular breathing
Laryngeal dyspnoea
Laryngeal oedema
Laryngospasm
Laryngotracheal oedema
Mouth swelling
Nasal obstruction
Oedema mouth
Oropharyngeal oedema
Oropharyngeal spasm
Oropharyngeal swelling
Pharyngeal oedema
Pharyngeal swelling
Respiratory arrest
Respiratory distress
Respiratory failure
Reversible airways obstruction
Sensation of foreign body
Sneezing
Stridor

Swollen tongue	Tracheal oedema
Tachypnoea	Upper airway obstruction
Throat tightness	Vaccine associated enhanced respiratory disease
Tongue oedema	Wheezing
Tracheal obstruction	
Category C	
Allergic oedema	Oedema
Angioedema	Oedema blister
Circumoral swelling	Periorbital oedema
Erythema	Periorbital swelling
Eye oedema	Pruritis
Eye pruritis	Pruritis allergic
Eye swelling	Rash
Eyelid oedema	Rash erythematous
Face oedema	Rash pruritic
Flushing	Skin swelling
Injection site urticaria	Swelling
Lip oedema	Swelling face
Lip swelling	Swelling of eyelid
Nodular rash	Urticaria
Ocular hyperaemia	Urticaria papular
Category D	
Blood pressure decreased	Cardiovascular insufficiency
Blood pressure diastolic decreased	Diastolic hypotension
Blood pressure systolic decreased	Hypotension
Cardiac arrest	Hypotensive crisis
Cardio-respiratory arrest	Post procedural hypotension

Note that if the MedDRA® version is increased from 25.1 during the study, any changes to the terms in the above categories should be applied.

The following **algorithmic approach** will be applied: A or (B and C) or [D and (B or C)], i.e.

If a participant has a TEAE which codes to a PT included in Category A, then the event will be flagged as an anaphylactic reaction. Note that participants with a TEAE coded to a PT='Type 1

hypersensitivity' will also be flagged as having a hypersensitivity reaction as this PT is also included in the Category A narrow search for the 'Hypersensitivity' SMQ.

OR

If a participant has a TEAE which codes to a PT included in Category B **AND** has a TEAE which codes to a PT included in Category C**, and both TEAEs have the same start date**, then both events will be flagged as anaphylactic reactions.

OR

If a participant has a TEAE which codes to a PT included in Category D **AND** has (either a TEAE which codes to a PT included in Category B **OR** a TEAE which codes to a PT included in Category C), **and both TEAEs have the same start date**, then both events will be flagged as anaphylactic reactions.

13.2 SAP Amendment 1 Changes

The main rationale for SAP Amendment 1 is to include details on the additional key derived and component exploratory variables required based on the results from the analyses of historical tumor biopsy samples in Part B. It was decided that these additional variables were needed to improve the interpretability of the test results received from the laboratory. This SAP amendment also provides some clarifications relating to the handling of data for the purpose of summarizing safety and exploratory anti-tumor activity endpoints.

The key changes are summarized in the table below (note that additional minor corrections and clarifications were also applied in this amendment but are not included in this table).

Section	Description of Change
1	The versions and dates of supporting study documentation were updated.
5.1	An update was made to the example illustrating the definition of a complete cycle of UCB6114.
7	TFD/TPI compliance calculation and corresponding definitions were updated.
8.1	The additional summary of the total number of doses of study treatment received was included.
8.2	Rules for handling missing relationship to study treatment for an adverse event were updated.
8.4.2	Clarification on the handling of triplicate ECG measurements was included.
9.1.2	Updates were added for more clarification on how C_{min} and C_{max} is to be derived.
9.2	Details on the analysis of the historical tumor biopsy samples was included together with rules for defining key and component derived variables based on the test results received from the laboratory. These variables were considered important for clearer interpretation of these results from data listings.

Section	Description of Change
9.3	A predefined fold-increase of 1.80 was included.
10.1.2	Rules for applying the protocol-defined window around the post-Baseline tumor assessments (scheduled and unscheduled) for the purpose of summarizing the investigator's overall tumor response assessment were included.
General	MedDRA® version number was updated to the latest version (25.1) throughout the document.

STATISTICAL ANALYSIS PLAN SIGNATURE PAGE

This document has been reviewed and approved per the Review and Approval of Clinical Documents Standard Operating Procedures. Signatures indicate that the final version of the Statistical Analysis Plan (SAP) or amended SAP is released for execution.

STATISTICAL ANALYSIS PLAN

PART C

DOSE ESCALATION (COMBINATION THERAPY)

Study: ONC001

Product: UCB6114

A PHASE 1/2 OPEN-LABEL, MULTICENTER STUDY TO ASSESS THE SAFETY, PHARMACOKINETICS, AND ANTITUMOR ACTIVITY OF UCB6114 ADMINISTERED INTRAVENOUSLY TO PARTICIPANTS WITH ADVANCED SOLID TUMORS

SAP/Amendment Number	**Date**
Version 1.0	20 August 2021
Amendment 1 Version 1.0	13 October 2023

Confidentiality Statement

TABLE OF CONTENTS

LIST OF ABBREVIATIONS

AE	adverse event
AESI	adverse event of special interest
ADA	anti-drug (UCB6114) antibody
ADaM	Analysis Data Model
ALP	alkaline phosphatase
ALQ	above limit of quantification
ALT	alanine aminotransferase
AST	aspartate aminotransferase
BLQ	below limit of quantification
BMI	body mass index
BOR	best overall response
CA	cancer
CDISC	Clinical Data Interchange Standards Consortium
CDMS	clinical data management system
cGremlin-1	circulating gremlin-1
CI	confidence interval
COVID-19	coronavirus disease 2019
CPPC	CDMS postproduction change
CR	complete response
CS	clinically significant
CRC	colorectal adenocarcinoma
CSR	clinical study report
ctDNA	circulating tumor DNA
CTMS	clinical trial management system
DCR	disease control rate
DEM	data evaluation meeting
DES	DLT Evaluable Set
DLT	dose limiting toxicity
DOR	duration of response
ECG	electrocardiogram
ECOG	Eastern Cooperative Oncology Group
eCRF	electronic case report form
EMA	European Medicines Agency
ES	enrolled set
EudraCT	European Union Drug Regulating Authorities Clinical Trials
FAP	fibroblast activation protein
FDA	Food and Drug Administration
Gastric cancer	gastric adenocarcinoma
GEJ cancer	adenocarcinoma of the gastroesophageal junction
geoCV	geometric coefficient of variation

geoMean	geometric mean
hh:mm	hours:minutes
H & E	hematoxylin and eosin
HLT	high level term
IHC	immunohistochemistry
ICH	International Council for Harmonization
IM	invasive margin
iv	intravenous
IPD	important protocol deviations
LLOQ	lower limit of quantification
LLT	low level term
LVEF	left ventricular ejection fraction
MedDRA®	Medical Dictionary for Regulatory Activities
mFOLFOX6	modified FOLFOX 6 regimen (leucovorin 400mg/m^2 on Day 1, 5-fluorouracil 400mg/m^2 on Day 1 + 1200mg/m^2/day on Day 1 and Day 2, and oxaliplatin 85mg/m^2 on Day 1)
MTD	maximum tolerated dose
mTPI	modified toxicity probability interval
n	number of study participants
NCI CTCAE	National Cancer Institute Common Terminology Criteria for AEs
NC	not calculable
NCS	not clinically significant
NEst	not estimable
NV	no value
ORR	objective tumor response rate
OS	overall survival
PCS	potentially clinically significant
PD	pharmacodynamic(s)
PDILI	potential drug-induced liver injury
PDS	pharmacodynamic set
PK	pharmacokinetic(s)
PKS	pharmacokinetic set
PFS	progression-free survival
PPS	per-protocol set
PR	partial response
PT	preferred term
PTEN	phosphatase and tensin homolog
Q2W	every 2 weeks
QTcF	QT interval corrected for heart rate using Fridericia's formula
RECIST	Response Evaluation Criteria in Solid Tumors
RP2D-F	recommended Phase 2 dose of UCB6114 when used in combination with mFOLFOX6
SAE	serious adverse event

SAP	statistical analysis plan
SD	stable disease
SDTM	Study Data Tabulation Model
SFU	safety follow-up
SI	International System of Units
SMAD4	mothers against decapentaplegic homolog 4
SMC	Safety Monitoring Committee
SoC	standard of care
SOC	system organ class
SS	safety analysis set
SSC	Study Steering Committee
TEAE	treatment-emergent adverse event
TEMA	treatment-emergent markedly abnormal
TFL	Table, Figure and Listing
TNM	TNM Classification of Malignant Tumors
TPS	tumor proportion score
UK	United Kingdom
ULN	upper limit of normal
US	United States
WHODD	World Health Organization Drug Dictionary

1. INTRODUCTION

The purpose of this statistical analysis plan (SAP) is to provide all information that is necessary to perform the required statistical analysis of the dose escalation (combination therapy) module (Part C) of study ONC001. It also describes the summary tables, figures and listings (TFLs) to be generated for Part C according to

Protocol amendment 6, dated 26 June 2023;

Electronic case report form (eCRF) (Clinical Data Management System [CDMS] postproduction change [CPPC] #14, version 23.0, dated 14 April 2023);

UCB's standards for TFL shells version 2023Q1;

Part A TFL shells, final version 2.4, dated 04 July 2023 (under development);

Part B and C Mocks draft version 1.3, dated 13 March 2023 (under development);

Part A, B and C List of TFLs (LoT) draft version 1.2, dated 04 July 2023 (under development);

UCB's Derivation of Efficacy Endpoints document, version 0.6, dated 21 January 2022.

Unless specified in the sections below, Part C of the study will be analyzed as described in the most recent version of the protocol. If a future protocol amendment necessitates a substantial change to the analysis of the Part C study data, this SAP will be amended accordingly. In addition, if the methodology for the analysis of key study endpoints must be modified or updated prior to the final database lock for Part C of this study, a SAP amendment will be required. Protocol amendments that do not affect the statistical analysis will not necessitate an amendment to the SAP. If, after database lock, additional analyses are required to supplement the planned analyses described in this SAP, these changes will be described in the clinical study report (CSR) together with the associated rationale.

Note that there may be a number of data cut-offs defined prior to the final database lock for Part C due to the regulatory safety reporting requirements for this study.

The content of this SAP is compatible with the International Council for Harmonization (ICH)/Food and Drug Administration (FDA) E9 Guidance (ICH-E9).

UCB is the Sponsor and ICON PLC is the contract research organization (CRO) for this study.

2. PROTOCOL SUMMARY

2.1 Study objectives

2.1.1 Primary objective

The primary objective of Part C (dose escalation module) of this study is to characterize the safety profile of UCB6114 administered in combination with oxaliplatin, leucovorin, and 5-fluorouracil (administered as mFOLFOX6 regimen) as standard of care (SoC) therapy in participants with locally advanced or metastatic colorectal adenocarcinoma, gastric adenocarcinoma, and adenocarcinoma of the gastroesophageal junction.

2.1.2 Secondary objective

The secondary objective of Part C of this study is to characterize the pharmacokinetics (PK) of UCB6114 administered in combination with mFOLFOX6 SoC regimen in participants with locally advanced or metastatic colorectal adenocarcinoma, gastric adenocarcinoma, and adenocarcinoma of the gastroesophageal junction.

2.1.3 Exploratory/Tertiary objectives

The exploratory/tertiary objectives of Part C of this study are:

- To document any antitumor activity observed with UCB6114 administered in combination with mFOLFOX6 SoC regimen according to relevant Response Evaluation Criteria in Solid Tumors (RECIST) criteria;
- To explore pharmacodynamics (PD) biomarkers of UCB6114 administered in combination with mFOLFOX6 SoC regimen;
- To evaluate the immunogenicity of UCB6114 administered in combination with mFOLFOX6 SoC regimen.

2.2 Study endpoints

2.2.1 Safety endpoints

2.2.1.1 Primary safety endpoints

The primary safety endpoints for Part C of this study are the incidence and severity of treatment-emergent adverse events (TEAEs) (including serious adverse events [SAEs]) from the first dose of UCB6114 on Day 1 of Cycle 1 to the Safety Follow-up (SFU) visit, and the incidence of dose limiting toxicities (DLTs) from the first dose of UCB6114 on Day 1 of Cycle 1 to the end of the DLT Observation Period (Day 28 of Cycle 1).

2.2.1.2 Other safety endpoints

The following other safety data will be assessed during Part C of the study to further support the characterization of the safety profile of UCB6114 administered in combination with mFOLFOX6 regimen:

- Clinical laboratory data (hematology, serum chemistry, coagulation and urinalysis);
- Vital signs (systolic and diastolic blood pressure, pulse rate, respiratory rate, and body temperature);
- 12-lead electrocardiogram (ECG);
- Echocardiogram (left ventricular ejection fraction [LVEF]);
- Eastern Cooperative Oncology Group (ECOG) performance status;
- Physical examination.

2.2.2 Pharmacokinetic and pharmacodynamic endpoints

2.2.2.1 Secondary pharmacokinetic endpoint

The secondary PK endpoint in Part C is the UCB6114 concentration by scheduled assessment for each UCB6114 dose level.

2.2.2.2 Exploratory pharmacokinetic endpoints

[redacted] will be exploratory PK endpoints in Part C.

2.2.2.3 Exploratory pharmacodynamic endpoints

The following PD endpoints will be assessed in Part C and reported separately outside of the CSR:

- Change in protein marker levels in blood by scheduled assessment and UCB6114 dose level;
- Change in circulating tumor deoxyribonucleic acid (ctDNA) levels in blood by scheduled assessment and UCB6114 dose level.

2.2.2.4 Exploratory immunogenicity endpoints

Immunogenicity in Part C will be explored using anti-drug (UCB6114) antibody (ADA) sample status and participant classification, and changes in titer over time. Potential relationships between ADA and PK, PD, anti-tumor activity and safety may also be explored but these analyses will be reported separately outside of the CSR.

2.2.3 Efficacy endpoints

2.2.3.1 Exploratory antitumor activity endpoints

Antitumor activity in Part C will be explored using the following endpoints:

- Objective tumor response rate (ORR);
- Disease control rate (DCR);
- Duration of antitumor response (DOR);
- Progression-free survival (PFS);
- Overall survival (OS).

2.2.3.2 Other exploratory efficacy endpoint

To further explore efficacy in Part C of the study, changes from Baseline in the ECOG performance status scale will be assessed.

2.3 Study design and conduct

Study ONC001 is a multicenter, nonrandomized, open-label, Phase 1/2 study evaluating the safety, PK, efficacy (as assessed by antitumor activity), PD, biomarkers, and immunogenicity (ADA activity) of intravenous (iv) UCB6114 as monotherapy and in combination with selected SoC regimens in study participants with advanced solid tumors.

The study has a modular design including up to 3 dose escalation modules (Parts A, B, and C), 1 dose adaptation module (Part A1), and up to 4 dose expansion modules (Parts D, E, F, and G). Depending on emerging data, not all modules may open. This SAP is focused only on the

ascending dose escalation module of the study evaluating UCB6114 in combination with mFOLFOX6 SoC regimen (Part C).

Part C consists of a Screening Period (28 days), a Treatment Period (consisting of 28-day cycles), a SFU visit (approximately 30 days after the last dose of UCB6114), and a Final Visit (approximately 3 months after the last dose of UCB6114).

In Part C, eligible participants with unresectable locally advanced or metastatic colorectal adenocarcinoma, gastric adenocarcinoma, or adenocarcinoma of the gastroesophageal junction will receive UCB6114 as an iv infusion in combination with mFOLFOX6 chemotherapy. During the Treatment Period, UCB6114 will be administered as an iv infusion every 2 weeks (Q2W) followed by iv oxaliplatin, leucovorin, and 5-fluorouracil Q2W on a 28-day cycle. Modified FOLFOX 6 (mFOLFOX6) will be administered at the recommended SoC dose: oxaliplatin 85mg/m^2 iv infusion on Day 1, leucovorin 400mg/m^2 iv infusion on Day 1, 5-fluorouracil 400mg/m^2 iv bolus on Day 1, followed by 5-fluorouracil 1200mg/m^2/day continuous infusion on Days 1 and 2 (2400mg/m^2 over 46 hours). The starting dose and schedule of UCB6114 will depend on the dose level evaluated in Cohort 3 of Part A (anticipated to be 500mg Q2W iv), the emerging safety profile of UCB6114 monotherapy, and any predicted overlapping toxicities with mFOLFOX6. Up to 3 dose levels (anticipated to be 500mg, 1000mg, and 2000mg administered Q2W iv) will be explored and up to 27 participants may be enrolled. Dose escalation decisions in this module will be guided by a model-based estimation of the probability of DLT in Cycle 1.

Part C will be undertaken using the modified toxicity probability interval (mTPI) method. The mTPI design uses a Bayesian decision framework to inform dose-escalation and dose de-escalation decisions. A target DLT rate of 25% with an equivalence interval (20% to 30%) will be used to estimate the maximum tolerated dose (MTD) of combined regimen during dose escalation. For all UCB6114 dose levels, enrolled participants will be treated in cohorts of 2 to 4 participants (target of 3), who can be treated in parallel. Each UCB6114 dose level may have more than one cohort and will have a minimum of 3 and maximum of 9 evaluable participants. For further detail on the mTPI method, the calculated model-based dose-escalation/dose de-escalation decisions to help inform the Safety Monitoring Committee (SMC)'s decision, and the determination of the MTD, please refer to Section 4.1.3.2.2 of the protocol. Detail on the operating characteristics for the mTPI design is included in Section 2.4 below.

