Clinical Study Protocol

Title Page

Clinical Study Protocol Title:	A randomized, open label, 3-arm Phase 3 study of precemtabart tocentecan with or without bevacizumab compared to trifluridine/tipiracil plus bevacizumab in participants with previously treated metastatic colorectal cancer (PROCEADE-CRC-03)
Study Number:	MS914001_0002
Protocol Version:	23 February 2026, Version 3.0
Study Phase:	Phase 3
Brief Title:	Phase 3 study of precemtabart tocentecan with or without bevacizumab compared to trifluridine/tipiracil plus bevacizumab in participants with previously treated metastatic colorectal cancer
Acronym or Abbreviation:	PROCEADE-CRC-03
Coordinating Investigator:	Kanwal Raghav, MD, MBBS The University of Texas MD Anderson Cancer Center, Houston, Texas, US
Sponsor Name and Legal Registered Address:	Sponsor: Affiliates of Merck KGaA, Darmstadt, Germany For all countries, except the US and Canada: Merck Healthcare KGaA, Darmstadt, Germany an affiliate of Merck KGaA, Darmstadt, Germany Frankfurter Strasse 250 64293 Darmstadt, Germany Local Sponsor for Sites in Japan: Merck Biopharma Co., Ltd. Japan an affiliate of Merck KGaA, Darmstadt, Germany Azabudai Hills Mori JP Tower 26F, 1-3-1 Azabudai, Minato-ku, Tokyo 106-0041, Japan In the US and Canada: EMD Serono Research & Development Institute, Inc. an affiliate of Merck KGaA, Darmstadt, Germany 45A Middlesex Turnpike Billerica, MA, 01821, USA

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Keywords	CEACAM5, antibody-drug conjugate, exatecan, M9140, Precem-TcT, Stage 4

Protocol Amendment Summary of Changes

Version Number	Type	Version Date
3.0	Global Amendment	23-February-2026
2.0	Global Amendment	17-December-2025
1.0	Original Protocol	12-December-2025

Protocol Version 3.0 (23 February 2026)

Overall Rationale for the Amendment

The protocol was amended to remove anticoagulants and thrombolytic agents from exclusion criterion #21, add sepsis as potential risk for Precem-TcT, and update the AESI definition.

Section # and Name	Description of Change	Brief Rationale
2.3.1 Risk Assessment	Added sepsis as potential risk for Precem-TcT.	To include the latest safety update.
5.1 Inclusion Criteria 5.2 Exclusion Criteria 6.9.2 Prohibited Medicines	• Specified that "For participants receiving anticoagulants, adequate therapeutic levels as applicable, are required before randomization" (inclusion criterion #6) • Removal of anticoagulants and thrombolytic agents from exclusion criterion #21, and modifications accordingly in Section 6.9.2.	To clarify the eligibility criteria for participants receiving anticoagulants, and in related sections.
1.2 Schedule of Activities 8.6 Biomarkers Appendix 7 Country and Regional Specific Requirements	Added that there are no age restrictions for FFPE tissue block samples, and if only slides are provided, tumor sections must be fresh.	For clarification.
7.2 Participant Discontinuation / Withdrawal from the Study	Deleted references to optional biological samples as these will not be collected in the study.	For clarification.
8.3.7 Adverse Events of Special Interest	AESIs to be collected for all study interventions.	To enable the evaluation of safety signals across the 3 arms in the same manner.
Appendix 5 Clinical Laboratory Tests	Clarified that estimated creatinine clearance at Screening will be based on central assessment of creatinine level.	For clarification.
Appendix 7 Country and Regional Specific Requirements	Deleted the specific requirements for Taiwan related to the minimum age (≥ 20 years) to sign the ICF.	To correct as the minimum age is currently ≥ 18 years, consistent with Section 5.1.
Throughout	Minor editorial and document formatting revisions.	Minor, therefore, have not been summarized.

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Protocol Summary

1 Synopsis

Clinical Study Protocol Title: A randomized, open label, 3-arm Phase 3 study of precemtabart tocentecan with or without bevacizumab compared to trifluridine/tipiracil plus bevacizumab in participants with previously treated metastatic colorectal cancer (PROCEADE-CRC-03)

Brief Title: Phase 3 study of precemtabart tocentecan with or without bevacizumab compared to trifluridine/tipiracil plus bevacizumab in participants with previously treated metastatic colorectal cancer

Rationale: The overall rationale for conducting this study is to address the significant unmet medical need in patients with previously treated metastatic colorectal cancer (mCRC), who have limited treatment options, by investigating the efficacy of precemtabart tocentecan (Precem-TcT) in those patients.

Single agent Precem-TcT has shown encouraging clinical activity in 3L CRC in terms of overall response rate, median progression-free and overall survival. Precem-TcT, with or without bevacizumab has demonstrated a manageable safety profile, consistent with exatecan toxicity with no new, unexpected AEs observed.

Thus, an overall positive benefit-risk ratio justifies the administration of Precem-TcT with or without bevacizumab in participants with mCRC.

Objectives and Estimands:

Objectives	Endpoints	Further Estimand Attributes
Primary		
• To demonstrate improvement in OS with Precem-TcT as single agent compared to FTD-TPI plus bevacizumab. • To demonstrate improvement in OS with Precem-TcT in combination with bevacizumab compared to FTD-TPI plus bevacizumab.	Endpoint: OS is defined as the time from date of randomization to death.	Population: Patients with previously treated mCRC who have been exposed to no more than 2 regimens of systemic therapies that include all standard of care cytotoxic agents and biologic agents according to the molecular profile of their tumor. Treatment: Precem-TcT as single agent or Precem-TcT in combination with bevacizumab vs. FTD-TPI plus bevacizumab. Intercurrent Event Strategy: The endpoint will be analyzed regardless of whether the following intercurrent events had occurred (treatment-policy strategy): • Treatment discontinuation • Start of subsequent anticancer therapy Population-Level Summary: Hazard Ratio

Objectives	Endpoints	Further Estimand Attributes
Secondary		
• To evaluate OS of Precem-TcT as single agent and of Precem-TcT in combination with bevacizumab.	Endpoint: Same as in the primary objective.	Population/Treatment/Intercurrent Event Strategy/Population-Level Summary: Same as in the primary objective.
• To demonstrate improvement in PFS with Precem-TcT as single agent compared to FTD-TPI plus bevacizumab. • To demonstrate improvement in PFS with Precem-TcT in combination with bevacizumab compared to FTD-TPI plus bevacizumab.	Endpoint: PFS is defined as the time from randomization to the first occurrence of any of the following events (occurring within 2 scheduled PFS assessments after last evaluable assessment or randomization): • Disease Progression by Investigator assessment. • Death from any cause.	Treatment/Population/Intercurrent Event Strategy/Population-level Summary: Estimand as defined for main analysis in the primary objective, except for the following change: Intercurrent Event Strategy: Start of subsequent anticancer therapy will be analyzed according to hypothetical strategy, i.e. tumor assessments/deaths after start of subsequent anticancer therapy will not be considered for analysis.
• To evaluate PFS of Precem-TcT as single agent and of Precem-TcT in combination with bevacizumab.	Endpoint: PFS is defined as the time from randomization to the first occurrence of any of the following events (occurring within 2 scheduled PFS assessments after last evaluable assessment or randomization): • Disease Progression by Investigator assessment. • Death from any cause.	Treatment/Population/Intercurrent Event Strategy/Population-level Summary: Estimand as defined for main analysis in the primary objective, except for the following change: Intercurrent Event Strategy: Start of subsequent anticancer therapy will be analyzed according to hypothetical strategy, i.e. tumor assessments/deaths after start of subsequent anticancer therapy will not be considered for analysis.
• To assess improvement in OR with Precem-TcT as single agent compared to FTD-TPI plus bevacizumab. • To assess improvement in OR with Precem-TcT in combination with bevacizumab compared to FTD-TPI plus bevacizumab. • To evaluate OR of Precem-TcT as single agent and of Precem-TcT in combination with bevacizumab.	Endpoint: OR according to RECIST V1.1 assessed by Investigator prior to documented PD.	Population/Treatment: Same as in the primary objective. Intercurrent Event Strategy: • Discontinuation of treatment is considered irrelevant in defining the treatment effect of interest and the endpoint will be analyzed regardless of the occurrence of the intercurrent event (treatment-policy strategy, i.e. ignoring intercurrent event) • Response to treatment prior to start of subsequent anti-cancer therapy is of interest and tumor assessments after the intercurrent event will be ignored (while-not-treated with subsequent anti-cancer therapy strategy) Population-Level Summary: OR

Objectives	Endpoints	Further Estimand Attributes
• To evaluate DoR of Precem-TcT as single agent and of FTD-TPI plus bevacizumab. • To evaluate DoR of Precem-TcT in combination with bevacizumab and of FTD-TPI plus bevacizumab. • To evaluate DoR of Precem-TcT as single agent and of Precem-TcT in combination with bevacizumab.	DoR according to RECIST v1.1 by Investigator assessment, is defined as time from first documentation of objective response to PD or death (due to any cause), occurring within 2 scheduled tumor assessments after last evaluable assessment.	Population: Same as in the primary objective and with objective response according to RECIST V1.1. Treatment: As in the primary objective. Intercurrent Event Strategy: Start of subsequent anticancer therapy will be analyzed according to hypothetical strategy, i.e. tumor assessments/deaths after start of subsequent anticancer therapy will not be considered for analysis. Population-Level Summary: KM estimates
• To evaluate the safety and tolerability with Precem-TcT as single agent compared to FTD-TPI plus bevacizumab. • To evaluate the safety and tolerability with Precem-TcT in combination with bevacizumab compared to FTD-TPI plus bevacizumab. • To evaluate the safety and tolerability with Precem-TcT as single agent compared to Precem-TcT in combination with bevacizumab.	Endpoints: Occurrence of AEs and treatment-related AEs.	Population: Same as in the primary objective.
To characterize the PK profile of Precem-TcT (conjugated antibody and unconjugated payload) as single agent or in combination with bevacizumab.	Endpoints: PK parameters of Precem-TcT (conjugated antibody and unconjugated payload), such as C_{EOI} and $C_{trough.}$	
To characterize the immunogenicity of Precem-TcT.	ADA against Precem-TcT: incidence and titer, as measured by ADA assays.	
To evaluate quality of life with Precem-TcT as single agent or Precem-TcT in combination with bevacizumab compared to FTD-TPI plus bevacizumab using EORTC QLQ-C30 during the investigational treatment phase.	Change from baseline in Global Health Status, physical and role functioning subscale scores of EORTC QLQ-C30 over time up to Cycle 6.	Population: Same as in the primary objective. Intercurrent Event Strategy: • Permanent discontinuation of investigational treatment (while on treatment strategy) • Death: while alive strategy Population-Level Summary: Difference of least squares mean change from baseline

ADA = antidrug antibody; DoR = duration of response; EORTC = European Organization for Research and Treatment of Cancer; FTD-TPI = trifluridine/tipiracil; KM = Kaplan-Meier; mCRC = metastatic colorectal cancer; OR = odds ratio; Precem-TcT = precemtabart tocentecan; QLQ = Quality of Life Questionnaire.

Overall Design: This is a prospective, controlled, open label, randomized, 3-arm parallel group, global Phase 3 study. The study will evaluate the efficacy and safety of Precem-TcT with or without bevacizumab compared to trifluridine/tipiracil (FTD-TPI) plus bevacizumab in participants with mCRC, who were intolerant/refractory to or progressed after systemic therapies.

Brief Summary:

This study aims to address the unmet medical need of patients with mCRC who have previously been treated with irinotecan, oxaliplatin, a fluoropyrimidine, and bevacizumab, by demonstrating an OS prolongation with Precem-TcT as single agent or Precem-TcT in combination with bevacizumab compared to FTD-TPI plus bevacizumab.

- Study duration (per participant): On average approximately 19 months for Arms 1 and 2 and 14 months for Arm 3 (including Screening, Treatment, and Follow-up period).
- Visit Frequency: Approximately every 3 weeks (Arms 1 and 2) and every 2 weeks for Arm 3.

Number of Participants: Approximately 1,020 participants will be randomized.

Study Intervention Groups and Duration:

Participants who meet the eligibility criteria will be randomized using permuted block allocation in a 1:1:1 ratio between

- Arm 1: single agent Precem-TcT
- Arm 2: Precem-TcT in combination with bevacizumab
- Arm 3: FTD-TPI in combination with bevacizumab

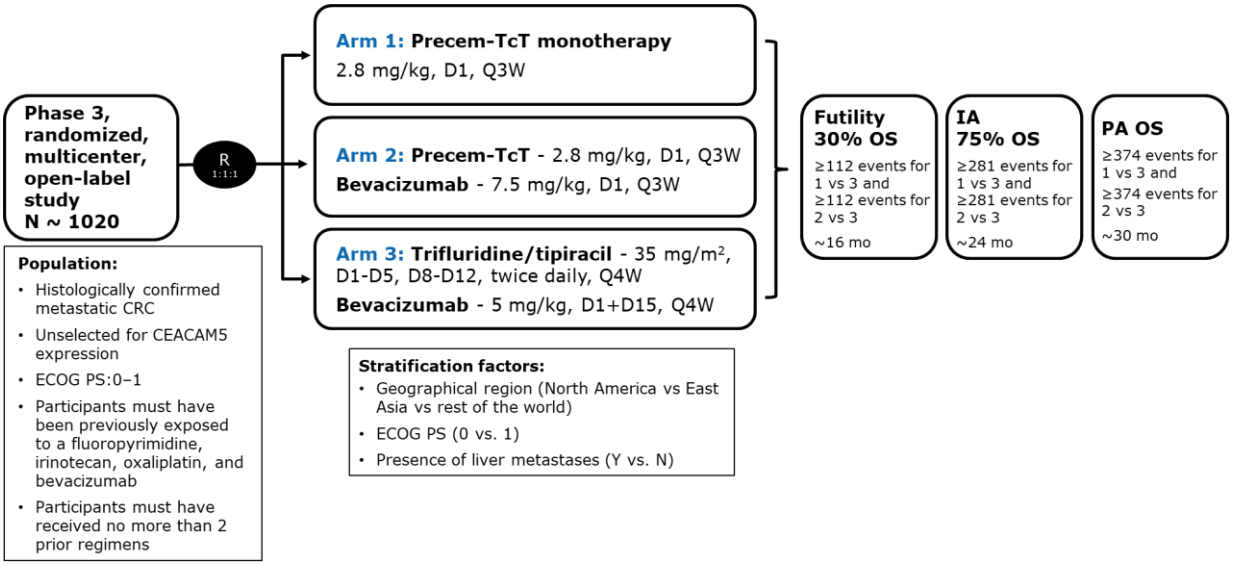
Randomization will be stratified according to geographical region (North America, East Asia, and rest of the world), ECOG PS (0 vs. 1) and presence of liver metastases at the time of randomization (yes vs. no).

Treatment will continue until disease progression, death, unacceptable toxicity, withdrawal of consent, or any criterion for treatment discontinuation, whatever comes first.

Data and Safety Monitoring /Other Committee: Yes

1.1 Schema

Figure 1 Study Schema



CEACAM = carcinoembryonic antigen-related cell adhesion molecules; D = day; ECOG PS = Eastern Cooperative Oncology Group Performance Status; IA = interim analysis; mCRC = metastatic colorectal cancer; mo = months; OS = overall survival; PA = primary analysis; Precem-TcT = precemtabart tocentecan; q3w = every 3 weeks; q4w = every 4 weeks; R = randomization.

1.2 Schedule of Activities

1.2.1 Arm 1: Precemtabart Tocentecan Monotherapy

Table 1 Schedule of Activities of Precemtabart Tocentecan Monotherapy q3w (Arm 1)

Assessments & Procedures	**Precem-TcT Monotherapy (Arm 1) 1 Cycle = 21 Days**															
Cycle	**Screening**		**1**			**2**		**3**		**4-6**		**≥ 7**	**EoSI**	**Safety FU**	**Survival Follow-up**	**Notes**
Cycle Day			**1**	**8**	**15**	**1**	**15**	**1**	**15**	**1**	**15**	**1**	≤ 7 days after decision of treatment discontinuation	30 days after last dose	Every 90 days after Safety FU	
Visit Window (days)	Up to 28 days before C1D1	Up to 7 days before C1D1	-	**±2**	**±2**	**±2**	**±2**	**±2**	**±2**	**±2**	**±2**	**±2**		**±3**	**±14**	
Informed consent	X															
Inclusion and exclusion criteria	X		X													Recheck before randomization
Randomization			X													Within 3 days before or on C1D1.
Study intervention: Precem-TcT			X			X		X		X		X				Dosing q3w (see Section 6.1.1.1).
Demography	X															
Physical examination		X	X	X	X	X		X		X		X	X			2-day window allowed prior to C1D1. See Section 8.2.1.
Past and current medical history	X															
Disease history	X															
Prior anticancer therapies	X															

Assessments & Procedures	**Precem-TcT Monotherapy (Arm 1) 1 Cycle = 21 Days**															
Cycle	**Screening**		**1**			**2**		**3**		**4-6**		**≥ 7**	**EoSI**	**Safety FU**	**Survival Follow-up**	**Notes**
Cycle Day			**1**	**8**	**15**	**1**	**15**	**1**	**15**	**1**	**15**	**1**	≤ 7 days after decision of treatment discontinuation	30 days after last dose	Every 90 days after Safety FU	
Visit Window (days)	Up to 28 days before C1D1	Up to 7 days before C1D1	-	**±2**	**±2**	**±2**	**±2**	**±2**	**±2**	**±2**	**±2**	**±2**		**±3**	**±14**	
Archival tumor tissue collection	X															If archival tumor tissue is not available, fresh biopsy sample is required. See Section 8.6 for further details.
Pregnancy test (POCBP only)		X	X					X		X		X	X	X		Serum only at Screening. Urine or serum on all other visits allowed. During treatment period to be performed on D1 of every other cycle starting on C1D1 (see Section 8.2.4).
HIV, hepatitis B, and C screening	X															HIV: at the Investigator's discretion unless locally required.
Hematology and biochemistry		X	X	X	X	X	X	X	X	X	X	X	X	X		2-day window allowed prior to C1D1. See Section 8.2.4 and Appendix 5.
Coagulation		X	X			X		X		X		X	X			
CRP		X	X			X		X		X		X	X			
Iron deficiency testing (ferritin, TSAT)	X															See Section 8.2.4 and Appendix 5.

Assessments & Procedures	**Precem-TcT Monotherapy (Arm 1) 1 Cycle = 21 Days**														
Cycle	**Screening**		**1**			**2**		**3**		**4-6**		**≥ 7**	**EoSI**	**Safety FU**	**Survival Follow-up**	**Notes**
Cycle Day			**1**	**8**	**15**	**1**	**15**	**1**	**15**	**1**	**15**	**1**	≤ 7 days after decision of treatment discontinuation	30 days after last dose	Every 90 days after Safety FU	
Visit Window (days)	Up to 28 days before C1D1	Up to 7 days before C1D1	-	**±2**	**±2**	**±2**	**±2**	**±2**	**±2**	**±2**	**±2**	**±2**		**±3**	**±14**	
Routine urinalysis		X	X			X		X		X		X	X			2-day window allowed prior to C1D1. Urinalysis per dipstick testing. Microscopic examination if blood or protein abnormality. Protein analysis if dipstick 2+ (see Section 8.2.4 and Appendix 5).
ECOG performance status		X	X			X		X		X		X	X	X		2-day window allowed prior to C1D1.
Vital signs		X	X	X	X	X	X	X	X	X	X	X	X	X		Weight and BMI will be assessed at Screening and on D1 of each cycle (2-day window prior to D1 allowed). Height is only assessed at Screening (see Section 8.2.2).
12-lead ECG	X		X					X		X		X	X	X		During treatment period to be performed on D1 of every other cycle starting on C1D1 (see Section 8.2.3).
CT Scan / MRI	At Screening and for response assessment via RECIST V1.1; tumors will be assessed every 6 weeks (± 7 days) following the C1D1 visit until the 7th scheduled tumor scan (i.e. from screening until Evaluation 6 inclusive), subsequently every 12 weeks (± 7 days), until radiologic disease progression, death, lost to follow-up, withdrawal of consent, or End of Study, whichever comes first, regardless of study intervention delays, discontinuation, or subsequent anticancer therapies (Section 8.1.1).															Window for the Screening tumor assessment is up to 14 days before C1D1.

Assessments & Procedures	**Precem-TcT Monotherapy (Arm 1) 1 Cycle = 21 Days**															
Cycle	**Screening**		**1**			**2**		**3**		**4-6**		**≥ 7**	**EoSI**	**Safety FU**	**Survival Follow-up**	**Notes**
Cycle Day			**1**	**8**	**15**	**1**	**15**	**1**	**15**	**1**	**15**	**1**	≤ 7 days after decision of treatment discontinuation	30 days after last dose	Every 90 days after Safety FU	
Visit Window (days)	Up to 28 days before C1D1	Up to 7 days before C1D1	-	**±2**	**±2**	**±2**	**±2**	**±2**	**±2**	**±2**	**±2**	**±2**		**±3**	**±14**	
EQ-5D-5L		X	X			X		X		X		X	X			Screening assessment before randomization and within 7 days prior C1D1. See Section 8.1.2.
EORTC QLQ-C30		X	X			X		X		X		X	X			
EORTC QLQ C30 (7-question subset only)				X	X		X		X		X					
Custom EORTC form (5 questions)		X	X	X	X	X	X	X	X	X	X	X	X			
PK	See Table 2 for sampling timepoints and Sections 8.4 and 8.6.															
ADA																
Serum biomarker sample																See Appendix 7 for China-specific guidance.
Subsequent anticancer therapies														X	X	
Survival Follow-up															X	Will be done (e.g. by phone) until death or EOS, whichever comes first. See also Section 4.4.
AE and SAE review	<==========															From the time of signing ICF to Safety Follow-up Visit.
Concomitant medication and procedures review	<==========															

ADA = antidrug antibody; AE = adverse event; BMI = body mass index; C = cycle; CRP = C-reactive protein; CT = computed tomography; D = day; ECG = electrocardiogram; ECOG PS = Eastern Cooperative Oncology Group Performance Status; EORTC = European Organization for Research and Treatment of Cancer; EoS = end of study; EoSI = end of study intervention; FU = follow-up; ICF = Informed Consent Form; MRI = magnetic resonance imaging; PK = pharmacokinetics; POCBP = participants of childbearing potential; Precem-TcT = precemtabart tocentecan; PRO = patient-reported outcomes; q3w =every 3 weeks; QLQ = quality of life questionnaire; SAE = serious adverse event; TSAT = transferrin saturation.

Table 2 **Schedule of PK, Serum Biomarkers, and ADA Assessments for Precemtabart Tocentecan Monotherapy (Arm 1)**

Visit Day	Time h (± h)	PK Precem-TcT	Serum Biomarker	ADA	Notes
Screening			X		Up to 28 days before C1D1.
C1D1	**Predose (-4 / 0)**	X	X	X	At visits where assessment time points for vital signs, ECG, and PK coincide, vital signs, and ECG are performed before PK sampling. All timepoints are based on the start of Precem-TcT infusion. Actual collection dates and times should be recorded in the CRF along with the times of start and EOI. An additional unscheduled serum biomarker sample is required in case a CR has been observed. It should be collected as soon as possible after the tumor assessment. Serum Biomarker: See Appendix 7 for China-specific guidance.
	EOI (within 0.25 of EOI)	X			
C1D8	**168 (± 48)**	X			
C1D15	**336 (± 48)**	X			
C2D1	**Predose (-4 / 0)**	X	X	X	
C3D1	**Predose (-4 / 0)**	X	X	X	
	EOI (within 0.25 of EOI)	X			
C3D15	**336 (± 48)**	X			
C4D1	**Predose (-4 / 0)**	X	X	X	
From C8D1 onwards, every 4 cycles on D1 until treatment discontinuation	**Predose (-4 / 0)**	X	X	X	
EoSI visit	**Within 7 days after decision to discontinue treatment**	X	X	X	

ADA = antidrug antibodies; C = cycle; CR = complete response; CRF = case report form; D = day; ECG = electrocardiogram; EOI = end of infusion; EoSI = end of study intervention; PK = pharmacokinetics; Precem-TcT = precemtabart tocentecan.

1.2.2 Arm 2: Precemtabart Tocentecan plus Bevacizumab

Table 3 Schedule of Activities of Precemtabart Tocentecan plus Bevacizumab q3w (Arm 2)

Assessments and Procedures	**Precem-TcT Plus Bevacizumab (Arm 2) 1 Cycle = 21 Days**														**Notes**
Cycle	**Screening**		**1**			**2**		**3**		**4-6**		**≥ 7**	**EoSI**	**Safety FU**	**Survival Follow-up**	
Cycle Day			**1**	**8**	**15**	**1**	**15**	**1**	**15**	**1**	**15**	**1**	≤7 days after decision of treatment discontinuation	30 days after last dose	Every 90 days after Safety FU	
Visit Window (days)	Up to 28 Days Before C1D1	Up to 7 Days Before C1D1	**-**	**±2**	**±2**	**±2**	**±2**	**±2**	**±2**	**±2**	**±2**	**±2**		**±3**	**±14**	
Informed consent	X															
Inclusion and exclusion criteria	X		X													Recheck before randomization.
Randomization			X													Within 3 days before or on C1D1.
Study intervention Precem-TcT and bevacizumab			X			X		X		X		X				Dosing q3w (see Section 6.1.1).
Demography	X															
Physical examination		X	X	X	X	X		X		X		X	X			2-day window allowed prior to C1D1. See Section 8.2.18.2.1.
Past and current medical history	X															
Disease history	X															
Prior anticancer therapies	X															

Assessments and Procedures	**Precem-TcT Plus Bevacizumab (Arm 2) 1 Cycle = 21 Days**														**Notes**
Cycle	**Screening**		**1**			**2**		**3**		**4-6**		**≥ 7**	**EoSI**	**Safety FU**	**Survival Follow-up**	
Cycle Day			**1**	**8**	**15**	**1**	**15**	**1**	**15**	**1**	**15**	**1**	≤7 days after decision of treatment discontinuation	30 days after last dose	Every 90 days after Safety FU	
Visit Window (days)	Up to 28 Days Before C1D1	Up to 7 Days Before C1D1	**-**	**±2**	**±2**	**±2**	**±2**	**±2**	**±2**	**±2**	**±2**	**±2**		**±3**	**±14**	
Archival tumor tissue collection	X															If archival tumor tissue is not available, fresh biopsy sample is required. See Section 8.6 for further details.
Pregnancy test (POCBP only)		X	X					X		X		X	X	X		Serum only at Screening. Urine or serum on all other visits allowed. During treatment period to be performed on D1 of every other cycle starting on C1D1 (see Section 8.2.4).
HIV, hepatitis B, and C screening	X															HIV: at the Investigator's discretion unless locally required.
Hematology and biochemistry		X	X	X	X	X	X	X	X	X	X	X	X	X		2-day window allowed prior to C1D1. See Section 8.2.4 and Appendix 5.
Coagulation		X	X			X		X		X		X	X			
CRP		X	X			X		X		X		X	X			
Iron deficiency testing (ferritin, TSAT)	X															See Section 8.2.4 and Appendix 5.

Assessments and Procedures	**Precem-TcT Plus Bevacizumab (Arm 2) 1 Cycle = 21 Days**														**Notes**
Cycle	**Screening**		**1**			**2**		**3**		**4-6**		**≥ 7**	**EoSI**	**Safety FU**	**Survival Follow-up**	
Cycle Day			**1**	**8**	**15**	**1**	**15**	**1**	**15**	**1**	**15**	**1**	≤7 days after decision of treatment discontinuation	30 days after last dose	Every 90 days after Safety FU	
Visit Window (days)	Up to 28 Days Before C1D1	Up to 7 Days Before C1D1	**-**	**±2**	**±2**	**±2**	**±2**	**±2**	**±2**	**±2**	**±2**	**±2**		**±3**	**±14**	
Routine urinalysis		X	X			X		X		X		X	X			2-day window allowed prior to C1D1. Urinalysis per dipstick testing. Microscopic examination if blood or protein abnormality. Protein analysis if dipstick 2+ (see Section 8.2.4 and Appendix 5).
ECOG performance status		X	X			X		X		X		X	X	X		2-day window allowed prior to C1D1.
Vital signs		X	X	X	X	X	X	X	X	X	X	X	X	X		Weight and BMI will be assessed at Screening and on D1 of each cycle (2-day window prior to D1 allowed). Height is only assessed at Screening (see Section 8.2.2)
12-lead ECG	X		X					X		X		X	X	X		During treatment period to be performed on D1 of every other cycle starting on C1D1 (see Section 8.2.3).
CT Scan / MRI	At Screening and for response assessment via RECIST v1.1; tumors will be assessed every 6 weeks (± 7 days) following the C1D1 visit until the 7th scheduled tumor scan (i.e. from screening until Evaluation 6 inclusive), subsequently every 12 weeks (± 7 days), until radiologic disease progression, death, lost to follow-up, withdrawal of consent, or End of Study, whichever comes first, regardless of study intervention delays, discontinuation, or subsequent anticancer therapies (Section 8.1.1).															Window for the Screening tumor assessment is up to 14 days before C1D1.
EQ-5D-5L		X	X			X		X		X		X	X			Screening assessment before randomization and
EORTC QLQ-C30		X	X			X		X		X		X	X			

Assessments and Procedures	**Precem-TcT Plus Bevacizumab (Arm 2) 1 Cycle = 21 Days**															**Notes**
Cycle	**Screening**		**1**			**2**		**3**		**4-6**		**≥ 7**	**EoSI**	**Safety FU**	**Survival Follow-up**	
Cycle Day			**1**	**8**	**15**	**1**	**15**	**1**	**15**	**1**	**15**	**1**	≤7 days after decision of treatment discontinuation	30 days after last dose	Every 90 days after Safety FU	
Visit Window (days)	Up to 28 Days Before C1D1	Up to 7 Days Before C1D1	**-**	**±2**	**±2**	**±2**	**±2**	**±2**	**±2**	**±2**	**±2**	**±2**		**±3**	**±14**	
EORTC QLQ C30 (7-question subset only)				X	X		X		X		X					within 7 days prior C1D1. See Section 8.1.2
Custom EORTC form (5 questions)		X	X	X	X	X	X	X	X	X	X	X	X			
PK	See Table 4 for sampling timepoints and Sections 8.4 and 8.3.78.6.															
ADA																
Serum biomarker sample																See Appendix 7 for China-specific guidance.
Subsequent anticancer therapies														X	X	
Survival Follow-up															X	Will be done (e.g. by phone) until death or EOS, whichever comes first. See also Section4.4.
AE and SAE review	<==========															From the time of signing ICF to Safety Follow-up Visit
Concomitant medication and procedures review	<==========															

ADA = antidrug antibody; AE = adverse event; BMI = body mass index; C = cycle; CRP = C-reactive protein; CT = computed tomography; D = day; ECG = electrocardiogram; ECOG PS = Eastern Cooperative Oncology Group Performance Status; EORTC = European Organization for Research and Treatment of Cancer; EoS = end of study; EoSI = end of study intervention; FU = follow-up; ICF = Informed Consent Form; MRI = magnetic resonance imaging; PK = pharmacokinetics; POCBP = participants of childbearing potential; Precem-TcT = precemtabart tocentecan; PRO = patient-reported outcomes; q3w =every 3 weeks; QLQ = quality of life questionnaire; SAE = serious adverse event; TSAT = transferrin saturation.

Table 4 **Schedule of PK, Serum Biomarkers, and ADA Assessments of Precemtabart Tocentecan q3w plus Bevacizumab (Arm 2)**

Treatment Day	Time h (± h)	PK Precem-TcT	Serum Biomarkers	ADA[a]	Notes
Screening			X		Up to 28 days before C1D1.
C1D1	**Predose (-4 / 0)**	X	X	X	At visits where assessment for vital signs, ECG, and PK time points coincide, vital signs, and ECG are performed before PK sampling. All timepoints are based on the start of Precem-TcT infusion. Actual collection dates and times should be recorded in the CRF along with the times of start and EOI. [a] only ADA against Precem-TcT will be measured. An additional unscheduled serum biomarker sample is required in case a CR has been observed. It should be collected as soon as possible after the tumor assessment. Serum Biomarker: See Appendix 7 for China-specific guidance.
	EOI (within 0.25 of EOI)	X			
C1D8	**168 (± 48)**	X			
C1D15	**336 (± 48)**	X			
C2D1	**Predose (-4 / 0)**	X	X	X	
C3D1	**Predose (-4 / 0)**	X	X	X	
	EOI (within 0.25 of EOI)	X			
C3D15	**336 (± 48)**	X			
C4D1	**Predose (-4 / 0)**	X	X	X	
From C8D1 onwards, every 4 cycles on D1 until treatment discontinuation	**Predose (-4 / 0)**	X	X	X	
EoSI visit	**Within 7 days after decision to discontinue treatment**	X	X	X	

ADA = antidrug antibodies; C = cycle; CR = complete response; CRF = case report form; D = day; ECG = electrocardiogram; EOI = end of infusion; EoSI = end of study intervention; PK = pharmacokinetics; Precem-TcT = precemtabart tocentecan.

