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

PROTOCOL ONC001 – AMENDMENT 6

PHASE 1/2

SHORT TITLE:

An open-label, multicenter, first in human study in participants with advanced solid tumors treated with UCB6114

Sponsor:

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PROTOCOL AMENDMENT SUMMARY OF CHANGES TABLE

Document History		
Document	**Date**	**Type of amendment**
Protocol Amendment 6	26 Jun 2023	Substantial
Protocol Amendment 5	14 Jan 2022	Substantial
Protocol Amendment 4	17 Jun 2021	Substantial
Protocol Amendment 3.2 (UK)	07 Apr 2021	Substantial
Protocol Amendment 3.1 (US)	24 Mar 2021	Not applicable
Protocol Amendment 3	07 Jan 2021	Substantial
Protocol Amendment 2	12 Oct 2020	Substantial
Protocol Amendment 1	11 Jun 2020	Substantial
Original Protocol	14 Oct 2019	Not applicable

Amendment 6 (26 Jun 2023)

Overall Rationale for the Amendment

The overall rationale for Amendment 6 is to provide clarity for the suspension of the study and to reflect the ability to stop either the entire study or individual study part.

This amendment is considered to be substantial based on the criteria set forth in Article 10(a) of Directive 2001/20/EC of the European Parliament and the Council of the European Union.

Section # and Name	Description of Change	Brief Rationale
6.7 Criteria for study hold or dosing stoppage 11.6 Appendix 6: Rapid Alert Procedures	Clarification that either the entire study or an individual Study Part can be suspended. Clarification of the process for study/individual Study Part hold/potential restart when criteria for study/individual Study Part suspension are met.	To clarify the study/Study Part hold procedures
1.3 Schedule of Activities 9.8 Pharmacodynamics	Footnotes j and n of Table 1-6 (Part A1, Cohort 3) have been updated to clarify when blood sample for PK and cGremlin should be collected with regards to biopsy. Footnotes o and p of Table 1-7 (Part B) and Table 1.8 (Part C) has been updated to clarify when blood samples for ADA, circulating gremlin-1 and ctDNA analysis are to be collected. In line with this change, a footnote has been added for Table 9-9 and Table 9-21.	Clarification
Global	Correction of typographical errors.	Correction

SERIOUS ADVERSE EVENT REPORTING

Serious adverse event reporting (24h)	
Fax	**Europe and Rest of the World:** +32 2 386 24 21 **US and Canada:** +1 800 880 6949 or +1 866 890 3175
Email	PSRapidalert@ucb.com
Phone	**UCB Study Physician:** [redacted] UCB Celltech, 208 Bath Rd, Slough, Berkshire, SL1 3WE, UK **24h Rapid Response Helpline:** +448081640230

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1 PROTOCOL SUMMARY

1.1 Synopsis

Protocol title: A Phase 1/2 open-label, multicenter study to assess the safety, pharmacokinetics (PK), and antitumor activity of UCB6114 administered intravenously (iv) to participants with advanced solid tumors.

Short Title: An open-label, multicenter, first in human (FIH) study in participants with advanced solid tumors treated with UCB6114.

Rationale: Gremlin-1, secreted by the tumor stroma, binds to bone morphogenetic proteins (BMPs) and antagonizes signaling, thereby allowing tumor cell expansion, renewal, and a more mesenchymal phenotype. By blocking this gremlin-1 BMP antagonism, UCB6114 is expected to restore BMP signaling, limit tumor cell expansion, and favor a more epithelial phenotype. Gremlin-1 messenger ribonucleic acid (mRNA) has been shown to be expressed in >60% of colorectal, pancreatic, and esophageal cancer cases and approximately 50% of bladder, breast, and lung cancer cases (Sneddon et al, 2006). It has also been shown to be a key driver in hereditary mixed polyposis syndrome (HMPS) (Jaeger et al, 2012), a rare and severe premalignant condition characterized by the development of mixed morphology colorectal tumors. Despite advances in the treatment regimens in the last decade, there is still a large unmet need in the therapy of cancer types mentioned above. For example, in colorectal cancer (CRC), nearly 25% will present with metastatic disease and 40% to 50% of those initially diagnosed with early-stage disease will eventually develop metastatic disease (Moriarity et al, 2016).

UCB6114 is a fully human immunoglobulin G4 (IgG4) monoclonal antibody (mAb), optimized for neutralizing activity against the human gremlin-1 protein, for the treatment of advanced solid tumors. Based on the mechanism of action of UCB6114 and previously generated nonclinical data, it is believed that UCB6114 could potentially represent an advance in the treatment of advanced solid tumors. This supports the testing of the objectives of this FIH study, which are to evaluate the safety, PK, and antitumor activity of iv UCB6114 and identify the recommended Phase 2 dose (RP2D) for UCB6114 when administered as monotherapy or in combination with standard of care (SOC) in participants with advanced solid tumors.

Objectives and endpoints

Study objectives and endpoints for the dose escalation and expansion modules are presented in Table 1-1 (Part A and Part A1), Table 1-2 (Part B and Part C), and Table 1-3 (Parts D, E, F, and G), respectively. The overarching objective of this study is to determine the RP2D for monotherapy (RP2D-M) and for combination therapy. This will be determined using the totality of data generated based on the objectives in Table 1-1 (Part A and Part A1), Table 1-2 (Part B and Part C), and Table 1-3 (Parts D, E, F, and G).

Table 1-1: Objectives and endpoints for the dose escalation module (Part A) and the dose optimization module (Part A1)

Objectives	Endpoints
Primary	
To characterize the safety profile of UCB6114 as monotherapy	Incidence of TEAEs Severity of TEAEs Incidence of DLTs
Secondary	
To characterize the PK of UCB6114 administered as monotherapy	UCB6114 concentration by scheduled assessment and cohort
Tertiary/exploratory	
To document any antitumor activity observed with UCB6114 according to relevant RECIST criteria	Antitumor activity as indicated by: • ORR • DCR • DOR • PFS • OS
To explore PD biomarkers of UCB6114	• Change in transcriptional and protein marker levels in blood and tumor tissue by scheduled assessment and cohort • Change in ctDNA levels in blood by scheduled assessment and cohort
To evaluate the incidence, emergence, and impact of ADA	ADA (anti-UCB6114 antibody) titer and sample status by scheduled assessment

ADA=antidrug antibody; ctDNA= circulating tumor DNA; DCR=disease control rate; DOR=duration of antitumor response; DLT=dose-limiting toxicity; ORR=objective response rate; OS=overall survival; PD=pharmacodynamic(s); PFS=progression-free survival; PK=pharmacokinetic(s); RECIST=Response Evaluation Criteria in Solid Tumors; TEAE=treatment-emergent adverse event

Table 1-2: Objectives and endpoints for the dose escalation modules in Part B and Part C

Objectives	Endpoints
Primary	
To characterize the safety profile of UCB6114 administered in combination with selected SOC regimens	Incidence of TEAEs Severity of TEAEs Incidence of DLTs
Secondary	
To characterize the PK of UCB6114 administered in combination with selected SOC regimens	UCB6114 concentration by scheduled assessment and dose level
Tertiary/exploratory	
To document any antitumor activity observed with UCB6114 administered in combination with selected SOC regimens according to relevant RECIST criteria	Antitumor activity as indicated by: • ORR • DCR • DOR • PFS • OS
To explore PD biomarkers of UCB6114 administered in combination with selected SOC regimens	• Change in protein marker levels in blood by scheduled assessment and dose level • Change in ctDNA levels in blood by scheduled assessment and dose level
To evaluate the immunogenicity of UCB6114 administered in combination with selected SOC regimens	ADA (anti-UCB6114 antibody) titer and sample status by scheduled assessment

ADA=antidrug antibody; ctDNA= circulating tumor DNA; DCR=disease control rate; DLT=dose-limiting toxicity; DOR=duration of antitumor response; ORR=objective response rate; OS=overall survival; PD=pharmacodynamic(s); PFS=progression-free survival; PK=pharmacokinetic(s); RECIST=Response Evaluation Criteria in Solid Tumors; SOC=standard of care; TEAE=treatment-emergent adverse event

Table 1-3: Objectives and endpoints for the expansion modules in Parts D, E, F, and G

Objectives	Endpoints
Primary	
To assess preliminary antitumor activity of UCB6114 when administered as monotherapy (Part D and Part E) or in combination with selected SOC regimens (Part F and Part G) according to relevant RECIST criteria	Antitumor activity as indicated by ORR
Secondary	
To characterize the safety profile of UCB6114 as monotherapy or in combination with selected SOC regimens	• Incidence of TEAEs • Severity of TEAEs
To document any antitumor activity observed with UCB6114 when administered as monotherapy or in combination with selected SOC regimens	Antitumor activity as indicated by: • DCR • DOR • PFS • OS
Tertiary/exploratory	
To explore PD biomarkers of UCB6114 administered as monotherapy or in combination with selected SOC regimens	Change in transcriptional and protein marker levels in blood and tumor tissue by scheduled assessment
To characterize the PK of UCB6114 administered as monotherapy or in combination with selected SOC regimens	UCB6114 concentration by scheduled assessment and dose level
To evaluate the immunogenicity of UCB6114 administered as monotherapy or in combination with selected SOC regimens	ADA (anti-UCB6114 antibody) titer and sample status by scheduled assessment

ADA=antidrug antibody; DCR=disease control rate; DOR=duration of antitumor response; ORR=objective response rate; OS=overall survival; PD=pharmacodynamic(s); PFS=progression-free survival; PK=pharmacokinetic(s); RECIST=Response Evaluation Criteria in Solid Tumors; SOC=standard of care; TEAE=treatment-emergent adverse event

Overall design

ONC001 is a multicenter, nonrandomized, open-label, Phase 1/2 study evaluating the safety, PK, efficacy (as assessed by antitumor activity), pharmacodynamics (PD), biomarkers, and immunogenicity (as assessed by antidrug antibody[ADA] participant classification) of iv UCB6114 as monotherapy (Parts A, A1, D, and E) or in combination with selected SOC regimens (Parts B, C, F, and G) in participants with advanced solid tumors. The RP2D-M or RP2D of iv UCB6114 for each combination therapy under evaluation will also be determined.

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 expansion modules (Parts D, E, F, and G) (see Table 4-1). Depending on emerging data, not all modules may open.

After completion of Part A, specific characteristics of modules subsequent to Part A will be described in planned protocol amendments. The updated characteristics will include, but not be limited to, tumor type selection, participant inclusion/exclusion criteria, route and frequency of study medication administration, and selection of the SOC treatment regimen.

Part A consists of a Screening Period, Treatment Period (consisting of 28-day cycles), a Safety Follow-Up (SFU) Visit, and a Final Visit, as shown in Table 1-4 and Figure 1-2. During the Treatment Period, UCB6114 is administered by iv infusion on Days 1 and 15 of each cycle, until the occurrence of progressive disease, unacceptable toxicity, or withdrawal of consent. The full Schedule of Activities is provided in Table 1-4.

Part A1 may commence after the fifth cohort in Part A (2000mg, every 2 weeks [Q2W]) has been determined to be [redacted] (ie, DLT incidence <33%, see Section 4.1.2.4). Based on emerging data from Part A, this module will evaluate different frequencies of dosing (eg, every 3 weeks [Q3W], every 4 weeks [Q4W]) and different durations of infusion (Figure 1-3). Four different dosing schedules (cohorts) have been defined:

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

In Part A1, as all cohorts will receive a new dose formulation, Cohort 1 will repeat the dosing schedule of Part A Cohort 5.

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 is administered as iv infusion as per defined dosing schedules until the occurrence of progressive disease, unacceptable toxicity, or withdrawal from the study. The full Schedule of Activities is provided in Table 1-5 and Table 1-6.

Part B consists of a Screening Period, Treatment Period (consisting of 28-day cycles), a SFU Visit, and a Final Visit, as shown in Table 1-7 and Figure 1-4 During the Treatment Period, UCB6114 will be administered in combination with trifluridine/tipiracil (TFD/TPI; TAS-102; Lonsurf®). UCB6114 will be administered as an iv infusion every 2 weeks (Q2W), while TFD/TPI will be administered orally twice daily (bid) within 1 hour of completion of morning

and evening meals on Days 1 to 5 and Days 8 to 12 (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. For administration at home on Cycle 1 Day 1, eligibility must be confirmed within 3 days prior to Day 1 dosing as per the Schedule of Assessments.

Trifluridine/tipiracil will be administered at the recommended standard of care dose. The starting dose of UCB6114 in Part B 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 TFD/TPI. The full Schedule of Activities is provided in Table 1-7.

Part C consists of a Screening Period, Treatment Period (consisting of 28-day cycles), a SFU Visit, and a Final Visit, as shown in Table 1-8 and Figure 1-5. 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/m^2/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. The full Schedule of Activities is provided in Table 1-8.

If any participant withdraws early, the site will attempt to contact the participant and facilitate completion of the SFU Visit and the Final Visit.

The end of the study is defined as the date of the Final Visit/last contact of the last participant in the study.

Number of participants

Overall, approximately 150 to 250 participants will be assigned to study treatment. Enrollment is anticipated to last 3 years.

The planned number of study participants for each study part is provided below.

Part A – Dose escalation (monotherapy)

Up to 42 eligible participants will be assigned to study treatment.

Part A1 – Dose optimization (monotherapy)

Up to 32 eligible participants will be assigned to study treatment.

Part B – Dose escalation (combination therapy)

Up to 27 eligible participants will be assigned to each combination therapy regimen to be explored.

Part C – Dose escalation (combination therapy)

Up to 27 eligible participants will be assigned to each combination therapy regimen to be explored.

Part D and Part E – Monotherapy expansion

Up to 15 eligible participants each will be assigned to study treatment in Part D and Part E.

Up to 15 additional participants each may be enrolled in Part D and Part E (ie, a total sample size of up to 30 participants in each expansion cohort, depending on emerging data).

Part F and Part G – Combination therapy expansion

Up to 15 eligible participants each will be assigned to study treatment in Part F and Part G.

Up to 15 additional participants each may be enrolled in Part F and Part G (ie, a total sample size of up to 30 participants in each expansion cohort, depending on emerging data).

Treatment groups and duration

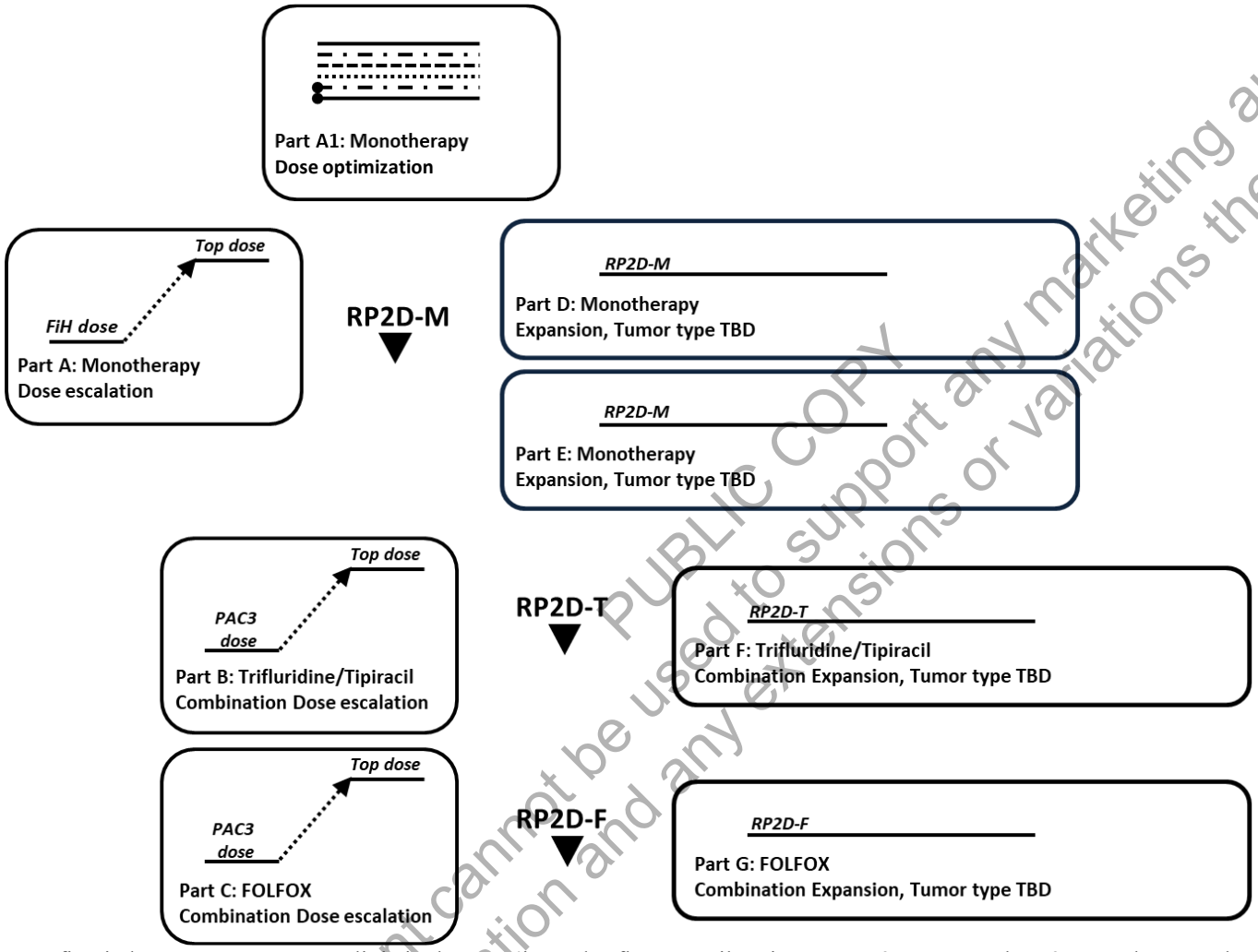
Participants will continue treatment with study medication until disease progression, unmanageable toxicity, criteria for discontinuation are met, or withdrawal of consent.

Where possible, participants will attend an SFU Visit approximately 30 days after discontinuation of study treatment and a Final Visit approximately 3 months after discontinuation of study treatment. The Final Visit may be undertaken by phone, where applicable.

1.2 Schema

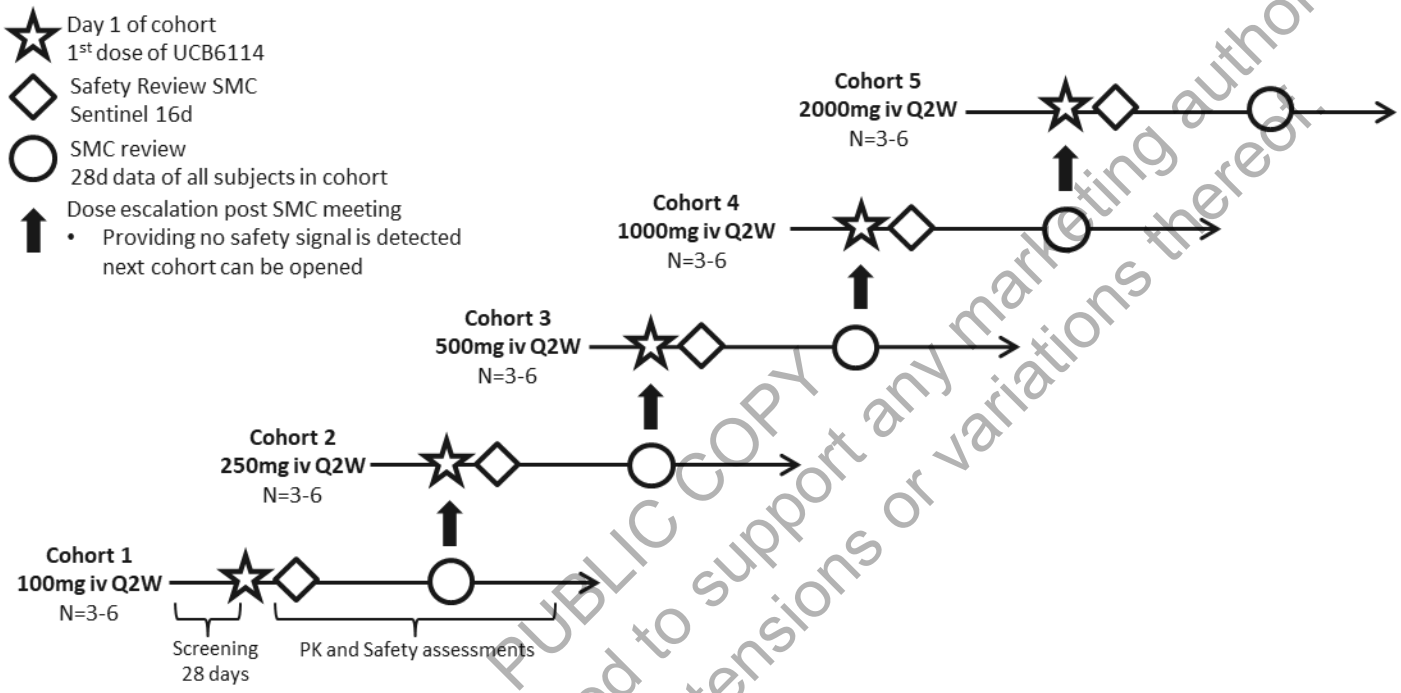
A schematic of the study design is shown in Figure 1-1 and a detailed description of Part A is shown in Figure 1-2. A detailed schematic of Part A1 is shown in Figure 1-3. A detailed schematic of Part B is shown in Figure 1-4. A detailed schematic of Part C is shown in Figure 1-5.

Figure 1-1: ONC001 study design



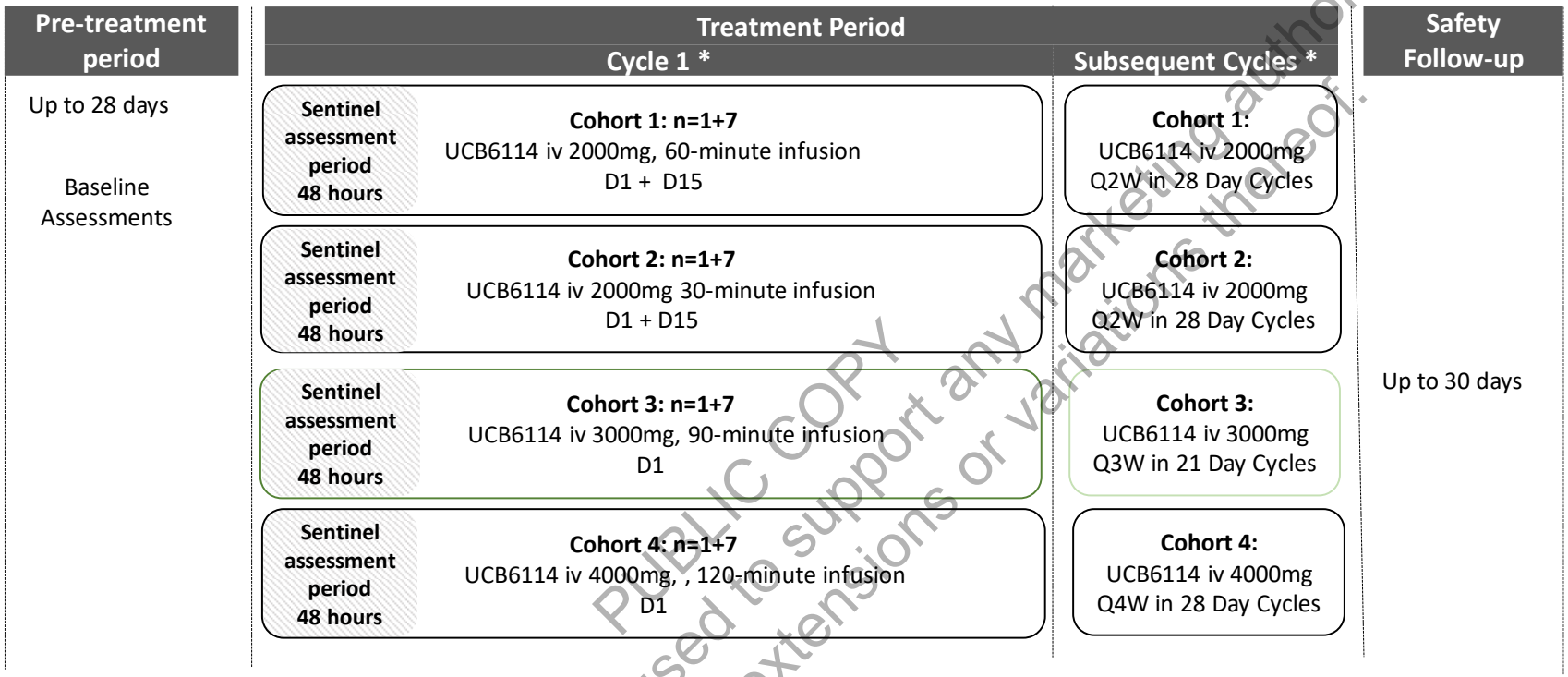
FIH=first in human; FOLFOX=oxaliplatin, leucovorin, and 5-fluorouracil regimen; PAC3=Part A Cohort 3; PD=pharmacodynamics; PK=pharmacokinetics; RP2D-F=Recommended phase 2 dose in combination with FOLFOX; RP2D-M=Recommended phase 2 dose for monotherapy based on acceptable safety and tolerability profile and PK, may also include available PD data; RP2D-T=Recommended phase 2 dose in combination with TFD/TPI; TBD=to be determined; TFD/TPI=trifluridine/tipiracil

Figure 1-2: ONC001 Part A cohorts



d=days; iv=intravenous; PK=pharmacokinetic(s); Q2W=every 2 weeks; SMC=Safety Monitoring Committee
Note: The SMC may add up to 2 additional cohorts based on emerging data, not to exceed 2000mg iv Q2W.

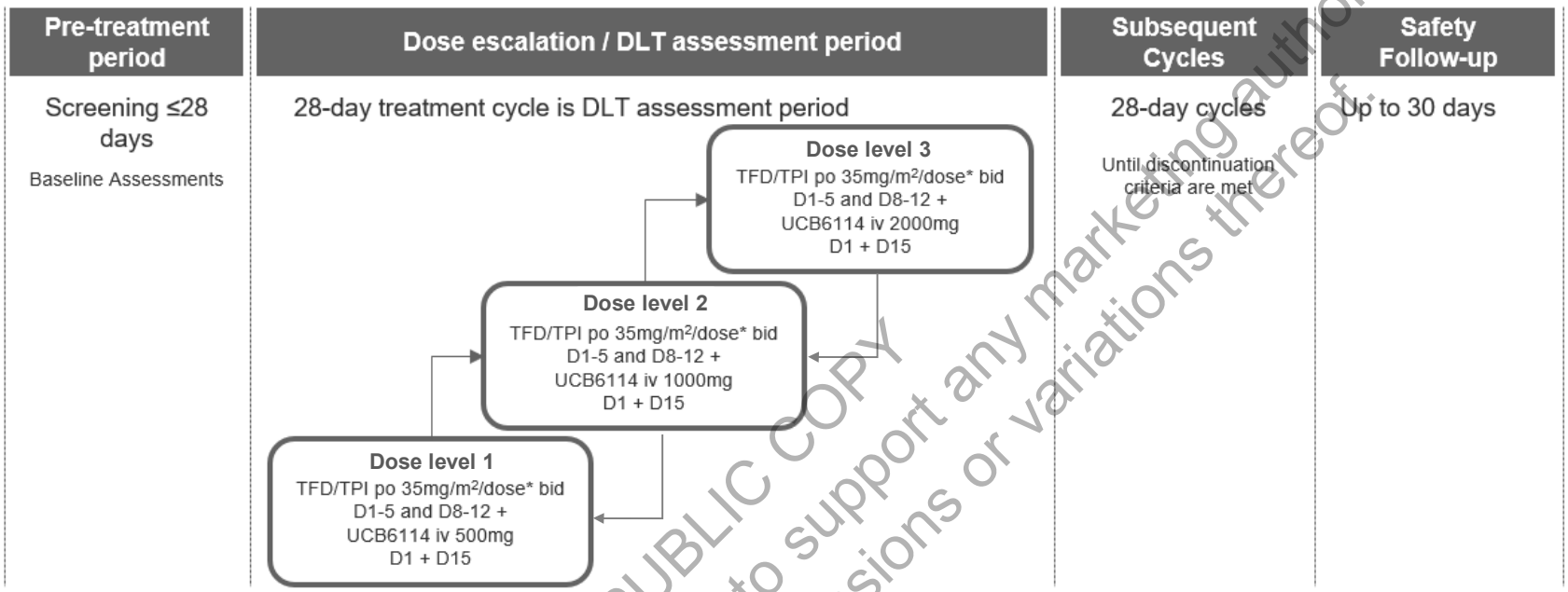
Figure 1-3: ONC001 Part A1



* Cohorts 1, 2, and 4: 28-day treatment cycles; Cohort 3: 21-day treatment cycles

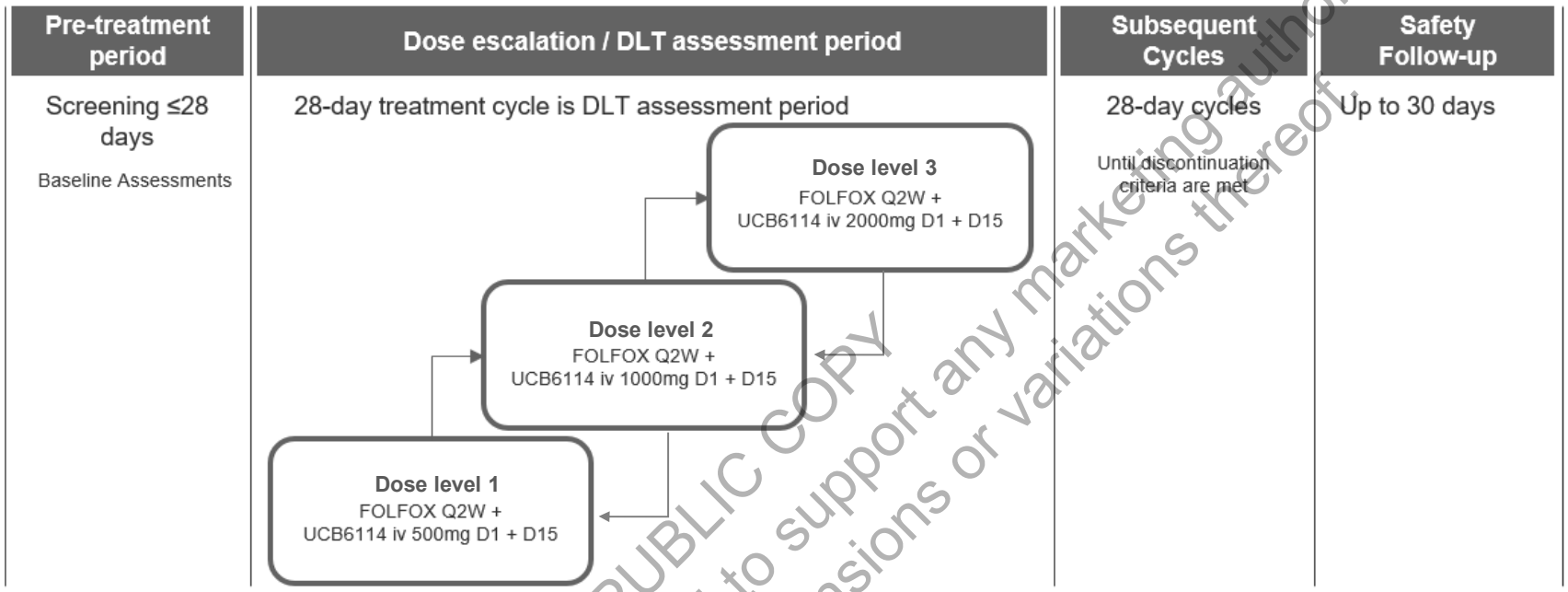
D=day; iv=intravenous; Q2W=every 2 weeks; Q3W=every 3 weeks; Q4W=every 4 weeks

Figure 1-4: ONC001 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: Dose levels may have 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.

Figure 1-5: ONC001 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: Dose levels may have 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.

1.3 Schedule of Activities

The Schedule of Activities for Part A (monotherapy dose escalation) is provided in Table 1-4.

Table 1-4: Schedule of Activities for Part A (monotherapy dose escalation)

Assessments	Screening[a]		Treatment[a]												SFU Visit[a]	Final Visit[a]
			Cycle 1 (28 days)					Cycle 2 (28 days)				Cycle 3 onwards[c] (28 days)			Within 30 days after last dose[f]	3 months after last dose[f]
Cycle day	-28 to -1	-14 to -1	1[d]	2/3	8	15[d]/16	22	1[d]	8	15[d]	22[e]	1[d]	15[d]	22		
Informed consent[g]	X															
Eligibility assessment	X	X	X[ee]													
Demographic data and height	X															
Medical/surgical/cancer history/ concomitant disease and current medical status.	X		X													
ECG[h]		X	X		X	X[z]	X	X		X		X	X		X	
Pregnancy test, if applicable[i]		X	X			X[z]		X		X		X	X		X	X
Study medication (UCB6114) administration[j]			X			X[z]		X		X		X	X			
Physical examination and weight[gg]		X[k]	X		X	X	X	X		X		X	X		X	
Vital signs (BP, HR, RR, and temperature)[l]		X	X	X	X	X	X	X	X	X		X	X		X	
ECOG performance status		X	X		X	X[z]	X	X		X		X	X		X	

Table 1-4: Schedule of Activities for Part A (monotherapy dose escalation)

Assessments	Screening[a]		Treatment[a]												SFU Visit[a]	Final Visit[a]
			Cycle 1 (28 days)					Cycle 2 (28 days)				Cycle 3 onwards[c] (28 days)				
Cycle day	-28 to -1	-14 to -1	1[d]	2/3	8	15[d]/16	22	1[d]	8	15[d]	22[e]	1[d]	15[d]	22	Within 30 days after last dose[f]	3 months after last dose[f]
Urinalysis[m]		X[k]	X[k]			X[z]		X		X		X	X		X	
Urinalysis for urinary markers of bone turnover[n]			X			X[z]		X				X			X	
Hematology		X[k]	X[k]		X	X[z]	X	X	X	X	X	X	X		X	
Blood chemistry		X[k]	X[k]		X	X[z]	X	X	X	X	X	X	X		X	
Coagulation		X[k]	X[k]			X[z]		X				X			X	
Blood collection for serum markers of bone turnover[n]			X			X[z]		X				X			X	
[redacted]																
Blood collection for immunogenicity (ADA)[p,q,r]			X[r]			X[z]	X	X				X			X	
Blood collection for circulating gremlin-1 analysis[n, r,dd]			X	X[s]		X[z]		X				X			X	
Blood collection for serum protein/proteomic analysis[n]			X			X[z]		X				X			X	

Table 1-4: Schedule of Activities for Part A (monotherapy dose escalation)

Assessments	Screening[a]		Treatment[a]												SFU Visit[a]	Final Visit[a]
			Cycle 1 (28 days)					Cycle 2 (28 days)				Cycle 3 onwards[c] (28 days)			Within 30 days after last dose[f]	3 months after last dose[f]
Cycle day	-28 to -1	-14 to -1	1[d]	2/3	8	15[d]/16	22	1[d]	8	15[d]	22[e]	1[d]	15[d]	22		
Blood collection for transcriptomic analysis[n]			X			X[z]		X				X			X	
Blood collection for genetic analysis			X													
Blood collection for ctDNA analysis			X			X[z]		X				X[aa]			X	
Echocardiogram		X						X				X[bb]			X	
Tumor assessments[cc]	X[t]										X[u]			X[v]	X[cc]	
Tumor biopsy for PD analysis[w]	X						X									
Historical tumor sample (from prior to entry into study) if available[x]	X															
Concomitant medication	X	X	Recorded throughout												X	
Adverse events (including DLT in Cycle 1)	X	X	Recorded throughout												X[y]	
Survival census[ff]															X	X

AE=adverse event; ALP=alkaline phosphatase; ALT=alanine transaminase; ANC=absolute neutrophil count; AST=aspartate transaminase; COVID-19=SARS-CoV2 (COVID-19) pandemic; CR=complete response; CT=computed tomography; ctDNA=circulating tumor DNA; ECG=electrocardiogram; ECOG=Eastern Cooperative Oncology Group; h=hours; hCG=human chorionic gonadotropin; iv=intravenous; LDH=lactate dehydrogenase; MRI=magnetic resonance imaging; PD=pharmacodynamic(s); PK=pharmacokinetic(s); PR=partial response; PSA=prostate specific antigen; RBC=red blood cell; SFU=Safety Follow-Up; SMC=Safety Monitoring Committee; WBC=white blood cell

[a] Allowed visit window: ± 2 days (unless specified otherwise). Note: Day 2 of Cycle 1 must occur on the scheduled day relative to Day 1, due to the PK sampling. See PK schedule for allowed sample windows for PK. If needed in context of the COVID-19 pandemic, assessments currently scheduled for Day -28 to Day-1 and assessments scheduled for Screening Days -14 to -1 may be combined into 1 visit conducted within 14 days of first dose.

[b] Deleted.

[c] From Cycle 3 and Cycle 4 onwards, visits on Day 22 may be omitted at the discretion of the investigator and based on toxicity seen at Cycle 1 and 2, unless these visits were required for tumor assessments, or participant assessment.

[d] The following safety assessments will be performed predose: physical examination, vital signs, hematology, blood chemistry, coagulation, urinalysis, pregnancy testing, ECOG performance status, echocardiograms, and ECG. All other safety assessments will be performed postdose.

[e] The visit on Day 22 may take place at any point from Day 21 to Day 28 of Cycle 2; tumor assessments should take place within this window at the investigator's discretion.

[f] When participants are unable to attend the SFU or Final Visit, it will not be considered a protocol deviation.

[g] Informed consent must be given before any study-specific Screening procedures are performed.

[h] ECGs are to be performed in triplicate with the participant in a supine position after a minimum of 5 min rest. When ECG coincides with PK (and PD), the ECG should be performed first. On Days 1 and 15 of Cycle 1, triplicate ECGs should be performed 3 times: the first predose; the second at the end of the infusion; and the third 8 hours after the end of the infusion. For all other cycles, triplicate ECGs should be performed predose.

[I] Pregnancy tests measure serum or urine ß-hCG. Serum tests should be performed at Screening and visit immediately before the investigational product administration on Day 1 Cycle 1. Serum or urine pregnancy tests must be performed prior to dosing on dosing days. Additional pregnancy tests should also be performed during the study if indicated.

[j] UCB6114 is administered as an iv infusion on Days 1 and 15 of each cycle, until the occurrence of progressive disease, unacceptable toxicity, or withdrawal of consent.

[k] Physical examination, weight, and laboratory tests (hematology, blood chemistry, coagulation, and urinalysis), may be repeated within 72h prior to Cycle 1 Day 1 for any borderline assessments identified at Days -14 to -3. Laboratory tests (hematology, blood chemistry, coagulation, and urinalysis) do not have to be repeated on Day 1 predose if performed within 72h of starting dosing. Laboratory tests (hematology, blood chemistry, coagulation, and urinalysis) may be obtained 24h prior to the scheduled visit and may be obtained at local laboratories.

[l] Vital signs on treatment days will be assessed at multiple time points in a semi-supine position after 5 minutes of rest: predose, 10min (±5min) and 30min (±10min) after the start of the infusion, at the end of the infusion (+15min); and at 1h (+15min) after the end of the infusion. In addition, on Cycle 1 Day 1 vital signs will also be assessed at 2 hours (+1h) and 8 hours (+2h) after the end of the infusion, to correspond with PK time points; vital signs will be assessed prior to collection of PK samples.

[m] Urinalysis parameters include specific gravity, pH, glucose, protein, ketones, blood, bilirubin, urobilinogen, nitrite, leukocyte esterase by dipstick. If there are abnormalities in urine dipstick blood or protein results, microscopic analysis should be performed (including crystals).

[n] Samples will only be collected up to and including Cycle 4.

[redacted]

[q] At visits where UCB6114 is administered, ADA samples will be collected predose as described in Section 9.10.

[r] The Cycle 1 predose samples may be used for data integrity and assay verification purposes.
[s] The sample will be collected on Day 2 only.
[t] Screening tumor assessments including contrast–enhanced spiral CT or MRI scan of the chest, abdomen, pelvis, and any other areas of known or suspected disease, must be obtained within 42 days prior to starting study medication. If there is a contraindication to iodinated iv contrast, chest CT should be performed without iv contrast and MRI scans (with gadolinium chelate contrasts) of the abdomen and pelvis may be used instead of CT scans of the abdomen and pelvis. A CT or MRI scan that is dated prior to consent (up to 42 days prior to starting study medication) for this study may be used as the Screening assessment, where this has been performed as per standard care or at the end of a prior research study. The same method of assessment is to be used per participant for the duration of study participation.
[u] Further tumor assessments are to be performed between Days 21 and 28 of every even cycle (±2 days).
[v] Tumor assessments are to be completed on even cycles.
[w] If there are accessible tumor lesions, optional biopsies may be performed at Screening and at Cycle 1 Day 22. The allowed time-window for collection of the Cycle 1 Day 22 sample is from Cycle 1 Day 22 up to Cycle 2 Day 22.
[x] If an historical tumor biopsy specimen obtained prior to the participant's entry into the study (eg, at the time of diagnosis) is available, samples of this tissue will be requested for PD analysis.
[y] Follow-up of AEs: AEs will be recorded up to 30 days after the last dose of study medication. After that time, any unresolved drug-related AEs should be followed until resolution or stabilization of the AE to obtain the date of resolution/stabilization (this follow-up can be via routine clinic visits or correspondence with a treating physician or other healthcare professional).
[z] Assessed on Day 15 only of Cycle 1.
[aa] Only at Day 1 of Cycle 3.
[bb] Echocardiograms are to be completed on even cycles from Cycle 3 onwards.
[cc] Tumor assessment at SFU is not required if the participant has withdrawn due to progressive disease or if the previous tumor assessment was within 42 days of SFU visit.
[dd] At visits where UCB6114 is administered, circulating gremlin-1 samples will be collected predose as described in Section 8.8.1.
[ee] Cycle 1 Day 1, the eligibility assessment will be performed predose.
[ff] Survival census will be performed at SFU and participants will also be contacted to ascertain their survival status 3 months after last dose.
[gg] A complete physical examination is to be performed at Screening and on Cycle 1 Day 1 predose. Physical examinations will be symptom-directed and performed prior to administration of UCB6114 on all other visits.

The Schedule of Activities for Part A1 (monotherapy dose optimization) is provided in Table 1-5 (Cohorts 1, 2 and 4) and Table 1-6 (Cohort 3).

Table 1-5: Schedule of Activities for Part A1 – Cohorts 1, 2, 4

Assessments	Screening		Treatment						SFU Visit	Final Visit
	-28 to -1	-14 to -1	Cycle 1 (28 days)		Cycle 2 (28 days)		Cycle 3 onwards (28 days)		Within 30 days after last dose	3 months after last dose
Cycle day			**1**	**15**	**1**	**15**	**1**	**15**		
Informed consent[a]	X									
Eligibility assessment[b]	X	X	X							
Demographic data and height	X									
Medical/surgical/cancer history/ concomitant disease and current medical status.	X		X							
ECG[c]	X		X		X		X		X	
Pregnancy test, if applicable[d]	X		X		X		X		X	X
UCB6114 - **Cohort 1 (Q2W)**			X	X	X	X	X	X		
UCB6114 – **Cohort 2 (Q2W)**			X	X	X	X	X	X		
UCB6114 – **Cohort 4 (Q4W)**			X		X		X			
Physical examination and weight[e]	X		X	X	X	X	X	X[f]	X	
Vital signs (BP, HR, RR, and temperature)[g]	X		X	X	X	X	X	X[f]	X	
ECOG performance status	X		X		X		X		X	
Urinalysis[h]	X		X	X	X	X	X	X[f]	X	
Hematology[i]	X		X	X	X	X	X	X[f]	X	
Chemistry[i]	X		X	X	X	X	X	X[f]	X	
Coagulation[i]	X		X		X		X		X	

Table 1-5: Schedule of Activities for Part A1 – Cohorts 1, 2, 4

Assessments	Screening		Treatment						SFU Visit	Final Visit
	-28 to -1	-14 to -1	Cycle 1 (28 days)		Cycle 2 (28 days)		Cycle 3 onwards (28 days)		Within 30 days after last dose	3 months after last dose
Cycle day			**1**	**15**	**1**	**15**	**1**	**15**		
Echocardiogram[j]	X						X		X	
Immunogenicity (ADA)[l]			X		X		X		X	
Tumor assessment[m]	X		Every 8 weeks from Day 1						X	
Concomitant medication	X		Recorded throughout						X	
Adverse Events (including DLT in Cycle 1)[n]	X		Recorded throughout						X	
Survival census									X	X
Biomarker analyses										
Blood collection for circulating gremlin-1 analysis[o]			X	X	X		X		X	
Blood collection for serum protein/proteomic analysis[p]		X		X	X		X		X	
Blood collection for transcriptomic analysis[p]		X		X	X		X		X	
Blood collection for genetic analysis		X								
Blood collection for ctDNA analysis		X		X	X		X		X	
Tumor biopsy for PD analysis[q]	X			X						
Historical tumor sample (from prior to entry into study) if available[r]	X									

ADA=anti-drug antibodies; AE=adverse event; BP= blood pressure; CT=computed tomography; ctDNA=circulating tumor DNA; h=hours; DLT=Dose limiting toxicity; ECG=electrocardiogram; ECOG=Eastern Cooperative Oncology Group; HR=heart rate; min=minutes; MRI=magnetic resonance imaging; PD=pharmacodynamic(s); PK=pharmacokinetic(s); Q2W=every 2 weeks; Q4W=every 4 weeks; RR= respiratory rate; SFU=Safety Follow Up;

Note: The allowed visit window is ± 2 days (unless specified otherwise). All assessments are to be performed prior to dosing with UCB6114 (unless specified otherwise)

[a] Informed consent must be given before any study-specific Screening procedures are performed.