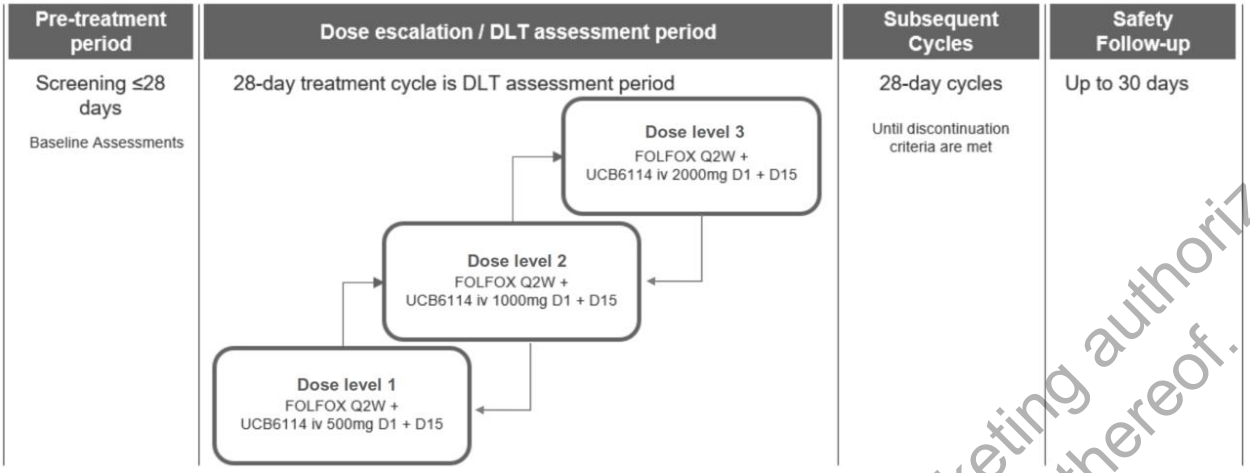
The planned duration of UCB6114 in Part C is 2 cycles. Participants may remain on study for additional cycles if they are receiving therapeutic benefit or until they fulfill one of the criteria for study discontinuation. Participants will continue treatment until disease progression, unmanageable toxicity, or withdrawal of consent. Upon discontinuation of treatment, participants will be referred to appropriate follow-up care per the investigator's judgement.

From Part C, a recommended Phase 2 dose for UCB6114 in combination with mFOLFOX6 (RP2D-F) will be determined based upon the totality of information, including the safety profile, PK data, PD biomarker data, and available antitumor activity.

Part C of the study is planned to be conducted at study sites in the United Kingdom (UK) and United States (US).

A schematic diagram of Part C of the study is provided in Figure 2-1.

Figure 2-1: Study Schematic for Part C



D=Day; DLT=dose-limiting toxicity; mFOLFOX6=leucovorin 400mg/m^2 on Day 1, 5-fluorouracil 400mg/m^2 on Day 1 + 1200mg/m^2/day on Day 1 and Day 2, and oxaliplatin 85mg/m^2 on Day 1; iv=intravenous; Q2W=every 2 weeks. mTPI= modified toxicity probability interval
Notes: A dose level may be given in more than 1 cohort
Escalation to the next dose level or de-escalation to the previous dose level will be guided by the mTPI algorithm.

A Study Steering Committee (SSC) will be implemented prior to the start of Part C. Part C of ONC001 is planned to be initiated after all participants in Cohort 3 of Part A have completed the 28-day DLT assessment period and after consultation with the SMC , the when the SCC provided a recommendation to dose escalate to the next protocol-defined level in Part A of the study. The SSC members will include the coordinating investigator, supporting co-investigators, and clinical experts not involved in the study. The medical, scientific, and clinical study expertise of the SSC will assist the Sponsor in identifying and resolving any study related issues, such as study design, study implementation and conduct, and data analysis and reporting.

During the Treatment Period, UCB6114 will be administered as an iv infusion Q2W followed by iv oxaliplatin, leucovorin, and 5-fluorouracil (FOLFOX) Q2W on a 28-day cycle. Modified FOLFOX 6 (mFOLFOX6) will be administered at the recommended standard of care dose: oxaliplatin 85mg/m^2 iv infusion on Day 1, leucovorin 400mg/m^2 iv infusion on Day 1, 5-fluorouracil 400mg/m^2 iv bolus on Day 1, followed by 5-fluorouracil 1200mg/m2/day continuous infusion on Days 1 and 2 (2400mg/m^2 over 46 hours). The starting dose of UCB6114 in Part C will depend on the dose level evaluated in Cohort 3 of Part A (anticipated to be 500mg Q2W iv), and the emerging safety profile of UCB6114 monotherapy, including any overlapping toxicity with the mFOLFOX6 regimen.

It is expected that up to 3 dose levels of UCB6114 will be explored in combination with the mFOLFOX6 SoC regimen. However, additional dose levels may be added based on emerging data and recommendations of the SMC. Dose escalation steps are currently planned at a maximum of 2-fold. Escalating dose levels in Part C will not exceed a dose level tested and considered safe by the SMC to allow dose escalation in monotherapy (Part A).

Eligible participants who withdraw from the study before receiving study treatment will be replaced. Participants who fail to receive the second planned dose of UCB6114 within 7 days of

the scheduled administration day during the 28-day DLT Observation Period for reasons not related to toxicity will be replaced by a new participant in that cohort. Safety data for replaced participants will be included in the data listings and in the summary tables, as applicable.

2.4 Determination of sample size

No formal statistical sample size calculation has been performed for the dose escalation modules in study ONC001.

The number of participants likely to be enrolled in Part C depends on how many dose levels are needed to define the RP2D-F for combination therapy. In Part C, up to 27 eligible participants will be enrolled. It is expected that up to 3 dose levels of UCB6114 will be explored in combination with the mFOLFOX6 dosing regimen, respectively. However, additional dose levels may be added based on emerging data and recommendations of the SMC.

Between 3 and 9 participants are expected to be enrolled for each dose level of UCB6114 depending on the observed toxicity/observation of DLTs. An administrative decision to stop enrolling into Part C may be made by the Sponsor at any time. "Dose level" refers to a particular UCB6114 dose, that can be given to one or more cohorts, not necessarily consecutive.

The operating characteristics of the mTPI design were evaluated using a simulation approach under four scenarios (see Table 2-1) and based on no DLTs observed in the first 2 cohorts in Part A monotherapy treatment (UCB6114 100mg and 250mg). The results of this evaluation can be seen in Table 2-2.

Table 2–1: Scenarios used for evaluating the operating characteristics of the mTPI design. Orange cells indicate the correct decision assuming a maximum tolerated toxicity of 25% (equivalence limits 20%, 30%)

	Probability of a DLT			
UCB6114 Dose	**Scenario 1**	**Scenario 2**	**Scenario 3**	**Scenario 4**
Dose 1 (500 mg)	0.05	0.05	0.15	0.25
Dose 2 (1000 mg)	0.05	0.15	0.25	0.35
Dose 3 (2000 mg)	0.05	0.25	0.35	0.50

Table 2–2: Evaluation of the operating characteristics of the mTPI design with a target maximum tolerated toxicity of 25%, using 5000 simulated trials for each scenario. Orange cells indicate the correct decision.

	Scenario 1	**Scenario 2**	**Scenario 3**	**Scenario 4**
Final UCB6114 Dose Selected	**% of Simulations (Number of Simulations)**			
Dose 1 (500 mg)	3.9% (196)	5.2% (262)	31.6% (1580)	53.3% (2666)

Dose 2 (1000 mg)	3.9% (195)	35.1% (1755)	40% (1999)	26.7% (1337)
Dose 3 (2000 mg)	91.4% (4571)	58.9% (2947)	21.6% (1080)	3.8% (191)
Overly Toxic at First Cohort	0.8% (38)	0.7% (36)	6.7% (336)	15.2% (758)
Overly Toxic after First Cohort	0	0	0.1% (5)	1% (48)

3. DATA ANALYSIS CONSIDERATIONS

3.1 General presentation of summaries and analyses

All TFLs will be produced by ICON PLC using SAS® Version 9.4 or higher (SAS Institute, Cary, North Carolina, USA). ICON PLC will also produce the analysis datasets which will adhere to the Clinical Data Interchange Standards Consortium (CDISC) guidance documents for Analysis Data Model (ADaM) and follow the Sponsor's interpretation. General statistical and reporting conventions will follow the current UCB Global Conventions Document Version 1.1.

Data will be summarized by UCB6114 dose level (treatment group), visit and timepoint, as applicable. All relevant reported and derived data will be listed and will be presented by treatment group, study participant and visit, as applicable.

Categorical variables will be summarized using frequency counts and percentages. Unless otherwise stated, the denominator for the percentages will be based on the number of participants in the respective analysis set, treatment group, visit and timepoint (as applicable) with non-missing data.

When reporting frequency counts and percentages, the following rules apply:

- For categories where all participants fulfill certain criteria, the percentage value will be displayed as 100;
- For categories where zero participants fulfill certain criteria, there will be no percentage displayed;
- All other percentage displays will use 1 decimal place.

Summary statistics will be presented for continuous variables including number of participants (n), arithmetic mean, standard deviation, median, minimum and maximum. 95% confidence intervals (CIs) for the arithmetic mean may also be included depending on the variable and where stated in the SAP. Geometric mean (geoMean), geometric coefficient of variation (geoCV) and 95% CI for the geoMean will also be presented in the summaries of UCB6114 concentration data. In all relevant outputs the 95% confidence limits will be restricted to the possible values that the variable can take.

When reporting descriptive statistics for data other than UCB6114 concentration data, the following rules will apply:

- n will be an integer;
- Mean (arithmetic and geometric), standard deviation, median and quartiles will use 1 decimal place more, or 1 significant figure more – depending on the reporting format of

the original data – than the original data. Original data may be data as reported directly onto the eCRF or summary data based on data reported onto the eCRF (e.g. mean of triplicates or percentage change from Baseline);

- Confidence intervals will be presented to the same number of decimal places as the value around which the CI is constructed;
- Minimum and maximum will be reported using the same number of decimal places or significant figures as the original value;
- A minimum of 3 values are required to calculate summary statistics. If only 2 values are available, then these should be presented as the minimum and maximum with other summary statistics reported as missing ("- ");
- If no participants have data at a given timepoint, then only n=0 will be presented;
- Percentage change from Baseline values will be calculated and displayed to 1 decimal place in the listings. In the summaries, where applicable, the mean, standard deviation and median percentage change from Baseline values will be presented to 2 decimal places and the minimum and maximum values presented to 1 decimal place.

When reporting individual UCB6114 concentration data in listings and figures, and presenting summary statistics in tables, the following rules will apply:

- UCB6114 concentration data should be reported in the listings to the same level of precision as received from the bioanalytical laboratory;
- Missing data should be reported as 'NV' (no value) in the listings;
- Concentrations below the lower limit of quantification (LLOQ) should be reported as BLQ (below the limit of quantification) in the listings;
- BLQ values prior to C_{max} should be set to 0 for purposes of plotting a figure (to capture lag-time);
- Actual sampling times will be used in the spaghetti plots of individual PK concentrations over time, and nominal sampling times will be used in the summaries of geoMean concentrations over time;
- UCB6114 concentration data should be plotted on both linear and semi-logarithmic scales;
- To calculate summary statistics, BLQ values should be set to half the LLOQ value and missing values should be excluded;
- When the total number of BLQ and missing values exceeds one third of the total then only minimum and maximum should be reported for this timepoint. Other summary statistics should be reported as missing ("-"). The minimum should be reported as BLQ;
- When the mean value includes one or more replaced BLQ values then a footnote should be included to say "contains one or more BLQ values replaced by half the LLOQ value";
- A minimum of 3 values are required to calculate summary statistics. If only 2 values are available, then these should be presented as the minimum and maximum with other summary statistics reported as missing ("- ");
- If no participants have data at a given timepoint, then only n=0 will be presented;

- Summary statistics for UCB6114 concentration data will be reported to the same level of precision as the individual data for the minimum and maximum, and to 1 additional decimal place or 1 additional significant figure – depending on the reporting format of the original data with a maximum of 3 significant figures - for the mean (arithmetic and geometric), median and standard deviation. The 95% CI for the geoMean will use the same number of decimal places or significant figures as the geoMean. It will be left blank if the geoCV is 0;
- Geometric coefficient of variation will be reported as a percentage to 1 decimal place. The geoCV will be calculated using the following formula where SD is the standard deviation from the log-transformed da data:

$$GeoCV(\%) = \sqrt{\exp SD^2 - 1} \times 100$$

When reporting PK parameters in listings and figures, and presenting summary statistics in tables, the following rules will apply:

[redacted]

3.2 General study level definitions

3.2.1 First and last dose of study treatment

For each participant the start of study treatment is defined as the date and time of the first dose of UCB6114. This will be considered as the starting point of the combination therapy.

Similarly, for each participant, the last dose of study treatment will be the date of the last dose of UCB6114.

3.2.2 Relative day and time

For each participant, the relative day of an event or assessment will be derived using the earliest date of their first dose of UCB6114 as reference.

Relative days for an event or assessment occurring before the date of first dose are calculated as follows:

Relative Day = Event/Assessment Date - Date of First Dose of UCB6114

The relative day for an event or assessment occurring on the date of first dose is 1. The relative day for an event or assessment occurring on or after the first dose to the date of the last dose of UCB6114 will be calculated as follows:

Relative Day = (Event/Assessment Date - Date of First Dose of UCB6114) + 1

For events or assessments occurring after the date of the last dose of UCB6114, relative day will be prefixed with '+' in the data listings and will be calculated as follows:

Relative Day = Event/Assessment Date – Date of Last Dose of UCB6114

There is no relative Day 0. Relative day will not be calculated in cases where dates are partial and should be presented as "--" in the relevant data listing.

Relative time of TEAEs recorded on, but not limited to, the day of UCB6114 infusion (Days 1 and 15 of each cycle) will be derived in minutes as follows using the infusion start time as reference:

Relative Time of TEAE = Onset Time of TEAE – Start Time of UCB6114 Infusion

Relative times of PK and PD sampling will be derived in hours using the end of infusion times on the day of UCB6114 dosing as reference, i.e. on Days 1 and 15 of each cycle:

Relative Sampling Time = Sampling Time – End Time of UCB6114 Infusion

3.2.3 Study periods

Part C of the study will consist of the following study periods:

- Screening Period – up to 28 days;
- Treatment Period – Successive 28-day cycles of study treatment (UCB6114 will be administered as an iv Q2W dose on Day 1 and Day 15 of each cycle followed by iv oxaliplatin, leucovorin, and 5-fluorouracil (mFOLFOX6) Q2W on a 28-day cycle. Modified FOLFOX 6 will be administered at the recommended SoC dose: oxaliplatin 85mg/m^2 iv infusion on Day 1, leucovorin 400mg/m^2 iv infusion on Day 1, 5-fluorouracil 400mg/m^2 iv bolus on Day 1, followed by 5-fluorouracil 1200mg/m^2/day continuous infusion on Days 1 and 2 (2400mg/m^2 over 46 hours), continuing until disease progression, unmanageable toxicity, or participant withdrawal. Within the first cycle of the Treatment Period, a 28-day DLT Observation Period is defined to determine safety events for dose escalation decisions using mTPI;
- Safety Follow-up Period – up to 30 days after the last dose of UCB6114.

There will be a further extended follow-up period, up to 3 months after the last dose of UCB6114, at which time the Final Visit will be performed.

For each participant, the end of the Treatment Period is defined by the date of their last dose of UCB6114.

The end of Part C of the study is defined by the date of the Final Visit for the last participant (3 months after the last participant's last dose of UCB6114), or the date of the SFU visit, if they discontinue prior to attending the Final Visit, or their last contact date if they discontinue early from the study without attending the SFU visit.

3.2.4 Visits

Unless otherwise specified, in the TFLs, visits will be labelled as follows (as applicable) using timepoints as recorded in the database:

Screening
Baseline
Cycle 1, Day X
Cycle 2, Day X
Cycle 3, Day X
Cycle 4, Day X
Cycle X, Day X
Etc.
SFU
Final Visit

3.3 Definition of Baseline values

Baseline in Part C will be the last available value prior to the first dose of UCB6114. Both scheduled and unscheduled values, as well as any repeated values, should be used when defining Baseline.

Measurement-specific Baseline definitions are presented in Table 3-1.

Table 3-1: Definition of Baseline

Measurement	Definition of Baseline
Echocardiogram (LVEF) Tumor assessments (antitumor activity)	Screening value
12-lead ECG Physical examination and weight Vital signs Clinical laboratory data ECOG performance status	Predose value obtained on Cycle 1, Day 1, or, if missing, Screening value
Serum and urinary markers of bone turnover Circulating gremlin-1 (cGremlin-1) Immunogenicity (ADA)	Predose sample value obtained on Cycle 1, Day 1

ADA=anti-drug (UCB6114) antibody; ECG=electrocardiogram; ECOG=Eastern Cooperative Oncology Group; LVEF=left ventricular ejection fraction.

3.4 Protocol deviations

Per ICH definition, important protocol deviations (IPDs) are a subset of protocol deviations that may significantly impact the completeness, accuracy, and/or reliability of the study data or that

may significantly affect a participant's rights, safety, or well-being. The criteria for identifying potentially important protocol deviations will be defined within the IPD specifications document.

For Part C of this study, IPDs will be categorized as follows:

- Inclusion/exclusion criteria deviations
- Incorrect treatment or dose administered
- Procedural non-compliance
- Prohibited concomitant medication use (see Section 6.5.6 of the protocol)
- Withdrawal criteria deviation

All protocol deviations will be reviewed as part of the ongoing data cleaning process and Data Evaluation Meetings (DEMs), and decisions made on whether they should be considered important or not, and whether they warrant a participant's exclusion from an analysis set, or partial exclusion from an analysis due to being an IPD (e.g. prohibited concomitant medication use). Multiple DEMs will be scheduled prior to the final database lock for Part C, in line with regulatory safety reporting requirements, with the final one held after all data have been verified/coded/entered into the database.

More specifically, participants who have IPDs relating to dosing of UCB6114 (e.g. interrupted, discontinued and missed infusion, incomplete/incorrect dose administered, additional dose received, or infusions administered outside of the defined visit window) will be reviewed at the DEM for potential exclusion of UCB6114 concentration data from the by-visit summaries at an individual visit or from the visit at which the dosing deviation was observed onwards.