1.2.3 Arm 3: Trifluridine/Tipiracil plus Bevacizumab

Table 5 Schedule of Activities of Trifluridine/Tipiracil plus Bevacizumab (Arm 3)

Assessments & Procedures	**Trifluridine/Tipiracil Plus Bevacizumab (Arm 3) 1 Cycle = 28 Days**															
Cycle	**Screening**		**1**			**2**		**3**		**4-6**		**≥ 7**		**EoSI**	**Safety FU**	**Survival Follow-up**	**Notes**
Cycle Day			**1**	**8**	**15**	**1**	**15**	**1**	**15**	**1**	**15**	**1**	**15**	≤7 days after decision of treatment discontinuation	30 days after last dose	Every 90 days after Safety FU	
Visit Window (days)	Up to 28 Days Before C1D1	Up to 7 Days Before C1D1	**-**	**±2**	**±2**	**±2**	**±2**	**±2**	**±2**	**±2**	**±2**	**±2**	**±2**		**±3**	**±14**	
Informed consent	X																
Inclusion and exclusion criteria	X		X														Recheck before randomization.
Randomization			X														Within 3 days before or on C1D1.
Study intervention bevacizumab			X		X	X	X	X	X	X	X	X	X				Dosing q2w (D1 and D15 within a 4-week cycle).
Study intervention FTD-TPI			Oral intake of FTD-TPI bid on D1 to D5 and D8 to D12, q4w.														See Sections 6.1.1 and 6.4 for details on dosing and dosing diary.
Demography	X																
Physical examination		X	X	X	X	X		X		X		X		X			2-day window allowed prior to C1D1. See Section 8.2.1.
Past and current medical history	X																
Disease history	X																
Prior anticancer therapies	X																

Assessments & Procedures	**Trifluridine/Tipiracil Plus Bevacizumab (Arm 3) 1 Cycle = 28 Days**															
Cycle	**Screening**		**1**			**2**		**3**		**4-6**		**≥ 7**		**EoSI**	**Safety FU**	**Survival Follow-up**	**Notes**
Cycle Day			**1**	**8**	**15**	**1**	**15**	**1**	**15**	**1**	**15**	**1**	**15**	≤7 days after decision of treatment discontinuation	30 days after last dose	Every 90 days after Safety FU	
Visit Window (days)	Up to 28 Days Before C1D1	Up to 7 Days Before C1D1	**-**	**±2**	**±2**	**±2**	**±2**	**±2**	**±2**	**±2**	**±2**	**±2**	**±2**		**±3**	**±14**	
Archival tumor tissue collection	X																If archival tumor tissue is not available, fresh biopsy sample is required. See Section 8.6 for further details.
Pregnancy test (POCBP only)		X	X					X		X		X		X	X		Serum only at Screening. Urine or serum on all other visits allowed. During treatment period to be performed on D1 of every other cycle starting on C1D1 (see Section 8.2.4).
HIV, hepatitis B, and C screening	X																HIV: at the Investigator's discretion unless locally required.
Hematology		X	X	X	X	X	X	X	X	X	X	X	X	X	X		2-day window allowed prior to C1D1. See Section 8.2.4 and Appendix 5.
Biochemistry		X	X	X	X	X	X	X	X	X	X	X		X	X		
Coagulation		X	X			X		X		X		X		X			
CRP		X	X			X		X		X		X		X			
Iron deficiency testing (ferritin, TSAT)	X																See Section 8.2.4 and Appendix 5.
Routine urinalysis		X	X			X		X		X		X		X			2-day window allowed prior to C1D1. Urinalysis per dipstick testing. Microscopic examination if blood or protein abnormality. Protein analysis if dipstick 2+ (see Section 8.2.4 and Appendix 5).
ECOG performance status		X	X			X		X		X		X		X	X		2-day window allowed prior to C1D1.

Assessments & Procedures	**Trifluridine/Tipiracil Plus Bevacizumab (Arm 3) 1 Cycle = 28 Days**															
Cycle	**Screening**		**1**			**2**		**3**		**4-6**		**≥ 7**		**EoSI**	**Safety FU**	**Survival Follow-up**	**Notes**
Cycle Day			**1**	**8**	**15**	**1**	**15**	**1**	**15**	**1**	**15**	**1**	**15**	≤7 days after decision of treatment discontinuation	30 days after last dose	Every 90 days after Safety FU	
Visit Window (days)	Up to 28 Days Before C1D1	Up to 7 Days Before C1D1	**-**	**±2**	**±2**	**±2**	**±2**	**±2**	**±2**	**±2**	**±2**	**±2**	**±2**		**±3**	**±14**	
Vital signs		X	X	X	X	X	X	X	X	X	X	X	X	X	X		Weight will be assessed at Screening and on D1 and D15 of each cycle (2-day window prior to D1 allowed). BSA will be assessed at Screening and on D1 of each cycle (2-day window prior D1 allowed) (see Section 6.1.1). Height is only assessed at Screening (see Section 8.2.2).
12-lead ECG	X		X					X		X		X		X	X		During treatment period to be performed on D1 of every other cycle starting on C1D1 (see Section 8.2.3).
CT Scan / MRI	At Screening and for response assessment via RECIST v1.1; tumors will be assessed every 6 weeks (± 7 days) following the C1D1 visit until the 7th tumor scan (Screening, Evaluation 1, Evaluation 2, Evaluation 3, Evaluation 4, Evaluation 5, and Evaluation 6). Subsequent tumor assessments will be done every 12 weeks (± 7 days) until radiologic disease progression, death, lost to follow-up, withdrawal of consent, or End of Study, whichever comes first, regardless of study intervention delays, discontinuation, or subsequent therapies (Section 8.1.1).																Window for the Screening tumor assessment is up to 14 days before C1D1.
EQ-5D-5L		X	X			X		X		X		X		X			Screening assessment before randomization and within 7 days prior to C1D1. See Section 8.1.2.
EORTC QLQ-C30		X	X			X		X		X		X		X			
EORTC QLQ C30 (7-question subset only)				X	X		X		X		X		X				
Custom EORTC form (5 questions))		X	X	X	X	X	X	X	X	X	X	X	X	X			

Assessments & Procedures	**Trifluridine/Tipiracil Plus Bevacizumab (Arm 3) 1 Cycle = 28 Days**															
Cycle	**Screening**		**1**			**2**		**3**		**4-6**		**≥ 7**		**EoSI**	**Safety FU**	**Survival Follow-up**	**Notes**
Cycle Day			**1**	**8**	**15**	**1**	**15**	**1**	**15**	**1**	**15**	**1**	**15**	≤7 days after decision of treatment discontinuation	30 days after last dose	Every 90 days after Safety FU	
Visit Window (days)	Up to 28 Days Before C1D1	Up to 7 Days Before C1D1	**-**	**±2**	**±2**	**±2**	**±2**	**±2**	**±2**	**±2**	**±2**	**±2**	**±2**		**±3**	**±14**	
Serum biomarker sample	X		X			X		X		X		X		X			From C4D1 onwards, every 4 cycles on D1 until treatment discontinuation. An additional unscheduled serum biomarker sample is required in case a CR has been observed. It should be collected as soon as possible after the tumor assessment. See Appendix 7 for China-specific guidance.
Subsequent anticancer therapies															X	X	
Survival Follow-up																X	Will be done (e.g. by phone) until death or EOS, whichever comes first. See also Section 4.4.
AE and SAE review	<==========																From the time of signing ICF to Safety Follow-up Visit.
Concomitant medication and procedures review	<==========																

ADA = antidrug antibody; AE = adverse event; BMI = body mass index; C = cycle; CRP = C-reactive protein; CT = computed tomography; D = day; ECG = electrocardiogram; ECOG PS = Eastern Cooperative Oncology Group Performance Status; EORTC = European Organization for Research and Treatment of Cancer; EoS = end of study; EoSI = end of study intervention; FTD-TPI = trifluridine/tipiracil; FU = follow-up; ICF = Informed Consent Form; MRI = magnetic resonance imaging; PK = pharmacokinetics; POCBP = participants of childbearing potential; Precem-TcT = precemtabart tocentecan; PRO = patient-reported outcomes; q2w = every 2 weeks; q4w = every 4 weeks; QLQ = quality of life questionnaire; SAE = serious adverse event; TSAT = transferrin saturation.

2 Introduction

Precemtabart tocentecan (Precem-TcT, formerly known as M9140) is an ADC specific to CEACAM5 (also known as CEA or CD66) with the TOP1 inhibitor exatecan as payload. The molecule is a fully homogenous product comprising 8 exatecan molecules per antibody, linked via a β-glucuronidase-cleavable linker.

Precem-TcT is being developed for the treatment of patients with advanced solid tumors.

Detailed information on the chemistry, pharmacology, efficacy, and safety of Precem-TcT is provided in the IB.

2.1 Study Rationale

The overall rationale for conducting this study is to address the unmet medical need in patients with mCRC who have limited treatment options, as outlined below, by investigating the efficacy of Precem-TcT in those patients:

- CEACAM5 is a well-known member of the CEACAM family. CEACAM5 has limited expression in adult normal tissues, but is expressed at high levels in various adenocarcinomas, particularly in CRC, GC, GEJC, NSCLC, and pancreatic cancers; therefore, it provides an attractive target for the development of ADCs, such as Precem-TcT.

- In in vivo studies in patient-derived xenograft models, administration of Precem-TcT demonstrated strong antitumor activity in CRC, GC, PDAC, and NSCLC tumors expressing CEACAM5. In addition, the bystander effect observed with Precem-TcT is expected to further enhance antitumor activity (Raab-Westphal 2024).

- Utilizing a proprietary IHC assay for semiquantitative CEACAM5 detection, CEACAM5^{high} is defined as a 2+/3+ membrane staining intensity in 50% or more of tumor cells. Based on this threshold in in-house prevalence analyses, 99% of CRC cases (n=89) were classified as CEACAM5^{high}, supporting an all-comer approach in this indication (Sponsor data on file).

- Precem-TcT, either as single agent or in combination with bevacizumab has demonstrated a manageable toxicity profile, consistent with exatecan toxicity with no new, unexpected AEs observed (Kopetz 2025a; Kopetz 2025b; Kopetz 2025c; Sponsor data on file). Precem-TcT-related AEs can be adequately managed with routine clinical supportive measures.

- Single agent Precem-TcT has shown encouraging efficacy in a heavily pretreated CRC population with ORR, mPFS and mOS that benchmarks very well with currently approved SoC therapies (Kopetz 2025a; Kopetz 2025c).

The outcome for patients with mCRC who have been exposed to irinotecan, oxaliplatin, 5-FU, and a VEGF inhibitor remains poor. Median OS with SoC approved therapies remains below 1 year and ORR is 1-6%. Thus, a high unmet medical need remains for that population.

Thus, an overall positive benefit-risk ratio justifies the administration of Precem-TcT either as single agent or in combination with bevacizumab in patients with mCRC without need to test for CEACAM5 expression.

2.2 Background

Outcome for patients with mCRC in 3L setting, who have been already exposed to irinotecan, oxaliplatin, 5-FU, and a VEGF inhibitor remains poor. Single agent approved therapies such as regorafenib, FTD-TPI, and fruquintinib have limited efficacy with an ORR of ≈2% and less than 3 months OS prolongation vs. placebo (Dasari 2023; Mayer 2015; Grothey 2013). The combination of FTD-TPI with bevacizumab has reported an ORR of approximately 6% while mOS still remains below 1 year (Prager 2023). Thus, a high unmet need exists for those patients.

Precem-TcT belongs to a class of highly potent biopharmaceutical ADCs, designed as targeted therapy for the treatment of solid cancer, and is the first anti-CEACAM5 ADC with the TOP1 inhibitor exatecan as payload that enters Phase 3 development in mCRC. CEACAMs are a family of 12 immunoglobulin-related proteins physiologically expressed on many epithelial tissues, where they act as modulators of different processes such as cell adhesion, differentiation, proliferation, and survival (Tchoupa 2014). CEACAM5 has limited expression in adult normal tissues but is expressed at high levels in adenocarcinomas, particularly in CRC; therefore, it provides an attractive target for the development of ADCs, such as Precem-TcT.

Precem-TcT is a recombinant human IgG1 monoclonal antibody with reduced effector functions, coupled to a potent TOP1 inhibitor payload, exatecan, with a high drug-to-antibody ratio of 8. The primary mechanism of action of Precem-TcT is targeted killing of tumor cells expressing CEACAM5 by affecting DNA replication and transcription. Upon CEACAM5 binding, the target-ADC complex is internalized into the cell and translocated to the lysosomal compartment where the linker is enzymatically cleaved and the cytotoxic substance exatecan is released from the ADC to induce tumor cell death. Exatecan is a camptothecin derivative that acts as an inhibitor of the enzyme TOP1, comparable to known chemotherapeutics like irinotecan and topotecan. TOP1 relaxes supercoiled DNA during replication and transcription by DNA nicking. TOP1 inhibitors are extensively used to treat a diverse range of cancers and act by trapping the TOP1-DNA cleavage complexes, which results in DNA damage during replication or transcription, thereby leading to tumor cell death (Pommier 2006; Mitsui 1995).

As of 02 September 2025, clinical data from ongoing Part 2A (2.8 mg/kg q3w DL) of the Precem TcT PROCEADE-CRC-01 (MS202329_0001; NCT05464030) Phase 1 study in heavily previously treated patients with mCRC have shown an ORR of 31.0% (95% CI: 15.3–50.8; confirmed: 20.7% [95% CI: 8.0–39.7]), and a median PFS of 6.9 months (95% CI: 4.4, 9.5), while median OS was not reached, after a median follow-up of 13.1 months (Kopetz 2025a, Kopetz 2025c). These results benchmark well with all approved treatment options in that setting (Dasari 2023, Mayer 2015, Grothey 2013, Prager 2023). Moreover, Precem-TcT has shown a more favorable tolerability profile compared to approved therapies in that setting, with hematological toxicities being the only severe toxicity observed.

2.3 Benefit/Risk Assessment

More detailed information about the known and expected benefits and risks and reasonably expected adverse events of Precem-TcT may be found in Section 4.2 and the IB. Based on the available nonclinical and clinical data to date, the conduct of the study, as specified in this protocol, is considered justified.

2.3.1 Risk Assessment

Table 6 Identified and Potential Risks and Their Management

Identified and Potential Risks of Clinical Significance	Summary of Data/Rationale for Risk	Mitigation Strategy
Study Intervention: Precem-TcT		
Identified Risks		
Hematologic toxicity (i.e. anemia, neutropenia, leukopenia, febrile neutropenia, and neutropenic infectious complications, thrombocytopenia, lymphopenia)	**Precem-TcT** Clinical findings (PROCEADE-CRC-01 Study, dose escalation and dose expansion): • Most common hematologic Grade ≥ 3 TEAEs: neutrophil count decreased/neutropenia, anemia, white blood cell count decreased/leukopenia, and platelet count decreased/thrombocytopenia Cynomolgus monkeys: • Changes in hematolymphoid system (bone marrow, thymus, spleen, and lymph nodes) at Precem-TcT doses ≥ 30 mg/kg • Transient decrease of reticulocytes and neutrophils at Precem-TcT doses ≥ 10 mg/kg, • RBC mass reduction (RBC, Ht, Hb) in females only at Precem-TcT doses ≥ 24 mg/kg **Exatecan** Clinical findings (Rowinsky 2005; de Jager 2000): • Principal DLT: myelosuppression, particularly neutropenia • Anemia, thrombocytopenia, lymphopenia may also occur less frequently	• Inclusion criteria requiring adequate hematologic function. • BMI cap-based dosing to prevent excessive exposure and potential increased risk for TRAEs in obese participants. • Close monitoring of hematology parameters throughout the study. • Recommendation for use of G-CSF as primary or secondary prophylaxis, as per Section 6.5.2. • Hematologic toxicity events should be managed and treated appropriately (e.g. hematopoietic growth factors or blood transfusion treatment) based on Investigator's judgment and guidance from Sections 6.5 and 7.1.
Gastrointestinal toxicity (i.e. diarrhea, constipation, nausea, vomiting, stomatitis)	**Precem-TcT** Clinical findings (PROCEADE-CRC-01 Study, dose escalation and dose expansion): • Most common TEAEs: nausea, vomiting, and diarrhea (majority of cases are mild to moderate [Grade 1 and 2]) Cynomolgus monkeys: • Changes of the digestive tract (e.g. mucosal atrophy of colon and larynx, atrophy of acinar cells of the exocrine pancreas) at Precem-TcT	• Inclusion criteria requiring adequate organ function and biochemistry. • Exclusion criteria: Participants with ileus Grade >1 or chronic inflammatory bowel disease (e.g. ulcerative colitis, Crohn's disease) and/or bowel obstruction, or participants with chronic gastrointestinal disorders • Mandatory antiemetic prophylaxis

Identified and Potential Risks of Clinical Significance	Summary of Data/Rationale for Risk	Mitigation Strategy
	doses ≥30 mg/kg, occasionally with diarrhea **Exatecan** Clinical findings (Rowinsky 2005; de Jager 2000): • GI toxicity very common • Generally mild to moderate (nausea and vomiting)	(see Section 6.5.5.1). Routine monitoring of AEs and SAEs throughout the study. These GI AEs should be treated according to best medical practice and guidance from Sections 6.5.4 and 6.5.5.1. Treatment of stomatitis is at the discretion of Investigators and according to institutional guidelines or guidance from Sections 6.5 and 7.1.
Fatigue	**Precem-TcT** Clinical findings (PROCEADE-CRC-01 Study, dose escalation and dose expansion): • Fatigue: mild to moderate (Grade 1 and 2) **Exatecan** Clinical findings (Rowinsky 2005; de Jager 2000): • Fatigue: mild to moderate (Grade 1 and 2)	Management based on Investigator's clinical judgment.
Potential Risks		
Sepsis	**Precem-TcT** Clinical findings: • Sporadic cases of sepsis in conjunction with treatment-related neutropenia and febrile neutropenia have been reported. However, all cases had other etiologies which may have contributed to the development of sepsis. **Exatecan** A potential consequence of exatecan-related neutropenia or febrile neutropenia due to biological plausibility and reports from clinical studies with exatecan.	Strict eligibility criteria requiring adequate organ function and no active or uncontrolled infection. Close monitoring and treatment of hematological toxicities based on Investigator's judgment and guidance from Sections 6.5 and 7.1. Recommendation for use of G-CSF as primary or secondary prophylaxis, as per Section 6.5.2.
Infusion-related reactions (e.g. itching, flushing, hives, chills, fever, back pain, hypotension, anaphylactic shock)	As for any biological therapeutic agent. **Precem-TcT** Clinical findings (PROCEADE-CRC-01 Study, dose escalation and dose expansion): • 1 case of Grade 2 IRR reported out of 40 participants treated with Precem-TcT in Part 1 of PROCEADE-CRC-01 study; 2 cases of Grade 1 IRR were reported in Part 2A, 1 case of Grade 2 IRR in Part 2B and 1 case of Grade 1 IRR in Part 2C2 of PROCEADE-CRC-01 study.	Exclusion of participants with history of severe hypersensitivity to the study intervention or to one or more of the excipients used. Severe hypersensitivity requires immediate discontinuation of study intervention, treatment according to the institutional guidelines and monitoring until the condition resolves. Participants should remain at the clinical site for at least 1 h after completion of the infusion on C1D1 and C2D1 to be monitored for any symptoms of IRR. If the participant experiences an IRR during Cycle 1 or 2, a 1-hour post-administration monitoring will be required for all the following cycles.

Identified and Potential Risks of Clinical Significance	Summary of Data/Rationale for Risk	Mitigation Strategy
Genotoxicity and teratogenicity	Exatecan is regarded as genotoxic and teratogenic.	Strict contraception/barrier requirements included in eligibility criteria (Sections 5.1 and 8.2.5). Pregnancy information collection, monitoring, and reporting (Section 8.3.4).
Drug-drug interactions (DDIs)	Precem-TcT payload is metabolized by CYP450 (3A4 and to a minor extent 1A2 isozymes) and is expected to be cleared mainly via metabolism and to a minor extent by renal clearance. Based on in vitro evaluation, Precem-TcT is a P-gp substrate; however, risk of DDI with P-gp inhibitors is assessed to be low.	• Strong CYP3A4 inhibitors are prohibited (Section 6.9.2 and Appendix 6). • Moderate CYP3A4 inhibitors should be avoided unless no alternative treatment exists. If coadministered, to be used cautiously with close monitoring of AEs. • Strong CYP1A2 inhibitors should be avoided unless no alternative treatment exists. If coadministered, to be used cautiously with close monitoring of AEs.
Alopecia	Commonly reported in clinical studies with exatecan. As of current DCO, approximately 8% of alopecia was reported from PROCEADE-CRC-01 study (Part 2A).	Education and supportive care (e.g. use of cosmetic and hair growth topical treatment) for participant comfort.
Risk Associated with Study Procedures		
Blood sampling	Blood sampling is required for participants as detailed in the SoA. These are considered essential for the study's scientific objectives and individual participant monitoring in terms of safety. Blood sampling carries a risk of adverse events including pain, bruising, bleeding, redness and swelling of the site/vein, and infection.	Minimization of blood sampling was thoughtfully considered during protocol development weighing risk to participants versus achievement of the study's scientific objectives and individual participant monitoring in terms of safety.
Tumor biopsy	Fresh tumor biopsies will be required for the study, if no archival tumor tissue is available, as detailed in the SoA and inclusion criteria. Biopsies carry a risk of AEs including bleeding and infection.	Investigators are expected to use clinical judgment and not to proceed with the biopsy if clinically contraindicated.
Other		
Diagnostic imaging assessments performed as indicated in the SoA in Section 1.2.	Risks of diagnostic imaging primarily arise from exposure to ionizing radiation. These mainly comprise low risk of induction of new malignancy. Alternative methodology can use MRI for most–but not all–scans, however exposure to high intensity magnetic fields can dislodge metallic implants such as cochlear implants and aneurism clips.	The frequency and type of imaging assessments were designed to minimize exposure to radiation to the minimum necessary for adequate assessment. There is an option that participants may be imaged using MRI for many, but not all study assessments. MRI does not use ionizing radiation, so radiation risks are avoided. However, participants with metallic implants with potential to move or become hot should not be exposed to MRI.

Identified and Potential Risks of Clinical Significance	Summary of Data/Rationale for Risk	Mitigation Strategy
Reactions to imaging contrast agents (e.g. rash, itching, or kidney function impairment)	Most CT scans use iodinated contrast media, which have a dose-independent risk of hypersensitivity, and also can provoke renal failure in patients with low GFR. The risk of death from hypersensitivity is less than 1 in 100,000 with modern contrast media. Most MRI scans use gadolinium-based contrast media which also have potential for hypersensitivity, but do not exhibit cross-reactivity with iodinated contrast media. In patients with poor renal function, gadolinium is occasionally associated with a risk of nephrogenic systemic fibrosis, and, in addition, gadolinium can accumulate in normal organs, including the brain, although no definite clinical syndrome has been associated with the latter.	Patients at risk of hypersensitivity reactions, to iodinated contrast media, such as those with a previous reaction or atopic history, should be considered for MRI: if not suitable, premedication should be considered. Those with poor renal function should be appropriately considered. Resuscitation equipment must be available whenever contrast media are administered.

AE = adverse event; CRC = colorectal cancer; CSF = colony-stimulating factor; CT = computed tomography; CYP: cytochrome 450; DDI = drug-drug interactions; DLT: dose-limiting toxicity; GI: gastrointestinal; GFR = growth factor receptor; Hb: hemoglobin; Ht: hematocrit; IRR = infusion-related Reactions; MRI: magnetic resonance imaging; RBC: red blood cells; SAE = serious adverse event; TEAE = treatment-emergent adverse event; TRAE = treatment-related adverse Event. .

The most common TEAEs observed in the FIH study PROCEADE-CRC-01 (dose optimization Part 2A) were anemia, neutrophil count decreased/neutropenia, nausea, platelet count decreased/thrombocytopenia, white blood cell count decreased and fatigue. The most common severe (Grade ≥ 3) TEAEs were neutrophil count decreased/neutropenia, anemia, white blood cell count decreased, and platelet count decreased/thrombocytopenia (Kopetz 2025a).

Risk mitigation measures are built into the study design. These include use of appropriate inclusion/exclusion criteria, G-CSF and antiemetic prophylaxis and close follow-up of the participants with regular safety visits and measurement of blood values. Further, lifestyle restrictions, regular monitoring (clinical and laboratory parameters), guidance on dose modification in the event of an adverse reaction, and review of emerging data at specified timepoints by the external DMC to ensure that the risks are adequately managed and acceptable.

Some of the most frequently observed adverse reactions across clinical trials, based on data from over 5,700 patients with various malignancies receiving bevacizumab, were hypertension, fatigue, or asthenia, diarrhea, and abdominal pain. The most serious adverse reactions across clinical trials using bevacizumab are GI perforations, hemorrhage, and arterial thromboembolism. Refer to the applicable local prescribing information for the full list of adverse reactions, as well as further information on the safety profile of bevacizumab.

When Precem-TcT is combined with bevacizumab, the emerging safety data from PROCEADE-CRC-01 study (Part 2C1) suggests a tolerability profile consistent with that of individual drugs. The most common TEAEs are nausea, neutropenia/neutrophil count decrease and anemia, while the most common severe (Grade ≥ 3) TEAES are neutropenia/neutrophil count decrease, platelet count decrease/thrombocytopenia and anemia (refer to the IB for additional information). Based

on preliminary limited PK data, exposure of Precem-TcT and bevacizumab in combination setting is evaluated to be consistent with respective monotherapies (Sponsor data on file).

The safety profile of FTD-TPI in combination with bevacizumab is based on the data from 246 patients with mCRC in the Phase 3 clinical study (SUNLIGHT; Prager 2023). The most common adverse reactions (≥ 30%) were neutropenia (69% [48% Grade ≥ 3]), fatigue (35% [3% Grade ≥ 3]), and nausea (33% [1% Grade ≥ 3]). The most common adverse reactions (≥ 2%) that resulted in treatment discontinuation, dose reduction, dose delay, or dose interruption of FTD-TPI when used in combination with bevacizumab were neutropenia, fatigue, thrombocytopenia, nausea, and anemia. When FTD-TPI is used in combination with bevacizumab, the frequency of the following adverse reactions was increased compared to FTD-TPI as monotherapy: neutropenia (69% vs 53%), severe neutropenia (48% vs 34%), thrombocytopenia (24% vs 16%), stomatitis (11% vs 6%). Refer to the applicable local prescribing information for further information on the safety profile of FTD-TPI.

2.3.2 Benefit Assessment

The target population of this study has a high unmet medical need due to limited established therapeutic options in the late lines setting of mCRC (Section 2.2). Precem-TcT may meet this unmet medical need due to its properties to selectively target CEACAM5-expressing tumor cells to deliver its cytotoxic payload to tumor cells by direct binding and its bystander effect. The high prevalence of high CEACAM5 expression (99% of mCRC samples evaluated [N=89]), (defined as a 2+/3+ membrane staining intensity in ≥ 50% of tumor cells utilizing a proprietary IHC assay), in mCRC allows to investigate Precem-TcT in patients with mCRC without need to test for CEACAM5 expression.

Existing clinical data of single agent Precem-TcT q3w from the dose escalation and dose optimization parts of the PROCEADE-CRC-01 study as well as data in combination with bevacizumab q3w from the same study (n≈120), have shown a manageable safety profile consistent with exatecan toxicity with no new, unexpected AEs observed, and promising preliminary antitumor activity in heavily previously treated patients with mCRC, as outlined in Section 2.2.

Bevacizumab, and FTD-TPI are approved agents for the treatment of CRC and are part of SoC combination regimen for the treatment of 3L mCRC patients. Their use in mCRC is recommended by both NCCN and ESMO clinical guidelines (NCCN CRC guidelines 2025, ESMO CRC guidelines 2023).

2.3.3 Overall Benefit: Risk Conclusion

Considering the measures taken to minimize risk to participants in this study, and the promising clinical efficacy data observed in the PROCEADE-CRC-01 study, the potential risks identified in association with Precem-TcT either as single agent or in combination with bevacizumab are justified by the anticipated benefits that may be afforded to participants with mCRC who were intolerant/refractory to or had progressive disease after 2 prior lines of SoC therapy depending on local standards and availability.