[b] Eligibility must be confirmed prior to proceeding to tumor biopsy and on Cycle 1 Day 1 prior to dosing with UCB6114.

[c] ECGs are to be performed at screening; during Cycle 1 prior to dosing, at the end of the infusion, and 2h after the end of infusion; during each subsequent cycle prior to dosing with UCB6114 on Day 1. Electrocardiograms are to be performed in triplicate with the participant in a supine position after a minimum of 5min rest. When ECG coincides with PK (and PD), the ECG should be performed first.

[d] Serum pregnancy test must be performed at screening. Serum or urine pregnancy test must be performed prior to dosing on Day 1 of each cycle. Additional pregnancy tests should also be performed during the study if indicated.

[e] A complete physical examination is to be performed at Screening and on Cycle 1 Day 1 prior to dosing with UCB6114. Physical examination will be symptom-directed and performed prior to administration of UCB6114 on all other visits.

[f] Assessments to be performed on dosing day only. Not applicable for Cohort 4.

[g] On treatment days, vital signs will be assessed at multiple time points in a semi-supine position after 5min of rest: prior to dosing, 10min (±5min) and 30min (±10min) after the start of the infusion, at the end of the infusion (+15min) and 2h after the end of the infusion (+15min). In addition, on Cycle 1 Day 1, vital signs will also be assessed at 5h (+2h) after the end of the infusion. Vital signs will be assessed prior to collection of PK samples.

[h] If there are abnormalities in urine dipstick, a microscopic analysis should be performed (including crystals). Urinalysis does not have to be repeated on Cycle 1 Day 1 predose if performed within 72h of starting dosing.

[i] Laboratory tests (hematology, blood chemistry, and coagulation) do not have to be repeated on Day 1 predose if performed within 72h of starting dosing. They may be obtained 24h prior to the scheduled visit and may be obtained at local laboratories.

[j] During the treatment period, echocardiograms are to be completed at the beginning of Cycle 3 (± 7 days), as clinically indicated afterwards, and at the SFU Visit.

[redacted]

[l] Immunogenicity (ADA) samples will be collected on Cycle 1 Day 1, Cycle 2 Day 1, Cycle 3 Day 1, and Day 1 of every third cycle thereafter (i.e. cycle 6, 9 etc.) and at the SFU Visit.

[m] Tumor assessments including spiral CT or MRI scan of the chest, abdomen, and any other area of known or suspected disease, must be obtained at Screening. A CT or MRI scan that is dated prior to consent (up to 42 days prior to starting IMP) for this study may be used as the Screening assessment, where this has been performed as per standard of care or at the end of a prior study. The same method of assessment is to be used per participant for the duration of study participation. Tumor assessments are to be performed every 8 weeks from Day 1 (± 7 days). Tumor assessment at SFU is not required if the participant has withdrawn due to progressive disease or if the previous tumor assessment was within 42 days of SFU visit.

[n] Follow-up of AEs: AEs will be recorded up to 30 days after the last dose of study medication. After that time, any unresolved drug-related AEs should be followed until resolution or stabilization of the AE to obtain the date of resolution/stabilization (this follow-up can be via routine clinic visits or correspondence with a treating physician or other healthcare professional).

[o] Blood samples for circulating gremlin-1 analysis will be collected at Cycle 1 Day 1, pre-dose (within 30 min prior to dosing), end of infusion (+15min), and 4h (+1h) post-infusion as well as at Day 15 at predose (within 30min prior to dosing) or on day of visit if a non-dosing day. At all subsequent cycles, blood samples will be collected at Day 1 predose (within 30min prior to dosing) and at the SFU Visit; for Cycle 3 only, an additional 4h (+1h) postdose sample should be taken on Day 1. An additional sample should also be collected on the day of on-treatment biopsy (only if taking place on a day where no PK samples are scheduled).

[p] To be confirmed based on Part A Cohorts 1 to 3 analysis.
[q] Baseline biopsy should be collected between Day -28 and Day -1. Whenever possible, on-treatment biopsy should be performed within 2 weeks post Cycle 1 Day 15 (ie, between Cycle 1 Day 15 and Cycle 2 Day 1). If on-treatment biopsy occurs a non-dosing day, an additional PK and an additional cGremlin-1 samples should be collected on the day of biopsy.
[r] If an historical tumor biopsy specimen obtained prior to the participant's entry into the study (eg, at the time of diagnosis) is available, samples of this tissue will be requested for PD analysis at the time of consent.

Table 1-6: Schedule of Activities for Part A1 – Cohort 3

Assessments	**Screening**		**Treatment**						**SFU Visit**	**Final Visit**
	-28 to -1	**-14 to -1**	**Cycle 1 (21 days)**		**Cycle 2 (21 days)**		**Cycle 3 onward (21 days)**		**Within 30 days after last dose**	
Cycle day			**1**	**15**	**1**	**15**	**1**	**15**		
Informed consent[a]	X									
Eligibility assessment[b]	X	X	X							
Demographic data and height	X									
Medical/surgical/cancer history/ concomitant disease and current medical status.	X		X							
ECG[c]	X		X		X		X		X	
Pregnancy test, if applicable[d]	X		X		X		X		X	X
UCB6114 - **Schedule 3 (Q3W)**			X		X		X			
Physical examination and weight[e]	X		X		X		X		X	
Vital signs (BP, HR, RR, and temperature)[f]	X		X		X		X		X	
ECOG performance status	X		X		X		X		X	
Urinalysis[g]	X		X		X		X		X	
Hematology[h]	X		X		X		X		X	
Chemistry[h]	X		X		X		X		X	

Table 1-6: Schedule of Activities for Part A1 – Cohort 3

Assessments	Screening		Treatment						SFU Visit	Final Visit
	-28 to -1	-14 to -1	Cycle 1 (21 days)		Cycle 2 (21 days)		Cycle 3 onward (21 days)		Within 30 days after last dose	
Cycle day			**1**	**15**	**1**	**15**	**1**	**15**		
Coagulation[h]	X		X		X		X		X	
Echocardiogram[i]	X						X		X	
[redacted]										
Immunogenicity (ADA)			X		X		X[k]		X	
Tumor assessment[l]	X		Every 8 weeks from Day 1						X	
Concomitant medication	X		Recorded throughout						X	
Adverse Events (including DLT in Cycle 1)[m]	X		Recorded throughout						X	
Survival census									X	X
Biomarker studies										
Blood, collection for circulating gremlin-1 analysis[n]			X	X	X		X		X	
Blood collection for serum protein/proteomic analysis[o]		X			X		X		X	
Blood collection for transcriptomic analysis[o]		X			X		X		X	
Blood collection for genetic analysis		X								
Blood collection for ctDNA analysis		X			X		X		X	
Tumor biopsy for PD analysis[p]	X				X					
Historical tumor sample (from prior to entry into study) if available[q]	X									

ADA=anti-drug antibodies; AE=adverse event; BP= blood pressure; CT=computed tomography; ctDNA=circulating tumor DNA; h=hours; DLT=Dose limiting toxicity; ECG=electrocardiogram; ECOG=Eastern Cooperative Oncology Group; HR=heart rate; min=minutes; MRI=magnetic resonance imaging; PD=pharmacodynamic(s); PK=pharmacokinetic(s); Q3W=every 3 weeks; RR= respiratory rate; SFU=Safety Follow Up;
Note: The allowed visit window is ± 2 days (unless specified otherwise). All assessments are to be performed prior to dosing with UCB6114 (unless specified otherwise)

[a] Informed consent must be given before any study-specific Screening procedures are performed.

[b] Eligibility must be confirmed prior to proceeding to tumor biopsy and on Cycle 1 Day 1 prior to dosing with UCB6114.

[c] ECGs are to be performed at screening; during Cycle 1 prior to dosing, at the end of the infusion, and 2h after the end of infusion; during each subsequent cycle prior to dosing with UCB6114 on Day 1. Electrocardiograms are to be performed in triplicate with the participant in a supine position after a minimum of 5min rest. When ECG coincides with PK (and PD), the ECG should be performed first.

[d] Serum pregnancy test must be performed at screening. Serum or urine pregnancy test must be performed prior to dosing on Day 1 of each cycle. Additional pregnancy tests should also be performed during the study if indicated.

[e] A complete physical examination is to be performed at Screening and on Cycle 1 Day 1 prior to dosing with UCB6114. Physical examination will be symptom-directed and performed prior to administration of UCB6114 on all other visits.

[f] On treatment days, vital signs will be assessed at multiple time points in a semi-supine position after 5min of rest: prior to dosing, 10min (±5min) and 30min (±10min) after the start of the infusion, at the end of the infusion (+15min) and 2h after the end of the infusion (+15min). In addition, on Cycle 1 Day 1, vital signs will also be assessed at 5h (+2h) after the end of the infusion. Vital signs will be assessed prior to collection of PK samples.

[g] If there are abnormalities in urine dipstick, a microscopic analysis should be performed (including crystals). Urinalysis does not have to be repeated on Cycle 1 Day 1 predose if performed within 72h of starting dosing.

[h] Laboratory tests (hematology, blood chemistry, and coagulation) do not have to be repeated on Day 1 predose if performed within 72h of starting dosing. They may be obtained 24h prior to the scheduled visit and may be obtained at local laboratories.

[i] During the treatment period, echocardiograms are to be completed at the beginning of Cycle 3 (± 7 days), as clinically indicated afterwards, and a the SFU Visit.

[redacted]

[k] Immunogenicity (ADA) samples will be collected on Cycle 1 Day 1, Cycle 2 Day 1, Cycle 3 Day 1, and Day 1 of every third cycle thereafter (i.e. cycle 6, 9 etc.) as well as at the SFU Visit.

[l] Tumor assessments including spiral CT or MRI scan of the chest, abdomen, and any other area of known or suspected disease, must be obtained at Screening. A CT or MRI scan that is dated prior to consent (up to 42 days prior to starting IMP) for this study may be used as the Screening assessment, where this has been performed as per standard of care or at the end of a prior study. The same method of assessment is to be used per participant for the duration of study participation. Tumor assessments are to be performed every 8 weeks from Day 1 (± 7 days). Tumor assessment at SFU is not required if the participant has withdrawn due to progressive disease or if the previous tumor assessment was within 42 days of SFU Visit.

[m] Follow-up of AEs: AEs will be recorded up to 30 days after the last dose of study medication. After that time, any unresolved drug-related AEs should be followed until resolution or stabilization of the AE to obtain the date of resolution/stabilization (this follow-up can be via routine clinic visits or correspondence with a treating physician or other healthcare professional).

[n] Blood samples for circulating gremlin-1 analysis will be collected at Cycle 1 Day 1 at predose (within 30min prior to dosing), end of infusion (+15min), and 4h (+1h) post-infusion. An additional sample should be collected on Day 15 post-infusion on day of visit.. In all subsequent cycles blood samples will be collected

at Day 1 predose (within 30min prior to dosing) and at the SFU Visit; for Cycle 3 only an additional 4h (+1h) sample should 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 PK samples are scheduled).

[o] To be confirmed based on Part A Cohort 1 to 3 analysis.

[p] Baseline biopsy should be collected between Day -28 and Day -1. Whenever possible, on-treatment biopsy should be performed within 2 weeks post Cycle 2 Day 1 (ie, between Cycle 2 Day 1 and Cycle 2 Day 15). If on-treatment biopsy occurs a non-dosing day, an additional PK and an additional cGremlin-1 samples should be collected on the day of biopsy.

[q] If an historical tumor biopsy specimen obtained prior to the participant's entry into the study (eg, at the time of diagnosis) is available, samples of this tissue will be requested for PD analysis at the time of consent.

The Schedule of Activities for Part B is provided in Table 1-7.

Table 1-7: Schedule of Activities for Part B

Procedure	Screening		Treatment						SFU Visit	Final Visit
			Cycle 1 & Cycle 2 (28 days)				Cycle 3 onwards (28 days)			
Cycle day	-28 to -1	-3 to -1	1	8	15	22	1	15	Within 30 days after final dose	3 months after final dose
Informed consent[a]	X									
Eligibility assessment[b]	X	X	X[g]							
Demographic data and height	X									
Medical/surgical/cancer history/concomitant disease and current medical status	X		X[g]							
ECG[c]	X	X	X		X		X		X	
Pregnancy test, if applicable[d]	X	X	X				X		X	X
TFD/TPI dispensing[e]		X	X							
TFD/TPI administration	TFD/TPI is administered orally twice daily on Days 1 to 5 and Days 8 to 12 of each cycle									
UCB6114 administration	UCB6114 is administered as an iv infusion on Days 1 and 15 of each cycle									
Physical examination and weight[f]	X	X	X	X[g]	X	X[g]	X	X	X	
Vital signs (BP, HR, RR, and temperature)[h]	X	X	X	X[g]	X	X[g]	X	X	X	
ECOG performance status[h]	X	X	X	X[g]	X	X[g]	X	X	X	
Urinalysis[i]	X	X	X		X	X	X		X	
Urinalysis for urinary markers of bone turnover			X		X		X		X	
Hematology[k]	X	X	X	X	X	X	X	X	X	
Blood chemistry[l]	X	X	X	X	X	X	X	X	X	
Coagulation[m]	X	X	X		X[g]		X		X	

Table 1-7: Schedule of Activities for Part B

Procedure	Screening		Treatment						SFU Visit	Final Visit
			Cycle 1 & Cycle 2 (28 days)				Cycle 3 onwards (28 days)			
Cycle day	-28 to -1	-3 to -1	1	8	15	22	1	15	Within 30 days after final dose	3 months after final dose
Blood collection for serum markers of bone turnover			X		X		X		X	
[redacted]										
Blood collection for immunogenicity (ADA)			X				X[p]		X	
Blood collection for circulating gremlin-1 analysis	X	X[o]	X[o,q]		X[q]		X[p,q]		X	
Blood collection for genetic analysis	X	X[o]								
Blood collection for ctDNA analysis	X	X[o]	X[o]		X		X		X	
Echocardiogram	X						X[u]		X	
Tumor assessments[r]	X		Every 8 weeks from Day 1						X	
Historical tumor sample if available[s]	X									
Concomitant medication	X		Recorded throughout						X	
Adverse events[t]	X		Recorded throughout						X	
Survival census									X	X

ADA=antidrug antibody; AE=adverse event; ALP=alkaline phosphatase; BP=blood pressure; CT=computed tomography; ctDNA=circulating tumor DNA; DLT=dose-limiting toxicity; ECG=electrocardiogram; ECOG=Eastern Cooperative Oncology Group; h=hour(s); HR=heart rate; iv=intravenous; min=minute(s); MRI=magnetic resonance imaging; PD=pharmacodynamic(s); PK=pharmacokinetic(s); RR=respiratory rate; TFD/TPI= trifluridine/tipiracil; SFU=Safety Follow-Up

Note: The allowed visit window is ±2 days (unless specified otherwise). All assessments are to be performed prior to dosing with IMP (unless specified otherwise).

[a] Informed consent must be given before any study-specific Screening procedures are performed.

[b] Eligibility must be confirmed within 3 days prior to starting any IMP. Confirmation does not have to be repeated on Day 1 predose if it was performed within 3 days prior to starting any IMP.

[c] ECGs are to be performed prior to dosing with IMP in triplicate with the participant in a supine position after a minimum of 5 minutes of rest. ECGs are to be performed in Screening and do not have to be repeated on Day 1 predose if performed within 3 days prior to starting any IMP. On Days 1 and 15 of Cycle 1 only, ECGs will also be performed at multiple timepoints in relation to dosing with UCB6114 (pre-infusion, end of infusion, and at 2 hours post infusion). When ECG coincides with blood collection for PK (and PD), the ECG should be performed first.

[d] Serum pregnancy test must be performed in Screening and does not have to be repeated on Day 1 predose if performed within 3 days prior to starting any IMP. If a serum pregnancy test was performed at Screening more than 3 days prior to starting any IMP, a urinary pregnancy test can be performed on Day 1 prior to dosing with any IMP. A serum or urinary test can be performed on all other visits.

[e] TFD/TPI can be dispensed once eligibility is confirmed (see footnote b).

Table 1-7: Schedule of Activities for Part B

Procedure	Screening		Treatment						SFU Visit	Final Visit
			Cycle 1 & Cycle 2 (28 days)				Cycle 3 onwards (28 days)			
Cycle day	-28 to -1	-3 to -1	1	8	15	22	1	15	Within 30 days after final dose	3 months after final dose

[f] A complete physical examination is to be performed in Screening and does not have to be repeated on Day 1 predose if performed within 3 days prior to starting any IMP. Physical examinations will be symptom-directed and performed prior to administration of IMP on all other visits.

[g] Not to be done in Cycle 2.

[h] Vital signs and ECOG performance status are to be performed in Screening and do not have to be repeated on Day 1 predose if performed within 3 days prior to starting any IMP. Vital signs on treatment days with UCB6114 will be assessed at multiple time points in a semi-supine position after 5min of rest: predose, 10min (±5min) and 30min (±10min) after the start of the infusion, at the end of the infusion (+15min); and at 1h (+15min) after the end of the infusion. In addition, on Cycle 1 Day 1 vital signs will be assessed at 2h (+1h) and 5h (+1h) after the end of the infusion.

[i] Urinalysis is to be performed in Screening and does not have to be repeated on Day 1 predose if performed within 3 days prior to starting any IMP. If there are abnormalities in urine dipstick, a microscopic analysis should be performed (including crystals).

[j] Deleted

[k] Hematology is to be performed in Screening and does not have to be repeated on Day 1 predose if performed within 3 days prior to starting any IMP. At all other visits, the hematology sample may be obtained 24h prior to the scheduled visit.

[l] Blood chemistry is to be performed in Screening and does not have to be repeated on Day 1 if performed within 3 days prior to dosing with any IMP. At all other visits blood, the chemistry sample may be obtained 24h prior to the scheduled visit. In the case of 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.

[m] Coagulation is to be performed in Screening and does not have to be repeated on Day 1 pre-dose if performed within 3 days prior to starting any IMP. At all

[redacted]

[o] No sample required if done previously.

[p] To be completed in Cycle 3 and thereafter in even cycles only (i.e., Cycle 4, 6)

[q] Sample for circulating gremlin-1 will be collected at the same time as PK samples (ie, 30 minutes prior to dosing with UCB6114).

[r] Tumor assessments including spiral CT or MRI scan of the chest, abdomen, pelvis, and any other areas of known or suspected disease, must be obtained at Screening. A CT or MRI scan that is dated prior to consent (up to 42 days prior to starting IMP) for this study may be used as the Screening assessment, where this has been performed as per standard care or at the end of a prior research study. The same method of assessment is to be used per participant for the duration of study participation. Tumor assessments are to be performed every 8 weeks from Day 1 (±7 days). Tumor assessment at SFU is not required if the participant has withdrawn due to progressive disease or if the previous tumor assessment was within 42 days of SFU visit.

[s] If an historical tumor biopsy specimen obtained prior to the participant's entry into the study (eg, at the time of diagnosis) is available, samples of this tissue will be requested for PD analysis.

[t] Including DLT in Cycle 1. Follow-up of AEs: AEs will be recorded up to 30 days after the final dose of IMP. After that time, any unresolved drug-related AEs should be followed until resolution or stabilization of the AE to obtain the date of resolution/stabilization (this follow-up can be via routine clinic visits or correspondence with a treating physician or other healthcare professional).

Table 1-7: Schedule of Activities for Part B

Procedure	Screening		Treatment						SFU Visit	Final Visit
			Cycle 1 & Cycle 2 (28 days)				Cycle 3 onwards (28 days)			
Cycle day	-28 to -1	-3 to -1	1	8	15	22	1	15	Within 30 days after final dose	3 months after final dose

[u] During the treatment period, echocardiograms are to be completed at the beginning of Cycle 3 (±7 days), as clinically indicated afterwards, and at the SFU Visit.

The Schedule of Activities for Part C is provided in Table 1-8. The Schedule of Activities for modules subsequent to Parts A, B, and C will be defined in a planned protocol amendment.

Table 1-8: Schedule of Activities for Part C

Procedure	Screening		Treatment						SFU Visit	Final Visit
	-28 to -1	-14 to -1	Cycle 1 & Cycle 2 (28 days)				Cycle 3 onwards (28 days)		Within 30 days after final dose	3 months after final dose
Cycle day			1	8	15	22	1	15		
Informed consent[a]	X									
Eligibility assessment[b]	X	X	X[g]							
Demographic data and height	X									
Medical/surgical/cancer history/concomitant disease and current medical status	X		X[g]							
ECG[c]		X	X		X		X	X	X	
Pregnancy test, if applicable		X[d]	X				X		X	X
UCB6114 administration			UCB6114 is administered as an iv infusion on Days 1 and 15 of each cycle							
mFOLFOX6 administration			mFOLFOX6 is administered iv starting on Days 1 and 15 of each cycle[e]							
Physical examination and weight[f]		X	X	X[g]	X	X[g]	X	X	X	
Vital signs (BP, HR, RR, and temperature)[h]		X	X	X[g]	X	X[g]	X	X	X	
ECOG performance status		X	X	X[g]	X	X[g]	X	X	X	
Urinalysis[i]		X	X		X	X	X		X	
Urinalysis for urinary markers of bone turnover			X		X		X		X	
Blood collection for serum markers of bone turnover			X		X		X		X	
Hematology[k]		X	X	X	X	X	X	X	X	
Blood chemistry[l]		X	X	X	X	X	X	X	X	
Coagulation[m]		X	X		X[g]		X		X	
[redacted]										
Blood collection for immunogenicity (ADA)			X				X[p]		X	
Blood collection for circulating gremlin-1 analysis	X	X[o]	X[o, q]		X[q]		X[p,q]		X	
Blood collection for genetic analysis	X	X[o]								
Blood collection for ctDNA analysis	X	X[o]	X[o]		X		X		X	

Table 1-8: Schedule of Activities for Part C

Procedure	Screening		Treatment						SFU Visit	Final Visit
	-28 to -1	-14 to -1	Cycle 1 & Cycle 2 (28 days)				Cycle 3 onwards (28 days)		Within 30 days after final dose	3 months after final dose
Cycle day			1	8	15	22	1	15		
Echocardiogram	X						X[u]		X	
Tumor assessments[r]	X		Every 8 weeks from Day 1						X	
Historical tumor sample if available[s]	X									
Concomitant medication	X	X	Recorded throughout						X	
Adverse events [t]	X	X	Recorded throughout						X	
Survival census									X	X

ADA=antidrug antibody; AE=adverse event; BP=blood pressure; CT=computed tomography; ctDNA=circulating tumor DNA; DLT=dose-limiting toxicity; ECG=electrocardiogram; ECOG=Eastern Cooperative Oncology Group; HR=heart rate; iv=intravenous; 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; MRI=magnetic resonance imaging; PD=pharmacodynamic(s); PK=pharmacokinetic(s); RR=respiratory rate; SFU=Safety Follow-Up

Note: The allowed visit window is ±2 days (unless specified otherwise). All assessments are to be performed prior to dosing with UCB6114 (unless specified otherwise).

[a] Informed consent must be given before any study-specific Screening procedures are performed.

[b] Eligibility must be confirmed on Cycle 1 Day 1 prior to dosing with any IMP.

[c] ECGs are to be performed prior to dosing with UCB6114 in triplicate with the participant in a supine position after a minimum of 5 minutes of rest. On Days 1 and 15 of Cycle 1 only, ECGs will also be performed at the end of infusion and at 2 hours after the infusion of UCB6114. When ECG coincides with blood collection for PK (and PD), the ECG should be performed first.

[d] Serum pregnancy tests must be performed at Screening. Serum or urine pregnancy test must be performed on dosing days prior to dosing with any IMP. Tests should also be performed during the study if indicated.

[e] The infusions will begin on Day 1 and Day 15 and continue over 46 hours, thus ending on Days 3 and 17, respectively.

[f] A complete physical examination is to be performed at Screening and on Cycle 1 Day 1 prior to dosing with UCB6114. Physical examinations will be symptom-directed and performed prior to administration of UCB6114 on all other visits.

[g] Not to be done in Cycle 2.

[h] Vital signs on treatment days will be assessed at multiple time points in a semi-supine position after 5 minutes of rest: prior to dosing with UCB6114, 10min (±5min) and 30min (±10min) after the start of the infusion, at the end of the infusion (+15min), and at 1h (+15min) after the end of the infusion of UCB6114. In addition, on Cycle 1 Day 1 vital signs will be assessed at 2 hours (+1h) and 5 hours (+1h) after the end of the infusion of UCB6114.

[i] If there are abnormalities in urine dipstick, a microscopic analysis should be performed (including crystals). Urinalysis does not have to be repeated on Cycle 1 Day 1 predose if performed within 72h of starting dosing. At all other visits, the urinalysis sample may be obtained 24h prior to the scheduled visit.

[j] Deleted

[k] Hematology does not have to be repeated on Day 1 predose if performed within 72h of starting dosing. At all other visits, the hematology sample may be obtained 24h prior to the scheduled visit.

Table 1-8: Schedule of Activities for Part C

Procedure	Screening		Treatment						SFU Visit	Final Visit
	-28 to -1	-14 to -1	Cycle 1 & Cycle 2 (28 days)				Cycle 3 onwards (28 days)		Within 30 days after final dose	3 months after final dose
Cycle day			1	8	15	22	1	15		

[l] Blood chemistry does not have to be repeated on Day 1 predose if performed within 72h of starting dosing. At all other visits, the blood chemistry sample may be obtained 24h prior to the scheduled visit. In the case of 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.

[m] Coagulation does not have to be repeated on Day 1 predose if performed within 72h of starting dosing. At all other visits, the coagulation sample may be obtained 24h prior to the scheduled visit.

[redacted]

[o] No sample required if done previously.

[p] To be completed in Cycle 3 and thereafter in even cycles only (i.e., Cycle 4, 6)

[q] Sample for circulating gremlin-1 will be collected at the same time as PK samples (ie, 30 minutes prior to dosing with UCB6114).

[r] Tumor assessments including spiral CT or MRI scan of the chest, abdomen, pelvis, and any other areas of known or suspected disease, must be obtained at Screening. A CT or MRI scan that is dated prior to consent (up to 42 days prior to starting IMP) for this study may be used as the Screening assessment, where this has been performed as per standard care or at the end of a prior research study. The same method of assessment is to be used per participant for the duration of study participation. Tumor assessments are to be performed every 8 weeks from Day 1 (±7 days). Tumor assessment at SFU is not required if the participant has withdrawn due to progressive disease or if the previous tumor assessment was within 42 days of the SFU visit.

[s] If an historical tumor biopsy specimen obtained prior to the participant's entry into the study (eg, at the time of diagnosis) is available, samples of this tissue will be requested for PD analysis.

[t] Including DLT in Cycle 1. Follow-up of AEs: AEs will be recorded up to 30 days after the final dose of IMP. After that time, any unresolved drug-related AEs should be followed until resolution or stabilization of the AE to obtain the date of resolution/stabilization (this follow-up can be via routine clinic visits or correspondence with a treating physician or other healthcare professional).

[u] During the treatment period, echocardiograms are to be completed at the beginning of Cycle 3 (±7 days), as clinically indicated afterwards, and at the SFU Visit.

2 INTRODUCTION

2.1 Study rationale

UCB6114 is a fully human IgG4P mAb optimized for neutralizing activity against the human gremlin-1 protein and is currently under development for advanced solid tumors. Gremlin-1, secreted by the tumor stroma, binds to BMP and antagonizes signaling, thereby allowing tumor cell expansion, renewal, and a more mesenchymal phenotype. By blocking this gremlin-1 BMP antagonism, UCB6114 is expected to restore BMP signaling, limit tumor cell expansion, and favor a more epithelial phenotype. Gremlin-1 has been shown to be expressed in multiple solid tumor types, with mRNA expression being observed in >60% of colorectal, pancreatic, and esophageal cases. Despite advances in the treatment regimens in the last decade, there is still a large unmet need in the therapy of cancer types mentioned above. Expression data in human tumor models, together with nonclinical evidence, suggests a therapeutic potential of UCB6114 and supports its proposed initial clinical investigation in participants with advanced solid tumors.

The primary objectives of this study are to characterize the safety profile (dose escalation modules of this study), to assess preliminary antitumor activity (expansion modules of this study), and to determine the RP2D of iv UCB6114 as monotherapy and in combination with selected SOC regimens. In addition, the PK, PD, PD biomarker profiles, and ADA of iv UCB6114 will be assessed.

The scientific rationale for the study design is presented in Section 4.2.

2.2 Background

Gremlin-1 has an essential role in skeletal development and homeostasis, and in kidney development (Khokha et al, 2003). The protein is highly conserved between species. Gremlin-1 has several cellular signaling mechanisms (Brazil et al, 2015). The most well-described role for gremlin-1 is as a high affinity antagonist regulating the activity of BMPs 2, 4, and 7, members of the transforming growth factor-β superfamily (Mulloy and Rider, 2015). Gremlin-1 has also been reported to bind to the vascular endothelial growth factor receptor 2, however the functional relevance is currently unclear. Further described roles for gremlin-1 include binding to slit guidance ligand 1 and 2 (Slit1 and Slit2) and facilitating their binding to the roundabout receptor which leads to inhibition of monocyte chemotaxis, as well as associating to fibrillin microfibers and activating Slug expression, leading to epithelial–mesenchymal transition and mesothelioma cell survival (Mulloy et al, 2015).

Gremlin-1 mRNA has been shown to be expressed in >60% of colorectal, pancreatic, and esophageal cancer cases and in approximately 50% of bladder, breast, and lung cancer cases (Sneddon et al, 2006). It has also been shown to be a key driver in HMPS (Jaeger et al, 2012), a rare and severe premalignant condition characterized by the development of mixed morphology colorectal tumors. It was demonstrated in this condition that there is a 4000-fold increase in gremlin-1 mRNA caused by a 40kb duplication in the gremlin-1 promotor region.

In mouse models of HMPS and CRC, the murinized version of UCB6114, Ab7326 mIgG1, has demonstrated the ability to inhibit disease pathology and profoundly extends the lifespan of mice. Long-term treatment of the *Apc*^{Min} mouse model of CRC with Ab7326 mIgG1 initiated at 6 or 16 weeks of age had a consistent effect on polyp development, allowing prolonged survival of animals through reduced tumor burden. In a highly aggressive model of CRC with

established disease, the combination of Ab7326 mIgG1 antibody together with cytotoxic chemotherapy was efficacious, whereas either individual agent alone was not.

The nonclinical safety program for UCB6114 comprised two 13-week Good Laboratory Practice (GLP) compliant repeated iv dose toxicity studies at dose levels of 30mg/kg and 150mg/kg, one in cynomolgus monkeys and the other in rats. No adverse effects, related to the mechanism of action (MoA) of UCB6114, were observed in any of the toxicology, safety pharmacology, and immunotoxicology parameters examined in cynomolgus monkeys or in male rats. In female rats, histopathological changes were noted in the ovaries, mammary gland, adrenal gland, and pituitary. No histopathological changes were noted in the cynomolgus monkey (females and males) and male rats. The endocrine changes in the female rats are considered related to the MoA of UCB6114 through BMPs effects in ovarian function and this pattern of changes occurs commonly in rats, particularly in aging Sprague Dawley rats. The potential effects on ovarian function in the rat led to an anovulatory state (lack of corpora lutea and cystic follicles) with a series of downstream rat-specific effects in the uterus, vagina, and mammary gland. Rodents are known to be specifically sensitive to hormonal changes and related impact on the hypothalamic-pituitary-adrenal (HPA)-mammary axis. The findings noted at the end of the main phase were either not observed or noted at comparable incidence to the control group at the end of the recovery period (Day 183).

For more detailed information regarding the nonclinical program, see the current Investigator's Brochure (IB).

2.3 Benefit/risk assessment

This is the first study of UCB6114 in humans. Nonclinical studies demonstrate that UCB6114 binds to gremlin-1, inhibits its pharmacological activity, and has antitumor activity in several in vivo mouse cancer models. Gremlin-1 is also known to be expressed in a range of human tumors and high expression has been associated with a poor prognosis in multiple tumor types. Taken together these data indicate that UCB6114 could play a role in treating a range of solid tumors.

No adverse effects, related to the MoA of UCB6114, were observed in any of the toxicology, safety pharmacology, and immunotoxicology parameters examined in cynomolgus monkeys or in male rats. In female rats, histopathological changes were noted in the ovaries, mammary gland, adrenal gland, and pituitary. No histopathological changes were noted in the cynomolgus monkey (females and males) and male rats. The endocrine changes in the female rats were considered related to the MoA of UCB6114 through BMPs effects in ovarian function and this pattern of changes occurs commonly in rats, particularly in aging Sprague Dawley rats. The potential effects on ovarian function in the rat led to an anovulatory state (lack of corpora lutea and cystic follicles) with a series of downstream rat-specific effects in the uterus, vagina, and mammary gland. Rodents are known to be specifically sensitive to hormonal changes and related impact on the HPA-mammary axis. The findings noted at the end of the main phase were either not observed or noted at comparable incidence to the control group at the end of the recovery period (Day 183). These drug-related changes are considered pharmacologically-related and shown to be reversible, and do not preclude further development of this molecule in the oncology indication.

The FIH start dose (Part A, UCB6114 monotherapy) is anticipated to have a >100-fold safety margin based on the outcome of the 13-week GLP toxicity study in rats (the most sensitive species).

In Part A, a number of safeguards are in place to minimize risk to study participants which reflect the state of knowledge of the study medication. There are detailed selection criteria and the study is designed using a sequential dose-escalation strategy (modified rolling-6), with at least 16 days elapsing between the first and subsequent participants enrolled in each cohort.

In Part A1, alternative dosing schedules have been determined based upon the currently available data, including the safety profile, pharmacokinetic (PK) data, pharmacodynamic (PD) biomarker data, and available anti-tumor activity. A number of safety measures are in place to minimize the risk to study participants. Each of the 4 cohorts incorporates a sentinel participant. The enrollment of a sentinel participant has been included as an additional risk mitigation measure to monitor potential infusion reactions and other potential acute adverse events as UCB6114 will be administered with a new dose formulation (all cohorts), with a shorter infusion time (Cohort 2), or higher initial dose (Cohorts 3 and 4) than previously administered in Part A of the study. Each sentinel participant will be assessed for at least 48 hours following the first treatment administration before further participants within the same cohort can be enrolled.

Parts B and C will use the modified toxicity probability interval (mTPI) design to guide dose escalation. The mTPI design replaces the algorithmic rules that are based on events (ie, 0 of 3, 1 of 3, 2 of 3, and 3 of 5) with a model-based inference on the toxicity probability intervals. The number of observed dose-limiting toxicities (DLTs) within a dose level will be used to calculate the probability that the current dose level under consideration is within the underdosing, equivalent dosing, or overdosing range relative to the prespecified target toxicity considered acceptable for the disease setting.

The target toxicity specified within this protocol (25%) results in a more conservative set of escalation rules as compared with an algorithmic approach in that a single DLT observed in the first cohort of 3 will result in a recommendation to treat the next cohort of participants at the same dose level rather than a recommendation to dose escalate. Consequently, the mTPI will treat fewer participants at doses above the maximum tolerated dose (MTD) and generally yields higher probabilities in identifying the true MTD.

Dose escalation between cohorts in Part A, Part B, and Part C will follow clearly defined criteria including a review by a Safety Monitoring Committee (SMC), with a dose de-escalation, if appropriate. In consultation with the SMC, a Study Steering Committee (SSC) will recommend to the Sponsor the dose and dosing regimen to be taken forward for the combination therapy dose escalation modules (Part B and C). The dosing schedules in Part A1 have been designed to achieve similar exposures at steady-state to those deemed sufficiently safe by the SMC in Part A. There are also clearly defined criteria for stopping dosing and participant withdrawal.

Targeted therapies have progressed current treatment of advanced solid tumors, increasing survival rates in combination with cytotoxic chemotherapy. Despite the advances in therapy, the paucity of approved agents for progressive disease constitutes an important medical need that needs to be addressed.

There is the potential for UCB6114 to be a beneficial treatment for patients with advanced solid tumors both in the context of this study and the wider clinical development program. Therefore,

taking into account the above considerations, the benefit/risk is considered favorable for the clinical study ONC001.

More detailed information about the preclinical pharmacology activity, potential benefits, and potential adverse events (AEs) of UCB6114 may be found in the current IB.

3 OBJECTIVES AND ENDPOINTS

Study objectives and endpoints for the dose escalation and expansion modules are presented in Table 3-1 (Part A and Part A1), Table 3-2 (Part B and Part C), and Table 3-3 (Parts D, E, F, and G), respectively. The overarching objective of this study is to determine the RP2D for monotherapy (RP2D-M) and for combination therapy. This will be determined using the totality of data generated based on the objectives in and Table 3-1 (Part A and Part A1), Table 3-2 (Part B and Part C), and Table 3-3 (Parts D, E, F, and G).

Table 3-1: Objectives and endpoints for the dose escalation module (Part A) and the dose optimization module (Part A1)

Objectives	Endpoints
Primary	
To characterize the safety profile of UCB6114 as monotherapy	Incidence of TEAEs Severity of TEAEs Incidence of DLTs
Secondary	
To characterize the PK of UCB6114 administered as monotherapy	UCB6114 concentration by scheduled assessment and cohort
Tertiary/exploratory	
To document any antitumor activity observed with UCB6114 according to relevant RECIST criteria	Antitumor activity as indicated by: • ORR • DCR • DOR • PFS • OS
To explore PD biomarkers of UCB6114	• Change in transcriptional and protein marker levels in blood and tumor tissue by scheduled assessment and cohort • Change in ctDNA levels in blood by scheduled assessment and cohort
To evaluate the incidence, emergence, and impact of ADA	ADA (anti-UCB6114 antibody) titer and sample status by scheduled assessment

ADA=antidrug antibody; ctDNA= circulating tumor DNA; DCR=disease control rate; DOR=duration of antitumor response; DLT=dose-limiting toxicity; ORR=objective response rate; OS=overall survival; PD=pharmacodynamic(s); PFS=progression-free survival; PK=pharmacokinetic(s); RECIST=Response Evaluation Criteria in Solid Tumors; TEAE=treatment-emergent adverse event

Table 3-2: Objectives and endpoints for the dose escalation modules in Part B and Part C

Objectives	Endpoints
Primary	
To characterize the safety profile of UCB6114 administered in combination with selected SOC regimens	Incidence of TEAEs Severity of TEAEs Incidence of DLTs
Secondary	
To characterize the PK of UCB6114 administered in combination with selected SOC regimens	UCB6114 concentration by scheduled assessment and dose level
Tertiary/exploratory	
To document any antitumor activity observed with UCB6114 administered in combination with selected SOC regimens according to relevant RECIST criteria	Antitumor activity as indicated by: • ORR • DCR • DOR • PFS • OS
To explore PD biomarkers of UCB6114 administered in combination with selected SOC regimens	• Change in protein marker levels in blood by scheduled assessment and dose level • Change in ctDNA levels in blood by scheduled assessment and dose level
To evaluate the immunogenicity of UCB6114 administered in combination with selected SOC regimens	ADA (anti-UCB6114 antibody) titer and sample status by scheduled assessment

ADA=antidrug antibody; ctDNA= circulating tumor DNA; DCR=disease control rate; DLT=dose-limiting toxicity; DOR=duration of antitumor response; ORR=objective response rate; OS=overall survival; PD=pharmacodynamic(s); PFS=progression-free survival; PK=pharmacokinetic(s); RECIST=Response Evaluation Criteria in Solid Tumors; SOC=standard of care; TEAE=treatment-emergent adverse event

Table 3-3: Objectives and endpoints for the expansion modules in Parts D, E, F, and G

Objectives	Endpoints
Primary	
To assess preliminary antitumor activity of UCB6114 when administered as monotherapy (Part D and Part E) or in combination with selected SOC regimens (Part F and Part G) according to relevant RECIST criteria	Antitumor activity as indicated by ORR
Secondary	
To characterize the safety profile of UCB6114 as monotherapy or in combination with selected SOC regimens	• Incidence of TEAEs • Severity of TEAEs
To document any antitumor activity observed with UCB6114 when administered as monotherapy or in combination with selected SOC regimens	Antitumor activity as indicated by: • DCR • DOR • PFS • OS
Tertiary/exploratory	
To explore PD biomarkers of UCB6114 administered as monotherapy or in combination with selected SOC regimens	Change in transcriptional and protein marker levels in blood and tumor tissue by scheduled assessment
To characterize the PK of UCB6114 administered as monotherapy or in combination with selected SOC regimens	UCB6114 concentration by scheduled assessment and dose level
To evaluate the immunogenicity of UCB6114 administered as monotherapy or in combination with selected SOC regimens	ADA (anti-UCB6114 antibody) titer and sample status by scheduled assessment

ADA=antidrug antibody; DCR=disease control rate; DOR=duration of antitumor response; ORR=objective response rate; OS=overall survival; PD=pharmacodynamic(s); PFS=progression-free survival; PK=pharmacokinetic(s); RECIST=Response Evaluation Criteria in Solid Tumors; SOC=standard of care; TEAE=treatment-emergent adverse event

4 STUDY DESIGN

4.1 Overall design

ONC001 is a multicenter, nonrandomized, open-label, Phase 1/2 study evaluating the safety, PK, and antitumor activity of iv UCB6114 in 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 expansion modules (Parts D, E, F, and G) (see Section 1.2). Depending on emerging data, not all modules may open.

After completion of Part A, Part A1, Part B, and Part C, specific characteristics of modules subsequent to Part A, Part A1, Part B, and Part C will be described in planned protocol amendments. The updated characteristics will include, but not be limited to, tumor type selection, participant's inclusion/exclusion criteria, route and frequency of study medication administration, and selection of the SOC treatment regimen.

There are 8 different study modules for dose escalation and expansion, which are shown in Table 4-1.

Table 4-1: Study modules for dose escalation and expansion

Module	Module description
Part A	Dose-escalation to identify the RP2D-M, based on emerging safety, PK, PD, and antitumor effect data. Participants will receive UCB6114 Q2W via iv infusion. The starting dose will be escalated (or de-escalated) stepwise in successive cohorts of 3 to 6 evaluable participants (modified rolling-6 design) (see Section 4.1.2), until the RP2D-M is determined. Up to 42 participants may be enrolled.
Part A1	Dose-optimization to evaluate alternative dosing schedules for UCB6114 administered as monotherapy in participant with unresectable locally advanced or metastatic colorectal adenocarcinoma, gastric adenocarcinoma, adenocarcinoma of the gastroesophageal junction, or pancreatic cancer. Based on emerging data from Part A, this module will evaluate a new dose formulation, different frequencies of dosing (eg, Q3W, QW4), and different time of infusion. Up to 32 participants may be enrolled.
Part B	Dose-escalation with TFD/TPI in participants with unresectable locally advanced or metastatic colorectal adenocarcinoma, gastric adenocarcinoma, or adenocarcinoma of the gastroesophageal junction to identify the RP2D-T. The starting dose of UCB6114 in Part B 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 TFD/TPI. It is expected that 2 or 3 dose levels of UCB6114 will be explored. The starting dose will be escalated stepwise in successive cohorts of 2 to 4 evaluable participants (mTPI design), until the RP2D-T is determined. Up to 27 participants may be enrolled.
Part C	Dose-escalation with mFOLFOX6 in participants with unresectable locally advanced or metastatic colorectal adenocarcinoma, gastric adenocarcinoma, and adenocarcinoma of the gastroesophageal junction to identify the RP2D-F. 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. The starting dose and dose escalation scheme may differ from that evaluated in Part B. It is expected that 2 or 3 dose levels of UCB6114 will be explored. The starting dose will be escalated stepwise in successive cohorts of 2 to 4 evaluable participants (mTPI design), until the RP2D-F is determined. Up to 27 participants may be enrolled.
Part D	Expansion module to explore the safety and antitumor activity of UCB6114 as monotherapy with the RP2D-M dosing regimen. It is planned to evaluate 15 participants with a selected recurrent/metastatic tumor type 1 (to be decided based on emerging internal and external data). Up to 15 additional participants may be enrolled depending on the observed antitumor activity (total sample size of up to 30 participants).