Any protocol deviations that are considered related to coronavirus disease 2019 (COVID-19) will be reviewed on an ongoing basis in case they collectively or individually give reason to consider a protocol amendment (e.g. study design changes or changes to primary analysis methods etc.). To facilitate this ongoing review, protocol deviations will be categorized as 'related to COVID-19' within the Clinical Trial Management System (CTMS) (ICOTrial). The COVID-19-related IPDs will then be listed separately for review and discussion at the DEMs.

3.5 Analysis sets

3.5.1 Enrolled Set (ES)

The Enrolled Set (ES) consists of all study participants who sign the Informed Consent Form.

This analysis set includes screening failures and will be used for the summary of disposition of study participants and for selected data listings (which will include all available data for the screening failures).

3.5.2 Safety Analysis Set (SS)

The Safety Analysis Set (SS) consists of all study participants who receive at least 1 full or partial dose of UCB6114.

This analysis set will be used for the reporting of demographic, baseline characteristics, safety and immunogenicity data. All summaries of the exploratory antitumor activity endpoints will be repeated for the SS as a sensitivity analysis.

3.5.3 Per-protocol Set (PPS)

The Per-protocol Set (PPS) consists of all study participants in the SS who do not have IPDs that may substantially affect antitumor activity. Potential exclusions will be reviewed at the DEMs and a final determination of the composition of this analysis set will be made prior to the final database lock for Part C.

The PPS will be the primary analysis set for the analysis of the exploratory antitumor activity endpoints.

3.5.4 Pharmacokinetic Set (PKS)

The Pharmacokinetic Set (PKS) consists of all study participants in the SS who have at least 1 evaluable postdose UCB6114 concentration sample (i.e. a sample which is above the lower limit of quantitation and for which the date and time of the sample and prior date and time of dosing are known). Additional participants or specific samples may be excluded from the PKS at the discretion of the Advanced Modeling and Simulation scientist/Quantitative Clinical Pharmacologist at UCB.

Pharmacokinetic analysis will be performed for the PKS.

3.5.5 Anti-drug Antibody Set (ADAS)

The Anti-drug Antibody Set (ADAS) consists of all study participants in the SS who have at least 1 evaluable ADA assessment.

Immunogenicity analyses will be performed for the ADAS.

3.5.6 Pharmacodynamic Set (PDS)

The Pharmacodynamic Set (PDS) consists of all study participants in the SS who have at least 1 evaluable PD assessment (where appropriate, the sample should be above the lower limit of quantitation and the date and time of the sample should be known).

Pharmacodynamic analysis will be performed for the PDS.

3.5.7 DLT Evaluable Set (DES)

The DLT Evaluable Set (DES) will include all study participants who, during the DLT assessment period receive the planned dose of UCB6114 and at least 80% of the planned dose of mFOLFOX6 or stopped treatment because of a DLT.

The DES will be used by the SMC for all dose escalation/de-escalation decision making.

3.6 Treatment assignment and treatment groups

In Part C, it is planned that study participants will be dosed with UCB6114 Q2W at ascending dose levels in combination with mFOLFOX6 SoC regimen. Treatment groups will be defined by each UCB6114 dose level and will be presented in ascending order and labelled in the TFLs as illustrated in Table 3-2.

Table 3-2: Treatment Group Labels

Cohort/UCB6114 Dose Level	Planned Treatment Group Label
Dose Level 1 (any cohort)	UCB6114 500mg + mFOLFOX6
Dose Level 2 (any cohort)	UCB6114 1000mg + mFOLFOX6
Dose Level 3 (any cohort)	UCB6114 2000mg + mFOLFOX6

UCB6114 dose level will be referred to as 'treatment group' from this point onwards in the SAP and in the TFLs.

Note that the actual dose levels and treatment group labels may change depending on whether MTD condition is met. Further, additional dose levels may be included based on emerging data.

3.7 Center pooling strategy

Each study site will contribute to the summaries of data from Part C according to the number of evaluable participants recruited; no separate summaries for each site will be presented.

3.8 Coding dictionaries

Adverse events and medical history will be coded by UCB, using the latest available version of the Medical Dictionary for Regulatory Activities (MedDRA®) (Version 25.1 or higher). The National Cancer Institute Common Terminology Criteria for AEs (Version 5.0) (NCI CTCAE) dictionary will also be used by the investigator to assign CTCAE severity grades to each adverse event (AE) and will be merged with the clinical database to define a CTCAE code and term to be used in the summaries of TEAEs by maximum CTCAE severity grade.

Medications (including prior anti-cancer systemic therapies) will be coded according to the World Health Organization Drug Dictionary (WHODD) (Version SEP/2020). Medical procedures will not be coded.

The versions of the coding dictionaries used will be displayed in the relevant TFLs.

3.9 Changes to protocol-defined analyses

The following changes to the protocol have been incorporated into the SAP:

- Other safety data have not been defined as safety endpoints in the protocol, e.g. clinical laboratory data, vital signs, ECG, echocardiogram, ECOG performance status and physical examination. These have been listed in Section 2.2.1 of the SAP as 'other safety endpoints' to support the characterization of the safety profile of UCB6114 and to provide supporting evidence of any measurements that are deemed abnormal and clinically significant and reported as an AE.
- ECOG performance status is defined as an efficacy assessment in Section 9.6.2 of the protocol, however, it will also be assessed from a safety perspective in Part C. The SAP therefore includes ECOG performance status as both a safety endpoint (Section 2.2.1) and an exploratory efficacy endpoint (changes from Baseline during Part C in Section 2.2.3).

- Section 9.4.2.1 of the protocol does not explicitly define the analysis set to be used for the antitumor activity endpoints but defines the denominator as the number of treated participants, which matches the protocol definition for the SS in Section 9.1 of the protocol. The SAP has been written to clarify that the PPS will be the primary analysis set for the analysis of the antitumor activity endpoints (Section 3.5.3) and that the SS will be used for the sensitivity analysis (Section 3.5.2).

4. STATISTICAL/ANALYTICAL ISSUES

4.1 Adjustments for covariates

Not applicable.

4.2 Handling of dropouts or missing data

There will be no imputation of missing data unless otherwise stated in the sections below.

4.2.1 Pharmacokinetics and pharmacodynamics

The reporting and handling of missing values and values that are BLQ in the TFLs is described in Section 3.1. Zero values will be assumed at the predose timepoint on Day 1 of Cycle 1.

4.2.2 Safety laboratory data

The rules for handling values that are BLQ in the safety laboratory data will be the same as those described for PK data in Section 3.1. Any values above the limit of quantification (ALQ) will be assigned as the value of upper limit of quantification.

4.2.3 Dates and times

Partial dates may be imputed for the following reasons:

- Classification of adverse events (AEs) as treatment-emergent;
- Classification of medications recorded on the concomitant medications log as prior or concomitant;
- Calculation of time since initial diagnosis, time since completion of most recent line of anti-cancer therapy and time since progression/relapse on most recent line of anti-cancer therapy.

Imputed dates will not be shown in the listings; all dates will be displayed as reported in the database.

The following rules will be applied for partial onset/start dates:

- If only the month and year are specified and the month and year of the first dose of UCB6114 is not the same as the month and year of the start date then the 1st of the month will be used, or the date of the Screening visit if this is later (if the latter imputation results in an end date that is earlier than the start date, then the 1st of the month will be used);
- If only the month and year are specified and the month and year of the first dose of UCB6114 is the same as the month and year of the start date, then the date of the first

dose of UCB6114 will be used. If this results in an imputed start date that is after the specified end date, then the 1st of the month will be used, or the date of Screening if this is later (if the latter imputation results in an end date that is earlier than the start date, then the 1st of the month will be used). If the imputed date is the same date as the date of the first dose of UCB6114 then, for AEs, the event will be regarded as treatment-emergent. For medications, the medication will be classified as concomitant;

- If only the year is specified, and the year of the first dose of UCB6114 is not the same as the year of the start date then January 01 will be used;
- If only the year is specified, and the year of the first dose of UCB6114 is the same as the year of the start date, then the date of the first dose of UCB6114 will be used. If this results in an imputed start date that is after the specified end date, then January 01, or the date of the Screening visit if this is later will be used (if the latter imputation results in an end date that is earlier than the start date, then January 01 will be used). If the imputed date is the date of the first dose of UCB6114 then, for AEs, the event will be regarded as treatment-emergent. For medications, the medication will be classified as concomitant;
- If the onset/start date is completely missing then the onset/start date will be imputed to the date of first dose of UCB6114 and therefore, for AEs, the event will be regarded as treatment-emergent and, for medications, the medication will be classified as concomitant.

The following rules will be applied to partial end/stop dates:

- If only the month and year are specified, then the last day of the month will be used;
- If only the year is specified, then December 31 of the known year will be used;
- If the stop date is completely unknown, the stop date will not be imputed.

Note that the start date or stop date of a prior medication (partial or otherwise) should not be imputed past the Screening date - 1.

In addition to onset and stop dates, the onset and end times of AEs occurring on the day of UCB6114 infusion will be collected on the eCRF. Onset and end times may also be recorded for other AEs that do not occur on the same day as the UCB6114 infusion. The duration of AEs with onset and end times will be calculated in days and hours:minutes (hh:mm) as:

Duration of AE = End Date and Time – Onset Date and Time

In cases where only the onset and stop dates are recorded for an AE, the duration of an AE will be calculated in days as:

Duration of AE = (Stop Date – Onset Date) + 1

Note that for participants who have an AE which starts and stops on the same day, but with only a start time or only a stop time recorded, it will be assumed that their AE started from 00:00 (if no start time is recorded) and ended at 23:59 (if no stop time is recorded) on that day.

If the date of a participant's initial diagnosis is incomplete, it will be imputed to the most recent feasible date for the calculation of time since initial diagnosis as follows:

- If only the day is missing, it will be imputed to the last day of the known month;

- If the day and month are missing, it will be imputed to December 31 in the known year;
- If the date of initial diagnosis is completely missing, then time since initial diagnosis will not be calculated.

The above date imputation rules will be applied to partially missing stop dates of a participant's last prior anti-cancer systemic therapy as well as partially and completely missing dates of progression/relapse on last prior anti-cancer systemic therapy.

In cases where the stop date of a participant's last prior anti-cancer systemic therapy and/or a participant's date of progression on last line of prior anti-cancer systemic therapy is completely missing, the participant's Screening date - 1 will be used in the calculation of the time since completion of most recent line of prior anti-cancer systemic therapy and the time since progression/relapse on most recent line of prior anti-cancer systemic therapy, respectively. Note that partial dates will not be imputed as a participant's first dose of UCB6114 in the calculation of time since initial diagnosis, time since completion of most recent line of prior anti-cancer systemic therapy and time since progression/relapse on most recent line of prior anti-cancer systemic therapy.

4.2.4 Impact of COVID-19

The FDA and European Medicines Agency (EMA) have provided guidance (see references listed in Section 12) to help assure the safety of all trial participants, maintaining compliance with good clinical practice (GCP), and minimizing risks to trial integrity during the COVID-19 pandemic. At the time of writing this SAP, the impact of the pandemic is still evolving and regulators continue to clarify their position, and how to handle missing or delayed assessments resulting from the pandemic is part of the risk assessment of the impact of COVID-19 on trial integrity. For this purpose, the impact at a visit level will be assessed by data collected on a specific COVID-19 impact eCRF form and protocol deviations related to COVID-19. Due to the timing of the start-up of recruitment of participants into this study, the consequences for Part C are not expected to be significant and, as a result, no details on strategies for handling missing data are included in this version of the SAP. However, should the ongoing review of COVID-19-related protocol deviations suggest that the impact is more significant than expected, e.g. in the case of a new wave, the SAP may be updated to include further details of handling missing data and/or any sensitivity analyses required. Note that there are no guidelines regarding how much missing data is too much, and there is no proportion of missing data under which valid results and preservation of study power can be guaranteed. In accordance with the EMA guidance, an independent Data Monitoring Committee (DMC) may be convened to make an assessment regarding the scientific integrity of the study.

4.3 Handling of repeated and unscheduled measurements

All repeated and unscheduled measurements will be presented in the data listings, where applicable. Repeated measurements are defined as more than 1 measurement at the same timepoint. For example, the same laboratory parameters assessed twice using the same batch of blood samples due to issues with the first assessment. The following general rules will apply to all repeated and unscheduled measurements:

- Unscheduled and repeated measurements prior to the first dose of UCB6114 will be used in the determination of Baseline and hence in the calculation of summary statistics at Baseline;
- Unscheduled and repeated measurements performed after the first dose of UCB6114 will not be included in the calculation of change from Baseline, summary measures such as minimum, maximum, average and last post-Baseline value calculated for the summaries of laboratory data (see Section 8.3), vital signs (see Section 8.4.1) and 12-lead ECG (see Section 8.4.2), or summary statistics, i.e. only the scheduled measurements will be used and summarized. Similarly, only scheduled visits will be used in the summaries of shifts from Baseline to the worst post-Baseline CTCAE severity grade for laboratory data (see Section 8.3).
- For the summaries of the investigator's overall tumor response assessment, protocol-defined windows will be applied to all post-Baseline tumor assessments (scheduled or unscheduled, but excluding tumor assessments performed at the SFU visit), as detailed in Section 10.1.2. Those tumor assessments which fall outside of the window will be considered as unscheduled assessments and not included in the summaries.
- Best overall response, DOR and PFS derivations will use data from all scheduled and unscheduled tumor assessments.
- All data from unscheduled visits will, however, be included on the relevant data listings.

4.4 Handling of measurements obtained for early withdrawals

Participants who withdraw early from the study for any reason will be asked to return to the clinic to complete the SFU visit. The SFU procedures performed at this visit are as shown in the Schedule of Activities in the protocol and will be summarized together with all other SFU visit data in the tables.

4.5 Interim analyses and data monitoring

No formal interim analyses are planned during Part C of this study.

A SSC will be implemented prior to the start of Part C. In consultation with the SMC, the SSC will recommend to the Sponsor the dose and dosing regimen to be taken forward for Part C. The SSC members will include the coordinating investigator, supporting co-investigators, and clinical experts not involved in the study. The medical, scientific, and clinical study expertise of the SSC will assist the Sponsor in identifying and resolving any study related issues, such as study design, study implementation and conduct, and data analysis and reporting.

The SMC already established for Part A of the study comprising investigators from UK sites participating in Part A and key Sponsor personnel, will continue as the SMC for Part B as long as they are actively enrolling study participants into the study. In addition, investigators from US sites who are actively enrolling participants into Part C of the study will also become members of the SMC for Part C.

Responsibilities of the SMC for Part C include:

- Review of safety data for study participants including review and provision of adjudication of individual DLTs, if needed;
- Review of available PK and PD biomarker data;
- Make dose escalation recommendations;
- Determination of the MTD, if applicable.

The SMC will convene after the last participant in a given cohort has completed the required 28-day DLT Observation Period. The SMC will decide whether to halt dose escalation, further expand the dose level to gain additional safety data, or determine the next dose level to be tested.

All data presented to the SMC will be cumulative in order that the members can review and discuss the data in its totality at the end of all completed cohorts, i.e. all safety information beyond Cycle 1 for all previous cohorts will be presented cumulatively for review during each subsequent SMC meeting.

In addition to the planned SMC data review meetings, the Sponsor and the SMC will have the ability to hold/request *ad hoc* meetings should they be deemed necessary (e.g. if safety concerns arise during Part C of the study and/or during other ongoing nonclinical and clinical studies).

4.6 Multicenter studies

Part C of this study is planned to be conducted at study sites in the UK and US. With the exception of participant disposition, no summaries will be presented by site.

4.7 Multiple comparisons/multiplicity

Not applicable.

4.8 Use of an efficacy subset of participants

The PPS will be used as the primary analysis set for the summaries of the exploratory antitumor activity endpoints in Part C.

4.9 Active-control studies intended to show equivalence

Not applicable.

4.10 Examination of subgroups

Not applicable.

5. STUDY POPULATION CHARACTERISTICS

5.1 Study participant disposition

The number of study participants who were screened for Part C of this study, the number and percentage of screen failures and the primary reasons for screen failure will be summarized for the ES. A listing of participants who did not meet the eligibility criteria for Part C will also be presented for the ES. In addition, the disposition of study participants screened and who received study treatment will be summarized by site. This table will include, for each site and overall, site

number, principal investigator name, the dates of the first participant in and the last participant out, the number of participants screened (ES), the number of screen failures, the number of participants who were treated (SS) and included in the PPS, PKS, ADAS and PDS. Disposition in each analysis set across all study sites will be summarized by treatment group.

The number of study participants who received study treatment and the primary reason for discontinuation of study treatment during Part C will be summarized by treatment group, together with the number and percentage of participants who continued participation in the study after discontinuation of study treatment (at subsequent scheduled visits and/or SFU visit and Final Visit). This summary will be based on the SS.

The number of study participants enrolled into Part C, who were screen failures as well as the number of eligible participants who were assigned to a study cohort but not treated will be presented for the ES. For those participants who did not receive study treatment, the reasons for early discontinuation from the study will be summarized.

Of those participants who received UCB6114, the number and percentage of participants who completed the study (i.e. participants who received at least 2 complete cycles of UCB6114 and attended the SFU visit), who received at least 2 complete cycles of UCB6114 but who did not attend the SFU visit and who discontinued early from Part C, together with the primary reasons for study discontinuation will be presented for all participants.

The number and percentage of participants who discontinued due to AEs will be summarized separately for all participants, based on the SS. This will be used for European Union Drug Regulating Authorities Clinical Trials (EudraCT) reporting.

The following study disposition tables will also be presented by gastric adenocarcinoma, adenocarcinoma of the gastroesophageal junction (Gastric/GEJ-Cancer) and colorectal adenocarcinoma (CRC) tumor type depending on the number of participants with specific tumor types.

- Disposition and Reasons for Discontinuation of Study Treatment;
- Disposition and Reasons for Discontinuation of Study Treatment;
- Discontinuation of the Study Due to AEs.