3 Objectives and Estimands

Objectives	Endpoints	Further Estimand Attributes	Ref. #
Primary			
• To demonstrate improvement in OS with Precem-TcT as single agent compared to FTD-TPI plus bevacizumab. • To demonstrate improvement in OS with Precem-TcT in combination with bevacizumab compared to FTD-TPI plus bevacizumab.	Endpoint: OS is defined as the time from date of randomization to death.	Population: Patients with previously treated mCRC who have been exposed to no more than 2 regimens of systemic therapies that include all standard of care cytotoxic agents and biologic agents according to the molecular profile of their tumor. Treatment: Precem-TcT as single agent or Precem-TcT in combination with bevacizumab vs. FTD-TPI plus bevacizumab. Intercurrent Event Strategy: The endpoint will be analyzed regardless of whether the following intercurrent events had occurred (treatment-policy strategy): • Treatment discontinuation • Start of subsequent anticancer therapy Population-Level Summary: Hazard Ratio	1a
Secondary			
• To evaluate OS of Precem-TcT as single agent and of Precem-TcT in combination with bevacizumab.	Endpoint: Same as #1a	Population/Treatment/Intercurrent Event Strategy/Population-Level Summary::: Same as #1a	1b
• To demonstrate improvement in PFS with Precem-TcT as single agent compared to FTD-TPI plus bevacizumab. • To demonstrate improvement in PFS with Precem-TcT in combination with bevacizumab compared to FTD-TPI plus bevacizumab.	Endpoint: PFS is defined as the time from randomization to the first occurrence of any of the following events (occurring within 2 scheduled PFS assessments after last evaluable assessment or randomization): • Disease Progression by Investigator assessment. • Death from any cause.	Treatment/ Population/Intercurrent Event Strategy/Population-level Summary: Estimand as defined for main analysis #1a, except for the following change: Intercurrent Event Strategy: Start of subsequent anticancer therapy will be analyzed according to hypothetical strategy, i.e. tumor assessments/deaths after start of subsequent anticancer therapy will not be considered for analysis.	2a

Objectives	Endpoints	Further Estimand Attributes	Ref. #
• To evaluate PFS of Precem-TcT as single agent and of Precem-TcT in combination with bevacizumab.	Endpoint: Same as #2a	Population/ Treatment/ Intercurrent Event Strategy/ Population-Level Summary: Same as #2a	2b
• To assess improvement in OR with Precem-TcT as single agent compared to FTD-TPI plus bevacizumab. • To assess improvement in OR with Precem-TcT in combination with bevacizumab compared to FTD-TPI plus bevacizumab. • To evaluate OR of Precem-TcT as single agent and of Precem-TcT in combination with bevacizumab.	Endpoint: OR according to RECIST V1.1 assessed by Investigator prior to documented PD	Population/Treatment: Same as #1a Intercurrent Event Strategy: • Discontinuation of treatment is considered irrelevant in defining the treatment effect of interest and the endpoint will be analyzed regardless of the occurrence of the intercurrent event (treatment-policy strategy, i.e. ignoring intercurrent event) • Response to treatment prior to start of subsequent anti-cancer therapy is of interest and tumor assessments after the intercurrent event will be ignored (while-not-treated with subsequent anti-cancer therapy strategy) Population-Level Summary: Odds Ratio	3
• To evaluate DoR of Precem-TcT as single agent and of FTD-TPI plus bevacizumab. • To evaluate DoR of Precem-TcT in combination with bevacizumab and of FTD-TPI plus bevacizumab. • To evaluate DoR of Precem-TcT as single agent and of Precem-TcT in combination with bevacizumab.	DoR according to RECIST V1.1 by Investigator assessment, is defined as time from first documentation of objective response to PD or death (due to any cause), occurring within 2 scheduled tumor assessments after last evaluable assessment.	Population: Same as #1a and with objective response according to RECIST V1.1. Treatment/ Intercurrent Event Strategy: Same as #2a Population-Level Summary: KM estimates	4
• To evaluate the safety and tolerability with Precem-TcT as single agent compared to FTD-TPI plus bevacizumab. • To evaluate the safety and tolerability with Precem-TcT in combination with bevacizumab compared to FTD-TPI plus bevacizumab.	Endpoints: Occurrence of AEs and treatment-related AEs.	Population: Same as #1a	5

Objectives	Endpoints	Further Estimand Attributes	Ref. #
• To evaluate the safety and tolerability with Precem-TcT as single agent compared to Precem-TcT in combination with bevacizumab.			
To characterize the PK profile of Precem-TcT (conjugated antibody and unconjugated payload) as single agent or in combination with bevacizumab.	Endpoints: PK parameters of Precem-TcT (conjugated antibody and unconjugated payload), such as C_{EOI} and $C_{trough.}$		6
To characterize the immunogenicity of Precem-TcT.	ADA against Precem-TcT: incidence and titer, as measured by ADA assays.		7
To evaluate quality of life with Precem-TcT as single agent or Precem-TcT in combination with bevacizumab compared to FTD-TPI plus bevacizumab using EORTC QLQ-C30 during the investigational treatment phase.	Change from baseline in Global Health Status, physical, and role functioning subscale scores of EORTC QLQ-C30 over time up to Cycle 6.	Population: Same as #1a Intercurrent Event Strategy: • Permanent discontinuation of investigational treatment (while on treatment strategy) • Death: while alive strategy Population-Level Summary: Difference of least squares mean change from baseline	8
Tertiary/Exploratory			
To describe patient-reported outcomes over time, with Precem-TcT as single agent or Precem-TcT in combination with bevacizumab compared to FTD-TPI plus bevacizumab during the investigational treatment phase.	Score change from baseline, over time in: • EORTC QLQ-C30 domain scores (except for GHS, Physical, and role functioning) • EQ-5D-5L domain and VAS scores • Custom EORTC form item scores [abdominal pain, bloating, frequent bowel movements].		9

Objectives	Endpoints	Further Estimand Attributes	Ref. #
To describe tolerability in terms of patient-reported adverse symptoms over time, with Precem-TcT as single agent or Precem-TcT in combination with bevacizumab compared to FTD-TPI plus bevacizumab during the investigational treatment phase.	Scores over time in: • EORTC- QLQ-C30 item scores [fatigue, nausea, vomiting, diarrhea, decreased appetite, and constipation] • Custom EORTC form mouth soreness item score • Custom EORTC form overall side-effect burden item score (Q168).		10
To investigate the relationship between CEACAM5 expression in tumor tissue and efficacy parameters.	Endpoints: Indicators of clinical activity. Biomarkers: Expression of CEACAM5 in tumor tissue.		11
To evaluate in serum samples additional biomarkers and their relationship to clinical response and/or for further disease characterization.	Endpoints: Indicators of clinical activity. Biomarkers: Biomarkers in serum samples.		12

ADA = antidrug antibody; AE = adverse event; CEACAM5: Carcinoembryonic Antigen-Related Cell Adhesion Molecule 5; DoR = duration of response; ECG: electrocardiogram; EORTC = European Organization for Research and Treatment of Cancer; FTD-TPI = trifluridine/tipiracil; Precem-TcT = precemtabart tocentecan; KM = Kaplan-Meier; mCRC = metastatic colorectal cancer; OR = odds ratio; OS = overall survival; PD = progressive disease; PFS = progression-free survival; RECIST = response evaluation criteria in solid tumor; TEAE: treatment-emergent; VAS, Visual Analogue Scale.

4 Study Design

4.1 Overall Design

Study Design	Prospective, controlled, randomized, 3-arm, parallel group, international Phase 3
Control Method	Active control; FTD-TPI plus bevacizumab
Single or Multicenter	Multicenter
Study Population Type	Participants with mCRC, who were intolerant to or whose disease was refractory to or progressed after no more than 2 previous regimens of systemic therapies.
Level and Method of Blinding	Open label

Bias Minimalization Method(s)	• Study intervention assignment/ randomization via IRT. • Aggregate results by treatment group will not be produced during the study conduct, except for external DMC analyses. Access to data produced for external DMC purposes or aggregated data produced for futility and interim analysis purposes will be strictly controlled, with all findings and documents resulting from the review of this data stored in a secure environment until the primary analysis is produced. • An external DMC will perform data reviews on a regular basis to identify any biases or ethical concerns that may arise during the study. The external DMC will also review the totality of available safety and efficacy data produced at the preplanned timepoints of futility and interim analysis. Ad hoc meetings can be scheduled if this is requested by the Sponsor or the external DMC. • Analysis of the efficacy results will follow the Intention-to-Treat Analysis principle: participants will be analyzed based on their original group assignment, regardless of whether they completed the study or adhered to the treatment protocol. • The Sponsor will designate a central laboratory alongside local laboratories to oversee the monitoring of critical safety laboratory parameters (Section 4.1). • Tumor assessment images will be collected for retrospective assessment by an IRC, if requested.
Study Intervention Assignment Method	Participants will be randomized in a 1:1:1 ratio to • Arm 1: Single agent Precem-TcT • Arm 2: Precem-TcT plus bevacizumab • Arm 3: FTD-TPI plus bevacizumab Randomization will be stratified according to geographical region (North America, East Asia, and rest of the world), ECOG PS (0 vs. 1) and presence of liver metastases at the time of randomization (yes vs. no). Randomization will take place once the consented participant has completed all the necessary screening assessments and is deemed eligible for study participation. Randomization must occur within 3 days before the planned C1D1 study intervention date.
Data and Safety Monitoring/Other Committee:	External DMC, Firewall Team, SSC, and if requested, 2 IRCs (one for reviewing ILD cases, and another for retrospective review of tumor assessment images). See Appendix 2 for details.

Total Duration of Study Participation per Participant	Study duration per participant is estimated to be on average approximately 19 months for Arms 1 and 2 and approximately 14 months for Arm 3 (including Screening, Treatment, and Follow-up period).
Screening, Treatment, and Follow-up Periods	The study includes the following periods: **Screening** will be performed within 28 days prior to first dose of study intervention. **Treatment** will begin with the first dose of study intervention administration. Participants in ▪ Arm 1 will receive Precem-TcT q3w ▪ Arm 2 will receive Precem-TcT in combination with bevacizumab q3w ▪ Arm 3 will receive FTD-TPI administered orally bid on days 1 through 5 and on days 8 through 12 every 28 days and bevacizumab administered iv q2w. Treatment will continue until disease progression, death, unacceptable toxicity, withdrawal of consent, or any criterion for treatment discontinuation, whichever comes first. If treatment is discontinued without radiologic disease progression, tumor assessment will continue until radiologic progression, death, lost to follow-up, withdrawal of consent, or End of Study, whichever comes first, regardless of any subsequent anticancer therapies. **End of Study Intervention visit** occurs within 7 days after decision to discontinue study intervention. **Safety Follow-up visit:** 30 (±3) days after last dose of study intervention. Safety Follow-up visit is not required in case the EoSI visit falls on the same time window (30 ± 3 days after last dose of study intervention) as the Safety Follow-up visit. **Survival Follow-up**: after the Safety Follow-up visit, Survival follow-up will be conducted every 90 days (± 14 days) and can be done remotely (e.g. by phone) until death, withdrawal of consent, or End of Study, whichever comes first (see Section 4.4).
Provisions for Study Extension or Entry into Rollover Studies	See Section 6.7.
Adaptive Aspects of Study Design	Not applicable

The study plans to randomize approximately 1,020 adult participants (approximately 340 per arm) of all sexes. The stratification factors for the randomization are listed above.

The primary analysis will be triggered once approximately 374 OS events have been observed for the 2 comparisons of each of the investigational arms versus the SoC. Beforehand, 2 interim analyses are planned: an early futility analysis (nonbinding) based on an IF of approximately 30% (112/374), and an efficacy interim analysis with an IF of approximately 75% (281/374). Each of these predefined analyses will be performed simultaneously regarding the hypothesis testing of the 2 comparisons (Section 9.4.4).

The study will employ competitive recruitment and thus enrollment will be monitored, and appropriate measures may be applied to limit enrollment in certain countries and/or regions to obtain a study population representative across the participating global regions (for example, Asian vs non-Asian countries).

4.2 Scientific Rationale for Study Design

This study is designed as a prospective, controlled, randomized, open label, 3-arm parallel group, Phase 3 study aiming to demonstrate an OS prolongation of single agent Precem-TcT (Arm 1) or Precem-TcT plus bevacizumab (Arm 2) vs. FTD-TPI plus bevacizumab as control arm (Arm 3) in participants with previously treated mCRC.

Precem-TcT as single agent has shown promising antitumor efficacy in heavily pretreated patients with mCRC (Section 2.2). Maintenance of VEGF inhibition with bevacizumab across treatment lines, beyond disease progression has been shown to offer clinical benefits in patients with mCRC (Bennouna 2013, Prager 2023). Clinical data suggest that when Precem-TcT is combined with bevacizumab there is no meaningful change in the incidence or severity of AEs related to either Precem-TcT or bevacizumab (for further details refer to the IB, Sponsor data on file).

Given the encouraging preliminary, single agent efficacy data of Precem-TcT and the potential improved outcome with the addition of bevacizumab, both single agent and combination with bevacizumab in comparison to SoC are considered as promising and the aim of the study is to obtain confirmatory evidence to support regulatory filing for both. Thus, a 3-arm study design is proposed.

The SUNLIGHT Phase 3 study has shown that FTD-TPI in combination with bevacizumab leads to superior OS vs FTD-TPI alone. Moreover, the combination of FTD-TPI and bevacizumab offers numerically better ORR, mPFS, and mOS, compared to all other approved treatment options in that disease setting and is the preferred treatment option for 3L CRC according to NCCN guidelines 2025 and ESMO guidelines (Cervantes 2024). Thus, the combination of FTD-TPI plus bevacizumab is considered an adequate control arm for this study.

According to FDA's guidance *"Clinical trial endpoints for the approval of cancer drugs and biologics - Guidance for Industry"* and to EMA's *"Guidelines on the evaluation of anticancer medicinal products in man. Appendix 1: Methodological consideration for using progression-free survival (PFS) or disease-free survival in confirmatory trials"* OS is considered the most reliable cancer endpoint. It is a precise and easy to measure endpoint, documented by the date of death,

while bias is not a factor in its measurement. When studies can be conducted to adequately assess survival, it is the preferred endpoint for randomized controlled studies.

Due to the difference between the experimental and control arms in terms of mode of administration (iv vs. oral administration) and the different cycle duration (21 days in Arm 1 and Arm 2 vs. 28 days in Arm 3), the study will be performed in an open label design.

The selected stratification factors ensure a balanced allocation of participants to treatment groups:

- **Geographical Region** (North America, East Asia, and rest of the world): to ensure that representation from the 3 main geographical regions included in the study is well balanced across all 3 arms.
- **ECOG Performance Status** (0 vs 1): is among the strongest predictors of outcome for patients with metastatic cancer (Kohne 2002, Jang 2014). In actively treated patients with mCRC, low PS is associated with higher rates of AEs and is predictive of inferior survival outcomes (Mitry 2004, Sanoff 2008, Stillwell 2011).
- **Presence of Liver Metastases** (Yes vs No): a pooled analysis of 17,924 patients with mCRC across 26 trials has demonstrated that liver metastases is a poor prognostic factor for mCRC increasing from 1L to ≥ 3L (Cohen 2024), representing an appropriate stratification factor in the assessment of patient outcome.

4.2.1 Patient Input into Study

Patient Advisory Boards were conducted before the start of the study with patients and caregivers from the US, UK, Spain, Brazil, and Japan, consisting of individuals with lived experience of the condition under investigation. In-depth interviews with patients and caregivers were conducted to obtain qualitative insights into their experiences, expectations, and needs pertaining to the study and to inform the development of patient-centered materials.

Patients' feedback on study design, study drug, eligibility criteria, duration and visit schedule, assessments, patient support, and the ICF was sought and suggestions from these discussions were thoughtfully considered and implemented where possible. Examples include assistance for travel, input into ICF language, and design of patient materials.

4.3 Justification for Dose

4.3.1 Arm 1: Precemtabart Tocentecan Monotherapy

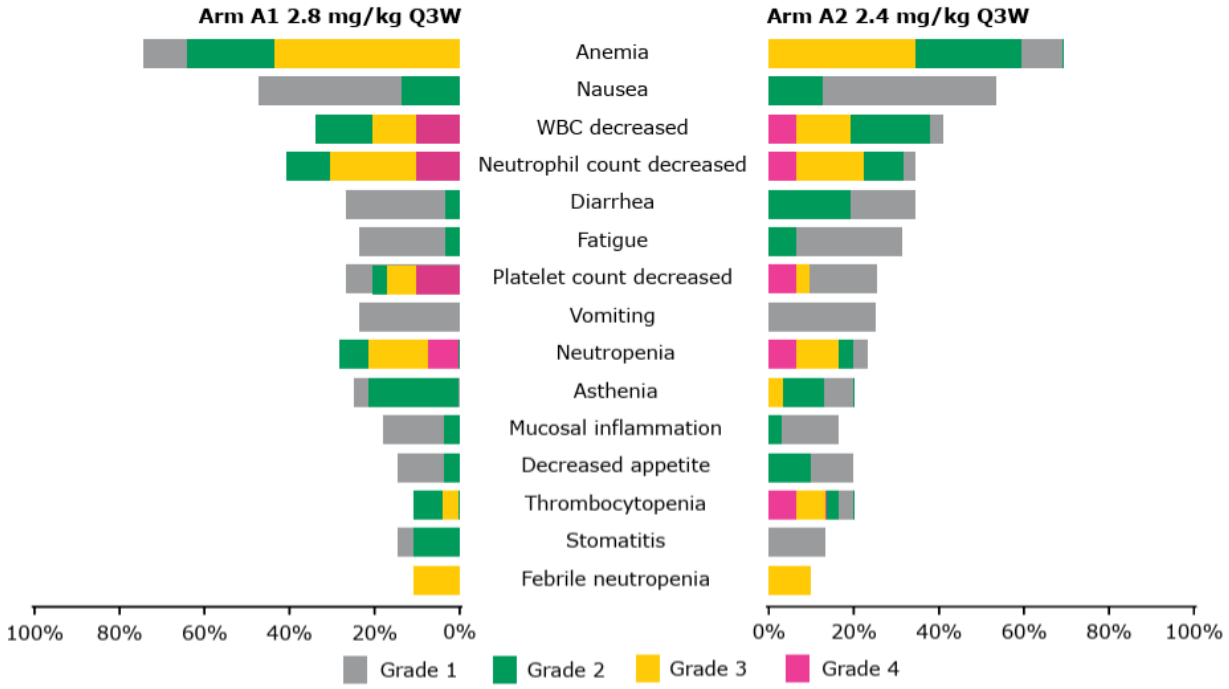
Based on a Totality of Evidence approach including PK, efficacy and safety data integrated through longitudinal PK/PD and exposure-response analyses in patients with mCRC, the proposed dosage of Precem-TcT for this study is 2.8 mg/kg q3w.

The dose escalation part of PROCEADE-CRC-01 study has declared 2.8 mg/kg as the maximum tolerated dose. Dose levels of 2.4 mg/kg and 2.8 mg/kg were selected for the expansion part of the study, which included a randomized dose optimization part (Part 2A). Thus, 60 patients with mCRC were randomized in a 1:1 ratio to receive Precem-TcT at a dose of 2.8 mg/kg (n = 29) or

2.4 mg/kg (n = 31). At the latest data cutoff (2 September 2025), the median treatment duration was 7.1 months in the 2.8 mg/kg arm and 5.3 months in the 2.4 mg/kg arm. A total of 5 patients (8.3%; 2/29 in 2.8 mg/kg DL and 3/31 in 2.4 mg/kg DL) were still under treatment.

Clinical data from the dose optimization part have demonstrated that tolerability of Precem-TcT was consistent with the tolerability profile reported in exatecan Phase 1 studies, with no new unexpected AEs observed. Hematological toxicities were the only severe (Grade ≥ 3) TRAEs observed. GI toxicities were mostly mild to moderate (only Grade 1-2) and there were no ILD or ocular toxicities. Tolerability profile was similar between 2.4 mg/kg and 2.8 mg/kg dose levels and no notable differences were observed in terms of both incidence and severity of TRAEs between the 2 arms (Figure 2). Safety profile at 2.8 mg/kg is considered acceptable following multicycle administration with high relative dose intensity (2.6 mg/kg) and low incidence of dose modifications/reductions (27.6%) at the proposed Phase 3 dosage. PRO CTCAE assessments do not indicate any greater burden of AEs from a participant perspective at 2.8 mg/kg vs. 2.4 mg/kg.

Figure 2 **Most common TEAEs by Grade (≥10% of patients) in 2.4 mg/kg and 2.8 mg/kg DLs in PROCEADE-CRC-01 (cutoff date 02 September 2025)**



As of 02 September 2025, 9 participants in the 2.8 mg/kg DL and 4 participants in the 2.4 mg/kg DL had a PR. Confirmed PRs were reported for 6 participants in the 2.8 mg/kg DL and 2 participants in the 2.4 mg/kg DL, leading to an ORR of 20.7% (95% CI 8, 39,7) and 6.5% (95% CI 0.8, 21.4), respectively (per RECIST V1.1 as assessed by Investigators). Median PFS was 6.9 months (95% CI 4.4, 9.5) and 7 months (95% CI 3.1, 9.7) in the 2.8 mg/kg and 2.4 mg/kg DL, respectively. The median OS was not reached in the 2.8 mg/kg (95% CI 8.7, NE) and 10.6 months (95% CI 7.0, NE) in the 2.4 mg/kg DL after median follow-up of 13.1 months.

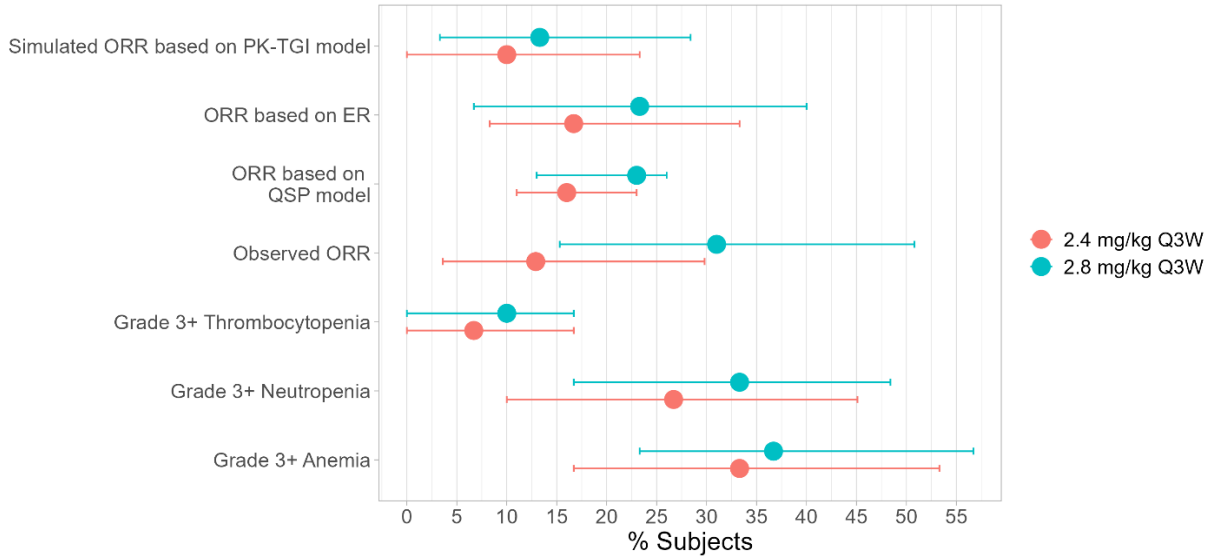
Population PK analyses were conducted with the totality of available Precem-TcT PK data across the dose range of 0.6 to 3.2 mg/kg in dose escalation and dose optimization parts (based on interim data snapshot of 25 March 2025) to characterize the PK of conjugated antibody and unconjugated exatecan. Given the small difference (<20% difference) between the 2 dose levels of 2.4 and 2.8 mg/kg q3w relative to the interindividual variability in PK (%CV of IIV in baseline clearance of conjugated antibody = 56%), systemic exposures were overlapping, with slightly higher exposures for the conjugated antibody at 2.8 mg/kg compared to 2.4 mg/kg. The population PK model was able to describe the data adequately and was utilized to generate individual exposures based on empirical Bayesian estimates for exposure-response analyses. Covariates such as body weight, baseline tumor size, albumin, ALP, and bilirubin were identified as statistically significant covariates, but the magnitudes of their impact on exposures of Precem-TcT were not considered clinically relevant. At the proposed dosage of 2.8 mg/kg, systemic exposures of both the conjugated antibody and unconjugated exatecan were generally consistent and largely overlapping over the distribution of body weight (34.6 to148 kg), age (28 to79 years), sex, race (Asian vs non-Asian), bilirubin (up to 1.5 x ULN) and eGFR (53.2 to 133.2 mL/min/1.73 m^2), supporting the suitability of a common Phase 3 dosage without the need for additional adjustments for these intrinsic/extrinsic factors. Furthermore, to protect participants with obesity (body mass index (BMI) > 30 kg/m^2) from excessive exposures and potential increased risk for TEAEs that could potentially result from mg/kg dosing, a maximum absolute dose limit (dose cap) was implemented for participants whose BMI is greater than 30 kg/m^2 in the Phase 1 study. The dose cap will remain applicable to this study.

Longitudinal semi mechanistic PK/PD models were developed and validated to describe the time course of tumor growth inhibition and hematological safety parameters (ANC, platelets, and hemoglobin). Model-based clinical trial simulations indicated a similar reduction in hematological parameters between 2.8 mg/kg and 2.4 mg/kg, with largely overlapping 95% prediction intervals.

Observed efficacy (ORR) in the randomized dose optimization evaluation of the PROCEADE-CRC-01 study, and consistent evidence for exposure-related efficacy in 3 complementary approaches to E-R analyses (logistic regression driven by ADC cycle 1 AUC, longitudinal PK/tumor growth inhibition modeling, and quantitative systems pharmacology (QSP) modeling integrating preclinical and clinical data), support numerically higher efficacy at 2.8 mg/kg vs. 2.4 mg/kg dose group.

Considering a Totality of Evidence approach, integrated population analyses suggest similar tolerability and numerically higher clinical antitumor activity at 2.8 mg/kg q3w compared to 2.4 mg/kg q3w (Figure 3). Taken together, the results of the randomized dose optimization evaluation coupled with integrated quantitative pharmacological analyses of the clinical PK, safety and efficacy data and supporting nonclinical data collectively provide the scientific rational in support of the benefit/risk profile of the proposed dosage of 2.8 mg/kg q3w of Precem-TcT monotherapy in Arm 1.

Figure 3 **Simulated and Observed ORR and Simulated Grade 3 and Above Hematological Toxicities (Median and 95% PI) at 2.4 and 2.8 mg/kg Q3W Dosage Using PopPK/PD, QSP, and ER Analyses**



Observed ORR (with 95% binomial confidence interval [CI]) is the observed unconfirmed ORR in the dose optimization cohort. All other rates are simulated (median and 95% predicted interval [PI]) using the respective models.

4.3.2 Arm 2: Precemtabart Tocentecan plus Bevacizumab

Emerging clinical data from Part 2C1 of Study PROCEADE-CRC-01 show that, when Precem-TcT is administered in combination with bevacizumab, there is no meaningful change in the incidence or severity of AEs related to either Precem-TcT or bevacizumab and the tolerability profile remains consistent with the tolerability profile of the individual drugs (refer to the IB).

Based on preliminary limited PK data, exposure of Precem-TcT and bevacizumab in combination is evaluated as consistent with the respective monotherapies (Sponsor data on file). Thus, 2.8 mg/kg of Precem-TcT plus 7.5 mg/kg of bevacizumab q3w will be used as the dose of Arm 2 of this study.

4.3.3 Arm 3: Trifluridine/Tipiracil plus Bevacizumab

Participants allocated to Arm 3 of the study will receive the approved doses of FTD-TPI plus bevacizumab. In combination, the starting dose of FTD-TPI in adults is 35 mg/m^2/dose orally bid on Days 1 to 5 and Days 8 to 12 of a 28-day cycle and the dose of bevacizumab is 5 mg/kg iv q2w (refer to local prescribing information).

4.4 End of Study Definition

The end of the study is defined globally as the date of the last follow-up of the last participant still in follow-up (including a contact via phone or the date of the last contact attempt if the last participant is declared lost to follow-up) or after a maximum of 24 months after the first study intervention of the last participant randomized, whichever occurs first.

At the time of Futility/Interim Analysis before completion of the study, and after consulting with the external DMC, the Sponsor may reassess the further need of specific study activities or may decide on immediate discontinuation or shortening of specific assessments (see Appendix 2 "Study and Site Closure" for more details).

If the end of study is reached or the Sponsor decides to terminate the study at any time, see Section 6.7 for further information regarding access to study intervention after end of study.

A participant has completed the study if one of the following occurs:

- Participant dies
- Participant withdraws consent from the study (see Section 7.2)
- Participant is lost to follow-up (see Section 7.3)
- Study is completed or discontinued.

5 Study Population

The criteria in Sections 5.1 and 5.2 are designed to enroll only individuals who are appropriate for the study; thereby, ensuring the study fulfills its objectives. All relevant medical and nonmedical conditions are considered when deciding whether an individual is suitable for this study.

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

Before performing any study assessments that are not part of the individual's routine medical care, the Investigator will confirm that the individual has provided written informed consent, as indicated in Appendix 2.

5.1 Inclusion Criteria

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

Category	Criterion Number	Criterion
Age	1.	Are ≥ 18 years of age at the time of signing the informed consent (see Appendix 7 for country-specific age requirements).
Type of Participant and Disease Characteristics	2.	a) Participants with documented histopathological diagnosis of mCRC, who were intolerant to, or whose disease was refractory to, or progressed after systemic therapies that **must** have included (provided there is no medical contraindication, and these agents are locally approved and available): i) a fluoropyrimidine, irinotecan, a platinum agent (e.g. oxaliplatin) ii) an anti-EGFR agent (if clinically indicated, i.e. RAS/BRAF wt and left-sided tumors) iii) an immune checkpoint inhibitor for participants with a known MSI-H status iv) encorafenib and cetuximab or encorafenib, cetuximab, and binimetinib for participants with known BRAF V600E mutation v) a HER-2 targeted therapy (e.g. trastuzumab plus tucatinib) for participants with known HER-2 positive CRC vi) a NTRK inhibitor (e.g. larotrectinib and entrectinib) for participants with NTRK gene fusion-positive CRC. b) Participants **must** have received previous treatment with bevacizumab c) Participants must have received and progressed on no more than 2 previous systemic treatment regimens in the metastatic setting. Notes: • A (neo)adjuvant therapy with disease progression / relapse during or within 6 months after regimen completion is considered as 1 regimen line in the metastatic setting. • A re-introduction of a removed agent which is part of a combination regimen (e.g. oxaliplatin from FOLFOX) due to disease progression / relapse will be counted as an additional regimen line.

Category	Criterion Number	Criterion
		• Changes of regimen components (e.g. due to unacceptable toxicity) without signs of progression will not be counted as an additional regimen line.

Sex and Contraception/ Barrier Requirements	3.	Participants of any sex and gender are eligible for this study.
		The Investigator confirms that each participant agrees to use appropriate contraception and barriers, if applicable. The contraception, barrier, and pregnancy testing requirements are described in Section 8.2.5 and Appendix 3.
		Contraceptive use will be consistent with local regulations on contraception methods for clinical study participants (see Appendix 8 for Japan-specific requirements).
		A **male** study participant:
		• Agrees to the following during the study intervention period and for at least 6 months after the last dose of study intervention
		  ○ Refrains from donating semen.
		  ○ Abstains from intercourse with a POCBP.
		  ▪ If engaging in intercourse with a POCBP or engaging in any activity that allows for exposure to ejaculate, uses an external condom and counsels the partner to use a highly effective contraceptive method, as specified in Appendix 3.
		A **female** study participant:
		• Is not breastfeeding
		• Is not pregnant
		• If a POCBP, uses a highly effective contraceptive method, with low user dependency, as specified in Appendix 3 for the time periods, specified in Section 8.2.5.
		The Investigator evaluates the effectiveness of the contraceptive method in relationship to the first dose of study intervention. The Investigator reviews the medical history, menstrual history, and recent sexual activity to decrease the risk for inclusion of an individual with an early undetected pregnancy.

Informed Consent	4.	Are capable of giving signed informed consent, as indicated in Appendix 2, which includes compliance with the requirements and restrictions listed in the ICF and this protocol.

Category	Criterion Number	Criterion
ECOG Performance Status	5.	≤ 1
Hematologic Function	6.	Is adequate, as indicated by: • Platelet count ≥ 100,000/μL (no transfusion in the past 3 weeks before randomization) • Hemoglobin ≥ 9.0 g/dL (no transfusion in the past 3 weeks before randomization) • ANC ≥ 1,500/μL (no hematopoietic growth factors or G-CSF in the past 3 weeks before randomization) • INR ≤ 1.5 × ULN. For participants receiving anticoagulants, adequate therapeutic levels as applicable, are required before randomization
Hepatic Function	7.	Is adequate, as defined by a total bilirubin level ≤ 1.5 × ULN, an AST level ≤ 2.5 × ULN, and an ALT level ≤ 2.5 × ULN • For documented Gilbert's Syndrome, a total bilirubin < 3 × ULN is accepted • For participants with liver metastases, AST and ALT < 5 × ULN is accepted
Renal Function	8.	Is adequate, as defined by creatinine clearance of ≥ 30 mL/min by calculation using Cockcroft-Gault formula: CrCl (mL/min) = {((140–age (years)) × weight (kg)) / (72 × Serum creatinine (mg/dL))} × 0.85 (if female)
Tumor Tissue collection	9.	Archival FFPE tumor tissue is required. If archived tumor material is not available, fresh biopsy is required.
Lesion	10.	Have measurable or evaluable, non-measurable disease as defined by RECIST v1.1.
Other	11.	Participants must be able to swallow oral tablets, and to comply with the study requirements for all scheduled evaluations.

5.2 Exclusion Criteria

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

Category	Criterion Number	Criterion
Medical Conditions	1.	If AEs related to previous therapies have not recovered to Grade ≤1 by NCI-CTCAE v6.0 (except for lymphopenia, Grade 2 peripheral neuropathy, Grade 2 alopecia, Grade 2 lab abnormalities that are clinically not relevant, and Grade 2 AEs from prior immune checkpoint inhibitor therapy that are not relevant as an exclusion criterion per Investigator's assessment [e.g. stable, substituted hypothyroidism]).
	2.	Participant has a history of additional malignancy within 3 years before randomization (exceptions are squamous and basal cell carcinomas of the skin and carcinoma in situ of the cervix, benign prostate neoplasm/hypertropia).
	3.	Participants with known brain metastases, except those meeting both of the following criteria: a) clinically stable brain metastases, i.e. without evidence of progression by imaging for at least 4 weeks prior to randomization. b) No ongoing neurological symptoms that are related to the brain localization of the disease (sequelae that are a consequence of the treatment of the brain metastases are acceptable). Note: participants with leptomeningeal disease are excluded regardless of clinical stability.
	4.	Abdominal fistula, gastrointestinal perforation, or intra-abdominal abscess within the past 6 months prior to randomization.
	5.	Participants with ileus Grade > 1, or chronic inflammatory bowel disease (e.g. ulcerative colitis, Crohn's disease) and/or bowel obstruction, or participants with chronic gastrointestinal disorders that, in the Investigator's opinion, might significantly interfere with proper absorption of the study treatments.