Table 4-1: Study modules for dose escalation and expansion

Module	Module description
Part E	Expansion module to explore the safety and antitumor activity of UCB6114 as monotherapy with the RP2D-M dosing regimen in an alternative selected tumor type (tumor type 2). It is planned to evaluate 15 participants with a selected recurrent/metastatic tumor type 2 (to be decided based on emerging internal and external data). Up to 15 additional participants may be enrolled depending on the observed antitumor activity (total sample size of up to 30 participants).
Part F	Expansion module to explore the safety and antitumor activity of UCB6114 in combination with the SOC regimen tested in Part B (RP2D-T). It is planned to evaluate UCB6114 plus SOC in 15 participants with a selected recurrent/metastatic tumor type. Up to 15 additional participants may be enrolled depending on the observed antitumor activity (total sample size of up to 30 participants).
Part G	Expansion module to explore the safety and antitumor activity of UCB6114 in combination with the SOC regimen tested in Part C (RP2D-F). It is planned to evaluate 15 participants with a selected recurrent/metastatic tumor type. Up to 15 additional participants may be enrolled depending on the observed antitumor activity (total sample size of up to 30 participants).

iv=intravenous(ly); 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; mTPI= modified toxicity probability interval; QW=once weekly; Q2W=every 2 weeks; Q3W=every 3 weeks; PD=pharmacodynamics; PK=pharmacokinetics; RP2D-F=recommended Phase 2 dose of UCB6114 when used in combination with FOLFOX; RP2D-M=recommended Phase 2 dose for monotherapy; RP2D-T=recommended Phase 2 dose of UCB6114 when used in combination with TFD/TPI; sc=subcutaneous; SOC=standard of care; TFD/TPI=trifluridine/tipiracil

In Part A, each cohort will include 3 to 6 participants. Dose escalation (or de-escalation) will be guided by safety assessments and available PK data. At each dose level, PD samples will be collected to evaluate the PK/PD relationship.

In Part A, eligible participants will receive UCB6114 as an iv infusion every 2 weeks (Q2W) as monotherapy. UCB6114 will be administered as a flat dose (ie, not adjusted for weight or body surface area [BSA]) unless emerging data indicate that weight- or BSA-based dosing would be more appropriate. Doses of UCB6114, ranging from 100mg to 2000mg (corresponding to approximately 1 to 30mg/kg) (Table 6-5) may be explored. Five dose levels are planned; however, an additional 2 dose levels may be added based on emerging data. Dose escalation steps are currently planned at a maximum of 2.5-fold; however, may be adjusted based on observed PK in the preceding cohort(s) and will not exceed 5-fold. Up to 42 participants may be enrolled.

The planned duration of treatment is 2 cycles. Participants may, however, remain on 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 discontinuation. Upon discontinuation of treatment, participants will be referred to appropriate follow-up care per the investigator's judgment.

Part A will include participants with tumor types associated with expression of *GREM1* mRNA. These tumor types include bladder urothelial carcinoma, breast invasive carcinoma, colorectal

adenocarcinoma, esophageal carcinoma, head and neck squamous cell carcinoma, lung adenocarcinoma, lung squamous cell carcinoma, pancreatic adenocarcinoma, prostate adenocarcinoma, and stomach adenocarcinoma based on *GREM1* expression data from Sneddon et al, 2006 and the Cancer Genome Atlas (The Cancer Genome Atlas, 2019).

From Part A, a RP2D for UCB6114 monotherapy (RP2D-M) will be selected based upon the totality of information, including the safety profile, PK profile, and available antitumor activity and PD data. The start of any modules subsequent to Part A (monotherapy dose escalation) will be reliant on module-specific criteria and the approval of planned protocol amendments.

Part A1 will be initiated after Cohort 5 of Part A (2000mg Q2W) has been determined to be [redacted] (ie, DLT incidence <33%, see Section 4.1.2.4). Eligible participants with unresectable locally advanced or metastatic colorectal adenocarcinoma, gastric adenocarcinoma, adenocarcinoma of the gastroesophageal junction, or pancreatic cancer will receive iv infusion of UCB6114 as monotherapy. Four alternative dosing schedules (cohorts) have been planned and will explore shorter infusion time, and less frequent administration (Table 6-6). Each cohort will enroll 8 participants including 1 sentinel participant. Up to 32 participants may be enrolled.

Part B and Part C of ONC001 are planned to be initiated after Cohort 3 of Part A has completed the 28-day DLT assessment period and once the SMC has provided a recommendation to dose escalate to the next protocol-defined level in Part A of the study. For all dose levels, participants will be treated in cohorts of 2 to 4 (target of 3), each dose level will have a minimum of 3 and a maximum of 9 participants (Section 4.1.4.2.2 [Part B] and Section 4.1.5.2.2 [Part C]).

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 initial 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 TFD/TPI. Up to 3 dose levels (anticipated to be 500mg, 1000mg, and 2000mg administered Q2W iv) are planned (Section 4.3.3). Up to 27 participants are planned. Dose escalation decisions in this module will be guided by a model-based estimation of the probability of DLT in Cycle 1.

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. The initial 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) are planned (Section 4.3.3). Up to 27 participants are planned. Dose escalation decisions in this module will be guided by a model-based estimation of the probability of DLT in cycle 1.

In the expansion modules, the RP2D from the respective escalation modules (Part A through Part C) will be tested either as monotherapy in selected tumor types (Part D and Part E) or in combination with SOC (Part F and Part G). Participants recruited to these modules must have at least 1 measurable tumor lesion according to relevant Response Evaluation Criteria in Solid Tumors (RECIST).

Participants will continue treatment until disease progression, unmanageable toxicity, criteria for discontinuation are met, or withdrawal of consent.

In the dose escalation modules, the decision to proceed to the next dose cohort will occur once all participants in the preceding cohort have been monitored for a minimum of 28 days (ie, 1 cycle). However, all available safety data (both within the cohort and from preceding cohorts) will be taken into consideration when dose escalation decisions are made.

In the expansion modules, response will be assessed after completion of 2 cycles of treatment (ie, 4 doses on Q2W dosing regimen) and at regular intervals thereafter.

4.1.1 Study oversight

Study safety oversight will be performed via an SMC as well as regular safety conference calls in Part A , and by an SMC and an SSC, as well as regular safety conference calls, once modules subsequent to Part A commence.

Safety monitoring committee

A SMC will be established for Part A and will comprise key Sponsor personnel and Investigators from participating sites. Once modules subsequent to Part A commence, the members of the SMC will include Investigators who are actively enrolling study participants into the study.

Responsibilities of the SMC include:

- Review of safety data for study participants including review and provision of adjudication of individual DLTs, when applicable.
- Review of available PK and PD biomarker data.
- Make dose escalation recommendations, dosing schedule recommendations, recommendations to continue the study as planned or with protocol adjustments, if needed.
- Determination of the MTD, if applicable.

Study steering committee

An SSC will be implemented prior to the start of modules subsequent to Part A. 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 study related issues, such as study design, study implementation and conduct, and data analysis and reporting. In consultation with the SMC, the SSC will recommend to the Sponsor the dose and dosing regimen to be taken forward for Part B and Part C.

4.1.2 Part A – Monotherapy dose escalation

In Part A of the study, 3 to 6 participants will be enrolled per dose level using a modified rolling-6 design. 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 treatment related AEs. Each sentinel participant will be assessed for at least 24 hours following second treatment administration 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 (Figure 4-1). Should the sentinel participant experience a DLT, then participants 2 and 3 will be enrolled and observed for 16 days (Figure 4-2). Escalation can be performed when 3/3, 4/4, 5/5, 5/6, or 6/6 participants are evaluated without 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 occurs when 2 or more participants experience a DLT at the first dose level.

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 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 (ie, 1 cycle), before dose escalation is considered. The second participant in any new cohort should also not be dosed until the first participant has received at least 2 doses and been observed for a minimum of 16 days (ie, 24 hours following the second treatment administration). All participants will remain in the hospital or study site's standard monitoring facility for continuous monitoring for the first 24 hours following the first dose; at subsequent doses, the participant may remain at the hospital or study site's standard monitoring facility at the investigator's discretion.

4.1.2.1 SMC

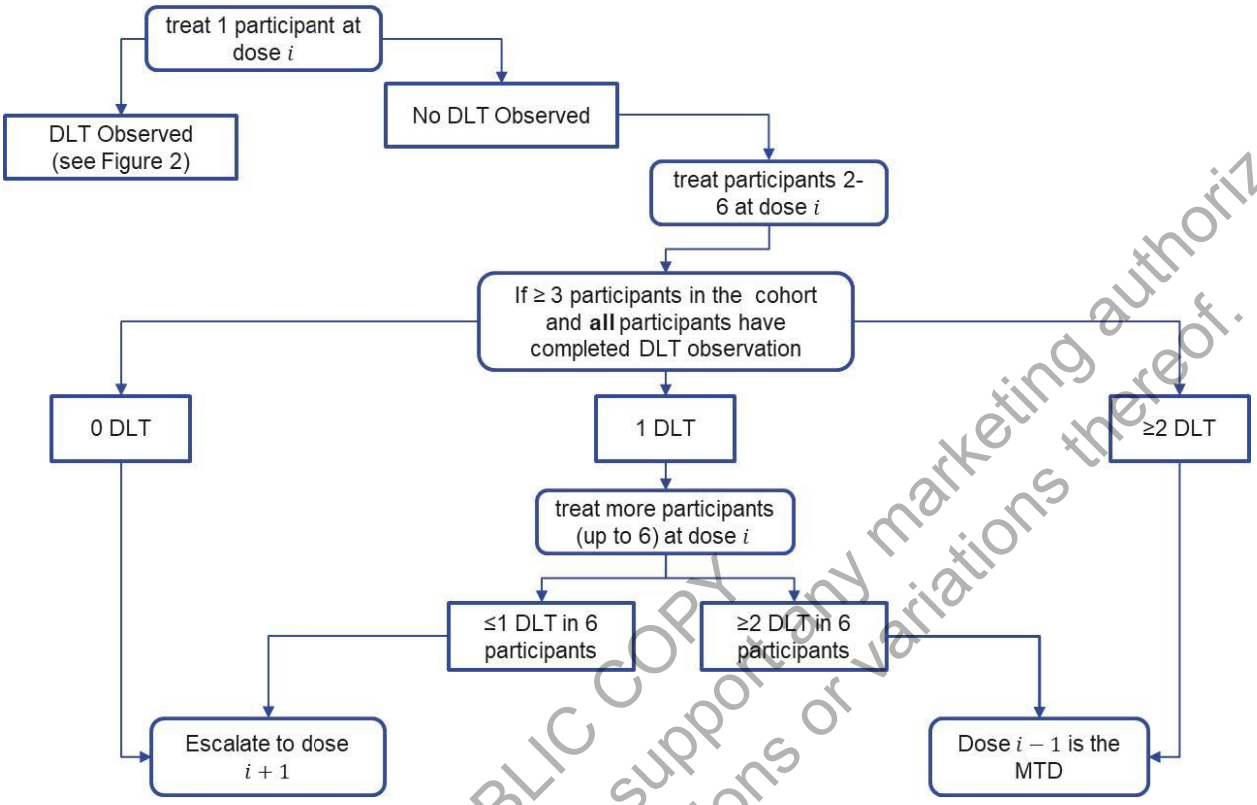
Once the last participant in a given cohort has completed the required 28-day DLT Observation Period, an SMC meeting will be convened to review all safety data, available PK data, and any available PD data. The SMC will decide whether to halt dose escalation, further expand the cohort to gain additional safety data, or determine the next dose level to be tested. Details are described in an SMC Charter.

4.1.2.2 Dose escalation criteria

Dose-limiting toxicities observed in the full 28 days of Cycle 1 will be used to decide whether escalation to the next dose level may take place or whether cohort expansion or dose de-escalation should occur. However, all available safety data (both within the cohort and from preceding cohorts) will be taken into consideration when making such decisions.

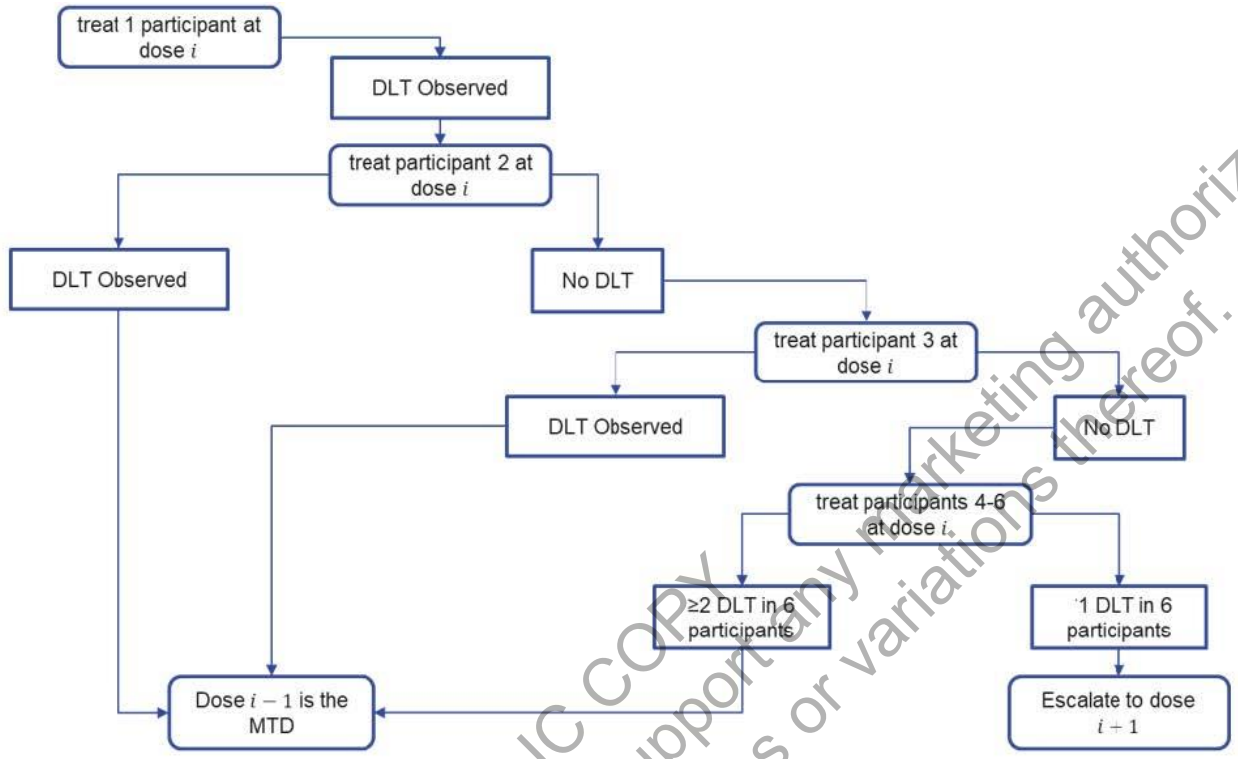
Dose-limiting toxicities may not be encountered in this study. There is no intention to continue dose escalation until an MTD can be established. The decision-making guidelines for dose escalation are shown in Figure 4-1 (no DLT was observed in the sentinel participant) and Figure 4-2 (a DLT was observed in the sentinel participant). The SMC will make dose escalation decisions based upon review of safety data and available PK data after all participants in a cohort complete at least the first treatment cycle (28 days) or have discontinued.

Figure 4-1: Dose escalation decision making: no DLT observed in sentinel participant



DLT=dose-limiting toxicity; MTD=maximum tolerated dose
Note: Figure 2 is shown in Figure 4-2.

Figure 4-2: Dose escalation decision making: DLT observed in sentinel participant



DLT=dose-limiting toxicity; MTD=maximum tolerated dose

4.1.2.3 Dose de-escalation following initial dose level

The SMC will determine if a dose de-escalation may be warranted, for example, if DLTs are observed in ≥2 participants in Cohort 1.

4.1.2.4 Dose-limiting toxicity determination and maximum tolerated dose definition

Dose-limiting toxicity is defined as an AE that is at least possibly related to the study medication that occurs during Cycle 1 and fulfills any one of the following criteria:

1. Grade 3 or 4 nonhematological toxicity according to the National Cancer Institute (NCI) Common Terminology Criteria for AEs (CTCAE Version 5.0) except for alopecia (of any severity or duration), or nausea, vomiting, or diarrhea that reverses to Grade ≤2 within 24 hours with appropriate medical therapy.
2. Grade 3 or 4 biochemical abnormality that persists despite maximal supportive treatment or biochemical abnormalities that is symptomatic and nontransient (does not return to baseline within 24 hours, with or without appropriate supplementation).
3. Any Grade ≥3 hematological toxicity of >5 days duration or febrile neutropenia (absolute neutrophil count [ANC]<1000/mm^3 with a single temperature of >38.3°C or sustained temperature ≥38°C for more than one hour), infection (documented clinically or

microbiologically) with Grade 3 or 4 neutropenia, thrombocytopenia with bleeding or requiring platelet transfusion, or Grade 4 thrombocytopenia.

4. Prolonged Grade 2 diarrhea (>7 days) despite adequate antidiarrheal medication, or multiple Grade 1or 2 toxicities (eg, Grade 1 or 2 diarrhea, vomiting, rash, and fatigue) may also be considered dose-limiting if considered so by the investigator.

Investigators, in consultation with the study physician or medically qualified designee, can declare a DLT if a participant is experiencing toxicity and treatment cannot be continued without exposing the participant to excessive risk.

The MTD is considered to be the dose level immediately below that which results in a DLT incidence of 33% or higher.

4.1.2.5 Defining the recommended Phase 2 dose for monotherapy

The RP2D-M will be defined when all participants in Part A have completed a minimum of 28 days of treatment (ie, 1 Cycle) or have discontinued prematurely (Table 1-4). All safety, PK, available PD biomarker, ADA, and antitumor activity data will be used to select the RP2D-M.

The RP2D-M will not exceed the MTD (if an MTD is established). Pharmacodynamic effects consistent with the mechanism of action of UCB6114 and/or clinical evidence of antitumor activity may also help determine the RP2D-M.

4.1.3 Part A1 – Dose optimization (alternative dosing schedules)

Part A1 is a multicenter, non-randomized, open-label, dose optimization module of Study ONC001 to evaluate alternative dosing schedules and infusion times for UCB6114 administered as monotherapy in patients with unresectable locally advanced or metastatic colorectal cancer, gastric cancer, cancer of the gastro-esophageal junction, or pancreatic cancer.

Part A1 may commence after the fifth cohort in Part A (Cohort 5) is considered sufficiently [redacted] by the SMC (DLT rate less than 33%). The planned dose optimization scheme for Part A1 will assess the safety and tolerability of the drug new 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 Q3W (90-minute iv infusion), 21-day treatment cycle
- Cohort 4: 4000mg Q4W (120-minute iv infusion), 28-day treatment cycle

Details of each planned cohort are provided in Table 6-6.

Up to 32 participants will be allocated 1:1:1:1 to one of the 4 cohorts, with each cohort enrolling 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. Each sentinel participant will be assessed for at least 48 hours following the first administration of UCB6114 in the first cycle and the SMC will convene before 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 observation period. If deemed necessary, an additional SMC meeting can convene after 75% of the participants have completed the required observation period. If 1 DLT, or more, (refer to 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 study can continue as planned.

If 3 or more participants experience DLT(s) in a given cohort, no further participants will be enrolled in the cohort and the dosing schedule will be considered to be unacceptably toxic.

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

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

4.1.4 Part B – Dose escalation with TFD/TPI

Part B is a single arm open-label multiple ascending dose-escalation module of ONC001 evaluating UCB6114 in combination with TFD/TPI to identify the recommended Phase 2 dose of UCB6114 when used in combination with TFD/TPI (RP2D-T). Up to 27 participants with unresectable locally advanced or metastatic colorectal adenocarcinoma, gastric adenocarcinoma, or adenocarcinoma of the gastroesophageal junction will be enrolled.

Part B of ONC001 is planned to be initiated after Cohort 3 of Part A has completed the 28-day DLT assessment period and once the SMC has provided a recommendation to dose escalate to the next protocol-defined level in Part A of the study.

During the Treatment Period, UCB6114 will be administered in combination with TFD/TPI. UCB6114 will be administered as an iv infusion every 2 weeks (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 (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. For administration at home on Cycle 1 Day 1, eligibility must be confirmed within 3 days prior to Day 1 dosing as per the Schedule of Assessments.

Trifluridine/tipiracil will be administered at the recommended standard of care dose. The starting dose of UCB6114 in Part B 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 TFD/TPI.

Part B will be undertaken using the mTPI method. A target DLT rate of 25% with an equivalence interval (20% to 30%) will be used to estimate the MTD during dose escalation. For all dose levels, enrolled participants will be treated in cohorts of 2 to 4 participants (target of 3), who can

be treated in parallel. Each dose level may have more than one cohort and will have a minimum of 3 evaluable participants.

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).

The decision to dose escalate, have no change in dose, or dose de-escalate in the next cohort will occur once all participants in the preceding cohort have been monitored for a minimum of 28 days (ie, 1 cycle). All available safety data (both within the cohort and from preceding cohorts and other parts of the study) will be taken into consideration when dose escalation decisions are made. The dose justification is given below in Section 4.3.3.

The planned duration of treatment is 2 cycles. Participants may, however, remain in the study for additional cycles if they are receiving therapeutic benefit (SD, PR, or CR) or until they fulfill one of the criteria for study discontinuation (Section 7.2). 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 RP2D-T for UCB6114 in combination with TFD/TPI will be determined based upon the totality of information, including the safety profile, PK data, PD biomarker data, and available antitumor activity.

4.1.4.1 Study oversight

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.

Safety conference calls with investigators and key Sponsor personnel will be held regularly.

4.1.4.2 Dose-limiting toxicity and maximum tolerated dose definition and determination

4.1.4.2.1 Definition of DLT

Dose-limiting toxicity is defined as one of the following toxicities (according to the NCI CTCAE Version 5.0) occurring during the DLT assessment window (Days 1 to 28 of Cycle 1) that is at least possibly related to UCB6114:

- Grade ≥4 neutropenia (ANC <500/μL) lasting ≥7 days
  - In the event of CTCAE Grade 4 neutropenia, full blood count must be performed on the seventh day after the onset of the event to determine if a DLT has occurred
- Grade ≥3 neutropenia complicated by fever (≥38° C) or infection
- Grade 3 thrombocytopenia with bleeding or requiring platelet transfusion or Grade 4 thrombocytopenia
- Any Grade ≥3 non-hematological event with the following exceptions:

- Grade 3 nausea, vomiting, diarrhea, or fatigue that resolves to Grade ≤2 within 24 hours of implementing optimal supportive care
- Grade 3 laboratory abnormality that is asymptomatic and also deemed by the investigator to not be clinically significant

Investigators, in consultation with the medical monitor, can declare a DLT if a participant is experiencing toxicity and treatment cannot be continued without exposing the participant to excessive risk.

4.1.4.2.2 Determination of maximum-tolerated dose

For every dose levels, participants will be treated in cohorts of 2 to 4 (target of 3), each dose level will have a minimum of 3 and a maximum of 9 participants.

The target rate of DLTs is 25% (equivalence interval 20% to 30%). The target rate will define the MTD of the combination regimen (UCB6114 given in combination with TFD/TPI).

The mTPI method relies upon a statistical probability algorithm, calculated using data from all participants treated in prior and current cohorts at the same dose level, to determine whether future cohorts should be dose escalated, have no change in dose, or be dose de-escalated. The dose escalation will stop if any of the following criteria is met:

- The maximum sample size has been reached (27 participants total)
- At least 9 participants have been accumulated on a dose that is predicted to be the MTD
- All doses explored appear to be overly toxic and the MTD cannot be determined
- The escalation would exceed a dose level tested and considered safe by the SMC in monotherapy (Part A)

The mTPI design uses a Bayesian decision framework to inform dose-escalation and dose de-escalation decisions. These rules are conceptually similar to those used by the 3+3 design. The model-based dose-escalation decisions to help inform the final decision by the SMC can be precalculated under the mTPI design and are presented in a 2-way table (Table 4-2).

Table 4-2: Part B dose escalation/de-escalation schema for mTPI design[a]

Number of DLTs	Number of participants treated at dose level						
	3	4	5	6	7	8	9
0	E	E	E	E	E	E	E
1	S	S	S	S	E	E	E
2	D	D	S	S	S	S	S
3	DR	DR	DR	D	S	S	S
4		DR	DR	DR	DR	DR	D
5			DR	DR	DR	DR	DR
6				DR	DR	DR	DR

D=de-escalate to next lower dose; DLT=dose-limiting toxicity; DR=the current dose is unacceptably toxic; E=escalate to next higher dose; mTPI= modified toxicity probability interval; S=stay at current dose
[a] Target toxicity=0.25

Table 4-2 has the following interpretation (using 3 and 6 treated participants as examples):

With 3 participants treated at current dose level:

- 0 DLTs = escalate
- 1 DLT = remain at the current dose
- 2 DLTs = de-escalate
- 3 DLTs = de-escalate and consider current dose as unacceptably toxic

With 6 participants treated at current dose level:

- 0 DLTs = escalate
- 1 to 2 DLTs = remain at the current dose
- 3 DLTs = de-escalate
- >3 DLTs = de-escalate and consider current dose as unacceptably toxic

4.1.4.3 Definition of recommended Phase 2 dose in combination with TFD/TPI

The RP2D-T will be defined after all participants evaluable for DLT assessment in Part B have completed a minimum of 28 days of treatment (ie, 1 cycle). The RP2D-T will not exceed the RP2D-M or the MTD (if an MTD is established). The definition of the RP2D-T will take into account the safety profile, PK, PD biomarkers, and any antitumor effect data.

4.1.5 Part C – Dose escalation with mFOLFOX6

Part C is a single arm, open-label, multiple ascending dose-escalation module of ONC001 evaluating UCB6114 in combination with a mFOLFOX6 to identify the recommended Phase 2 dose of UCB6114 when used in combination with mFOLFOX6 (RP2D-F). Up to 27 participants

with unresectable locally advanced or metastatic colorectal adenocarcinoma, gastric adenocarcinoma, and adenocarcinoma of the gastroesophageal junction will be enrolled.

Part C of ONC001 is planned to be initiated after Cohort 3 of Part A has completed the 28-day DLT assessment period and once the SMC has provided a recommendation to dose escalate to the next protocol-defined level in Part A of the study. Eligible participants will receive UCB6114 as an iv infusion Q2W in combination with iv mFOLFOX6 (Q2W) on a 28-day cycle. A mFOLFOX6 regimen 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/m^2/day continuous infusion on Day 1 and Day 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.

Part C will be undertaken using the mTPI method. A target DLT rate of 25% with an equivalence interval (20% to 30%) will be used to estimate MTD during dose escalation. For all dose levels, enrolled participants will be treated in cohorts of 2 to 4 participants (target of 3), who can be treated in parallel. Each dose level may have more than one cohort and will have a minimum of 3 evaluable participants.

It is expected that up to 3 dose levels of UCB6114 will be explored in combination with the selected mFOLFOX6 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 C will not exceed a dose level tested and considered safe by the SMC to allow dose escalation in monotherapy (Part A).

The decision to dose escalate, have no change in dose, or dose de-escalate in the next cohort will occur once all participants in the preceding cohort have been monitored for a minimum of 28 days (ie, 1 cycle). All available safety data (both within the cohort and from preceding cohorts and other parts of the study) will be taken into consideration when dose escalation decisions are made. The dose justification is given below in Section 4.3.3.

The planned duration of treatment is 2 cycles. Participants may, however, remain in the study for additional cycles if they are receiving a therapeutic benefit (SD, PR, or CR) or until they fulfill one of the criteria for study discontinuation (Section 4.3.3). Participants will continue treatment until disease progression, unmanageable toxicity, or withdrawal of consent. Upon discontinuation from treatment, participants will be referred to appropriate follow-up care per the investigator's judgment.

From Part C, a RP2D-F for UCB6114 in combination with mFOLFOX6 will be determined based upon the totality of information, including the safety profile, PK data, PD biomarker data, and available antitumor activity.

4.1.5.1 Study oversight

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.

Safety conference calls with investigators and key Sponsor personnel will be held regularly.

4.1.5.2 Dose-limiting toxicity determination and maximum tolerated dose definition

4.1.5.2.1 Definition of DLT

Dose-limiting toxicity is defined as one of the following toxicities (according to the NCI CTCAE Version 5.0) occurring during the DLT assessment window (Days 1 to 28 of Cycle 1) that is at least possibly related to UCB6114:

- Grade ≥4 neutropenia (ANC <500/μL) lasting ≥7 days
  - In the event of CTCAE Grade 4 neutropenia, full blood count must be performed on the seventh day after the onset of the event to determine if a DLT has occurred
- Grade ≥3 neutropenia complicated by fever (≥38° C) or infection
- Grade 3 thrombocytopenia with bleeding or requiring platelet transfusion or Grade 4 thrombocytopenia
- Any Grade ≥3 non-hematological event with the following exceptions:
  - Grade 3 nausea, vomiting, diarrhea, or fatigue that resolves to Grade ≤2 within 24 hours of implementing optimal supportive care
  - Grade 3 laboratory abnormality that is asymptomatic and also deemed by the investigator to not be clinically significant

Investigators, in consultation with the medical monitor, can declare a DLT if a participant is experiencing toxicity and treatment cannot be continued without exposing the participant to excessive risk.

4.1.5.2.2 Determination of maximum-tolerated dose

For every dose levels, participants will be treated in cohorts of 2 to 4 (target of 3), each dose level will have a minimum of 3 and a maximum of 9 participants.

The target rate of DLTs is 25% (equivalence interval 20% to 30%). The target rate will define the MTD of the combination regimen (UCB6114 given in combination with mFOLFOX6).

The mTPI method relies upon a statistical probability algorithm, calculated using data from all participants treated in prior and current cohorts at the same dose level, to determine whether future cohorts should be dose escalated, have no change in dose, or be dose de-escalated. The dose escalation will stop if any of the following criteria are met:

- The maximum sample size has been reached (27 participants total)
- At least 9 participants have been accumulated on a dose that is predicted to be the MTD
- All doses explored appear to be overly toxic and the MTD cannot be determined
- The escalation would exceed a dose level tested and considered safe by the SMC in monotherapy (Part A)

The mTPI design uses a Bayesian decision framework to inform dose-escalation and de-escalation decisions. These rules are conceptually similar to those used by the 3+3 design. The

dose-escalation decisions can be pre-calculated under the mTPI design and are presented in a 2-way table (Table 4-3).

Table 4-3: Part C dose escalation/de-escalation schema for mTPI design[a]

Number of DLTs	Number of participants treated at dose level						
	3	4	5	6	7	8	9
0	E	E	E	E	E	E	E
1	S	S	S	S	E	E	E
2	D	D	S	S	S	S	S
3	DR	DR	DR	D	S	S	S
4		DR	DR	DR	DR	DR	D
5			DR	DR	DR	DR	DR
6				DR	DR	DR	DR

D=de-escalate to next lower dose; DLT=dose-limiting toxicity; DR=the current dose is unacceptably toxic; E=escalate to next higher dose; mTPI= modified toxicity probability interval; S=stay at current dose
[a] Target toxicity=0.25

Table 4-3 has the following interpretation (using 3 and 6 treated participants as examples):

With 3 participants treated at current dose level:

- 0 DLTs = escalate
- 1 DLT = remain at the same dose
- 2 DLTs = de-escalate
- 3 DLTs = de-escalate and consider current dose as intolerable

With 6 participants treated at current dose level:

- 0 DLTs = escalate
- 1 to 2 DLTs = remain at the same dose
- 3 DLTs = de-escalate
- >3 DLTs = de-escalate and consider current dose as intolerable

4.1.5.3 Defining the recommended Phase 2 dose in combination with mFOLFOX6

The RP2D-F will be defined after all participants evaluable for DLT assessment in Part C have completed a minimum of 28 days of treatment (ie, 1 cycle). The RP2D-F will not exceed the RP2D-M or the MTD (if an MTD is established). The definition of the RP2D-F will take into account the safety profile, PK, PD biomarkers, and any antitumor effect data.

4.1.6 Part D – Monotherapy 1 expansion

Part D can be initiated as soon as the RP2D-M is determined in Part A, or commencement may be delayed until evaluation of other schedules or routes of administration in Part A1.

4.1.7 Part E – Monotherapy 2 expansion

Part E can be initiated as soon as the RP2D-M is determined in Part A, or commencement may be delayed until evaluation of other schedules or routes of administration in Part A1.

4.1.8 Part F – Combination 1 expansion

Part F can be initiated as soon as the RP2D-T is determined in Part B.

4.1.9 Part G – Combination 2 expansion

Part G can be initiated as soon as the RP2D-F is determined in Part C.

4.1.10 Tumor type selection for modules post-Part A

The tumor types to be explored in the modules following Part A will be selected based upon the following:

- Data collected through Part A
- Evolving preclinical and translational data
- Literature data on the role of gremlin-1 in specific tumors
- Feasibility of enrollment

The protocol may be amended to replace the tumor types based on emerging data.

4.2 Scientific rationale for study design

This is a modular study comprising dose escalation and expansion modules.

The first dose escalation module of the study is an open-label, nonrandomized modified rolling-6 design (an algorithm-based extension of the 3+3 design which is a standard practice in Phase 1 oncology studies) in participants with advanced solid tumors, where UCB6114 will be administered as monotherapy.

Two additional dose escalation modules will explore combination regimens (Part B and Part C). These will use the mTPI design to guide dose escalation (Ji and Wang, 2013). This design has a low risk of exposing participants to doses above the MTD and yields high probabilities for identifying the correct MTD.

The planned monotherapy expansion modules and combination expansion modules will allow the simultaneous evaluation of multiple tumor types and standard of care regimens, replacing separate Phase 2 studies that would have followed after identification of the RP2D. Combining dose escalation and the expansion modules under one protocol will allow multiple hypotheses to be addressed (ie, different tumor types, doses) and potentially expedite development and approval of UCB6114.

4.2.1 Rationale for Part A

The rationale for Part A is provided in Section 2.1.

The tumor types for Part A were selected based on the reported prevalence of detectable expression and/or expression level of *GREM1* mRNA and include bladder urothelial carcinoma, breast invasive carcinoma, colorectal adenocarcinoma, esophageal carcinoma, head and neck

squamous cell carcinoma, lung adenocarcinoma, lung squamous cell carcinoma, pancreatic adenocarcinoma, prostate adenocarcinoma, and stomach adenocarcinoma.

4.2.2 Rationale for Part A1

GREM1 mRNA expression has been reported in more than half of tissue samples from colorectal and pancreatic cancer (Sneddon et al, 2006). Upregulated gremlin-1 expression has been linked to a more advanced tumor stage and poor clinical prognosis in gastric cancer (Sun et al, 2020). In CRC, high levels of *GREM1* expression were associated with a shorter disease-free survival when compared with low levels of *GREM1* expression (Davis et al, 2015; Dutton et al, 2019).

Part A1 will be conducted in participants with colorectal-, gastric-, gastroesophageal junction or, pancreatic cancer and will evaluate alternative dosing schedules and duration of infusion to allow for future combination regimens with UCB6114 and a range of other treatments. Part A1 will use modifications to the 5th dose-level in Part A (2000mg Q2W) should this be determined to be [redacted] (i.e. DLT incidence <33%, see Section 4.1.2.4).

4.2.3 Rationale for Part B and Part C

UCB nonclinical data showed that, in the *Apc^{Min};Vil1-Grem-1* model of CRC in late stage, disease established mice, the combination of 5-fluorouracil and the murinized version of UCB6114, Ab7326 mIgG1, significantly prolonged mouse lifespan. This supports the evaluation of UCB6114 in selected gastrointestinal cancer types in combination with a fluoropyrimidine-based chemotherapy.

Trifluridine/tipiracil chemotherapy is used in different lines of treatment which depends on the tumor type, the patients' comorbidities, and personal preferences. As no overlapping toxicity is expected, in Part B the dose escalation of UCB6114 will start in combination with therapeutic doses of the TFD/TPI chemotherapy, with the expectation that participants will benefit from the standard of care chemotherapy.

The mFOLFOX6 chemotherapy regimen, consisting of leucovorin, 5-fluorouracil, and oxaliplatin, has been evaluated in CRC for more than 15 years and is commonly used in a variety of gastrointestinal cancers, including CRC and gastric- and gastroesophageal junction adenocarcinoma. The mFOLFOX6 chemotherapy regimen is used in different lines of treatment which depends on the tumor type, the patients' comorbidities, and personal preferences. As no overlapping toxicity is expected, in Part C the dose escalation of UCB6114 will start in combination with therapeutic doses of the mFOLFOX6 chemotherapy, with the expectation that participants will benefit from the standard of care chemotherapy.

4.2.4 Dosing strategy

The monotherapy dose escalation module (Part A) will systematically evaluate the safety, tolerability, and PK of UCB6114 at increasing dose levels.

The planned dose escalation steps are given in Table 6-5. In the event that exposure is substantially lower than anticipated, dose escalations will still not exceed a 5-fold increase. Doses will be administered every 2 weeks by iv infusion.

In Part A, the SMC will decide on the dose escalation steps (see Section 4.1.2.1). Based upon the emerging data, the SMC may decide to add up to 2 additional dose levels and/or schedules. Doses above 2000mg iv Q2W will be subject to a substantial amendment.

The combination dose escalation modules (Part B and Part C) will start with the Part A Cohort 3 dose of UCB6114. Depending on the eventual determination of the RP2D-M from Part A, this starting dose could represent 25% to 100% of the RP2D-M. Doses of UCB6114 in the combination dose escalation modules will not exceed the MTD if an MTD is determined. Combination agents will be given at the approved doses and schedules.

The RP2D-M will be used in the monotherapy expansion modules (Part D and Part E) and the RP2D in combination therapy will be used for the combination expansion modules (Part F and Part G).

4.3 Justification for dose

4.3.1 Starting dose in Part A

The rationale to start at UCB6114 100mg administered iv Q2W in Part A is based on the following:

- The maintenance of a predicted suppression of gremlin-1 associated with antitumor activity (prolonged survival; predicted 95% suppression across the dosing interval) observed in nonclinical pharmacology models assuming a low level of gremlin-1 ([redacted]) in human and a slow gremlin-1 turnover rate [redacted]) based on a PK/PD model scaled to human developed using single ascending dose data from cynomolgus monkeys.
- The low risk of UCB6114's mechanism of action (antagonism of gremlin-1) and the class of molecule (fully human IgG4P), in combination with the lack of relevant adverse findings from the nonclinical 13-week GLP toxicity studies.

When Ab7326 mIgG1 (murinized version of UCB6114) was dosed iv at 30mg/kg twice weekly (BIW) in the *Apc*^{Min}/*Vil1-Grem1* model, or 30mg/kg once weekly (QW) in the *Vil1-Grem1* model, a significantly increased survival over vehicle control was observed. Lower doses had reduced antitumor activity or had no effect, whereas higher doses did not appear to further increase survival. The human exposures at this dose level are anticipated to be lower than the exposures achieved at the efficacious doses identified in the nonclinical pharmacology models. These models are known to highly over-express gremlin-1 mRNA and may have much higher levels of gremlin-1 protein present than in patients with advanced solid tumors; therefore, the human exposures required for antitumor activity are anticipated to be lower. The median average concentration at steady state ($C_{av,ss}$) anticipated following 100mg iv Q2W is 20.4µg/mL, which corresponds to a concentration 10-fold greater than the cellular IC_{50} for the ID-1 reporter assay (an in vitro assay measuring the functional inhibition of BMP signaling by gremlin-1). The FIH starting dose is anticipated to have a >100-fold safety margin based on the outcome of the 13-week GLP toxicity studies in cynomolgus monkeys and rats. Further details regarding dose modification are provided in Section 6.6.

4.3.2 Doses in Part A1

Part A1 will be initiated after Cohort 5 of Part A, with dosing schedules that aim to maintain a similar exposure at steady state (average UCB6114 concentration at steady-state; $C_{av,ss}$; see Table 6-5) to the Part A Cohort 5 dose of 2000mg Q2W iv. Cohort 1 will assess safety, PK and PD of the new dose formulation. Cohorts 2 to 4 will assess shorter infusion time and less frequent administration.

4.3.3 Starting doses for UCB6114 and standard of care regimens in Part B and Part C

4.3.3.1 UCB6114 dosing

In both Part B and Part C, UCB6114 will be administered by iv infusion on Days 1 and 15 of each cycle. The starting dose 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 which may overlap with expected toxicities associated with TFD/TPI (Part B) or mFOLFOX6 (Part C). The rationale for the UCB6114 starting dose in combination with TFD/TPI (Part B) or mFOLFOX6 (Part C) is based on:

- Nonclinical safety studies of UCB6114, which demonstrated no toxicities (with the possible exception of reproductive findings in female rats) that would overlap with those commonly seen with cytotoxic chemotherapy.
- A review of dosing targeted and cytotoxic drug combinations between 2010 and 2013 which showed that for combinations involving an antibody as the targeted agent, 69 out of 121 studies (57%; 37 out of 68 drug combinations) could give both agents at 100% of the recommended dose (Nikanjam et al, 2016).
- A nonclinical study of Ab7326 mIgG1 in the *Apc^{Min};Vil1-Grem-1* mouse model, in which the lowest monotherapy dose that showed qualitative improvement in survival was 15mg/kg BIW subcutaneously (sc) (for 6 weeks followed by 15mg/kg QW sc thereafter) when dosing from an age of 21 days. A clinical dose of UCB6114 of 1000mg Q2W iv is expected to provide similar exposure in humans as the 15mg/kg BIW dose achieved in mice. The combination UCB6114 start dose of 500mg Q2W iv is expected to provide an exposure approximately 50% of this.
- A nonclinical study of Ab7326 mIgG1 in the *Apc^{Min};Vil1-Grem-1* mouse model, in which 30mg/kg BIW sc (for 6 weeks followed by 30mg/kg QW thereafter) given in combination with 5-fluorouracil increased survival relative to either monotherapy when dosing from an age of 35 days (which is close to the point where untreated mice are sacrificed on humane grounds). The combination UCB6114 start dose of 500mg Q2W iv is expected to provide an exposure approximately 25% of this.

Considering the above points, a start dose of UCB6114 of 500mg Q2W iv in combination with TFD/TPI (Part B) or FOLOFX (Part C) is expected to have an adequate safety profile and is expected to provide approximately 25% of the exposure that was associated with increased survival in combination with 5-fluorouracil in the mouse model.

As no significant difference in survival was observed between doses of 30 and 60mg/kg BIW sc of Ab7326 mIgG1 in the *Apc^{Min};Vil1-Grem-1* mouse model, doses of UCB6114 higher than 2000mg Q2W iv in humans are not likely warranted as monotherapy or in combination. Therefore, evaluation of 3 UCB6114 dose-levels escalated in combination with TFD/TPI (Part B) or mFOLFOX6 (Part C), anticipated to be 500mg, 1000mg, and 2000mg administered Q2W iv, is proposed.

4.3.3.2 Standard of Care regimen dosing

There are no planned escalations of the standard of care regimen doses. Dose modifications based on toxicity are described in Section 6.6.

4.3.3.2.1 Part B

In Part B, TFD/TPI will be given orally bid on Days 1 to 5 and Days 8 to 12 of each 28-day treatment cycle. The starting dose of TFD/TPI in adults is 35mg/m^2/dose administered orally bid on Days 1 to 5 and Days 8 to 12 of each 28-day cycle. The dosage is calculated according to body surface area (BSA) (Table 4-4). The dosage must not exceed 80mg/dose (based on the trifluridine component).

Table 4-4: TFD/TPI dosage calculation

Starting dose	BSA (m^2)	Dose (mg)	Tablets per dose		Total daily dose (mg)
			15mg/6.14mg	20mg/8.19mg	
35 mg/m^2	< 1.07	35	1	1	70
	1.07 to 1.22	40	0	2	80
	1.23 to 1.37	45	3	0	90
	1.38 to 1.52	50	2	1	100
	1.53 to 1.68	55	1	2	110
	1.69 to 1.83	60	0	3	120
	1.84 to 1.98	65	3	1	130
	1.99 to 2.14	70	2	2	140
	2.15 to 2.29	75	1	3	150
	≥2.30	80	0	4	160

BSA=body surface area

The tablets must be swallowed whole with a glass of water within 1 hour of completion of the morning and evening meals. Study participants will be instructed to swallow the required number of tablets at approximately the same times on each day. Study participants will be instructed to wash their hands before and after taking the drug. The TFD/TPI tablets may be dispensed to the study participants once predose assessments are completed and eligibility is confirmed, up to 3 days prior to Day 1 (Table 1-7). The sites can, however, choose to do all assessments on Day 1, prior to dosing of any study medication.

Participants must not retake doses of TFD/TPI that are vomited or were missed and should continue with the next scheduled dose. If tablets are handled by anyone other than the participant, this person must wear gloves.

4.3.3.2.2 Part C

In Part C, mFOLFOX6 will be administered iv every 2 weeks in 28-day treatment cycles. Dosing will be based on calculated body surface area and will consist of 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 Day 1 and 2 (2400mg/m^2 over 46 hours).

The recommended administration of mFOLFOX6 is shown in Table 4-5.

Table 4-5: mFOLFOX6 dosing

Drug	Dose	Administration
Oxaliplatin[a]	85mg/m^2	iv in 250 to 500mL glucose 5% over 2 hours
Leucovorin[a]	400mg/m^2	iv in 250mL glucose 5% over 2 hours
5-Fluorouracil	400mg/m^2	iv bolus
5-Fluorouracil	2400mg/m^2	iv over 46 hours via an infusor

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(ly)

[a] Oxaliplatin and leucovorin may be infused over the same two-hour period by using a Y-site connector placed immediately before the infusion site.

Within the study, mFOLFOX6 is administered every 14 days in 28-day treatment cycles up to a maximum of 6 cycles.

Antiemetic premedication prior to administration of chemotherapy is recommended and sites should follow their institutional standard of care.

4.4 End of study definition

The end of the study is defined as the date of the last visit of the last participant in the study.