Visits impacted by COVID-19 will be listed for the ES. This listing will include, visit, visit date, relative day, impact category (e.g. visit performed out of window, visit performed by telephone, visit not done, missed study drug administration/dispensation, termination of study participation), relationship to COVID-19 (confirmed COVID-19 infection, suspected COVID-19 infection, general circumstances around COVID-19 or other) and a narrative for the event. The number and percentage of participants with visits impacted by COVID-19 will be presented by treatment group and by impact category. This summary will be presented for the different relationships to COVID-19. The denominator for the percentage calculations will be the number of participants in the SS.

In addition, the following listings will be presented:

- Study participant disposition (ES);
- Study treatment discontinuation (SS);

- Study discontinuation (ES);
- Visit dates (ES);
- Participant analysis sets and exclusions from analysis sets (ES)*.

*DES is not included in this listing as it is only relevant for the SMC, and not required for the CSR.

The listing of study participant disposition will include the date of informed consent, date and time of first and last dose of study treatments (UCB6114, mFOLFOX6 SoC regimen), date of early study discontinuation (if applicable) and primary reason for discontinuation.

Separate listings of UCB6114 and mFOLFOX6 study treatment discontinuation will include date and time of first and last dose of UBC6114 and individual oxaliplatin, leucovorin and 5-fluorouracil treatments, date of decision to discontinue study treatments and primary reason for discontinuation of each study treatment, date of clinical progression (if applicable), number of doses of study treatment received (based on 2 doses per cycle for UCB6114 and mFOLFOX6 SoC regimen), total dose of study treatment received across all cycles for UCB6114 and mFOLFOX6 SoC regimen, number of complete cycles of study treatment received, and whether or not the participant had continued participation in the study (at subsequent visits, the SFU visit or the Final Visit).

Note that a participant is deemed to have completed a full cycle of study treatment if they received the planned dose of UCB6114 on Days 1 and 15 of the cycle (i.e. the infusion was not permanently discontinued due to an AE or other reason such that less than the planned dose was received) and a decision was not made to discontinue UCB6114 up to and including Day 28 relative to Day 1 of the cycle. This will be derived based on a participant's last dose of UCB6114 and whether or not the participant attended the visit at which they were scheduled to receive their next dose of UCB6114. For example, if a participant received UCB6114 on Day 1 and Day 15 of Cycle 1 and attended the clinic for their UCB6114 infusion on Day 1 of Cycle 2 then the participant will be counted as having completed Cycle 1. If the participant did not attend Day 1 of a subsequent cycle, then it is likely that a decision was made to discontinue their UCB6114 treatment and/or the study. Therefore, the date that the decision was made to discontinue UCB6114 will be used to determine whether the participant completed a cycle of study treatment. If a decision was made to discontinue UCB6114 on >Day 28 relative to Day 1 of the particular cycle then the participant will be counted as having completed the cycle. For any interim deliveries at a data cut-off, if the participant did not attend Day 1 of their next cycle and there was no decision to discontinue UCB6114, then the latest date available for that participant should be used to determine whether they have completed a 28-day cycle.

Whether or not a participant has completed the study is defined as having received at least 2 complete cycles of UCB6114 and attended the SFU visit. The investigator will record a study participant's disposition status at study termination according to this definition of a 'completed' participant, however, a study completion flag will also be programmatically derived based on the relevant data on the database and the above rules for defining completion of a full cycle of UCB6114.

The listing of study discontinuation will include the primary reason for early study discontinuation, the number of cycles of UCB6114 received, and the total number of days on UCB6114.

5.2 Protocol deviations

Important protocol deviations will be identified and classified by the deviation types defined in the IPD specification document, as per Section 3.4.

A listing of all IPDs identified at the DEM will be presented for all study participants based on the SS and will include the deviation type and description. In addition, a listing of all protocol deviations related to COVID-19 (whether considered important or not) will be presented for the SS. The number and percentage of participants in the SS with IPDs will be summarized by treatment group and for all participants for each deviation type. The number and percentage of participants who were excluded from the PPS will also be presented. The denominator for the percentage calculations will be the number of participants in the SS. A summary will also be presented for all protocol deviations related to COVID-19, all IPDs related to COVID-19 and all IPDs related to COVID-19 leading to exclusion from the PPS.

6. DEMOGRAPHICS AND OTHER BASELINE CHARACTERISTICS

6.1 Demographics

A by-participant listing of demographics will be presented based on the ES. This will include the year of birth, age (as entered by investigator in the eCRF in years), sex, race, ethnicity, height (in cm), weight (in kg) and body mass index (BMI, in kg/m^2). Height will be the measurement obtained at the Screening visit and weight will be the last non-missing value prior to the first dose of study treatment.

The BMI will be derived in the database using the height and weight measurements recorded at the Screening visit and will be automatically reported to 1 decimal place on the eCRF.

All demographic characteristics (except for date of birth) will be summarized by treatment group and for all study participants based on the SS. The summary of age will include descriptive statistics and categorical summaries, the latter based on requirements for EudraCT and clinicaltrials.gov reporting. In addition, summaries will be presented by Gastric/GEJ-Cancer and CRC tumor type depending on the number of participants with specific tumor types.

For the EudraCT reporting, the categories will include:

- 18 to <65 years;
- 65 to <85 years.

For clinicaltrials.gov reporting, the categories will include:

- ≤18 years;
- 19 to <65 years;
- ≥65 years.

Childbearing potential and method of birth control will be listed for the ES.

6.2 Cancer history

All cancer history data for Part C participants will be listed for the ES. This listing will include date of initial diagnosis, tumor type, TNM Classification of Malignant Tumors (TNM) classifications and stage, Duke's score (participants with colorectal adenocarcinoma only), histological and cytological diagnosis details (as relevant), whether the participant had any metastases and associated anatomical location, and whether the participant had received any prior anti-cancer therapies (including the number of lines of any prior systemic therapies, prior radiation therapies and prior anti-cancer surgeries).

Time since initial diagnosis (calculated in months using date of Screening visit and date of initial diagnosis and multiplying the duration in days by 12/365.25), tumor type, T, N, and M classifications and TNM stage, Duke's score (participants with colorectal adenocarcinoma only), presence of metastases and anatomical location of metastases will be summarized by treatment group and for all study participants based on the SS. In the summaries of categorical variables, percentages will be calculated based on the number of study participants with non-missing data. Further, for the Duke's score, the denominator for the percentage calculation will be the number of study participants with colorectal adenocarcinoma.

Cancer history will be presented by Gastric/GEJ-Cancer and CRC tumor type depending on the number of participants with specific tumor types.

6.3 Prior anti-cancer therapy

Details recorded for each line of prior anti-cancer systemic therapy received by a study participant will be listed for the ES. This listing will include the line and type of systemic therapy, intent, drug name and dose, formulation, indication (current/ultimate), start and end dates, number of cycles received and the number of days per cycle, the participant's best response and the date of that best response, reason for discontinuation and whether the participant had disease progression prior to the next line of systemic therapy. If there was progression, then the date of progression will also be listed. In addition, time from completion of the last prior anti-cancer systemic therapy to the start of UCB6114, whether the participant had progression after the last line of systemic therapy and, if so, the time from progression to the start of UCB6114 will be derived and listed.

For those participants in the ES who received prior radiotherapy, the following data will be listed: treatment site, type of radiotherapy, intent, settings (concurrent with other anti-cancer systemic therapy or stand-alone radiation therapy), and, if concurrent radiotherapy, the anti-cancer systemic therapy line that the radiotherapy was given with and the drug name. In addition, the start and stop dates, total cumulative dose (if known), number of fractions (if known), the participant's best response to radiotherapy and whether the tumor at the treatment site had progressed since radiotherapy will be included in this listing.

A further listing of prior anti-cancer radiotherapy with systemic therapy regimens will be presented for participants in the ES who had concurrent prior systemic therapy and radiotherapy as their prior anti-cancer therapy. This listing will include the relevant data described above together with the participant's best response to that regimen.

Date of surgery/procedure, anatomical location, description of the surgical procedure and whether the tumor was completely removed will be listed for those study participants in the ES who had prior anti-cancer surgeries or procedures.

The following summaries of prior anti-cancer therapy regimens and surgeries will be presented by treatment group and for all participants for the SS:

- Number of prior anti-cancer therapy regimens (0, 1, 2, 3, >3) (including all anti-cancer systemic therapy lines given alone and concurrently with radiotherapy)
- Best response to the most recent prior anti-cancer therapy regimen
- Number of prior anti-cancer systemic therapy + radiotherapy regimens (0, 1, 2, 3, >3)
- Best response to the most recent anti-cancer systemic therapy + radiotherapy regimen
- Reasons for discontinuation of the most recent line[a]
- Time from completion of most recent line[a] to the start of UCB6114 (<1 month, 1-<3 months, 3-6 months, >6 months)[b]
- For participants that progressed after their most recent line[a], the time from progression to the start of UCB6114 (<1 month, 1-<3 months, 3-6 months, >6 months)[b]
- Number of prior anti-cancer radiotherapies (including radiotherapies given alone and concurrently with anti-cancer systemic therapy) (0, 1, 2, >2)
- Number of prior anti-cancer surgeries and procedures (0, 1, 2, >2)

[a] Most recent line is the last prior anti-cancer therapy regimen received which may be a prior anti-cancer systemic therapy given alone or concurrently with radiotherapy.
[b] 1 month = 30 days.

Time from completion and time from progression relative to the last line of anti-cancer systemic therapy will also be summarized using frequency counts and percentages as well as summary statistics.

The number and percentage of participants with any prior anti-cancer systemic therapy, and any prior anti-cancer systemic therapy given concurrently with radiotherapy will be summarized for the SS by treatment group and for all participants, and by WHODD Anatomical Main Group [Level 1 term text], Pharmacological Subgroup [Level 3 term text] and PT.

Prior anti-cancer therapy will be presented by Gastric/GEJ-Cancer and CRC tumor type depending on the number of participants with specific tumor types.

6.4 Cancer status at Screening

The current cancer status of study participants at entry into Part C of this study will be assessed at the Screening visit and listed for the ES. This listing will include tumor type, T, N and M classifications and TNM stage, Duke's score (participants with colorectal adenocarcinoma only), histological and cytological diagnosis details (as relevant), whether the participant has any metastases and associated anatomical location, whether the tumor is recurrent and whether the participant had relapsed from their last line of anti-cancer therapy.

Tumor type, T, N, and M classifications and TMN stage, Duke's score (participants with colorectal adenocarcinoma only), presence of metastases and anatomical location of metastases, and time since relapse on last line of therapy (calculated in days using the date of the Screening visit and date of relapse) will be summarized by treatment group and for all study participants based on the SS. In the summaries of categorical variables, percentages will be calculated based on the number of study participants with non-missing data. Further, for Duke's score, the denominator for the percentage calculation will be the number of study participants with colorectal adenocarcinoma.

Cancer status will be presented by Gastric/GEJ-Cancer and CRC tumor type depending on the number of participants with specific tumor types.

6.5 Medical history and concomitant diseases

Medical history will be listed for the ES and summarized by MedDRA® system organ class (SOC) and preferred term (PT) by treatment group and for all study participants for the SS. The reported term will be included in the listing. Previous medical history (any previous medical conditions with a stop date prior to the start of UCB6114) and ongoing medical history (any ongoing medical conditions with a missing stop date but recorded as ongoing on the eCRF) will be summarized separately. These summaries will include the number and percentage of study participants and will be sorted alphabetically by SOC and by descending incidence of PT within each SOC, based on the incidence in all study participants.

Non-anti-cancer procedure history will be listed for the ES and concomitant medical procedures performed during the study will be listed for the SS.

Medical history and concomitant disease will be presented by Gastric/GEJ-Cancer and CRC tumor type depending on the number of participants with specific tumor types.

6.6 Prior and concomitant medications

Prior medications will include any medications that started prior to the date of the first dose of UCB6114. This will include medications that started prior to the first dose of UCB6114 and continued after.

Concomitant medications will include medications with a start date on or after the first dose of UCB6114 and prior to the date of the last dose of UCB6114 + 30 days, and whose stop date is either missing, or on or after the date of the first dose of UCB6114. Any medications with a start date prior to the first dose of UCB6114 and a stop date after, or continued to be ongoing during the study, will also be classified as concomitant medications. Medications with a start date > 30 days after the last dose of UCB6114 will be considered as post-study medications and will not be included in the summaries of concomitant medication.

Any medication that started prior to, and stopped after the first dose of UCB6114 or continued to be ongoing during the study, will be classified as both prior and concomitant.

Any medications with missing start dates will be classified as both prior and concomitant.

Any medications with partially missing dates will be handled as described in Section 4.2.3 to classify them as prior or concomitant provided that a stop date is not present or a stop date is present but prior to the first dose of UCB6114.

All medications (prior, concomitant and post-study) will be listed for the ES. Any prohibited concomitant medications, rescue medications or steroid use will be identified via a medical review and flagged in this listing.

Prior and concomitant medications (per the definitions above) will be summarized for the SS by treatment group and by WHODD Anatomical Main Group [Level 1 term text], Pharmacological Subgroup [Level 3 term text] and PT. The reported term will be included in the listing. Separate summaries will be presented for prior medications and concomitant medications. As per the definitions above, prior medications which continued into the Treatment Period will also be classified as concomitant and will be included in both summaries.

All tabulations will be sorted alphabetically by Level 1 term, alphabetical Level 3 term within Level 1 and decreasing frequency of PT in all study participants.

A glossary of all prior and concomitant medications will be presented for the SS including the Anatomical Main Group (Level 1), Pharmacological Subgroup (Level 3), PT and reported term.

Prior and concomitant medications will be presented by Gastric/GEJ-Cancer and CRC tumor type depending on the number of participants with specific tumor types.

7. MEASUREMENTS OF TREATMENT COMPLIANCE

During Part C of this study, administration of study treatment will be performed via iv infusion/bolus at the study site under the supervision of the designated site personnel and in compliance with the Guideline for First in Human clinical studies (EMEA/CHMP/SWP/28367/07Rev. 1). Compliance will be monitored at the site through a review of accountability logs which will be used to record study treatment dispensing and return information to ensure that each study participant received the correct dose level of all components of the combination therapy, i.e. UCB6114 and each component of mFOLFOX6.

Any dosing deviations will be reviewed as IPDs at the DEMs and assessed for possible impact on the PPS and PKS. If considered important, these deviations will be included in the summary and listing of IPDs.

8. SAFETY ANALYSES

All safety summaries and listings will be presented by treatment group based on the SS, unless otherwise stated.

All safety summaries may be presented by Gastric/GEJ-Cancer and CRC tumor type depending on the number of participants with specific tumor types.

8.1 Extent of exposure

A combination of study treatments is administered in Part C, and exposure to UCB6114, oxaliplatin, leucovorin and 5-fluorouracil will be summarized and listed separately.

Details on UCB6114 administration on Day 1 and Day 15, oxaliplatin+leucovorin infusion on Day 1 and Day 15, 5-fluorouracil bolus on Day 1 and Day 15 and 5-fluorouracil infusion on Day 2 and Day 16 of each cycle will be listed. This listing will be split into two parts. The first part

will include the start and stop dates and times of infusion, duration of infusion, infusion rate, whether the infusion was temporarily stopped/interrupted, whether the infusion was permanently discontinued and, if this was the case, whether the interruption or permanent discontinuation was due to an AE or other reason. The second part of this listing will include, for each visit, and for each study treatment, infusion site, total volume delivered, volume infused, planned total dose and total dose actually administered at infusion. In addition, the percentage of planned dose received, total dose administered across all cycles, number of complete cycles of UCB6114 received and the total number of doses of UCB6114 received will be listed.

The percentage of planned dose received will be calculated for UCB6114 and each component of mFOLFOX6 for each study participant at each dosing visit within each cycle as follows:

$$Percentage\ of\ Planned\ Dose\ Received = 100 \times \frac{Total\ Dose\ Administered}{Planned\ Total\ Dose}$$

Actual duration of infusion will be calculated in minutes for UCB6114 and each component of mFOLFOX6 only for those study participants who did not have any temporary interruption(s) of their infusion using the infusion start and stop times and included on this listing. Length of interruption(s) will be calculated for those study participants who had temporary interruption(s) of their infusion.

Extent or duration of exposure will be calculated and summarized separately for UCB6114 and the components of mFOLFOX6. Frequency counts and percentages for the number of complete cycles of UCB6114 received (0, 1, 2, 3, 4, >4) and summary statistics for the total dose of UCB6114 and the components of mFOLFOX6 received across all cycles, the total number of doses of UCB6114 and the components of mFOLFOX6 received, and the total duration of exposure to each will be presented.

Total duration of exposure will be calculated in days as follows:

$$Total\ Duration\ of\ Exposure = (Date\ of\ Last\ Dose - Date\ of\ First\ Dose) + 30$$

Note that 30 days is added to this calculation to account for a participant's continued exposure to UCB6114 and the components of mFOLFOX6 following their last dose of study treatment.

Note that a participant is deemed to have completed a full cycle of UCB6114 if they receive the planned dose of UCB6114 on Day 1 and Day 15 of each cycle and a decision was not made to discontinue UCB6114 up to and including Day 28 relative to Day 1 of a cycle.

8.2 Adverse events

The primary safety endpoints for Part C of this study are the incidence and severity of TEAEs (including SAEs) from the first dose of UCB6114 treatment on Day 1 of Cycle 1 until the end of the SFU Period (up to 30 days following the last dose of UCB6114), and the incidence of DLTs from the first dose of UCB6114 on Day 1 of Cycle 1 until the end of the DLT Observation Period (Day 28 of Cycle 1).