Category	Criterion Number	Criterion
	6.	a. Congestive heart failure (NYHA ≥ II), uncontrolled cardiac arrhythmia, unstable angina, myocardial infarction, coronary revascularization procedure, cerebral vascular accident, transient ischemic attack, thrombotic or hemorrhagic event, hemoptysis or any other significant cardiovascular condition or event within 180 days of randomization. b. Calculated QTc average using QTcF > 470 msec.
	7.	Uncontrolled concurrent illness (e.g. serious uncontrolled diabetes [fasted blood glucose > 250 mg/dL], or psychiatric illness/social situations that would limit compliance with the study requirements).
	8.	Active or prior ILD/pneumonitis. History of idiopathic pulmonary fibrosis, obliterative bronchiolitis, or idiopathic pneumonitis. History of prior resolved radiation pneumonitis is allowed.
	9.	Active or uncontrolled infection, e.g. requiring systemic antibiotics, antivirals, or antifungals. Participants with localized fungal infections of skin or nails may be eligible following discussion with the Medical Monitor. The following exceptions apply: • HIV infection: o Participants on ART must have a CD4+ T-cell count > 350 cells/µL at time of screening. o Participants on ART must have achieved and maintained virologic suppression defined as confirmed HIV RNA < 50 copies/mL or below the limit of detection by locally available assay at the time of screening and for at least 12 weeks prior to screening. o Participants on ART must have been on a stable regimen, without changes in drugs or dose adjustment, for at least 4 weeks prior to Cycle 1 Day 1 of study treatment. o The ART regimen must not contain any prohibited medications that may interfere with exatecan metabolism. • HBV infection: Participants are eligible with the following:

Category	Criterion Number	Criterion
		○ Anti-HBsAg+ and anti-HBc- (prior HBV vaccination status). ○ HBsAg- and anti-HBc+ (i.e. have cleared HBV infection) meeting the below conditions. ○ HBsAg+ with chronic HBV infection (lasting 6 months or longer) meeting the below conditions. ○ Conditions: ▪ HBV DNA viral load < 2000 IU/mL. ▪ Normal ALT and AST or, if liver metastases are present, abnormal results of AST/ALT < 3 × ULN, which are not attributable to HBV infection. ▪ Start or maintain antiviral treatment if clinically indicated as per the Investigator. ○ For Japan-specific measures regarding HBV infection see Appendix 7. • HCV infection: Participants are eligible if they have been treated and cured as demonstrated clinically and by viral serologies.
	10.	Estimated life expectancy of < 4 months.
	11.	Major surgery, unhealed wound following surgery, significant traumatic injury, or drainage for ascites, pleural effusion, or pericardial fluid within 4 weeks, prior to randomization, or an anticipated need for major surgery during the study.
	12.	History of severe hypersensitivity/allergic reactions to prior therapies with biologicals or to any of the study interventions (Precem-TcT, bevacizumab, FTD-TPI) or their excipients.
	13.	Uncontrolled hypertension (defined as either systolic blood pressure ≥ 150 mmHg and/or diastolic blood pressure ≥ 100 mmHg), based on average of readings according to ACC/AHA, despite antihypertensive treatment.
	14.	Participants with proteinuria > 2 g/24 hours (24-h urine collection is required only if dipstick is 2+).

Category	Criterion Number	Criterion
	15.	Any other contraindication present in the local product information of bevacizumab or FTD-TPI.
Prior/Concomitant Therapy	16.	Systemic steroid or other immunosuppressive therapy taken within 7 days prior to randomization. Inhaled steroids, topical steroids, or intra articular steroid injections are permitted in the study (Section 6.9.1). Brief, limited use of systemic corticosteroids (less than 7 days) is also permitted where such use is considered standard of care (e.g. for COPD exacerbation).
	17.	Participants currently receiving or unable to stop using prohibited medication (within prohibited window) prior to randomization as defined in Section6.9.2.
	18.	Received growth factors (including EPO, darbepoetin, G-CSF, GM-CSF, and platelet stimulators [e.g. eltrombopag, romiplostim, or IL-11]) or transfusions within 3 weeks prior to randomization.
	19.	Prior treatment with FTD-TPI, CEACAM5-targeting therapy (e.g. anti-CEACAM5 ADC), or with an ADC with a TOP1 inhibitor payload (e.g. trastuzumab deruxtecan).
	20.	Received chemotherapy, radiation therapy (except limited local palliative RT), biological therapy (e.g. antibodies) or any other anticancer therapy or investigational drugs, within 3 weeks or 5 half-lives, whichever is shorter, before randomization. Participation in a study without IMP administration such as noninterventional or epidemiological studies, or in a study follow-up, is allowed.
	21.	Participants with evidence of bleeding diathesis or coagulopathy.

5.3 Lifestyle Considerations

5.3.1 Meals and Dietary Restrictions

Participants will be instructed to refrain from consumption of CYP3A4 inhibitors such as herbal supplements (e.g. essiac tea) and foods or drinks with CYP3A4 inhibition potential (i.e. grapefruits and grapefruit juice, Seville oranges, pomelos, starfruits) starting at least 7 days before the first administration of any study intervention (all arms) and during the study intervention (Arm 1 and Arm 2) (see Appendix 6 for details).

5.3.2 Caffeine, Alcohol, Tobacco, and Cannabinoid

- During each dosing period, participants will be instructed to abstain from ingesting caffeine- or xanthine-containing products (e.g. coffee, tea, cola drinks, and chocolate) for 6 hours prior to ECG and vital sign assessments.
- During each dosing period, participants will be instructed to abstain from alcohol and cannabinoid-containing products for 12 hours prior to ECG and vital sign assessments.
- Participants who nicotine-containing products (including nicotine patches) will be instructed that their use will not be permitted while they are in the clinical unit.

5.3.3 Activity

Participants will be instructed to abstain from strenuous exercise for 4 hours before each blood collection for clinical laboratory tests. Nonstrenuous activities performed at a leisurely, comfortable pace and without moderate or strenuous physical exertion, such as leisurely walks, tai chi, or gentle yoga are allowed.

5.4 Screen Failures

Individuals who do not meet the criteria for participation in this study (screen failure) may be rescreened before randomization, if the condition leading to screen failure has resolved and after discussion with the Medical Monitor. Rescreened participants will be assigned a new participant number. Only one rescreening is allowed. The participant will be flagged in the eCRF as having been rescreened.

Screen failures are participants who have signed the ICF and for whom a study-specific identification number has been assigned (screened participants) but who were not randomized because they failed to meet the eligibility criteria or discontinued study participation during the Screening period for other reason(s).

Retesting of participants in case of physical and/or laboratory parameters abnormalities will be allowed within the Screening period.

Beyond the Screening period, participants may be rescreened in certain circumstances for enrolment into the study:

- A participant consented to participate, met the eligibility criteria but was delayed in starting due to a change in situation (e.g. family issues, request for attending a private matter, etc.).
- A participant failed eligibility due to an acute event that resolved or was stabilized with medications.
- Reversible causes of screening failure that were adequately treated and/or resolved.

All assessments should be repeated according to instructions provided for the initial screening (see Section 1.2).

6 Study Intervention(s) and Concomitant Therapies

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

6.1 Study Intervention(s) Administration

Study Intervention(s) Administered

Intervention Name/ INN	Precemtabart tocentecan	Bevacizumab	Trifluridine/tipiracil
Intervention Description	2.8 mg/kg iv q3w (Arm 1 and Arm 2)	7.5 mg/kg iv q3w (Arm 2) 5 mg/kg iv q2w (Arm 3)	35 mg/m^2 orally bid on days 1–5 and 8–12 every 28 days.
Type	Antibody-drug conjugate	Antibody	Chemotherapy
Dose Formulation	Freeze-dried powder for concentrate for solution for infusion	Concentrate for solution for infusion	Film-coated tablet
Unit Dose Strength(s)	10 mg/mL	25 mg/mL	• 15 mg trifluridine/6.14 mg tipiracil • 20 mg trifluridine/8.19 mg tipiracil
Dose Amount	2.8 mg/kg	7.5 mg/kg (Arm 2) 5 mg/kg (Arm 3)	35 mg/m^2 (based on the trifluridine component)
Dose Regimen	q3w	q3w (Arm 2) q2w (Arm 3)	bid on days 1–5 and 8–12 every 28 days
Route of Administration	Intravenous	Intravenous	Oral
Use	Experimental	Experimental (Arm 2) Comparator (Arm 3)	Comparator
Clinical Study Use Drug, for studies with Japanese sites	Main Test Drug	Concomitant Drug (Arm 2) Control Drug (Arm 3)	Control Drug
IMP or NIMP/AxMP	IMP	IMP	IMP
Sourcing	Provided by the Sponsor	Provided by the Sponsor	Provided locally from the hospital pharmacies of the clinical sites or centrally by Sponsor/CRO or designee.
Packaging and Labeling	Precem-TcT will be provided in vials. Each vial will be packed and labeled per country-specific requirement(s) and GMP Guidelines.	Bevacizumab will be provided and labeled per country-specific requirement(s) and GMP Guidelines.	Trifluridine/tipiracil will be provided and labeled per country-specific requirement(s) and GMP Guidelines.

Study Arm(s)

Arm Name	Arm 1: Precemtabart Tocentecan Monotherapy	Arm 2: Precemtabart Tocentecan plus Bevacizumab	Arm 3: Trifluridine/tipiracil plus Bevacizumab
Arm Type	Experimental	Experimental	Active Comparator

Arm Description	Precemtabart tocentecan 2.8 mg/kg q3w	Precemtabart tocentecan 2.8 mg/kg q3w Bevacizumab 7.5 mg/kg q3w	Trifluridine/tipiracil 35 mg/m^2 bid on days 1–5 and 8–12 every 28 days Bevacizumab 5 mg/kg q2w

6.1.1 Dosage and Administration of Precemtabart Tocentecan, Bevacizumab, and Trifluridine/Tipiracil

In all 3 arms, treatment as described below will continue until disease progression, unacceptable toxicity, death, withdrawal of consent or any criterion for treatment discontinuation (Section 7.1). After the discontinuation of the study interventions, participant's treatment is left to the physician's discretion.

Further details about study intervention preparation and administration are provided in the Pharmacy Manual.

6.1.1.1 Arm 1: Single-agent Precem-TcT

Precem-TcT will be given at the dose of 2.8 mg/kg on Day 1 of each 21-day cycle. Precem-TcT should be given as an iv infusion (approximately 1-h infusion duration) on Day 1 of each cycle. See Section 6.5.5.1 for prophylaxis of Precem-TcT-induced nausea and vomiting.

Participants will remain at the clinical site for at least 1 h after completion of the infusion on C1D1 and C2D1 to be monitored for any symptoms of IRR. If the participant experiences an IRR during C1 or C2, a 1-h post-administration monitoring will be required for all the following cycles. See Section 6.5.6.18.2.2 for recommendations on monitoring IRR symptoms during and after Precem-TcT infusion.

- The dose to be administered to each participant will be calculated based on the participant's weight using 1 decimal place for weight:

  Dose (mg) = Dose Level (mg/kg) x body weight (kg)

- Details about requirements for dose recalculation in case of weight changes will be described in the Pharmacy Manual.
- BMI should be calculated with the following formula:

  BMI (kg/m^2) = weight (kg) / (height [m])^2.

- Height (in m) should be provided with 2 decimal places and BMI (in kg/m^2) with 1 decimal place. E.g. for a participant with weight of 70.2 kg and height of 1.75 m the BMI would be calculated as follows:

  70.2 kg/(1.75 m × 1.75 m) = 22.9 kg/m^2.

- The BMI calculation to determine the dose will be provided by the IRT.
- For participants whose BMI is greater than 30 kg/m^2, the Investigator should use a weight that, based on the participant's height, corresponds to a maximum BMI of 30 kg/m^2.

The dose is calculated according to the following formula if BMI is greater than 30 kg/m^2:

Dose (mg) = Dose Level (mg/kg) x 30 (kg/m^2) × (height [m])^2.

6.1.1.2 Arm 2: Precem-TcT in Combination With Bevacizumab

Precem-TcT will be administered as described in Section 6.1.1.1.

Bevacizumab will be administered at the dose of 7.5 mg/kg on D1 of each 21-day cycle.

- Bevacizumab should be given as an iv infusion at least 30 minutes after completion of Precem-TcT administration. The initial dose should be delivered over 90 minutes. If the first infusion is well tolerated, the second infusion may be administered over 60 minutes. If the 60-minute infusion is well tolerated, all subsequent infusions may be administered over 30 minutes. It should not be administered as an iv push or bolus. If the participant was previously exposed to bevacizumab with no tolerability issues during infusion, the initial infusion time can be reduced to 30 minutes.
- The dose (in mg) to be administered to each participant will be calculated based on the participant's weight using 1 decimal place for weight.

  Dose (mg) = Dose Level (mg/kg) x body weight (kg).

6.1.1.3 Arm 3: Trifluridine/Tipiracil in Combination with Bevacizumab

The recommended starting dose of FTD-TPI in adults, as monotherapy or in combination with bevacizumab, is 35 mg/m^2 dose administered orally twice daily on Days 1 to 5 and Days 8 to 12 of each 28-day cycle.

- The BSA will be calculated by the IRT using the following DuBois formula (all BSA calculations are rounded to 2 decimal places) (Du Bois 1916):
  BSA (m²) = ([Body Weight (kg)]$^{0.425}$ x [Height (cm)]$^{0.725}$) x 0.007184.
- The doses will be calculated by the IRT.
- Details about requirements for dose recalculation in case of BSA changes will be described in the Pharmacy Manual.
- The dose must not exceed 80 mg/dose.
- No increase in FTD-TPI dose due to increase in BSA is permitted.
- FTD-TPI should be taken with a glass of water within 1 hour after completion of morning and evening meals.
- FTD-TPI should only be given on Days 1 through 5 and Days 8 through 12 of each cycle. If doses are missed or held on those days, the participant should not make up for missed doses. Extension of study treatment into Days 6 to 7 or into the rest period (Days 13 through 28) is not permitted.

Table 7 Starting Dose Calculation for FTD-TPI According to BSA

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

Table 8 Dose Reductions of FTD-TPI According to BSA[a]

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

Reduced dose	BSA (m^2)	Dose in mg (2x daily)	Tablets per dose (2x daily)		Total daily dose (mg)
			15 mg/6.14 mg	20 mg/8.19 mg	
Level 3 dose reduction: From 25 mg/m^2 to 20 mg/m^2					
20 mg/m^2	< 1.14	20	0	1	40
	1.14 - 1.34	25[a]	2[b]	1[b]	50[b]
	1.35 - 1.59	30	2	0	60
	1.60 - 1.94	35	1	1	70
	1.95 - 2.09	40	0	2	80
	2.10 - 2.34	45	3	0	90
	≥ 2.35	50	2	1	100

[a] For participants with renal impairment (CrCl < 30 mL/min) see Section 6.5.1 and local product information.

[b] At a total daily dose of 50 mg, participants should take 1 x 20 mg/8.19 mg tablet in the morning and 2 x 15 mg/6.14 mg tablets in the evening.

Bevacizumab will be administered at the dose of 5 mg/kg on D1 and D15 of each 28-day cycle.

- Bevacizumab should be given as an iv infusion. The initial dose should be delivered over 90 minutes. If the first infusion is well tolerated, the second infusion may be administered over 60 minutes. If the 60-minute infusion is well tolerated, all subsequent infusions may be administered over 30 minutes. It should not be administered as an iv push or bolus. If the participant was previously exposed to bevacizumab with no tolerability issues during infusion, the initial infusion time can be reduced to 30 minutes.
    - The dose (in mg) to be administered to each participant will be calculated based on the participant's weight using 1 decimal place for weight.

      Dose (mg) = Dose Level (mg/kg) x body weight (kg).

6.2 Study Intervention(s) Preparation, Handling, Storage, and Accountability

The Investigator, institution, or the head of the medical institution (where applicable) is responsible for study intervention accountability, reconciliation, and record maintenance (i.e. receipt, reconciliation, and final disposition records).

- Upon receipt of the study intervention(s), the Investigator or designee will confirm appropriate temperature conditions have been maintained during transit and any discrepancies are reported and resolved before use. Also, the responsible person will check for accurate delivery. Further guidance and information for study intervention accountability are provided in the Pharmacy Manual.
- Only participants enrolled in the study may receive study intervention(s) and only authorized site staff may supply it. All study intervention(s) will be stored in a secure, environmentally controlled, and monitored (manual or automated) area, per the labeled storage conditions, and with access limited to the Investigator and authorized site staff.

- Dispensing will be recorded on the appropriate accountability forms so that accurate records will be available for verification at each monitoring visit.
- Study intervention(s) accountability records at the study site will include the following:
  - Confirmation of receipt, in good condition, and in the defined temperature range.
  - The inventory provided for the clinical study and prepared at the site.
  - The dose(s) each participant used during the study.
  - The disposition (including return, if applicable) of any unused study intervention(s).
  - Dates, quantities, batch numbers, medication vials and container numbers, expiry dates, and the participant numbers.
- The Investigator site will maintain records which adequately documents that participants were provided the doses specified in this protocol, and all study intervention(s) provided were fully reconciled.
- Unused study intervention(s) will not be discarded or used for any purpose other than the present study. No study intervention that is dispensed to a participant may be redispensed to a different participant.
- A Study Monitor will periodically collect the study intervention(s) accountability forms.
- Further guidance and information for the final disposition of unused study intervention(s) are provided in the Pharmacy Manual.

6.3 Measures to Minimize Bias: Study Intervention Assignment and Blinding

6.3.1 Study Intervention Assignment

After confirmation of participant's eligibility and within 3 days prior to study intervention administration, participants will be centrally allocated to either Arm 1, Arm 2, or Arm 3 in a 1:1:1 ratio using an IRT and per a computer-generated randomization list. Randomization will be stratified according to geographical region (North America, East Asia, and rest of the world), ECOG PS (0 vs. 1) and presence of liver metastases (yes vs. no) at the time of randomization.

The IRT will be used to assign unique participant numbers, allocate participants to study intervention group at the randomization, and study intervention to participants at each study intervention visit.

Before the study is initiated, the directions for the IRT will be provided to each site. The site will contact the IRT prior to starting study intervention administration for each participant.

6.3.2 Blinding

This is an open label study.

Analyses by treatment arm during the ongoing study will be conducted by an external SDAC for review by the external DMC, while the Sponsor remains blinded to the results. Access to the data analyses generated for DMC purposes will be strictly controlled. All findings and documents resulting from the DMC's review will be securely stored until the primary analysis is completed or a decision regarding unblinding is made.

A Firewall Team will be established prior to any interim analysis (see Appendix 2). The Firewall Team will consist of a limited number of individuals not involved in the study's design, conduct, or analysis. A Firewall Team Charter will govern the access and responsibilities of the team members. To mitigate the risk of influence, knowledge of the Firewall Team's membership and at Sponsor's side the charter will be restricted to those directly interacting with the team. This structured approach is essential for maintaining the integrity and validity of the study outcomes.

If any boundaries are crossed during the interim analysis, or if the DMC recommends stopping or modifying the study, the Chair of the external DMC will notify the Firewall Team. Following this notification, access to study results by treatment arm may be granted to the Firewall Team, facilitating informed decision-making by the Sponsor. Additional details will be outlined in both the external DMC and Firewall Team charters.

Additionally, PK data may be made available prior to DBL to an external CRO (who will be firewalled) to frontload population PK analyses; details will be described in additional documents.

Assignment Method Retention

This is an open label study.

6.4 Study Intervention Compliance

In this study, participants treated in Arm 1 and Arm 2 will receive the study intervention(s) at the investigational site. Participants in Arm 3 will receive bevacizumab at the investigational site and FTD-TPI will be either received directly from the Investigator or designee, under medical supervision (during visits) or will be self-administered at home.

When participants are dosed at the site, they will receive study intervention directly from the Investigator or designee, under medical supervision. The date and time of each dose, if applicable, administered in the clinic will be recorded in the source documents and recorded in the CRF. A member of the study site staff other than the person administering the study intervention will confirm the study intervention dose and study participant identification at the time of dosing.

Participants will be instructed by the Investigator/designee regarding off-site self-administration of FTD-TPI and asked to record self-administration in a dosing diary. When participants self-administer FTD-TPI at home, compliance will be assessed at each visit to the investigational site. Compliance will be assessed by the Investigator or a designated person during the site visits by reviewing the dosing diary, direct questioning, and counting of returned tablets during the site visits and will be documented in the source documents and eCRF. Any deviation(s) from the prescribed dosage regimen are recorded in the CRF.

A record of the number of FTD-TPI tablets dispensed to and taken by each participant will be maintained and reconciled with study intervention and compliance records. Intervention start and stop dates, including dates for intervention delays and/or dose reductions will be recorded in the CRF.

6.5 Dose Modification

6.5.1 Dose Modification of Study Interventions

Individual dose modifications, interruptions, or discontinuations for Precem-TcT are listed in Table 9, for bevacizumab in Table 10, and for FTD-TPI in Table 8, Table 11, and Table 12.

- Investigators are encouraged to discuss with Medical Monitor before implementation of dose modifications.

- Before starting a new treatment cycle, all toxicities related to study treatment must have resolved according to the tables below, except for toxicities considered by the Investigator to be unlikely to become serious or life-threatening.

- If the toxicities do not resolve during the given cycle according to the tables below, the start of the next cycle must be delayed for a maximum of 28 days from the scheduled start date of the next cycle. If more than 28 days are needed to recover from a study intervention-related event, the participant will be discontinued from the study intervention as described in Section 7.1. Exception may be allowed for circumstances where the participant has previously benefited from study intervention, is expected to continue to benefit from resumed study intervention, and toxicity risks can be appropriately mitigated with dose modifications and/or supportive interventions, after discussion with medical monitor.

- Participants may have bevacizumab withheld or discontinued permanently and continue Precem-TcT or FTD-TPI alone in Arms 2 and 3, respectively, if this is deemed beneficial for the participant according to the Investigator's clinical judgment.

- If a participant needs to withhold or discontinue Precem-TcT or FTD-TPI (Arms 2 and 3), then the participant will respectively withhold or discontinue from bevacizumab as well.

- For Precem-TcT, 2 dose reductions are permitted, to dose levels of 2.4 mg/kg and subsequently 1.8 mg/kg.

- For FTD-TPI a maximum of 3 dose reductions are permitted, of 5 mg/m^2 decrement each, to a minimum dose of 20 mg/m^2 twice daily.

- Once a minimal dose level has been reached, subsequent AEs attributed to Precem-TcT or FTD-TPI requiring dose reductions will result in permanent discontinuation.

- In participants with severe renal impairment (CrCl 15-29 mL/min), FTD-TPI dose will be adjusted to 20 mg/m^2 twice daily, with one dose reduction to a minimum of 15 mg/m^2. FTD-TPI will not be administered to participants with a CrCl < 15 mL/min.

- Dose reduction for AEs is not recommended for bevacizumab. In case of toxicity that is considered related to bevacizumab and in the opinion of the Investigator bevacizumab continuation may put participant's safety at risk, bevacizumab should be temporarily suspended or permanently discontinued as described in the local prescribing information and Table 10.

- For all agents dose re-escalation is not permitted after it has been reduced.

6.5.1.1 Precemtabart Tocentecan

Table 9 Dose Modifications and Temporary/Permanent Treatment Discontinuation of Precem-TcT

Specifics	Toxicity (NCI-CTCAE V6.0 Grade)	Criteria for permanent discontinuation or dose interruption and modification
Hematological Toxicity		
Neutrophils count decreased: < 1,000 - 500/mm^3; < 1.0 - 0.5 x 10^9/L).	Grade 2	Withhold Precem-TcT until resolution or recovery to Grade ≤ 1 and start G-CSF. Upon recovery, restart Precem-TcT at the same dose with prophylactic administration of G-CSF (see Section 6.5.2).
Neutrophils count decreased: (< 500/mm^3; < 0.5 x 10^9/L).	Grade 3-4	Withhold Precem-TcT until recovery to Grade ≤ 1 and start G-CSF. **First occurrence:** Upon recovery, restart Precem-TcT at the same dose with prophylactic administration of G-CSF (see Section 6.5.2). **Second occurrence:** Upon recovery, reduce Precem-TcT dose to 2.4 mg/kg for all subsequent cycles with prophylactic administration of G-CSF (see Section 6.5.2). **Subsequent recurrence:** Upon recovery, reduce Precem-TcT dose to 1.8 mg/kg for all subsequent cycles with prophylactic administration of G-CSF (see Section 6.5.2).
Febrile neutropenia: i.e. ANC < 1,000/mm^3 with single temperature of 38.3°C [101°F] or a sustained temperature of ≥ 38°C [100.4°F] for >1 h.	Grade 3-4	**First occurrence:** Withhold Precem-TcT and treat with G-CSF (see Section 6.5.2) until complete resolution. Upon recovery, reduce Precem-TcT dose to 2.4 mg/kg for all subsequent cycles with prophylactic administration of G-CSF (see Section 6.5.2). **In case of recurrence**: permanently discontinue Precem-TcT.
Anemia: Hgb < 8.0 g/dL; < 4.9 mmol/L; < 80 g/L; transfusion indicated.	Grade 3	**First occurrence:** Withhold Precem-TcT until recovery to ≤ Grade 2. Support with blood products as needed. Upon recovery, resume Precem-TcT at the same dose with blood product support as needed.
Anemia: Life-threatening consequences, urgent intervention indicated.	Grade 4	**First occurrence:** Withhold Precem-TcT until recovery to Grade ≤ 2, then reduce dose to 2.4 mg/kg for all subsequent cycles with blood product support as needed, at Investigator's discretion. **In case of recurrence:** Permanently discontinue Precem-TcT.

Specifics	Toxicity (NCI-CTCAE V6.0 Grade)	Criteria for permanent discontinuation or dose interruption and modification
Thrombocytopenia (with platelet count < 50,000/mm^3 - 25,000/mm^3) without clinically significant bleeding		Withhold Precem-TcT until recovery to Grade ≤ 2. Upon recovery, restart Precem-TcT at the same dose.
Thrombocytopenia (< 7 days) with platelet count < 25,000/mm^3 **without clinically significant bleeding.**		Withhold Precem-TcT until recovery to Grade ≤ 2. Upon recovery, restart Precem-TcT at the same dose.
Long-lasting thrombocytopenia (≥ 7 days) with platelet count < 25,000/mm^3 **without clinically significant bleeding**		**First occurrence:** Withhold Precem-TcT until recovery to baseline or Grade ≤ 2 and reduce Precem-TcT dose to 2.4 mg/kg for all subsequent cycles. **Second occurrence:** withhold Precem-TcT until recovery to baseline or Grade ≤ 2 and reduce Precem-TcT dose to 1.8 mg/kg for all subsequent cycles. **In case of recurrence** at 1.8 mg/kg: Permanently discontinue Precem-TcT.
Thrombocytopenia with clinically significant bleeding.	Grade ≥ 3	**First occurrence:** In cases of Grade ≥ 3 that are associated with significant bleeding withhold Precem-TcT until recovery to Grade ≤ 2 and then reduce Precem-TcT dose to 2.4 mg/kg for all subsequent cycles. **In case of recurrence**: Permanently discontinue Precem-TcT.
Non-hematological		
Diarrhea/Colitis: Increase of ≥7 stools per day over baseline; hospitalization indicated; severe increase in ostomy output compared to baseline; requires iv intervention; limiting self-care ADL.	Grade 3	• Withhold Precem-TcT until recovery to Grade ≤ 1. • If resolved within 2 weeks from the day of onset, reduce Precem-TcT dose to 2.4 mg/kg. • If not resolved within 2 weeks from the day of the onset or there is a recurrence, permanently discontinue Precem-TcT. Appropriate antidiarrheal therapy must be initiated immediately in accordance with institutional guidelines (see Section 6.5.4).
Diarrhea/Colitis: Life-threatening consequences, urgent intervention indicated.	Grade 4	• Permanently discontinue Precem-TcT. • Appropriate antidiarrheal therapy must be initiated immediately in accordance with institutional guidelines (see Section 6.5.4).
IRRs	Grade 1	• If IRR is observed during Precem-TcT administration, the infusion rate should be reduced by 50% and participants should be closely monitored. • If no other reactions appear, the subsequent infusion could be resumed at the initial planned speed.

Specifics	Toxicity (NCI-CTCAE V6.0 Grade)	Criteria for permanent discontinuation or dose interruption and modification
	Grade 2	• Administration of Precem-TcT should be interrupted briefly. • Consider symptomatic treatment (e.g. antihistamines, NSAIDs, narcotics, iv fluids; see Section 6.5.6.1 and Table 16). • If the event resolves or improves to Grade 1, Precem-TcT infusion can be restarted at a 50% reduced infusion rate. • Subsequent Precem-TcT infusions should be conducted at the reduced rate. • Additional premedication can be considered for subsequent Precem-TcT infusions according to Investigator's clinical judgment.
	Grade ≥ 3 (including anaphylaxis/anaphylactic reactions)	• Administration of Precem-TcT should be discontinued immediately and permanently. • Urgent intervention indicated. Antihistamines, steroids, epinephrine, bronchodilators, vasopressors, intravenous fluid therapy, oxygen inhalation etc., should be administered as clinically indicated.

Other non-hematological toxicities
• For ILD, see Section 6.5.3
• For diarrhea, see Section 6.5.4
• For nausea/vomiting, see Section 6.5.5
	Grade 2-3	• Decide if type of AE requires withholding Precem-TcT after discussion with Medical Monitor. If so, withhold Precem-TcT until recovery to baseline or Grade ≤ 1.
		  • If resolved within 2 weeks from the day of onset, reduce Precem-TcT dose to 2.4 mg/kg.
		  • If not resolved within 2 weeks from the day of onset, consider permanent discontinuation of Precem-TcT according to the Investigator's clinical judgment and Medical Monitor consultation.
		  • If there is a recurrence that resolves within 2 weeks, withhold Precem-TcT until recovery to baseline or Grade ≤ 1.and further reduce Precem-TcT dose to 1.8 mg/kg.

	Grade 4	**First occurrence:** • Withhold Precem-TcT until recovery to baseline or Grade ≤ 1 and implement dose reduction as for Grade 3. Permanent Precem-TcT discontinuation should be considered. **Second occurrence:** Permanently discontinue Precem-TcT.

AE = adverse event, ANC = absolute neutrophil count, G-CSF = granulocyte colony-stimulating factor, GI = gastrointestinal, Hb = hemoglobin, ILD; interstitial lung disease; IRR = infusion-related reaction, IV, intravenous; NSAID = nonsteroidal anti-inflammatory drug; NCI-CTCAE, common terminology criteria for adverse events; Precem-TcT = precemtabart tocentecan.

6.5.1.2 Bevacizumab

Table 10 Temporary/Permanent Discontinuation of Bevacizumab for Bevacizumab-related Toxicities

Specifics	Toxicity[a]	Dose Interruption and Modification[b]
GI perforations and fistula	• GI perforations, Grade ≥ 1 • Tracheoesophageal fistula, Grade ≥ 1 • Fistula, Grade 4 • Fistula perforation involving any internal organ, Grade ≥ 1	Discontinue bevacizumab
Wound healing complications	• Wound healing complications requiring medical intervention • Necrotizing fasciitis	Discontinue bevacizumab
Hemorrhage	Grade ≥ 3	Discontinue bevacizumab
	Recent history of hemoptysis of ½ teaspoon (2.5 mL) or more	Withhold bevacizumab
Thromboembolic events	Arterial thromboembolism, Grade ≥ 3	Discontinue bevacizumab
	Venous thromboembolism, Grade ≥ 4	Discontinue bevacizumab
Hypertension	• Hypertensive crisis • Hypertensive encephalopathy	Discontinue bevacizumab
	Hypertension, Grade ≥ 3	Withhold bevacizumab, if not controlled with medical management. Resume once controlled
Posterior reversible encephalopathy syndrome	Grade ≥1	Discontinue bevacizumab
Renal injury and proteinuria	Nephrotic syndrome	Discontinue bevacizumab
	Proteinuria greater than or equal to 2 g per 24 h in the absence of nephrotic syndrome	Withhold bevacizumab until proteinuria less than 2 g per 24 h
Infusion-related reaction	Mild, clinically insignificant	Decrease infusion rate
	Mild or Moderate, clinically significant	Interrupt infusion, resume at a decreased rate of infusion after symptoms resolve
	Severe	Discontinue bevacizumab
Congestive heart failure	Any Grade	Discontinue bevacizumab
Anaphylaxis	Grade ≥ 3	Discontinue bevacizumab

GI = gastrointestinal, Hb = hemoglobin,

[a] NCI-CTCAE per bevacizumab local prescribing information.

[b] For any cases not covered in the table above, or if there is a discrepancy between the dose modification guidelines provided in this table and local product information or clinical practices, the more conservative approach should be followed.