5 STUDY POPULATION

Prospective approval of protocol deviations to recruitment and enrollment criteria, also known as protocol waivers or exemptions, is not permitted.

The study population is defined separately for each study module and is presented in Table 5-1.

Table 5-1: Study population

Study module	Population
Part A: Monotherapy dose escalation	Participants with recurrent or metastatic advanced solid tumors resistant or refractory to standard treatment from a variety of tumors types associated with gremlin-1 mRNA expression (ie, bladder urothelial carcinoma, breast invasive carcinoma, colorectal adenocarcinoma, esophageal carcinoma, head and neck squamous cell carcinoma, lung adenocarcinoma, lung squamous cell carcinoma, pancreatic adenocarcinoma, prostate adenocarcinoma and stomach adenocarcinoma)
Part A1: Monotherapy dose optimization	Participants with unresectable locally advanced or metastatic colorectal adenocarcinoma, gastric adenocarcinoma, adenocarcinoma of the gastroesophageal junction, or pancreatic cancer
Part B: Combination dose escalation with TFD/TPI	Participants with unresectable locally advanced or metastatic colorectal adenocarcinoma, gastric adenocarcinoma, or adenocarcinoma of the gastroesophageal junction

Study module	Population
Part C: Combination dose escalation with mFOLFOX6	Participants with unresectable locally advanced or metastatic colorectal adenocarcinoma, gastric adenocarcinoma, or adenocarcinoma of the gastroesophageal junction
Part D: Monotherapy expansion	Participants with recurrent or metastatic advanced solid tumor type selected
Part E: Monotherapy expansion	Participants with recurrent or metastatic advanced solid tumor type selected
Part F: Combination therapy expansion	Participants with recurrent or metastatic advanced solid tumor type selected
Part G: Combination therapy expansion	Participants with recurrent or metastatic advanced solid tumor type selected

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; mRNA=messenger ribonucleic acid; TFD/TPI=trifluridine/tipiracil

5.1 Inclusion criteria

5.1.1 Part A

Participants are eligible to be included in **Part A** of the study only if all of the following criteria apply:

Age

1. Participant must be at least 18 years of age inclusive, at the time of signing the informed consent.

Type of participant and disease characteristics

2a. Participant has a histologically and/or cytologically confirmed diagnosis of one of the following advanced solid tumor types: colorectal adenocarcinoma, esophageal carcinoma, head and neck squamous cell carcinoma, lung adenocarcinoma, lung squamous cell carcinoma, pancreatic adenocarcinoma, prostate adenocarcinoma, stomach adenocarcinoma, bladder urothelial carcinoma, or breast invasive carcinoma.

3b. Participant has advanced disease (ie, unresectable locally recurrent or metastatic) and had access to approved therapies.

4. Participant has measurable or non-measurable disease as defined by the relevant RECIST (Appendix 9, Section 11.9).

5. Participant has a performance status of ≤1 on the Eastern Cooperative Oncology Group (ECOG) scale (Appendix 8, Section 11.8).

6. Participant has discontinued all previous therapies for cancer (with exception of treatments defined in Section 6.5.1), including chemotherapy, radiotherapy, cancer-related hormonal therapy, or other investigational therapy for a minimum of 28 days or 5 half-lives (whichever is shorter) (6 weeks for mitomycin-C or nitrosoureas) prior to study enrollment and recovered from the acute effects of therapy.

7. Participant has an estimated life expectancy of ≥12 weeks.
8. Participant has adequate bone marrow function, including the following:
   a. Absolute neutrophil count ≥1.5x10^9/L.
   b. Platelet count ≥100x10^9/L.
   c. Hemoglobin ≥9.0g/dL (or 5.5mmol/L).

   Participants with hemoglobin ≥8g/dL but <9g/dL may receive erythrocyte transfusions to achieve a hemoglobin level ≥9.0 g/dL. Initial treatment must not begin until 2 days after the erythrocyte transfusion and after the confirmation of hemoglobin ≥9.0g/dL.

Contraception

9. A male participant must agree to use contraception as detailed in Appendix 4 (Section 11.4) of this protocol during the treatment period and for at least 3 months after the last dose of study treatment and refrain from donating sperm during this period.
10. A female participant is eligible to participate if she is not pregnant (see Appendix 4 [Section 11.4]), not breastfeeding, and at least one of the following conditions applies:
    a. Not a woman of childbearing potential as defined Appendix 4 (Section 11.4).
    OR
    b. A woman of childbearing potential who agrees to follow the contraceptive guidance in Appendix 4 (Section 11.4) during the treatment period and for at least 3 months after the last dose of study treatment.

Informed consent

11. Participant is capable of giving signed informed consent which includes compliance with the requirements and restrictions listed in the Informed Consent Form (ICF) and in this protocol.

5.1.2 Part A1

Participants are eligible to be included in **Part A1** of the study only if all of the following criteria apply:

Age

1. Participant must be at least 18 years of age inclusive, at the time of signing the informed consent.

Type of participant and disease characteristics

2. Participant has histologically and/or cytologically confirmed diagnosis of one of the following advanced solid tumor types: colorectal adenocarcinoma, gastric adenocarcinoma, adenocarcinoma of the gastroesophageal junction, or pancreatic cancer.
3. Participant has advanced disease (ie, unresectable locally recurrent or metastatic).
4. Participant must have received and is refractory or intolerant to standard therapy appropriate for the tumor type.

5. Participant has measurable or non-measurable disease as defined by the relevant RECIST (Appendix 9, Section 11.9).
6. Participant has a performance status of ≤1 on the Eastern Cooperative Oncology Group (ECOG) scale (Appendix 8, Section 11.8).
7. Participant must have tumor lesion(s) or metastases amenable to biopsy, excluding bone metastases, as confirmed by a radiologist, if appropriate, and as deemed safe by the Investigator.
8. Participant must consent to the mandatory pretreatment and on-treatment tumor biopsies.
9. Participant has discontinued all previous therapies for cancer (with exception of treatments defined in Section 6.5.2), including chemotherapy, radiotherapy, cancer-related hormonal therapy, or other investigational therapy for a minimum of 28 days or 5 half-lives (whichever is shorter) (6 weeks for mitomycin-C or nitrosoureas) prior to start of study medication and recovered from the acute effects of therapy.
10. Any clinically significant treatment-related toxicity from prior therapy must have resolved to Grade ≤1 prior to study entry, with the exception of alopecia.
11. Participant has an estimated life expectancy of ≥12 weeks.

Contraception

12. A male participant must agree to use contraception as detailed in Appendix 4 (Section 11.4) of this protocol during the treatment period and for at least 3 months after the last dose of study treatment and refrain from donating sperm during this period.
13. A female participant is eligible to participate if she is not pregnant (see Appendix 4 [Section 11.4]), not breastfeeding, and at least one of the following conditions applies:
    a. Not a woman of childbearing potential as defined in Appendix 4 (Section 11.4).

       OR

    b. A woman of childbearing potential who agrees to follow the contraceptive guidance in Appendix 4 (Section 11.4) during the treatment period and for at least 3 months after the last dose of study treatment.

Informed consent

14. Participant is capable of giving signed informed consent which includes compliance with the requirements and restrictions listed in the Informed Consent Form (ICF) and in this protocol.

5.1.3 Part B

Participants are eligible to be included in **Part B** of the study only if all of the following criteria apply:

Age

1. Participant must be at least 18 years of age inclusive, at the time of signing the ICF.

Type of participant and disease characteristics

2. Participant has a histologically and/or cytologically confirmed diagnosis of one of the following advanced solid tumor types: colorectal adenocarcinoma, gastric adenocarcinoma, or adenocarcinoma of the gastroesophageal junction.

3a. Participant has advanced disease (ie, unresectable locally advanced or metastatic).

4a. Participants must have received, or be intolerant to, or deemed not suitable for, at least 2 prior regimens of treatment, including the following standard of care anti-cancer treatments (where such treatments are available as standard of care):

   a. Participants with colorectal cancer: fluoropyrimidine-, oxaliplatin-, and irinotecan-based chemotherapy, an anti-vascular endothelial growth factor biological therapy, and, if RAS wild-type, an anti-epidermal growth factor receptor (EGFR) therapy, or if microsatellite instability high/deficient mismatch repair (MSI-H/dMMR) immunotherapy (eg, nivolumab, pembrolizumab and ipilimumab).

   b. Participants with gastric or gastroesophageal junction adenocarcinoma: fluoropyrimidine, a platinum, either a taxane or irinotecan, ramucirumab, and, if appropriate, human EGFR 2/neu-targeted therapy.

5. Participant has measurable or nonmeasurable disease as defined by the relevant RECIST.

6. Participant has a performance status of ≤1 on the ECOG scale.

7. Participant has discontinued all previous therapies for cancer (with exception of treatments defined in Section 6.5.3), including chemotherapy, radiotherapy, cancer-related hormonal therapy, or other investigational therapy for a minimum of 28 days or 5 half-lives (whichever is shorter) (6 weeks for mitomycin-C or nitrosoureas) prior to start of study medication and recovered from the acute effects of therapy.

   Any clinically significant treatment-related toxicity from prior therapy must have resolved to Grade ≤1 prior to study entry, with the exception of alopecia.

8. Participant has an estimated life expectancy of ≥12 weeks.

Contraception

9. A nonsterilized male participant with female partners of reproductive potential must agree to use contraception during the Treatment Period and for at least 6 months after the final dose of study treatment and must refrain from donating sperm during this period.

   A female participant is eligible to participate if she is not pregnant, not breastfeeding, and at least one of the following conditions applies:

   a. Not a woman of childbearing potential as defined in Appendix 4 (Section 11.4).
   OR

   b. A woman of childbearing potential who agrees to follow the contraceptive guidance in Appendix 4 (Section 11.4) during the Treatment Period and for at least 6 months after the final dose of study treatment.

Informed consent

10. Participant is capable of giving signed informed consent which includes compliance with the requirements and restrictions listed in the ICF and in this protocol.

5.1.4 Part C

Participants are eligible to be included in **Part C** of the study only if all of the following criteria apply:

Age

1. Participant must be at least 18 years of age inclusive, at the time of signing the ICF.

Type of participant and disease characteristics

2. Participant has a histologically and/or cytologically confirmed diagnosis of one of the following advanced solid tumor types: colorectal adenocarcinoma, gastric adenocarcinoma, or adenocarcinoma of the gastroesophageal junction.

3a. Participant has advanced disease (ie, unresectable locally advanced or metastatic) not amenable to curative treatment.

4. Participants must have received, or be intolerant to, or deemed not suitable for at least 1 prior line of standard anti-cancer treatment in the locally advanced or metastatic setting.

5. Participant has measurable or nonmeasurable disease as defined by the relevant RECIST.

6. Participant has a performance status of ≤1 on the ECOG scale.

7. Participant has discontinued all previous therapies for cancer (with exception of treatments defined in Section Section 6.5.4), including chemotherapy, radiotherapy, cancer-related hormonal therapy, or other investigational therapy for a minimum of 28 days or 5 half-lives (whichever is shorter) (6 weeks for mitomycin-C or nitrosoureas) prior to start of study medication.

   Any clinically significant treatment-related toxicity from prior therapy must have resolved to Grade ≤1 prior to study entry, with the exception of alopecia.

8. Participant has an estimated life expectancy of ≥12 weeks.

Contraception

9. A nonsterilized male participant with female partners of reproductive potential must agree to use contraception during the treatment period and for at least 6 months after the final dose of study treatment and must refrain from donating sperm during this period.

   A female participant is eligible to participate if she is not pregnant, not breastfeeding, and at least one of the following conditions applies:

   a. Not a woman of childbearing potential as defined in Appendix 4 (Section 11.4).
   OR

   b. A woman of childbearing potential who agrees to follow the contraceptive guidance in Appendix 4 (Section 11.4) during the Treatment Period and for at least 6 months after the final dose of study treatment.

Informed consent

10. Participant is capable of giving signed informed consent which includes compliance with the requirements and restrictions listed in the ICF and in this protocol.

Inclusion criteria for Parts D, E, F, and G will be defined in a protocol amendment.

5.2 Exclusion criteria

5.2.1 Part A

Participants are excluded from **Part A** of the study if any of the following criteria apply:

Medical conditions

1. Participant has any medical or psychiatric condition that, in the opinion of the investigator, could jeopardize or would compromise the study participant's ability to participate in this study.

2. Deleted.

3. Participant has a known hypersensitivity to any components of the study medication or comparable drugs (eg, monoclonal antibodies, drugs targeting BMP signaling pathway).

4. Active and clinically significant bacterial, fungal, or viral infection, known infections with hepatitis B, hepatitis C, known human immunodeficiency virus, or acquired immunodeficiency syndrome related illness.

5. Deleted.

6. Participants with known tuberculosis (TB) infection, at high risk of acquiring TB infection, with latent TB infection, or current or history of nontuberculous mycobacteria infection.

7a. Symptomatic central nervous system (CNS) malignancy or metastases. Screening of asymptomatic participants without history of CNS metastases is not required. Participants with asymptomatic CNS lesions should have completed standard therapy for their CNS lesions prior to study enrollment.

8. Current hematologic malignancies, for example acute or chronic leukemia.

9. Chronic underlying infection (for example, unhealed draining abscess, fistula) that, in the view of the investigator, should preclude the participant from enrolling in the study.

10. Prior organ or allogeneic stem-cell transplantation.

11. Moderate or severe cardiovascular disease including:

    a. Presence of cardiac disease, including a myocardial infarction within 6 months prior to study entry, unstable angina pectoris, New York Heart Association Class III/IV congestive heart failure, or uncontrolled hypertension.

    b. Documented major electrocardiogram (ECG) abnormalities at the investigator's discretion (for example, symptomatic or sustained atrial or ventricular arrhythmias, second- or third-degree, atrioventricular block, bundle branch blocks, ventricular hypertrophy).

c. Major abnormalities documented by echocardiography (for example, moderate or severe heart valve function defect and/or left ventricular ejection fraction <50%), evaluation based on the institutional lower limit of normal.

d. Participant has experienced any of the following during the last 6 months: coronary/peripheral bypass graft, cerebrovascular accident, transient ischemic attack, deep vein thrombosis, or symptomatic pulmonary embolism.

12. Alanine transaminase (ALT) or aspartate aminotransferase (AST) are ≥2xULN (if liver metastases are present: ≥5xULN).

13. Alkaline phosphatase (ALP) is ≥3xULN (if liver metastases are present: ≥5xULN).

14. Bilirubin ≥1.5xULN (isolated bilirubin >1.5xULN is acceptable if bilirubin is fractionated and direct bilirubin <35%).

15a. Current or chronic history of liver disease, or known hepatic or biliary abnormalities other than liver metastases (with the exception of Gilbert's syndrome, asymptomatic gallstones, or biliary stent provided bilirubin levels do not exceed limits as per Exclusion Criterion #14).

For study participants with a baseline result ≥2xULN for ALT, AST, or ≥3xULN ALP, or ≥1.5xULN total bilirubin, the presence of liver metastases must be recorded in the electronic Case Report Form (eCRF).

16b. QTc >450msec (note: The QTc is the QT interval corrected for heart rate according to Fridericia's formula [QTcF]; it is either machine-read or manually over-read).

Prior/Concomitant therapy

17. Participant is taking a prohibited medication or has taken a prohibited medication as defined in Section 6.5.5.

18. Treatment with biologic agents (such as monoclonal antibodies including marketed drugs) within 28 days prior to dosing.

Prior/Concurrent clinical study experience

19a. Current enrollment or past participation within the last 28 days before signing of consent in this or any other clinical study involving an IMP.

Other exclusions

20. Participant has impaired renal function as indicated by serum creatinine >1.5xULN.

21. Participant has experienced any major surgery within 28 days prior to the first administration of the medication under investigation in the study.

22a. International normalized ratio (INR), prothrombin time (PT), or activated partial thromboplastin time (aPTT) as follows:

- In the absence of therapeutic intent to anticoagulate the participant:
  - INR >1.5xULN or PT >1.5xULN or aPTT >1.5xULN, or

- In the presence of therapeutic intent to anticoagulate the participant: INR or PT or aPTT not within therapeutic limits (according to the medical standards at the institution) or participant has not been on a stable dose of anticoagulant for at least 2 weeks prior to dosing.

5.2.2 Part A1

Participants are excluded from **Part A1** of the study if any of the following criteria apply:

Medical conditions

1. Participant has any medical or psychiatric condition that, in the opinion of the Investigator, could jeopardize or would compromise the study participant's ability to participate in this study.
2. Participant has a known hypersensitivity to any components of the study medication or comparable drugs (eg, monoclonal antibodies, drugs targeting BMP signaling pathway).
3. Active and clinically significant bacterial, fungal, or viral infection, known infections with hepatitis B, hepatitis C, known human immunodeficiency virus, or acquired immunodeficiency syndrome related illness.
4. Participants with known tuberculosis (TB) infection, at high risk of acquiring TB infection, with latent TB infection, or current or history of nontuberculous mycobacteria infection.
5. Symptomatic central nervous system (CNS) malignancy or metastases. Screening of asymptomatic participants without history of CNS metastases is not required. Participants with asymptomatic CNS lesions should have completed standard therapy for their CNS lesions prior to study enrollment.
6. Current hematologic malignancies, for example acute or chronic leukemia.
7. Participants with evidence or history of bleeding diathesis.
8. Chronic underlying infection (for example, unhealed draining abscess, fistula) that, in the view of the Investigator, should preclude the participant from enrolling in the study.
9. Prior organ or allogeneic stem-cell transplantation.
10. Moderate or severe cardiovascular disease including:
    a. Presence of cardiac disease, including a myocardial infarction within 6 months prior to study entry, unstable angina pectoris, New York Heart Association Class III/IV congestive heart failure, or uncontrolled hypertension.
    b. Documented major electrocardiogram (ECG) abnormalities at the Investigator's discretion (for example, symptomatic or sustained atrial or ventricular arrhythmias, second- or third-degree, atrioventricular block, bundle branch blocks, ventricular hypertrophy).
    c. Major abnormalities documented by echocardiography (for example, moderate or severe heart valve function defect and/or left ventricular ejection fraction <50%), evaluation based on the institutional lower limit of normal.

d. Participant has experienced any of the following during the last 6 months: coronary/peripheral bypass graft, cerebrovascular accident, transient ischemic attack, deep vein thrombosis, or symptomatic pulmonary embolism.

Organ Function

11. Participant has inadequate bone marrow function, including the following:
    a. ANC<1.5x10^9/L.
    b. Platelet count<100x10^9/L.
    c. Hemoglobin<9.0g/dL (or 5.5mmol/L).
12. Prothrombin time or aPTT outside normal range, or international normalized ratio (INR) ≥1.5.
13. Participant has impaired renal function as indicated by serum creatinine >1.5x upper limit of normal (ULN) or calculated creatinine clearance of <50mL/min on the bases of the Cockroft-Gault glomerular filtration rate estimation (Appendix 2 [Section 11.2] with formula).
14. Alanine transaminase (ALT) or aspartate aminotransferase (AST) are ≥2xULN (if liver metastases present ≥5xULN).
15. Bilirubin ≥1.5xULN
16. Current or chronic history of liver disease, or known hepatic or biliary abnormalities other than liver metastases (with the exception of Gilbert's syndrome, asymptomatic gallstones, or biliary stent provided bilirubin levels do not exceed limits as per Exclusion Criterion #12).
17. QTc >450msec (note: The QTc is the QT interval corrected for heart rate according to Fridericia's formula [QTcF]; it is either machine-read or manually over-read).

Prior/Concomitant therapy

18. Participant is taking a prohibited medication or has taken a prohibited medication as defined in Section 6.5.6.
19. Participant is receiving therapeutic or prophylactic anticoagulation therapy.
20. Treatment with biologic agents (such as monoclonal antibodies including marketed drugs) within 28 days prior to dosing.

Prior/Concurrent clinical study experience

21. Current enrollment in another clinical study, unless it is an observational (noninterventional) clinical study or the follow-up period of an interventional study.

5.2.3 Part B

Participants are excluded from **Part B** of the study if any of the following criteria apply:

Medical conditions

1. Participant has any medical or psychiatric condition that, in the opinion of the investigator, could jeopardize or would compromise the study participant's ability to participate in this study.

2a. Participant has a known hypersensitivity to any study medications or components of the study medications or comparable drugs (eg, trifluridine or tipiracil hydrochloride, monoclonal antibodies, drugs targeting BMP signaling pathway).

3. Participant is unable to swallow tablets.

4. Participant has hereditary problems of galactose intolerance, total lactase deficiency, or glucose-galactose malabsorption.

5. Participant has active and clinically significant bacterial, fungal, or viral infection, known infections with hepatitis B, hepatitis C, known human immunodeficiency virus, or acquired immunodeficiency syndrome related illness.

6. Participant has known TB infection, is at high risk of acquiring TB infection, or has current or history of nontuberculous mycobacteria infection.

7a. Participant has symptomatic CNS malignancy or metastases. Screening of asymptomatic participants without history of CNS metastases is not required. Participants with asymptomatic CNS lesions should have completed standard therapy for their CNS lesions prior to study enrollment.

8. Participant has current hematologic malignancies, eg, acute or chronic leukemia.

9. Participant has chronic underlying infection (eg, unhealed draining abscess, fistula) that, in the view of the investigator, should preclude the participant from enrolling in the study.

10. Participant has prior organ or allogeneic stem-cell transplantation.

11. Participant has moderate or severe cardiovascular disease including:

    a. Presence of cardiac disease, including a myocardial infarction within 6 months prior to study entry, unstable angina pectoris, New York Heart Association Class III/IV congestive heart failure, or uncontrolled hypertension.

    b. Documented major ECG abnormalities at the investigator's discretion (for example, symptomatic or sustained atrial or ventricular arrhythmias, second- or third-degree atrioventricular block, bundle branch blocks, ventricular hypertrophy).

    c. Major abnormalities documented by echocardiography (for example, moderate or severe heart valve function defect and/or left ventricular ejection fraction <50%), evaluation based on the institutional lower limit of normal.

    d. Participant has experienced any of the following during the last 6 months: coronary/peripheral bypass graft, cerebrovascular accident, transient ischemic attack, deep vein thrombosis, or symptomatic pulmonary embolism.

12. Participant has experienced any major surgery within 28 days prior to the first administration of the medication under investigation in the study.
13. Participant has serum potassium, magnesium, or calcium levels outside the institutional normal limits.

    Participants with electrolyte levels outside of the normal range will be eligible if these values are corrected upon retesting following any necessary supplementation.

Organ function

14. Participant has inadequate bone marrow function, including the following:
    a. ANC $<1.5x10^9$/L
    b. Platelet count $<100x10^9$/L
    c. Hemoglobin <9.0g/dL (or 5.5mmol/L)

    Participants with hemoglobin ≥8.0g/dL but <9.0g/dL may receive erythrocyte transfusions to achieve a hemoglobin level ≥9.0g/dL. Initial treatment must not begin until 2 days after the erythrocyte transfusion and after the confirmation of hemoglobin ≥9.0g/dL.
15. Participant has impaired renal function as indicated by serum creatinine >1.5x upper limit of normal (ULN) or calculated creatinine clearance of <50mL/min on the bases of the Cockroft-Gault glomerular filtration rate estimation (Appendix 2 [Section 11.2] with formula).
16. Alanine transaminase or AST are ≥2xULN (if liver metastases are present: ≥5xULN).

    For study participants with a baseline result ≥2xULN for ALT and/or AST, the presence of liver metastases must be recorded in the eCRF.
17. Bilirubin ≥1.5xULN
18. Current or chronic history of liver disease or known hepatic or biliary abnormalities other than liver metastases (with the exception of Gilbert's syndrome, asymptomatic gallstones, or biliary stent, provided bilirubin levels do not exceed limits as per Exclusion Criterion #17).
19. International normalized ratio, PT, or aPTT as follows:
    a. In the absence of therapeutic intent to anticoagulate the participant, INR or PT or aPTT >1.5xULN, or
    b. In the presence of therapeutic intent to anticoagulate the participant, INR or PT or aPTT not within therapeutic limits (according to the medical standards at the institution) or participant has not been on a stable dose of anticoagulant for at least 2 weeks

20b. QTc >450msec (note: The QTc is the QTcF; it is either machine-read or manually over-read).

Prior/Concomitant therapy

21. Participant is taking a prohibited medication or has taken a prohibited medication as defined in Section 6.5.7 within 28 days of starting study treatment.
22. Participant has received prior treatment with TFD/TPI.

23. Administration of a live, attenuated vaccine (eg, live attenuated influenza vaccine [LAIV], measles, mumps, and rubella [MMR], varicella; FluMist®) within 28 days of starting study treatment and for up to 3 months after the final dose of IMP or anticipation that such vaccine will be required during the study.

Prior/Concurrent clinical study experience

24. Current enrollment in another clinical study, unless it is an observational (noninterventional) clinical study or the follow-up period of an interventional study.

5.2.4 Part C

Participants are excluded from **Part C** of the study if any of the following criteria apply:

Medical conditions

1. Participant has any medical or psychiatric condition that, in the opinion of the investigator, could jeopardize or would compromise the study participant's ability to participate in this study.

2a. Participant has a known hypersensitivity to any study medications or components of the study medications or comparable drugs (eg, oxaliplatin, fluorouracil, calcium folinate/leucovorin, monoclonal antibodies, drugs targeting BMP signaling pathway).

3. Participant has a history of hypersensitivity to oxaliplatin or other platinum-based drugs.

4. Participant has active and clinically significant bacterial, fungal, or viral infection, known infections with hepatitis B, hepatitis C, known human immunodeficiency virus, or acquired immunodeficiency syndrome related illness.

5. Participants has known TB infection, is at high risk of acquiring TB infection, or has current or history of nontuberculous mycobacteria infection.

6a. Participant has symptomatic CNS malignancy or metastases. Screening of asymptomatic participants without history of CNS metastases is not required. Participants with asymptomatic CNS lesions should have completed standard therapy for their CNS lesions prior to study enrollment.

7. Participant has current hematologic malignancies, eg, acute or chronic leukemia.

8. Participant has chronic underlying infection (eg, unhealed draining abscess, fistula) that, in the view of the investigator, should preclude the participant from enrolling in the study.

9. Participant has prior organ or allogeneic stem-cell transplantation.

10. Participant has moderate or severe cardiovascular disease including:
    a. Presence of cardiac disease, including a myocardial infarction within 6 months prior to study entry, unstable angina pectoris, New York Heart Association Class III/IV congestive heart failure, or uncontrolled hypertension.
    b. Documented major ECG abnormalities at the investigator's discretion (for example, symptomatic or sustained atrial or ventricular arrhythmias, second- or third-degree atrioventricular block, bundle branch blocks, ventricular hypertrophy).

c. Major abnormalities documented by echocardiography (for example, moderate or severe heart valve function defect and/or left ventricular ejection fraction <50%), evaluation based on the institutional lower limit of normal.

d. Participant has experienced any of the following during the last 6 months: coronary/peripheral bypass graft, cerebrovascular accident, transient ischemic attack, deep vein thrombosis, or symptomatic pulmonary embolism.

11. Participant has experienced any major surgery within 28 days prior to the first administration of the medication under investigation in the study.

12. Participant has serum potassium, magnesium, or calcium levels outside the institutional normal limits.

Participants with electrolyte levels outside of the normal range will be eligible if these values are corrected upon retesting following any necessary supplementation.

Organ function

13a. Participant has inadequate bone marrow function, including the following:

a. ANC <$2.0x10^9$/L

b. Platelet count <$100x10^9$/L

c. Hemoglobin <9.0g/dL (or 5.5mmol/L)

Participants with hemoglobin ≥8.0g/dL but <9.0g/dL may receive erythrocyte transfusions to achieve a hemoglobin level ≥9.0g/dL. Initial treatment must not begin until 2 days after the erythrocyte transfusion and after the confirmation of hemoglobin ≥9.0g/dL.

14. Participant has impaired renal function as indicated by serum creatinine >1.5x upper limit of normal (ULN) or calculated creatinine clearance of <50mL/min on the bases of the Cockroft-Gault glomerular filtration rate estimation (Appendix 2 [Section 11.2] with formula).

15. Alanine transaminase or AST are ≥2xULN (if liver metastases are present: ≥5xULN).

For study participants with a Baseline result ≥2xULN for ALT and/or AST, the presence of liver metastases must be recorded in the eCRF.

16. Bilirubin ≥1.5xULN.

17. Current or chronic history of liver disease or known hepatic or biliary abnormalities other than liver metastases (with the exception of Gilbert's syndrome, asymptomatic gallstones, or biliary stent, provided bilirubin levels do not exceed limits as per exclusion criterion #16).

18. International normalized ratio, PT, or aPTT as follows:

a. In the absence of therapeutic intent to anticoagulate the participant, INR or PT or aPTT >1.5xULN, or

b. In the presence of therapeutic intent to anticoagulate the participant, INR or PT or aPTT not within therapeutic limits (according to the medical standards at the institution) or participant has not been on a stable dose of anticoagulant for at least 2 weeks

19b. QTc >450msec (note: The QTc is the QTcF; it is either machine-read or manually over-read).

Prior/Concomitant therapy

20. Known dihydropyrimidine dehydrogenase deficiency or thymidylate synthetase gene polymorphism predisposing the participant to 5-fluorouracil toxicity.
21. Participant is taking a prohibited medication or has taken a prohibited medication as defined in Section 6.5.8 within 28 days of starting study treatment.
22. Administration of a live, attenuated vaccine (eg, LAIV, MMR, varicella; FluMist®) within 28 days of starting study treatment and for up to 3 months after the final dose of IMP, or anticipation that such vaccine will be required during the study.

Prior/Concurrent clinical study experience

23. Current enrollment in another clinical study, unless it is an observational (noninterventional) clinical study or the follow-up period of an interventional study.

Other exclusions

24. Participant has known or suspected pernicious anemia or other anemias due to vitamin B12 deficiency.

Exclusion criteria for Parts D, E, F, and G will be defined in a subsequent protocol amendment.

5.3 Lifestyle restrictions

No restrictions are required.

5.4 Screen failures

Prior to dosing, the study physician or medically qualified designee will assess participant eligibility and confirm suitability for study treatment. Screen failures are defined as participants who consent to participate in the clinical study but are not subsequently assigned to study treatment. A minimal set of screen failure information is required to ensure transparent reporting of screen failure participants to meet the Consolidated Standards of Reporting Trials publishing requirements and to respond to queries from regulatory authorities. Minimal information includes demography, screen failure details, eligibility criteria, and any serious adverse event (SAE).

Due to the ongoing COVID-19 pandemic, or a potential re-emergence of COVID-19, some participants may be unable to complete Screening procedures (for instance, due to local pandemic restrictions or the need to self-isolate following close contact exposure). These participants should be considered screen failures. These and other individuals who do not fully meet the criteria for participation in this study (screen failure) may be rescreened at the discretion of the investigator and by agreement with the Sponsor on a case-dependent nature (dependent on the reason for the initial screen failure).

6 STUDY TREATMENTS

Study treatment is defined as any investigational treatment(s), marketed product(s), placebo, or medical device(s) intended to be administered to a study participant according to the study protocol.

6.1 Treatments administered

6.1.1 Part A

In Part A, UCB6114 will be administered as described in the Schedule of Activities (Table 1-4). A summary of the study treatment to be administered is provided in Table 6-1.

Table 6-1: Treatments administered in Part A

IMP	UCB6114
Type	Drug
Dose formulation	UCB6114 [redacted]
Unit dose strength(s)	100mg/mL
Dosage level(s)	100mg, 250mg, 500mg, 1000mg, and 2000mg. Doses will be administered Q2W
Route of administration	iv infusion
Use	Experimental
Sourcing	IMP will be supplied by UCB Clinical Trial Supply or designee.
Packaging and labeling	Study intervention will be provided in 100mg/mL solution in glass vials. Each vial will be labeled as required per country requirement.

IMP=investigational medicinal product; iv=intravenous(ly); Q2W=every 2 weeks

6.1.2 Part A1

A new dose formulation will be used in Part A1. UCB6114 will be administered as described in the Schedule of Activities (Table 1-5 and Table 1-6) and as per defined cohort (Table 6-6). A summary of the study treatment to be administered is provided in Table 6-2.

Table 6-2: Treatments administered in Part A1

IMP	UCB6114
Type	Drug
Dose formulation (new)	UCB6114 [redacted]
Unit dose strength(s)	100mg/mL
Dosage level(s)	2000mg, 3000mg, 4000mg. Doses will be administered Q2W, Q3W, or Q4W as per defined cohort
Route of administration	iv infusion
Use	Experimental
Sourcing	IMP will be supplied by UCB Clinical Trial Supply or designee.
Packaging and labeling	Study intervention will be provided in 100mg/mL solution in glass vials. Each vial will be labeled as required per country requirement.

IMP=investigational medicinal product; iv=intravenous(ly); Q1W=one weekly; Q2W=every 2 weeks, Q3W=every 3 weeks, Q4W=every 4 weeks.

6.1.3 Part B

UCB6114 and TFD/TPI will be administered as described in the Schedule of Activities for Part B (Table 1-7). A summary of the study treatments to be administered in Part B is provided in Table 6-3.

Table 6-3: Study treatments in Part B

Product Name	**UCB6114**	**Lonsurf®**
Intervention name	UCB6114	Trifluridine/tipiracil (active ingredients: trifluridine and tipiracil hydrochloride)
Type	Drug	Drug
Dose formulation	Solution for injection/infusion containing UCB6114 at 100mg/mL (as in Part A); for excipients see below	Film-coated tablets containing Trifluridine (15 or 20mg) and tipiracil (6.14mg or 8.19mg); for excipients see below
Unit dose strength(s)	100mg/mL	Lonsurf 15mg/6.14mg (white); Lonsurf 20mg/8.19mg (pale red)
Dosage level(s)	Planned dose levels: 500mg Q2W 1000mg Q2W 2000mg Q2W	35mg/m^2/dose administered bid on Days 1 to 5 and Days 8 to 12 of each 28-day cycle, not to exceed 80mg per dose.
Route of administration	iv infusion	Oral

Product Name	**UCB6114**	**Lonsurf®**
Use	Experimental	Experimental (combination product)
IMP and NIMP	IMP	IMP
Sourcing	Will be supplied by UCB Clinical Trial Supply or designee	Provided centrally by the Sponsor or locally by the study site, subsidiary, or designee.
Packaging and labeling	UCB6114 will be provided as a 100mg/mL solution in glass vials. Each vial will be labeled as required per country requirements.	Lonsurf will be provided in its original packaging. All IMP will be labeled as required per country requirements.
Excipients	[redacted]	Tablet core Lactose monohydrate Starch, pregelatinized (maize) Stearic acid Film coating Lonsurf 15mg/6.14mg film-coated tablets Hypromellose Macrogol (8000) Titanium dioxide (E171) Magnesium stearate Lonsurf 20mg/8.19mg film-coated tablets Hypromellose Macrogol (8000) Titanium dioxide (E171) Iron oxide red (E172) Magnesium stearate Printing ink Shellac Iron oxide red (E172) Iron oxide yellow (E172) Titanium dioxide (E171) Indigo carmine aluminium lake (E132) Carnauba wax Talc
Current/Former name or alias	Not applicable	TAS-102

bid=twice daily; HCl=hydrochloride; IMP=investigational medicinal product; iv=intravenous(ly); NIMP=non-investigational medicinal product; Q2W=every 2 weeks

6.1.4 Part C

UCB6114 and mFOLFOX6 chemotherapy will be administered as described in the Schedule of Activities for Part C (Table 1-8). UCB6114 must always be administered prior to mFOLFOX6 chemotherapy.

A summary of the study treatment to be administered in Part C is provided in Table 6-4.

Table 6-4: Treatments administered in Part C

Product Name	UCB6114	Oxaliplatin	Leucovorin	Fluorouracil
Intervention name	UCB6114	Part of mFOLFOX6 chemotherapy regimen	Part of mFOLFOX6 chemotherapy regimen	Part of mFOLFOX6 chemotherapy regimen
Type	Drug	Drug	Drug	Drug
Dose formulation	Solution for injection/infusion containing UCB6114 at 100mg/mL, (as in Part A) for excipients see below	Concentrate for solution for infusion containing oxaliplatin (5mg/mL), for excipients see below	Solution for injection containing leucovorin (10mg/mL), for excipients see below	Solution for injection containing fluorouracil (25 or 50mg/mL), for excipients see below
Unit dose strength(s)	100mg/mL	5mg/mL	10mg/mL	25mg/mL; 50mg/mL
Dosage level(s)	Planned dose levels: 500mg Q2W 1000mg Q2W 2000mg Q2W	85mg/m^2 Q2W	400mg/m^2 Q2W	400mg/m^2 Q2W, followed by 1200mg/m^2/day on Day 1 and 2 (2400mg/m^2 over 46 hours)
Route of administration	iv infusion	iv infusion	iv infusion	iv bolus, then continuous infusion via infusor
Use	Experimental	Experimental (as part of mFOLFOX6 chemotherapy)	Experimental (as part of mFOLFOX6 chemotherapy)	Experimental (as part of mFOLFOX6 chemotherapy)
IMP	IMP	IMP	IMP	IMP
Sourcing	Will be supplied by UCB Clinical Trial Supply or designee	Provided centrally by the Sponsor or locally by the study site, subsidiary, or designee.	Provided centrally by the Sponsor or locally by the study site, subsidiary, or designee.	Provided centrally by the Sponsor or locally by the study site, subsidiary, or designee.

Table 6-4: Treatments administered in Part C

Product Name	UCB6114	Oxaliplatin	Leucovorin	Fluorouracil
Packaging and labeling	UCB6114 will be provided in 100mg/mL solution in glass vials. Each vial will be labeled as required per country requirement.	Oxaliplatin will be provided in its original packaging. All IMP will be labeled as required per country requirements.	Leucovorin will be provided in its original packaging. All IMP will be labeled as required per country requirements.	Fluorouracil will be provided in its original packaging. All IMP will be labeled as required per country requirements.
Excipients	[redacted]	Water for injection	Sodium chloride Water for injection	Sodium hydroxide Water for injection
Current/Former name(s) or alias(es)	Not applicable	Eloxatin®	Calcium folinate	5-fluorouracil, 5-FU

FU=fluorouracil; IMP=investigational medicinal product; iv=intravenous(ly); 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; Q2W=every 2 weeks

6.2 Preparation, handling, storage, and accountability requirements

6.2.1 UCB6114

The 100mg/mL solution will be diluted to a concentration calculated to give the planned dose over a constant infusion duration. Details of the dilution factors and the infusion rates to achieve this are given in the investigational medicinal product (IMP) Handling Manual.

Study drug product (ie, IMP) must be stored under refrigerated conditions (2°C to 8°C/35.6°F to 46.4°F). Further instructions regarding drug preparation and dosing will be contained in the IMP Handling Manual, which will be provided to each clinical site.

The investigator (or designee) must confirm appropriate temperature conditions have been maintained during transit for all study treatment received and any discrepancies are reported and resolved before use of the study treatment.

Only participants enrolled in the study may receive study treatment and only authorized site staff may supply or administer study treatment. All study treatments must be stored in a secure, temperature controlled, and monitored (manual or automated) area in accordance with the labeled storage conditions with access limited to the investigator and authorized site staff.

The investigator, institution, or the head of the medical institution (where applicable) is responsible for study treatment accountability, reconciliation, and record maintenance (ie, receipt, reconciliation, and final disposition records).

In case an out-of-range temperature is noted, it must be immediately reported as per instructions contained in the IMP Handling Manual.

Further guidance and information for the final disposition of unused study treatment are provided in the IMP Handling Manual.

Preparation, handling, storage and accountability requirements are described in the IMP Handling Manual.

6.2.2 TFD/TPI

Please refer to the prescribing information or the Summary of Product Characteristics (SmPC) for details on formulations and storage.

6.2.3 mFOLFOX6

Please refer to the prescribing information or SmPC for the individual components for details on formulations and storage.

6.2.4 Drug accountability

Accountability logs will be used to record study medication dispensing and return information on a by-participant basis and will serve as source documentation during the course of the study. Details of any study medication lost, damaged (due to breakage or wastage), not used, partially used, disposed of at the study site, or returned to the Sponsor or designee must also be recorded on the appropriate forms. All supplies and pharmacy documentation must be made available throughout the study for UCB (or designee) to review.

The investigator (or designee) is responsible for retaining all used, unused, and partially used containers of study medication until returned or destroyed.

The investigator may assign some of the investigator's duties for drug accountability at the study site to an appropriate pharmacist/designee.

The investigator must ensure that the study medication is used only in accordance with the protocol.

Periodically, and/or after completion of the clinical phase of the study, all used (including empty containers)/partially used, unused, damaged, and/or expired study medication must be reconciled and either destroyed at the site according to local laws (in which case the site should provide the appropriate certification or confirmation of destruction), regulations, and UCB Standard Operating Procedures, or returned to UCB (or designee). Investigational medicinal product intended for the study cannot be used for any other purpose than that described in this protocol.

6.3 Measures to minimize bias: Randomization and blinding

This is an open-label study.

6.4 Treatment compliance

Study participant compliance in Parts A, A1, and C will be ensured by the administration of study medication by designated site personnel. Drug accountability must be recorded on the accountability log.

Study participant compliance for UCB6114 in Part B will be ensured by the administration of study medication by designated site personnel and drug accountability must be recorded on the accountability log. Study participant compliance for TFD/TPI in Part B will be evaluated through the use of a participant diary and the drug accountability log on which the number of TFD/TPI tablets dispensed and the number of unused tablets returned will be recorded. Drug accountability must be performed in the presence of the participant in order to obtain any explanations regarding discrepancies with the dosing regimen.

Drug accountability must be recorded on the accountability log.

6.5 Concomitant medication(s)/treatment(s)

Permitted and prohibited concomitant medications during Part A, Part A1, Part B, and Part C are defined below. Permitted concomitant medications for subsequent modules Part A1, Part D, Part E, Part F, and Part G will be described in subsequent protocol amendments.

6.5.1 Permitted concomitant treatments (medications and therapies) during Part A

The following concomitant medications are permitted during Part A of the study:

- Medications intended solely for supportive care (eg, treatments for nausea, vomiting, and diarrhea)
- Therapeutic use of steroids equivalent to prednisone ≤10mg/day
- Bisphosphonate therapy
- Hormonal contraceptives/hormonal replacement therapy

- Continuation of gonadotropin-releasing hormone (GnRH) agonist therapy for participants with prostate cancer
- Continuation of antiestrogen therapy (eg, aromatase inhibitor) for participants with breast cancer

6.5.2 Permitted concomitant treatments (medications and therapies) during Part A1

The following concomitant medications are permitted during Part A1 of the study:

- Medications intended solely for supportive care (eg, treatments for nausea, vomiting, and diarrhea)
- Therapeutic use of steroids equivalent to prednisone ≤10mg/day
- Bisphosphonate therapy or therapy with RANK ligand inhibitor
- Hormonal contraceptives/hormonal replacement therapy
- Palliative radiotherapy to specific sites of disease is permitted if considered medically necessary by the investigator. Palliative radiotherapy specifically refers to radiotherapy for symptom relief only.
- Participants who experience infusion-associated symptoms may be treated symptomatically as per standard practice.

6.5.3 Permitted concomitant treatments (medications and therapies) during Part B

The following concomitant medications and/or treatments are permitted during Part B of the study:

- Medications intended solely for supportive care (eg, treatments for nausea, vomiting, and diarrhea).
- Bisphosphonate therapy or therapy with RANK ligand inhibitor.
- Hormonal contraceptives/hormonal replacement therapy.
- Therapeutic use of steroids equivalent to prednisone ≤10mg/day.
- Palliative radiotherapy to specific sites of disease is permitted if considered medically necessary by the investigator. Palliative radiotherapy specifically refers to radiotherapy symptom relief only.
- Participants who experience infusion-associated symptoms may be treated symptomatically as per standard practice.
- Granulocyte colony-stimulating factor (G-CSF) or pegylated G-CSF for the management of neutropenia related toxicities. (Note: prophylactic pegylated G-CSF in Cycle 1 is not permitted.)

6.5.4 Permitted concomitant treatments (medications and therapies) during Part C

The following concomitant medications and/or treatments are permitted during Part C of the study:

- Medications intended solely for supportive care (eg, treatments for nausea, vomiting, and diarrhea).
- Bisphosphonate therapy or therapy with RANK ligand inhibitor.
- Hormonal contraceptives/hormonal replacement therapy.
- Therapeutic use of steroids equivalent to prednisone ≤10mg/day.
- Palliative radiotherapy to specific sites of disease is permitted if considered medically necessary by the investigator. Palliative radiotherapy specifically refers to radiotherapy symptom relief only.
- Participants who experience infusion-associated symptoms may be treated symptomatically as per standard practice.
- Granulocyte colony-stimulating factor (G-CSF) or pegylated G-CSF for the management of neutropenia related toxicities. (Note: prophylactic pegylated G-CSF in Cycle 1 is not permitted.)

6.5.5 Prohibited concomitant treatments (medications and therapies) during Part A

The following concomitant medications are prohibited during Part A of the study:

- Any concurrent anticancer treatment within 28 days or 5 half-lives (whichever is shorter) prior to first dose of study medication (eg, cytoreductive therapy, radiotherapy [with the exception of palliative bone-directed radiotherapy], immunotherapy, biological therapy, or cytokine therapy [with the exception of erythropoietin])
- Any investigational drug within 28 days prior to start of study medication
- Herbal remedies or vitamins used as anticancer treatments
- Any herbal remedies with immunostimulating properties (eg, mistletoe extract) or known to potentially interfere with major organ function (eg, hypericin)

Concomitant treatment considered necessary for the participant's well-being may be given at the discretion of the investigator but should be discussed with the study physician or medically qualified designee whenever possible. If there is a clinical indication for one of these medications specifically prohibited during the study, discontinuation from the study medication may be required.