All AEs in Part C of the study will be coded using MedDRA® and classified as pre-treatment and treatment-emergent relative to the first infusion of UCB6114. Adverse events with a start date prior to the first dose of UCB6114 will be defined as pre-treatment AEs. A TEAE is defined as any AE with a start date on or after the first dose of UCB6114 up until the last dose of UCB6114

+ 30 days. A pre-treatment AE which increases in severity on or after the first dose of UCB6114 will also be counted as a TEAE. Note that in this case, the pre-existing AE will have a stop date and an outcome of 'worsened' and a new AE (with the same verbatim) will be entered with the same start date and the increased severity recorded on the eCRF. Any AE (including SAEs) with an onset date later than the last dose of UCB6114 + 30 days will not be considered as treatment-emergent and therefore will not be included in the tabulations of TEAEs. These AEs will be considered as post-study AEs and will be listed only. Where onset dates are missing or partially missing, AEs will be assumed to be treatment-emergent, unless there is clear evidence to suggest that the AE started prior to the first dose of UCB6114 and it has not increased in severity. Missing or partially missing dates for AEs will be handled as described in Section 4.2.3. All AEs for a participant will be recorded in the eCRF from the time of informed consent until completion or early discontinuation of Part C of this study. Serious adverse events are to be reported up to 30 days after the Final Visit (i.e. up to 150 days after the last dose of UCB6114).

Adverse events will be assigned an NCI CTCAE severity grade (Grade 1/Grade 2/Grade 3/Grade 4/Grade 5), where possible. If a CTCAE toxicity grading is not possible, then the intensity of the AE (mild/moderate/severe) will be recorded on the eCRF. If the AE is not gradable, is serious, and is considered as life threatening, then the intensity for this AE will be missing and one of the reasons for seriousness will be recorded as life threatening. Adverse events will also be categorized according to their relationship to UCB6114 and/or individual components of mFOLFOX6 treatment (related/not related), and whether the event is a DLT, as judged by the investigator. A DLT is defined as a TEAE at least possibly related to UCB6114 that occurs during Cycle 1 and fulfills any of the criteria listed in Section 4.1.4.2.1 of the protocol. The investigator is expected to record whether an AE is a DLT on the eCRF.

An overview of the number and percentage of participants who experience TEAEs will be presented. This summary will include the number and percentage of participants with any TEAEs, serious TEAEs, related TEAEs (related to UCB6114 only, related to UCB6114 and/or mFOLFOX6, and related to each of oxaliplatin, leucovorin or 5-fluorouracil), discontinuations from study treatment (UCB6114 and mFOLFOX6, mFOLFOX6 only, oxaliplatin, leucovorin or 5-fluorouracil) due to TEAE(s), discontinuations from the study due to TEAE(s), CTCAE Grade ≥ 3 TEAEs, CTCAE Grade ≥3 related TEAEs (related to UCB6114 only, related to UCB6114 and/or mFOLFOX6, and related to each of oxaliplatin, leucovorin or 5-fluorouracil), DLTs, AEs leading to death and TEAEs leading to death; event counts will also be included against each of these categories. The overview of TEAEs will be presented by Gastric/GEJ-Cancer and CRC tumor type depending on the number of participants with specific tumor types.

In addition, the following summaries will be presented by SOC, high level term (HLT) and PT, and where indicated also by Gastric/GEJ-Cancer and CRC tumor type depending on the number of participants with specific tumor types:

- Incidence of TEAEs (overall and by tumor type);
- Incidence of serious TEAEs (overall and by tumor type);
- Incidence of non-serious TEAEs (overall and by tumor type);
- Incidence of TEAEs leading to a temporary interruption of UCB6114 infusion and/or dose reduction (overall and by tumor type);

- Incidence of TEAEs leading to a temporary interruption of oxaliplatin infusion and/or dose reduction (overall and by tumor type);
- Incidence of TEAEs leading to a temporary interruption of leucovorin infusion and/or dose reduction (overall and by tumor type);
- Incidence of TEAEs leading to a temporary interruption of 5-fluorouracil bolus or infusion and/or dose reduction (overall and by tumor type);
- Incidence of TEAEs leading to discontinuation of UCB6114 and mFOLFOX6 (overall and by tumor type);
- Incidence of TEAEs leading to discontinuation of mFOLFOX6 only (overall and by tumor type);
- Incidence of TEAEs leading to discontinuation of oxaliplatin (overall and by tumor type);
- Incidence of TEAEs leading to discontinuation of leucovorin (overall and by tumor type);
- Incidence of TEAEs leading to discontinuation of 5-fluorouracil (overall and by tumor type);
- Incidence of TEAEs leading to discontinuation of study (overall and by tumor type);
- Incidence of DLTs (separately for during the 28-day DLT Observation Period and after the 28-day DLT Observation Period) (overall and by tumor type);
- Incidence of adverse events of special interest (AESIs) (Hy's Law – see Section 8.2.1 below) (overall and by tumor type);
- Incidence of UCB6114 infusion-related reactions (defined as any TEAE with a PT from both a narrow and broad scope search of category A terms of the 'Hypersensitivity' Standardized MedDRA® Query (SMQ) – see Section 8.2.2) (overall and by tumor type);
- Incidence of TEAEs by maximum CTCAE severity grade (overall and by tumor type);
- Incidence of TEAEs related to UCB6114 only by maximum CTCAE severity grade (overall and by tumor type);
- Incidence of TEAEs related to UCB6114 and/or mFOLFOX6 by maximum CTCAE severity grade (overall and by tumor type);
- Incidence of TEAEs by maximum relationship to UCB6114 only (overall and by tumor type);
- Incidence of TEAEs by maximum relationship to UCB6114 and/or mFOLFOX6 (overall and by tumor type);
- Incidence of TEAEs by relationship to UCB6114 only;
- Incidence of TEAEs by relationship to UCB6114 and/or mFOLFOX6;
- Incidence of serious TEAEs by relationship to UCB6114 only;
- Incidence of serious TEAEs by relationship to UCB6114 and/or mFOLFOX6;
- Incidence of non-serious TEAEs by relationship to UCB6114 only;

- Incidence of non-serious TEAEs by relationship to UCB6114 and/or mFOLFOX6;
- Incidence of fatal TEAEs by relationship to UCB6114 only;
- Incidence of fatal TEAEs by relationship to UCB6114 and/or mFOLFOX6;
- Incidence and event rate of TEAEs by treatment-emergent ADA positivity.

The following summary will be presented by SOC and PT for EudraCT reporting:

- Incidence of non-serious TEAEs above the threshold of 5% of participants in any treatment group.

The above summaries of TEAEs will be ordered alphabetically by SOC, alphabetically by HLT within SOC and decreasing incidence of PT events within SOC /HLT in all study participants. For tables including only the number and percentage of participants, summaries will be ordered alphabetically by SOC, alphabetically by HLT within SOC and decreasing incidence of participants with each PT within SOC /HLT in all study participants.

The incidence of TEAEs by maximum CTCAE severity grade will be presented by CTCAE term. CTCAE term will be obtained from the NCI CTCAE Version 5.0 via a mapping of MedDRA® lower level terms. This summary will be ordered by decreasing incidence of participants with each CTCAE term in all study participants.

Summary tables will contain frequency counts and percentages, and the number of events, where applicable. A study participant who experiences the same event multiple times will be counted only once in the frequency counts for the PT, but all events will be included.

In the summaries of TEAEs by relationship, participants will be counted in “Not related” and “Related” categories (or “Missing” in the case where an event has a missing relationship). A study participant who experiences the same event multiple times will be included in the most related category for the summaries by maximum relationship.

In the overview summary of TEAEs, participants will be counted as having at least one TEAE with CTCAE severity grade ≥3, and in the summary of TEAEs by maximum CTCAE severity grade, participants will be counted as having at least one TEAE in the following categories: ‘Grade 1’, ‘Grade 2’, ‘Grade 3’, ‘Grade 4’, ‘Grade 5’, ‘Grade 3 or 4’ and ‘Grade >=3’. Events for which no CTCAE severity grade is recorded by the investigator but an intensity is recorded instead, the intensity of this event will be assigned to a CTCAE severity grade for the purpose of these summaries, i.e. ‘Mild’ will be included as ‘Grade 1’, ‘Moderate’ will be included as ‘Grade 2’, ‘Severe’ will be included as ‘Grade 3’, ‘Life Threatening’ will be included as ‘Grade 4’ and, if the participant dies due to the event, it will be included as ‘Grade 5’. The determination of whether the event is life threatening or results in death will be based on the reason for seriousness recorded as life-threatening or death on the eCRF, or on the event having a fatal outcome. Otherwise, if both the CTCAE severity grade and intensity is missing then the CTCAE severity grade in these summaries will be missing. A study participant who experiences the same event multiple times will be included in the highest severity grade category in the summary of TEAEs by maximum CTCAE severity grade.

A glossary of all AEs will be presented including the MedDRA® SOC, HLT, PT, reported term and low level term (LLT).

A listing of all AEs will be presented by study participant for the ES. The listing will include the onset date and stop date of the event (including relative days) and also the onset times and stop times of events where available. Period of onset of AEs will also be presented on this listing.

Period of onset of AEs will be defined as follows for the purpose of the listing:

- If the AE has an onset date prior to the date of the Screening visit, then Period=Pre-study;
- If the AE has an onset date on or after the date of the Screening visit and has an onset date and time prior to the start time of UCB6114 infusion on Day 1 of Cycle 1 then Period=Screening;
- If the AE has an onset date and time on or after the start time of UCB6114 infusion on Day 1 of Cycle 1 and up to the date and time of the start of Cycle 2 (i.e. prior to the start time of the UCB6114 infusion on Day 1 of Cycle 2) then Period=Cycle 1
- If the AE has an onset date and time on or after the start time of UCB6114infusion on Day 1 of Cycle 2 and up to the date and time of the start of Cycle 3 (i.e. prior to the start time of the UCB6114 infusion on Day 1 of Cycle 3) then Period=Cycle 2;
- Same as above for subsequent cycles (Cycle 3 etc.);
- If the AE has an onset date after the last dose of UCB6114up to and including 30 days after the last dose of UCB6114, then Period=SFU;
- If the event has an onset date after the 30-day period following the last dose of UCB6114, then Period=Post-study.

The listing of all AEs will also include the AE duration (derived in days, hh:mm for AEs with onset and stop times recorded and derived in days for all other AEs with only onset and stop dates recorded), days since start of UCB6114 infusion (time if an onset time is recorded, days otherwise), seriousness and reason for seriousness, CTCAE severity grade, intensity (where a CTCAE severity grade is not recorded), pattern of event, relationship to UCB6114 and mFOLFOX6 and action taken with UCB6114 and mFOLFOX6 (including other action taken), the outcome of the AE, whether an autopsy was performed and cause of death. In addition, the listing will flag AEs that led to discontinuation from the study, TEAEs, AESIs, SAEs, led to UCB6114 infusion-related reactions, and DLTs. Whether an AE is related to a concomitant medication, (and separately whether it is related to the COVID-19 vaccination), the names of any co-suspect medications will also be listed.

Separate listings of all SAEs, TEAEs leading to discontinuation of UCB6114 and mFOLFOX6, TEAEs leading to discontinuation of mFOLFOX6 only, TEAEs leading to discontinuation of each component of mFOLFOX6 and TEAEs leading to discontinuation of the study will also be presented.

All deaths that occur on study (defined as during study treatment or within 30 days of the latest dose of UCB6114) will be listed separately. This listing will include the primary cause of death and the number of days between the date of the last dose of UCB6114 and death, defined as

$$Days\ since\ last\ dose = (Date\ of\ death - Date\ of\ latest\ dose\ of\ UCB6114\ )$$

8.2.1 Adverse events of special interest

An AESI is any AE that a regulatory authority has mandated be reported on an expedited basis, regardless of the seriousness, expectedness, or relatedness of the AE to the administration of a UCB product/compound.

For ONC001, potential Hy's Law is used to identify AESIs and is defined using the laboratory data and the following potential drug-induced liver injury (PDILI) criteria:

- ≥3x upper limit of normal (ULN) alanine aminotransferase (ALT) *or* aspartate aminotransferase (AST) with coexisting ≥2xULN total bilirubin in the absence of ≥2xULN alkaline phosphatase (ALP), with no alternative explanation for the biochemical abnormality;
- Study participants who have evidence of liver metastases may be considered to have an alternate etiology for the described laboratory abnormalities.

All AESIs will be flagged on the listing of AEs.

8.2.2 Infusion-related reactions

Infusion-related reactions are defined as hypersensitivity reactions, anaphylactic reactions and cytokine release syndrome with onset within 24 hours after the start of the UCB6114 infusion.

All potential infusion-related reactions will be identified programmatically and will then undergo medical review for confirmation based on participant characteristics and other signs and symptoms. The final assessment from the medical review will be used in the programming to ensure that all infusion-related reactions are flagged correctly in the listings and included in the relevant summaries.

Hypersensitivity reactions will be programmatically identified as any TEAE with a PT from both a narrow and broad scope search of category A terms of the 'Hypersensitivity' SMQ.

Anaphylactic reactions will be programmatically identified using an algorithmic approach based on the 'Anaphylactic Reaction' SMQ. Further details on this algorithm are given in Section 11. Note that if the MedDRA® version is increased from 25.1 during the study, any changes to the terms included in the 'Anaphylactic Reaction' SMQ should be applied.

Cytokine release syndrome will be programmatically identified as any TEAE with a PT of 'Cytokine release syndrome' from the broad scope search of category A terms of the 'Hypersensitivity' SMQ. Since this disorder is characterized by fever, headache, tachycardia, hypotension, rash, tachypnoea and/or hypoxia, a further medical review of participants with these events occurring within 24 hours after infusion of UCB6114 will be performed to confirm any further infusion-related reactions.

Note that any other AEs (i.e. not identified as infusion-related reactions using the rules above) which result in a temporary interruption or permanent discontinuation of a UCB6114 infusion will not be considered as an infusion-related reaction.

8.3 Clinical laboratory evaluations

The use of multiple local laboratories (1 per site in the UK and US) in Part C of this study has meant that results have been recorded in different units and with reference to different normal ranges, and further, for some laboratory tests, different normal ranges have been applied to males

and females and age groups. As a first step to ensure comparability of laboratory results, results and normal ranges will be converted to the same International System of Units (SI) units using UCB's standard conversion factors. This will be programmed at the Study Data Tabulation Model (SDTM) level. Note though that the simple conversion to SI units does not represent a full homogenization of results from different local laboratories using different methods. To ensure full comparability, the observed laboratory results will be normalized to a unique set of standard reference ranges using the location-scale normalization formula (Chuang-Stein, 1992) which normalizes all results in relation to a standard set of reference ranges (for hematology, clinical chemistry and coagulation parameters):

$$s = L_S + (x - L_X)\frac{(U_S - L_S)}{(U_X - L_X)}$$

and when the standard lower limit is 0: $s = x\frac{U_S}{U_X}$ where:

s = normalized observed value
x = original observed value in SI units
L_S = Lower Limit of the reference range chosen to be the standard reference range
U_S = Upper Limit of the reference range chosen to be the standard reference range
L_X = Lower Limit of the reference range associated with the original observed value in SI units (local laboratory reference range)
U_X = Upper Limit of the reference range associated with the original observed value in SI units (local laboratory reference range)

This transformation preserves the distance of the original laboratory result from the lower limit of normal as a multiple of the specified standard reference range.

Note that the choice of the standard reference range is arbitrary, however, the most recent reference ranges used by ICON Central Laboratories (including the age and gender specific reference ranges for parameters, where available) will be used to normalize the results in this study.

Normalization of the laboratory results will be performed in the ADaM programming by ICON.

All laboratory data (hematology, serum chemistry and coagulation) and changes from Baseline for numeric variables will be listed for participants who have at least one value outside of the reference range. All urinalysis data will be listed for all participants. Data will be listed by study participant, laboratory panel, laboratory parameter and visit within each treatment group. Any laboratory measurements that are BLQ or ALQ will be handled as described in Section 4.2.2. For the relevant numeric laboratory parameters, the reference ranges supplied by the local analytical laboratory will be used to flag values outside the reference range as low or high in this listing. For the parameters for which the local laboratory cannot supply the reference ranges, the reference ranges provided by ICON Central Laboratories will be used instead. A listing of all laboratory results outside of the reference range will also be presented. The reference ranges will also be reported in the listings.

In addition, for the relevant hematology, clinical chemistry and coagulation laboratory tests, CTCAE severity grades (Grade 1, Grade 2, Grade 3, Grade 4) will be applied (where possible) in

the ADaM programming according to NCI CTCAE Version 5.0, and these grades will also be listed for the relevant laboratory parameters. Note that Grade 0 will be applied in cases where a result is normal for the relevant laboratory test and Grade 5 is not applicable in the grading of laboratory data.

Observed values and changes from Baseline in the hematology, serum chemistry and coagulation parameters presented below in Table 8-1 will be summarized at each visit. In addition, for each of these parameters, the Baseline value, the minimum, maximum, average and last post-Baseline value for each participant will be summarized by cycle using descriptive statistics. These post-Baseline summary measures will be calculated based on all available scheduled postdose values within each cycle, i.e. from Day 8 of the current cycle up to Day 1 (pre-UCB6114) of the subsequent cycle. The last value in a cycle will be the predose value of the subsequent cycle where a subsequent cycle occurs, otherwise it will be the value at the last scheduled assessment. If only one value is available then the average will not be calculated and presented but this value will be used for the minimum, maximum and last post-Baseline summary measures. These summary measures for each cycle will also be listed.

The summaries of normalized hematology, serum chemistry and coagulation values and changes from Baseline will also be presented by Gastric/GEJ-Cancer and CRC tumor type depending on the number of participants with specific tumor types.

For those laboratory parameters with a CTCAE toxicity assigned, shift tables for the change from Baseline in CTCAE severity grade at each visit and to the worst post-Baseline CTCAE severity grade during the Treatment Period will be presented.