6.5.1.3 Trifluridine/Tipiracil

Table 11 Dose Interruption and Resumption Criteria of FTD-TPI for Hematological Toxicities Related to Myelosuppression

Parameter	Interruption criteria	Resumption criteria[a]
Neutrophils	< 0.5 x 10^9/L	≥ 1.5 x 10^9/L
Platelets	< 50 x 10^9/L	≥ 75 x 10^9/L

[a] Resumption criteria apply to the start of the next cycle for all participants regardless of whether or not the interruption criteria were met.

Table 12 Dose Interruption and Resumption Criteria of FTD-TPI in Case of Hematological and Non-hematological Adverse Reactions

Adverse reaction[a]	Recommended dose modifications
• Febrile neutropenia • Neutropenia (< 0.5 x 10^9/L) or thrombocytopenia (< 25 × 10^9/L) that results in more than 1 week's delay in start of next cycle • Non-hematologic Grade 3 or Grade 4 adverse reaction; 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 5 mg/m^2/dose from the previous dose level (Table 8). • Dose reductions are permitted to a minimum dose of 20 mg/m^2/dose twice daily (or 15 mg/m^2/dose twice daily in severe renal impairment). • Do not increase dose after it has been reduced.

[a] NCI-CTCAE per FTD/TPI local prescribing information.

If the participant recovers from toxicities requiring treatment interruption:

- During the active treatment intake period of a cycle (treatment D1-D12):
  - if no dose reduction is required, FTD-TPI may be resumed during that cycle. Missed doses must not be caught up.
  - if a dose reduction is required, FTD-TPI should be resumed at the start of the next treatment cycle at the appropriate dose level.

- During the rest period (D13-28):
  - start the next cycle on schedule at the appropriate FTD-TPI dose level.

6.5.2 Prophylaxis and Management of Neutropenia

Hematological toxicities, including neutropenia and febrile neutropenia, were the most common severe AEs reported with single agent Precem-TcT treatment in the dose escalation and dose optimization parts of the PROCEADE-CRC-01 clinical study (refer to the IB and Section 2.3.1). In most cases, the onset of neutropenia was observed around D15. Similarly, neutropenia and severe neutropenia were reported in patients receiving FDP-TPI in combination with bevacizumab in the SUNLIGHT study (Prager 2023). In both the PROCEADE-CRC-01 and the SUNLIGHT studies, concomitant G-CSF was administered as required to prevent and manage neutropenia.

Therefore, the Sponsor recommends the use of primary or secondary G-CSF prophylaxis (preferably long-acting G-CSF) in this study, as per local and international guidelines (Aapro 2011; NCCN Hematopoietic Growth Factors 2025; Smith 2015; Greil 2007) and according to the Investigator's clinical judgment.

Given the observed late onset of neutropenia around D15 of a 21-day cycle with Precem-TcT, the Investigators may consider adjusting the usual G-CSF administration to around D8, in participants receiving Precem-TcT.

According to the NCCN guidelines, participants with ≥1 of the following risk factors should be assessed for prophylactic use of G-CSF:

- Prior chemotherapy or radiation therapy
- Persistent neutropenia
- Bone marrow involvement by tumor
- Recent surgery and/or open wounds
- Liver dysfunction (bilirubin > 2.0 x ULN)
- Renal dysfunction (creatinine clearance < 50 mL/min)
- Age > 65 years receiving full chemotherapy dose intensity

For participants who have experienced a febrile neutropenia or a neutropenic event that can impact planned dosing of study treatment, G-CSF should be used for all subsequent treatment cycles. Risk for development of neutropenia and febrile neutropenia should be reassessed before each treatment administration for every participant.

For management of febrile neutropenia and related infections with antibiotics, see Section 6.9.2 and Appendix 6 for medications that should be avoided or prohibited.

6.5.3 Management of Interstitial Lung Disease/Pneumonitis

ILD/pneumonitis has not been observed in preclinical studies or in the Phase 1 study with Precem-TcT (Section 2.3.1) and, therefore, is considered unlikely for Precem-TcT. ILD/pneumonitis has not been described for bevacizumab or FTD-TPI. On the other hand, since ILD/pneumonitis has been described for other ADCs, as a precaution, the study protocol provides guidance for management of ILD/pneumonitis.

All potential ILD/pneumonitis cases will be reported as an AESI or SAE (if seriousness criteria are fulfilled; see Section 8.3 and Appendix 4). All relevant clinical information, prior relevant study images, and imaging evaluations for ILD/pneumonitis will be collected for an ILD IRC (see Appendix 2).

If a participant develops an acute onset of new or worsening pulmonary condition, other related signs/symptoms such as dyspnea, cough or fever, or radiographic changes potentially consistent

with ILD/pneumonitis, interrupt treatment with Precem-TcT and rule out ILD/pneumonitis as soon as possible with a workup that should include the following:

- pulse oximetry (SpO2)
- clinical laboratory tests including complete blood count, biochemistry, CRP, serology tests, and blood culture
- high-resolution CT scan
- pulmonologist consultation (infectious diseases consultation as clinically indicated)
- bronchoscopy with bronchoalveolar lavage if clinically indicated and feasible
- arterial blood gases, pulmonary function tests, as well as one blood sample collection for PK and exploratory biomarker analysis should be considered.

Pulmonary toxicities related to bevacizumab or FTD-TPI, which might include a similar workup, should be addressed according to management guidance for non-hematological toxicity, and local prescribing information.

If the event is confirmed to have an etiology other than Precem-TcT-related ILD/pneumonitis, follow the appropriate management guidance.

If ILD/pneumonitis is considered related to Precem-TcT, follow the management guidance as outlined in Table 13.

Table 13 Management of ILD/Pneumonitis Considered Related to Precem-TcT.

ILD / Pneumonitis Severity (NCI CTCAE V6.0)	Management
Grade 1 Asymptomatic	• Consider corticosteroid (e.g. ≥ 0.5 mg.kg/day prednisone or equivalent) until improvement. Followed by gradual taper over at least 4 weeks • Interrupt Precem-TcT until the event is fully resolved to Grade 0 • If resolved ≤ 28 days from day of onset, maintain dose • If resolved in > 28 days from day on onset, reduce Precem-TcT dose to 2.4 mg/kg *Notes: Grade 0 refers to full resolution of ILD/pneumonitis, including the disappearance of radiological findings associated with active ILD/pneumonitis. Residual scarring or fibrosis following recovery of ILD/pneumonitis is not considered to be active disease.* *As per Section 7.1, if the start of the next cycle is delayed ≥ 28 days, the participant will discontinue Precem-TcT.* • Monitor and closely follow-up clinically with pulse oximetry (SpO2) in 2 to 7 days • Consider follow-up imaging in 1 to 2 weeks (or as clinically indicated) • If worsening despite initiation of corticosteroids, then follow guidance for Grade ≥ 2, according to clinical presentation
Grade 2 Mildly symptomatic	• Permanently discontinue Precem-TcT • Promptly start corticosteroids at ≥ 1 mg/kg/day with gradual taper over ≥ 4 weeks • Monitor symptoms closely • Re-image as clinically indicated • If worsening or no improvement in clinical or diagnostic observations in 5 days:

	• Consider increasing dose of corticosteroids (e.g. 2 mg/kg/day prednisone or equivalent) and administration to switch to iv • Reconsider additional workup for alternative etiologies

Grade 3 or 4
Severe or life-threatening
	• Permanently discontinue Precem-TcT
	• Hospitalization is required
	• Promptly start corticosteroids. Begin high-dose pulse therapy (e.g. iv methylprednisolone 500-1,000 mg/day for 3 days), followed by ≥ 1.0 mg/kg/day prednisone (or equivalent), with a gradual taper over ≥ 4 weeks
	• Re-image as clinically indicated
	• If no improvement within 3 to 5 days:
	  • Reconsider additional workup for alternative etiologies
	  • Consider other immunosuppressants and/or treat per local practice

6.5.4 Management of Diarrhea

Diarrhea has been identified as risk with Precem-TcT treatment (Section 2.3.1) and is also a common adverse reaction with FTD-TPI. Although diarrhea related to Precem-TcT and FTD-TPI is mainly mild to moderate (Grade 1-2), chemotherapy-induced diarrhea and its complications may result in treatment delays and interruptions, decrease compliance, and impact the quality of life, as well as become serious and potentially life-threatening, which may compromise long-term outcomes. Therefore, the following principles for management of diarrhea will apply:

- Educate participants and their families about the seriousness of chemotherapy-induced diarrhea.
- Instruct participants to contact study site staff at the first sign of loose stools and to record the number of stools, reporting any symptoms of complicated diarrhea (Table 14).
- Provide dietary guidance for managing diarrhea and supply loperamide (or standard antidiarrheal therapy), instructing participants on its use at the first sign of diarrhea.
- Monitor the participant's fluid and electrolyte balance, intervening with fluids and electrolyte replacement as needed (Benson III 2004).
- For study intervention delays, interruptions, and dose modifications, see Section 6.5.1 and Table 9.
- Guidelines for management of diarrhea are described in Table 14, and may be adapted according to institutional practice.
- For concomitant medications that might be used, such as antibiotics, see Section 6.9.2 and Appendix 6 for medications that should be avoided or prohibited.

Table 14 Management of Diarrhea.

Diarrhea Severity (NCI CTCAE V6.0)	Management
Mild to moderate diarrhea: Grade 1 or 2, without complications	• Initiate dietary modifications and standard antidiarrheal therapy, such as loperamide (4 mg initially, then 2 mg every 4 h or after each unformed stool, not exceeding 16 mg/day). • If diarrhea resolves, continue dietary modifications while gradually reintroducing solid foods. Discontinue antidiarrheal therapy after 12 h of being diarrhea-free.

Diarrhea Severity (NCI CTCAE V6.0)	Management
	• If diarrhea persists for over 24 h, increase the loperamide dose to 2 mg every 2 h and consider oral antibiotics for infection prophylaxis. • If diarrhea continues after 48 h, start a second-line antidiarrheal agent.
Complicated diarrhea: Grade 3 or 4, or Grade 1 or 2 diarrhea accompanied by any of the following symptoms: • Fever, sepsis, moderate to severe cramping • Grade 2 nausea/vomiting • Decreased performance status • Neutropenia • Hematochezia • Dehydration	• iv fluids. • Octreotide starting at 100 to 150 µg sc tid or iv (25 to 50 µg/h) for severe dehydration, with dose escalation up to 500 µg until diarrhea is controlled. • Administration of antibiotics (e.g. fluoroquinolone). • Conduct stool workup (for blood, fecal leukocytes, *C. difficile, Salmonella, E. coli, Campylobacter,* and infectious colitis), complete blood count, and electrolyte profile. • Continue interventions until the participant has been diarrhea-free for 24 h.

6.5.5 Management of Nausea and Vomiting

6.5.5.1 Precemtabart Tocentecan

Nausea and vomiting have been identified as risks with Precem-TcT treatment (Section 2.3.1). According to MASCC/ESMO consensus recommendation (Jordan 2023), Precem-TcT may be considered of low emetogenic risk (10% to 30% risk of emesis). Based on guidelines of chemotherapy-induced nausea and vomiting (NCCN Antiemesis 2025, Herrstedt 2024), prior to each dose of Precem-TcT, participants will receive prophylactic premedication at Day 1 with a 5 HT3 receptor antagonist ± dexamethasone, followed at Days 2 and 3 by continuation of either a 5-HT3 receptor antagonist or dexamethasone (Table 15). Additional antiemetic agents may be used, according to individual participant's needs, physician's discretion, and institutional practices. If NK1 receptor antagonists are used, see Section 6.9.2 and Appendix 6 for medications that should be avoided.

Table 15 Prophylaxis of Precem-TcT-induced Nausea and Vomiting.

Day 1	Days 2 and 3
5-HT3 receptor antagonist such as • palonosetron 0.25 mg iv qd • ondansetron 16-24 mg po qd, or 8-16 mg iv qd • dolasetron 100 mg po qd • granisetron 10 mg sc qd, or 2 mg po qd, or 3.1 mg/24 h transdermal patch applied 24 to 48 h before Precem-TcT dosing with or without dexamethasone 12 mg po or iv qd	5-HT3 receptor antagonist* such as • ondansetron 8 mg or 16 mg po bid or 8-16 mg iv qd • dolasetron 100 mg po qd • granisetron 1-2 mg po OR dexamethasone 8 mg po or iv daily

*No further 5-HT3 receptor antagonist is required if palonosetron or granisetron extended release (sc or transdermal patch) were administered on Day 1.

6.5.5.2 Trifluridine/Tipiracil

Nausea and vomiting are common adverse reactions for FDT-TPI, which is considered of low/minimal emetogenic potential, according to MASCC/ESMO consensus recommendation (Jordan 2023). Therefore, antiemetic medicines should be administered as needed. If indicated, a single antiemetic agent, such as dexamethasone, a 5-HT3 receptor antagonist or a dopamine receptor antagonist, such as metoclopramide may be considered for prophylaxis. The antiemetic will be administered during the days of FDP-TPI dosing, before the FTD-TPI intake. For further details on the management of FDP-TPI-induced nausea, refer to the local product information.

6.5.5.3 All Study Interventions

For all study interventions, the following apply:

- If a participant experiences acute or delayed nausea or vomiting despite the use of appropriate antiemesis prophylaxis as described above, then antiemetic prophylaxis needs to be adjusted for all subsequent cycles with the addition of another agent from a different drug class, or administration of a higher-level antiemetic regimen.

- In case a participant experiences anticipatory nausea and vomiting, benzodiazepines are recommended.

6.5.6 Prophylaxis and Management of Infusion-Related Reactions

6.5.6.1 Precemtabart Tocentecan

Premedication for prophylaxis of IRRs can be considered according to the physician's judgment prior to each subsequent dose of Precem-TcT for participants who have experienced Grade 2 IRR.

Table 16 Premedication for Prophylaxis of IRRs

Premedication Regimen and Recommended Doses	
Premedication	Corticosteroids: • Equivalent to 80-100 mg iv methylprednisolone, approximately 0.5 to 2 h prior to the start of Precem-TcT administration. • Corticosteroids premedication may be omitted in participants with insulin-dependent diabetes.
	Antihistamine (H1 antagonist): • Equivalent to 25-50 mg iv diphenhydramine, approximately 0.5 h prior to the start of Precem-TcT administration.
Additional premedication (*to add at any time during the study at the Investigator's discretion)*	Antihistamine (H2 antagonist) • Equivalent to 50 mg iv ranitidine or 20 mg iv famotidine or equivalent, approximately 0.5 h prior to the start of Precem-TcT administration.
	Acetaminophen: • 1,000 mg iv (where available, or po), or equivalent, approximately 0.5 h prior to the start of Precem-TcT administration.

Note: Doses may be adjusted based on institutional practices.

6.5.6.2 Bevacizumab

Participants receiving bevacizumab may be at risk of developing infusion/hypersensitivity reactions (including anaphylactic shock). Close observation of the patient during and following the administration of bevacizumab is recommended as expected for any infusion of a therapeutic humanized monoclonal antibody. If a reaction occurs, the infusion should be discontinued, and appropriate medical therapies should be administered. A systematic premedication is not warranted.

6.6 Retreatment Criteria

Not applicable.

6.7 Continued Access to Study Intervention After the End of the Study

Participants may be offered continued access to the study intervention that they received after study completion, when appropriate, according to local regulations and within defined limitations and as described below.

Rollover studies, patient support or access programs, marketed product, or single-patient poststudy access may be implemented when further research data on efficacy is not needed. Under this mechanism, the participant still receiving study intervention may be provided with the study intervention outside of the clinical study. The following prerequisites should be met: the benefits will outweigh the risks, the participant and the treating physician will comply with any legal and regulatory requirement, and there are no appropriate alternative treatments available.

Collection of safety data will continue, as specified in a safety reporting agreement with the treating physician outside of the CRF.

6.8 Treatment of Overdose

Even if not associated with an AE or SAE, any overdose is recorded in the CRF and reported to Global Patient Safety in an expedited manner. Overdoses are reported in the Safety Overdose case report form, as detailed in Appendix 4.

6.8.1 Precemtabart Tocentecan

Any dose of Precem-TcT greater than 10% than the calculated dose for that particular administration within a 24-hour time period will be considered an overdose.

The Sponsor does not recommend specific treatment for an overdose. For treating an overdose, the Investigator will use their clinical judgment, considering the symptoms and any site procedures or standards.

6.8.2 Trifluridine/Tipiracil

An overdose with FTD-TPI is defined as taking a dose beyond the recommended dose in one day or beyond the recommended total dose in each cycle (i.e. 35 mg/m²/dose or >170 mg/day) as assigned by the IRT. The highest dose of FTD-TPI administered in clinical studies was 180 mg/m^2 per day. The adverse drug reactions reported in association with overdoses were consistent with the established safety profile, being bone marrow suppression the primary anticipated complication. There is no known antidote available in case of FTD-TPI overdose. Overdose should be managed aggressively with close monitoring and administration of prophylactic and symptomatic therapies to prevent or correct potential side effects.

6.8.3 Bevacizumab

Any dose of bevacizumab greater than 10% than the calculated dose for that particular administration will be considered an overdose. The highest dose of bevacizumab tested in humans (20 mg/kg of body weight, iv q2w) was associated with severe migraine in several patients.

6.9 Concomitant Therapy

Record in the CRF all concomitant therapies (e.g. medicines or nondrug interventions) used from the signing of the ICF until the Safety Follow-up Visit at the timepoints specified in the SoA including any changes.

Contact the Medical Monitor for any questions on concomitant or prior therapy.

6.9.1 Permitted Medicines

Permitted medicines are the following:

- Prophylactic antiemetic agents according to Section 6.5.5.
- Primary or secondary prophylactic administration of G-CSF according to Section 6.5.2 and international scientific guidelines and local clinical practice (Crawford 2010, Aapro 2006, Smith 2015).
- Antidiarrheal therapy (e.g. loperamide) should be used in accordance with Section 6.5.4 and with the prescribing information or institutional guidelines.
- Inhaled steroids, topical steroids, or intra articular steroid injections are permitted in the study. Brief, limited use of systemic corticosteroids (< 7 days) is also permitted where such use is considered standard of care (e.g. for COPD exacerbation).
- IRR prophylaxis treatment is allowed according to Section 6.5.6.
- Vaccines: Investigators should assess prior to or at the beginning of the screening period, whether a participant should be vaccinated before receiving the first dose of IMP against a specific infectious disease, that may be a significant risk to the participant during the study. This assessment should include also for example the risk of COVID-19 infection or monkeypox infection. In general, Investigators may take into consideration that the vaccination effect may

be reduced in patients with cancer and may not lead to protection depending on the extent of the immunocompromised state of the participant including the impact of prior therapies.

Any medicines that are considered necessary to protect the participant's welfare in emergencies may be given at the Investigator's discretion, regardless of if it results in a protocol deviation.

6.9.2 Prohibited Medicines

If not otherwise specified, prohibited medications should not be used until the Safety Follow-up Visit.

- Participants may not receive any other anticancer therapy (e.g chemotherapy, biological therapies, hormonal therapies, alternative traditional medicines [e.g. herbal medicines, traditional Chinese medicines]), investigational therapeutic agents, or surgery of anticancer intent.
- Concomitant use of corticosteroids in a dose ≥ 10 mg per day of prednisone or equivalent when administered for ≥ 7 days. If the Investigator deems that corticosteroid use is needed in a higher dose or longer duration (e.g. for toxicity management, AE or intercurrent disease), the Medical Monitor must be consulted.
- Live vaccines are prohibited during the 28 days prior to C1D1 and during the whole study, as they may cause severe vaccine-induced infections in immunocompromised individuals. Non-live vaccines are prohibited during the 14 days prior to C1D1 and during the ± 5 days of each subsequent study intervention administration.
- Growth factors (including EPO, darbepoetin, G-CSF, GM-CSF, and platelet stimulators [e.g. eltrombopag, romiplostim, or IL-11]) or transfusions within 3 weeks prior to randomization.
- Radiotherapy. Exception: palliative stereotactic radiotherapy to known metastatic sites as long as it does not interrupt any study intervention for longer than the maximum time specified in the dose modification section (Section 6.5.1) and does not affect assessment of the response.
- All strong CYP3A4 inhibitors taken < 7 days prior to the first dose of study intervention (all arms) and during the study (Arm 1 and Arm 2). For a listing refer to Appendix 6 (https://www.fda.gov/drugs/drug-interactions-labeling/drug-development-and-drug-interactions-table-substrates-inhibitors-and-inducers).
- Participants will be instructed to refrain from consumption of any herbal/natural products which are potential CYP3A4 inhibitors (e.g. essiac tea) starting at least 7 days before the first administration of any study intervention (all arms) and during the study (Arm 1 and Arm 2).
- In Arm 1 and Arm 2, moderate CYP3A4 inhibitors should be avoided unless no alternative treatment exists. If coadministered, to be used cautiously with close monitoring of AEs.
- In Arm 1 and Arm 2, strong CYP1A2 inhibitors should be avoided unless no alternative treatment exists. If coadministered, to be used cautiously with close monitoring of AEs.
- For details on drug-drug interactions and prohibited medications with bevacizumab and FTD-TPI, refer to the local product information.

6.9.3 Other

- Arm 2 and Arm 3: Treatment with bevacizumab should be interrupted for elective surgery.
- Concomitant use of dietary supplements, medications not prescribed by the Investigator and alternative/complementary treatment (e.g. traditional Chinese medicines) are not recommended.

7 Discontinuation of Study Intervention and Participant Discontinuation/Withdrawal

Discontinuation of specific sites or of the entire study is specified in Appendix 2.

7.1 Discontinuation of Study Intervention

A participant may withdraw from receiving study intervention at any time, at their own request or at the discretion of the Investigator for safety, behavioral, compliance, or administrative reasons (e.g. disruption of operations due to natural disasters, interruption of lab or facility accreditation, participant moving to another country, resignation of key staff).

If study intervention is permanently discontinued, the participant will remain in the study to be evaluated for the End of Study Intervention (EoSI) and Safety Follow-up Visit as well as Survival Follow-up. The SoA indicates data to be collected at the time of discontinuation of study intervention and follow-up and for any further evaluations that need to be completed.

If a participant withdraws from receiving study intervention and attending study visits but remains in the study, long-term follow-up of survival data will continue.

Participants must be withdrawn from any study intervention if any of the following occurs:

- A participant's study intervention should be discontinued if the Investigator believes that for safety reasons (e.g. AE) it is in the participant's best interest.
- Liver Clinical Safety Laboratory Tests Stopping Criteria fulfilled (Section 7.1.1).
- Cardiac Safety Stopping Criteria being fulfilled (Section 7.1.2).
- The participant becomes pregnant.
- At the participant's request (withdrawal of consent or withdrawal of study intervention).
- If Precem-TcT and FTD-TPI treatment is delayed >28 days from the scheduled start date of the next cycle (regardless of bevacizumab treatment), treatment will be discontinued. Exception may be allowed for circumstances where the participant has previously benefited from study intervention, is expected to continue to benefit from resumed study intervention, and toxicity risks can be appropriately mitigated with dose modifications and/or supportive interventions, after discussion with the Medical Monitor.
- If the administration of a prohibited concomitant medication becomes necessary during the study, the Medical Monitor will be contacted first to discuss whether study intervention will be discontinued.

- Occurrence of disease progression according to RECIST V1.1.
- Noncompliance with the study intervention or failure to attend scheduled assessments that are deemed necessary for the participant's safety or study integrity for more than 28 days.

7.1.1 Liver Clinical Safety Laboratory Tests Stopping Criteria

The Investigator is required to discontinue study intervention for abnormal liver function when a participant meets 1 of the conditions outlined below or if the Investigator believes that it is in best interest of the participant.

All events of ALT/AST ≥ 3 × ULN and bilirubin ≥ 2 × ULN (> 35% direct bilirubin), without initial findings of cholestasis (elevated serum ALP) or ALT > 3 × ULN and INR > 1.5, if INR measured (not because of anticoagulants), and for which an alternative etiology has not been identified (such as viral hepatitis A, B, or C; preexisting or acute liver disease; disease under evaluation, or another drug capable of causing the observed injury).

Such cases may indicate potential severe liver injury (possible Hy's Law) and will be reported as an SAE.

7.1.2 Cardiac Safety Stopping Criteria

If a clinically significant finding is identified (including changes from baseline in QT interval corrected using Fridericia's formula [QTcF]) by > 60 ms or above 500 ms after start of study intervention, the Investigator or qualified designee upon consultation with the Medical Monitor will determine if the participant can continue in the study and if any change in participant management is needed. While increases in QT/QTc to > 500 ms or of > 60 ms over baseline are commonly used as thresholds for potential discontinuation, the exact criteria chosen for this study will depend on the risk-benefit level considered appropriate for the participant in question. This review of the ECG at the time of collection will be documented. Any new clinically relevant finding is reported as an AE.

7.1.3 Temporary Discontinuation

The dose of any study intervention must be withheld in case any of the situations described in Table 9, Table 10, Table 11, and Table 12 (Section 6.5) is fulfilled.

Before starting a new treatment cycle, all toxicities related to study treatment must have resolved according to Table 9, Table 10, Table 11, and Table 12 (except for toxicities considered by the Investigator to be unlikely to become serious or life-threatening).

7.2 Participant Discontinuation/Withdrawal from the Study

- A participant may discontinue from the study at any time, at their own request and for any reason or at the discretion of the Investigator for any reason if deemed that it is in the best interest of the participant, study, or both. In case of withdrawal, participants will be asked to

continue safety and survival follow-up, which includes the collection of data on survival and subsequent anticancer therapy.

- At the time of study discontinuation, if possible, a discontinuation visit will be conducted, as listed in the SoA. The SoA specifies the data to collect at study discontinuation and follow-up, and any additional evaluations that need to be completed.
- If the participant withdraws consent and wants to discontinue from the study, any data collected up to the date of withdrawal may still be used and analyzed, but no future data can be collected, except for the date of death from death registries when collection of this information is permitted. Any biological samples collected up to the date of study withdrawal may be retained and continued to be used for the purposes the participant originally consented, unless the participant specifically requests that certain samples be destroyed, or local laws require their immediate destruction. The results from these analyses will remain as part of the overall study data.
- Participants who discontinue from study intervention(s) will continue to be followed up for safety and survival.
- All possible efforts should be made to carry out the necessary follow-up visits, with particular emphasis on gathering Survival Follow-up information following the discontinuation of the study intervention.

7.3 Lost to Follow-Up

- If a participant fails to return to the clinic for a required study visit, the site will contact them or their family and reschedule the missed visit as soon as possible, counsel them on the importance of maintaining the assigned visit schedule and determine if they want to or will continue in the study.
- If the site is unable to contact the participant for long-term follow-up, the site will continue attempts to contact them or their family.
- The date of death may be collected from public records or by other means where allowed by local law/regulations.
- A participant is not considered as "lost to follow-up" until after study completion and the study site has been unable to reach them despite multiple attempts during the study or long-term follow-up. All contact attempts will be documented in the participant's medical records. The specific contact methods that will be used are in the operations manual.

8 Study Assessments and Procedures

- Study assessments and procedures and their timing are summarized in the SoA.
- No protocol waivers or exemptions are allowed.
- Immediate safety concerns are discussed with the Sponsor immediately upon occurrence or awareness to determine if the participant will continue or discontinue study intervention.
- Adherence to the study design requirements, including those specified in the SoA, is essential and required for study conduct.

- All screening evaluations will 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, to confirm eligibility, and if applicable, record reasons for screening failure.
- Prior to performing any study assessments that are not part of the participant's routine medical care, the Investigator will obtain written informed consent as specified in Appendix 2.
- Procedures conducted as part of the participant's routine medical care and obtained before signing of the ICF may be used for screening or baseline purposes provided the procedures met the protocol-specified criteria, were performed within the time frame defined in the SoA, and if reviewed and approved by the Sponsor.
- Where allowed by local law/regulations, samples collected during this clinical study may be transferred to a biobank and used for future research outside the clinical protocol when additional consent for this purpose is given. Transfer to the biobank will be documented and any testing of coded biobank samples will **not** be reported in the CSR.
- Where available and permitted by local regulations and site policies, participants may have access to televisit functionality, enabling them to connect with the site via telephone or video call for non-mandatory consultations (e.g. for adverse event reporting or clarification of questions) and survival follow-up. However, televisits cannot be utilized for the remaining visits and assessments outlined in the SoA. Updated survival status may be requested between scheduled study visits or contacts upon Sponsor notification.

8.1 Efficacy Assessments and Procedures

8.1.1 Tumor Assessments

Efficacy assessments and procedures and their timing are summarized in Section 1.2.

Tumor assessments will be performed at baseline prior to the start of study intervention, and then every 6 weeks (± 7 days) following the C1D1 visit until the 7th scheduled tumor scan (i.e. from screening until Evaluation 6 inclusive). Subsequent scheduled tumor assessments will be done every 12 weeks (± 7 days) until disease progression according to RECIST V1.1, death, lost to follow-up, withdrawal of consent, or End of Study, whichever comes first, regardless of study intervention delays, discontinuation, or subsequent anticancer therapies.

Approved study imaging modalities consist of CT, MRI and/or PET CT scan. CT is mandatory for chest imaging. If PET CT is used, CT moiety must be of diagnostic quality. Hybrid images should not be used for measurement. Regular scheduled as well as unscheduled on-study tumor assessments should use approved study imaging modalities. Imaging of the chest/abdomen/pelvis must be acquired. A brain CT/MRI scan will be performed if clinically indicated or for participants with known brain metastasis at baseline, as well as at any time during the study if new or worsening brain disease is suspected (Appendix 8). All scans performed at Screening must be repeated at subsequent visits for tumor assessment (exception: normal baseline brain scan with no new signs suggesting new brain disease). In general, lesions detected at Screening should be followed using the same imaging methodology and preferably the same imaging equipment at subsequent tumor

evaluation visits. New lesions seen on modalities other than CT, MRI, or the CT moiety of PET CT should be confirmed using study imaging modalities.

8.1.2 Patient-Reported Outcomes

PROs are relevant to mCRC as patients with CRC report more comorbidities and poorer HRQoL compared with patients with other common cancers. HRQoL is particularly important in the management of patients receiving later-line treatment and end-of-life care for mCRC (Fakih 2024). CRC and its treatments may adversely affect different dimensions of HRQoL, especially physical, social, economic, family, and medical aspects (Bonnetain 2017). A disease conceptual model of patient experience with mCRC identified 58 signs and symptoms with a total of 35 impacts reported by patients with mCRC ranging from interference with daily activities and impact on cognitive functioning to financial impacts and impact on social life (Guillemin 2024).

The proposed combination of PRO instruments is informed by the purpose of capturing both potential treatment-specific, cancer-specific, and CRC-specific dimensions through nonpreference-based questionnaires as well as the preference-based EQ-5D-5L to inform health economic modeling for health state utility estimates.

8.1.2.1 Administration of the PRO Questionnaires

The EORTC QLQ-C30, EQ-5D-5L, and a custom EORTC form will be administered according to the schedule shown in Table 1, Table 3, and Table 5.

Participants should read and complete the PRO instrument independently. Whenever possible, the PRO assessments should be completed prior to administration of study intervention. Questionnaires should also be completed by participants prior to any clinical tumor assessment and/or receiving results of any test, including disease status. PRO instruments should be completed in the following order: EQ-5D-5L, EORTC QLQ-C30, and custom EORTC form when all assessments are required. Completion of all questionnaires is expected to take 30 minutes in total. For mid-cycle assessments on Cycle 8 and/or Cycle 15, questionnaires are to be completed in the following order: EORTC QLQ C30 7-question set followed by custom EORTC form (5 questions).

Particular attention should be devoted to maximizing compliance. The CRO and the Sponsor will review compliance rates on a regular basis. PROs will not be reviewed or used to inform care decisions nor for safety purposes.

Participants should receive a short electronic training before completing the questionnaires for the first time. Participants should complete the questionnaires in a quiet, private area and any form of influence on their answers (e.g. conferring with relatives or study personnel) should be avoided to ensure participant’s privacy and absence of bias.

The questionnaires will be completed using an electronic device.