6.5.6 Prohibited concomitant treatments (medications and therapies) during Part A1

The following concomitant medications are prohibited during Part A1 of the study:

- Any concurrent anticancer treatment within 28 days or 5 half-lives (whichever is shorter) prior to first dose of study medication (eg, cytoreductive therapy, radiotherapy [with the exception of palliative bone-directed radiotherapy], immunotherapy, biological therapy, or cytokine therapy [with the exception of erythropoietin])
- Any investigational drug within 28 days prior to start of study medication
- Herbal remedies or vitamins used as anticancer treatments
- Any herbal remedies with immunostimulating properties (eg, mistletoe extract) or known to potentially interfere with major organ function (eg, hypericin)
- Any anticoagulation therapy until after biopsies are obtained

Concomitant treatment considered necessary for the participant's well-being may be given at the discretion of the Investigator but should be discussed with the study physician or medically qualified designee whenever possible. If there is a clinical indication for one of these medications specifically prohibited during the study, discontinuation from the study medication may be required.

6.5.7 Prohibited concomitant treatments (medications and therapies) during Part B

The following concomitant medications are prohibited during Part B of the study:

- Any concurrent anticancer treatment within 28 days or 5 half-lives (whichever is shorter) prior to first dose of study medication (eg, cytoreductive therapy, radiotherapy immunotherapy, biologic therapy, or cytokine therapy [with the exception of erythropoietin])
- Treatment with mitomycin C or nitrosoureas within 6 weeks of starting study medication
- Any investigational drug within 28 days prior to start of study medication
- Herbal remedies or vitamins used as anticancer treatments
- Any herbal remedies with immunostimulating properties (eg, mistletoe extract) or known to potentially interfere with major organ function (eg, hypericin)

Concomitant treatment considered necessary for the participant's well-being may be given at the discretion of the investigator but should be discussed with the study physician or medically qualified designee whenever possible. If there is a clinical indication for one of these medications specifically prohibited during the study, discontinuation from the study medication may be required.

6.5.8 Prohibited concomitant treatments (medications and therapies) during Part C

The following concomitant medications are prohibited during Part C of the study:

- Any concurrent anticancer treatment within 28 days or 5 half-lives (whichever is shorter) prior to first dose of study medication (eg, cytoreductive therapy, radiotherapy immunotherapy, biologic therapy, or cytokine therapy [with the exception of erythropoietin])
- Treatment with mitomycin C or nitrosoureas within 6 weeks of starting study medication
- Any investigational drug within 28 days prior to start of study medication
- Herbal remedies or vitamins used as anticancer treatments
- Any herbal remedies with immunostimulating properties (eg, mistletoe extract) or known to potentially interfere with major organ function (eg, hypericin)

The following should be avoided during Part C of the study:

- Concurrent administration of 5-fluorouracil and CYP2C9 substrates. Five-fluorouracil is a CYP2C9 inhibitor and possible drug interaction with 5-fluorouracil and CYP2C9 substrates has been reported.
  - Possible drug interaction with oxaliplatin, 5-fluorouracil, and warfarin has been reported. For participants maintained on warfarin, weekly INR is recommended until a stable warfarin dose is established, and then every 2 weeks.
  - Possible drug interaction with 5-fluorouracil and phenytoin or fosphenytoin has been reported and may occur at any time. Close monitoring is recommended; 5-fluorouracil may increase the serum concentration of these 2 agents.
- Concomitant administration of medicinal product with a known potential to prolong the QT interval as QT interval prolongation and ventricular arrhythmias can occur with oxaliplatin.
- Co-administration of medicinal products known to be nephrotoxic.

Concomitant treatment considered necessary for the participant's well-being may be given at the discretion of the investigator but should be discussed with the study physician or medically qualified designee whenever possible. If there is a clinical indication for one of these medications specifically prohibited during the study, discontinuation from the study medication may be required.

6.5.9 Vaccines

Administration of live attenuated vaccines is not allowed during the conduct of the study and for up to 3 months after the final dose of IMP.

Administration of non-live vaccines is allowed during the study at the discretion of the Investigator.

Administration of any other vaccine not mentioned above may be allowed following discussion with the Medical Monitor.

6.5.10 Rescue medication

There are no absolute restrictions on the use of concomitant rescue medications for participants whose condition deteriorates during the course of the study. While the objectives of the study should be protected as much as possible through observance of restrictions detailed, the well-being of the participant will always take priority, and participants should be managed as deemed appropriate by the investigator. The anticipated use of any prohibited medications should be discussed with the study physician or medically qualified designee first, whenever possible.

The date and time of rescue medication administration as well as the name and dosage regimen of the rescue medication must be recorded.

6.6 Dose modification

6.6.1 Part A and Part A1

The justification for the UCB6114 start dose for Part A is presented in Section 4.3.1.

In Part A, the decision to proceed to the next dose level (either an escalation or a de-escalation) will be made by the SMC based on safety, and available preliminary PK and/or PD data obtained in at least 3 participants at the prior dose level (Section 4.1.2.1). Further data obtained from any previous dose level may also contribute to this decision.

The planned escalation scheme is given in Section 6.6.1.1.

6.6.1.1 Dose escalation scheme

A summary of the planned UCB6114 dose levels for dose escalation in Part A is provided in Table 6-5. A dose range up to 2000mg Q2W iv was selected based on the following:

1. Exposure and predicted gremlin-1 suppression levels associated with antitumor activity at different dose levels in nonclinical pharmacology models
2. Pharmacokinetics of UCB6114 in cynomolgus monkeys scaled to humans
3. Findings of 13-week GLP toxicity studies in cynomolgus monkeys and rats

Table 6-5: Dose escalation steps and justification (Part A)

Cohort[a]	Dose (mg) [approximate mg/kg[b]]	Predicted $C_{av,ss}$ [90% prediction interval] (µg/mL)[c]	Justification
1	100 [1.4]	20.4 [13.4-31.0]	The starting dose of 100mg Q2W iv was selected as described in Section 4.3.1. The anticipated safety margin is >100-fold.
2	250 [3.6]	51.3 [33.5-77.5]	Corresponds to a 2.5-fold increase over the first dose level and will give similar inhibition should the turnover half-life of gremlin-1 in humans be [redacted].
3	500 [7.1]	102 [67.0-155.0]	Corresponds to a 2-fold increase over the previous dose level.

Table 6-5: Dose escalation steps and justification (Part A)

Cohort[a]	Dose (mg) [approximate mg/kg[b]]	Predicted $C_{av,ss}$ [90% prediction interval] (µg/mL)[c]	Justification
4	1000 [14.3]	204 [134.0-310.0]	The lowest dose to show qualitative improvement in survival in the *Apc^{Min};Vil1-Grem-1* model was 15mg/kg BIW. A dose of 1000mg Q2W is expected to provide similar exposure in humans. Also, assuming a gremlin-1 level of 100ng/mL and a turnover half-life of 2h in humans, 1000mg Q2W iv is predicted to inhibit approximately 95% of circulating gremlin-1. The anticipated safety margin is >10-fold at this dose level.
5	2000 [28.6]	408 [268.0-620.0]	A dose of 30mg/kg BIW in *Apc^{Min};Vil1-Grem-1* model showed improved survival compared with the control. A dose of 2000mg iv Q2W is expected to provide similar exposure in humans. No difference was observed between 30 and 60mg/kg BIW in the *Apc^{Min};Vil1-Grem-1* model, and therefore, higher doses are likely not warranted.

BIW=twice weekly; $C_{av,ss}$=average concentration at steady state; h=hour; iv=intravenous(ly); PK=pharmacokinetic(s); Q2W=every 2 weeks

[a] Dose levels administered may be adapted according to emerging data, eg, dose escalation or de-escalation to an intermediate dose level. Not all dose levels listed may be evaluated in this study.

[b] Approximate mg/kg doses based on a 70kg person.

[c] Predicted $C_{av,ss}$ was calculated from estimated cynomolgus monkey PK parameters following a single administration (UCB Research Study NCD3086) scaled to humans and predicted at steady state. The estimated between-subject variability of clearance (coefficient of variation of 26.3%) was assumed to apply to human study participants.

The proposed dose escalation and dose schedule may be adapted based on the following:

- Cohort-by-cohort safety assessment and available PK data
- Any available PD biomarker data
- Data collected in ongoing nonclinical studies

Characterization of the dose-concentration-effect relationship (ranging from potential minimum effective doses to maximum effective doses) is important to determine the therapeutic window for UCB6114 for later clinical development.

After the fifth cohort in Part A has been determined, an additional module (Part A1) has been included to evaluate alternative dosing schedules (see Table 6-6). The rationale for Part A1 includes the following:

- Evaluation of a less frequent (Q3W or Q4W) dosing schedule is considered desirable to enable UCB6114 to be combined with a range of other treatments or to reduce patient burden.
- Administration with a shorter infusion time may be desirable to reduce patient's burden.

The dosing schedules planned in Part A1 are given in Table 6-6.

Table 6-6: Planned dose optimization scheme for Part A1

Cohort	Dosing and infusion time	Purpose
Cohort 1[a]	2000mg Q2W 60-minute iv infusion (33.33mg/min) 28-day treatment cycles	To assess safety, PK and PD of 2000mg dose of new dose formulation.
Cohort 2	2000mg Q2W 30-minute iv infusion (66.67mg/min) 28-day treatment cycles	To establish a shorter infusion time (30 minutes) to reduce the burden/allow for easier combination with other anti-tumor agents.
Cohort 3	3000mg Q3W 90-minute iv infusion (33mg/min) 21-day treatment cycles	To assess safety, PK and PD of less frequent dosing to allow combination with anti-tumor agents given in a 3-weekly cycle.
Cohort 4	4000mg Q4W 120-minutes iv infusion (33mg/min) 28-day treatment cycles	To assess less frequent dosing to allow combination with SOC treatments given in a 4-weekly cycle.

[a] Reference, ie, same dosing schedule as in Part A Cohort 5 but with new dose formulation. All subsequent cohorts will receive the new dose formulation.
iv=intravenous(ly); min=minute(s); PD=pharmacodynamics; PK=pharmacodynamics; Q2W=every 2 weeks; Q3W=every 3 weeks; Q4W=every 4 weeks, SOC=standard of care

6.6.1.2 Within participant dose modification in Part A

For participants who experience dose-limiting toxicity, dose adjustments are permitted if it is considered in the best interest of the participant to continue therapy at the discretion of the investigator, in consultation with the Sponsor.

Participants who fail to receive the second planned dose of UCB6114 within 7 days of the scheduled administration day, during the DLT Observation Period, for reasons not related to toxicity will be replaced by a new participant in that cohort. The replaced participant may still continue participation in the study. Safety data for replaced participants will be included in all summary data and any DLTs experienced by the replaced participant will contribute to determination of MTD (Part A) or suitability of the dosing schedule (Part A1).

6.6.1.3 Within participant dose modification in Part A1

Dose adjustments and/or changes in dosing schedule are not permitted.

6.6.2 Part B

The justification for the UCB6114 start dose for Part B is presented in Section 4.3.3.2.1.

In Part B, the decision to proceed to the next dose level (either an escalation or a de-escalation) will be made by the SMC as described in Section 4.1.4.1. Further data obtained from any previous dose level may also contribute to this decision.

The planned dose escalation scheme is given in Section 6.6.2.1.

6.6.2.1 Dose escalation scheme

A summary of the planned UCB6114 dose levels for dose escalation in Part B is provided in Table 6-7.

Table 6-7: Dose escalation steps and justification (Part B)

Dose Level	Dose (mg)	Justification
1	500	The starting dose selected for Part B is the Part A Cohort 3 dose (anticipated to be 500mg Q2W iv); see Section 4.3.3.1 for details.
2	1000	The lowest dose to show a qualitative improvement in survival in the *Apc^{Min};Vil1-Grem-1* model was 15mg/kg of Ab7326 mIgG1 administered BIW sc as monotherapy from an age of 21 days. A dose of 1000mg Q2W iv is expected to provide similar exposure in humans. A dose of 1000mg is expected to provide an exposure approximately 50% of that given in combination with 5-fluorouracil where survival relative to either monotherapy was increased in the *Apc^{Min};Vil1-Grem-1* model when dosing from an age of 35 days (30mg/kg BIW sc [for 6 weeks followed by 30mg/kg QW thereafter]).
3	2000	A dose of 2000mg is expected to provide the same exposure in humans as that given in combination with 5-fluorouracil where survival relative to either monotherapy was increased in the *Apc^{Min};Vil1-Grem-1* model when dosing from an age of 35 days. In a separate study where Ab7326 mIgG1 was administered as monotherapy from an age of 21 days, no difference was observed between 30 and 60mg/kg BIW sc in the *Apc^{Min};Vil1-Grem-1* model, and therefore, higher doses of UCB6114 are likely not warranted.

BIW=twice weekly; h=hour; iv=intravenous(ly); PK=pharmacokinetic(s); Q2W=every 2 weeks; sc=subcutaneous(ly)

6.6.2.2 UCB6114 dose modifications

Study participants who experience Grade 4 (life-threatening) nonhematologic toxicity, including diarrhea and mucositis, which is at least possibly related to UCB6114, will be discontinued from treatment.

Treatment with UCB6114 may temporarily be suspended for up to 3 weeks beyond the scheduled treatment day until toxicities are resolved to CTCAE Grade 2 or less. If UCB6114 is

held for more than 3 weeks beyond the scheduled treatment day, then the participant will be discontinued from treatment and will be followed up for safety and efficacy per the Schedules of Activities for Part A (Table 1-4), Part B (Table 1-7), and Part C (Table 1-8).

For permitted adjustments of the infusion rate in case of AEs refer to the IMP Handling Manual. Participants who experience severe or life-threatening infusion-related events (CTCAE Grade 3 or 4) will not receive further infusions. Hypersensitivity/infusion-related events should be managed per institutional guidelines. Premedication with steroids may be administered at the discretion of the investigator.

6.6.2.3 TFD/TPI dose modifications

Dose modifications for TFD/TPI-related AEs are allowed as described below. A maximum of 3 dose reductions are permitted to a minimum of 20mg/m^2/dose.

Participants who permanently discontinue TFD/TPI treatment due to TFD/TPI-related toxicity will have the option to continue treatment with UCB6114 alone if, in the view of the investigator, the participant is deriving benefit.

In the case of hematological toxicities, TFD/TPI treatment may be interrupted or resumed according to the criteria stated in Table 6-8. In the case of hematological and nonhematological toxicities, the dose may be modified according to the criteria stated in Table 6-9. Reductions will be made in accordance with BSA (Table 6-10).

Table 6-8: TFD/TPI dose interruption and resumption criteria for hematological toxicities

Parameter	Interruption criteria	Resumption criteria[a]
Neutrophils	<0.5x10^9/L	≥1.5x10^9/L
Platelets	<50x10^9/L	≥75x10^9/L

TFD/TPI=trifluridine/tipiracil
[a] Resumption criteria applied to the start of the next cycle for all participants regardless of whether the interruption criteria were met.

Table 6-9: TFD/TPI dose modifications in case of hematological and non-hematological toxicities

Adverse reaction	Recommended dose modifications
Febrile neutropenia. CTCAE Grade 4 neutropenia (<0.5x10^9/L) or thrombocytopenia (<25x10^9/L) that results in more than 1 week's delay in start of next cycle. CTCAE Grade 3 or Grade 4 nonhematologic AEs; except for Grade 3 nausea and/or vomiting controlled by antiemetic therapy or diarrhea responsive to antidiarrheal medicinal products.	Interrupt dosing until toxicity resolves to Grade 1 or baseline. When resuming dosing, decrease the dose level by 5mg/m^2/dose from the previous dose level (Table 6-10). Dose reductions are permitted to a minimum dose of 20mg/m^2/dose bid. Do not increase dose after it has been reduced.

AE=adverse event; bid=twice daily; CTCAE= Common Terminology Criteria for Adverse Events; TFD/TPI=trifluridine/tipiracil

Table 6-10: TFD/TPI dose reductions according to body surface area

Reduced dose	BSA (m^2)	Dose (mg)	Tablets per dose		Total daily dose (mg)
			15mg/6.14mg	20mg/8.19mg	
Level 1 dose reduction: from 35mg/m^2 to 30mg/m^2					
30mg/m^2	<1.09	30	2	0	60
	1.09 to 1.24	35	1	1	70
	1.25 to 1.39	40	0	2	80
	1.40 to 1.54	45	3	0	90
	1.55 to 1.69	50	2	1	100
	1.70 to 1.94	55	1	2	110
	1.95 to 2.09	60	0	3	120
	2.10 to 2.28	65	3	1	130
	≥2.29	70	2	2	140
Level 2 dose reduction: from 30mg/m^2 to 25mg/m^2					
25mg/m^2	<1.10	25[a]	2[a]	1[a]	50[a]
	1.10 to 1.29	30	2	0	60
	1.30 to 1.49	35	1	1	70
	1.50 to 1.69	40	0	2	80
	1.70 to 1.89	45	3	0	90
	1.90 to 2.09	50	2	1	100
	2.10 to 2.29	55	1	2	110
	≥2.30	60	0	3	120
Level 3 dose reduction: from 25mg/m^2 to 20mg/m^2					
20mg/m^2	<1.14	20	0	1	40
	1.14 to 1.34	25[a]	2[a]	1[a]	50[a]
	1.35 to 1.59	30	2	0	60
	1.60 to 1.94	35	1	1	70
	1.95 to 2.09	40	0	2	80
	2.10 to 2.34	45	3	0	90
	≥2.35	50	2	1	100

BSA=body surface area; TFD/TPI=trifluridine/tipriacil
[a] At a total daily dose of 50mg, study participants should take 1x20mg/8.19mg tablet in the morning and 2x15mg/6.14mg tablets in the evening.

6.6.3 Part C

The justification for the UCB6114 start dose for Part C is presented in Section 4.3.3.2.2.

In Part C, the decision to proceed to the next dose level (either an escalation or a de-escalation) will be made by the SMC as described in Section 4.1.5.1). Further data obtained from any previous dose level may also contribute to this decision.

The planned escalation scheme is given in Section 6.6.3.1.

6.6.3.1 Dose escalation scheme

A summary of the planned UCB6114 dose levels for dose escalation in Part C is provided in Table 6-11.

Table 6-11: Dose escalation steps and justification (Part C)

Dose Level	Dose (mg)	Justification
1	500	The starting dose selected for Part C is the Part A Cohort 3 dose (anticipated to be 500mg Q2W iv); see Section 4.3.3.1 for details.
2	1000	The lowest dose to show a qualitative improvement in survival in the *Apc^{Min};Vil1-Grem-1* model was 15mg/kg of Ab7326 mIgG1 administered BIW sc as monotherapy from an age of 21 days. A dose of 1000mg Q2W iv is expected to provide similar exposure in humans. A dose of 1000mg is expected to provide an exposure approximately 50% of that given in combination with 5-fluorouracil where survival relative to either monotherapy was increased in the *Apc^{Min};Vil1-Grem-1* model when dosing from an age of 35 days (30mg/kg BIW sc [for 6 weeks followed by 30mg/kg QW thereafter]).
3	2000	A dose of 2000mg is expected to provide the same exposure in humans as that given in combination with 5-fluorouracil where survival relative to either monotherapy was increased in the *Apc^{Min};Vil1-Grem-1* model when dosing from an age of 35 days. In a separate study where Ab7326 mIgG1 was administered as monotherapy from an age of 21 days, no difference was observed between 30 and 60mg/kg BIW sc in the *Apc^{Min};Vil1-Grem-1* model, and therefore, higher doses of UCB6114 are likely not warranted.

BIW=twice weekly; h=hour; iv=intravenous(ly); PK=pharmacokinetic(s); Q2W=every 2 weeks; sc=subcutaneous(ly)

6.6.3.2 UCB6114 dose modifications

Study participants who experience Grade 4 (life-threatening) nonhematologic toxicity, including diarrhea and mucositis, which is at least possibly related to UCB6114, will be discontinued from treatment.

Treatment with UCB6114 may temporarily be suspended for up to 3 weeks beyond the scheduled treatment day until toxicities are resolved to CTCAE Grade 2 or less. If UCB6114 is

held for more than 3 weeks beyond the scheduled treatment day, then the participant will be discontinued from treatment and will be followed up for safety and efficacy per the Schedule of Activities.

For permitted adjustments of the infusion rate in case of AEs, refer to the IMP Handling Manual. Participants who experience severe or life-threatening infusion-related events (Grade 3 or 4) will not receive further infusions. Hypersensitivity/infusion-related events should be managed per institutional guidelines. Premedication with steroids may be administered at the discretion of the investigator.

6.6.3.3 mFOLFOX6 dosing

Please refer to the individual package inserts for details on formulations and storage.

Antiemetic premedication prior to administration of chemotherapy is recommended and sites should follow their institutional standard of care.

The recommended administration of mFOLFOX6 is shown in Table 6-12.

Table 6-12: mFOLFOX6 dosing

Drug	Dose	Administration
Oxaliplatin[a]	85mg/m^2	iv in 250 to 500mL glucose 5% over 2 hours
Leucovorin[a]	400mg/m^2	iv in 250mL glucose 5% over 2 hours
5-Fluorouracil	400mg/m^2	iv bolus
5-Fluorouracil	2400mg/m^2	iv over 46 hours via an infusor

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(ly)

[a] Oxaliplatin and leucovorin may be infused over the same two-hour period by using a Y-site connector placed immediately before the infusion site.

Within the study, mFOLFOX6 is administered every 14 days in 28-day treatment cycles up to a maximum of 6 cycles.

6.6.3.4 mFOLFOX6 dose modifications

Dose modifications for mFOLFOX6-related AEs are allowed as described below. A maximum of 2 dose level reductions are permitted.

Participants who permanently discontinue treatment (all or individual drugs of the mFOLFOX6 regimen) due to toxicity will be considered for continuation of treatment with UCB6114 if, in the view of the investigator, the participant is deriving benefit.

Dose levels for individual drugs are as follows:

- Oxaliplatin:
  - Starting dose: 85mg/m^2
  - Dose Level -1: 65mg.m^2
  - Dose Level -2: 50mg/m^2
- 5-fluorouracil iv bolus:

- Starting dose: 400mg/m^2
- Dose Level -1: 320mg/m^2
- Dose Level -2: 200mg/m^2

- 5-fluorouracil infusion over 46 hours:
  - Starting dose: 2400mg/m^2
  - Dose Level -1: 2000mg/m^2
  - Dose Level -2: 1600mg/m^2

No dose adjustments are required for leucovorin.

6.6.3.4.1 Dose modifications for neurological toxicity

If neurological symptoms (ie, paresthesia, dysesthesia) occur, oxaliplatin dosage adjustments should be made as outlined in Table 6-13. No dose adjustments of 5-fluorouracil are recommended for neurotoxicity.

Table 6-13: Dose modification for oxaliplatin-related neurological toxicity

CTCAE (v5.0) Toxicity grade	Duration of toxicity	
	Transient (≥1 day and ≤14 days)	Persistent (present at start of next treatment)
1	Maintain dose level	Maintain dose level
2	Maintain dose level	Reduce 1 dose level
3	1st time: reduce one dose level 2nd time: reduce one dose level	Discontinue
4	Discontinue	Discontinue

CTCAE=Common Terminology Criteria for Adverse Events

6.6.3.4.2 Dose modifications for hematological toxicity

Recommended dose modifications for oxaliplatin and 5-fluorouracil for hematological toxicity are outlined in Table 6-14.

Table 6-14: Dose modification for hematological toxicity

Prior to Dosing (Day 1 or Day 15)	Toxicity		Dose level for subsequent cycles	
	CTCAE (V5.0) Toxicity Grade	ANC (x10^9/L)	Oxaliplatin	5-Fluorouracil
If ANC <1.2 on Day 1 or Day 15, hold treatment and perform weekly blood counts.	1	≥1.2	Maintain dose level	Maintain dose level
	2	1.0 to <1.2	Maintain dose level	Maintain dose level
	3	0.5 to <1.0	Reduce 1 dose level	Maintain dose level

Table 6-14: Dose modification for hematological toxicity

Prior to Dosing (Day 1 or Day 15)	Toxicity		Dose level for subsequent cycles	
If ANC is ≥1.2 within 2 weeks, proceed with treatment at a dose level according to the lowest ANC result of the delayed weeks. If ANC remains <1.2 after 2 weeks, discontinue treatment.	4	<0.5	Reduce 1 dose level	Omit iv bolus and reduce infusion 1 dose level
	CTCAE (V5.0) Toxicity Grade	**Platelets (x 10^9/L)**	**Oxaliplatin**	**5-Fluorouracil**
If platelets <75 on Day 1 or Day 15, hold treatment. Perform weekly blood counts. If platelets ≥75 within 2 weeks, proceed with treatment at a dose level according to the lowest platelets result of the delayed weeks. If platelets remain <75 after 2 weeks, discontinue treatment.	1	≥75	Maintain dose level	Maintain dose level
	2	50 to <70	Maintain dose level	Maintain dose level
	3	10 to <50	Reduce 1 dose level	Maintain dose level
	4	<10	Reduce 2 dose levels	Maintain dose level

ANC=absolute neutrophil count; CTCAE= Common Terminology Criteria for Adverse Events; iv=intravenous(ly)

6.6.3.4.3 Dose modifications for non-hematological, non-neurological toxicity

Recommended dose modifications for non-hematological, non-neurological toxicity are outlined in Table 6-15. Along with dose modifications, supportive treatment should be initiated per institutional guidelines.

Table 6-15: Dose modification for non-hematological, non-neurological toxicity

Prior to Dosing (Day 1 or Day 15)	Toxicity		Dose level for subsequent cycles	
	CTCAE (V5.0) Toxicity Grade	**Diarrhea**	**Oxaliplatin**	**5-Fluorouracil**
If diarrhea ≥2 on Day 1 or Day 15, hold treatment. Perform weekly assessments. If diarrhea is <Grade 2 within 2 weeks, proceed with treatment at a dose level according to the highest Grade experienced.	1	Increase of <4 stools/day, or mild increase in colostomy output	Maintain dose level	Maintain dose level
	2	Increase of 4 to 6 stools/day, or moderate increase in colostomy output; limiting instrumental ADL	Maintain dose level	Maintain dose level
	3	Increase of ≥7 stools/day; hospitalization indicated; severe increase in	Maintain dose level	Reduce 1 dose level of iv bolus and infusion

Table 6-15: Dose modification for non-hematological, non-neurological toxicity

Prior to Dosing (Day 1 or Day 15)	Toxicity		Dose level for subsequent cycles	
If diarrhea remains ≥Grade 2 after 2 weeks, discontinue treatment.		colostomy output; limiting self-care ADL		
	4	Life threatening consequences; urgent intervention indicated	Reduce 1 dose level	Reduce 1 dose level of iv bolus and infusion
	CTCAE (V5.0) Toxicity Grade	**Stomatitis/Mucositis**	**Oxaliplatin**	**5-Fluorouracil**
If stomatitis ≥Grade 2 on Day 1 or Day 15, hold treatment. Perform weekly assessments. If stomatitis <Grade 2 within 2 weeks, proceed with treatment at a dose level according to the highest Grade experienced. If stomatitis remains >Grade 2 after 2 weeks, discontinue treatment.	1	Minimal symptoms with normal oral intake	Maintain dose level	Maintain dose level
	2	Moderate pain, analgesics indicated; altered oral intake	Maintain dose level	Maintain dose level
	3	Severe pain; unable to adequately aliment or hydrate orally	Maintain dose level	Reduce 1 dose level of iv bolus and infusion
	4	Life-threatening consequences, urgent intervention indicated	Reduce 1 dose level	Reduce 1 dose level of iv bolus and infusion

ADL=activities of daily living; CTCAE= Common Terminology Criteria for Adverse Events; iv=intravenous(ly)

6.7 Criteria for study hold or dosing stoppage

Detailed procedures for reporting SAEs and other safety events (including Rapid Alert Procedures) that may meet study or individual study part hold criteria are provided in Appendix 6 (Section 11.6).

The study or individual study part will be immediately suspended (ie, any participant who has not received dose(s) of UCB6114 at the time of study/study part suspension will not be administered UCB6114) if 1 or more study participants develop any of the following AEs deemed to be at least possibly related to UCB6114 administration by the investigator and the sponsor:

- Death
- Life-threatening organ failure requiring intervention to prevent death or permanent disability (eg, respiratory failure requiring ventilation, renal failure requiring dialysis, heart failure requiring hemodynamic support).

The SMC will be consulted for both study/study module suspension and potential restart (details can be found in the SMC charter).

The management of ongoing participants may be discussed on an individual basis with the inverstigator and the participants taking into account the benefit/ risk assessment, unless asked by the SMC and/or a regulatory authority/ies not to do so.

Enrolment of new participants into the study or individual study module will not be restarted until:

- Sponsor and the SMC have agreed a risk mitigation strategy which meets the requirements of any regulatory authority/ies to whom details of the AE have been submitted, and
- Based on local policies, the Independent Ethics Committees (IECs)/Institutional Review Boards (IRBs) have been notified, and
- Where applicable, regulatory authorities have been notified and have approved a substantial amendment for study restart.

6.8 Treatment after the end of the study

The planned duration of study treatment is 2 cycles. Participants may, however, remain on study for additional cycles if they are receiving therapeutic benefit (SD, PR, or CR) or until they fulfill one of the criteria for study discontinuation. Upon discontinuation of treatment, participants will be referred to appropriate follow-up care per the investigator's judgment.

7 DISCONTINUATION OF STUDY MEDICATION AND PARTICIPANT DISCONTINUATION/WITHDRAWAL

7.1 Discontinuation of study medication

The IMP will be discontinued if any of the stopping criteria are met or if the participant is withdrawn from the study (see Section 7.2).

7.1.1 Liver Chemistry Stopping Criteria

The threshold of laboratory abnormalities for a potential case of drug-induced liver injury depends on the participant's individual baseline values and underlying conditions. Participants who present with the following laboratory abnormalities should be evaluated further to definitively determine the etiology of the abnormal laboratory values:

- Participants with AST or ALT and total bilirubin baseline values within the normal range who subsequently present with AST or ALT ≥3xULN concurrent with a total bilirubin ≥2xULN.
- For participants with pre-existing ALT OR AST OR total bilirubin values above the ULN, the following threshold values should be used in the definition mentioned above:
  - For participants without liver metastases: AST or ALT value ≥2 times the baseline values *AND* ≥3xULN
  - For participants with liver metastases: AST or ALT value ≥2 times the baseline values AND ≥8xULN

Concurrent with

- For participants with preexisting values of total bilirubin above the normal range: Total bilirubin ≥2 times the baseline values OR if the value reaches ≥3xULN (whichever is lower).

The participant should return to the investigational site and be evaluated as soon as possible, preferably within 24 hours from awareness of the abnormal results. This evaluation should include laboratory tests, detailed history and physical assessment, and the possibility of hepatic neoplasia (primary or secondary) should be considered. In addition to repeating measurements of AST and ALT, laboratory tests should include albumin, creatine kinase, total bilirubin, direct and indirect bilirubin, gamma-glutamyl transferase, prothrombin time/international normalized ratio, and ALP. A detailed history, including relevant information, such as review of ethanol, acetaminophen, recreational drug and supplement consumption, family history, occupational exposure, sexual history, travel history, history of contact with a jaundiced person, surgery, blood transfusion, history of liver or allergic disease, and work exposure, should be collected. Further testing for acute hepatitis A, B, or C infection and liver imaging (eg, biliary tract) may be warranted. All cases confirmed on repeat testing as meeting the laboratory criteria defined above, with no other cause for liver function test abnormalities identified at the time should be considered potential Hy's Law cases irrespective of availability of all the results of the investigations performed to determine etiology of the abnormal liver function tests. Such potential Hy's Law cases should be reported as SAEs.

Interruption of the study medication should be considered by the investigator when a participant meets one of the conditions outlined above.

7.1.2 QTc Stopping Criteria

A participant who meets either bulleted criterion based on the average of triplicate ECG readings will be withdrawn from study medication.

- QTc >500msec OR Uncorrected QT >600msec

- Change from baseline of QTc >60msec

For participants with underlying bundle branch block, follow the discontinuation criteria listed in Table 7-1.

Table 7-1: Bundle Branch Block discontinuation criteria

Baseline QTc with Bundle Branch Block	Discontinuation QTc threshold with Bundle Branch Block
< 450msec	> 500msec
450 to 480msec	≥ 530msec

If a clinically significant finding is identified (including, but not limited to, changes from baseline in QTcF after enrollment), the investigator, study physician, or medically qualified designee will determine if the participant can continue in the study and if any change in participant management is needed. This review of the ECG printed at the time of collection must be documented. Any new clinically relevant finding should be reported as an AE.

See the Schedules of Activities for Part A (Table 1-4), Part A1 (Table 1-5 and Table 1-6), Part B (Table 1-7), and Part C (Table 1-8) for data to be collected at the time of treatment discontinuation and follow-up and for any further evaluations that need to be completed.

7.1.3 Other criteria for discontinuation of study medication

Participants must discontinue study treatment if they experience any of the following:

1. There is confirmation of a pregnancy during the study, as evidenced by a positive pregnancy test.
2. The participant experiences unacceptable toxicity.
   - For information on dose delays due to drug-related toxicity, see Section 6.6.1 (Part A and Part A1), Section 6.6.2 (Part B), and Section 6.6.3 (Part C). Participants will discontinue treatment, unless, in the opinion of the investigator, they are experiencing clinical benefit and it is in their best interest to continue treatment. For these participants, treatment may continue at a reduced dose at the discretion of the investigator and Sponsor.
3. The participant has documented evidence of progressive disease.
   - Participants with progressive disease before the end of Cycle 1 may be discontinued from study medication at the discretion of the investigator. Participants with progressive disease beyond Cycle 1 will be discontinued from study medication. In cases where progression is not clear and, in the opinion of the investigator, the participant may be having clinical benefit, the participant may continue treatment, but must be reimaged within 2 cycles of treatment.
4. The participant, for any reason, requires treatment with another therapeutic agent or modality for his/her cancer (with the exception of palliative bone-directed radiotherapy). In this case, discontinuation from the study treatment must occur before introduction of the new agent or modality.

5. Participant takes prohibited concomitant medications as defined in this protocol.

Participants who discontinue the study medication and/or study early will have end-of-study (SFU) procedures performed as shown in the Schedules of Activities for Part A (Table 1-4), Part A1 (Table 1-5 and Table 1-6), Part B (Table 1-7), and Part C (Table 1-8).

See the Schedules of Activities for Part A (Table 1-4), Part A1 (Table 1-5 and Table 1-6), Part B (Table 1-7), and Part C (Table 1-8) for data to be collected at the time of study treatment discontinuation and follow-up and for any further evaluations that need to be completed.

7.1.4 Temporary discontinuation of study medication

A treatment dose may be withheld if a participant experiences toxicity as described in Section 6.6.1.2 (Part A), Section 6.6.1.3 Part A1), Section 6.6.2.2 (Part B), and Section 6.6.3.1 (Part C).

Participants who fail to receive the second planned dose of UCB6114 within 7 days of the scheduled administration day during the DLT Observation Period for reasons not related to toxicity will be replaced by a new participant in that cohort.

Treatment with UCB6114 may temporarily be suspended for up to 3 weeks beyond the scheduled treatment day until toxicities are resolved to CTCAE Grade 2 or less. If UCB6114 is held for more than 3 weeks beyond the scheduled treatment day, then the participant will be discontinued from treatment and will be followed up for safety per schedule of assessment.

7.2 Participant discontinuation/withdrawal from the study

The criteria for enrollment must be followed explicitly. A Treatment Allocation/Enrolment Plan and management process (IVRS) may be utilized to ensure strict compliance.

Participants are free to withdraw from the study at any time, without prejudice to their continued care.

A participant may withdraw from the study at any time at his/her own request, or may be withdrawn at any time at the discretion of the investigator for safety or compliance reasons.

Participants should be withdrawn from the study if any of the following events occur:

1. Participant withdraws his/her consent.
2. Participant develops an illness or comorbidity that would interfere with his/her continued participation.
3. The investigator considers it in the best interest of the participant to be withdrawn. If this decision is made because of an SAE or a clinically significant laboratory value, then appropriate supportive measures are to be taken. UCB or its designee is to be alerted immediately.
4. Participant is noncompliant with the study visit schedule.

If the participant withdraws consent for disclosure of future information, the Sponsor may retain and continue to use any data collected before such a withdrawal of consent.

If a participant withdraws from the study, he/she may request destruction of any samples taken and not tested, and the investigator must document this in the site study records.

If any participant withdraws/is withdrawn from the study, the site will attempt to contact the participant and facilitate completion of the SFU Visit and the Final Visit. However, participants will not be followed up if they have withdrawn their consent to do so.

The primary reason for withdrawal from the study should be documented on the appropriate eCRF page.

Investigators should inform the study physician or medically qualified designee in the event that a participant is withdrawn from the study.

Participants who withdraw from the study before receiving study medication will be replaced.

7.3 Lost to follow up

A participant will be considered lost to follow-up if he or she repeatedly fails to return for an SFU and is unable to be contacted by the study site.

The following actions must be taken if a participant fails to return to the clinic for a required study visit:

- The site must attempt to contact the participant and reschedule the missed visit as soon as possible and counsel the participant on the importance of maintaining the assigned visit schedule and ascertain whether or not the participant wishes to and/or should continue in the study.
- Before a participant is deemed lost to follow-up, the investigator, study physician, or medically qualified designee must make every effort to regain contact with the participant (at least 1 phone call and 1 written message to the participant), and document his/her effort (date and summary of the phone call and copy of the written message in the source documents), to complete the final evaluation. All results of these evaluations and observations, together with a narrative description of the reason(s) for removing the participant, must be recorded in the source documents. The eCRF must document the primary reason for withdrawal.

Should the participant continue to be unreachable, he/she will be considered to have withdrawn from the study with a primary reason of lost to follow-up documented in the eCRF.

7.4 COVID-19 Pandemic

In the context of the COVID-19 pandemic, investigators should have individualized benefit-risk discussions with study participants during Screening and the course of the study. Such discussions should take into consideration the ongoing assessment of the study participant's medical status as well as the COVID-19 pandemic status in the geographic region. Investigators must elicit from the participant any suspected or known exposure to COVID-19 or a confirmed COVID-19 positive diagnosis. To accommodate potential COVID-19 restrictions, the study procedures may be adapted. Such adaptations may include replacing in-clinic visits with video consultations, flexibility in the timing and/or location of assessment collection, and any other changes deemed necessary until such restrictions are lifted. Clinical sites may arrange for virtual study visits or home visits to continue collection of safety and PK data. Participants who miss doses due to a positive COVID-19 diagnosis or a known exposure may continue in the study if, in the opinion of the investigator, they are experiencing clinical benefit and it is in their best interest to continue treatment. A study participant may resume treatment after missing doses due to COVID-19 pandemic restrictions, exposure, or infection provided that the protocol-defined

study drug discontinuation criteria are not met. In such cases, the investigator should assess all available medical information prior to re-initiating dosing. In the event of a temporary dosing stop due to COVID-19, participants who were enrolled prior to stop may receive home or virtual visits to continue collection of safety and PK data. Adverse events associated with COVID-19 are discussed in Section 9.2.

Any changes to the study to manage the impact of COVID-19 will be communicated to the regulatory authorities according to local guidance.

8 STUDY AND SITE DISCONTINUATION

The investigator or UCB have the right to stop or terminate the study at any time, for any ethical, medical, or scientific reason, while considering the rights, safety, and well-being of the participant(s).

Study site participation may be discontinued if UCB, the investigator, the IRB/ethical review board, or the regulatory authority deems it necessary for any scientific, medical, or ethical reason. The study will be discontinued if UCB, while considering the rights, safety, and wellbeing of the participant(s), deems it necessary for any scientific, medical, or ethical reason.

9 STUDY ASSESSMENTS AND PROCEDURES

Study procedures and their timing are summarized in the Schedules of Activities for Part A (Table 1-4), Part A1 (Table 1-5 and Table 1-6), Part B (Table 1-7), and Part C (Table 1-8). Study procedures and their timing for modules subsequent to Parts A, A1, B, and C will be described in a planned protocol amendment.

Protocol waivers or exemptions are not allowed.

Immediate safety concerns should be discussed with the Sponsor immediately upon occurrence or awareness to determine if the participant should continue or discontinue study treatment.

Adherence to the study design requirements, including those specified in the Schedules of Activities for Part A (Table 1-4), Part A1 (Table 1-5 and Table 1-6), Part B (Table 1-7), and Part C (Table 1-8), is essential and required for study conduct.

All Screening evaluations must be completed and reviewed to confirm that potential participants meet all eligibility criteria. The investigator will maintain a Screening log to record details of all participants screened and to confirm eligibility or record reasons for Screening failure, as applicable.

Procedures conducted as part of the participant's routine clinical management (eg, blood count) and obtained before signing of the ICF may be utilized for Screening or baseline purposes provided the procedures met the protocol-specified criteria and were performed within the time frame defined in the Schedules of Activities for Part A (Table 1-4), Part A1 (Table 1-5 and Table 1-6), Part B (Table 1-7), or Part C (Table 1-8), as applicable.

In **Part A**, the maximum amount of blood collected from each participant during Screening will be approximately 8 to 10mL. In the case of liver function abnormalities considered potential Hy's Law cases where the liver-specific ALP must be separated from the total ALP in participants with bone metastases, an additional volume of 2mL of blood will be collected.

The maximum amount of blood collected from each participant over the duration of Cycle 1 of Part A are indicated in Table 9-1.

Table 9-1: Total blood volume collected during Cycle 1 of Part A

Sample	Number of samples	Volume of sample	Total blood volume
Hematology	4	<2mL	8mL
Biochemistry	4	<2mL	8mL
Coagulation	2	<2mL	4mL
Pregnancy (if applicable)[a]	1	2mL	2mL
[redacted]			
Pharmacodynamics (PD)	12	various (2.5 to 20mL)	83.5mL
Immunogenicity (ADA)	3	5mL	15mL
Total	38	-	180.5mL

ADA=antidrug antibody
Note: Repeat or unscheduled samples may be taken in addition, for safety reasons or for technical issues with the samples.
[a] This volume could be increased by 2mL per visit if serum pregnancy test is performed instead of urine for second pregnancy assessment during this cycle.

The maximum amount of blood collected from each participant during Cycle 2 of Part A will be approximately 82.5mL. This volume could be increased by up to 4mL if serum pregnancy test is performed instead of urine pregnancy test.

The maximum amount of blood collected from each participant during Cycle 3 of Part A will be approximately 72.5mL, and the maximum amount of blood collected from each participant from Cycle 4 onwards will be approximately 52.5mL. This volume could be increased by up to 4mL per cycle if serum pregnancy test is performed instead of urine pregnancy test

The maximum amount of blood collected from each participant during the SFU of Part A will be approximately 51.5mL.

In **Part A1**,

- The maximum amount of blood collected from each participant during **Screening** will be approximately 42 to 44mL (if pregnancy test is applicable). In the case of liver function abnormalities considered potential Hy's Law cases where the liver-specific ALP must be separated from the total ALP in participants with bone metastases, an additional volume of 2mL of blood will be collected.
- The maximum amount of blood collected from each participant over the duration of **Cycle 1** is indicated in Table 9-2.
- The maximum amount of blood collected from each participant during **Cycle 2** will be approximately 51.5mL for Cohorts 1, 2 and 4, and 47.5mL for Cohort 3. This volume could be increased by up to 2mL if serum pregnancy test is performed instead of urine pregnancy test.

- The maximum amount of blood collected from each participant during **Cycle 3** will be approximately 60.5mL for Cohorts 1 and 2, and 56.5mL for Cohorts 3 and 4. This volume could be increased by up to 2mL per cycle if serum pregnancy test is performed instead of urine pregnancy test. If the on-treatment biopsy is not performed an additional volume of up to 9mL could be collected for additional PK and circulating Gremlin-1 assessment.
- The maximum amount of blood collected from each participant from **Cycle 4 onwards** will be approximately 46.5mL for Cohorts 1 and 2, and 42.5mL for Cohorts 3 and 4. This volume will be increased by up to 7mL (2mL per cycle if serum pregnancy test is performed instead of urine pregnancy test and 5mL every third cycle [Cycle 6, Cycle 9] for immunogenicity).
- The maximum amount of blood collected from each participant during the SFU Visit will be approximately 47.5mL.

Table 9-2: Total blood volume collected during Cycle 1 of Part A1

Cohorts / Sample	Volume of sample	Cohorts 1, 2, 4		Cohort 3	
		N° of samples	Total blood volume	N° of samples	Total blood volume
Hematology	<2mL	2	<4mL	1	<2mL
Biochemistry	<2mL	2	<4mL	1	<2mL
Coagulation	<2mL	1	2mL	1	2mL
Pregnancy (if applicable)[a]	2mL	1	2mL	1	2mL
[redacted]					
PD	various (2.5 to 20mL)	7	43.5mL	4	16mL
Immunogenicity (ADA)	5mL	1	5mL	1	5mL
Total	-	-	**80.5mL**	-	**49mL**

ADA=antidrug antibody; N°=number; PD=pharmacodynamics; PK=pharmacokinetics
[a] This volume could be increased by 2mL per visit if serum pregnancy test is performed instead of urine for second pregnancy assessment during this cycle.
Note: Repeat or unscheduled samples may be taken in addition, for safety reasons or for technical issues with the samples.