Table 8-1: Clinical Laboratory Assessments

Laboratory Assessment	Laboratory Parameters
Hematology	Platelet Count, RBC Count, Hemoglobin, Hematocrit, RBC Indices (MCV, MCH, MCHC), WBC Count with Differential (Absolute Neutrophils, Absolute Lymphocytes, Absolute Monocytes, Absolute Eosinophils, Absolute Basophils)
Clinical Chemistry	ALT, AST, ALP[a] , Bicarbonate, Sodium, Potassium, Magnesium, Chloride, Calcium, Total Bilirubin, BUN or Urea, Serum Creatinine, Glucose (non-fasted), Phosphorus or Phosphate, Albumin, Total Protein, Uric Acid, Amylase, GGT, Cholesterol, Creatine Kinase, CRP, LDH, Lipase, Triglycerides
Coagulation	aPTT and either prothrombin time or INR
Routine Urinalysis	Specific Gravity, pH, Glucose, Protein, Blood, Ketones, Bilirubin, Urobilinogen, Nitrite, Leukocyte Esterase by Dipstick Microscopic Examination (if blood or protein is abnormal, including crystals)
Screening Tests	Pregnancy tests: FSH and estradiol (for women of non-childbearing potential only); serum or urine hCG pregnancy test (for women of childbearing potential) Bone turnover markers: blood BAP, blood CTx, urinary NTx and urinary CTxII Tumor markers: e.g. PSA, CA125, CA19-9

ALP=alkaline phosphatase; ALT=alanine aminotransferase; aPPT=activated partial thromboplastin time; AST=aspartate aminotransferase; BAP=bone alkaline phosphatase; BUN=blood urea nitrogen; CA=cancer antigen; CRP=C-reactive protein; CTx=C-terminal telopeptide; FSH=follicle-stimulating hormone; GGT=gamma glutamyl transferase; hCG=human chorionic gonadotropin; INR=international normalized ratio; LDH=lactate dehydrogenase; MCH=mean corpuscular hemoglobin; MCHC=mean corpuscular hemoglobin concentration; MCV=mean corpuscular volume; NTx=N-terminal telopeptide; PSA=prostate specific antigen; RBC=red blood cell; WBC=white blood cell.
a including liver-specific ALP for use in assessing participants with bone metastases at Screening. In the case of bone metastases liver function abnormalities considered potential Hy's law cases, the liver-specific ALP must be separated from the total in participants with bone metastases and used to assess the liver function instead of the total ALP

The screening laboratory tests included above in Table 8-1 will be listed only.

Liver function abnormalities will be defined using the following criteria:

- ALT or AST ≥2xULN
- ALT or AST ≥3xULN
- Total bilirubin ≥2xULN
- Total bilirubin ≥3xULN
- ALT or AST ≥5xULN
- ALT or AST ≥8xULN

- ALT or AST ≥3xULN AND total bilirubin ≥2xULN (>35% direct bilirubin)

For the subgroups of participants with liver metastases and without liver metastases at Baseline, the number and percentage of participants in each liver function abnormality category will be summarized at each visit.

In addition, participants with PDILI criteria are those that fulfill the following laboratory data (based on liver function tests) criteria at a visit:

- AST or ALT and total bilirubin within the normal range at Baseline and AST or ALT ≥3xULN concurrent with total bilirubin ≥2xULN;
- AST, ALT or total bilirubin above ULN at Baseline and AST or ALT ≥2 times Baseline values AND AST or ALT ≥3xULN (participants without liver metastases at Baseline)/AST or ALT ≥8xULN (participants with liver metastases at Baseline) concurrent with total bilirubin above ULN at Baseline and total bilirubin ≥2 times Baseline value or ≥3xULN (whichever is lower).

All relevant laboratory data collected for participants with a PDILI event (i.e. liver function tests) will be listed at the visits at which at least one of the above criteria was fulfilled.

The number and percentage of participants meeting different combinations of the ALT, AST and total bilirubin criteria defined above will be summarized by treatment group. This summary will be presented for all participants as well as for the subgroups of participants who had liver metastases at Baseline and participants without liver metastases at Baseline.

A separate listing will also be produced containing drug-induced liver injury -relevant family medical history, lifestyle data (alcohol consumption or drug abuse in the previous 6 months), hepatic event supplemental medical history and any hepato-toxic medications taken for participants in the SS with a PDILI event.

8.4 Vital signs, physical findings, and other observations related to safety

8.4.1 Vital signs

Vital signs will be measured in a semi-supine position after 5 minutes rest and will include:

- Systolic and diastolic blood pressure;
- Pulse rate;
- Oral body temperature;
- Respiratory rate.

On UCB6114 dosing visits (Days 1 and 15 of each cycle), vital signs will be assessed at multiple timepoints relative to the UCB6114 infusion: predose, 10 minutes (±5 minutes) and 30 minutes (±10 minutes) after the start of the infusion, at the end of the infusion (+15 minutes); and at 1 hour (+15 minutes) after the end of the infusion. In addition, on Cycle 1 Day 1, vital signs will also be assessed at 2 hours (+1 hour) and 5 hours (+1 hours) after the end of the infusion. All vital signs measurements will be performed prior to the collection of PK samples.

At all other scheduled visits (Day 8, and 22 of Cycle 1 and Days 1), vital signs will be measured prior to UCB6114 dosing on dosing days. At the SFU visit, vital signs measurements will be taken prior to PK sampling.

Observed vital sign measurements and changes from Baseline will be listed by visit and timepoint and summarized using descriptive statistics. In addition, for each of the vital signs, the Baseline value, the minimum, maximum, average and last post-Baseline value for each participant will be calculated based on all available scheduled postdose values during each cycle up to the predose value on Day 1 of the subsequent cycle and will be summarized by cycle using descriptive statistics. The last value in a cycle will be the predose value of the subsequent cycle where a subsequent cycle occurs, otherwise it will be the value at the last scheduled assessment. If only 1 value is available then the average will not be calculated and presented but this value will be used for the minimum, maximum and last post-Baseline summary measures. These summary measures for each cycle will also be listed.

For the multiple vital signs measurements on treatment days (i.e. on Days 1 and 15 of each cycle), changes from the predose value will be calculated at each postdose timepoint and summarized using descriptive statistics.

For each vital signs parameter, the mean (±standard deviation) change from Baseline value will be plotted over scheduled visit and timepoint with treatment group overlaid on the same plot.

The incidence of treatment-emergent markedly abnormal (TEMA)/ potentially clinically significant (PCS) vital signs based on blood pressure and pulse rate measurements will be summarized by visit and timepoint using frequency counts and percentages. The criteria for identifying a TEMA/PCS are included in Table 8-2.

Table 8-2: TEMA/PCS Criteria for Vital Signs

Variable (unit)	Low[a]	High[a]
Systolic Blood Pressure (mmHg)	Value <90 and ≥20 decrease from Baseline	Value >140 and ≥20 increase from Baseline
Diastolic Blood Pressure (mmHg)	Value <50 and ≥15 decrease from Baseline	Value >90 and ≥15 increase from Baseline
Pulse Rate (bpm)	Value <45 and ≥15 decrease from Baseline	Value >90 and ≥15 increase from Baseline

bpm=beats per minute; PCS=potentially clinically significant; mmHg=millimeter of mercury; TEMA=treatment-emergent markedly abnormal.
a Both conditions must be satisfied for a measurement to be considered PCS.

8.4.2 12-Lead Electrocardiograms

Electrocardiograms will be performed at each visit and timepoint in triplicate with the participant in a supine position after a minimum of 5 minutes rest.

On Days 1 and 15 of Cycle 1 only, ECGs will be performed in triplicate at multiple timepoints relative to UCB6114 dosing (predose, end of infusion, and 2 hours after the end of infusion). When ECG measurements coincide with blood sampling for PK (and PD), ECG will be

performed first. On Days 1 and 15 of Cycle 2 and on Day 1 of all subsequent cycles, ECGs will be performed in triplicate prior to UCB6114 dosing. At the SFU visit, ECGs will be performed once in triplicate prior to PK sampling.

All ECGs will be evaluated for any clinically relevant changes by the investigator.

Electrocardiograms will also be collected for central reading, the data from which will be analyzed separately.

All summaries and listings of ECG data will be based on the local (site) 12-lead ECG measurements.

The following ECG parameters will be reported:

- PR interval;
- QT interval;
- QRS interval;
- QTcF interval (QT corrected for heart rate using Fridericia's formula [QTcF]);
- Heart rate.

Observed values and changes from Baseline in these ECG parameters will be listed and summarized by visit using descriptive statistics. The mean of the triplicate measurements taken for each parameter will be used in the summary at each visit and timepoint. If less than 3 of the triplicate measurements are taken then the mean of the available measurements will be used (if only 1 of the 3 triplicate measurements is available, then this value will be used in the summaries). The Baseline value will be the mean of the last scheduled or unscheduled triplicate measurements taken prior to first dose of UCB6114 on Day 1 of Cycle 1. If no predose triplicate measurements are taken then the mean of the triplicate measurements taken at Screening will be used. The mean of only the scheduled triplicate measurements at each Post-Baseline visit and timepoint will be included in the summary. In addition, for each of the ECG parameters, the minimum, maximum, average and last post-Baseline value for each participant will be calculated based on the mean of the triplicate of all available scheduled postdose measurements during each cycle up to the predose value on Day 1 of the subsequent cycle, and will be summarized by cycle using descriptive statistics. The last value in a cycle will be the predose mean triplicate value of the subsequent cycle where a subsequent cycle occurs, otherwise it will be the mean triplicate value at the last scheduled assessment. If only 1 mean triplicate value is available then the average will not be calculated and presented but this value will be used for the minimum, maximum and last post-Baseline value summary measures. These summary measures for each cycle will also be listed.

For the multiple ECGs performed on Days 1 and 15 of Cycle 1, changes from the predose value will be calculated at each postdose timepoint and summarized using descriptive statistics.

Mean (±standard deviation) change from Baseline in QTcF will be plotted over scheduled visit with treatment groups overlaid on the same plot. Individual observed values of QTcF will be presented over actual time in a spaghetti plot.

The following cut-points in QTcF will be applied for observed data and changes from Baseline:

For observed QTcF data:

- <450 msec;
- ≥450 to <480 msec;
- ≥480 to <500 msec;
- ≥500 msec.

For changes from Baseline in QTcF:

- <30 msec;
- ≥30 to <60 msec;
- ≥60 msec.

The incidence of participants in each of these categories will be summarized using frequency counts and percentages by visit.

A listing of 12-lead ECG abnormal findings will be presented.

Electrocardiograms will also be collected for central reading; however, these data will be reported in an addendum to the CSR.

8.4.3 Echocardiogram

Echocardiograms will be performed at the Screening visit, at Cycle 3 Day 1 (+/- 7 days), as clinically indicated afterwards, and at the SFU Visit.

All details on the echocardiogram assessments performed at each visit will be listed including the observed LVEF measurements and changes from Baseline, as well as information on whether the result was normal, abnormal not clinically significant (NCS) or abnormal clinically significant (CS).

Observed values and changes from Baseline in LVEF will be summarized by visit using descriptive statistics. In addition, shift tables for the change from Baseline in normal, abnormal NCS, abnormal CS LVEF results will be summarized by visit.

Mean (±standard deviation) change from Baseline in LVEF will be plotted over scheduled visit with treatment groups overlaid on the same plot. Individual observed LVEF results will be presented over actual time in a spaghetti plot.

8.4.4 ECOG performance status

ECOG performance status will be listed by participant and visit and will be summarized using frequency counts and percentages. A shift table summarizing the changes from Baseline to each post-Baseline visit will also be presented. Further detail on the ECOG performance scale, the listings and summaries are included in Section 10.2.

8.4.5 Physical examination

Physical examination abnormalities from the complete physical examination performed at Screening and predose on Day 1 of Cycle 1, and from the symptom-directed physical examinations performed at other visits (predose on dosing visits), will be listed.

9. PHARMACOKINETICS AND PHARMACODYNAMICS

9.1 Pharmacokinetics

9.1.1 Secondary pharmacokinetic endpoint

[redacted]

9.1.2 Exploratory pharmacokinetic endpoints

[redacted]

[redacted]

9.2 Pharmacodynamics

The following exploratory PD and biomarker endpoints will be obtained from blood and urine samples which will be analyzed at a number of external laboratory vendors:

- Serum markers of bone turnover;
- Urinary markers of bone turnover;
- cGremlin-1;
- Genetic analysis;
- ctDNA.

The impact of UCB6114 on bone turnover will be explored using the serum and urinary markers provided by the analytical laboratory. These markers will be listed for the SS and summarized descriptively over time for the PDS by dose level (treatment group), as described for the clinical laboratory parameters in Section 8.3. For each marker of bone turnover, the mean (±standard deviation) value and the mean (±standard deviation) change from Baseline value will be plotted over scheduled visit with treatment group overlaid on the same plot.

cGremlin-1 will be reported as concentration in blood by nominal (scheduled) assessment and dose level. Concentrations of cGremlin-1 will be listed for the SS and summarized for the PDS using descriptive statistics by dose level (treatment group) and nominal (scheduled) sampling timepoints (n, arithmetic mean, standard deviation, median, minimum, maximum, geoMean, geoCV and 95% CI for the geoMean [assuming lognormally distributed data]). Changes from Baseline will also be summarized. Individual study participant cGremlin-1 concentration-time profiles will be displayed graphically in spaghetti plots and geoMean cGremlin-1 concentration and 95% CI will be plotted at each nominal (scheduled) timepoint with treatment group overlaid on the same plot.

Serum protein analysis, genetic analysis and the analysis of the test results from the blood samples taken for ctDNA will be performed and reported separately outside of the CSR.

Hematoxylin and eosin (H & E) staining and immunohistochemistry (IHC) will be used to analyze any available historical tissue biopsy samples obtained prior to a participant's entry into the study (e.g. at the time of diagnosis).

Test results from the H & E staining and for target genes, phosphatase and tensin homolog (PTEN), Ki67 (cellular marker for proliferation in tumors), Gremlin-1, mothers against decapentaplegic homolog 4 (SMAD4) and fibroblast activation protein (FAP) will be listed by variable and sample analyzed (multiple tissue samples from a tumor biopsy may have been analyzed for a participant) for the SS. No summaries of these data will be generated due to the

expected small numbers of historical biopsy samples analyzed for each dose level (treatment group).

The following key/component variables will be derived based on H & E staining, PTEN, Ki67, Gremlin-1 and FAP test results. No derived variables will be generated for SMAD4; only raw test results will be listed. Note that multiple tissue samples from a tumor biopsy may have been analyzed for a participant and therefore multiple test results will be presented in the listings.

H & E: Tissue Integrity (Percentage of Necrosis in Tumor Area)

In order to assess tissue integrity, percentage of necrosis in the tumor area will be categorized as '<20%' and '>=20%'. If percentage of necrosis data are missing but other H & E staining and IHC data are available for a participant (i.e. the participant had historical tumor biopsy sample(s) analyzed), then the result will be categorized as 'Not Done'.

This categorical variable will be listed together with all other H & E test results.

PTEN: Tissue Sample Quality Control

The presence of staining of intrinsic control elements on the slides together with the level of staining intensity will be used to determine the tissue sample quality control.

If staining of intrinsic control elements on stained slides='YES' and staining intensity of intrinsic control elements on stained slides is 1, 2 or 3 then the tissue sample quality control is 'Good', otherwise if the staining intensity of intrinsic control elements=0 then the tissue sample quality control is 'Questionable'. If staining of intrinsic control elements on stained slides='NOT PRESENT' then the tissue sample quality control is 'No staining present'. If both variables are missing but other IHC results are available (i.e. the participant had historical tumor biopsy sample(s) analyzed), then the result will be categorized as 'Not done'.

This categorical variable will be listed together with the presence/absence of staining of intrinsic control elements on the slides, the level of staining intensity, staining pattern, staining artifacts and any assay-specific comments. Since the percent of tumor cells with staining intensity 0/1/2/3 and the H-score (test results for which will be provided by the laboratory) are less relevant to assessing the quality control of the tissue sample, these raw test results will not be listed.

Ki67 – Proliferative Activity of the Tumor

In order to assess the proliferative activity of the tumor mass, cellular proliferation reflected by the number of Ki67-positive cell objects in the tumor region divided by the total number of cell objects in the tumor region will be categorized as '<=10%' or '>10%' with the latter category indicating an actively/moderately proliferating tumor. If the test result is 'NOT EVALUABLE' or missing but IHC results are available (i.e. the participant had historical tumor biopsy sample(s) analyzed), then the result will be categorized as 'Not done'.

This categorical variable will be listed together with all other Ki67 raw test results.

Gremlin-1: Cytoplasmic Histoscore

The cytoplasmic histoscore will be calculated as a weighted score based on the percentage of tumor cells with Gremlin-1 cytoplasmic staining intensity 1, 2 or 3 as follows:

(1 x percent tumor cells with Gremlin-1 cytoplasmic staining intensity 1) + (2 x percent tumor cells with Gremlin-1 cytoplasmic staining intensity 2) + (3 x percent tumor cells with Gremlin-1 cytoplasmic staining intensity 3).

The cytoplasmic histoscore will be missing if the participant had a historical biopsy tumor sample analyzed but there are no test results for percent tumor cells with Gremlin-1 cytoplasmic staining intensity 1, 2 or 3.

The cytoplasmic histoscore will be listed together with all other Gremlin-1 raw test results.

FAP

From the image analysis of FAP-stained slides, the tumor will be classified into 2 regions: the cancer (CN) tumor region and the invasive margin (IM) region using a pre-established digital automated algorithm. The IM region is usually a small proportion of the whole tumor and, per standard procedures at the analytical laboratory, will be identified first. As a result, there is a risk that some parts of the CN tumor region may be inaccurately classified as part of the IM region, particularly in cases when the tumor is small. Therefore, instead of using the results for the percentage of high, medium and low intensity FAP provided by the laboratory, a decision was made to back-calculate the areas of the CN tumor region and the IM region and add these together in order to re-calculate the percentage of high, medium and low intensity FAP in the whole tumor.

These back-calculated results and derived variables based on FAP test results are defined in Table 9-1.

Table 9-1: FAP Derived Variables

Variable No.	FAP Derived Variable	Description and Calculation
1[a]	Total Analyzed Tumor Area (um^2)	This is the total tumor area (um^2) across the CN tumor region and the IM region and will be calculated as the sum of the areas of the CN tumor region (um^2) and the IM region (um^2) where a non-missing numeric test result is available for both the area of the CN tumor region and the area of the IM region. Note that, in cases where no IM region is defined, the area of the IM region will be recorded as 0 or 'NOT APPLICABLE', or may be missing. If the area of the IM region is recorded as 'NOT APPLICABLE' or is missing, then 0 will be assumed in this calculation and the total analyzed tumor area will be equal to the area of the CN tumor region.