8.1.2.2 EORTC QLQ-C30

The EORTC QLQ-C30 is a cancer-specific health-related QOL questionnaire that has been widely used in clinical studies (Kluetz 2016). It is a self-reporting 30-item generic instrument which assesses 5 functional multi-item scales (physical, role, emotional, cognitive, social), 8 symptom scales (fatigue, nausea and vomiting, pain, dyspnea, insomnia, appetite loss, constipation, diarrhea), financial difficulties and a GHS/QoL scale. The responses to the functional and symptom scale items are scored from 1 to 4, whereas the responses to the GHS/QoL scale are scored from 1 to 7. The recall period is one week. Development and validation of the EORTC QLQ-C30 has been well documented as a reliable and valid measure of QOL in patients with cancer (Aaronson 1993) with widespread use in Europe and the US.

The following subset of 7 questions from the EORTC QLQ C30 informing the evaluation of tolerability objective, will be assessed at additional timepoints (see Table 1, Table 3, and Table 5):

- Have you felt weak?
- Were you tired?
- Have you felt nauseated?
- Have you vomited?
- Have you had diarrhea?
- Have you lacked appetite?
- Have you been constipated?

8.1.2.3 EQ-5D-5L

The EQ-5D-5L is a 6-item instrument developed by the EuroQol Group as a measure of health-related quality of life that can be used in a wide range of health conditions and treatments. The EQ-5D-5L consists of a descriptive system (5 items) and a single item EQ VAS. The descriptive system comprises 5 dimensions: mobility, self-care, usual activities, pain/discomfort, and anxiety/depression. The EQ VAS records the participant's self-rated health on a vertical VAS. The EQ-5D-5L has 5 response categories: no problems, slight problems, moderate problems, severe problems, and extreme problems. The participant is asked to indicate their health state by ticking the box next to the most appropriate statement in each of the 5 dimensions. The responses to each of the 5 dimensions (ranging from 1 to 5) are summarized into a 5-digit profile, which can be converted into a preference-weighted index value and is a key component for discussions with access decision makers.

8.1.2.4 Custom EORTC Form

The custom EORTC form was derived from the EORTC item library and includes 5 questions assessing various symptoms specific to CRC, or its treatment, and a question on side-effect burden:

- Did you have abdominal pain?
- Did you have a bloated feeling in your abdomen?

- Have you experienced frequent bowel movements?
- Have you had soreness in your mouth?
- To what extent have you been troubled with side effects from your treatment? [Q168]

Note: The mouth soreness [Have you had soreness in your mouth], and side-effect burden [Q168] questions will inform evaluation of tolerability objective.

8.2 Safety Assessments and Procedures

The safety profile of the study intervention will be assessed through the recording, reporting, and analysis of baseline medical conditions, AEs, physical examination findings, vital signs, electrocardiograms, ECOG performance status, and laboratory tests.

Comprehensive assessment of any potential toxicity experienced by each participant will be conducted starting when the participants give informed consent and throughout the study. The Investigator will report any AEs, whether observed by the Investigator or reported by the participant; the reporting period is specified in Section 8.3.

8.2.1 Physical Examinations

- A complete physical examination will include, at a minimum, assessments of the cardiovascular, respiratory, GI, skin, and neurological systems.
- Investigators will pay special attention to clinical signs related to previous serious illnesses and AEs requiring a dose modification (Section 6.5).

8.2.2 Vital Signs

- Blood pressure and participant's position during measurement; pulse; respiratory rate; temperature and location of measurement as indicated in the SoA (Section 1.2); weight and BMI (at Screening and Day 1 of each cycle), and height (at Screening only) will be measured. In Arm 3 BSA will also be measured (at Screening and Day 1 of each cycle).
- Blood pressure and pulse measurements will be preceded by at least 5 minutes of rest for the participant in a quiet setting without distractions (e.g. television, cell phones), in the sitting or semirecumbent position and measured with an automated device. Manual techniques will be used only if an automated device is not available.
- Vital signs will consist of 1 pulse and 3 blood pressure measurements (3 consecutive blood pressure readings will be recorded at intervals of at least 1 minute). The average of the 3 blood pressure readings will be recorded on the CRF.

8.2.3 Electrocardiograms

Single 12-lead ECGs will be obtained as outlined in the SoA using an ECG machine that automatically measures heart rate, PR, QRS, and QT. Also, QTcF, and RR will be automatically measured (preferred) or it will be calculated if the ECG machine cannot measure it automatically.

The ECG should be performed after at least 10 minutes rest in a recumbent or semirecumbent position and, if possible, prior to blood sampling. ECGs will be read locally and should be assessed on the day of collection and on dosing days before study drug administration by a physician or a qualified delegate according to the site's policy.

Investigators should assess if a finding is clinically significant, including changes from baseline in QTcF by > 60 ms or above 500 ms after start of study intervention. In case of a clinically significant finding, Investigators should interrupt study treatment until further clinical evaluation (Section 7.1.2). ECGs should be repeated if QTcF is outside the range until resolution. Additional ECGs can be performed as clinically indicated.

8.2.4 Clinical Safety Laboratory Tests

Blood and urine samples will be collected for the clinical laboratory tests listed in Appendix 5 at the time points listed in the SoA. All samples will be clearly identified.

Additional tests may be performed at any time during the study, as determined necessary by the Investigator or required by local regulations and results should be recorded in the CRF as unscheduled visits.

The tests will be performed by a central laboratory designated by the Sponsor and/or by a local laboratory, according to instructions shown in Appendix 5.

If both local and central samples are required, they will be obtained at the same time and assessed for the required analytes described in Appendix 5. Investigators will have access to the central laboratory results.

Laboratory tests performed centrally will be used to assess the eligibility of participants during Screening, except for tests which will be performed only locally: urinalysis, pregnancy, and optional HIV. Local laboratory results may be supportive to assess the eligibility of participants, only in case the central laboratory test results are not available in a timely fashion for the planned randomization and start of study intervention dates, and in consultation with the Medical Monitor.

Overall, after randomization, local laboratory results will be used for management of participants and safety assessments. Central laboratory results may support management of participants and safety assessments, as feasible. The Investigators will review each local laboratory result and document the review. The local laboratory results will be filed with the source documents and will be recorded in the eCRF. Any abnormal local laboratory tests results meeting the AE or SAE definition (see Appendix 4) will be reported by the Investigator.

8.2.5 Time Period for Use of Contraception Methods

The contraception, barrier, and pregnancy testing requirements for female study participants are as follows:

Before the first dose of the study intervention, if using hormonal contraception:

- Has completed at least one 28-day cycle of an oral contraception pill and either had or has begun her menses; **OR**,

- Has used a depot contraceptive or extended-cycle oral contraceptive for least 28 days and has a documented negative pregnancy test using a highly sensitive assay.

During the study intervention and up to 9 months after the last dose of study intervention agree to use highly effective contraception methods (Appendix 3) and not to donate eggs (ova, oocytes) for reproduction.

Requirements for male study participants are detailed in Section 5.1.

8.3 Adverse Events, Serious Adverse Events, and Other Safety Reporting

- The definitions of an AE, SAE, and SUSAR are in Appendix 4.
- The Investigator and any qualified designees (e.g. Subinvestigators) are responsible for detecting, documenting, and recording events that meet the definition of an AE or SAE. The Investigator remains responsible for following up all AEs and AEs that are serious, considered related to the study intervention or study procedures, or that caused the participant to discontinue the study intervention or study, as specified in Section 8.3.2.
- Requests for follow-up will usually be made via the Sponsor or CRO-designated study team member, although in exceptional circumstances the Global Patient Safety department may contact the Investigator directly to obtain further information or to discuss the event.
- The method of recording, evaluating, and assessing causality of AEs and SAEs and the procedures for completing and transmitting SAE reports are in Appendix 4.
- All AEs and SAEs will be collected from the signing of the ICF until the safety follow-up visit or the initiation of new anticancer therapy, whichever occurs first, at the timepoints specified in the SoA (Section 1.2). Beyond this reporting period, any new unsolicited SAEs that the Investigator spontaneously reports to the Sponsor will be collected and processed.
- All SAEs will be recorded and reported to the Sponsor or designee immediately and under no circumstance will this exceed 24 hours, as indicated in Appendix 4. The Investigator will submit any updated SAE data to the Sponsor within 24 hours of it being available using the same procedure that was used for the initial report.
- The Investigator is not obligated to actively solicit information on AEs or SAEs after the end of study participation. However, they will promptly notify the Sponsor if they learn of any SAE, including a death, at any time after a participant has been discharged from the study, and they consider the event to be reasonably related to the study intervention or study participation.

8.3.1 Method of Detecting Adverse Events and Serious Adverse Events

At each study visit, the participant will be queried on changes in their condition.

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.

The method of recording, evaluating, and assessing causality of AEs and SAEs and the procedures for completing and transmitting SAE reports are in Appendix 4.

8.3.2 Follow-up of Adverse Events and Serious Adverse Events

After the initial AE/SAE report, the Investigator is required to proactively follow each participant at subsequent visits/contacts. All SAEs, and AESIs (as defined in Section 8.3.7), will be followed until resolution, stabilization, the event is otherwise explained, or the participant is lost to follow-up (as defined in Section 7.3). Reasonable attempts to obtain this information will be made and documented. It is also the Investigator's responsibility to ensure that any necessary additional therapeutic measures and follow-up procedures are performed. Further information on follow-up procedures is in Appendix 4.

8.3.3 Regulatory Reporting Requirements for Serious Adverse Events

- Prompt notification by the Investigator to the Sponsor of an SAE (particularly life-threatening and deaths) is essential so that legal obligations and ethical responsibilities toward the safety of participants and the safety of a study intervention 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 intervention under clinical investigation.
    - SUSARs will be reported to regulatory agencies, as soon as possible but no later than 7 calendar days after the Sponsor first becomes aware that a case qualifies as fatal or life-threatening.
    - SUSARs will be reported to regulatory agencies, as soon as possible but no later than 15 calendar days after the Sponsor first becomes aware that a case qualifies as nonfatal or nonlife-threatening.
- An Investigator or Subinvestigator who receives an Individual Case Safety Report describing a SUSAR or other specific safety information (e.g. Emerging Safety Issue Report, summary or listing of SAEs/SUSARs) from the Sponsor will read it and confirm completion of this activity. This information will be filed in the Investigator's Site File, and the IRB/IEC will be notified, if appropriate, according to applicable local laws/regulations and site SOPs. For studies in EU/EEA and submitted under the EU Clinical Trial Regulation 536/2014, SUSARs will be reported centrally via the EudraVigilance database to Health Authorities by the Sponsor.
- In this global clinical multicenter study, the Sponsor is in the best position to determine an unanticipated problem (as defined in US Regulations 21 CFR 312.66). The Sponsor will immediately notify all Investigators of findings that could adversely affect the safety of participants, impact the conduct of the study, or alter the IRB's approval/favorable opinion to continue the study. An unanticipated problem is a serious adverse event that by its nature,

incidence, severity, or outcome has not been identified in the current version of the risk analysis report, specified in Section 2.3.

8.3.4 Pregnancy

- Details of all pregnancies in participants and, if indicated, participant's partners will be collected after the start of study intervention and until 9 months after the last dose of study intervention, for participants, and until 6 months after the last dose of study intervention, for participant's partners.
- If a pregnancy occurs in the participant, the Investigator will record in the CRF, the pregnancy test information and action taken (e.g. withdrawal from study due to pregnancy).
- If a pregnancy occurs in the participant or the partner, it will be reported within 24 hours after awareness to the Sponsor on the appropriate paper report form. For a partner pregnancy, the form is completed after obtaining the necessary signed partner's informed consent.
- 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. Abnormal pregnancy outcomes (e.g. spontaneous abortion, fetal death, stillbirth, congenital anomalies, ectopic pregnancy) are considered and reported as SAEs. A spontaneous abortion (occurring at < 22 weeks gestational age) or stillbirth (occurring at > 22 weeks gestational age) is always considered to be an SAE and will be reported as such.
- If pregnancy complications occur in the pregnant partner or in the child/fetus, these will be reported to the Sponsor on the appropriate paper form. For a partner pregnancy, the form is completed after obtaining the necessary signed partner's informed consent.
- The participant/partner will be followed to determine the outcome of the pregnancy. The Investigator will collect follow-up information on the participant/partner and the neonate, and the information will be forwarded to the Sponsor. Generally, follow-up will not be required for longer than 6 to 8 weeks beyond the estimated delivery date for a healthy newborn. In case of a congenital anomaly or other illness of the newborn, follow-up will continue until the illness has resolved or there is a definite outcome of the event.
- Any post study pregnancy related SAE considered reasonably related to the study intervention by the Investigator will be reported to the Sponsor as specified in Section 8.3.3. While the Investigator is not obligated to actively seek this information in former study participants/partner, they may learn of an SAE through spontaneous reporting.
- Any participant who becomes pregnant while participating in the study will discontinue study intervention.

8.3.5 Cardiovascular and Death Events

No dedicated collection of cardiovascular TEAEs is planned for this study. Potential cardiovascular AEs will be recorded according to standard TEAE documentation and reporting process. Death will not be collected as SAE but only be recorded as outcome of a TEAE.

8.3.6 Disease-Related Events and/or Disease-Related Outcomes Not Qualifying as AEs or SAEs

The following DREs are common in participants with mCRC and can be serious/life-threatening:

- Progressive disease

Because these events are typically associated with the disease under study, they will not be reported according to the standard process for expedited reporting of SAEs even though the event may meet the definition of an SAE. These events will be recorded as part of the secondary endpoints.

However, the event will be recorded and reported as an AE/SAE (instead of a DRE) as defined in Appendix 4.

8.3.7 Adverse Events of Special Interest

For this study, AESI(s) are as follows:

- Febrile neutropenia
- Any Grade ≥ 2 bleeding associated with Grade ≥ 3 thrombocytopenia
- ILD/pneumonitis

The Investigator must report any AESI to the Sponsor as specified in Appendix 4.

8.4 Pharmacokinetics

8.4.1 Blood Sampling and Bioanalysis

- Samples are collected only where allowed by local law/regulations.
- The actual date and time (24-hour clock time) of:
  - Each sample collection
  - Study intervention administration prior to sample collection

  will be recorded in the CRF to determine the elapsed time of sampling in relation to the administration of study intervention.
- Whole blood samples will be collected for measurement of Na-heparin plasma concentrations of Precem-TcT (conjugated antibody and unconjugated payload). Collection times are specified in the SoA.
- The quantification of Precem-TcT (conjugated antibody and unconjugated payload) in plasma will be performed using validated methods.
- Remaining samples collected for bioanalytical measurements may also be used for evaluating additional metabolites, immunogenicity, and safety or efficacy aspects related to concerns arising, or exploratory biomarkers during or after the study. Retention time and possible analyses of samples after the end of study are specified in the respective ICF.
- Details on processes for collection and handling of these samples are in the Laboratory Manual.

8.4.2 PK Parameters

- The following PK parameters for Precem-TcT (conjugated antibody and unconjugated payload) will be calculated, when appropriate:

Symbol	Definition
C_{eoi}	The observed concentration at the end of the infusion period.
C_{trough}	The concentration observed at the end of a dosing interval immediately before next dosing.

- Other PK parameters might be added based on emerging data. Details will be in the IAP.

- Listing of PK concentrations at each timepoint will be provided and summary statistics will be reported. When the actual sampling time is missing, calculations will be performed using the scheduled time. For samples to be collected within a time range the nominal midpoint will be used for PK evaluation, in case where the actual sampling time is missing. There will be no further imputation of missing data. Details will be provided in the IAP.

- Concentration data will be used for integrated data analyses across studies, such as population PK, and exposure-response analyses of efficacy, and safety analyses. Full details of the planed population PK, population pharmacokinetics/pharmacodynamics, and exposure-response modeling will be described in separate analysis plans. Results will be reported separately from the CSR.

8.5 Pharmacogenetics

Not applicable.

8.6 Biomarkers

- Samples are collected only where it is allowed by local law/regulations. See Appendix 7 for biomarker analyses performed in People's Republic of China.
- The following participant samples for biomarker research will be collected from all participants in this study. Collection times are specified in the SoA.
  - Tumor tissue samples will be tested retrospectively for expression of CEACAM5 to correlate expression levels with response to Precem-TcT or further clinical endpoints, using a Sponsor's proprietary test. There are no age restrictions for FFPE tissue block samples; however, tumor sections must be prepared fresh prior to shipment if only slides are provided. Bone biopsies, fine needle aspirates, and cell blocks are not suitable tumor tissue samples for examining CEACAM5 expression and will not be accepted. Details are described in the Laboratory Manual. Additional biomarkers (protein or mRNA expression, genetic mutations/aberrations) may be tested to evaluate their role in response to Precem-TcT or to further characterize the disease.
  - Serum samples will be collected pre- and on-treatment to have the opportunity to investigate baseline and under treatment levels of e.g. protein, RNA, DNA, or metabolite markers to evaluate impact on PK and/or treatment response or to further characterize the disease.

- Retention time and possible analyses of samples after the end of study are specified in the respective ICF.
- Details on processes for collection and handling of these samples are specified in the Laboratory Manual.

8.7 Immunogenicity Assessments

Participants who are pre-existing positive, transient treatment-emergent positive, or persistent treatment-emergent positive for ADA will be listed. Titers of ADA-positive samples will be reported. The impact of ADA formation on PK may be explored as permitted by the data. The details will be described in the IAP.

- The Sponsor considers Precem-TcT as a low-medium risk drug for immunogenicity-related clinical sequalae, considering the following:
  - Mechanism of action: Precem-TcT works as a CEACAM5 targeting ADC, killing tumor cells through the cytotoxic payload exatecan. The mode of action is considered low risk for ADA development or ADA-related clinical sequelae.
  - Structure: Precem-TcT is an IgG1 based ADC. Therefore, it does not have any endogenous counterpart. The likelihood of ADA incidence is considered to be comparable to other humanized monoclonal antibodies. The immunogenicity of Precem-TcT has been monitored during the dose escalation in study PROCEADE-CRC-01 with no sign of immunogenicity-related clinical sequalae.
  - Treatment route and patient population: The iv route is generally considered to be the least likely to elicit an immune response. Furthermore, it is not expected that the patient population to be treated with Precem-TcT would have an activated immune system (e.g. as in certain infections or autoimmune diseases), therefore, the patient population is not at high risk of developing immunity against Precem-TcT.
- Samples are collected only where allowed by local law/regulations.
- Whole blood samples will be collected for detection of antibodies against Precem-TcT in plasma. Collection times are specified in the SoA.
- The detection of antibodies to Precem-TcT will be performed using a validated assay method with tiered testing of screening, whole drug (Precem-TcT) confirmation and titration. Confirmed positive antibodies may be further characterized.
- Where allowed by local law/regulations, remaining samples collected for analysis of anti-Precem-TcT antibodies may also be used to evaluate Precem-TcT concentration or exploratory biomarkers during or after the study.
- Details on processes for collection and handling of these samples are in the Laboratory Manual. Retention time and possible analyses of samples after the end of study are specified in the respective ICF.

8.8 Health Economics

Healthcare resource utilization data are not collected in this study.

9 Statistical Considerations

The study will be considered positive if at least one of the primary null hypotheses, H_{0A1}^{OS} or H_{0A2}^{OS} as outlined in Section 9.1, is rejected. The hypothesis for the primary objective will be tested for statistical significance to demonstrate an improvement in the primary endpoint OS for Precem-TcT as single agent compared to FTD-TPI plus bevacizumab, or for Precem-TcT in combination with bevacizumab compared to FTD-TPI plus bevacizumab. The study is designed to conduct the following analyses simultaneously, triggered by the respective number of OS events for both two-arm comparisons: an early futility analysis based on an IF of approximately 30%, an efficacy interim analysis with an IF of approximately 75%, and the primary analysis which will be triggered once approximately 374 events have been observed for each of the 2-arm comparisons. The statistical testing of effect sizes between the Precem-TcT groups is not included in the confirmatory analysis. Should both investigational arms show superiority over FTD-TPI plus bevacizumab, a thorough benefit-risk assessment will be conducted, which will inform any potential recommendations for clinical practice and guide future treatment decisions.

If either of the OS null hypotheses is rejected in favor of one of the Precem-TcT groups, the key secondary efficacy endpoint, PFS will subsequently be tested for the corresponding Precem-TcT arm against FTD-TPI plus bevacizumab.

All other analyses of secondary endpoints, as well as the evaluation of the 2 investigational arms for OS and PFS, will be provided along with respective confidence intervals of any effect sizes for exploratory purposes only.

Further details of the planned statistical analyses are given in the IAP.

9.1 Statistical Hypotheses

9.1.1 Primary Hypotheses

The primary hypotheses to demonstrate superiority for the primary endpoint of OS between the 2 investigational arms and FTD-TPI plus bevacizumab are as follows:

- for comparing Arm 1 (A1, Precem-TcT monotherapy) versus Arm 3 (A3, FTD-TPI plus bevacizumab)

$$H_{0A1}^{OS}: \lambda_{A1}^{OS}(t) = \theta\lambda_{A3}^{OS}(t), \theta \geq 1 \text{ versus } H_{1A1}^{OS}: \lambda_{A1}^{OS}(t) = \theta\lambda_{A3}^{OS}(t), \theta < 1,$$

- for comparing Arm 2 (A2, Precem-TcT plus bevacizumab) versus Arm 3 (A3, FTD-TPI plus bevacizumab)

$$H_{0A2}^{OS}: \lambda_{A2}^{OS}(t) = \theta\lambda_{A3}^{OS}(t), \theta \geq 1 \text{ versus } H_{1A2}^{OS}: \lambda_{A2}^{OS}(t) = \theta\lambda_{A3}^{OS}(t), \theta < 1,$$

where $\lambda_{\square}^{OS}$(t) represents the hazard at time t and θ the unknown constant of proportionality of hazards in the treatment arms corresponding to the hazard ratio of OS.

9.1.2 Secondary Efficacy Hypotheses

Secondary efficacy testing will be done for the key secondary endpoint of PFS between the 2 investigational arms and FTD-TPI plus bevacizumab as follows:

- for comparing Arm 1 (A1, Precem-TcT monotherapy) versus Arm 3 (A3, FTD-TPI plus bevacizumab)

$$H_{0A1}^{PFS}: \lambda_{A1}^{PFS}(t) = \theta\lambda_{A3}^{PFS}(t), \theta \geq 1 \text{ versus } H_{1A1}^{PFS}: \lambda_{A1}^{PFS}(t) = \theta\lambda_{A3}^{PFS}(t), \theta < 1,$$

- for comparing Arm 2 (A2, Precem-TcT plus bevacizumab) versus Arm 3 (A3, FTD-TPI plus bevacizumab)

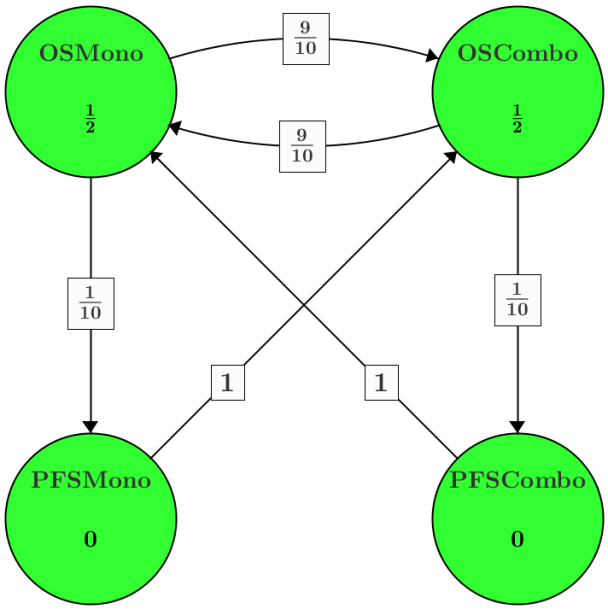
$$H_{0A2}^{PFS}: \lambda_{A2}^{PFS}(t) = \theta\lambda_{A3}^{PFS}(t), \theta \geq 1 \text{ versus } H_{1A2}^{PFS}: \lambda_{A2}^{PFS}(t) = \theta\lambda_{A3}^{PFS}(t), \theta < 1,$$

where $\lambda_{\square}^{PFS}$(t) represents the hazard at time t and θ the unknown constant of proportionality of hazards in the treatment arms corresponding to the hazard ratio of PFS.

9.1.3 Testing Strategy

The testing strategy to control the family-wise type I error rate (FWER) for the comparisons of the Arm 1 or Arm 2 vs Arm 3 for the primary endpoint OS and the key secondary efficacy endpoint PFS is based on the following graphical approach (Maurer 2013):

Figure 4 **Testing strategy for the primary endpoint OS and key secondary endpoint PFS**



OS/PFS Mono: OS/PFS comparison of Arm 1 (Precem-TcT monotherapy) versus Arm 3 (FTD-TPI plus bevacizumab),
OS/PFS Combo: OS/PFS comparison of Arm 2 (Precem-TcT plus bevacizumab) versus Arm 3 (FTD-TPI plus bevacizumab).

The primary endpoint of OS for Arm 1 compared to Arm 3 will be tested first at a one-sided alpha/2 level (1.25%). The OS of Arm 2 compared to Arm 3 will then be tested using the remaining one-sided alpha level (also alpha/2).

If the comparison between Arm 1 and Arm 3 shows statistical significance, PFS for Arm 1 vs Arm 3 can be tested with a one-sided type 1 error of 0.125% (1/10 of alpha/2). Additionally, a type 1 error of 2.375% can be utilized for the second OS test (Arm 2 compared to Arm 3). If both OS and PFS tests are positive for Arm 1 vs Arm 3, the full one-sided alpha of 2.5% can be applied for the second OS test (Arm 2 compared to Arm 3). If the first test is not statistically significant, the second test will be conducted at the alpha/2 level.

If the first test comparing Arm 1 versus Arm 3 is not statistically significant, but the second test comparing Arm 2 versus Arm 3 is significant, the loop-back feature will allow for a retest of Arm 1 versus Arm 3 with a one-sided type 1 error of 2.375% and the testing of PFS between Arm 2 and Arm 3 with a one-sided type 1 error of 0.125%. The same rules outlined for the previous testing will apply here.

Interim Analysis

An interim analysis for efficacy is planned; therefore, all significance levels mentioned above will be adjusted according to the Lan-DeMets method, employing O'Brien-Fleming-like boundaries based on the information fraction used during the interim analysis.

Secondary Objectives regarding the Assessments of OS and PFS

The assessment of the 2 investigational arms (Arm 1 versus Arm 2) regarding OS and PFS is specified as part of the secondary objectives. The respective analyses will be descriptive, and no formal statistical comparison is planned. The treatment effect of Precem-TcT plus bevacizumab versus Precem-TcT monotherapy will be estimated using stratified Cox regression analysis, and the estimated hazard ratio (HR) will be reported along with the corresponding 95% confidence interval. Ties will be handled by replacing the proportional hazards model by the discrete logistic model as the tie-handling method within the Cox model (refer to Collett 2014, chapter 3.3.2).

Additionally, KM estimates will be calculated, and KM curves will be generated to visualize the survival data. Should both investigational arms demonstrate superiority over FTD-TPI plus bevacizumab a thorough benefit-risk assessment will be conducted, which will inform any potential recommendations for clinical practice and guide future treatment decisions.

9.2 Sample Size Determination

Based on the primary endpoint of OS, the sample size is determined for testing the null hypotheses, taking into account the following design parameters and assumptions:

- Allocation ratio of 1:1:1 of Arm 1 to Arm 2 to Arm 3.
- One-sided alpha of 2.5%; for each of the 2 comparisons (Arm 1 vs. Arm 3 and Arm 2 vs. Arm 3) a type 1 error of 1.25% and a power of 90% are considered.
- Assumed effect size with a HR of 0.686 based on a median OS time of 12 months for Arm 3 (FTD-TPI plus bevacizumab; Section 9.2.1) vs a median OS time of 17.5 months for Arm 1 (Precem-TcT monotherapy) as well as for Arm 2 (Precem-TcT plus bevacizumab).
- Log-rank test as the primary test statistic for the comparison of 2 treatment arms.
- A non-binding futility analysis with an IF of 30% and a predefined futility boundary as a HR of 0.98.
- An interim efficacy analysis with an IF of 75% using an alpha spending according to Lan-DeMets with O´Brien-Fleming-like boundaries.
- Assumed enrollment of the participants within 18 months and a study duration of 30 months with a dropout rate of 5% per 12 months.

The sample size calculation is based on a two-arm comparison, where both study interventions (Arm 1: mono and Arm 2: combo) are compared separately to Arm 3 (FTD-TPI plus bevacizumab). The overall one-sided alpha of 2.5% is divided into 1.25% for each comparison. Since the effect sizes for Arm 1 vs. Arm 3 and Arm 2 vs. Arm 3 are assumed to be identical (see Section 9.2.1, Justification of Assumptions below), the required number of participants and events are the same.

To demonstrate that one of the study interventions (Arm 1 or Arm 2) is superior to FTD-TPI plus bevacizumab (Arm 3) concerning the primary endpoint of OS, 374 OS events across the 2 respective treatment arms are required for the primary analysis. This will ensure a power of 90%

(using a log-rank test) with a one-sided type 1 error of 1.25%, based on an expected hazard ratio (HR) of 0.686 (assuming median OS times of 12 months for A3 and 17.5 months for both Arm 1 and Arm 2). Considering a 5% dropout rate per 12 months, approximately 680 participants need to be randomized for the two-arm comparison, resulting in a total sample size of 1,020 participants (Table 19, Table 20, Table 21, Table 22, and Section 9.4.4).

9.2.1 Justification of Assumptions

The study aims to demonstrate an OS prolongation, hypothesizing a median OS difference of 5.5 months (17.5 months vs. 12 months) between either of the Precem-TcT arms and FTD-TPI plus bevacizumab arm. The efficacy boundary for the primary analysis is defined by a HR of 0.79, indicating an expected OS difference of >3 months, based on the assumed median OS time of 12 months for FTD-TPI plus bevacizumab. While the observed median OS time from published data for FTD-TPI plus bevacizumab (Prager 2023) is 10.8 months (with a 95% confidence interval of 9.4 to 11.8 months), using a slightly higher estimate of 12 months allows for a conservative approach in sample size calculations. This provides a buffer against potential variability in participant outcomes and enhances the robustness of the study findings. A prolongation of >3 months is considered clinically relevant as it leads to a median OS time of ≈15-17.5 months that is clearly above the OS range with current standard treatment options (Mayer 2015, Grothey 2013, Prager 2023, Dasari 2023). Moreover, an OS prolongation of ≥ 3 months for tumor types/settings where OS with control treatment is < 12 months is considered as clinically relevant according to the ESMO Magnitude of Clinical Benefit Scale (Cherny 2015).

For the investigational arms, a median OS time of 17.5 months was utilized for both the monotherapy arm (Arm 1) and the combination therapy arm (Arm 2). By using a median OS time of 17.5 months, the study design aims to enhance the likelihood of achieving a statistically significant and clinically meaningful effect size. In summary, the assumption of a median OS time of 17.5 months for the investigational arms is based on limited available clinical data, the need for a clinically relevant target, and the desire to ensure that the study is adequately powered to demonstrate meaningful treatment effects.

9.2.2 Assumptions for Key Secondary Endpoint PFS

Furthermore, for the key secondary efficacy endpoint PFS the following assumptions were considered:

- Allocation ratio of 1:1:1 of Arm 1 to Arm 2 to Arm 3 as mentioned above.
- Sample Size of 340 participants in each arm as determined based on OS.
- One-sided type I error of 0.125% is considered in case OS is tested positive.
- Assumed effect size with a HR of 0.622 based on a median PFS time of 5.6 months for Arm 3 (FTD-TPI plus bevacizumab) vs a median PFS time of 9 months for Arm 1 (Precem-TcT monotherapy) as well as for Arm 2 (Precem-TcT plus bevacizumab).
- Log-rank test as the test statistic for the comparison of 2 treatment arms.

- An interim efficacy analysis at Month 24 (simultaneously with OS IA) using an alpha spending according to Lan-DeMets with O'Brien-Fleming-like boundaries.
- Assumed enrollment of the participants within 18 months and a study duration of 30 months with a dropout rate of 5% per 12 months.

The operating characteristics for PFS are displayed in Table 19 (Section9.4.4).

9.3 Analysis Sets

The analysis sets are specified below.

Analysis Set	Description
SCR	All participants who provided informed consent, regardless of the participant's randomization and study intervention status in the study.
FAS	The FAS will include all randomized participants. Participant will be analyzed according to the treatment assigned at randomization as per the Intention-to-Treat (ITT) principle.
SAF	All participants who were administered any dose of any study intervention. Analyses will consider participants as treated.
PK	The PKAS will consist of all participants, who receive any dose of study intervention, and provide at least 1 measurable postdose concentration. A measurement BLQ is considered a valid measurement. Participants will be analyzed per the actual study intervention they received.
Immunogenicity	All participants who receive any dose of Precem-TcT and have at least 1 valid ADA result. All ADA analyses will be based on this analysis set.