In **Parts B and C**, the maximum amount of blood collected from each participant during Screening will be approximately 38.5mL. In the case of liver function abnormalities considered potential Hy's Law cases where the liver-specific ALP must be separated from the total ALP in participants with bone metastases, an additional volume of 2mL of blood will be collected.

The maximum amount of blood collected from each participant over the duration of Cycle 1 of Parts B and C is indicated in Table 9-3.

Table 9-3: Total blood volume collected during Cycle 1 of Parts B and C

Sample	Number of samples	Volume of sample	Total blood volume
Hematology	4	<2mL	8mL
Biochemistry	4	<2mL	8mL
Coagulation	2	<2mL	4mL
[redacted]			
Pharmacodynamics (PD)	4	various (4 to 20mL)	32mL
Immunogenicity (ADA)	1	5mL	5mL
Total	19	-	77mL[a]

Note: Repeat or unscheduled samples may be taken in addition, for safety reasons or for technical issues with the samples.
[a] This volume could be increased by 2mL per visit at which serum pregnancy test is performed

The maximum amount of blood collected from each participant during Cycle 2 will be approximately 101mL. This volume could be increased by up to 2mL if serum pregnancy test is performed instead of urine pregnancy test.

The maximum amount of blood collected from each participant during subsequent cycles and the SFU will be approximately 44mL. This volume could be increased by up to 2mL per cycle if serum pregnancy test is performed instead of urine pregnancy test.

9.1 Safety assessments

Planned time points for all safety assessments are provided in the Schedules of Activities for Part A (Table 1-4), Part A1 (Table 1-5 and Table 1-6), Part B (Table 1-7), and Part C (Table 1-8). Safety assessments for Parts A1, D, E, F, and G will be described in a protocol amendment.

9.1.1 Physical examination

The investigator or other designated clinician will perform a complete physical examination at Screening and on Cycle 1 Day 1 predose (Part A, Part A1 and Part C) or within 3 days prior to administration of any IMP (Part B). Physical examination will be symptom-directed at all other visits.

A complete physical examination will include, at a minimum, head, eyes, ears, nose, and throat; general abdomen; lymph nodes; and cardiovascular, respiratory, gastrointestinal, neurological, musculoskeletal, hepatic, and genitourinary (as clinically indicated) systems. Weight will also be measured and recorded. Height will only be recorded at Screening.

Signs and symptoms of concomitant disease and/or conditions should also be assessed. Investigators should pay special attention to clinical signs related to previous serious illnesses.

Clinically relevant findings or worsening of previous findings will be recorded in the eCRF as an AE.

9.1.2 Vital signs

Vital signs will be measured in a semi-supine position after 5 minutes rest and will include temperature, systolic and diastolic blood pressure, pulse, and respiration rate. Vital sign measurements should be recorded prior to collection of PK samples.

9.1.3 Electrocardiograms

Triplicate 12-lead ECG will be obtained using an ECG machine that automatically calculates the heart rate and measures PR, QRS, and QT intervals. Refer to Section 7.1.2 for QTc withdrawal criteria and any additional QTc readings that may be necessary.

All ECG recordings should be taken with the study participant resting in the supine position for at least 5 minutes before the recording. When coinciding with blood sample draws for PK, ECG assessment should be performed prior to blood sample collection, such that the blood sample is collected at the nominal time.

The 3 ECG tracings should be obtained as closely as possible in succession, within 2 to 10 minutes at each time point.

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

Electrocardiograms may be collected for central reading. During the visit, the assessment of the ECG by the investigator or designee will be used to determine eligibility and continuation in the study.

9.1.4 Echocardiograms

Echocardiograms will be collected from all participants according to the Schedules of Activities for Part A (Table 1-4), Part A1 (Table 1-5 and Table 1-6), Part B (Table 1-7), and Part C (Table 1-8). Left ventricular ejection fraction will be measured and recorded in the eCRF expressed as a percentage.

9.1.5 Clinical safety laboratory assessments

Hematology, blood chemistry, coagulation, and urinalysis will be collected at the time points described in the Schedules of Activities for Part A (Table 1-4), Part A1 (Table 1-5 and Table 1-6), Part B (Table 1-7), and Part C (Table 1-8) and analyzed at a local laboratory. See Appendix 2 (Section 11.2) for the list of clinical laboratory tests to be performed.

The investigator must review the laboratory report, document this review, and record any clinically relevant changes occurring during the study in the AE section of the eCRF. The laboratory reports must be filed with the source documents. Clinically significant abnormal laboratory findings are those which are not associated with the underlying disease, unless judged by the investigator to be more severe than expected for the participant's condition.

Chemistry, hematology, and coagulation (where applicable) results should be available for review prior to infusion of treatment.

All laboratory tests with values considered clinically significantly abnormal during participation in the study or within 24 hours after the final dose of study medication should be repeated until the values return to normal or baseline or are no longer considered clinically significant by the investigator or study physician or medically qualified designee.

If such values do not return to normal/baseline within a period of time judged reasonable by the investigator, the etiology should be identified and the Sponsor notified.

All protocol-required laboratory assessments, as defined in Appendix 2 (Section 11.2), must be conducted in accordance with the laboratory manual and the Schedules of Activities for Part A (Table 1-4), Part A1 (Table 1-5 and Table 1-6), Part B (Table 1-7), and Part C (Table 1-8).

If laboratory values from nonprotocol-specified laboratory assessments performed at the institution's local laboratory require a change in participant management or are considered clinically significant by the investigator (eg, SAE or AE or dose modification), then the results must be recorded in the eCRF.

9.1.6 Pregnancy testing

Procedures for pregnancy testing and contraceptive use are provided in Appendix 4 (Section 11.4). Pregnancy testing should be collected as described in the Schedules of Activities for Part A (Table 1-4), Part A1 (Table 1-5 and Table 1-6), Part B (Table 1-7), and Part C (Table 1-8).

For female participants of childbearing potential, a serum pregnancy test with sensitivity of at least 25mIU/mL will be performed on 2 occasions prior to starting study therapy, as follows: once at the start of Screening and once at the Day 1 Cycle 1 visit immediately before the investigational product administration.

Following a negative pregnancy test result at Screening, appropriate contraception must be commenced, and another negative pregnancy test result will then be required at the Day 1 Cycle 1 Visit before the participant may receive the study treatment.

Serum or urine pregnancy tests will also be routinely repeated twice at every treatment cycle during the active Treatment Period, at the Final Visit, and additionally whenever 1 menstrual cycle is missed or when potential pregnancy is otherwise suspected. In the case of a positive pregnancy test, the participant will be withdrawn from treatment but may remain in the study (Section 9.2.5).

9.2 Adverse events and serious adverse events

Planned time points for AE and SAE reporting are provided in the Schedules of Activities for Part A (Table 1-4), Part A1 (Table 1-5 and Table 1-6),Part B (Table 1-7), and Part C (Table 1-8). Reporting of AEs and SAEs for Parts D, E, F, and G will be described in a protocol amendment.

The definitions of an AE or SAE can be found in Appendix 3 (Section 11.3).

Adverse events will be reported by the participant (or, when appropriate, by a caregiver, surrogate, or the participant's legally authorized representative).

The investigator, study physician, or medically qualified designee are responsible for detecting, documenting, and recording events that meet the definition of an AE or SAE and remain responsible for following up AEs that are serious, considered related to the study treatment (UCB6114, TFD/TPI [Part B], any individual component of mFOLFOX6 [Part C], or more than 1 of the treatments) or study procedures, or that caused the participant to discontinue the study treatment or study (see Section 7).

All non-serious events of COVID-19 or associated with COVID-19 should be reported as either "suspected COVID-19" or "confirmed COVID-19" utilizing the standard AE form. If additional assessments (e.g. additional labs) are performed by the site, they should be reported on unscheduled visit CRF pages per standard practice.

All serious events of COVID-19 or associated with COVID-19 should be reported as either "suspected COVID-19" or "confirmed COVID-19", along with additional relevant data, to UCB Patient Safety utilizing the electronic SAE form and in accordance to the timelines outlined within the protocol.

9.2.1 Time period and frequency for collecting AE and SAE information

All AEs and SAEs will be collected from the signing of the ICF until the follow-up visit at the time points specified in the Schedules of Activities for Part A (Table 1-4), Part A1 (Table 1-5 and Table 1-6), Part B (Table 1-7), and Part C (Table 1-8).

In order to ensure complete safety data collection, all AEs occurring during the study (ie, after the signing of the ICF), including any pretreatment and posttreatment periods required by the protocol, must be reported in the eCRF even if no study medication was taken but specific study procedures were conducted. This includes all AEs not present prior to the initial visit and all AEs that recurred or worsened after the initial visit.

All SAEs will be recorded and reported to the Sponsor or designee within 24 hours, as indicated in Appendix 3 (Section 11.3). The investigator will submit any updated SAE data to the Sponsor within 24 hours of it being available.

The investigator is specifically requested to collect and report to UCB (or its representative) any SAEs (even if the investigator is certain that they are in no way associated with the study medication), up to the Safety Follow-up Visit for each participant, and to also inform participants of the need to inform the investigator of any SAE within this period. Serious AEs that the investigator thinks may be associated with the study medication must be reported to UCB regardless of the time between the event and the end of the study.

The method of recording, evaluating, and assessing causality of AE and SAE and the procedures for completing and transmitting SAE reports are provided in Appendix 3 (Section 11.3).

9.2.2 Method of detecting AEs and SAEs

Care will be taken not to introduce bias when detecting AEs and/or SAEs. Open-ended and non-leading verbal questioning of the participant is the preferred method to inquire about AE occurrences.

9.2.3 Follow-up of AEs and SAEs

After the initial AE/SAE report, the investigator is required to proactively follow each participant at subsequent visits/contacts. All SAEs and non-serious AEs of special interest (as defined in Section 9.2.6 and Section 9.2.7, respectively), will be followed until resolution, stabilization, the investigator determines that it is no longer clinically significant, the event is otherwise explained, or the participant is lost to follow-up (as defined in Section 7.3. Further information on follow-up procedures for AEs and SAEs is given in Appendix 3 (Section 11.3).

9.2.4 Regulatory reporting requirements for SAEs

Prompt notification by the investigator to the Sponsor of an SAE is essential so that legal obligations and ethical responsibilities towards the safety of participants and the safety of a study treatment under clinical investigation are met.

The Sponsor has a legal responsibility to notify both the local regulatory authority and other regulatory agencies about the safety of a study treatment under clinical investigation. The Sponsor will comply with country-specific regulatory requirements relating to safety reporting to the regulatory authority, IRB/IEC, and investigators.

Investigator safety reports must be prepared for suspected unexpected serious adverse reactions according to local regulatory requirements and Sponsor policy and forwarded to investigators as necessary.

An investigator who receives an investigator safety report describing a SAE or other specific safety information (eg, summary or listing of SAEs) from the Sponsor will review and then file it along with the IB and will notify the IRB/IEC, if appropriate according to local requirements.

9.2.5 Pregnancy

Details of all pregnancies in female participants and female partners of male participants will be collected after the start of study treatment and until 3 months after the last study treatment administration.

If a pregnancy is reported, the investigator must immediately inform the Sponsor within 24 hours of learning of the pregnancy and should follow the procedures outlined in Appendix 4 (Section 11.4).

Female participants should be withdrawn from the study as soon as pregnancy is known (by positive pregnancy test), and the following should be completed:

- The participant should return for a Safety Follow-up Visit.
- The participant should immediately stop the intake of the study medication or be down-titrated as instructed at the Safety Follow-up Visit.
- A Final Visit should be scheduled 3 months after the participant has discontinued her study medication.

Abnormal pregnancy outcomes (eg, spontaneous abortion, fetal death, stillbirth, congenital anomalies, ectopic pregnancy) are considered SAEs.

9.2.6 Adverse events of special interest

An AE of special interest 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 UCB6114, the following event requires immediate reporting (within 24 hours regardless of seriousness) to UCB:

- Hy's Law
  - Potential Hy's Law, defined as ≥3xULN ALT or AST with coexisting ≥2xULN total bilirubin in the absence of ≥2xULN ALP, with no alternative explanation for the biochemical abnormality (ie, without waiting for any additional etiologic investigations to have been concluded). Follow-up information should be reported if an alternative etiology is identified during investigation and monitoring of the participant.
  - Study participants who have evidence of liver metastases may be considered to have an alternate etiology for the described laboratory abnormalities.

9.2.7 Adverse events of special monitoring

An AE of special monitoring is a product-specific AE, adverse reaction, or safety topic requiring special monitoring by UCB.

For UCB6114, no AEs of special monitoring have been identified.

9.2.8 Anticipated serious adverse events

To date, no humans have been exposed to UCB6114. Thus, no serious AEs with a possible causal relationship to the IMP (ie, suspected serious adverse reactions [SARs]) have been observed in humans. Therefore, all suspected SARs will be considered unexpected and will be reported as such.

Death due to disease progression will not be recorded as a SAE and will be recorded in the survival eCRF. However, if death might be due to other causes, it should be timely reported as a SAE.

9.2.9 Infusion-related reactions (hypersensitivity reactions)

Participants should be observed for at least 6 hours after the start of the first infusion and for 2 hours after the start of the subsequent infusions for symptoms like fever and chills or other infusion-related symptom. Interruption or slowing the rate of the infusion may help control such symptoms. The infusion may be resumed when symptoms abate.

If an infusion-related reaction occurs, the participant must be treated according to the best available medical practice.

Participants should be instructed to report any delayed reactions to the investigator immediately.

Ensure that medications to treat infusion-related reactions, and cardiopulmonary resuscitative equipment are available for immediate use prior to initiation of UCB6114.

In the event of an infusion-related reaction, temporarily stop the drug until resolution, then resume at a reduced infusion rate.

If an infusion is interrupted, it can be restarted if the investigator considers it appropriate to do so. In such instances, the total infusion time may exceed the planned infusion time in order to administer the entire planned dose. The chronology of these events should be recorded accurately

in the source data and eCRF. In addition, the PK sampling times should be adjusted to preserve the relationship of sampling times to the start of the infusion.

If an infusion-related reaction or anaphylaxis occurs, a blood sample will be collected from the study participant as soon as possible, while the event is ongoing, to investigate the nature of the reaction. Evaluation of drug-related hypersensitivity reaction may consist of diagnostic testing and continued monitoring. Further tests may include, but are not limited to cytokine measurements, immunoglobulin E levels, tryptase, complement parameters such as C3a, C5a measurements when there is a suspicion of Type I or III hypersensitivity reaction.

The results of all monitoring, including laboratory testing and other testing, should be made available to the study site and Sponsor.

Premedication to prevent the onset of infusion-related reactions may be allowed for individual study participants based on the Investigator recommendations and after consultation with the Sponsor and should be recorded in the eCRF.

Procedures for reporting infusion-related reactions are the same as those for AEs and SAEs, as described in Appendix 3 (Section 11.3).

9.3 Safety signal detection

Selected data from this study will be reviewed periodically to detect, as early as possible, any safety concern(s) related to the study medication so that investigators, study participants, regulatory authorities, and IRBs/IECs will be informed appropriately and as early as possible.

The study physician or medically qualified designee/equivalent will conduct an ongoing review of safety data as they become available and perform ongoing SAE reconciliations in collaboration with the Patient Safety representative.

As appropriate for the stage of development and accumulated experience with the study medication, medically qualified personnel at UCB may identify additional safety measures (eg, AEs, vital signs, laboratory or electrocardiogram [ECG] results) for which data will be periodically reviewed during the course of the study. For information regarding the SMC, see Section 4.1.1 (all parts), Section 4.1.2.1 (Part A), Section 4.1.3 (Part A1), Section 4.1.4.1 (Part B), and Section 4.1.5.1 (Part C).

9.4 Treatment of overdose

For this study, any dose of UCB6114 >20% above the prescribed dose within a 24-hour time period will be considered an overdose. Overdose events are only considered AEs or SAEs if there are associated clinical signs and symptoms.

No specific information is available on the treatment of overdose for UCB6114.

UCB6114 will not be self-administered by the study participant. In the event of inadvertently administering an overdose of UCB6114, the investigator should:

1. Contact the study physician or medically qualified designee immediately.
2. Closely monitor the participant for any AE/SAE and laboratory abnormalities until UCB6114 can no longer be detected systemically (at least 28 days).

[redacted]

4. Document the quantity of the excess dose as well as the duration of the overdose in the eCRF.

Decisions regarding dose interruptions or modifications will be made by the investigator in consultation with the study physician or medically qualified designee based on the clinical evaluation of the participant.

For this study, overdose of the SOC combination therapies in Part B (TFD/TPI) and Part C (mFOLFOX6) refers to the administration of a quantity of medicinal product given per administration or per day that is above the recommended dose according to the authorized product information. This shall also take into account cumulative effects due to overdose. Please refer to the respective product information or SmPC for overdose management information.

9.5 Pharmacokinetics

[redacted]

[redacted]

Table 9-4: Blood collection time points for PK analysis for Part A

[redacted]

Table 9-4: Blood collection time points for PK analysis for Part A

[redacted]

Table 9-5: Blood collection time points for PK analysis for Part A1

[redacted]

Table 9-6: Blood collection time points for PK analysis for Part B and Part C

[redacted]

9.6 Efficacy assessments

Planned time points for all tertiary/exploratory antitumor activity assessments are provided in the Schedules of Activities for Part A (Table 1-4), Part A1 (Table 1-5 and Table 1-6), Part B (Table 1-7), and Part C (Table 1-8). Primary, secondary, and tertiary/exploratory antitumor activity assessments for Parts A1, D, E, F, and G will be described in a protocol amendment.

9.6.1 Tumor assessments

Tumor assessments will be performed as outlined in the Schedules of Activities for Part A (Table 1-4), Part A1 (Table 1-5 and Table 1-6), Part B (Table 1-7), and Part C (Table 1-8). The same imaging technique used to characterize each identified and reported lesion at Baseline will be employed in subsequent tumor assessments.

Screening tumor assessments must be performed within 42 days prior to the first dose of UCB6114, and include at a minimum a computed tomography (CT) or magnetic resonance imaging (MRI) scan of the chest, abdomen, and pelvis (if relevant), and any other areas of known or suspected disease. A CT or MRI scan that is dated prior to consent for this study may be used as the Screening assessment, where this has been performed as per standard care or at the end of a prior research study

Thereafter, tumor assessments of the chest, abdomen, and pelvis (if applicable) and any other areas of disease found at Screening, or newly suspected at follow-up, are to be performed

between Days 21 and 28 of every even-numbered cycle and at the SFU Visit unless the participant has already withdrawn due to progressive disease or if the previous tumor assessment was within 6 weeks of SFU Visit.

Bone lesions can be assessed with CT and MRI. Further tests may be required for assessing bone lesions and they will be performed at the investigator's discretion and per clinical practice.

The method of tumor assessment should follow the RECIST (Version 1.1) criteria detailed in Appendix 9 (Section 11.9). If subcutaneous masses or nodes are palpable (eg, bulky) and are assessable by both clinical and radiographic techniques, the radiographic (CT/MRI) technique should be used for the assessment of target and non-target lesions. Assessment is to be performed at the site by appropriately qualified personnel (radiologist and clinical investigator) and results are to be recorded in the eCRF.

In the event of CR or PR, the tumor assessment should be confirmed. The confirmation assessment is done at least 4 weeks after the response is recorded, typically at the next scheduled assessment time point. If bone lesion assessments are a part of the tumor assessment, the bone assessments should be repeated at the time of the confirmation scan.

Any redacted scan data may be collected for verification/central reading.

9.6.2 ECOG Performance Status

Measures of ECOG Performance Status will be taken at visits outlined in the Schedules of Activities for Part A (Table 1-4), Part A1 (Table 1-5 and Table 1-6), Part B (Table 1-7), and Part C (Table 1-8). ECOG Performance Status will be determined according to the table provided in Appendix 8 (Section 11.8).

9.7 Genetics

Planned time points for all genetic assessments are provided in the Schedules of Activities for Part A (Table 1-4), Part A1 (Table 1-5 and Table 1-6), Part B (Table 1-7), and Part C (Table 1-8). Genetic assessments for Parts A1, D, E, F, and G will be defined in a protocol amendment.

Where local regulation and IEC allow, an 8.5mL blood sample for deoxyribonucleic acid (DNA) isolation will be collected from participants and may be used to perform genetic analysis to help understand a participant's response to UCB6114.

See Appendix 5 (Section 11.5) for information regarding genetic research. Details on processes for collection and shipment of these samples can be found in the laboratory manual.

9.8 Pharmacodynamics

Planned time points for all tertiary/exploratory PD assessments are provided in the Schedules of Activities for Part A (Table 1-4), Part A1 (Table 1-5 and Table 1-6), Part B (Table 1-7), and Part C (Table 1-8). All tertiary/exploratory PD assessments for Parts D, E, F, and G will be defined in a protocol amendment.

Blood samples for PD analysis will be collected at the time points discussed in the following sections.

Blood samples of various volumes may be collected for analysis in a range of PD assays (Table 9-1). In Part A, the number of blood samples and total volume collected per cycle and at the SFU Visit will be as follows:

- In Cycle 1, up to 12 blood samples totaling approximately 83.5mL
- In Cycle 2, up to 5 blood samples totaling approximately 35.5mL
- In Cycle 3, up to 5 blood samples totaling approximately 35.5mL
- In Cycle 4, up to 4 blood samples totaling approximately 15.5mL
- At the SFU Visit, up to 5 blood samples totaling approximately 35.5mL

In Part A1, the number of blood samples and total volume collected per cycle and at the SFU Visit will be as follows:

- In Screening, up to 4 blood samples totaling approximately 36 mL in each Cohort
- Cycle 1, up to 7 blood samples totaling approximately 43.5mL in Cohorts 1, 2, 4 and up to 4 blood samples totaling approximately 16mL in Cohort 3
- In Cycle 2, up to 4 blood samples totaling approximately 31.5mL in each Cohort
- In Cycle 3 up to 5 blood samples totaling approximately 35.5mL in each Cohort
- From Cycle 4 onwards and at the SFU Visit up to 4 blood samples totaling approximately 31.5mL in each Cohort

One additional sample for circulating gremlin-1 (4mL) may be taken on the day of the on-treatment biopsy if taking place on a day where no circulating gremlin-1 sample is scheduled.

In Parts B and C, the number of blood samples and total volume collected per cycle and at the SFU Visit will be as follows:

- In Screening, up to 3 blood samples totaling approximately 32.5mL
- In Cycle 1, up to 4 blood samples totaling approximately 32mL
- In Cycle 2, up to 6 blood samples totaling approximately 56mL
- From Cycle 3 onwards, up to 3 blood samples totaling approximately 28mL
- At the SFU Visit, up to 3 blood samples totaling approximately 28mL

Tumor biopsies will also be collected during the study (see Section 9.8.7).

9.8.1 Blood samples for circulating gremlin-1

Whole blood samples of approximately 4mL per time point will be collected and processed to serum for measurement of total circulating gremlin-1 levels. Sampling time points throughout the study are outlined in the Schedules of Activities for Part A (Table 1-4), Part A1 (Table 1-5 and Table 1-6), Part B (Table 1-7), and Part C (Table 1-8). Sampling collection times relative to dosing are detailed in Table 9-7 (Part A), in Table 9-8 (Part A1) and Table 9-9 (Part B and Part C).

Instructions pertaining to sample collection, processing, storage, labeling, and shipping are provided in the laboratory manual for this study.

Table 9-7: Sample time points for serum gremlin-1 analysis in Part A

Cycle	Day	Sampling time relative to dosing	Sampling time
Cycle 1	Day 1	Baseline	Predose
	Day 2	+24h	Postdose on Cycle 1 Day 1
	Day 15	Within 0.5h prior to dosing	Predose
Subsequent cycles (up to and including Cycle 4)	Day 1	Within 0.5h prior to dosing	Predose
SFU Visit	On day of visit	On day of visit	NA

h=hour; NA=not applicable; SFU=Safety Follow-Up
Note: The time window for blood sample collection at the 24h PD time point postdose (Cycle Day 2) is ± 0.5h.

Table 9-8: Sample time points for serum gremlin-1 analysis in Part A1

Cycle[a]	Day	Sampling time relative to dosing	Sampling time
Cycle 1	Day 1	Baseline	Predose
	Day 1	End of infusion (+15min)	Postdose
	Day 1	+4h (+1h)	Postdose
	Day 15[b]	Within 0.5h prior to dosing/day of visit	Predose/NA
Cycle 2	Day 1	Within 0.5h prior to dosing	Predose
Cycle 3	Day 1	Within 0.5h prior to dosing	Predose
	Day 1	+4h (+1h)	Postdose
Cycle 4 onwards	Day 1	Baseline	Predose
SFU Visit	On day of visit	On day of visit	NA

[a] An additional sample should also be collected on the day of the on-treatment biopsy (only if taking place on a day where no serum gremlin-1 samples are scheduled)
[b] Predose for a 2-weekly cycle (Cohorts 1 and 2) but on day of visit for a 3-weekly or a 4-weekly cycle (Cohorts 3 and 4)
h=hour; NA=not applicable; SFU=Safety Follow-Up

Table 9-9: Sample time points for serum gremlin-1 analysis in Part B and Part C

Cycle	Day	Sampling time relative to dosing with UCB6114	Sampling time
Screening	Once between Day -28 and -1	NA	NA
Cycle 1	Day 15	Within 0.5h prior to dosing	Predose
Cycle 2	Day 1	Within 0.5h prior to dosing	Predose
	Day 15	Within 0.5h prior to dosing	Predose
Cycle 3 (onward)[a]	Day 1	Within 0.5h prior to dosing	Predose
SFU Visit	On day of visit	On day of visit	NA

h=hour; NA=not applicable; SFU=Safety Follow-Up
[a] To be completed in cycle 3 and thereafter in even cycles only (ie, Cycle 4, 6)

9.8.2 Blood samples for serum protein analysis and blood transcriptomics

In Part A and Part A1, whole blood samples of approximately 5mL per time point will be collected and processed to serum for analysis of protein markers. An additional whole blood sample of 2.5mL per time point may also be collected for potential transcriptomic analysis. Samples for analysis of protein markers or potential transcriptomic analysis will not be obtained in Part B or Part C.

Sampling time points for these assays are detailed in Table 9-10 (Part A) and Table 9-11 (PartA1).

Instructions pertaining to sample collection, processing, storage, labeling, and shipping are provided in the laboratory manual for this study.

Table 9-10: Sample time points for serum protein analysis and blood transcriptomics in Part A

Cycle	Day	Sampling time relative to dosing	Sampling time
Cycle 1	Day 1	Baseline	Predose
	Day 15	Within 0.5h prior to dosing	Predose
Subsequent cycles (up to and including Cycle 4)	Day 1	Within 0.5h prior to dosing	Predose
SFU Visit	On day of visit	On day of visit	NA

h=hour; NA=not applicable; SFU=Safety Follow-Up

Table 9-11: Sample time points for serum protein analysis and blood transcriptomics in Part A1

Cycle	Day	Sampling time relative to dosing	Sampling time
2-weekly and 4-weekly cycles (Cohorts 1, 2 and 4)			
Screening	Day-14 to -1	Baseline	
Cycle 1	Day 15	Within 0.5h prior to dosing (Cohorts 1 and 2)/on day of visit (Cohort 4)	Predose(Cohorts 1 and 2)/ NA (Cohort 4)
Subsequent cycles	Day 1	Within 0.5h prior to dosing	Predose
SFU Visit	On day of visit	On day of visit	NA
3-weekly cycles (Cohort 3)			
Screening	Day-14 to -1	Baseline	
Cycle 2 onwards	Day 1	Within 0.5h prior to dosing	Predose
SFU Visit	On day of visit	On day of visit	NA

h=hour; NA=not applicable; SFU=Safety Follow-Up

9.8.3 Blood samples for circulating tumor DNA analysis

Whole blood samples of approximately 20mL per time point will be collected and processed for analysis of circulating tumor DNA (ctDNA).

Sampling time points are detailed in Table 9-12 (Part A), Table 9-13 (Part A1) and Table 9-14 (Part B and Part C).

Instructions pertaining to sample collection, processing, storage, labeling, and shipping are provided in the laboratory manual for this study.

Table 9-12: Sample time points for ctDNA analysis in Part A

Cycle	Day	Sampling time relative to dosing	Sampling time
Cycle 1	Day 1	Baseline	Predose
	Day 15	Within 0.5h prior to dosing	Predose
Subsequent cycles (up to and including Cycle 3)	Day 1	Within 0.5h prior to dosing	Predose
SFU Visit	On day of visit	On day of visit	NA

ctDNA=circulating tumor DNA; h=hour; NA=not applicable; SFU=Safety Follow-Up

Table 9-13: Sample time points for ctDNA analysis in Part A1

Cycle	Day	Sampling time relative to dosing	Sampling time
2-weekly and 4-weekly cycles (Cohorts 1, 2 and 4)			
Screening	Day-14 to -1	Baseline	
Cycle 1	Day 15	Within 0.5h prior to dosing (Cohorts 1 and 2)/on day of visit (Cohort 4)	Predose(Cohorts 1 and 2)/ NA (Cohort 4)
Subsequent cycles	Day 1	Within 0.5h prior to dosing	Predose
SFU Visit	On day of visit	On day of visit	NA
3-weekly cycles (Cohort 3)			
Screening	Day-14 to -1	Baseline	
Cycle 2 onwards	Day 1	Within 0.5h prior to dosing	Predose
SFU Visit	On day of visit	On day of visit	NA

h=hour; NA=not applicable; SFU=Safety Follow-Up

Table 9-14: Sample time points for ctDNA analysis in Part B and Part C

Cycle	Day	Sampling time relative to dosing with UCB6114	Sampling time
Screening	Once between Day -28 and -1	NA	NA
Cycle 1	Day 15	Within 0.5h prior to dosing	Predose
Cycle 2	Day 1	Within 0.5h prior to dosing	Predose
	Day 15	Within 0.5h prior to dosing	Predose
Cycle 3 (onward)	Day 1	Within 0.5h prior to dosing	Predose
SFU Visit	On day of visit	On day of visit	NA

ctDNA=circulating tumor DNA; h=hour; NA=not applicable; SFU=Safety Follow-Up

9.8.4 Blood samples for serum bone turnover markers

In Parts A, B, and C, whole blood samples of approximately 4mL per time point will be collected and processed to serum for analysis of circulating markers of bone turnover. Sampling time points throughout the study are outlined in the Schedules of Activities for Part A (Table 1-4), Part B (Table 1-7), and Part C (Table 1-8).

Sampling collection time points relative to dosing are detailed for Part A in Table 9-15 and for Parts B and C in Table 9-16.

Instructions pertaining to sample collection processing, storage, labeling, and shipping are provided in the laboratory manual for this study.

Table 9-15: Blood samples for serum bone turnover markers in Part A

Cycle	Day	Sampling time relative to dosing	Sampling time
Cycle 1	Day 1	Baseline	Predose
	Day 15	Within 0.5h prior to dosing	Predose
Subsequent cycles (up to and including Cycle 4)	Day 1	Within 0.5h prior to dosing	Predose
SFU Visit	On day of visit	On day of visit	NA

h=hour; NA=not applicable; SFU=Safety Follow-Up

Table 9-16: Blood samples for serum bone turnover markers in Parts B and C

Cycle	Day	Sampling time relative to dosing with UCB6114	Sampling time
Cycle 1	Day 1	Baseline	Predose
	Day 15	Within 0.5h prior to dosing	Predose
Cycle 2	Day 1	Within 0.5h prior to dosing	Predose
	Day 15	Within 0.5h prior to dosing	Predose
Subsequent cycles (from cycle 3 onwards)	Day 1	Within 0.5h prior to dosing	Predose
SFU Visit	On day of visit	On day of visit	NA

h=hour; NA=not applicable; SFU=Safety Follow-Up

9.8.5 Urine samples for urinary bone turnover markers

In Parts A, B, and C, urine samples of approximately 30mL per time point will be collected for analysis of urinary markers of bone turnover. Sampling time points throughout the study are outlined in the Schedules of Activities for Part A (Table 1-4), Part B (Table 1-7), and Part C (Table 1-8).

Sampling collection times relative to dosing are detailed for Part A in Table 9-17 and for Parts B and C in Table 9-18.

Instructions pertaining to sample collection processing, storage, labeling, and shipping are provided in the laboratory manual for this study.

Table 9-17: Urine samples for urinary bone turnover markers in Part A

Cycle	Day	Sampling time relative to dosing	Sampling time
Cycle 1	Day 1	Baseline	Predose
	Day 15	Within 0.5h prior to dosing	Predose
Subsequent cycles (up to and including Cycle 4)	Day 1	Within 0.5h prior to dosing	Predose
SFU Visit	On day of visit	On day of visit	NA

h=hour; NA=not applicable; SFU=Safety Follow-Up

Table 9-18: Urine samples for urinary bone turnover markers in Parts B and C

Cycle	Day	Sampling time relative to dosing with UCB6114	Sampling time
Cycle 1	Day 1	Baseline	Predose
	Day 15	Within 0.5h prior to dosing	Predose
Cycle 2	Day 1	Within 0.5h prior to dosing	Predose
	Day 15	Within 0.5h prior to dosing	Predose
Subsequent cycles (from cycle 3 onwards)	Day 1	Within 0.5h prior to dosing	Predose
SFU Visit	On day of visit	On day of visit	NA

h=hour; NA=not applicable; SFU=Safety Follow-Up

9.8.6 Blood samples for genetic analysis

An 8.5mL blood sample will be taken predose Cycle 1 Day 1 (Part A) or at Screening (Part A1, Part B and Part C) for genetic analysis as described in Section 9.7.

Instructions pertaining to sample collection, processing, storage, labeling, and shipping are provided in the laboratory manual for this study. A description of genetic analyses performed in this study is provided in Appendix 5 (Section 11.5).

9.8.7 Tumor biopsy for PD assessments and predictive biomarker assessments

In participants with a tumor that is accessible to biopsy and who have given informed consent, biopsies may be performed unless tissue collection carries a high risk of mortality or is otherwise contraindicated (to be determined at the discretion of the investigator).

- During Part A, these biopsies will be optional and collected at Screening and on Day 22.
- During Part A1, these biopsies will be mandatory and collected at the following time points:
  - After eligibility assessment and before study drug administration (Baseline) between Day-28 and Day -1.

– Within 2 weeks post Cycle 1 Day 15 for 2- or 4- weekly dosing schedule (ie, 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 for a 3-weekly dosing schedule (ie, between Cycle 2 Day 1 and Cycle 2 Day 15 for Cohort 3).

Note: An additional blood sample each for PK and cGremlin-1 should be collected on the day of biopsy but only in cases where samples for these endpoints are not already scheduled to be taken on the Day.

In addition, if a historical tumor biopsy specimen had been obtained prior to the study participant's entry into the study (eg, time of diagnosis), permission will be requested at the time of informed consent to use the biopsy for PD analysis.

- Tumor biopsies will not be obtained in Part B or Part C.

Biopsies will be performed according to standard clinical practice for the participant's indication and will be collected as outlined in the Schedules of Activities for Part A and Part A1 (Section 1.3).

Biopsy samples may be processed to RNA and/or formalin fixed and paraffin embedded. Ribonucleic acid samples may be used for transcriptomic analysis. Formalin-fixed and paraffin-embedded tissue may be used for transcriptomic analysis, immunohistochemistry, and/or protein expression analysis.

Excess tumor samples that remain after PD assessments have been performed may be retained while research on UCB6114 or study medications of this class continues, but no longer than 20 years (or other period according to local regulations). Tumor samples may be analyzed for additional biomarkers specifically related to the mechanism of action of UCB6114 or cancer biology as warranted by new preclinical discoveries and reports in the scientific literature.

Biopsy procedure in Part A1

The most suitable lesion(s) to be biopsied should discussed between the oncologist, radiologist, and/or colleague performing biopsy of cutaneous metastases or endoscopic biopsy, as appropriate.

Tumor biopsies are mandatory, however biopsies are to be performed, and the potentially required local anesthesia administered, only if considered to be of low risk to the participant, as determined by the Investigator and the health care professional performing the biopsy.

It is preferred that up to 5 cores per biopsy, 18-gauge in diameter and ≥1cm in length will be obtained during each procedure, if considered safe and feasible. A single baseline biopsy core transferred to neutral buffered formalin (NBF) will constitute a successful biopsy. If an initial attempt at a biopsy is unsuccessful, the patient will be given an option to proceed with a repeated attempt. If the baseline biopsy remains unsuccessful no further biopsies will be performed but the patient may remain on the study and receive study medication.

If the study participant chooses not to undergo biopsies subsequent to the baseline biopsy, he/she will be withdrawn from the study. Feasibility for the subsequent biopsies will be assessed by the Investigator/the health care professional performing the biopsy and should include a consideration of patient safety. If the subsequent biopsy is deemed to be unsafe and/or not feasible , the study participant may remain on study and receive study medication.

The lesion from which each biopsy is taken will be documented in the Tissue Acquisition Form, and, if possible, an attempt will be made to collect the on-treatment biopsies from the same lesion as the Baseline biopsy.

The use of imaging to facilitate biopsies will be decided by members of the Interventional Radiology team and may include ultrasound, CT scan, or MRI. Should a CT scan be needed for biopsy, the number of scans for each procedure will be limited to the minimum number and duration required to safely obtain the biopsy.

Instructions pertaining to sample collection, processing, storage, labeling, and shipping are provided in the biopsy manual for this study.

9.8.8 Historical tumor samples

If available, samples from study participants' stored historical tumor biopsy specimen from the time of diagnosis or subsequent surgery may be sent to the analyzing laboratory. These samples will be analyzed for transcriptional and/or protein expression and the results may be compared with those obtained from the on-study biopsies where available.

9.9 Biomarkers

Collection of samples for other biomarker research is also part of this study and is described in Section 9.8.

Planned tertiary/exploratory biomarker assessments for Parts D, E, F, and G will be defined in a protocol amendment.

9.10 Immunogenicity

Antibodies to UCB6114 will be evaluated in serum samples collected from all participants according to the Schedules of Activities for Part A (Table 1-4), Part A1 (Table 1-5 and Table 1-6), Part B (Table 1-7), and Part C (Table 1-8). On dosing days, these samples will be collected predose. These samples will be tested by the Sponsor or Sponsor's designee. All tertiary/exploratory ADA assessments for Parts D, E, F, and G will be described in a protocol amendment.

Serum samples will be screened for antibodies binding to UCB6114 and the titer of confirmed positive samples will be reported.

The detection and characterization of antibodies to UCB6114 will be performed using validated assays by or under the supervision of the Sponsor.

In Part A, a total of 3 samples of 5mL of blood will be collected for ADA analysis during the first cycle of treatment, for a total of 15mL (Table 9-19). One sample of 5mL of blood will be collected for ADA analysis during Cycles 2, 3, and 4. If a participant continues on study beyond Cycle 4, an additional 5mL blood sample for ADA analysis (with concomitant sample for PK analysis) will be collected every 3 months (Cycle 7, Cycle 10, etc). An additional 5mL blood sample for ADA will be taken at the SFU Visit.

In Part A1, 1 sample of 5mL of blood will be collected for ADA analysis on Day 1 of the first 3 cycles (Cycles 1 to 3) and on Day 1 of every third cycles thereafter (ie, Cycle 6, Cycle 9; Table 9-20). An additional 5mL blood sample for ADA will also be taken at the SFU Visit.

In Part B and Part C, 1 sample of 5mL of blood will be collected for ADA analysis during Cycle 1 and Cycle 2 (Table 9-21). From Cycle 3 onwards, an additional 5mL sample for ADA analysis (concomitant to a sample for PK analysis) will be collected in even-numbered cycles only (Cycle 4, Cycle 6, etc). An additional 5mL blood sample for ADA will also be taken at the SFU Visit.

Instructions pertaining to sample collection, processing, storage, labeling, and shipping are provided in the laboratory manual for this study.

Table 9-19: Blood sample time points for ADA analysis in Part A

Cycle	Day	Sampling time relative to dosing	Sampling time
Cycle 1	Day 1	Baseline	Predose
	Day 15	Within 0.5h prior to dosing	Predose
	Day 22	On day of visit (taken at same time ±5min as PK sample is collected)	On day of visit
Cycle 2	Day 1	Within 0.5h prior to dosing	Predose
Cycle 3	Day 1	Within 0.5h prior to dosing	Predose
Cycle 4	Day 1	Within 0.5h prior to dosing	Predose
Cycle 7 (onward)	Every 3 months	Within 0.5h prior to dosing	Predose
SFU Visit	On day of visit	On day of visit	NA

ADA=antidrug antibody; h=hour; NA=not applicable; SFU=Safety Follow-up

Table 9-20: Blood sample time points for ADA analysis in Part A1

Cycle	Day	Sampling time relative to dosing with UCB6114	Sampling time
Cycle 1	Day 1	Baseline	Predose
Cycle 2	Day 1	Within 0.5h prior to dosing	Predose
Cycle 3[a] onwards	Day 1	Within 0.5h prior to dosing	Predose
SFU Visit	On day of visit	NA	On day of visit

ADA=antidrug antibody; h=hour; NA=not applicable; SFU=Safety Follow-Up
[a] Cycle 3 and every third cycle thereafter (ie, Cycle 6, Cycle 9 etc.)

Table 9-21: Blood sample time points for ADA analysis in Part B and Part C

Cycle	Day	Sampling time relative to dosing with UCB6114	Sampling time
Cycle 1	Day 1	Baseline	Predose
Cycle 2	Day 1	Within 0.5h prior to dosing	Predose
Cycle 3 (onward)[a]	Day 1	Within 0.5h prior to dosing	Predose
SFU Visit	On day of visit	NA	On day of visit

ADA=antidrug antibody; h=hour; NA=not applicable; SFU=Safety Follow-Up
[a] To be completed in cycle 3 and thereafter in even cycles only (i.e., Cycle 4, 6).

10 STATISTICAL CONSIDERATIONS

A description of statistical methods follows and further details will be included in the Statistical Analysis Plan for each module.

10.1 Definition of analysis sets

Enrolled Set

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

Safety Set

The Safety Set (SS) will be used primarily for the analysis of safety data and will consist of all study participants who receive 1 or more full or partial doses of any study treatment.

Per-protocol Set

The Per-protocol Set (PPS) will include all study participants in the SS who do not have important protocol deviations that may substantially affect antitumor activity. The PPS will be the primary analysis set for the analysis of the exploratory antitumor activity endpoints.

Pharmacokinetic Set

The Pharmacokinetic Set (PKS) will include all study participants in the SS who have at least 1 evaluable PK concentration (ie, 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 Pharmacology scientist.

Pharmacokinetic analysis will be performed on the PKS.

ADA Set

The ADA Set (ADAS) will include all study participants in the SS who have at least 1 evaluable ADA assessment.

Immunogenicity analyses will be performed on the ADAS.

Pharmacodynamic Set

The Pharmacodynamic Set (PDS) will include 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 on the PDS.

DLT Evaluable Set

The DLT Evaluable Set (DES) will include all study participants who, during the DLT assessment period:

- Receive the planned dose of UCB6114 (Part A and Part A1)
- Receive the planned dose of UCB6114 and at least 80% of the planned dose of TFD/TPI (Part B)
- Receive the planned dose of UCB6114 and at least 80% of the planned dose of mFOLFOX6 (Part C)
- Stopped treatment because of a DLT (any part of the study)

The DES will be used by the SMC for all dose escalation/de-escalation decision making.

10.2 General statistical considerations

All analyses will be performed using SAS® Version 9.2 or higher (SAS Institute, Cary, NC, US).

Descriptive statistics will be used to provide an overview of the Baseline, safety, PK, PD, and other exploratory results. For categorical and ordinal variables, the number and percentage of participants in each category will be presented. The denominator for the percentages will be based on the number of participants appropriate for the purpose of analysis. Unless otherwise noted, all percentages will be expressed to 1 decimal place. For continuous variables, descriptive statistics will include, but will not be limited to, the number of participants, mean, median, standard deviation, minimum, and maximum.

Definitions of Baseline for each variable, as applicable, will be included in the SAPs for each module.

No formal hypothesis testing will be performed in Part A, Part A1, Part B or Part C.

10.3 Planned safety and other analyses

10.3.1 Safety analyses

Safety will be assessed by clinical review of all relevant parameters including AEs, SAEs, laboratory values, vital signs, echocardiograms, ECG results and physical examination. Eastern Cooperative Oncology Group performance status will also be assessed from a safety perspective. Unless specified otherwise, the safety analyses will be conducted for the SS defined in Section 10.1. The results of these analyses will be presented by study part. For the dose escalation modules of the study (Part A, B, and C) tabulations will be provided by dose level and overall. For the dose optimization module of the study (Part A1) tabulations will be provided by cohort and overall. For the expansion modules (Parts D, E, F, and G), tabulations will be

provided by tumor type and overall. Some safety analyses may be performed based on the dose escalation, optimization, and expansion modules combined.

Summary tables and listings will be provided for all reported TEAEs, defined as AEs that start on or after the first administration of study treatment up until the SFU visit. A pre-treatment AE which increases in severity on or after the first dose of study treatment will also be counted as a TEAE. The reported AE term will be assigned a standardized preferred term using the current version of the Medical Dictionary for Regulatory Activities (MedDRA).