Variable No.	FAP Derived Variable	Description and Calculation
		This variable will be missing if both the areas of the CN tumor region and IM region are missing, or if one or both are 'NOT EVALUABLE' or 'NOT DIAGNOSTIC'.
2	Measured Area of Weakly Stained FAP in the CN Tumor Region (um^2)	This is the back-calculated area of weakly stained FAP in the CN tumor region (weak positive) and will be calculated by multiplying the area of the CN tumor region (um^2) and the relative area of weakly stained FAP in the CN tumor region (%) where a non-missing numeric test result is available for both the area of the CN tumor region and the relative area of weakly stained FAP in the CN tumor region. This variable will be set to 0 if one or both are missing, 'NOT EVALUABLE' or 'NOT DIAGNOSTIC'.
3	Measured Area of Moderately Stained FAP in the CN Tumor Region (um^2)	This is the back-calculated area of moderately stained FAP in the CN tumor region (moderate positive) and will be calculated by multiplying the area of the CN tumor region (um^2) and the relative area of moderately stained FAP in the CN tumor region (%) where a non-missing numeric test result is available for both the area of the CN tumor region and the relative area of moderately stained FAP in the CN tumor region. This variable will be set to 0 if one or both are missing, 'NOT EVALUABLE' or 'NOT DIAGNOSTIC'.
4	Measured Area of Strongly Stained FAP in the CN Tumor Region (um^2)	This is the back-calculated area of strongly stained FAP in the CN tumor region (strong positive) and will be calculated by multiplying the area of the CN tumor region (um^2) and the relative area of strongly stained FAP in the CN tumor region (%) where a non-missing numeric test result is available for both the area of the CN tumor region and the relative area of strongly stained FAP in the CN tumor region. This variable will be set to 0 if one or both are missing, 'NOT EVALUABLE' or 'NOT DIAGNOSTIC'.
5	Measured Area of Weakly Stained FAP in the IM Region (um^2)	This is the back-calculated area of weakly stained FAP in the IM region (weak FAP-positive) and will be calculated by multiplying the area of the IM region (um^2) and the relative area of weakly stained FAP in the IM region (%) where a non-missing numeric test result is available for both the area of the IM region and the relative area of weakly stained FAP in the IM region. This variable will be set to 0 if one or both are missing, 'NOT EVALUABLE' or 'NOT DIAGNOSTIC'.

Variable No.	FAP Derived Variable	Description and Calculation
6	Measured Area of Moderately Stained FAP in the IM Region (um^2)	This is the back-calculated area of moderately stained FAP in the IM region (moderate FAP-positive) and will be calculated by multiplying the area of the IM region (um^2) and the relative area of moderately stained FAP in the IM region (%) where a non-missing numeric test result is available for both the area of the IM region and the relative area of moderately stained FAP in the IM region. This variable will be set to 0 if one or both are 'NOT EVALUABLE' or 'NOT DIAGNOSTIC'.
7[a]	Measured Area of Strongly Stained FAP in the IM Region (um^2)	This is the back-calculated area of strongly stained FAP in the IM region (strong FAP-positive) and will be calculated by multiplying the area of the IM region (um^2) and the relative area of strongly stained FAP in the IM region (%) where a non-missing numeric test result is available for both the area of the IM region and the relative area of strongly stained FAP in the IM region. This variable will be set to 0 if one or both are missing, 'NOT EVALUABLE' or 'NOT DIAGNOSTIC'.
8[a]	Total FAP-Positive Tumor Area (um^2)	This is the total FAP-positive area across the CN tumor region and the IM region (whole tumor) and will be calculated as the sum of component derived variables 2-7. If all 6 component variables are 0 then this derived variable will be missing.
9[a]	Total Measured Area of Weakly Stained FAP (um^2)	This is the total weak FAP-positive area across the CN tumor region and the IM region (whole tumor) and will be calculated as the sum of component FAP derived variables 2 and 5.
10[a]	Total Measured Area of Moderately Stained FAP (um^2)	This is the total moderate FAP-positive area across the CN tumor region and the IM region (whole tumor) and will be calculated as the sum of component FAP derived variables 3 and 6.
11[a]	Total Measured Area of Strongly Stained FAP (um^2)	This is the total strong FAP-positive area across the CN tumor region and the IM region (whole tumor) and will be calculated as the sum of component FAP derived variables 4 and 7.
12[a]	Total Relative Area of Weakly Stained FAP (%)	This is the percentage of weak FAP expression across the CN tumor region and IM region (whole tumor) and will be calculated using component FAP derived variables 1 and 9 as

Variable No.	FAP Derived Variable	Description and Calculation
		(Total Measured Area Of Weakly Stained FAP / Total Analyzed Tumor Area) x 100 If the total analyzed tumor area is missing then this variable cannot be calculated and will be missing.
13[a]	Total Relative Area of Moderately Stained FAP (%)	This is the percentage of moderate FAP expression across the CN tumor region and IM region (whole tumor) and will be calculated using component FAP derived variables 1 and 10 as (Total Measured Area Of Moderately Stained FAP / Total Analyzed Tumor Area) x 100 If the total analyzed tumor area is missing then this variable cannot be calculated and will be missing.
14[a]	Total Relative Area of Strongly Stained FAP (%)	This is the percentage of strong FAP expression across the CN tumor region and IM region (whole tumor) and will be calculated using component FAP derived variables 1 and 11 as (Total Measured Area Of Strongly Stained FAP / Total Analyzed Tumor Area) x 100 If the total analyzed tumor area is missing then this variable cannot be calculated and will be missing.
15[a]	Total Relative FAP-Positive Tumor Area (TPS) (%)	This is the total proportion score which is the percentage of FAP-positive area across the CN tumor region and the IM region (whole tumor) and will be calculated using component derived variables 1 and 8 as (Total FAP-Positive Tumor Area / Total Analyzed Tumor Area) x 100 If the total analyzed tumor area is missing then this variable cannot be calculated and will be missing.
16[a]	Total FAP Histoscore	This is a histoscore for the combined CN tumor region and IM region (whole tumor) and will be calculated as a weighted score based on component derived variables 12, 13 and 14 as (1 x Total Relative Area of Weakly Stained FAP) + (2 x Total Relative Area of Moderately Stained FAP) + (3 x Total Relative Area of Strongly Stained FAP).

CN=cancer; FAP=fibroblast activation protein, IM=invasive margin, TPS=total proportion score.
[a] Included in the listing of FAP test results.

The derived variables containing the [a] flag in Table 9-1 above will be listed together with information on staining artifacts and any assay-specific comments provided by the laboratory.

Further informal analyses may be performed to explore the relationship between the PD and biomarker endpoints with antitumor activity, ADA status, and also with key PK parameters. The PK-PD effects of UCB6114 may be assessed using a population analysis approach. These analyses will also be performed separately outside of the CSR and the details of analysis methods will be included in a separate analysis plan.

The incidence of available historical tumor biopsies will be summarized by treatment group. The incidence of PD samples taken from blood and urine will be summarized by cycle and treatment group.

9.3 Immunogenicity

Anti-drug (UCB6114) antibody status and classification, changes from Baseline in titer over time (Cycles 1, 2 and even cycles thereafter) and the incidence of treatment-emergent ADA positivity are exploratory immunogenicity endpoints in Part C of this study. Potential relationships between ADA and PK, PD, antitumor activity and safety will also be explored but this will be reported separately outside of the CSR.

Serum samples will be collected from all study participants for the measurement of ADA and the evaluation of immunogenicity according to the Schedule of Activities in the protocol.

All listings of ADA will be presented for the SS and summaries of the ADA data will be presented by treatment group for the ADAS.

Anti-drug (UCB6114) antibodies will be measured using a three-tiered assay approach: Screening assay, confirmatory assay and titration assay.

Samples will first be evaluated in the Screening assay using a false positivity rate of 5% (reported as ‘negative screen’ or ‘positive screen’), followed by analysis of screened positive samples in the confirmatory assay (which is a drug depletion assay) to confirm the positivity of the samples (reported as ‘negative immunodepletion’ or ‘positive immunodepletion’). Samples that are confirmed as positive in the confirmatory assay will be evaluated in a titration assay to assess the ADA level and this will be reported as titer (reciprocal dilution factor including minimum required dilution).

Anti-drug (UCB6114) antibody sample status will be determined as follows from the pre-treatment sample taken on Day 1 of Cycle 1 (Baseline) and all post-treatment (post-Baseline) samples.

- Sample values that are either ‘negative screen’ or ‘positive screen’ and ‘negative immunodepletion’ will be defined as **ADA negative**
- Sample values that are ‘positive screen’ and ‘positive immunodepletion’ will be defined as **ADA positive**

Anti-drug (UCB6114) antibody sample status will be listed for each participant at each visit by treatment group. This listing will include sampling dates and times, the Screening assay result, the confirmatory assay result and the derived ADA sample status. In addition, the titer from the titration assay (if applicable) will be listed together with the change from Baseline in titer. The number and percentage of participants with a positive or negative sample at each visit will be summarized by treatment group. Percentages will be calculated based on the number of participants with a non-missing/sufficient sample at the visit.

Based on the ADA status of the samples, study participants will be categorized according to the following 6 ADA classifications in Table 9-2:

Table 9-2: ADA Classifications

Classification	Classification Label	Definition
1	Pre-ADA negative – treatment induced ADA negative	Includes participants who have an ADA negative status at Baseline, or missing/insufficient Baseline sample, and an ADA negative status at all sampling timepoints post-Baseline (including SFU). Participants with missing post-Baseline samples are included as long as the missing samples do not result in an unmonitored period greater than 16 weeks.
2	Pre-ADA negative – treatment induced ADA positive	Includes participants who have an ADA negative status at Baseline, or missing/insufficient Baseline sample, and an ADA positive status at any sampling timepoint post-Baseline (including SFU).
3	Pre-ADA positive – treatment reduced ADA	Includes participants who have an ADA positive status at Baseline and an ADA negative status at all sampling timepoints post-Baseline (including SFU).
4	Pre-ADA positive – treatment unaffected ADA	Includes participants who have an ADA positive status at Baseline and an ADA positive status at any sampling timepoint post-Baseline (including SFU) with titer values of the same magnitude as Baseline (≤1.80 fold difference from the Baseline value) or with decreased titer values compared to Baseline (>1.80 fold decrease from the Baseline value).
5	Pre-ADA positive – treatment boosted ADA positive	Includes participants who have an ADA positive status at Baseline and an ADA positive status at any sampling timepoint post-Baseline (including SFU) with increased titer values compared to Baseline (>1.80 fold increase from the Baseline value).
6	Inconclusive	Includes participants who do not satisfy the criteria for classifications 1-5.

ADA=anti-drug (UCB6114) antibody; SFU=Safety Follow-up.
Note: The terminology 'treatment unaffected' is ambiguous as the criteria refers to ADA responses that are not increased upon dosing compared to Baseline level whereas titers may reduce.

A study participant will be classified as having **treatment-emergent ADA positivity** if they satisfy one of the following criteria:

- The Baseline result is ADA negative and at least one post-Baseline result is ADA positive (pre-ADA negative – treatment induced ADA positive) – ADA classification 2 in Table 9-2;
- The Baseline result is ADA positive and at least one post-Baseline result shows a pre-defined fold increase in titer from the Baseline value (the fold increase from Baseline required to meet this criterion will be defined with the development of the assay and will be included in the TFLs) (pre-ADA positive – treatment boosted ADA positive) – ADA classification 5 in Table 9-2.

Total anti-drug (UCB6114) antibody **incidence** will be determined by the number and percentage of participants with treatment-emergent ADA positivity (as defined above). The denominator for the percentage calculation will be the number of participants with at least one available/reported post-Baseline result.

Total **prevalence** of pre-anti-drug (UCB6114) antibody will be determined by the number and percentage of participants who are pre-ADA positive (i.e. participants who have a positive ADA status at Baseline). The denominator for the percentage calculation will be the number of participants with an available/reported Baseline sample result.

Total anti-drug (UCB6114) antibody **prevalence** will be determined by the number and percentage of participants with ADA classifications 2, 3 or 5 in Table 9-2 (i.e. an ADA positive status at any post-Baseline sampling timepoint. The denominator for the percentage calculation will be the number of participants with at least one available/reported sample result (either at Baseline and/or post-Baseline).

The ADA classification for each participant will be listed by treatment group. This listing will also include whether or not the participant achieved treatment-emergent ADA positivity (ADA incidence), whether the participant was pre-ADA positive (pre-ADA prevalence) and whether the participant had an ADA positive or negative status at any post-Baseline sampling timepoint (ADA prevalence). In addition, the visit at which the participant first achieved treatment-emergent ADA positivity will be included.

The number and percentage of participants in each of the 6 ADA classifications defined above in Table 9-2 will be presented by treatment group. Also, in this tabulation, ADA incidence and prevalence (as defined above) will be summarized.

The first occurrence of treatment-emergent ADA positivity (based on the criteria above) will be summarized using frequency counts and percentages at each post-Baseline visit by treatment group. This tabulation will include a count of the number of participants at each post-Baseline visit who fulfill at least one of the above defined criteria for treatment-emergent ADA positivity; participants will be counted in the numerator based on the earliest visit at which one of these criteria is fulfilled. At other visits, participants will be counted in the denominator (assuming an assessment of treatment-emergent positivity is available) and this will be used in the percentage calculations.

Individual study participant ADA titer profiles over actual time will be presented graphically on the linear and the semi-logarithmic scale. The linear scale plots will be repeated for the subset of participants who achieve treatment-emergent ADA positivity during Part C.

Mean (±standard deviation) C_{min} will be plotted by ADA sample status over nominal (scheduled) time with treatment groups overlaid on the same plot. On this plot, mean C_{min} at Cycle 1 Day 15 will be the mean of the derived C_{min} following the first dose of UCB6114 (as described in Section 9.1.2) and, thereafter from Cycle 2 Day 1, mean C_{min} will be the mean of the predose concentrations at the subsequent dosing visits.

10. EFFICACY ANALYSES

10.1 Antitumor activity

The analysis of antitumor activity is exploratory in Part C of this study.

10.1.1 Definitions of the antitumor activity endpoints

The following endpoints are defined based on RECIST (Version 1.1) which standardizes solid tumor measurements and provides guidelines for the objective assessment of changes in tumor size during anti-cancer treatment.

Appendix 9 (Section 11.9) of the protocol contains the RECIST 1.1 guidelines to be used in this study, adapted from Eisenhauer (2009), and includes the definitions of target and non-target lesions, the definitions of target and non-target lesion responses at each tumor assessment, the criteria for determining overall response at each tumor assessment based on target lesion response, non-target lesion response and the presence/absence of new lesions, and a participant's best overall response (BOR). Further details on the rules to apply in the derivation of BOR are included in the Derivation of Efficacy Endpoints document which has been developed to support this SAP.

At each post-Baseline tumor assessment, the investigator will record responses for target lesions and non-target lesions, whether or not there has been an appearance of any new lesions, and the participant's overall response based on their target lesion response, non-target lesion response and the presence/absence of new lesions. Note that target lesion response and non-target lesion response assessments will be based on the changes in the pre-existing lesions at Baseline and the appearance of new lesions will only factor in the determination of an overall response of PD at that tumor assessment visit (i.e. per Tables A and B in Section 11.9.2 of Appendix 9 of the protocol).

Objective response rate (ORR) is defined as the percentage of participants with a BOR of complete response (CR) or partial response (PR) during Part C.

Disease Control Rate (DCR) is defined as the percentage of participants with a BOR of CR, PR, or stable disease (SD) during Part C.

Best overall response (BOR) is defined for each study participant as the best overall tumor response from each tumor assessment (performed every 8 weeks from Day 1 of Cycle 1 (±7 days)) according to the RECIST criteria for changes in target and non-target lesions and the appearance of new lesions. Best overall response is determined from the start of study treatment (first dose of UCB6114) until documented objective disease progression or the date of

subsequent anti-cancer therapy (systemic therapy, surgery or radiotherapy for cancer), whichever occurs first. If anti-cancer therapy is started on the same day as a tumor assessment, then the overall response from that assessment will be used in the derivation of BOR. If a participant does not have objective disease progression or does not start a subsequent anti-cancer therapy then all tumor assessments up to the SFU visit will be included in the derivation of BOR. For a BOR of SD, a participant's tumor measurements must have met the SD criteria at least once after the start of study treatment at a minimum interval of no less than 49 days.

For this study, BOR determination requires confirmation of CR or PR responses at a subsequent assessment ≥4 weeks (28 days) after the criteria for CR or PR responses are first met, however, an unconfirmed BOR will also be derived for each participant for the purpose of reporting (as described below in Section 10.1.2). Table C in Appendix 11.9 of the protocol and Table 1 and subsequent text in the Derivation of Efficacy Endpoints document provides the derivation of BOR when confirmation of CR and PR responses are required. The definition of an unconfirmed BOR is also included in this document. Although the derivation of unconfirmed BOR does not include the requirement for a CR or PR response to be confirmed ≥4 weeks (28 days) after the initial response, a participant's CR or PR response may, in fact, be confirmed at a subsequent assessment ≥4 weeks (28 days) after the criteria for the CR or PR response are first met. Unconfirmed BOR will be referred to as BOR (confirmed or unconfirmed) throughout the rest of this document.

Confirmed BOR and BOR (confirmed or unconfirmed) will be derived programmatically based on the overall tumor assessment data recorded on the eCRF by the investigator.