ADA: anti-drug antibody; BLQ: below lower limit of quantification; PD: pharmacodynamics; PKAS: pharmacokinetic analysis set; Precem-TcT: precemtabart tocentecan.

9.4 Statistical Analyses

Analyses of all data will be performed by the Sponsor or its designee. The results will be reported in the Clinical Study Report. Details of the analyses of efficacy, safety, PK, and HRQOL will be described in the Integrated Analysis Plan, which will be finalized before the database lock for analysis.

To provide overall estimates of treatment effects, data will be pooled across study centers. The factor 'center' will not be considered in statistical models or for subgroup analyses due to the high number of participating centers in contrast to the anticipated small number of participants randomized at each center.

The primary analysis is based on using a stratified log-rank test with the following stratification factors:

- Geographical region (North America, East Asia, and rest of the world)
- ECOG PS (0 vs. 1)
- Presence of liver metastases (Yes vs. No)

In general, continuous variables will be summarized using number (n), mean, median, standard deviation, minimum, and maximum. Time-to-event data will be summarized based on Kaplan-Meier estimates, including but not limited to median (and 95% CI), frequency of participants with events, at risk, rate (and 95% CI) at predefined timepoints. Categorical variables will be summarized using frequency counts and percentages. Proportions are calculated based on the number of participants in the analysis set of interest, unless otherwise specified in the Integrated Analysis Plan. If not explicitly stated, no imputation is used in the analyses. All safety and efficacy endpoints will be summarized by treatment arm.

9.4.1 Efficacy Analyses

All analyses on efficacy endpoints are primarily done on the FAS. Participants will be analyzed according to the treatment assigned at randomization as per the ITT principle.

Details on the analyses for primary and key secondary efficacy estimands are shown in Table 17.

Table 17 Further Details on Statistical Analyses of Efficacy Estimands

Reference #	Category	Statistical Analysis
Primary		
1a–OS	Main	Population-Level Summary: OS between 2 treatment arms (Arm 1 vs Arm 3 and Arm 2 vs Arm 3) will be compared using a one-sided stratified log-rank test controlling for an overall one-sided type I error of 2.5% in a group-sequential design (see also Table 19, Table 21, and Table 22). The treatment effect will be evaluated in terms of the hazard ratio, including confidence interval (both adjusted and unadjusted), estimated by means of a Cox proportional hazards model, stratified by the randomization strata. Randomization strata will be taken as specified and documented in the IRT and each stratum will define a separate baseline hazard function. Ties will be handled by replacing the proportional hazards model by the discrete logistic model as the tie-handling method within the Cox model.
	Sensitivity 1	Rationale: Evaluate robustness of treatment effect toward IRT strata (as used for randomization) and corresponding eCRF variable(s) Sensitivity Analysis: Estimand as defined for main analysis, except for the following change: Population-Level Summary: Use strata from eCRF instead of IRT.
	Supplementary 1	Rationale: Explore interaction of treatment effect and selected baseline covariates Supplementary Analysis: Estimand as defined for main analysis, except for the following change: Population-Level Summary: Separately for each selected baseline covariate:

Reference #	Category	Statistical Analysis
		Interaction derived from unstratified Cox model including treatment effect, baseline covariate, and their interaction Wald-Test.
	Supplementary 2	Rationale: Explore homogeneity of treatment effect across subgroups defined by selected baseline covariates Supplementary Analysis: Estimand as defined for main analysis, except for the following change: Population-Level summary: Separately for each subgroup level (of selected baseline variables, e.g. age, sex, race, ethnicity, and tumor site): Treatment effect based on unstratified Cox model using treatment group as only covariate
Secondary		
1b -OS	Main	Population-Level Summary: The treatment effect will be evaluated in terms of the hazard ratio, including 95% confidence interval, estimated by means of a Cox proportional hazards model, stratified by the randomization strata. Randomization strata will be taken as specified and documented in the IRT and each stratum will define a separate baseline hazard function. Ties will be handled by replacing the proportional hazards model by the discrete logistic model as the tie-handling method within the Cox model.
2a - PFS	Main	Population-Level Summary: In case OS testing was positive, PFS between the respective 2 treatment arms (Arm 1 vs Arm 3 and/or Arm 2 vs Arm 3) will be compared using a one-sided stratified log-rank test controlling for an overall one-sided type I error of 0.125% in a group-sequential design (see also Table 20). The treatment effect will be evaluated in terms of the hazard ratio, including confidence interval, estimated by means of a Cox proportional hazards model, stratified by the randomization strata. Randomization strata will be taken as specified and documented in the IRT and each stratum will define a separate baseline hazard function. Ties will be handled by replacing the proportional hazards model by the discrete logistic model as tie-handling method within the Cox model.
	Supplementary 1	Rationale: Evaluation of the scientific question whether the drug improves PFS irrespective of subsequent anticancer therapy or long time-gap between PFS assessments (pure ITT analysis) Supplementary Analysis: Estimand as defined for main analysis, except for the following changes: Endpoint: Use all PFS events regardless of the time since last evaluable assessment or randomization.
	Supplementary 2	Rationale: Evaluation of the scientific question whether the drug improves PFS irrespective of subsequent anticancer therapy Supplementary Analysis: Estimand as defined for main analysis, except for the following change:

Reference #	Category	Statistical Analysis
		Intercurrent Event Strategy: The endpoint will be analyzed regardless of whether the intercurrent event 'Start of subsequent anticancer therapy' had occurred (treatment-policy strategy).
	Supplementary 3	Rationale: Explore homogeneity of treatment effect across subgroups defined by selected baseline covariates Supplementary Analysis: Estimand as defined for main analysis, except for the following change: Population-Level summary: Separately for each subgroup level (of selected baseline variables, e.g. age, sex, race, ethnicity, and tumor site): Treatment effect based on unstratified Cox model using treatment group as only covariate
2b - PFS	Main	Population-Level Summary: The treatment effect will be evaluated in terms of the hazard ratio, including 95% confidence interval, estimated by means of a Cox proportional hazards model, stratified by the randomization strata. Randomization strata will be taken as specified and documented in the IRT and each stratum will define a separate baseline hazard function. Ties will be handled by replacing the proportional hazards model by the discrete logistic model as tie-handling method within the Cox model.
3–OR	Main	Population-Level Summary: The confirmed OR rate (ORR) is the proportion of participants with confirmed OR in the analysis set. Confirmed OR status as assessed by Investigators will be compared between the 2 treatment arms by using a logistic regression model adjusted for randomization stratification factors. The same stratification factors used for the randomization will be applied to the analysis. The number of participants with confirmed OR will be presented along with the odds ratio and the corresponding 95% CI as well as the number and percentage of participants with a best overall response of confirmed CR, confirmed PR, SD, non-CR/non-PD, PD, and NE.
4–DoR	Main	Population-Level Summary: DoR is calculated for participants with confirmed objective response as the time from first documentation of confirmed objective response (CR or PR) to the date of first documentation of PD or death (due to any cause). If a participant has not had an event (PD or death), DoR is censored at the date of last adequate tumor assessment. Kaplan-Meier estimates (product-limit estimates) will be presented for the analysis of DoR, together with a summary of associated statistics (median, survival time and survival rate estimates at 3, 6, 12 months and every 6 months thereafter if applicable) including the corresponding 2-sided 95% CIs. DoR data will be censored on the date of the last non-missing tumor assessment for participants who do not have an event (PD or death) or for participants for which the event is reported after 2 or more missed subsequent scheduled tumor assessments or reported after start of subsequent anticancer therapy.
8 - HRQoL	Main	**Population-Level Summary:** Difference of least squared mean change from baseline until Cycle 6 based on mixed model for repeated measurements (MMRM).

Reference #	Category	Statistical Analysis
Exploratory		
9 - HRQoL	Explorative	Will be specified in the IAP finalized before database lock.

9.4.2 Safety Analyses

All safety analyses will be performed on the Safety Analysis Set. The analyses will be performed as a descriptive tabulation considering participants as actual treated.

Safety endpoints include AEs, clinical laboratory assessments, vital signs, ECG parameters, and ECOG PS. Table 18 provides more details on safety analyses.

Table 18 Statistical Analysis Methods for Safety Endpoints.

Reference #	Category	Statistical Analysis Methods
Secondary		
5 - Safety	Main	Safety will be analyzed on the Safety (SAF) population and will be based on all safety analysis reporting outcomes like AEs, AESIs, and laboratory tests outcomes. The safety endpoints will be tabulated using descriptive statistics. The incidence of AEs which includes AESIs, regardless of attribution, will be summarized by Preferred Term and System Organ Class (MedDRA Version 28.1 or higher) for each treatment arm, and described in terms of severity according to NCI-CTCAE V.6 grades and relationship to treatment. Summary and analysis of AEs will be performed based on the 3-tier approach (Crowe 2009). Further details will be provided in the Integrated Analysis Plan.

AE: adverse event, AESI: adverse events of special interest, CTCAE: Common Terminology Criteria for Adverse Events, IAP: Integrated Analysis Plan; MedRA, medical dictionary for regulatory activities.

9.4.3 Other Analyses

Details on the PK, pharmacogenomics, and exploratory biomarker analyses will be described in the IAP that will be finalized before database lock. Details on immunogenicity and exploratory biomarkers analyses will be provided and reported separately.

9.4.4 Sequence of Analyses

Regular safety review meetings of the external DMC are planned. Analyses will be conducted by an external SDAC. Access to data analyses generated for external DMC purposes, as well as aggregated data by treatment arms produced for futility and interim analyses, will be strictly controlled. All findings and documents resulting from the review of these data will be stored in a secure environment until the primary analysis is completed or a decision regarding unblinding is made. If any of the boundaries are crossed during the interim analyses, the external DMC Chair will notify the Firewall Team. Access to Restricted Information will be granted to the Firewall Team to assess aggregated study results with external DMC members, supporting informed Sponsor decision-making. Further details will be given in the external DMC Charter as well as in the Firewall Team Charter.

Regarding the primary endpoint, 3 comparative analyses are planned during the clinical study:

- **Futility analysis (non-binding) of OS:** An early futility analysis will be performed simultaneously for both investigational arms vs FTD-TPI plus bevacizumab once approximately 30% (112/374) of the required OS events are observed for each of the two-arm comparisons. A HR boundary of 0.98 was chosen for this analysis. The probability to cross the boundary under H_0 is 54.3%. The predictive probability of success to receive a positive outcome is 2.1% at the interim efficacy analysis (IF=75%) and 8.6% at the primary analysis (374 OS events) if a HR of 0.98 based on 112 OS events is observed at the time of the futility analysis (Kundu 2021). The futility analysis will be conducted by SDAC for the external DMC (Sections 4.1 and Appendix 2).

- **Interim analysis of OS:** An interim analysis will be triggered once approximately 75% of the required OS events (281/374) for the primary analysis are observed for each of the 2-arm comparison (see Table 19, Table 20, Table 21, and Table 22) for the critical values for the hypothesis testing). The interim analyses will be conducted SDAC for the external DMC (Sections 4.1 and Appendix 2) and will focus on primary endpoint analysis and supporting key secondary endpoints analyses. The primary intent of these analyses is to demonstrate that Precem-TcT as single agent or Precem-TcT in combination with bevacizumab prolongs OS compared to FTD-TPI plus bevacizumab. No early stopping of the study for efficacy is planned (i.e. the collection of study data will be continued). Provided that the results of the OS interim analysis are positive, the data may be used for regulatory and health technology assessment submissions purposes. This interim analysis will be conducted only if the anticipated duration between this interim analysis and the primary analysis, based on a forecast utilizing actual OS data, is at least 6 months. If this condition is not met, the interim analysis may be canceled. If OS is statistically significant, the corresponding PFS testing between those 2 arms will also be performed (see also Table 20).

- **Primary analysis of OS:** The primary analysis will be performed once approximately 374 OS events are observed for each of the two-arm comparison. The primary intent of this analysis is to demonstrate that Precem-TcT as single agent or Precem-TcT in combination with bevacizumab prolongs OS compared to FTD-TPI plus bevacizumab. If OS is statistically significant, the respective PFS testing between those 2 arms will also be performed to demonstrate that Precem-TcT as single agent or Precem-TcT in combination with bevacizumab prolongs PFS compared to FTD-TPI plus bevacizumab (see Table 19, Table 20, Table 21, and Table 22) for the critical values for the hypothesis testing). Analysis will be done on all endpoints. Results are planned to be used for regulatory and health technology assessment submissions.

The planned efficacy analyses with expected timing and corresponding operating characteristics are shown in Table 19.

Table 19 Planned Efficacy Analysis for OS with a One-Sided Type 1 Error of 1.25%, Expected Timing, and Operating Characteristics

Analysis (months)	No of events (IF)	HR boundary	p-value boundary (efficacy)[1]	Incremental probability crossing efficacy boundary (H1)[2]
OS futility (16)	112[3] (30%)	0.98 (futility)	NA	NA
OS IA (24)	281[3] (75%)	0.728 **(efficacy)[1]**	0.004	69.0%
OS PA (30)	374[3] (100%)	0.790 **(efficacy)[1]**	0.011	21.0%
Total:	**Sample Size: 680[3] / 1020[4]**			**Power: 90.0%**

H1: Alternative Hypothesis; HR: Hazard Ratio; IA: Interim Analysis; IF: Information Fraction; NA: Not applicable; OS: overall survival; PA: Primary Analysis.

[1] Alpha spending according to Lan-DeMets with O´Brien-Fleming-like boundaries

[2] Boundary Crossing Probability (incremental) at PA: The probability under the alternative hypothesis that the boundary will not be crossed at interim and will be crossed at PA. The sum over all time points is equal to the power

[3] Total number regarding two-arm comparison (investigational arm vs. FTD-TPI plus bevacizumab)

[4] Total number regarding all 3 treatment arms

Note: Decisions will be based on p-values with respect to actual number of events. Expected HRs under the assumption of an exponential distribution are only given as further information.

Analyses will be triggered by the respective numbers of OS events as mentioned above, while the significance boundaries are adjusted accordingly to control the family-wise error rate (FWER) at alpha/2 (1.25% one-sided) by using alpha spending according to Lan-DeMets with O'Brien-Fleming-like boundaries.

In case OS is statistically significant at IA for one of the investigational arms vs FTD-TPI plus bevacizumab then 1/10 of alpha/2 can be used for testing PFS in this investigational arm vs FTD-TPI plus bevacizumab (Table 20).

Table 20 Planned Efficacy Analysis for PFS with a One-Sided Type 1 Error of 0.125%, Expected Timing, and Operating Characteristics

Analysis (months)	No of events (IF)	HR boundary	p-value boundary (efficacy)[1]	Incremental probability crossing efficacy boundary (H1)[2]
PFS IA (24)	443[3] (83%)	0.727 **(efficacy)[1]**	0.0004	95.0%
PFS PA (30)	534[3] (100%)	0.768 **(efficacy)[1]**	0.0011	4.3%
Total:	**Sample Size: 680[3] / 1020[4]**			**Power: 99.3%**

H1: Alternative Hypothesis; HR: Hazard Ratio; IA: Interim Analysis; IF: Information Fraction; PA: Primary Analysis; PFS: progression-free survival.

[1] Alpha spending according to Lan-DeMets with O´Brien-Fleming-like boundaries

[2] Boundary Crossing Probability (incremental) at PA: The probability under the alternative hypothesis that the boundary will not be crossed at interim and will be crossed at PA. The sum over all time points is equal to the power

[3] Total number regarding 2-arm comparison (investigational arm vs. FTD-TPI plus bevacizumab)

[4] Total number regarding all 3 treatment arms

Note: Decisions will be based on p-values with respect to actual number of events. Expected HRs under the assumption of an exponential distribution are only given as further information.

In case OS is statistically significant at IA for one of the investigational arms vs FTD-TPI plus bevacizumab but not PFS then additional 9/10 of alpha/2 can be used for testing OS in the other investigational arm vs FTD-TPI plus bevacizumab (Table 21).

Table 21 Planned Efficacy Analysis for OS with a One-Sided Type 1 Error of 2.375%, Expected Timing, and Operating Characteristics

Analysis (months)	No of events (IF)	HR boundary	p-value boundary (efficacy)[1]	Incremental probability crossing efficacy boundary (H1)[2]
OS futility (16)	112[3] (30%)	0.98 (futility)	NA	NA
OS IA (24)	281[3] (75%)	0.754 **(efficacy)[1]**	0.009	78.2%
OS PA (30)	374[3] (100%)	0.810 **(efficacy)[1]**	0.021	14.8%
Total:	**Sample Size: 680[3] / 1020[4]**			**Power: 93.0%**

H1: Alternative Hypothesis; HR: Hazard Ratio; IA: Interim Analysis; IF: Information Fraction; NA: Not applicable; OS: overall survival; PA: Primary Analysis.

[1] Alpha spending according to Lan-DeMets with O´Brien-Fleming-like boundaries

[2] Boundary Crossing Probability (incremental) at PA: The probability under the alternative hypothesis that the boundary will not be crossed at interim and will be crossed at PA. The sum over all time points is equal to the power

[3] Total number regarding 2-arm comparison (investigational arm vs. FTD-TPI plus bevacizumab)

[4] Total number regarding all 3 treatment arms

Note: Decisions will be based on p-values with respect to actual number of events. Expected HRs under the assumption of an exponential distribution are only given as further information.

In case OS and PFS are statistically significant at IA for one of the investigational arms vs FTD-TPI plus bevacizumab, then the whole alpha of 2.5% can be used for the testing of the other investigational arm vs FTD-TPI plus bevacizumab (Table 22).

Table 22 Planned Efficacy Analysis for OS with a One-Sided Type 1 Error of 2.5%, Expected Timing, and Operating Characteristics

Analysis (months)	No. of events (IF)	HR boundary	p-value boundary (efficacy)[1]	Incremental probability crossing efficacy boundary (H1)[2]
OS futility (16)	112[3] (30%)	0.98 (futility)	NA	NA
OS IA (24)	281[3] (75%)	0.757 **(efficacy)[1]**	0.01	78.9%
OS PA (30)	374[3] (100%)	0.812 **(efficacy)[1]**	0.022	14.3%
Total	**Sample Size: 680[3] / 1020[4]**			**Power: 93.2%**

H1: Alternative Hypothesis; HR: Hazard Ratio; IA: Interim Analysis; IF: Information Fraction; NA: not applicable; OS: overall survival; PA: Primary Analysis.

[1] Alpha spending according to Lan-DeMets with O´Brien-Fleming-like boundaries

[2] Boundary Crossing Probability (incremental) at PA: The probability under the alternative hypothesis that the boundary will not be crossed at interim and will be crossed at PA. The sum over all time points is equal to the power

[3] Total number regarding 2-arm comparison (investigational arm vs. FTD-TPI plus bevacizumab)

[4] Total number regarding all 3 treatment arms

Note: Decisions will be based on p-values with respect to actual number of events. Expected HRs under the assumption of an exponential distribution are only given as further information.

At the time of analysis, all calculations must be updated based on the actual number of events.

10 References

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11 Appendices

Appendix 1 Abbreviations

1L	First Line
3L	Third Line
5-FU	5-Fluorouracil
5-HT3	5-hydroxytryptamine
ADA	Antidrug Antibody
ADC	Antibody-Drug Conjugate
AE	Adverse Event
AESI	Adverse Events of Special Interest
APAC	Asia-Pacific Region
BMI	Body Mass Index
BSA	Body Surface Area
C	Cycle
CDMO	Contract Development and Manufacturing Organization
CEA	Carcinoembryonic Antigen
CEACAM	Carcinoembryonic Antigen-Related Cell Adhesion Molecule 5
CRC	Colorectal Cancer
CRF	Case Report Form
CRO	Clinical Research Organization
CT	Computed Tomography, Chemotherapy
CYP	Cytochrome P450
DAR	Drug Antibody Rate
DL	Dose Level
DMC	Data Monitoring Committee
DoR	Duration of Response
ECG	Electrocardiogram
ECOG PS	Eastern Cooperative Oncology Group Performance Status
eCRF	Electronic Case Report Form
EGFR	Epidermal Growth Factor Receptor
EOI	End of Infusion
ESMO	European Society of Medical Oncology
FFPE	Formalin-fixed Paraffin-embedded
FIH	First-in-Human
FTD-TPI	Trifluridine/tipiracil

GC	Gastric Cancer
GCP	Good Clinical Practice
G-CSF	Granulocyte Colony-stimulating Factor
GEJC	Gastroesophageal Junction Cancer
GI	Gastrointestinal
GM-CSF	Granulocyte-macrophage Colony-stimulating Factor
HA	Health Authority
HBV	Hepatitis B Virus
HR	Hazard Ratio
HRQoL	Health-Related Quality of Life
IAP	Integrated Analysis Plan
IB	Investigator's Brochure
ICF	Informed Consent Form
IEC	Independent Ethics Committee
IF	Information Fraction
IHC	Immunohistochemistry
IL-11	Interleukin 11
ILD	Interstitial Lung Disease
IMP	Investigational Medicinal Product
INR	International Normalized Ratio
IRB	Institutional Review Board
IRC	Independent Review Committee
IRR	Infusion-Related Reactions
IRT	Interactive Response Technology
KM	Kaplan-Meier
MASCC	Multinational Association for Supportive Care in Cancer
mCRC	Metastatic Colorectal Cancer
MoA	Mechanism of Action
mOS	Median Overall Survival
MRI	Magnetic resonance imaging
MSI-H	Microsatellite Instability High
N	Number
NCCN	National Comprehensive Cancer Network
NCI-CTCAE	National Cancer Institute Common Terminology Criteria for Adverse Events

NSCLC	Non-small-cell Lung Cancer
NYHA	New York Heart Association
OR	Overall Response
ORR	Overall Response Rate
OS	Overall Survival
PD	Progressive Disease
PET	Positron Emission Tomography
PFS	Progression-free survival
PK	Pharmacokinetic
POCBP	Participants of Childbearing Potential
PR	Partial Response
PRO	Patient-reported Outcomes
QTc	Corrected QT interval
RECIST	Response Evaluation Criteria in Solid Tumor
SAE	Serious Adverse Event
SD	Stable Disease
SDAC	Statistical Data Analysis Center
SmPC	Summary of Product Characteristics
SoA	Schedule of Activities
SoC	Standard of Care
SSC	Study Steering Committee
SUSAR	Suspected Unexpected Serious Adverse Reactions
TEAE	Treatment-emergent Adverse Event
TRAE	Treatment-related Adverse Event
TOP1	Topoisomerase 1
VEGF	Vascular Endothelial Growth Factor

Appendix 2 Study Governance

Financial Disclosure

Investigators and Subinvestigators will provide the Sponsor with sufficient, accurate financial information, as requested, for the Sponsor to submit complete and accurate financial certification or disclosure statements to the appropriate regulatory authorities. This information is required during the study and for 1 year after completion of the study.

Informed Consent Process

- The Investigator or their representative will explain the nature of the study, including the risks and benefits, to the participant and answer all questions on the study.
- Participants will be informed that their participation is voluntary.
- Participants will be required to sign a statement of informed consent that meets the requirements of 21 CFR 50; local regulations; ICH guidelines; privacy and data protection requirements, where applicable; and the IRB/IEC or study center.
- The medical record will include a statement that written informed consent was obtained before the participant was enrolled in the study and the date the written consent was obtained. The authorized person obtaining the informed consent will also sign the ICF.
- If the ICF is updated during their participation in the study, participants will be reconsented to the most current, approved version.
- Participants will not need to be reconsented during Survival Follow-Up unless the changes to the ICF affect them. Participants who are rescreened are required to sign a new ICF.

Data Protection

- The Investigator and Sponsor will comply with all applicable regulations to protect personal data. If a data security breach occurs at the site, the Investigator will inform the Sponsor within 24 hours after becoming aware of the event. The Sponsor will manage the breach in accordance with their processes, including where applicable regulatory authority and/or IRB/IEC notification.
- Only the necessary data to meet the study objectives will be collected. Personal data will be kept only as long as needed and will be securely deleted or made anonymous afterwards.
- To keep personal data safe, security measures will be in place:
    - Only authorized people will have access to personal data, with regular checks to monitor who accesses it.
    - Personal data will be encrypted while being sent and stored to protect it from unauthorized access.
    - Personal data will be pseudonymized wherever possible, to reduce the risk of identification and to minimize exposure to personal data.

  - Personal data will be stored in safe locations using secure servers and cloud services that meet data protection standards Regular Security Assessments will be done to identify and address potential security risks.

- The Sponsor will assign a unique identifier to participants after obtaining their informed consent. Any participant records or datasets that are transferred to the Sponsor will contain the identifier only; participant names or any identifiable information will not be transferred.
- The Sponsor will inform participants that their personal study-related data will be used per local data protection and privacy laws. The level of disclosure will also be explained to the participant and pregnant partners (if applicable) who will be required to give consent for their data to be used, as specified in the informed consent.
- The participant will be informed that their medical records may be examined by Clinical Quality Assurance auditors or other Sponsor-appointed, authorized personnel, by appropriate IRB/IEC members, and by regulatory authority inspectors. All such persons will strictly maintain participants' confidentiality.

Study Administrative

The Coordinating Investigator listed on the title page represents all Investigators for decisions and discussions on this study, per ICH GCP. The Coordinating Investigator will provide expert medical input and advice on the study design and execution and is responsible for the review and signoff of the Clinical Study Report.

Several activities are outsourced to third-party service providers. These providers and activities include, but are not limited to a CRO, central laboratory, ePRO, IRT, imaging, and CDMO.

Study oversight committees will include SSC, external DMC, Firewall team, an IRC for ILD review, and an IRC for retrospective review of tumor assessments (at Sponsor's discretion).

Study Steering Committee

The SSC will ensure scientific validity of the entire study in an ongoing basis and assist the Sponsor in conducting the study, interpreting study data, and providing guidance on the implications and any additional analyses. Details will be provided in a separate SSC Charter.

External Data Monitoring Committee

An external DMC will be formed in this study before the randomization of the first participant. The external DMC will consist of expert members who are independent of the Sponsor. The members will be appointed by the Sponsor based on their expertise in clinical studies, biostatistics, and medical oncology. Members will not be Investigators in the study, nor will they have any conflict of interest with the Sponsor.

The external DMC will review the totality of available data produced on a regular basis and at the preplanned timepoints of futility and interim analysis. Ad hoc meetings can be scheduled if this is requested by the Sponsor or the external DMC.

Further details on the objectives, roles and responsibilities, operational procedures, data outputs, and data review are described in a separate external DMC Charter.

Firewall Team

The Firewall Team will consist of relevant Sponsor senior experts (as described in a dedicated Firewall Charter), who are independent of the study team, to review the external DMC recommendation(s) following interim analyses for futility as well as for efficacy with regards to the conduct of the study and according to the respective charters, preserving study integrity.

Independent Review Committee for Tumor Assessments

At Sponsor's discretion an IRC will perform a retrospective blinded central review of tumor assessment images of all participants. Details of structures and associated procedures will be defined in a separate Imaging Charter and Independent Review Charters, if applicable.

Independent Review Committee for ILD Review

An ILD IRC will be responsible for reviewing all cases of potential ILD/pneumonitis, in case they are observed. To ensure adequate and relevant independent evaluation, systematic additional data collection will be conducted for all cases that will be brought for review. The data to be reviewed will cover all relevant clinical information, prior relevant study images, and imaging evaluations for ILD/pneumonitis. The data collection and review will be triggered based on the AESI reporting of an ILD/pneumonitis, and with the support of a predefined list of preferred terms. The ILD IRC will review all cases on an ongoing basis. The details of the ILD IRC (membership, responsibilities, and working procedures) are described in its own charter, provided as a separate document.

Details of structures and associated procedures will be defined separately.

Regulatory and Ethical Considerations

- This study will be conducted in accordance with the protocol and the following:
  - Consensus ethical principles derived from international guidelines, including the Declaration of Helsinki and CIOMS International Ethical Guidelines
  - Applicable ICH GCP Guidelines
  - Applicable laws and regulations

    For studies with EU member states sites, with Regulation [EU] No 536/2014
- The protocol, protocol amendments (if applicable), ICF, IB, and other relevant documents (e.g. advertisements) will be submitted to an IRB/IEC for review and approval before the study is initiated.
- Any protocol amendments (i.e. changes to the protocol) will be documented in writing and, where applicable, require IRB/IEC approval before implementation of changes, except for changes necessary to eliminate an immediate hazard to study participants. When applicable, amendments will be submitted to the appropriate Health Authorities.

- The protocol and any applicable documentation will be submitted or notified to the Health Authorities in accordance with all local and national regulations for each site.

Emergency Medical Support

- The Sponsor or designee will provide Emergency Medical Support cards to participants for use during the study. These provide the means for participants to identify themselves as participating in a clinical study. Also, these give health care providers access to any information about this participation that may be needed to determine the course of medical treatment for the participant.
- The first point of contact for all emergencies will be the clinical study Investigator caring for the participant. Consequently, the Investigator agrees to provide their emergency contact information on the card. If the Investigator is available when an event occurs, they will answer any questions. Any subsequent action will follow the standard process established for Investigators.

When the Investigator is not available, the Sponsor provides the appropriate means to contact a Sponsor (or designee) physician. This includes provision of a 24-hour contact number at a call center, whereby the health care providers will be given access to the appropriate Sponsor (or designee) physician to assist with the medical emergency

Clinical Study Insurance and Compensation to Participants

Insurance coverage will be provided for each country participating in the study. Insurance conditions will meet good local standards, as applicable.

For Japan, the Sponsor is entirely responsible for AEs that are associated with this study and cause damage to the health of the participants, except for AEs caused by an intentional and/or significant deviation on the part of the Investigator, the study site, and/or the participant. The Sponsor takes out insurance to fulfill the responsibility.

Clinical Study Report

After completion of the study, the Sponsor will write a Clinical Study Report in consultation with the Coordinating Investigator following the guidance in ICH Topic E3, and it will be submitted in accordance with local regulations.

Publication

- 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 allows Merck to protect proprietary information and to provide comments.
- The Sponsor will comply with the requirements for publication of study results. Per standard editorial and ethical practice, the Sponsor will generally support publication of multicenter studies only in their entirety and not as individual site data.

- Authorship will be determined by agreement and in line with International Committee of Medical Journal Editors authorship requirements.

Dissemination of Clinical Study Data

- The Sponsor publicly discloses the design and results of clinical studies on platforms such as ClinicalTrials.gov, the CTIS, its clinical trial websites, and other relevant public registries and websites. This is done in compliance with the format, requirements, and timelines of the applicable local laws and regulations on clinical trial disclosure (e.g. Regulation [EU] No 536/2014).
- The results posting is carried out following the global completion of the study on CTIS, ensuring adherence to the relevant EU requirements for the disclosure of clinical trial information. No summary of intermediate data analyses as required per Art 37.8 of Regulation [EU] No 536/2014 will be submitted in CTIS in line with the exemption reasons #1 and #2 as explained in the Q&A document v7.1 (dated 27 March 2025), Question 6.6.
- The Sponsor also voluntarily discloses information beyond the scope of local laws and regulations, in accordance with its SOPs. The Sponsor always ensures that study results are disclosed in an objective, accurate, balanced, and comprehensive manner.
- Posted information is reviewed periodically to ensure it remains up to date.

Data Quality Assurance

- All participant study data will be recorded in the CRFs or transmitted to the Sponsor or designee electronically (e.g. laboratory data). The Investigator is responsible for verifying that data entries are complete, accurate, legible, and timely by physically or electronically signing the CRF. Details for managing CRFs are in the eCRF Completion Guidelines.
- For PRO data (e.g. QoL and pain assessments), ePRO will be used.
- The Investigator will maintain accurate documentation (source data) that supports the information in the CRF.
- The Investigator will permit study-related monitoring, quality assurance audits, IRB/IEC review, and regulatory agency inspections and provide direct access to the study file and source data.
- QTLs will be predefined and documented in the Trial Master File to help support the identification of systematic issues that could potentially impact participant safety and/or reliability of study results. These predefined parameters will be monitored during the study and important deviations from the QTL thresholds and remedial actions taken will be summarized in the Clinical Study Report.
- Monitoring details describing strategy, including definition of study critical data items and processes (e.g. risk-based initiatives in operations and quality such as Risk Management and Mitigation Strategies and Analytical Risk-Based Monitoring), methods, responsibilities, and requirements, including handling of noncompliance issues and monitoring techniques (central, remote, or on-site monitoring) are in the Monitoring Plan.