The causal relationship between the occurrence of an AE and study medication will be judged by the investigator. In the event that a participant experiences repeat episodes of the same AE, then the event with the highest CTCAE severity grade and strongest causal relationship to study medication will be used for purposes of incidence tabulations.

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, TFD/TPI [Part B], any individual component of mFOLFOX6 [Part C], or more than 1 of the treatments [Part B and Part C]), discontinuation due to TEAEs, CTCAE Grade 3 or 4 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 MedDRA System Organ Class, High Level Term and Preferred Term:

- Incidence of all TEAEs, serious TEAEs, and non-serious TEAEs
- Incidence of TEAEs by maximum relationship and maximum CTCAE severity grade
- Incidence of TEAEs leading to a temporary interruption and/or reduction in study treatment
- Incidence of TEAEs leading to discontinuation of study treatment
- Incidence of fatal TEAEs by relationship
- Incidence of adverse events of special interest (AESIs) (Hy's Law – see Section 9.2.6)
- Incidence of infusion-related (hypersensitivity) reactions

For the dose escalation and optimization modules, the observed DLT rate in each dose cohort will be calculated by the crude proportion of participants who experience DLT. Multiple concurrent AEs leading to DLT will be considered a single DLT.

Deaths that occur on study (defined as during treatment or within 30 days of treatment discontinuation) will be reported in a participant listing, which will include the primary cause of death and the number of days between the date of the final dose of study medication and death.

Observed values and changes from Baseline in clinical chemistry, hematology, urinalysis, and coagulation parameters 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 laboratory assessments performed at the scheduled time points common to all cycles of study treatment.

Laboratory values will be assigned severity grades when available using the NCI CTCAE criteria. Directional shifts in laboratory toxicity grades (comparing Baseline grade with worst post-Baseline grade) will be analyzed using standard shift tables, presenting the number and proportion of participants and their maximum grade shift. For analytes without a CTCAE severity grade assigned, the shift table will present directional shifts from Baseline to above or below the laboratory standard normal range using the maximum increase and/or decrease observed throughout the course of treatment/observation.

In addition, serial vital signs measurements will be obtained during participant's UCB6114 treatment and postdose (per the Schedules of Activities for Part A [Table 1-4], Part A1 [Table 1-5 and Table 1-6], Part B [Table 1-7], and Part C [Table 1-8]). On the first day of each participant's UCB6114 treatment, vital signs will be taken in conjunction with serial PK sampling. For each participant, the vital signs change from the predose value will be summarized in a descriptive manner.

In Part A, vital signs will be measured at multiple time points on treatment days (predose, 10min and 30min after the start of the infusion, at the end of infusion, and at 1 hour after the end of the infusion). In addition, on Cycle 1 Day 1, vital signs will also be assessed at 2 hours and 8 hours after the end of the infusion. On non-dosing visits, vital signs will be measured prior to PK sampling.

In Part A1, vital signs will be measured at multiple time points on treatment day (predose, 10 minutes and 30 minutes after the start of the infusion, at the end of the infusion and 2 hours after the end of the infusion. In addition, on Cycle 1 Day 1, vital signs will also be assessed at 5 hours after the end of the infusion.

In Part B and Part C, on Day 1 of Cycle 1, vital signs will be measured at multiple time points (per the Schedules of Activities for Part B [Table 1-7], and Part C [Table 1-8]). At all other scheduled visits (Day 8, 15, and 22 of Cycle 1 and Days 1 and 15 of all subsequent cycles of study treatment), vital signs will be measured prior to UCB6114 dosing on treatment days.

Observed vital sign measurements and changes from Baseline will be summarized by visit and timepoint 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 summarized by cycle using descriptive statistics. These post-Baseline summary measures will be calculated based on vital sign measurements performed at the scheduled time points common to all cycles of study treatment.

For the multiple vital sign measurements on Day 1 of Cycle 1, changes from the predose value will be calculated at each postdose time point and summarized using descriptive statistics.

In Part A, on Days 1 and 15 of Cycle 1, ECGs will be performed at multiple time points relative to the dose of study treatment (predose, end of infusion, and 8 hours post end of infusion prior to PK sampling). At all other dosing visits (Days 1 and 15 of all subsequent cycles of study treatment), ECGs will be performed predose. On non-dosing visits, ECGs will be performed prior to PK sampling.

In Part A1, ECGs will be performed at Screening; during Cycle 1 prior to dosing, at the end of the infusion, and 2 hours after the end of infusion; during each subsequent cycle prior to dosing with UCB6114 on Day 1.

In Part B and Part C, on Days 1 and 15 of Cycle 1, ECGs will be performed at multiple time points relative to dosing with UCB6114 (predose, end of infusion, and 2 hours post end of infusion prior to PK sampling). At all other UCB6114 dosing visits, ECGs will be performed prior to dosing with any study medication and as per Schedule of Activities.

Observed values and changes from Baseline for 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. In addition, for each of the ECG 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 ECG measurements performed at the scheduled time points common to all cycles of study treatment.

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

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

Physical examination data will be listed only.

Prior and concomitant medications will be coded to the generic term using the current version of the World Health Organization Drug Dictionary and will be tabulated by cohort and listed by participant.

10.3.2 Analysis of Baseline and Demographic Variables

Descriptive summaries of demographic and Baseline characteristics for participants in the SS will be presented. For the dose escalation modules (Parts A, B and C) and the dose optimization module (Part A1), Baseline and demographic data will be tabulated by cohort and overall. For Part B and Part C, summaries may be presented by tumor type depending on the number of participants with specific tumor types. For the expansion modules (Parts D, E, F and G), participants will be tabulated by tumor type and overall.

10.3.3 Other analyses

10.3.3.1 Analysis of PK endpoints

UCB6114 concentrations in blood will be listed for the SS and summarized descriptively for the PKS at each scheduled assessment by dose level. Where possible, key and other PK parameters will be determined after single and multiple doses using noncompartmental analysis and will also be summarized descriptively. Key and other PK parameters are described in Table 10-1 and will be calculated where possible.

Table 10-1: Pharmacokinetic parameters

[redacted]

10.3.3.1.1 Dose dependency

The dose-dependency of PK parameters may be assessed.

10.3.3.1.2 Population PK

The PK of UCB6114 administered as monotherapy in Part A and Part A1 may be assessed using a population analysis approach. [redacted]

10.3.3.2 Analysis of genetic endpoints

Possible relationships between variations in DNA sequence and the PD effects of UCB6114 will be explored using summary statistics and graphs.

The analysis method and results for all genetic analysis will be reported separately to the main clinical study report.

10.3.3.3 Analysis of PD endpoints

The PD variables from blood samples and optional tumor samples will be summarized descriptively by cancer type, dose level/schedule, treatment cycle, and overall. The relationship of PD variables with the tumor response to UCB6114 will be explored using summary statistics and graphs.

[redacted]

The analysis methods and results for all PD variables will be reported separately to the main clinical study report.

10.3.3.4 Analysis of biomarker endpoints

Biomarkers examined in this study will be analyzed as described in Section 10.3.3.3.

10.3.3.5 Analysis of immunologic endpoints

The ADA antibody status from the samples, participant classification according to ADA antibody status, changes from Baseline in titer over time, and the incidence of treatment-emergent ADA positivity will be summarized by timepoint. Potential relationships between ADA and PK, PD, antitumor activity, and safety will also be explored.

Hypersensitivity reactions are referenced in Section 10.3.1.

10.4 Planned efficacy/outcome analyses

10.4.1 Analysis of antitumor activity/outcome endpoint

The analysis of the primary antitumor activity/outcome endpoint in the expansion modules (Parts D, E, F, and G) will be the same as the analysis of the exploratory antitumor activity/outcome endpoints in the dose escalation modules and will be further described, as applicable, in a planned protocol amendment.

10.4.1.1 Antitumor activity endpoint definitions

The following are definitions of the antitumor activity endpoints:

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

Disease control rate (DCR) is defined as the percentage of participants with a BOR of CR, PR, or SD.

Best overall response is defined for each study participant as the best overall tumor response designation, as determined by the investigator according to relevant RECIST criteria, recorded between the first dosing date and the date of documented disease progression or the date of subsequent anticancer therapy (systemic medication, surgery, or radiotherapy for cancer), whichever occurs first. Complete response or PR determinations included in the BOR assessment

must be confirmed by a second scan ≥4 weeks after the criteria for response are first met. In addition, for a BOR of SD, tumor measurements must have met the criteria for stable disease (SD)at least once after the start of study treatment at a minimum interval of no less than 6 to 8 weeks. Table C in Section 11.9 (Appendix 9) provides the derivation of BOR when confirmation of CR and PR responses are required.

Duration of response (DOR) will be calculated for participants who achieve a CR or a PR and is defined as the time in days from the start date of the response to the first date that recurrent or progressive disease is objectively documented. For participants who die without objective disease progression, DOR will be censored on the date of death, regardless of cause. For participants who discontinue early without documented objective progressive disease, 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. A sensitivity analysis will be performed taking into account both objective progressive disease and clinical disease progression, as determined by the investigator, in the calculation of DOR.

Progression-free survival (PFS) is defined as the time in days from first dosing date to the date of the first documented objective disease progression or death due to any cause, whichever occurs first. Participants who died without a documented objective disease progression will be considered to have progressed on the date of their death. Participants who did not progress or die will be censored on the date of their last available (scheduled or unscheduled) tumor assessment. Participants who did not have any on-study tumor assessments and did not die will be censored on the date of their first dose of study treatment. Participants who discontinued early 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 started anti-cancer therapy 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. A sensitivity analysis will be performed taking into account both objective progressive disease and clinical disease progression, as determined by the investigator, in the calculation of PFS.

Overall Survival (OS) is defined for all participants in the study as the time in days from the date of first dosing 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 final dose of study treatment) and at the Final Visit (3 months after their final dose of study treatment); they will not be followed up beyond this time point. For participants who discontinued early from the study or discontinued study treatment due to disease progression and were not known to have died, OS will be censored on the date of last contact.

10.4.1.2 Analysis of the antitumor activity endpoints

Unless specified otherwise, the antitumor activity analyses will be conducted using the PPS with sensitivity analyses conducted using the SS (see Section 10.1). The results of these analyses will be presented for each study part.

Tumor response data, as determined using RECIST criteria, will be tabulated. Tabulations will be presented by dose level for each cohort.

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 (eg, extent of prior anti-cancer therapy).

For the antitumor activity endpoints ORR and DCR, the proportion of participants achieving response, and, if data allow, the exact 95% confidence interval for this proportion will be estimated using the Clopper-Pearson method and presented for the response rates.

Duration of response, PFS and OS will be summarized descriptively using the Kaplan-Meier method with 95% CIs calculated using Greenwood's formula. Duration of response and PFS rates at specific timepoints (3 months, 6 months, 12 months, etc.) will also be derived from the Kaplan-Meier estimation and presented together with associated 95% CIs.

A full discussion of statistical methodology will be provided in the SAPs for each module.

10.5 Handling of protocol deviations

After all data have been verified/coded/entered into a database, a data review will be performed. The purpose of this review will be to check all protocol deviations, define the PPS, and check the quality of the data. The review will also help decide how to manage problems in the participants' data (eg, missing values, withdrawals, dropouts, and protocol deviations). Accepted deviations from theoretical time points will be described in the appropriate documents and included in the Trial Master File. After the pre-analysis review, resolution of all issues, and documentation of all decisions, the database will be locked.

10.6 Handling of dropouts or missing data

Participants who withdraw from the study before receiving study medication will be replaced and will not be included in the safety or antitumor activity assessments. Safety analyses will be conducted on all participants who have received at least 1 dose of the study medication, regardless of whether they are deemed evaluable for the assessment of a dose level (ie, they receive the planned dose during Cycle 1 [2 treatment administrations]).

Any participant who is discontinued from the study before receiving all doses of UCB6114 in Cycle 1 will be deemed nonevaluable for assessment of a dose level and will be replaced unless they experience a DLT before withdrawal.

In the context of the COVID-19 pandemic, participants who miss doses due to a positive COVID-19 diagnosis or known or expected exposure may continue in the study if, in the opinion of the investigator, they are experiencing clinical benefit and it is in their best interest to continue treatment (see Section 7.1.4).

Nonevaluable participants may be replaced to ensure that at least 3 participants receive all assigned doses of therapy at each dose level/cohort, unless accrual to that cohort has stopped due to DLTs.

Further details on any imputation of missing data will be included in the SAPs for each module.

10.7 Planned interim analysis and data monitoring

No formal interim analysis will be conducted during this study; however, the SMC will regularly review all the safety, tolerability, and PK data as well as any available biomarker and ADA data for the dose escalation modules (Part A, Part B, Part C).

In Part A, Part B, and Part C, at the end of each cohort, the SMC will review all available safety, PK, ADA and biomarker data prior to any dose escalation/de-escalation decision. The composition and operation of the SMC will be clearly outlined in the SMC Charter. The PK data will be summarized after each cohort, in order to support escalation to the next proposed dose level.

In Part A1, the SMC will review all the safety and tolerability of the sentinel participant in each 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 observation period.

Before starting any subsequent study part, the Sponsor will review all available safety, tolerability, PK, and PD biomarker endpoints from other final or ongoing study part.

10.8 Determination of sample size

10.8.1 Dose escalation modules

The number of participants likely to be enrolled in Parts A, B, and C depends on how many dose levels are needed to define the RP2D-M and the RP2D for combination therapy.

In Part A, up to 42 eligible participants will be enrolled across 5 cohorts/dose levels. This assumes that all 5 planned dose levels are evaluated, that 1 dose level is added based on emerging data, and that, on average, each cohort includes an additional participant due to drop-out/replacement and/or the modified rolling-6 design.

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 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% (Mokdad et al, 2018). 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.

In Part B and Part C, up to 27 eligible participants will be enrolled. In both parts, it is expected that up to 3 dose levels of UCB6114 will be explored in combination with the standard TFD/TPI or FOLFOX dosing regimen, respectively. However, additional dose levels may be added based on emerging data and recommendations of the SMC. In each part of the study, between 3 and 9 participants are expected to be enrolled per dose level depending on the observed toxicity/observation of DLTs. An administrative decision to stop enrolling into Part B or Part C may be made by the Sponsor at any time.

10.8.2 Expansion modules

Participant numbers for Parts D, E, F, and G are based primarily on pragmatic considerations rather than formal statistical power considerations. A minimum sample size of 15 participants is proposed per expansion module (may be expanded to 30 participants). This sample size will allow the safety and antitumor activity of UCB6114 to be evaluated with reasonable confidence

prior to commencement of further clinical studies. Furthermore, based on well-established statistical principles (Gehan, 1961):

- If no responses are seen in the first 15 consecutive participants enrolled, the chances of a response rate >20% are <4%.
- If no responses are seen in 30 consecutive participants enrolled, the chances of a response rate >10% is <5%.

For Parts F and G, in which UCB6114 will be evaluated in combination with another agent/regimen, response rates may be higher depending on the participant population and combination agent/regimen chosen.

Accordingly, a clinically meaningful improvement in the response rate will be defined for Parts F and G based upon the tumor type, line of therapy, and current SOC response probability. A 2-stage design (Simon, 1989) will be used to expand the cohorts should the observed response rate exceed the SOC expected response plus the clinically meaningful improvement threshold.

11 SUPPORTING DOCUMENTATION AND OPERATIONAL CONSIDERATIONS

11.1 Appendix 1: Regulatory, ethical, and study oversight considerations

11.1.1 Regulatory and ethical considerations

The study will be conducted under the auspices of an IRB/IEC, as defined in local regulations, International Council for Harmonisation (ICH)-Good Clinical Practice (GCP), and in accordance with the ethical principles that have their origin in the Declaration of Helsinki.

The investigator/UCB will ensure that an appropriately constituted IRB/IEC that complies with the requirements of the current ICH-GCP version or applicable country-specific regulations will be responsible for the initial and continuing review and approval of the clinical study. Prior to initiation of the study, the investigator/UCB will forward copies of the protocol, ICF, IB, investigator's curriculum vitae (if applicable), advertisement (if applicable), and all other participant-related documents to be used for the study to the IRB/IEC for its review and approval.

Before initiating a study, the investigator will have written and dated full approval from the responsible IRB/IEC for the protocol.

The investigator will also promptly report to the IRB/IEC all changes in the study, all unanticipated problems involving risks to participants or others, and any protocol deviations, to eliminate immediate hazards to participants.

The investigator will not make any changes in the study or study conduct without IRB/IEC approval, except where necessary to eliminate apparent immediate hazards to the participants. For minor changes to a previously approved protocol during the period covered by the original approval, it may be possible for the investigator to obtain an expedited review by the IRB/IEC as allowed.

As part of the IRB/IEC requirements for continuing review of approved studies, the investigator will be responsible for submitting periodic progress reports to the IRB/IEC (based on IRB/IEC

requirements), at intervals appropriate to the degree of participant risk involved, but no less than once per year. The investigator should provide a final report to the IRB/IEC following study completion.

UCB (or its representative) will communicate safety information to the appropriate regulatory authorities and all active investigators in accordance with applicable regulatory requirements. The appropriate IRB/IEC will also be informed by the investigator or the Sponsor, as specified by the applicable regulatory requirements in each concerned country. Where applicable, investigators are to provide the Sponsor (or its representative) with evidence of such IRB/IEC notification.

11.1.2 Financial disclosure

Insurance coverage will be handled according to local requirements.

Finance and insurance are addressed in the investigator and/or contract research organization (CRO) agreements, as applicable.

11.1.3 Informed consent process

Participant's informed consent must be obtained and documented in accordance with local regulations, ICH-GCP requirements, and the ethical principles that have their origin in the principles of the Declaration of Helsinki.

Prior to obtaining informed consent, information should be given in a language and at a level of complexity understandable to the participant in both oral and written form by the investigator (or study physician or medically qualified designee). Each participant will have the opportunity to discuss the study and its alternatives with the investigator.

Prior to participation in the study, the ICF should be signed and personally dated by the participant, or his/her legal representative, and by the person who conducted the informed consent discussion (investigator, study physician, or medically qualified designee). The participant or his/her legal representative must receive a copy of the signed and dated ICF. As part of the consent process, each participant must consent to direct access to his/her medical records for study-related monitoring, auditing, IRB/IEC review, and regulatory inspection.

If the ICF is amended during the study, the investigator (or the Sponsor, if applicable) must follow all applicable regulatory requirements pertaining to the approval of the amended ICF by the IRB/IEC and use of the amended form.

11.1.4 Data protection

UCB staff (or designee) will affirm and uphold the participant's confidentiality. Throughout this study, all data forwarded to UCB (or designee) will be identified only by the participant number assigned at Screening.

The investigator agrees that representatives of UCB, its study physician or medically qualified designee, representatives of the relevant IRB/IEC, or representatives of regulatory authorities will be allowed to review that portion of the participant's primary medical records that directly concerns this study (including, but not limited to, laboratory test result reports, ECG reports, admission/discharge summaries for hospital admissions occurring during a participant's study participation, and autopsy reports for deaths occurring during the study).

The participant must be informed that his/her personal study-related data will be used by the Sponsor in accordance with local data protection law. The level of disclosure must also be explained to the participant.

The participant must be informed that his/her medical records may be examined by Clinical Quality Assurance auditors or other authorized personnel appointed by the Sponsor, by appropriate IRB/IEC members, and by inspectors from regulatory authorities.

11.1.5 Committees structure

The SMC will comprise key Sponsor personnel and investigators from participating sites (see Section 4.1.1). Full details of the exact SMC composition will be provided in the SMC Charter.

11.1.6 Data quality assurance

All participant data relating to the study will be recorded in eCRF unless transmitted to the Sponsor or designee electronically (eg, laboratory data). The investigator is responsible for verifying that data entries are accurate and correct by physically or electronically signing the eCRF.

The investigator must maintain accurate documentation (source data) that supports the information entered in the eCRF.

The investigator must permit study-related monitoring, audits, IRB/IEC review, and regulatory agency inspections and provide direct access to source data documents.

The Sponsor or designee is responsible for the data management of this study including quality checking of the data.

Study monitors will perform ongoing source data verification to confirm that data entered into the eCRF by authorized site personnel are accurate, legible, contemporaneous, original, and attributable from source documents; that the safety and rights of participants are being protected; and that the study is being conducted in accordance with the currently approved protocol and any other study agreements, ICH GCP, and all applicable regulatory requirements.

All essential documents must be retained by the investigator for the minimum retention period mandatory under the applicable local laws and regulations. The investigator will contact UCB for authorization prior to the destruction of any study records or in the event of accidental loss or destruction of any study records. The investigator will also notify UCB should he/she relocate or move the study-related files to a location other than that specified in the Sponsor's trial master file.

11.1.6.1 Electronic Case Report Form completion

The investigator is responsible for prompt reporting of accurate, complete, and legible data in the eCRFs and in all required reports.

Any change or correction to the eCRF after saving must be accompanied by a reason for the change.

Corrections made after the investigator's review and approval (by means of a password/electronic signature) will be reapproved by the investigator.

The investigator should maintain a list of personnel authorized to enter data into the eCRF.

Detailed instructions will be provided in the eCRF Completion Guidelines.

11.1.7 Source documents

All source documents must be accurate, clear, unambiguous, permanent, and capable of being audited. They should be made using some permanent form of recording (ink, typing, printing, optical disc). They should not be obscured by correction fluid or have temporary attachments (such as removable self-stick notes).

Source documents are original records in which raw data are first recorded. These may include hospital/clinic records, charts, diaries, x-rays, laboratory results, printouts, pharmacy records, care records, ECG, or other worksheets. Source documents should be kept in a secure, limited access area.

Source documents that are computer-generated and stored electronically must be printed for review by the monitor (eg, ECG reports). Once printed, these copies should be signed and dated by the investigator and become a permanent part of the participant's source documents. The investigator will facilitate the process for enabling the monitor to compare the content of the printout and the data stored in the computer to ensure all data are consistent.

Electronic data records, such as Holter monitor records or electroencephalogram records, must be saved and stored as instructed by UCB (or designee).

11.1.8 Study and site closure

Study site participation may be discontinued if UCB, the investigator, the IRB/ethical review board, or the regulatory authority deems it necessary for any scientific, medical, or ethical reason.

The study will be discontinued if UCB, while considering the rights, safety, and wellbeing of the participant(s), deems it necessary for any scientific, medical, or ethical reason.

The Sponsor designee reserves the right to close the study site or terminate the study at any time for any reason at the sole discretion of the Sponsor. Study sites will be closed upon study completion. A study site is considered closed when all required documents and study supplies have been collected and a study-site closure visit has been performed.

The investigator may initiate study-site closure at any time, provided there is reasonable cause and sufficient notice is given in advance of the intended termination.

Reasons for the early closure of a study site by the Sponsor or investigator may include but are not limited to:

- Failure of the investigator to comply with the protocol, the requirements of the IRB/IEC or local regulatory authorities, the Sponsor 's procedures, or GCP guidelines
- Inadequate recruitment of participants by the investigator
- Discontinuation of further study medication development

11.1.9 Publication policy

The results of this study may be published or presented at scientific meetings. If this is foreseen, the investigator agrees to submit all manuscripts or abstracts to the Sponsor before submission. This will allow the Sponsor to protect proprietary information and to provide comments.

The Sponsor will comply with the requirements for publication of study results. In accordance with standard editorial and ethical practice, the Sponsor will generally support publication of multicenter studies only in their entirety and not as individual site data. In this case, a coordinating investigator will be designated by mutual agreement.

Authorship will be determined by mutual agreement and in line with International Committee of Medical Journal Editors authorship requirements.

11.2 Appendix 2: Clinical laboratory tests

- Chemistry, hematology, and coagulation (as described in the Schedules of Activities for Part A [Table 1-4], Part A1 (Table 1-5 and Table 1-6), Part B [Table 1-7], and Part C [Table 1-8]) results should be available for review prior to administration of treatment.
- The tests detailed in the table below will be performed by the local or central laboratory. If the local or central laboratory results are used to make either a study treatment decision or response evaluation, the results must be entered into the eCRF.
- Protocol-specific requirements for inclusion or exclusion of participants are detailed in Section 5.1 and Section 5.2 of this protocol.
- Additional tests may be performed at any time during the study as determined necessary by the investigator or required by local regulations.

Protocol-Required Safety Laboratory Assessments

Laboratory Assessments	**Parameters**			
Hematology	Hemoglobin Hematocrit RBC count Platelet count	RBC Indices: MCV MCH MCHC	WBC Count with Differential: Absolute neutrophils Absolute lymphocytes Absolute monocytes Absolute eosinophils Absolute basophils	
Coagulation	aPTT and either PT or INR			
Clinical Chemistry[1]	ALT	AST	Alkaline phosphatase	Bicarbonate
	Sodium	Potassium	Magnesium	Chloride
	Calcium	Total bilirubin	BUN or urea	Glucose (non-fasted)
	Phosphorus or phosphate	Total protein	Uric acid	Amylase
	Albumin			
	GGT	Cholesterol	Creatine kinase	CRP
	LDH	Lipase	Triglycerides	Serum creatinine
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)			

Laboratory Assessments	Parameters
Other Tests	**Pregnancy tests:** • Follicle-stimulating hormone and estradiol (as needed in women of non-childbearing potential only) • Serum or urine hCG pregnancy test (as needed for women of childbearing potential) **Bone Turnover Markers:** • Blood BAP, blood CTx, urinary NTx and urinary CtxII (see Section 9.8) **Tumor markers** • eg, PSA, CA125, CA19-9 • If routinely measured, results of tumor markers will also be recorded in the eCRF when available during the participant's participation in the study. All study-required laboratory assessments will be performed by a local laboratory. The results of each test must be entered into the eCRF.

NOTES:

[1] Details of liver chemistry stopping criteria and required actions and follow-up assessments after liver stopping or monitoring event are given in Section 7.1.1 . All cases confirmed on repeat testing as meeting the laboratory criteria defined in Section 7.1.1, with no other cause for liver function test abnormalities identified at the time, should be considered potential Hy's Law cases irrespective of availability of all the results of the investigations performed to determine etiology of the abnormal liver function tests. Such potential Hy's Law cases should be reported as SAEs.

ALT=alanine aminotransferase; aPPT=activated partial thromboplastin time; AST=aspartate aminotransferase; BAP=bone alkaline phosphatase; BUN=blood urea nitrogen; eCRF=electronic Case Report Form; CRP=C-reactive protein; CTx=C-terminal telopeptide; GGT=gamma glutamyl transferase; hCG=human chorionic gonadotropin; INR=international normalized ratio; LDH=lactate dehydrogenase; NTX=N-terminal telopeptide; PSA=prostate specific antigen; PT=prothrombin time; RBC=red blood cell; ULN=upper limit of normal; SAE=serious adverse event; WBC=white blood cell

Investigators must document their review of each laboratory safety report.

The formula for the Cockroft-Gault glomerular filtration rate estimation is as follows:

$$\text{Creatinine Clearance (men)} = \frac{(140\text{-Age}) \times \text{Lean Body Weight [kilograms]}}{\text{Serum Creatinine (mg/dL)} \times 72}$$

$$\text{Creatinine Clearance (women)} = \frac{0.85 \times (140\text{-Age}) \times \text{Lean Body Weight [kilograms]}}{\text{Serum Creatinine (mg/dL)} \times 72}$$

Reference:

Gault MH, Longerich LL, Harnett JD, et al. Predicting glomerular function from adjusted serum creatinine (editorial). Nephron 1992;62:249.

11.3 Appendix 3: Adverse events – Definitions and procedures for recording, evaluating, follow-up, and reporting

Definition of AE

AE Definition
• An AE is any untoward medical occurrence in a patient or clinical study participant, temporally associated with the use of study medication, whether or not considered related to the study medication. • NOTE: An AE can therefore be any unfavorable and unintended sign (including an abnormal laboratory finding), symptom, or disease (new or exacerbated) temporally associated with the use of study medication.

Events Meeting the AE Definition
• Any abnormal laboratory test results (hematology, clinical chemistry, coagulation, or urinalysis) or other safety assessments (eg, ECG, radiological scans, vital signs measurements), including those that worsen from baseline, considered clinically significant in the medical and scientific judgment of the investigator (ie, not related to progression of underlying disease). • Exacerbation of a chronic or intermittent pre-existing condition including either an increase in frequency and/or intensity of the condition. • New conditions detected or diagnosed after study medication administration even though it may have been present before the start of the study. • Signs, symptoms, or the clinical sequelae of a suspected drug-drug interaction. • Signs, symptoms, or the clinical sequelae of a suspected overdose of either study medication or a concomitant medication. Overdose per se will not be reported as an AE/SAE unless it is an intentional overdose taken with possible suicidal/self-harming intent. Such overdoses should be reported regardless of sequelae. • "Lack of efficacy" or "failure of expected pharmacological action" per se will not be reported as an AE or SAE. Such instances will be captured in the antitumor activity assessments. However, the signs, symptoms, and/or clinical sequelae resulting from lack of antitumor activity will be reported as AE or SAE if they fulfil the definition of an AE or SAE.

Events NOT Meeting the AE Definition
• Medical or surgical procedure (eg, endoscopy, appendectomy): the condition that leads to the procedure is the AE. • Situations in which an untoward medical occurrence did not occur (social and/or convenience admission to a hospital). • Anticipated day-to-day fluctuations of pre-existing disease(s) or condition(s) present or detected at the start of the study that do not worsen.

Definition of SAE

If an event is not an AE per definition above, then it cannot be an SAE even if serious conditions are met (eg, hospitalization for signs/symptoms of the disease under study, death due to progression of disease).

An SAE is defined as any untoward medical occurrence that, at any dose:
a. Results in death
b. Is life-threatening The term 'life-threatening' in the definition of 'serious' refers to an event in which the participant was at risk of death at the time of the event. It does not refer to an event, which hypothetically might have caused death, if it were more severe.
c. Requires inpatient hospitalization or prolongation of existing hospitalization In general, hospitalization signifies that the participant has been detained (usually involving at least an overnight stay) at the hospital or emergency ward for observation and/or treatment that would not have been appropriate in the physician's office or outpatient setting. Complications that occur during hospitalization are AEs. If a complication prolongs hospitalization or fulfills any other serious criteria, the event is serious. When in doubt as to whether "hospitalization" occurred or was necessary, the AE should be considered serious. Hospitalization for elective treatment of a pre-existing condition that did not worsen from baseline is not considered an AE. Hospitalization for convenience/assessments and for convalescence is not considered an AE.
d. Results in persistent disability/incapacity • The term disability means a substantial disruption of a person's ability to conduct normal life functions. • This definition is not intended to include experiences of relatively minor medical significance such as uncomplicated headache, nausea, vomiting, diarrhea, influenza, and accidental trauma (eg, sprained ankle) which may interfere with or prevent everyday life functions but do not constitute a substantial disruption.
e. Is a congenital anomaly/birth defect
f. Important medical events: • Medical or scientific judgment should be exercised in deciding whether SAE reporting is appropriate in other situations such as important medical events that may not be immediately life-threatening or result in death or hospitalization but may jeopardize the participant or may require medical or surgical intervention to prevent one of the other outcomes listed in the above definition. These events should usually be considered serious.

- Examples of such events include, but are not limited to, potential Hy's law, invasive or malignant cancers, intensive treatment in an emergency room or at home for allergic bronchospasm, blood dyscrasias or convulsions that do not result in hospitalization, or development of drug dependency or drug abuse.

Recording and Follow-Up of AE and/or SAE

AE and SAE Recording

- When an AE/SAE occurs, it is the responsibility of the investigator to review all documentation (eg, hospital progress notes, laboratory reports, and diagnostics reports) related to the event.
- The investigator will then record all relevant AE/SAE information in the eCRF.
- It is **not** acceptable for the investigator to send photocopies of the participant's medical records to UCB/CRO in lieu of completion of the AE/SAE eCRF page.
- There may be instances when copies of medical records for certain cases are requested by the study physician or medically qualified designee. In this case, all participant identifiers, with the exception of the participant number, will be redacted on the copies of the medical records before submission to the study physician or medically qualified designee.
- The investigator will attempt to establish a diagnosis of the event based on signs, symptoms, and/or other clinical information. Whenever possible, the diagnosis (not the individual signs/symptoms) will be documented as the AE/SAE.

Assessment of Intensity

Each must be categorized using the National Cancer Institute Common Terminology Criteria for Adverse Events (NCI CTCAE) v 5.0 (https://ctep.cancer.gov/protocolDevelopment/electronic_applications/docs/CTCAE_v5_Quick_Reference_8.5x11.pdf).

Assessment of Causality

- The investigator is obligated to assess the relationship between study medication and each occurrence of each AE/SAE.
- A "reasonable possibility" of a relationship conveys that there are facts, evidence, and/or arguments to suggest a causal relationship, rather than a relationship cannot be ruled out.
- The investigator will use clinical judgment to determine the relationship.
- Alternative causes, such as underlying disease(s), concomitant therapy, and other risk factors, as well as the temporal relationship of the event to study medication administration will be considered and investigated.
- The investigator will also consult the IB and/or Product Information, for marketed products, in his/her assessment.
- For each AE/SAE, the investigator **must** document in the medical notes that he/she has reviewed the AE/SAE and has provided an assessment of causality.
- There may be situations in which an SAE has occurred and the investigator has minimal information to include in the initial report to UCB. However, **it is very important that the investigator always make an assessment of causality for every event before the initial transmission of the SAE data to UCB.**
- The investigator may change his/her opinion of causality in light of follow-up information and send a SAE follow-up report with the updated causality assessment.
- The causality assessment is one of the criteria used when determining regulatory reporting requirements.

Follow-up of AEs and SAEs

- The investigator is obligated to perform or arrange for the conduct of supplemental measurements and/or evaluations as medically indicated or as requested by a UCB representative to elucidate the nature and/or causality of the AE or SAE as fully as possible. This may include additional laboratory tests or investigations, histopathological examinations, or consultation with other health care professionals.
- An AE should be followed until it has resolved, has a stable sequelae, the investigator determines that it is no longer clinically significant, or the participant is lost to follow-up. This follow-up requirement applies to AEs, SAEs, and AEs of special interest.
- New or updated information will be recorded in the originally completed eCRF.
- The investigator will submit any updated SAE data to UCB within 24 hours of receipt of the information.

Reporting of SAEs

SAE Reporting to UCB via an Electronic Data Collection Tool
• The primary mechanism for reporting an SAE to UCB will be the electronic data collection tool. • If the electronic system is unavailable for more than 24 hours, then the site will use the paper SAE data collection tool (see next section). • The site will enter the SAE data into the electronic system as soon as it becomes available. • After the study is completed at a given site, the electronic data collection tool will be taken off-line to prevent the entry of new data or changes to existing data. • If a site receives a report of a new SAE from a study participant or receives updated data on a previously reported SAE after the electronic data collection tool has been taken off-line, then the site can report this information on a paper SAE form (see next section) or to the study physician or medically qualified designee by telephone. • Contacts for SAE reporting can be found on page 3.

SAE Reporting to UCB via Paper CRF
• Facsimile transmission of the SAE paper CRF is the preferred method to transmit this information to the UCB. • In rare circumstances and in the absence of facsimile equipment, notification by telephone is acceptable with a copy of the SAE data collection tool sent by overnight mail or courier service. • Initial notification via telephone does not replace the need for the investigator to complete and sign the SAE CRF pages within the designated reporting time frames. • Contacts for SAE reporting can be found on page 3.

11.4 Appendix 4: Contraceptive Guidance and Collection of Pregnancy Information

Definitions

Woman of Childbearing Potential

A woman is considered fertile following menarche and until becoming post-menopausal unless permanently sterile (see below).

Women in the following categories **are not considered women of childbearing potential**:

1. Premenarchal
2. Premenopausal female with 1 of the following:
   - Documented hysterectomy
   - Documented bilateral salpingectomy
   - Documented bilateral oophorectomy

   Note: Documentation can come from the site personnel's review of the participant's medical records, medical examination, or medical history interview.
3. Postmenopausal female
   - A postmenopausal state is defined as no menses for 12 months without an alternative medical cause. A high follicle stimulating hormone (FSH) level in the postmenopausal range may be used to confirm a postmenopausal state in women not using hormonal contraception or hormonal replacement therapy (HRT). However, in the absence of 12 months of amenorrhea, a single FSH measurement is insufficient.
   - Females on HRT and whose menopausal status is in doubt will be required to use one of the non-estrogen hormonal highly effective contraception methods if they wish to continue their HRT during the study. Otherwise, they must discontinue HRT to allow confirmation of postmenopausal status before study enrollment.

Contraception Guidance

Male participants

Male participants with female partners of childbearing potential are eligible to participate if they agree to ONE of the following during this study:

- Are abstinent from penile-vaginal intercourse as their usual and preferred lifestyle (abstinent on a long term and persistent basis) and agree to remain abstinent.
- Agree to use a male condom plus partner use of a contraceptive method with a failure rate of <1% per year as described in the table below when having penile-vaginal intercourse with a woman of childbearing potential who is not currently pregnant.

In addition, male participants must refrain from donating sperm for the duration of the study and after the final dose of study medication as follows:

1. For 3 months if participating in Part A or Part A1 of the study;
2. For 6 months if participating in Part B or Part C of the study.

Male participants with a pregnant or breastfeeding partner must agree to remain abstinent from penile-vaginal intercourse or use a male condom during each episode of penile penetration for the duration of the study and, after the final dose of study medication as follows:

1. For 3 months if participating in Part A or Part A1 of the study;
2. For 6 months if participating in Part B or Part C of the study.

Female participants

Female participants of childbearing potential are eligible to participate if they agree to use a highly effective method of contraception consistently and correctly as described in the table below.

It is currently unknown whether trifluridine/tipiracil (Lonsurf®) may reduce the effectiveness of hormonal contraceptives, and therefore women using hormonal contraceptives should add a barrier contraceptive method.

Highly Effective Contraceptive Methods

Highly Effective Contraceptive Methods That Are User Dependent[a] Failure rate of <1% per year when used consistently and correctly.
Combined (estrogen and progestogen containing) hormonal contraception associated with inhibition of ovulation[a] • Oral • Intravaginal • Transdermal
Progestogen only hormonal contraception associated with inhibition of ovulation • Oral • Injectable
Highly Effective Methods That Are User Independent[b]
Implantable progestogen only hormonal contraception associated with inhibition of ovulation • Intrauterine device (IUD) • Intrauterine hormone-releasing system (IUS) • Bilateral tubal occlusion
Vasectomized partner A vasectomized partner is a highly effective contraception method provided that the partner is the sole male sexual partner of the woman of childbearing potential and the absence of sperm has been confirmed. If not, an additional highly effective method of contraception should be used.
Sexual abstinence Sexual abstinence is considered a highly effective method only if defined as refraining from heterosexual intercourse during the entire period of risk associated with the study medication. The reliability of sexual

abstinence needs to be evaluated in relation to the duration of the study and the preferred and usual lifestyle of the participant.
NOTES: a) Typical use failure rates may differ from those when used consistently and correctly. Use should be consistent with local regulations regarding the use of contraceptive methods for participants participating in clinical studies. b) Hormonal contraception may be susceptible to interaction with the study medication, which may reduce the efficacy of the contraceptive method. In this case, 2 highly effective methods of contraception should be utilized during the treatment period and after the final dose of study medication, as follows: 1. For at least 3 months if participating in Part A or Part A1 of the study; 2. For at least 6 months if participating in Part B or Part C of the study.

Pregnancy testing

- Women of childbearing potential should only be included after a confirmed menstrual period and a negative highly sensitive serum pregnancy test.
- Additional pregnancy testing should be performed at each visit during the treatment period and within 30 days after the final dose of study medication and as required locally.
- Pregnancy testing will be performed whenever a menstrual cycle is missed or when pregnancy is otherwise suspected.
- Pregnancy testing, with a sensitivity of at least 25mIU/mL will be performed.

Male participants with partners who become pregnant

- The investigator will attempt to collect pregnancy information on any male participant's female partner who becomes pregnant while the male participant is in this study. This applies only to male participants who receive study medication.
- After obtaining the necessary signed informed consent from the pregnant female partner directly, the investigator will record pregnancy information on the appropriate form and submit it to the Sponsor within 24 hours of learning of the partner's pregnancy. The female partner will also be followed to determine the outcome of the pregnancy. Information on the status of the mother and child will be forwarded to the Sponsor. Generally, the follow-up will be at least 12 months after the delivery date. Any termination of the pregnancy will be reported regardless of fetal status (presence or absence of anomalies) or indication for the procedure.

Female participants who become pregnant

- Any female participant who becomes pregnant while participating in the study will discontinue study medication or be withdrawn from the study OR may request continuation of study medication.
- The investigator will collect pregnancy information on any female participant who becomes pregnant while participating in this study. Information will be recorded on the appropriate form and submitted to the Sponsor within 24 hours of learning of a participant's pregnancy. The participant will be followed to determine the outcome of the pregnancy. The investigator will collect follow-up information on the participant and the neonate, and the information will be forwarded to the Sponsor. Generally, the follow-up will be at least 12 months after

the delivery date. Any termination of pregnancy will be reported, regardless of fetal status (presence or absence of anomalies) or indication for the procedure.

- While pregnancy itself is not considered to be an AE or SAE, any pregnancy complication or elective termination of a pregnancy will be reported as an AE or SAE. A spontaneous abortion is always considered to be an SAE and will be reported as such. Any post-study pregnancy related SAE considered reasonably related to the study medication by the investigator will be reported to the Sponsor as described in Section 9.2.5. While the investigator is not obligated to actively seek this information in former study participants, he or she may learn of an SAE through spontaneous reporting.

11.5 Appendix 5: Genetics

Use and analysis of DNA

- Genetic variation may impact a participant's response to study medication, susceptibility to, and severity and progression of disease. Variable response to study medication may be due to genetic determinants that impact the mechanism of action of the drug; disease etiology; and/or molecular subtype of the disease being treated. Therefore, where local regulations and IRB/IEC allow, a blood sample will be collected for potential DNA analysis.
- DNA samples may be used for research related to UCB6114 and/or advanced solid tumors (locally recurrent or metastatic). They may also be used to develop tests/assays including diagnostic tests related to UCB6114 and/or interventions of this drug class and/or advanced solid tumors (locally recurrent or metastatic). Genetic research may consist of the analysis of one or more candidate genes or the analysis of genetic markers throughout the genome or analysis of the entire genome (as appropriate).
- DNA samples may be analyzed if it is hypothesized that this may help further understand the clinical data or help resolve issues with the clinical data; for example, PK outliers or potential safety observations.
- The samples may be analyzed as part of a multi-study assessment of genetic factors involved in the response to UCB6114 or study medications of this class to understand the participant's solid tumor or related conditions.
- The results of any genetic analyses will be reported separately.
- The Sponsor will store the DNA samples in a secure storage space with adequate measures to protect confidentiality.
- The samples will be retained while research on UCB6114 or study medications of this class continues, but no longer than 20 years (or other period according to local regulations).

11.6 Appendix 6: Rapid Alert Procedures

The aim of the Rapid Alert process is to stop the exposure to the study medication or concerned study procedure as soon as possible, following a confirmed or suspected safety issue, preventing its reoccurrence in other study participants as described in the Rapid Alert Team charter. Upon occurrence of an SAE and/or another safety event which may constitute a study/study part hold criterion, irrespective of its relationship with the study medication or the study conduct, the **investigator should notify the study Sponsor as soon as possible** (ideally within 2 hours of becoming aware of the event) by the following process:

1. A phone call to the study physician to alert them a safety event has been identified.
2. If the investigator is not able to reach the study physician, they should call the 24-hour rapid response helpline number. Upon receipt of a call from an investigator, the 24/7 helpline will contact a physician from UCB who will return the call to the investigator.
3. Additionally,

a. For UCB's RAVE® (ACQUIRE) study, complete the eCRF (S)AE page

   OR

b. For non UCB's RAVE (ACQUIRE) study or as back-up if UCB's RAVE® (ACQUIRE) is down, send a completed "Investigator (S)AE Report Form for Development Drug (For Rapid Alert Studies)" to the fax/email for Rapid Alert provided at the front of the protocol.

   The form should include assessed seriousness, severity, and causality and should be filed in the Study Investigator's File.

   Both the phone call and the completed form from the Investigator are crucial in assessing the safety of the study medication and in determining whether the event requires immediate action to place the study or individual study parts on hold and/or expedite reporting to the regulatory authorities. The (S)AE form should be completed in English and provided even if the data are incomplete, or if it is obvious that more data will be needed in order to draw any conclusions about the diagnosis or causality. Additional information (eg, laboratory reports) received by the investigator must be provided within 24 hours. All documents in the local language must be accompanied by a translation in English, or the relevant information included in the same document must be summarized in English in the (S)AE form.

During the call between the Investigator and the UCB physician the safety issue will be discussed to determine if there is sufficient evidence to declare a protocol hold criterion has been met for the entire study or for an individual study part. If the investigator and UCB physician agree a stopping criterion has not been met, dosing of the study may continue as per the study protocol and the discussion between the investigator and the UCB physician should be documented.

In all other circumstances, the investigator will be instructed to suspend dosing and the UCB physician will arrange an urgent, internal UCB Rapid Alert Team meeting. The Rapid Alert Team will review the information provided at the call along with the (S)AE form to determine whether or not a protocol hold criterion for the entire study or for an individual study part has been met. If it is determined that no criterion have been met, UCB will contact the investigator and inform them to recommence dosing. If it is determined a hold criterion has been met, UCB

will contact all investigators and notify them of the formal hold (please refer to Section 6.7 for further details).