Duration of response (DOR) will be calculated for participants with a BOR of confirmed CR or PR as the time in days from the start date of the confirmed CR or PR (e.g. the date of the first overall response of CR or PR, which is at least 4 weeks before a second overall response of CR or PR) to the first date that recurrent or progressive disease is objectively documented (i.e. according to the RECIST guidelines). This will be referred to as the duration of confirmed response and the following calculation will be performed:

$$\begin{aligned} &Duration\ of\ Confirmed\ Response \\ &\quad = (Date\ of\ First\ Objective\ Disease\ Progression \\ &\quad - Start\ Date\ of\ Confirmed\ CR\ or\ PR\ Response) + 1 \end{aligned}$$

Duration of response will also be calculated for participants with a BOR of CR or PR which is either confirmed or unconfirmed [DOR (confirmed or unconfirmed)] as the time in days from the start date of the CR or PR to the date of the first documented objective disease progression (i.e. according to the RECIST guidelines). The following calculation will be performed:

$$\begin{aligned} &DOR\ (Confirmed\ or\ Unconfirmed) \\ &\quad = (Date\ of\ First\ Objective\ Disease\ Progression \\ &\quad - Start\ Date\ of\ CR\ or\ PR\ Response) + 1 \end{aligned}$$

For the purpose of a sensitivity analysis of both duration of confirmed response and DOR (confirmed or unconfirmed), the above calculations will take into consideration the occurrence of both objective disease progression (per RECIST 1.1) and clinical disease progression (as described in Appendix 11.9 of the protocol and as determined by the investigator and recorded as a reason for study treatment discontinuation on the eCRF), whichever occurs first. If clinical

disease progression occurs on the same date that a participant's objective disease progression is determined, then the participant will be included in the sensitivity analyses as having objective disease progression.

The following calculations will therefore be performed for the sensitivity analyses:

$$Duration\ of\ Confirmed\ Response = (Date\ of\ First\ Objective\ or\ Clinical\ Disease\ Progression - Start\ Date\ of\ Confirmed\ CR\ or\ PR\ Response) + 1$$

$$DOR\ (Confirmed\ or\ Unconfirmed) = (Date\ of\ First\ Objective\ or\ Clinical\ Disease\ Progression - Start\ Date\ of\ CR\ or\ PR\ Response) + 1$$

For participants who die without objective disease progression, DOR will be censored on the date of death, regardless of cause. For a participant who discontinues early from Part C of the study with no objective disease progression, DOR will be censored on the date of their last available (scheduled or unscheduled) tumor assessment at which a lack of objective disease progression was determined. Participants who discontinue study treatment but who do not have documented objective disease progression (i.e. according to the RECIST guidelines), DOR will be censored at the date of their last available (scheduled or unscheduled) tumor assessment at which a lack of objective disease progression was determined. Such participants might include those that are ongoing in Part C at the time of any defined data cut-off. Likewise, participants who have not discontinued early and do not have disease progression after a confirmed or unconfirmed response, DOR will be censored at the date of their last available (scheduled or unscheduled) tumor assessment.

In the sensitivity analyses of duration of confirmed response and duration of unconfirmed response, the same censoring rules will apply except that the date of last contact will be used for the censoring of participants who discontinue early from Part C or complete Part C without objective disease progression, clinical disease progression or death.

Date of last contact will be the latest of the dates of premature study termination and of last contact recorded on Study Termination eCRF page, the date of death, the date of last dose of study treatment, the dates of all visits, AE start and end dates (with partial dates imputed as earliest possible) and the date of contact recorded on the Survival Safety Follow-up and Survival Final Follow-up eCRF forms.

Further details on the rules to apply in the derivation of DOR are included in the Derivation of Efficacy Endpoints document which has been developed to support this SAP.

Progression-free survival (PFS) will be calculated as the time in days from the first dose of study treatment to the date of the first documented objective disease progression (i.e. according to the RECIST guidelines), or death due to any cause, whichever occurs first. The following calculation will be performed:

$$PFS = (Date\ of\ Objective\ Progressive\ Disease/Death - Date\ of\ First\ Dose) + 1$$

Participants who die due to any cause without a documented objective disease progression will be considered to have progressed on the date of their death. Participants who do not have any post-Baseline tumor assessments will be censored on the date of their first dose of study treatment. Participants who discontinue early from Part C or discontinue study treatment without

documented objective disease progression or death, will be censored on the date of their last available (scheduled or unscheduled) tumor assessment at which a lack of objective disease progression was determined. Participants who start anti-cancer therapy during Part C without a prior documented objective disease progression will be censored on the date of their last available (scheduled or unscheduled) tumor assessment prior to the initiation of the subsequent anti-cancer therapy. If anti-cancer therapy starts on the same date as the participant's tumor assessment and determination of objective disease progression, or the participant's death (due to any cause), then the participant will not be censored and the participant will be included as having an uncensored event on this date. This censoring rule will also be applied to participants who are ongoing at any data cut-off for an analysis of Part C data who have no documented objective disease progression. The use of anti-cancer therapy during Part C will be identified via ongoing medical review of the concomitant medications together with the start dates of further anti-cancer therapy information recorded on the survival follow-up pages of the eCRF.

As a sensitivity analysis, PFS will also be calculated as the time in days from the first dose of study treatment to the date of the first documented objective disease progression (per RECIST 1.1), the date of clinical disease progression, as determined by the investigator, or the date of death due to any cause, whichever occurs first. Last contact date will be used for the censoring of participants still alive with no reported disease progression (objective or clinical). The same rules described above for the censoring of participants who start anti-cancer therapy will be applied in this sensitivity analysis.

Further details on the rules to apply in the derivation of PFS are included in the Derivation of Efficacy Endpoints document which has been developed to support this SAP.

Overall survival (OS) will be calculated as the time in days from the date of first dose of UCB6114 to the date of death from any cause. Participants will be followed up to ascertain their survival status at the SFU visit (within 30 days after their last dose of UCB6114) and at the Final Visit (3 months after their last dose of UCB6114); they will not be followed up beyond this timepoint.

The following calculation will be performed:

$$OS = (Date\ of\ Death - Date\ of\ First\ Dose\ of\ UCB6114) + 1$$

OS will be censored on the date of their last contact for participants who discontinue early from Part C of the study or who discontinue study treatment due to disease progression but continue in the study, are not known to have died.

Further details on the rules to apply in the derivation of OS are included in the Derivation of Efficacy Endpoints document which has been developed to support this SAP.

10.1.2 Analysis of the antitumor activity endpoints

The analyses of the antitumor activity endpoints in Part C will be performed for the PPS. As a sensitivity analysis, all analyses will be repeated for the SS. All listings will be presented for the SS. Summaries and listings will be presented by treatment group.

All lesion assessment data recorded at Baseline (Screening) and during the Treatment Period (every 8 weeks from Day 1 of Cycle 1 [±7 days]) will be listed separately for target lesions, non-target lesions and new lesions. Each post-Baseline tumor assessment will be labelled as 'Tumor Assessment 1, Tumor Assessment 2 etc. – see further details below). These listings will include

lesion number and lesion type (nodal/non-nodal), location, method of assessment, dimension (or an indication that the lesion is too small to measure, for target lesions only) and lesion response evaluation (for non-target lesions at post-Baseline assessments). The listing for target lesions will also include the derived eCRF component data used for the determination of the overall target lesion response at each post-Baseline assessment (e.g. sum of all dimensions across target lesions and percentage change from Baseline in the sum). In addition, the overall response assessment for target lesions and non-target lesions, as determined by the investigator, will be listed for each post-Baseline tumor assessment (Tumor Assessment 1, Tumor Assessment 2 etc.) together with the presence of new lesions and the overall response assessment.

The investigator's overall tumor response assessment will be summarized using frequency counts and percentages over time (tumor assessment). Post-Baseline tumor assessments are scheduled to be performed per protocol every 8 weeks from Day 1 (±7 days). For the purpose of this summary, the first post-Baseline tumor assessment (scheduled or unscheduled) will be assigned to 'Tumor Assessment 1' using the protocol-defined window of Day 50 to 64 (Day 57 ± 7 days) relative to Day 1 (first dose of UCB6114). For all subsequent post-Baseline tumor assessments (scheduled or unscheduled, but excluding tumor assessments performed at the SFU visit), these will be assigned to 'Tumor Assessment 2', 'Tumor Assessment 3' etc. using the protocol-defined window of Day 50-64 relative to the previous post-Baseline tumor assessment. If a post-Baseline tumor assessment is missed, then the scheduled day of the missed assessment will be used to window the next tumor assessment. In cases where a scheduled and unscheduled tumor assessment occurs in the same window, the investigator's overall tumor response at both assessments will be considered. If the overall tumor response is NE at one of the assessments, then the overall tumor response from the other assessment will be included in the summary table. If the overall tumor response is not NE at both assessments, then the tumor assessment that is closest to the target day of the tumor assessment will be included in the summary table. In the event that the two tumor assessments are equidistant from the target day of the tumor assessment and neither have an overall tumor response of NE, then the worst case overall tumor response will be included in the summary table. Otherwise, if the post-Baseline tumor assessment falls outside of the protocol-defined window, it will be classified as an unscheduled assessment and not included in the summary of overall tumor response. Bar charts will also be produced for overall tumor response rate by treatment group for each visit. In addition, waterfall plots of participants' percentage change from Baseline in the sum of dimensions for all target lesions will be presented by treatment group and visit. The individual participants' bars will be colored by overall tumor response at the visit.

Confirmed and unconfirmed BOR for each participant will be derived programmatically using the overall response assessments performed every 8 weeks from Day 1 of Cycle 1 (or at unscheduled timepoints) and the RECIST criteria. Whether a BOR of CR or PR is confirmed or unconfirmed will be indicated on this listing. Using a participant's BOR, whether the participant achieves an objective tumor response (i.e. a BOR of CR or PR) and/or disease control (i.e. a BOR of CR, PR or SD) during study treatment will be determined. These derived data will be listed for the SS.

Confirmed BOR and unconfirmed BOR will be summarized using frequency counts and percentages. Bar charts will also be produced for confirmed BOR and unconfirmed BOR by treatment group.

The number and percentage of participants achieving objective tumor response and disease control (ORR and DCR) based on confirmed BOR and BOR (confirmed or unconfirmed) will be presented and, if data allow, exact 95% CIs for binomial proportions will be calculated using the Clopper-Pearson method and presented for the response rates. In the calculation of ORR and DCR, the denominator will include all participants in the analysis set. Objective response rate and DCR (based on confirmed BOR and unconfirmed BOR) will also be summarized in bar charts by treatment group overall and by tumor type and ECOG performance status at Baseline.

In addition, waterfall plots of each participant's best percentage change from Baseline in the sum of the dimensions for all target lesions will be presented by treatment group overall and by tumor type and ECOG performance status at Baseline with the individual participants' bars colored by confirmed BOR and unconfirmed BOR.

The summaries and analyses of DOR, PFS and OS will be carried out as described below, if the data allow.

Duration of confirmed response, DOR (confirmed or unconfirmed) and PFS will be listed and summarized descriptively using Kaplan-Meier estimation. These summaries will be repeated for the sensitivity analyses of these endpoints (defined in Section 10.1.1 above) and will include the number and percentage of participants with the event, the number and percentage of participants censored, minimum and maximum values and Kaplan-Meier estimates of the 25th percentile, median, 75th percentile and corresponding 95% CIs calculated using Greenwood's formula. In addition, DOR and PFS rates at 3 months, 6 months and 9 months will be derived from the Kaplan-Meier estimation and presented together with associated 95% CIs.

Kaplan-Meier curves will be presented for duration of confirmed response and DOR (confirmed or unconfirmed) and PFS. Treatment groups will be overlaid on each plot.

Survival status collected on the eCRF at the SFU visit and at the Final Visit will be listed for each participant by treatment group. This listing will include the participant's survival status, date and cause of death, whether an autopsy was performed and date of autopsy, whether the participant had received any further antitumor treatment after the last dose of study treatment and the type of treatment, and whether the participant's disease had been assessed since the end of study treatment including method of assessment and the overall response.

Overall survival times will be listed and summarized descriptively using Kaplan-Meier estimation. Note that since participants are only followed up for survival until the Final Visit in Part C of the study, a summary of OS may not be meaningful (i.e. if no participants die then OS cannot be assessed).

Exploratory analyses of selected antitumor activity endpoints may be performed based on subgroups of participants in the SS. Data permitting, the subgroups will be defined based on participant, disease, and treatment history information (e.g. extent of prior anti-cancer therapy).

Additionally, the relationship of the antitumor activity variables with key PK parameters may be explored but this will be reported separately.

10.2 ECOG performance status

ECOG performance status is an additional efficacy assessment performed in Part C of this study and is defined in Table 10-1.

Table 10-1: ECOG Performance Status Scale

Grade	ECOG performance status scale
0	Fully active, able to carry on all pre-disease performance without restriction
1	Restricted in physically strenuous activity but ambulatory and able to carry out work of a light or sedentary nature (e.g. light housework, office work)
2	Ambulatory and capable of all self-care but unable to carry out any work activities. Up and about more than 50% of waking hours
3	Capable of only limited self-care, confined to bed or chair for more than 50% of waking hours
4	Completely disabled. Cannot carry out any self-care. Totally confined to bed or chair
5	Dead

ECOG=Eastern Cooperative Oncology Group.

ECOG performance status will be listed by treatment group at each visit for the SS.

ECOG performance status will be summarized as an ordinal categorical variable using frequency counts and percentages. Shift tables for the change from Baseline in each grade will be summarized by visit.

11. OTHER ANALYSES

Not applicable.

12. REFERENCES

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13. APPENDICES

13.1 SMQ algorithm for identification of anaphylactic reactions

Based on MedDRA® Version 25.1, the SMQ='Anaphylactic reaction' consists of 3 parts:

1) A **narrow search** containing PTs that represent core anaphylactic reaction terms:

Category A

Anaphylactic reaction
Anaphylactic shock
Anaphylactic transfusion reaction
Anaphylactoid reaction
Anaphylactoid shock
Circulatory collapse
Dialysis membrane reaction
Kounis syndrome
Procedural shock
Shock
Shock symptom
Type I hypersensitivity

2) A **broad search**:

Category B

Acute respiratory failure
Asthma
Bronchial oedema
Bronchospasm
Cardio-respiratory distress
Chest discomfort
Choking
Choking sensation
Circumoral oedema
Cough
Cough variant asthma
Cyanosis
Dyspnoea
Hyperventilation
Irregular breathing
Laryngeal dyspnoea
Laryngeal oedema
Laryngospasm
Laryngotracheal oedema
Mouth swelling
Nasal obstruction
Oedema mouth
Oropharyngeal oedema
Oropharyngeal spasm
Oropharyngeal swelling
Pharyngeal oedema
Pharyngeal swelling
Respiratory arrest
Respiratory distress
Respiratory failure
Reversible airways obstruction
Sensation of foreign body
Sneezing
Stridor
Swollen tongue
Tachypnoea
Throat tightness
Tongue oedema

Tracheal obstruction	Vaccine associated enhanced respiratory disease
Tracheal oedema	Wheezing
Upper airway obstruction	
Category C	
Allergic oedema	Oedema
Angioedema	Oedema blister
Circumoral swelling	Periorbital oedema
Erythema	Periorbital swelling
Eye oedema	Pruritis
Eye pruritis	Pruritis allergic
Eye swelling	Rash
Eyelid oedema	Rash erythematous
Face oedema	Rash pruritic
Flushing	Skin swelling
Injection site urticaria	Swelling
Lip oedema	Swelling face
Lip swelling	Swelling of eyelid
Nodular rash	Urticaria
Ocular hyperaemia	Urticaria papular
Category D	
Blood pressure decreased	Cardiovascular insufficiency
Blood pressure diastolic decreased	Diastolic hypotension
Blood pressure systolic decreased	Hypotension
Cardiac arrest	Hypotensive crisis
Cardio-respiratory arrest	Post procedural hypotension

Note that if the MedDRA® version is increased from 25.1 during the study, any changes to the terms in the above categories should be applied.

The following **algorithmic approach** will be applied: A or (B and C) or [D and (B or C)], i.e.

If a participant has a TEAE which codes to a PT included in Category A, then the event will be flagged as an anaphylactic reaction. Note that participants with a TEAE coded to a PT=’Type 1 hypersensitivity’ will also be flagged as having a hypersensitivity reaction as this PT is also included in the Category A narrow search for the ‘Hypersensitivity’ SMQ.

OR

If a participant has a TEAE which codes to a PT included in Category B **AND** has a TEAE which codes to a PT included in Category C**, and both TEAEs have the same start date**, then both events will be flagged as anaphylactic reactions.

OR

If a participant has a TEAE which codes to a PT included in Category D **AND** has (either a TEAE which codes to a PT included in Category B **OR** a TEAE which codes to a PT included in Category C), **and both TEAEs have the same start date**, then both events will be flagged as anaphylactic reactions.

13.2 SAP Amendment 1 Changes

The main rationale for SAP Amendment 1 is to include details on the additional key derived and component exploratory variables required based on the results from the analyses of historical tumor biopsy samples in Part C. It was decided that these additional variables were needed to improve the interpretability of the test results received from the laboratory. This SAP amendment also provides some clarifications relating to the handling of data for the purpose of summarizing safety and exploratory anti-tumor activity endpoints.

The key changes are summarized in the table below (note that additional minor corrections and clarifications were also applied in this amendment but are not included in this table).

Section	Description of Change
1	The versions and dates of supporting study documentation were updated.
5.1	An update was made to the example illustrating the definition of a complete cycle of UCB6114.
8.1	The additional summary of the total number of doses of study treatment received was included.
8.2	Rules for handling missing relationship to study treatment for an adverse event were updated.
8.4.2	Clarification on the handling of triplicate ECG measurements was included.
9.1.2	Updates were added for more clarification on how C_{min} and C_{max} is to be derived.
9.2	Details on the analysis of the historical tumor biopsy samples was included together with rules for defining key and component derived variables based on the test results received from the laboratory. These variables were considered important for clearer interpretation of these results from data listings.
9.3	A predefined fold-increase of 1.80 was included.

Section	Description of Change
10.1.2	Rules for applying the protocol-defined window around the post-Baseline tumor assessments (scheduled and unscheduled) for the purpose of summarizing the investigator's overall tumor response assessment were included.
General	MedDRA® version number was updated to the latest version (25.1) throughout the document.

STATISTICAL ANALYSIS PLAN SIGNATURE PAGE

This document has been reviewed and approved per the Review and Approval of Clinical Documents Standard Operating Procedures. Signatures indicate that the final version of the Statistical Analysis Plan (SAP) or amended SAP is released for execution.