If the investigator believes a protocol stopping criterion has been met for the entire study or for an individual study part, and they are unable to contact UCB prior to the next dose being due, they should postpone any further dosing until they have obtained feedback from UCB. In these circumstances dosing may be restarted if UCB and the investigator subsequently agree that no stopping criteria have been met.

11.7 Appendix 7: Country-specific Requirements

Not applicable.

11.8 Appendix 8: ECOG Performance Status Scale

ECOG Performance Status will be determined according to the following table:

Grade	ECOG performance status scale
0	Fully active, able to carry on all predisease performance without restriction
1	Restricted in physically strenuous activity but ambulatory and able to carry out work of a light or sedentary nature (eg, light housework, office work)
2	Ambulatory and capable of all selfcare 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 on any selfcare. Totally confined to bed or chair
5	Dead

ECOG=Eastern Cooperative Oncology Group

11.9 Appendix 9: RECIST v1.1 guidelines

Guidelines here have been adapted from Eisenhauer, 2009.

11.9.1 Measurability of tumor at Baseline

At Baseline, tumor lesions/lymph nodes will be categorized measurable or nonmeasurable as follows:

Measurable Lesions

Tumor lesions (extra/non-nodal lesions)

Lesions that can be accurately measured in ≥1 dimension (longest diameter in the plane of measurement) with a minimum size of

- 10mm or greater when assessed by CT or MRI (slice thickness no greater than 5mm)
- 10mm or greater when assessed by caliper (lesions which cannot be accurately measured with calipers should be recorded as nonmeasurable)
- 20mm by chest X-ray

Malignant lymph nodes (nodal lesions)

Malignant lymph nodes with the short axis 15mm or greater when assessed by CT (CT slice thickness recommended to be no greater than 5mm)

NOTE: The shortest axis is used as the diameter for malignant lymph nodes, longest axis for all other measurable lesions.

Nonmeasurable lesions

Nonmeasurable lesions will be considered as follows:

- All other lesions, including small lesions (extra/ non-nodal lesions) with longest diameter less than 10mm
- Malignant lymph nodes (nodal lesions) with ≥10 to <15mm short axis
- Truly nonmeasurable lesions: such as pleural or pericardial effusions, ascites, inflammatory breast disease, leptomeningeal disease, lymphangitic involvement of skin or lung, clinical lesions that cannot be accurately measured with calipers, abdominal masses identified by physical exam that are not measurable by reproducible imaging techniques.

Special considerations regarding lesion measurability

- Bone disease: Bone disease is nonmeasurable with the exception of soft tissue components that can be evaluated by CT or MRI and meet the definition of measurability at Baseline.
- Previous local treatment: A previously irradiated lesion (or lesion subjected to other local treatment) is non-measurable unless it has progressed since completion of treatment.

Normal sites

- Cystic lesions: Simple cysts should not be considered as malignant lesions and should not be recorded either as target or non-target disease. Cystic lesions thought to represent cystic metastases can be measurable lesions, if they meet the specific definition above. If non-cystic lesions are also present in the same patient, these are preferred as target lesions.
- Normal nodes: Nodes with short axis <10 mm are considered normal and should not be recorded or followed either as measurable or non-measurable disease.

Recording Tumor Assessments

All sites of disease must be assessed at Baseline. Baseline assessments should be done as close as possible to and prior to study start. For an adequate baseline assessment, all required scans must be done within 42 days prior to treatment and all disease must be documented appropriately. If a baseline assessment is inadequate, subsequent statuses generally should be indeterminate.

To assess objective response or future progression, overall tumor burden at Baseline should be estimated and compared to subsequent assessments.

Baseline documentation of target lesions

All measurable lesions up to a maximum of 2 lesions per organ and 5 lesions in total and representative of all involved organs should be identified as target lesions at Baseline. Target lesions should be selected on the basis of size (longest lesions) and suitability for accurate repeated measurements. Record the longest diameter of each lesion, except in the case of pathological lymph nodes for which the short axis should be recorded. The sum of the diameters

(longest for non-nodal lesions, short axis for nodal lesions) for all target lesions at Baseline will be the basis for comparison to assessments performed during the study.

- If two target lesions coalesce, the measurement of the coalesced mass is used. If a large target lesion splits, the sum of the parts is used.
- Measurements for target lesions that become small should continue to be recorded. If a target lesion becomes too small to measure, 0 mm should be recorded if the lesion is considered to have disappeared; otherwise a default value of 5 mm should be recorded.

NOTE: When nodal lesions decrease to <10 mm (normal), the actual measurement should still be recorded.

Baseline documentation of nontarget lesions

All nonmeasurable disease is nontarget. All measurable lesions not identified as target lesions are also included as non-target disease. Measurements are not required but rather assessments will be expressed as ABSENT, INDETERMINATE (not evaluable), PRESENT/NOT INCREASED (present), INCREASED (unequivocal progression). Multiple non-target lesions in one organ may be recorded as a single item on the eCRF (eg, 'multiple enlarged pelvic lymph nodes' or 'multiple liver metastases').

11.9.2 Objective response status at each evaluation

Disease sites must be assessed using the same technique used at baseline, including consistent administration of contrast and timing of scanning. If a change needs to be made, the case must be discussed with the radiologist to determine if substitution is possible. If not, subsequent objective statuses are indeterminate.

Target lesions

- Complete Response (CR): Complete disappearance of all target lesions with the exception of nodal disease. All target nodes must decrease to normal size (short axis <10 mm). All target lesions must be assessed.
- Partial Response (PR): Greater than or equal to 30% decrease under Baseline of the sum of diameters of all target measurable lesions. The short diameter is used in the sum for target nodes, while the longest diameter is used in the sum for all other target lesions. All target lesions must be assessed.
- Stable: Does not qualify for CR, PR or Progression. All target lesions must be assessed. Stable can follow PR only in the rare case that the sum increases by <20% from the nadir, but enough that a previously documented 30% decrease no longer holds.
- Progressive disease: 20% increase in the sum of diameters of target measurable lesions above the smallest sum observed (over Baseline if no decrease in the sum is observed during therapy), with a minimum absolute increase of 5 mm.
- Indeterminate. Progression has not been documented, and one or more target measurable lesions have not been assessed; or assessment methods used were inconsistent with those used at Baseline; or one or more target lesions cannot be measured accurately (eg, poorly

visible unless due to being too small to measure); or one or more target lesions were excised or irradiated and have not reappeared or increased.

Nontarget lesions

- CR: Disappearance of all nontarget lesions and normalization of tumor marker levels. All lymph nodes must be 'normal' in size (<10 mm short axis).
- NonCR/Nonprogressive disease: Persistence of any nontarget lesions and/or tumor marker level above the normal limits.
- Progressive disease: Unequivocal progression of pre-existing lesions. Generally, the overall tumor burden must increase sufficiently to merit discontinuation of therapy. In the presence of SD or PR in target disease, progression due to unequivocal increase in non-target disease should be rare.
- Indeterminate: Progression has not been determined and one or more non-target sites were not assessed or assessment methods were inconsistent with those used at Baseline.

New Lesions

The appearance of any new unequivocal malignant lesion indicates progressive disease. If a new lesion is equivocal, for example due to its small size, continued assessment will clarify the etiology. If repeat assessments confirm the lesion, then progression should be recorded on the date of the initial assessment. A lesion identified in an area not previously scanned will be considered a new lesion.

FDG-PET scanning can be used to complement CT scanning in assessments of progression (particularly possible "new" disease). New lesions on the basis of FDG-PET imaging can be identified according to the following algorithm:

- Negative FDG-PET at Baseline, with a positive FDG-PET at follow-up is a sign of progressive disease based on a new lesion.
- No FDG-PET at Baseline and a positive FDG-PET at follow-up:
  - If the positive FDG-PET at follow-up corresponds to a new site of disease confirmed by CT, this is progressive disease.
  - If the positive FDG-PET at follow-up is not confirmed as a new site of disease on CT, additional follow-up CT scans are needed to determine if there is truly progression occurring at that site (if so, the date of progressive disease will be the date of the initial abnormal FDG-PET scan).
  - If the positive FDG-PET at follow-up corresponds to a pre-existing site of disease on CT that is not progressing on the basis of the anatomic images, this is not progressive disease.

Supplemental Investigations

- If CR determination depends on a residual lesion that decreased in size but did not disappear completely, it is recommended the residual lesion be investigated with biopsy or fine needle aspirate. If no disease is identified, objective status is CR.

- If progression determination depends on a lesion with an increase possibly due to necrosis, the lesion may be investigated with biopsy or fine needle aspirate to clarify status.

Subjective progression

Participants requiring discontinuation of treatment without objective evidence of disease progression should not be reported as progressive disease on tumor assessment eCRFs. This should be indicated on the Study Medication Discontinuation eCRF page as Clinical Progression. Every effort should be made to document progressive disease even after discontinuation of treatment.

Evaluation of Response for an Individual Assessment Time Point

In order to determine tumor response, the sum of all target lesions is calculated at Baseline and at each subsequent time point (every 2 cycles in this study). Initially, a separate response for target lesions is determined using Table A. Finally, the best overall response is determined as a composite of the target and non-target responses using Table B.

Table A Objective Response Status at each Evaluation for Participants with Nontarget Disease Only

Nontarget diseases	New Lesions	Objective status
CR	No	CR
NonCR/nonprogressive disease	No	NonCR/nonprogressive disease
Indeterminate	No	Indeterminate
Unequivocal progression	Yes or No	progressive disease
Any	Yes	progressive disease

Table B Overall Response (Target and Nontarget) at Each Assessment Time Point

Target Lesions	Nontarget Lesions	New Lesions	Overall Response
CR	CR	No	CR
CR	NonCR/nonprogressive disease	No	PR
CR	Indeterminate or Missing	No	PR
PR	NonCR/nonprogressive disease, Indeterminate or Missing	No	PR
SD	NonCR/nonprogressive disease, Indeterminate or Missing	No	Stable
Indeterminate or Missing	Nonprogressive disease	No	Indeterminate
Progressive disease	Any	Yes or No	Progressive disease

Target Lesions	Nontarget Lesions	New Lesions	Overall Response
Any	Progressive disease	Yes or No	Progressive disease
Any	Any	Yes	Progressive disease

Best response determination in trials where confirmation of complete or partial response IS required: Complete or partial responses may be claimed only if the criteria for each are met at a subsequent time point as specified in the protocol (generally 4 weeks later). In this circumstance, the best overall response can be interpreted as in Table B.

Table C Best overall response when confirmation of CR and PR required

Overall response First time point	Overall response Subsequent time point	BEST overall response
CR	CR	CR
CR	PR	Stable Disease, progressive disease, or PR[a]
CR	Stable Disease	Stable disease provided minimum criteria for stable disease duration met, otherwise, progressive disease
CR	Progressive Disease	Stable disease provided minimum criteria for stable disease duration met, otherwise, progressive disease
CR	NE	Stable disease provided minimum criteria for stable disease duration met, otherwise, NE
PR	CR	PR
PR	PR	PR
PR	Stable Disease	Stable Disease
PR	Progressive Disease	Stable disease provided minimum criteria for stable disease duration met, otherwise, progressive disease
PR	NE	Stable disease provided minimum criteria for stable disease duration met, otherwise, NE
NE	NE	NE

CR=complete response; NE=nonevaluable; PR=partial response

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

11.10 Appendix 10: Abbreviations and Trademarks

ADA	antidrug antibody
ADAS	ADA Set
AE	adverse event
ALP	alkaline phosphatase
ALT	alanine aminotransferase
ANC	absolute neutrophil count
aPTT	activated partial thromboplastin time
AST	aspartate aminotransferase
bid	twice daily
BIW	twice a week
BMP	bone morphogenetic protein
BOR	best overall response
BSA	body surface area
CNS	central nervous system
CR	complete response
CRF	Case Report form
CRC	colorectal cancer
CRO	contract research organization
CTCAE	Common Terminology Criteria for Adverse Events
ctDNA	circulating tumor DNA
DCR	disease control rate
DES	DLT Evaluable Set
DLT	dose-limiting toxicity
DNA	deoxyribonucleic acid
DOR	duration of response
ECG	electrocardiogram
ECOG	Eastern Cooperative Oncology Group
eCRF	electronic Case Report form
EGFR	epidermal growth factor receptor
ES	Enrolled Set
FAS	Full Analysis Set

FIH	first in human
FOLFOX	oxaliplatin, leucovorin, and 5-fluorouracil (FOLFOX) regimen
GCP	Good Clinical Practice
G-CSF	granulocyte colony-stimulating factor
GLP	Good Laboratory Practice
GnRH	gonadotropin-releasing hormone
HMPS	hereditary mixed polyposis syndrome
HPA	hypothalamic-pituitary-adrenal
IB	Investigator's Brochure
ICF	Informed Consent Form
ICH	International Council for Harmonisation
IEC	Independent Ethics Committee
IgG4	human immunoglobulin G4
IMP	investigational medicinal product
INR	international normalized ratio
IRB	Institutional Review Board
iv	intravenous(ly)
LAIV	live attenuated influenza vaccine
mAb	monoclonal antibody
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)
MMR	measles, mumps, and rubella
MoA	mechanism of action
MRI	magnetic resonance imaging
mRNA	messenger ribonucleic acid
MTD	maximum tolerated dose
mTPI	modified toxicity probability interval
NBF	neutral buffered formalin
NCI	National Cancer Institute
ORR	objective response rate
OS	overall survival

PD	pharmacodynamic(s)
PDS	Pharmacodynamic Set
PFS	progression-free survival
PK	pharmacokinetic(s)
PKS	Pharmacokinetic Set
PPS	Per-protocol Set
PR	partial response
PT	prothrombin time
Q2W	every 2 weeks
Q3W	every 3 weeks
Q4W	every 4 weeks
QW	once weekly
QTcF	QT interval corrected for heart rate according to Fridericia's formula
RECIST	Response Evaluation Criteria in Solid Tumors
RP2D	recommended Phase 2 dose
RP2D-F	recommended Phase 2 dose of UCB6114 when used in combination with FOLFOX
RP2D-M	recommended Phase 2 dose for monotherapy
RP2D-T	recommended Phase 2 dose of UCB6114 when used in combination with TFD/TPI
SAE	serious adverse event
SAR	serious adverse reactions
sc	subcutaneous(ly)
SD	stable disease
SFU	Safety Follow-Up
SLIT1/2	slit guidance ligand 1/2
SMC	Safety Monitoring Committee
SmPC	Summary of Product Characteristics
SOC	standard of care
SS	Safety Set
SSC	Study Steering Committee
TFD/TPI	trifluridine/tipiracil
ULN	upper limit of normal

11.11 Appendix 11: Protocol amendment history

The Protocol Amendment Summary of Changes Table for the current amendment is located directly before the Table of Contents.

Amendment 5 (14 Jan 2022)

Overall Rationale for the Amendment

The overall rationale for Amendment 5 is to provide details for the conduct of Part A1 (dose optimization module), as summarized in the table below.

This amendment is considered to be substantial based on the criteria set forth in Article 10(a) of Directive 2001/20/EC of the European Parliament and the Council of the European Union.

Section # and Name	Description of Change	Brief Rationale
Global	Addition of text pertaining to dose optimization module Part A1 throughout the document, including the synopsis, objectives and endpoints, schema, schedules of activities, background, design, benefit-risk assessment, dose selection, selection and withdrawal criteria, treatments administered, concomitant medications, dose modifications, study assessments and procedures, statistical analyses, and appendices. When applicable, sections, tables and figures have been renumbered.	Addition to provide details for the conduct of Part A1 of the study
Global	Part A1 'dose adaptation module' was renamed 'dose optimization module' for clarity.	Clarification
1.1 Synopsis 3 Objectives and endpoints Global	In secondary and tertiary endpoints, the wording '*dose level*' was replaced by 'cohort' to cover both dose level in Part A and dosing schedule in Part A1. The changes were also applied throughout the document, where relevant.	Update of the endpoints to include Part A1's endpoints
4.1 Overall design	The description of the Safety Monitoring Committee (SMC) and Study Steering Committee (SSC) are applicable for all study parts; thus, the information has been moved up in a separate section. Subsequent sections have been renumbered. Treatment duration text was updated to include "***criteria for discontinuation are met"***, in line with the text provided in the study synopsis (new text in bold).	Simplification of the text Clarification

Section # and Name	Description of Change	Brief Rationale
4.2.3 Rationale for Part B and Part C	The rationale for selected indication for Part B and Part C was the same as for Part A1 and the corresponding text was moved from Section 4.2.3 to Section 4.2.2. It was clarified that Ab7326mIgG1 is the murinized version of UCB6114.	Clarification
5.2.3 Part B 5.2.4 Part C	A correction was made in the exclusion criteria for Part A (criterion #7a), Part B (criterion #7a) and Part C (criterion #6a): "*Screening of ~~symptomatic~~* ***asymptomatic*** *participants without history of CNS metastases is not required*".	Correction
9.2.8 Anticipated serious adverse events	Clarification that death due to disease progression will not be recorded as a SAE but will be recorded in a survival electronic case report form (eCRF).	Clarification
9.2.9 Infusion-related reactions (hypersensitivity reactions)	Clarifications of the procedures to be performed in case an infusion-related reaction occurs.	Clarification
10 Statistical considerations	Clarification that a SAP will be developed for each module.	Clarification
10.4 Analysis of the anti-tumor activity endpoints	Timepoints at which the duration of responses and PFS will be derived has been corrected to be in line with the statistical analysis plan.	Correction
Global	Correction of spelling, grammar, or typographical errors.	Correction
Document history	Type of amendment for protocol amendment 3.1 has been changed from 'substantial' to 'Not applicable' as the substantial/nonsubstantial classification is irrelevant in US.	Correction

Amendment 4 (17 June 2021)

Overall Rationale for the Amendment

The overall rationale for Amendment 4 is to incorporate regulatory agency-required local protocol amendments in 1 global amendment and perform some additional adjustments to the protocol. Summary of changes is given in the table below (changes already performed in one of the previous local amendments are identified by a footnote).

This amendment is considered to be substantial based on the criteria set forth in Article 10(a) of Directive 2001/20/EC of the European Parliament and the Council of the European Union.

Section # and Name	Description of Change	Brief Rationale
Title Page	Addition of the IND number.	Addition of the IND number.
Synopsis Table 1-2: Objectives and endpoints for the dose escalation modules in Part B and Part C 3. Objectives and endpoints Table 3-2: Objectives and endpoints for the dose escalation modules in Part B and Part C	Pharmacodynamic endpoint related to protein marker levels has been updated as follows: *"Change in protein marker levels in blood ~~and tumor tissue~~ by scheduled assessment and dose level".*	Correction as no tumor biopsies are requested in Parts B and C of the study.
4.1.1.4 Dose-limiting toxicity determination and maximum tolerated dose definition (Part A)	Update of the definition of DLTs to confirm that they include any AE **at least possibly related** to the study medication and fulfilling the specified criteria.[a]	Correction.
4.1.1.4 Dose-limiting toxicity determination and maximum tolerated dose definition (Part A)	Revision of the DLT definition for Part A (update of the febrile neutropenia definition as per CTCAE v5.0 and addition of Grade 4 thrombocytopenia).[a]	Correction.
4.1.3.2.1 Definition of DLT (Part B) 4.1.4.2.1 Definition of DLT (Part C)	Revision of the DLT definition for Part B and Part C (addition of any Grade 4 thrombocytopenia).[a]	Correction.
5. Study population 5.1.1 Part A 5.1.2 Part B 5.1.3 Part C	Revision of the eligibility criteria such that participants with locally advanced disease must also have unresectable disease (definition of the study population in Table 5.1; Part A: inclusion criterion #3b; Part B and Part C: inclusion criterion #3a).The precision was also added throughout the text when relevant.[a] The sentence at the end of Section 5.1.1, which mentioned that inclusion criteria for Parts A1, B, C, D, E, F, and G will be defined in a protocol amendment, has been moved at the end of Section 5.1.3; reference to Parts B and C has been deleted.	Clarification. Correction as inclusion criteria for Part B and Part C are now detailed in Sections 5.1.2 and 5.1.3.
5.1.2 Part B	Inclusion of ramucirumab as an option in the prior treatment regimen in Part B (inclusion criterion #4a).[a]	Clarification.

Section # and Name	Description of Change	Brief Rationale
5.2.1 Part A 5.2.2 Part B 5.2.3 Part C	Revision of the eligibility criteria to provide a single QTc cutoff, irrespective of the participant's sex (Part A: exclusion criterion #16b, Part B: exclusion criterion #20b, Part C: inclusion criterion #19b).[a] The sentence at the end of Section 5.2.1, which mentioned that exclusion criteria for Parts A1, B, C, D, E, F, and G will be defined in a protocol amendment, has been moved at the end of Section 5.2.3; reference to Parts B and C has been deleted.	Correction. Correction as exclusion criteria for Part B and Part C are now detailed in Sections 5.2.2 and 5.2.3.
5.2.2 Part B 5.2.3 Part C	Clarification that all participants with known hypersensitivity to any of the study medications will be excluded from the study (exclusion criterion #2a).[b]	Clarification of an exclusion criterion in Parts B and C.
5.2.3 Part C	Alignment with the UK prescribing information for oxaliplatin regarding the threshold for neutrophil count in exclusion criterion (exclusion criterion #13a).[b] Alignment with the UK prescribing information for calcium folinate regarding known or suspected pernicious anemia or other anemias due to vitamin B12 deficiency (addition of exclusion criterion #24).[b]	Update of exclusion criteria in Part C.
6.5.3 Permitted concomitant treatments (medications and therapies) during Part C 6.5.5 Prohibited concomitant treatments (medications and therapies) during Part B	Clarification that the following should be avoided in Part C:[a] • Concomitant administration of medicinal product with a known potential to prolong the QT interval • Concurrent administration of 5-fluorouracil and CYP2C9 substrates • Co-administration of medicinal products known to be nephrotoxic Title and text of Section 6.5.5 has been modified to remove the information pertaining only to Part C of the study. All the information applying to Part C has been copied or moved to a new section entitled***: 6.5.6 Prohibited concomitant treatments (medications and therapies) during Part C.***[a]	Clarification.

Section # and Name	Description of Change	Brief Rationale
6.5.7 Vaccines	Text has been corrected as follows: *"Administration of live ~~(including~~ attenuated~~)~~ vaccines is not allowed during the conduct of the study and for up to 3 months after the final dose of IMP.* *Administration of ~~inactivated~~ non-live vaccines is allowed during the study at the discretion of the Investigator."*	Correction.
6.6.2.2 UCB6114 dose modifications (Part B) 6.6.3.2 UCB6114 dose modifications (Part C)	Deletion of the following sentence: *"For participants who experience a DLT, dose adjustments are permitted if it is considered in the best interest of the participant to continue therapy at the discretion of the investigator, in consultation with the Sponsor."*[a]	Clarification.
6.6.2.2 UCB6114 dose modifications (Part B) 6.6.3.2 UCB6114 dose modifications (Part C)	Addition of any Grade 4 nonhematologic toxicity, including diarrhea and mucositis, which is at least possibly related to UCB6114 in the list of events leading to treatment discontinuation.[a]	Update the list of AEs leading to treatment discontinuation.
6.7 Criteria for study hold or dosing stoppage	Clarification that prior approval of a substantial amendment by the regulatory authorities is required for any study restart after defined stopping criteria have been met.[b]	Clarification.
9. Study assessments and procedures Table 9-2: Total blood volume collected during Cycle 1 of Parts B and C.	Revision of the maximum amount of blood collected from each participant at Screening, during Cycle 1 and Cycle 2, and at SFU. Blood sample for pregnancy test has been moved to the footnote of the table.	Correction/ clarification.
9. Study assessments and procedures Schedule of Activities Table 1-5 Schedule of Activities for Part B Table 1-6 Schedule of Activities for Part C	Update of the text to specify that liver specific ALP must be separated and used to assess the liver function instead of total ALP in participants with bone metastases and liver abnormalities considered as potential Hy's low cases. Update of Footnote l (Tables 1-5 and 1-6).	Update procedure for ALP assessment in case of liver abnormalities.

Section # and Name	Description of Change	Brief Rationale
9.5 Pharmacokinetics 9.10 Immunogenicity	Text pertaining to immunogenicity sampling was moved from the Section 9.5 Pharmacokinetics to the 9.10 Immunogenicity.	Clarification.
9.8.4 Blood samples for serum bone turnover markers Schedule of Activities Table 1-5 Schedule of Activities for Part B Table 1-6 Schedule of Activities for Part C	Deletion of the following sentence: *"Samples for analysis of circulating markers of bone turnover will not be obtained in Part B or Part C"* which was incorrect.[a] Deletion of the related footnote in the Schedule of Activities' tables (footnote j).[a]	Correction.
Schedule of Activities Table 1-5 Schedule of Activities for Part B Table 1-6 Schedule of Activities for Part C	Addition of the echocardiogram assessments in the study procedures for Part B and Part C to be in line with the assessments planned.[c] Addition of collection time-windows for blood PK sampling for Part B and Part C. Update in the time schedule of the vital sign measurements on Day 1 (2h [+1h] and 5h+ [1h] after the end of infusion)	Update Schedule of Activities for Part B and Part C.
11.4 (Appendix 4)	Update the contraceptive requirements for males in Parts B and C in relation to sperm donation and pregnant or breastfeeding partners (6 months compared to 3 months in Part A).[b] Addition of the recommendation to use a barrier contraceptive in addition to the use of hormonal contraceptive for woman of childbearing potential receiving Lonsurf® in the body text.[b] Clarification that effective contraceptive method should be utilized for at last 6 months for participant in Parts B and C (compared to 3 months in Part A)[b]	Alignment of the appendices' text with the exclusion criteria regarding contraception requirements. Clarification.

Section # and Name	Description of Change	Brief Rationale
1.3 Schedule of Activities	Correction of a few typographical and formatting errors, deletion of footnote which was not applicable for a specific assessment (Table 1.4 [Part A], footnote n for "Blood collection for genetic analysis"), and addition of an existing footnote to 2 of the current procedures (Table 1.5 [Part B] and 1.6 [Part C] footnote g added to Eligibility criteria and Medical history as they are not to be assessed in Cycle 2).	Correction.
4.1.3 Part B - Dose escalation with TFD/TPI 4.1.3.2.2 Determination of maximum-tolerated dose 4.1.4 Part C - Dose escalation with mFOLFOX6 4.1.4.2.2 Determination of maximum-tolerated dose Table 6-2 Study Treatments in Part B Table 6-3 Treatments administered in Part C 10.3.1 Safety analyses 10.7 Planned interim analysis and data monitoring 10.8.1 Dose escalation module	Clarification in the use of "cohort" and "dose level" for Part B and Part C.	Clarification.
1.2 Schema Figure 1.3 ONC001 Part B Figure 1.4 ONC001 Part C	Clarification in the schematic representation of the dose escalation/DLT assessment period: • "Cohort" replaced by "dose level", • Addition of the possibility of dose de-escalation • Clarification that each dose level can include more than one cohort of participants.	Clarification.
Global	The wording "Health Authorities" was replaced by "regulatory authorities". Correction of a few typographical and formatting errors.	Correction.

[a]This change has been previously implemented in protocol amendment 3.1 (US)
[b]This change has been previously implemented in protocol amendment 3.2 (UK)
[c]This change has been previously implemented in protocol amendment 3.1 (US) but the timepoints at which the assessment should be performed have been further updated

Amendment 3 (07 Jan 2021)

Overall Rationale for the Amendment

The overall rationale for Amendment 3 is to provide details for the conduct of Parts B and C, as summarized in the table below.

Section # and Name	Description of Change	Brief Rationale
Serious Adverse Event Reporting	Corrected 24h Rapid Response Helpline phone number.	Correction
Global	Added text pertaining to dose escalation (combination therapy) modules Part B and Part C throughout the document, including the synopsis, objectives and endpoints, schema, schedules of activities, background, design, benefit-risk assessment, dose selection, selection and withdrawal criteria, treatments administered, concomitant medications, dose modifications, and statistical analyses.	Addition to provide details for conduct of Part B and Part C of the study
Section 1.1 Synopsis, Rationale and Section 2.2 Background	Clarification of available literature on expression data in tumors.	Clarification
Section 1.1 Synopsis, Objectives and endpoints and Section 3 Objectives and endpoints	For better clarity, separated objectives and endpoints for Part A, A1, B, and C to 2 separate tables, one for Parts A and A1, and a second for Part B and C. Updated objectives and endpoints for Parts A and A1, and Parts B and C. Updated objectives and endpoints for Parts D, E, F, and G.	Clarification
Section 1.2 Schema	Updated Figure 1-1 to reflect changes to terminology in overall design.	Clarification
Section 2.1 Study rationale	Added text clarifying types of tumors selected for Part A.	Clarification

Section # and Name	Description of Change	Brief Rationale
Section 5.2.1 Exclusion Criteria Part A	Exclusion criterion 22 renumbered as 22a. Text has been corrected from: "In the presence of therapeutic intent to anticoagulate the participant: INR or PT and aPTT…" to "In the presence of therapeutic intent to anticoagulate the participant: INR or PT or aPTT…"	Correction
Section 6.1.1 Part A, Table 6-1 Treatments administered in Part A	Updated dose formulation row to clarify formulation.	Clarification
Section 9.5 Pharmacokinetics and Section 10.3.3.1 Analysis of PK endpoints	Moved text and table pertaining to PK analyses from Section 9.5 to Section 10.3.3.1.	Correction
Section 10.3.3.1 Analysis of PK endpoints	Added text specifying which PK concentrations will be disclosed on public registries for Part A, Part B, and Part C.	Addition
Global	Correction of spelling, grammar, or typographical errors.	Correction

Amendment 2 (12 Oct 2020)

Overall Rationale for the Amendment

The overall rationale for Amendment 2 is to clarify some of the study assessments and procedures and to add language related to the COVID-19 pandemic, as summarized in the table below. Minor (non-substantive) corrections to grammar and formatting are not captured in the table below.

Section # and Name	Description of Change	Brief Rationale
11.2. Appendix 2 Clinical laboratory tests	Separated the terms "phosphorus or phosphate" and "albumin"	These are separate assessments
7. Discontinuation of study medication and participant discontinuation/withdrawal	Section was restructured to clarify situations of: • participant discontinuation • treatment discontinuation • study/site discontinuation by sponsor	Restructuring provides additional clarity.

Section # and Name	Description of Change	Brief Rationale
5.2 Exclusion criteria	Added language to Criterion 15b clarifying that the presence of liver metastases must be recorded in the eCRF	Clarification
7.1.3 Other criteria for discontinuation of study medication	• Added language allowing palliative bone-directed radiotherapy as concomitant treatment • Defined taking prohibited medications as defined elsewhere in the protocol as a criterion for discontinuation of study medication	• Excepts palliative bone-directed radiotherapy from criteria for discontinuation of study medication • Clarification that prohibited medications leading to discontinuation of study medication are defined in elsewhere in the protocol
10.4.2.1. Antitumor activity endpoint definitions	Overall survival (OS) was originally measured from date of study enrollment to date of death. Revised to measure OS from the date of first dosing to date of death.	Alignment of start of time-to-event analysis for OS with the start of the time-to-event analysis for progression-free survival (PFS)
7.1.3 Other criteria for discontinuation of study medication	Excepted palliative bone-directed radiotherapy from criteria for discontinuation Added Criterion No 5	Allows participants who receive bone-directed radiotherapy to stay on treatment Adds taking prohibited concomitant medications to the criteria for discontinuation
7.1.4 Temporary discontinuation of study medication	Added language allowing temporary suspension of study medication for up to 3 weeks	Allows for suspension of treatment with study medication to resolve toxicities
7.2 Participant discontinuation/withdrawal from the study	Added clarification that site will attempt to contact participants who withdraw from the study to complete the SFU and Final Visits.	Clarification
7.4. COVID-19 Pandemic	Added a section on COVID-19 Pandemic	Gives guidance on how to adapt study processes, procedures, and timing to potential impacts of COVID-19
9.2 Adverse events and serious adverse events	Added language regarding collection of AEs and SAEs related to COVID-19	Gives guidance on how to report AEs and SAEs related to COVID-19

Section # and Name	Description of Change	Brief Rationale
9.2.5 Pregnancy	Replaced "early discontinuation visit" with "Safety Follow-up Visit" when specifying follow-up for positive pregnancy test	Accuracy
10.6. Handling of dropouts or missing data	Added language regarding missing doses due to the COVID-19 Pandemic	Clarification on missing doses due to COVID-19 Pandemic
Appendix 11. Protocol amendment history	In Amendment 1, the Summary of Changes table footnote "k" reference to Cycle 1 Day 15/16 was deleted.	Correction of an error in the Summary of Changes table from Amendment 1.
Table 1-3: Schedule of activities for Part A (monotherapy dose escalation)	Footnote "z" was added to the coagulation and ECOG assessments on Cycle 1 Day 15/16	Clarification that coagulation and ECOG in Cycle 1 is assessed on Day 15, not Day 16.
	Flexibility in assessment collection for PK sampling and Screening procedures to accommodate potential impacts of the COVID-19 pandemic	Allows flexibility in study procedures to accommodate potential impacts of the COVID-19 pandemic
	Added survival census to SFU Visit.	Consistency with CRF
	Added language to footnote "ff" clarifying survival census at SFU Visit.	Consistency with CRF
	Added language to Footnote "k" allowing collection of laboratory tests from local laboratories	Allows flexibility in collection of laboratory test
	Added language to footnote "o" expanding window of PK assessments scheduled for Day 16 to Day 21 in context of COVID-19	Allows flexibility in timing of PK assessments if needed in context of COVID-19
5.4 Screen failures	Language added to define screen failures due to impacts of the COVID-19 pandemic	Pandemic guidance for screen failures
5.2 Exclusion criteria	Exclusion Criterion No 5 was deleted	Removed need for Screening TB test of study participants
	Exclusion Criterion No 13 was modified to remove separate conditions for study participants with bone metastases	Removed separation of liver-specific AP from total AP for study participants with bone metastases

Amendment 1 (11 Jun 2020)

Overall Rationale for the Amendment

Section # and Name	Description of Change	Brief Rationale
Title page	Sponsor name has been updated.	Belgium has recently adopted a new Code of Companies and Associations, resulting in a mandatory change of the name of the legal form of the entity "*société privée à responsabilité limitée*", abbreviated "*SPRL*", to "*société à responsabilité limitée*", abbreviated "*SRL*".
Section 1.1, Synopsis	Number of participants statement updated.	For consistency with dose escalation text
	Timing of SFU visit updated and allowance for Final Visit to be conducted by phone.	Clarification
Section 1.2, Schema	Footnote to the schema has been updated.	Clarification
Section 1.3 Schedule of Activities	Cycle 2 Day 2 column and Cycle 3 onwards Day 8 column deleted as all assessments on those days have been deleted.	Reduction of participant assessment burden
	Blood collection for PK analysis row – samples deleted from Cycle 2 Day 2 and Final Visit.	Reduction of participant assessment burden
	Blood collection immunogenicity (ADA) row – samples deleted from Cycle 2 Day 15, Cycle 3 onwards Day 15, and Final Visit.	Reduction of participant assessment burden
	Added new row for blood collection for ctDNA analysis.	Addition
	Added new row for survival census.	Addition
	Added new row for coagulation.	Addition
	Footnote a was corrected to delete reference to Day 2 of Cycle 2.	For consistency with deletion of Cycle 2 Day 2 column
	Footnote b was deleted.	Clarification
	Footnote c was corrected to delete reference to Day 8 of Cycle 3 and Cycle 4 onwards.	For consistency with deletion of Cycle 3 Day 8 column

Section # and Name	Description of Change	Brief Rationale
	Footnote d has been added to the headings for columns Cycle 1 (Days 1 and 15), Cycle 2 (Day 15), and Cycle 3 onwards (Days 1 and 15) to specify timing of predose and postdose safety assessments at these visits.	Clarification
	Footnote d has been revised to include coagulation.	Addition
	Footnote h has been revised to specify timing of ECG assessments due to reduction in number of assessments.	Reduction of participant assessment burden
	Footnote i has been revised to clarify use of urine vs serum pregnancy assessments.	Clarification
	Footnote j has been revised to correct a grammatical error.	Correction of grammatical error
	Footnote k was added to the Cycle 1 Day 1 for the urinalysis, hematology, blood chemistry, and coagulation rows.	Clarification
	Footnote k was revised to add coagulation, Clarification of timing of Day 1 predose sample collection was added. Clarified that laboratory tests may be obtained 24h prior to the scheduled visit.	Clarification
	Footnote l has been revised to specify timing of vital sign assessments on Cycle 1 Day 1.	Clarification
	Footnote m has been revised to specify types of urine abnormalities that require microscopic analysis.	Clarification
	Footnote o has been revised to specify collection windows for end of infusion samples.	Clarification
	Footnote q has been revised to clarify collection of ADA samples.	Clarification
	Footnote r has been revised to add use of samples for assay verification .	Correction
	Footnote t has been revised to clarify timing of tumor assessments prior to starting study medication and to specify exception for prior CT or MRI scan.	Clarification
	Footnote z was added to specify which procedures are assessed Day 15 only of Cycle 1.	Clarification

Section # and Name	Description of Change	Brief Rationale
	Footnote aa was added to specify timing of ctDNA sampling on Cycle 3 onwards Day 1.	Addition
	Footnote bb was added to specify that echocardiograms will only be assessed at even-numbered cycles from Cycle 3 onwards.	Clarification
	Footnote cc was added to clarify requirements for tumor assessments at SFU visit.	Clarification
	Footnote dd was added to clarify when tumor assessment is not required at SFU Visit.	Clarification
	Footnote ee was added to specify predose eligibility assessment at Cycle 1 Day 1.	Addition
	Footnote ff was added to clarify liver laboratory assessments in the case of bone metastases.	Clarification
	Footnote gg was added to specify completion of survival census.	Addition
	Footnote hh was added to clarify timing of complete and symptom-directed physical examinations.	Clarification
Section 4.1 Overall design	Table 4-1, row for Part B: colorectal carcinoma changed to colorectal adenocarcinoma.	Consistency
	Sentence "Higher or lower doses may be considered based on emerging data." has been deleted.	For consistency with dose escalation text
	Pancreatic carcinoma changed to pancreatic adenocarcinoma.	Consistency
Section 4.1.1 Part A – Monotherapy dose escalation	Specified 16-day observation for participants who enroll after sentinel participant experiences a DLT.	Clarification
Section 4.2 Scientific rationale for study design	Clarification of design choices with expanded explanatory text.	Clarification
Section 4.2.1 Dosing strategy	Clarified SMC role in dose decisions and role in adding additional dose levels. Clarified that doses above 2000mg require an amendment.	Clarification
Section 5, Table 5-1 Study population	Row Part A: Term pancreatic carcinoma corrected to term pancreatic adenocarcinoma Rows Part B, Part D, and Part F: Term colorectal carcinoma corrected to colorectal adenocarcinoma.	Consistency

Section # and Name	Description of Change	Brief Rationale
Section 5.1 Inclusion criteria	Inclusion criterion 2 has been renumbered as 2a; terms pancreatic carcinoma and colorectal carcinoma corrected pancreatic adenocarcinoma and colorectal adenocarcinoma, respectively.	Consistency
	Inclusion criterion 3 has been renumbered as 3a and has been changed from “or” to “and”.	Clarification
Section 5.2 Exclusion criteria	Exclusion criterion 2 has been deleted.	Clarification
	Exclusion criterion 15 has been renumbered as 15a; and has been modified to add history of biliary stent.	Clarification
	Exclusion criterion 19 has been renumbered as 19a and has been modified to remove “or any other type of medical research”.	Correction
	New criterion: Exclusion criterion 20 has been added to specify criterion for renal function.	Ensure participants have adequate renal function
	New criterion: Exclusion criterion 21 has been added to exclude major surgery prior to study drug initiation.	Addition
	New criterion: Exclusion criterion 22 has been added to specify criteria for coagulation parameters.	
Section 6.2.1 Drug accountability	Drug accountability procedure changed to use of drug accountability logs instead of eCRF.	Correction
Section 6.4 Treatment compliance	Drug accountability procedure changed to use of drug accountability logs instead of eCRF.	Correction
Section 6.5.1 Permitted concomitant treatments (medications and therapies) during Part A	Term “concomitant” was deleted from last 2 bullets (redundant with sentence preceding bulleted list)	Correction
Section 6.6.1, Table 6-2 Dose escalation steps and justification	Footnote c was changed to spell out PK terms	Clarification
	List of abbreviations for table has been updated.	Correction
	Footnote d has been deleted as any doses higher than 2000mg would be subject to a substantial protocol amendment.	Clarification

Section # and Name	Description of Change	Brief Rationale
Section 8 Study assessments and procedures	Text has been added to specify the maximum amount of blood collected from participants during each part of the study.	Clarification
	Table 8-1, coagulation added to sample types; number and volumes of samples updated, total blood volumes updated.	Reduction of participant assessment burden
Section 8.1.1 Physical examination	Clarified timing of complete and symptom-directed physical examinations. Clarified that height will only be recorded at Screening.	Clarification
Section 8.1.5	Coagulation added to types of laboratory assessments.	
Section 8.1.6 Pregnancy testing	Text has been updated to reflect use of serum or urine pregnancy tests.	Clarification
Section 8.5, Table 8-2 Pharmacokinetic parameters	AUC_{tau} changed to $AUC_{0\text{-}336h}$.	Clarification
	Footnote a has been updated to reflect reporting.	Clarification
Section 8.5 Pharmacokinetics	Deleted PK sample collection from Final Visit.	Reduction of participant assessment burden
Section 8.5 Table 8-3, Blood collection time points for PK analysis	Cycle 1, Day 15 (samples 9 and 10), Day 16 (sample 11), and Day 22 (sample 12) sampling times and predose/postdose timepoints updated.	Correction
	Cycle 2, Day 1 (samples 13, 14, and 15) sampling times and predose/postdose timepoints updated.	Correction
	First note in footnotes updated to reflect number of samples and blood volumes.	Correction
	New note added to footnotes to specify predose sample summarization in statistical analysis.	Clarification
	Footnote a added to specify collection of Cycle 3 Day 1 PK sample in subjects who are not continuing treatment.	Addition
Section 8.6.1 Tumor assessments	Specified exception for prior CT or MRI scan. Moved tumor assessments from Final Visit to SFU visit.	Correction
Section 8.8 Pharmacodynamics	Blood volumes updated.	Correction
Section 8.8.3 Blood samples for circulating tumor DNA analysis	New section added.	Addition

Section # and Name	Description of Change	Brief Rationale
Section 8.8.4 Blood samples for serum bone turnover markers	Blood volume corrected.	Correction
Section 8.8.8 Historical tumor samples	Sentence regarding laboratory manual deleted.	To avoid confusion at sites
Section 8.10 Immunogenicity	Text updated to reflect reduction in total number of samples taken during Cycles 2, 3, and 4.	Reduction of participant assessment burden
	Table 8-9 Blood sample timepoints for ADA analysis: Deletion of Day 15 samples for Cycles 2, 3, and 4. Clarification of timing of sampling at SFU Visit. Comment column removed.	Clarification.
Section 9.1 Definition of analysis sets	Updated definitions of analysis sets, including deletion of FAS and addition of ADAS.	Consistency with SAP
Section 9.2 General statistical considerations	Added text omitted in error from original version of protocol.	Correction
Section 9.3.1 Safety analyses	Updated planned analyses. Updated vital signs information.	Consistency with SAP
Section 9.3.2 Analysis of Baseline and demographic variables	Clarification of study parts.	Clarification
9.3.3.1 Analysis of PK endpoints	Updated planned analyses.	Consistency with SAP
9.3.3.5 Analysis of immunological endpoints	Updated planned analyses.	Consistency with SAP
9.4.1 Analysis of primary antitumor activity/outcome endpoint	Updated terminology.	Consistency with SAP
9.4.2.1 Antitumor activity endpoint definitions	Clarification of definitions.	Consistency with SAP
9.4.2.2 Analysis of the antitumor activity endpoints	Updated planned analyses.	Consistency with SAP

Section # and Name	Description of Change	Brief Rationale
9.6 handling of dropouts or missing data	Noted that further details will be provided in SAP.	Clarification
Section 9.8.1 Dose escalation modules	Clarified text for addition of dose level based on emerging data.	Consistency with dose escalation scheme
Section 10.2 Appendix 2: Clinical laboratory tests	Added coagulation parameters as a row. Deleted coagulation tests from other Screening tests row. Changed "Other Screening Tests" to "Other Tests). BUN or urea creatinine changed to BUN or urea Added serum creatinine.	Clarification
Section 10.3	Added coagulation to abnormal laboratory test results bullet for events meeting the AE definition.	Clarification
Section 10.9, Appendix 9: RECIST v1.1 guidelines	Aligned text to be consistent with RECIST v1.1 guidelines and to the eCRF mapping of terms.	Alignment of text with RECIST v1.1 and eCRF
Section 10.10	Added aPTT, INR, and PT to list of abbreviations	Addition
Global	Correction of spelling, grammar, or typographical errors.	Correction

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SPONSOR DECLARATION

I confirm that I have carefully read and understand this protocol and agree to conduct this clinical study as outlined in this protocol and according to current Good Clinical Practice.

Approval Signatures

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