- The Sponsor or designee is responsible for data management of this study, including quality checking of the data and maintaining a validated database. Database lock will occur once quality control and quality assurance procedures have been completed. Details will be outlined in Data Management documents and procedures.
- Study Monitors will perform ongoing source data verification to confirm that data in the CRF are accurate, complete, and verifiable; that the safety and rights of participants are being protected; and that the study is being conducted per the currently approved protocol and any other study agreements, ICH GCP, and all applicable regulatory requirements.
- For studies with EU member states sites, the data will be collected and processed in accordance with Directive 95/46/EC.
- The Investigator will retain records and documents, including signed ICFs, pertaining to the conduct of this study for the required length of time after study completion, per all applicable regulations, institutional policies, or contractual agreement.
    - The archiving period is 25 years in EU member states.

Source Documents

- Source documents provide evidence for the existence of the participant and substantiate the integrity of the data collected.
- The Investigator will maintain source documents that support the data recorded in the CRFs.
- Data recorded on CRFs that are transcribed from source documents will be consistent with the source documents or the discrepancies will be explained. The Investigator may need to request previous medical records or transfer records, depending on the study. Also, current medical records will be available.
- Source documents are stored at the site for the longest possible time permitted by the applicable regulations, and/or as per ICH GCP guidelines, whichever is longer. The Investigator ensures that no destruction of medical records is performed without the Sponsor's written approval.
- Definition of what constitutes source data, and its origin is found in the Monitoring Plan.

Study and Site Start and Closure

- The study start date is when the first participant signs the Informed Consent Form.

Study and Site Closure

The Investigator may initiate site closure at any time, provided there is reasonable cause, and enough notice is given in advance of the intended closure.

Reasons for the early closure of a study site by the Sponsor or Investigator may include:

- Failure of the Investigator to comply with the protocol, the requirements of the IRB/IEC or local health authorities, the Sponsor's procedures, or GCP guidelines.
- Inadequate recruitment of participants by the Investigator.

- Discontinuation of further development of the Sponsor's compound.
- Based on a negative data analysis outcome of the study, or discontinuation of the development of the compound, the Sponsor may decide to immediately shorten timelines or stop non-patient-safety related assessments or sampling procedures with the intention to reduce study-related burden of the ongoing participants.

These assessments/procedures may include:

  - Long-term follow-up assessments/procedures
  - Collection of biological samples (e.g. blood and tissue)
  - Collection of blood samples for clinical laboratory tests for the central laboratory
  - Exploratory Measurements
  - PRO procedures

- The Sponsor will decide which study procedures/assessments that are not related to participant safety will be discontinued.

If the study is prematurely terminated or suspended, the Sponsor will promptly inform the Investigators, the IECs/IRBs, the regulatory authorities, and any third-party service providers of the reason for termination or suspension, as specified by the applicable regulatory requirements. The Investigator will promptly inform the participants and assure appropriate participant therapy and/or follow-up.

Appendix 3 Contraception and Barrier Requirements

Definitions:

Pregnant:

A participant of childbearing potential with a positive result from a highly sensitive hCG pregnancy test.

POCBP:

A participant is of childbearing potential (fertile) following menarche and until becoming postmenopausal unless permanently sterile, as specified below.

If fertility is unclear (e.g. amenorrhea in adolescents or athletes) and a menstrual cycle cannot be confirmed before the first dose of study intervention, consider additional evaluation.

Postmenopausal:

Postmenopausal is defined as no menses for at least 12 months. If menopausal status is in doubt, the participant will be required to use a highly effective contraceptive method, as specified below. FSH test is required to confirm postmenopause.

Permanent Sterilization:

Permanent sterilization includes:

- Documented hysterectomy
- Documented bilateral salpingectomy
- Documented bilateral oophorectomy

Documentation can come from the site personnel's review of the individual's medical records, medical examination, or medical history interview.

For individuals with permanent infertility due to an alternate medical cause other than the above, (e.g. Mullerian agenesis, androgen insensitivity), Investigator discretion applies to determine study entry.

Contraceptives Allowed During the Study

Highly Effective Methods - Low User Dependency

- Implantable progestogen-only hormone contraception associated with inhibition of ovulation
- IUD
- IUS
- Bilateral tubal occlusion
- Azoospermic partner (vasectomized or due to a medical cause): azoospermia is considered a highly effective contraceptive method provided the partner is the sole sexual partner of the POCBP and the absence of sperm has been confirmed. Otherwise, use an additional highly effective method of contraception. The spermatogenesis cycle is approximately 90 days.

Documentation can come from the site personnel's review of the individual's medical records, medical examination, or medical history interview.

Highly Effective Methods - User Dependent

- Combined (estrogen- and progestogen-containing) hormonal contraception associated with inhibition of ovulation:
  - Oral
  - Intravaginal
  - Transdermal
  - Injectable
- Progestogen-only hormone contraception associated with inhibition of ovulation:
  - Oral
  - Injectable
- Sexual abstinence: a highly effective method only if defined as refraining from intercourse during the entire period of risk associated with the study intervention. 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.

Barrier Methods

Barrier Methods (to be used in addition to a highly effective method):

- External or internal condom with or without spermicide.
- Cap, diaphragm, or sponge with spermicide.

Notes

Contraceptive use will be consistent with local regulations on contraceptive methods for clinical study participants. For country-specific contraception requirements or restrictions, see Appendix 7 where these are specified.

Highly effective methods are those with a failure rate of < 1% per year when used consistently and correctly. Typical use failure rates differ from those when used consistently and correctly.

Hormonal contraception may be susceptible to interaction with the study intervention(s), which may reduce the efficacy of the contraceptive method. As such, 1) barrier methods (external or internal condom with or without spermicide; cap, diaphragm, or sponge with spermicide) in addition to hormonal contraception or 2) a non-hormonal IUD will be used. If locally required, in accordance with CTFG guidelines, acceptable contraceptive methods are limited to those which inhibit ovulation as the primary mode of action.

Periodic abstinence (calendar, symptothermal, post-ovulation methods), withdrawal (coitus interruptus), spermicides only, and LAM are not acceptable methods of contraception for this study. External and internal condoms cannot be used together (due to risk of failure from friction).

Appendix 4 Adverse Events: Definitions and Procedures for Recording, Evaluating, Follow-up, and Reporting

AE Definition

AE Definition
• An AE is any untoward medical occurrence in a patient or clinical study participant, temporally associated with the use of study intervention, whether considered related to the study intervention or not. • 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 intervention. For surgical or diagnostic procedures, the condition/illness leading to such a procedure is considered as the AE rather than the procedure itself.
Events <u>Meeting</u> the AE Definition
• Any abnormal laboratory test results (e.g. hematology, clinical chemistry, or urinalysis) or other safety assessments (e.g. ECG, radiological scans, vital signs measurements), including those that worsen from baseline and are judged to be more severe than expected for the participant's condition per the Investigator's medical and scientific judgment, are considered clinically significant in the medical and scientific judgment of the Investigator (e.g. not related to progression of underlying disease, but may be leading to study intervention discontinuation). • 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 intervention 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 intervention or a concomitant medication. • "Lack of efficacy" or "failure of expected pharmacological action" per se will not be reported as an AE or SAE. However, the signs, symptoms, and/or clinical sequelae resulting from lack of efficacy will be reported as an AE or SAE if they fulfill the definition of an AE or SAE.
Events <u>NOT</u> Meeting the AE Definition
• Unless judged by the Investigator to be more severe than expected for the participant's condition, any clinically significant abnormal laboratory findings, other abnormal safety assessments that are associated with the underlying disease, the disease/disorder being studied within the expectedness for participant's condition, as judged by the Investigator. • Medical or surgical procedure (e.g. 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.

AE/SAEs Observed in Association with Disease Progression

Progression of the disease/disorder being studied assessed by measurement of lesions on radiographs or other methods as well as associated clinical signs or symptoms (including laboratory abnormalities) will not be reported as AEs/SAEs, unless the participant's general condition is more severe than expected for their condition and/or unless the outcome is fatal within the AE reporting period, as defined in Section 8.3.

SAE Definition

If an event is not an AE per the definition above, then it cannot be an SAE even if serious conditions are met (e.g. hospitalization for signs/symptoms of the disease under study, death due to progression of disease outside of the AE reporting period).

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 will be considered serious.
- Hospitalization for elective treatment of a pre-existing condition that did not worsen from baseline is not considered an AE.
- However, all events leading to unplanned hospitalizations or unplanned prolongation of an elective hospitalization must be documented and reported as SAEs.

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 (e.g. 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. Other situations

- Medical or scientific judgment will 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 1 of the other outcomes listed in the above definition. These events are usually considered as serious.
- Examples of such events include 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.

Any suspected transmission of an infectious agent via a study intervention is also considered an SAE for reporting purposes, as specified below for reporting SAEs or AESIs.

SUSAR Definition

A SUSAR is an adverse reaction that meets these 3 criteria: suspected, unexpected, and serious.

- Suspected: There is a reasonable possibility that the drug caused the adverse drug reaction.
- Unexpected: An adverse reaction, the nature or severity of which is not consistent with the applicable product information (e.g. the RSI, refer to glossary term in the IB or alternative documents, according to applicable regulatory requirements).
- Serious: Refer to SAE definition above.

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 (e.g. hospital progress notes, laboratory reports, and diagnostics reports) related to the event.
- The Investigator will then record all relevant AE/SAE information in the CRF.
- As needed, the Sponsor or designee may ask for copies of certain medical records (e.g. autopsy reports, supplemental lab reports, documents on medical history/concomitant medications, discharge letters), as supporting source documentation. All participant identifiers, except the participant number, will be redacted on these copies before submission to the Sponsor or 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.
- Specific guidance is in the CRF Completion and Monitoring Conventions.

Assessment of Intensity

- The Investigator will assess the intensity of each AE and SAE reported during the study and assign it to 1 of the following categories:

- Mild: A type of adverse event that is usually transient and may require only minimal treatment or therapeutic intervention. The event does not generally interfere with usual activities of daily living.
- Moderate: A type of adverse event that is usually alleviated with additional specific therapeutic intervention. The event interferes with usual activities of daily living, causing discomfort but poses no significant or permanent risk of harm to the research participant.
- Severe: A type of adverse event that interrupts usual activities of daily living, or significantly affects clinical status, or may require intensive therapeutic intervention.
- Do not confuse an AE that is assessed as severe with an SAE. Severe is a category used to rate the intensity of an event; both AEs and SAEs can be assessed as severe. An event is defined as "serious" when it meets at least 1 of the predefined criteria specified in the definition of an SAE, NOT when it is rated as severe.

Investigators will reference the NCI-CTCAE, version 6.0 (publication date: 22 July 2025), a descriptive terminology that can be used for AE reporting.

A general grading (severity/intensity; hereafter referred to as severity) scale is provided at the beginning of the above referenced document, and specific event grades are also provided.

If the severity for an AE is not specifically graded by NCI-CTCAE, the Investigator is to use the general NCI-CTCAE definitions of Grade 1 through Grade 5, using their best medical judgment.

The 5 general grades are:

- Grade 1 or Mild
- Grade 2 or Moderate
- Grade 3 or Severe
- Grade 4 or Life-threatening
- Grade 5 or Death

Any clinical AE with severity of Grade 4 or 5 must also be reported as an SAE. However, a laboratory abnormality of Grade 4, such as anemia or neutropenia, is considered serious only if the condition meets 1 of the serious criteria specified below.

If death occurs, the primary cause of death or event leading to death will be recorded and reported as an SAE. "Fatal" will be recorded as the outcome of this specific event and death will not be recorded as separate event. Only, if no cause of death can be reported (e.g. sudden death, unexplained death), the death per se might then be reported as an SAE.

Assessment of Causality

- The Investigator will assess the relationship between study intervention and each AE/SAE occurrence:

- Unrelated: Not reasonably related to the study intervention. AE could not medically (pharmacologically/clinically) be attributed to the study intervention. A reasonable alternative explanation will be available.
- Related: Reasonably related to the study intervention. AE could medically (pharmacologically/clinically) be attributed to the study intervention.

- 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 intervention administration will be considered and investigated.
- The Investigator will also consult the IB and/or Product Information, for marketed products, in their assessment.
- For each AE/SAE, the Investigator will document in the medical notes that they reviewed the AE/SAE and assessed causality.
- There may be situations when an SAE has occurred, and the Investigator has minimal information to include in the initial report to the Sponsor or its designee. To meet the reporting timeline, the causality assessment is not required for the initial report.
- The Investigator may change their causality assessment after considering follow-up information and send an SAE follow-up report with the updated causality assessment.
- The causality assessment is 1 of the criteria used when determining regulatory reporting requirements.

Follow-up of AEs and SAEs

- The Investigator will perform or arrange for the conduct of supplemental measurements and/or evaluations, as medically indicated or as requested by the Sponsor or designee 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.
- If a participant dies, for reasons not due to disease progression, during participation in the study or during a recognized follow-up period, the Investigator will provide Sponsor with a copy of any post-mortem findings including histopathology. New or updated information will be recorded in the originally completed CRF.
- The Investigator will submit any updated SAE data to the Sponsor or designee within 24 hours of receipt of the information.

Reporting of SAEs

SAE Reporting by an Electronic Data Collection Tool
• The primary mechanism for reporting an SAE in multicenter studies to the Sponsor or its designee will be the electronic data collection tool, with the exception of pregnancy and pregnancy complication reporting. • If the electronic system is unavailable, then the site will use the paper SAE form, specified below, to report the event within 24 hours. • The site will enter into the electronic system the SAE data within 24 hours after becoming aware of the event. It is expected that the Investigator/SubInvestigator signs off this data in the system and any relevant associated data (e.g. additional laboratory tests, medical records, diagnostic reports, histopathological examinations, or consultation with other health care professionals) will be entered as soon as it becomes available. • After the study is completed at a 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 or to the Sponsor's safety department. • By exception, an SAE (or follow-up information) may be reported by telephone. The site will complete the electronic SAE data entry immediately thereafter.
SAE Reporting by a Paper Form
• SAE reporting on a paper report form may be used as a back-up method for an EDC system failure. The paper form includes completion instructions for the Investigator, names, addresses, and telephone, and fax numbers. All information from the paper form will be transcribed into the electronic form as soon as the system becomes available. • The paper form will be transmitted to the Sponsor or its designee within 24 hours by email or facsimile (fax to mail). • In rare circumstances and in the absence of facsimile equipment, notification by telephone is acceptable with a copy of the form sent by overnight mail or courier service. • Initial notification via telephone does not replace the need for the Investigator to complete and sign the form within 24 hours after becoming aware of the event. • Additional documents (e.g. laboratory reports, autopsy report, hospital discharge letter) may also be required. The data provided will be consistent with the information in the CRF.

Reporting of AESIs

• The site will record nonserious and serious AESIs within 24 hours in the CRF, using the same process as stated in the above section entitled "Reporting of SAEs". Paper report forms may be used as a back-up method for an EDC system failure and will be transmitted to the Sponsor or its designee within 24 hours by facsimile (fax to mail) or email.

Appendix 5 Clinical Laboratory Tests

The protocol-required clinical laboratory assessments are in the following table. For detailed information about which Laboratory Assessments are required at each visit, see the SoA.

Category	Laboratory Assessment	Notes	Screening		Visits After Randomization	
			Central	Local	Central	Local
Biochemistry	Albumin			X		X
	Alanine aminotransferase		X	X	X	X
	Alkaline phosphatase		X	X	X	X
	Amylase		X	X	X	X
	Aspartate aminotransferase		X	X	X	X
	Total bilirubin	If total bilirubin is increased, indirect bilirubin is required. Testing both indirect and direct bilirubin upfront is acceptable.	X	X	X	X
	Blood urea nitrogen or urea		X	X	X	X
	Calcium	Ionized calcium is preferred.		X		X
	Magnesium			X		X
	Creatinine		X	X	X	X
	Estimated creatinine clearance (Cockcroft-Gault formula)	At Screening the central creatinine value will be used for calculation and reported in the CRF.	X			X
	C-reactive protein			X		X
	Gamma glutamyl transferase			X		X
	Glucose		X	X		X
	Lipase		X	X	X	X
	Potassium		X	X	X	X
	Sodium		X	X	X	X
	Protein			X		X
Coagulation	Prothrombin Intl. Normalized Ratio		X	X		X
	Activated partial thromboplastin time		X	X		X
Hematology	RBC		X	X	X	X
	Hematocrit		X	X	X	X
	Hemoglobin		X	X	X	X
	Ery. Mean corpuscular volume (MCV)		X	X	X	X
	Ery. Mean corpuscular hemoglobin (MCH)		X	X	X	X
	Leukocytes with Differential: Neutrophils (absolute)		X	X	X	X

Category	Laboratory Assessment	Notes	Screening		Visits After Randomization	
			Central	Local	Central	Local
	Lymphocytes (absolute) Monocytes (absolute) Eosinophils (absolute) Basophils(absolute)					
	Platelets		X	X	X	X
Iron deficiency Testing	Ferritin		X			
	Transferrin saturation		X			
Routine Urinalysis	Dipstick testing: Specific gravity, pH, glucose, protein, blood, ketones, bilirubin, urobilinogen, nitrite, leukocytes.			X		X
	Urine protein analysis in case of 2+ proteinuria dipstick.	If dipstick urinalysis shows 2+ proteinuria, at Screening, a 24-h urine collection is required. During study conduct UPCR may be used instead.		X		X
	Microscopic examination (if required)	Only required if blood or protein is abnormal in dipstick testing (blood 1+, protein 2+).		X		X
Contraception and Pregnancy	Serum or highly sensitive urine hCG pregnancy test (as needed for a POCBP).	Serum only at Screening. Urine or serum on all other visits allowed. If required by local regulations or the IRB/IEC, serum testing will be done instead.		X		X
Serology	HIV antibody	HIV screening is at the Investigator's discretion unless required locally.		X		
	Hepatitis B Virus (HBV) • Hepatitis B Virus Surface Antigen (HBsAg) • Hepatitis B Virus Surface Antibody (HBsAb) • Hepatitis B Virus Core Antibody (HBcAb) • Hepatitis B Virus DNA (HBV DNA) if HBsAg or HBcAb are positive	See Appendix 7 for Japan-specific information.	X			
	Hepatitis C Virus (HCV) • Hepatitis C Virus Antibody (HCVAb) • Hepatitis C Virus RNA (HCV RNA) if HCVAb is positive		X			

Appendix 6 List of Examples of Strong and Moderate CYP3A4 Inhibitors, and Strong CYP1A2 Inhibitors

CYP Isoform	
CYP3A4	**Examples of strong inhibitors include:**
	boceprevir, clarithromycin, cobicistat, danoprevir and ritonavir[a], elvitegravir and ritonavir[a], indinavir and ritonavir[a], idelalisib, itraconazole, ketoconazole, lopinavir and ritonavir[a], mibefradil (withdrawn in US), nefazodone paritaprevir and ritonavir and (ombitasvir and/or dasabuvir)[a], nelfinavir, posaconazole, ritonavir, saquinavir and ritonavir[a], telaprevir, tipranavir and ritonavir[a], telithromycin, troleandomycin, voriconazole
CYP3A4	**Examples of moderate inhibitors include:**
	aprepitant, atazanavir[a], ciprofloxacin, darunavir[a], diltiazem, dronedarone, erythromycin, fosaprepitant[b], fosnetupitant[c], fluconazole, isavuconazole, netupitant,, tofizopam, verapamil
CYP1A2	**Examples of strong inhibitors include:**
	ciprofloxacin, enoxacin, fluvoxamine

Source: https://www.fda.gov/drugs/drug-interactions-labeling/drug-development-and-drug-interactions-table-substrates-inhibitors-and-inducers

[a] Ritonavir is usually given in combination with other anti-HIV or anti-HCV drugs in clinical practice. Caution should be used when extrapolating the observed effect of ritonavir alone to the effect of combination regimens on CYP3A activities.

[b] Fosaprepitant is the prodrug of aprepitant and when administered intravenously is converted rapidly to aprepitant.

[c] Fosnetupitant is the prodrug of netupitant and when administered intravenously is converted rapidly to netupitant.

For details on drug-drug interactions and prohibited medications with bevacizumab and FTD-TPI, refer to the local product information.

Appendix 7 Country and Regional Specific Requirements

EU-specific Requirements

EU-specific requirements are listed below together with the applicable protocol sections.

Section 6.1, Study Intervention(s) Administration

According to EU Regulation 536/2014 (Annex VI, A1, paragraph 3), "The address and telephone number of the main contact shall not be required to appear on the label if subjects have been given a leaflet or card which provides these details and have been instructed to keep this in their possession at all times."

A Patient ID card is used in this study which contains information related to address and telephone number of the main contact for this study.

Section 8.3.3 Regulatory Reporting Requirements for Serious Adverse Events

For studies in EU/EEA and submitted under the EU Clinical Trial Regulation 536/2014, SUSARs will need to be reported centrally via the EV database to HA by the Sponsor.

France-specific Requirements

Section 5.2, Exclusion Criteria

- Persons under court protection, persons not affiliated to a social security system, protected adults.

This exclusion criterion is in accordance with Art. L. 1121-6, Art. L. 1121-8, Art. L. 1121-8-1.

Japan-specific Requirements

Japan-specific requirements are listed below together with the protocol sections where the information is applicable:

Section 5.1 Inclusion Criteria and Appendix 3 Contraception and Barrier Requirements

- The following highly effective contraception methods are not approved in Japan:
  - Implantable progestogen-only hormone contraception associated with inhibition of ovulation
- The following barrier methods are not approved in Japan:
  - Female condom with or without spermicide
  - Cap, diaphragm, or sponge with spermicide

Breastfeeding women who choose to stop breastfeeding can be enrolled in this study. (Breastfeeding may only be resumed 3 months after the end of treatment with the study

intervention). Participants who received bevacizumab may only resume breastfeeding after 6 months.

- Postmenopause is defined as no menses for at least 12 months. The onset of menopause caused by other medical conditions, such as side effects from antineoplastic agents, is excluded from this definition.

Section 5.2 Exclusion Criteria

#9. In Japan, participants are excluded if HbsAg+ or HBV DNA is ≥ 20 IU/mL (if HbcAb+ and/or HbsAb+). If HBV DNA is < 20 IU/mL for the participants who are HbcAb+ and/or HbsAb+, HBV DNA will be monitored during the study according to the "Guideline for prevention of immunosuppressive therapy/chemotherapy-induced reactivation of hepatitis B virus."

Section 6.8 Concomitant Therapy

Hematopoietic growth factors other than G-CSF have not been approved for events associated with cancer chemotherapy in Japan.

China-specific Requirements

China-specific requirements are listed below together with the protocol sections where the information is applicable:

Section 8.6 Biomarkers

- Collection of biological samples for biomarker research is part of this study. Samples are collected only where it is allowed by local law/regulations.
- The following participant samples for biomarker research will be collected from all participants in this study as specified in the Schedule of Activities and detailed in the Laboratory Manual.

Tumor tissue samples will be tested retrospectively for expression of CEACAM5 to correlate expression levels with response to Precem-TcT or further clinical endpoints, using a Sponsor's proprietary test. There are no age restrictions for FFPE tissue block samples; however, tumor sections must be prepared fresh prior to shipment if only slides are provided. Bone biopsies, fine needle aspirates, and cell blocks are not suitable tumor tissue samples for examining CEACAM5 expression and will not be accepted. Details are described in the Laboratory Manual.

Retention time and possible analyses of samples after the end of study are specified in the respective ICF.

Details on processes for collection and handling of tumor samples are specified in the Laboratory Manual.

No further exploratory biomarker analyses are planned.

South Korea-specific Requirements

South Korea-specific requirements are listed below together with the protocol sections where the information is applicable:

Section 5.1 Inclusion Criteria

1. Participants who are ≥ 19 years of age at the time of signing the informed consent.

Appendix 8 Response Evaluation Criteria in Solid Tumors (RECIST) Version 1.1

The text below is derived from Eisenhauer 2009 and Schwartz 2016.

Definitions:

Response and progression will be evaluated using the international criteria proposed by the RECIST Working Group (v 1.1). The RECIST criteria use changes in only a single diameter (unidimensional measurement) of the tumor lesions–for non-nodal lesions, this is the longest diameter and for nodal lesions it is the short axis diameter. Lesions are either measurable or nonmeasurable using the criteria below. The term "evaluable" in reference to measurability will not be used.

Measurable Disease:

Tumor (non-nodal) lesions will be accurately measured in at least 1 dimension–the longest diameter in the plane of measurement is recorded–with a minimum size of 10 mm by CT scan (irrespective of scanner type) and MRI (no less than double the slice thickness and a minimum of 10 mm).

Malignant lymph nodes will be considered pathologically enlarged and measurable, when the lymph node is ≥ 15 mm in short axis when assessed by CT scan. The recommended CT scan slice thickness will be no greater than 5 mm. At baseline and in follow-up, only the short axis will be measured and followed.

Nonmeasurable Disease:

All other lesions or sites of disease, including small lesions (i.e. longest diameter ≥ 10 to < 15 mm with older techniques or < 10 mm using spiral CT scan), are considered nonmeasurable disease. Leptomeningeal disease, ascites, pleural or pericardial effusion, inflammatory breast disease, lymphangitic involvement of skin or lung, abdominal masses/abdominal organomegaly identified by physical examination that are not measurable by reproducible imaging techniques are all nonmeasurable.

Bone Lesions:

- Bone scan, PET scan, or plain films are not considered adequate imaging techniques to measure bone lesions. However, these techniques can be used to confirm the presence or disappearance of bone lesions.
- Lytic bone lesions or mixed lytic-blastic lesions, with identifiable soft tissue components that can be evaluated by cross-sectional imaging techniques, such as CT or MRI, can be considered as measurable lesions if the soft tissue component meets the definition of measurability specified above.
- Blastic bone lesions are nonmeasurable.

Cystic Lesions:

- Lesions that meet the criteria for radiographically defined simple cysts will not be considered as malignant lesions (neither measurable nor nonmeasurable).
- Cystic lesions thought to represent cystic metastases can be considered as measurable lesions if they meet the definition of measurability specified above if no measurable noncystic lesions are present.

Lesions with Prior Local Treatment:

Tumor lesions situated in a previously irradiated area, or in an area subjected to other local regional therapy are normally not considered measurable unless there has been demonstrated progression in the lesion.

Target Lesions

All measurable lesions, up to a maximum of 2 lesions per organ and 5 lesions in total, will be identified as **target lesions**, and recorded and measured at baseline. Target lesions will be selected on the basis of their size (lesions with the longest diameter), be representative of all involved organs, but in addition will be those that lend themselves to reproducible repeated measurements.

Pathological lymph nodes which are defined as measurable and identified as target lesions will meet the criterion of a short axis of ≥ 15 mm by CT scan. Only the short axis of these nodes will contribute to the baseline sum. Radiologists normally use the short axis of the node as the diameter to judge if a node is involved by solid tumor. Nodal size is normally reported as 2 dimensions in the plane in which the image is obtained (for CT scan this is almost always the axial plane; for MRI the plane of acquisition may be axial, sagittal, or coronal). The smaller of these measures is the short axis. For example, an abdominal node which is reported as being 20 mm × 30 mm has a short axis of 20 mm and qualifies as a malignant, measurable node. In this example, 20 mm will be recorded as the node measurement. All other pathological nodes (those with short axis ≥ 10 mm but < 15 mm) will be considered nontarget lesions. Nodes that have a baseline short axis < 10 mm are considered nonpathological and will not be recorded or followed.

A sum of diameters (longest for non-nodal lesions, short axis for nodal lesions) for all target lesions will be calculated and reported as the baseline sum of diameters. The baseline sum of diameters will be used as reference to further characterize any objective tumor regression in the measurable dimension of the disease.

Nontarget Lesions:

All other lesions (or sites of disease) including pathological lymph nodes will be identified as nontarget lesions and will also be recorded at baseline. Measurements are not required, and these lesions will be followed as ‘present’, ‘absent’, or in rare cases ‘unequivocal progression’. In addition, it is possible to record multiple nontarget lesions involving the same organ as a single item in the CRF (e.g. “multiple enlarged pelvic lymph nodes” or “multiple liver metastases”). If

there are no target lesions, and the protocol permits entry of such patients, all baseline lesions will be non-target lesions.

GUIDELINES FOR EVALUATION OF MEASURABLE DISEASE:

All measurements will be recorded in metric notation, using calipers if clinically assessed. All baseline evaluations will be performed as close as possible prior to but never more than 2 weeks before randomization.

The same assessment method and technique will be used to characterize each identified and reported lesion at baseline and during follow-up, unless it is not pragmatic to do so (e.g. imaging done at another clinic). Imaging based evaluation will always be done rather than clinical examination unless the lesion(s) being followed cannot be imaged and are assessable by clinical examination.

CT, MRI: CT is the best currently available and reproducible method to measure lesions selected for response assessment. This guideline has defined measurability of lesions on CT scan based on the assumption that CT slice thickness is 5 mm or less. As is described in Appendix II of the original source article, when CT scans have slice thickness greater than 5 mm, the minimum size for a measurable lesion will be twice the slice thickness. MRI is also acceptable in certain situations but will not be used alone for chest imaging

Ultrasound: Ultrasound is not useful in assessment of lesion size and will not be used as a method of measurement. Ultrasound examinations cannot be reproduced in their entirety for independent review at a later date and because they are operator dependent, it cannot be guaranteed that the same technique and measurements will be taken from 1 assessment to the next. If new lesions are identified by ultrasound during the study, confirmation by CT or MRI is required. If there is concern about radiation exposure at CT, MRI may be used instead of CT in selected instances.

Endoscopy, laparoscopy: The use of these techniques for objective tumor evaluation is not advised. However, they can be useful to confirm complete pathological response when biopsies are obtained or to determine relapse in studies where recurrence following CR or surgical resection is an endpoint.

Tumor markers: Tumor markers alone cannot be used to assess objective tumor response. If markers are initially above the upper normal limit; however, they will normalize for a participant to be considered in CR.

Cytology, histology: These techniques can be used to differentiate between PR and CR in rare cases if required for this study (e.g. residual lesions in tumor types such as germ cell tumors, where known residual benign tumors can remain). When effusions are known to be a potential AE of treatment (e.g. with certain taxane compounds or angiogenesis inhibitors), the cytological confirmation of the neoplastic origin of any effusion that appears or worsens during treatment can be considered if the measurable tumor has met criteria for response or SD in order to differentiate between response (or SD) and PD.

RESPONSE CRITERIA

Evaluation of Target Lesions:

CR: Disappearance of all target lesions. Any pathological lymph nodes (whether target or nontarget) will have reduction in short axis to < 10 mm.

PR: At least a 30% decrease in the sum of diameters of target lesions, taking as reference the baseline sum diameters.

PD: At least a 20% increase in the sum of diameters of target lesions, taking as reference the smallest sum on study (this includes the baseline sum if that is the smallest on study). In addition to the relative increase of 20%, the sum will also demonstrate an absolute increase of at least 5 mm. The appearance of 1 or more new lesions is also considered progression.

SD: Neither sufficient shrinkage to qualify for PR nor sufficient increase to qualify for PD, taking as reference the smallest sum diameters while on study.

Lymph nodes*:* Lymph nodes identified as target lesions will always have the actual short axis measurement recorded (measured in the same anatomical plane as the baseline examination), even if the nodes regress to below 10 mm on study. When lymph nodes are included as target lesions, the "sum" of diameters may not be zero even if CR criteria are met, since a normal lymph node is defined as having a short axis of < 10 mm. CRFs or other data collection methods may therefore be designed to have target nodal lesions recorded in a separate section where, in order to qualify for CR, each node will achieve a short axis < 10 mm. For PR, SD, and PD, the actual short axis measurement of the nodes will be included in the sum of target lesions.

Target lesions that become "too small to measure": While on study, all lesions (nodal and non-nodal) recorded at baseline will have their actual measurements recorded at each subsequent evaluation. In cases where lesions or lymph nodes which are recorded as target lesions at baseline become "too small to measure". In cases where, in the opinion of the radiologist the lesion has likely disappeared, the measurement will be recorded as 0 mm. In cases where, in the opinion of the radiologist the lesion is believed to be present and is faintly seen but too small to measure, a default value of 5 mm will be assigned. If a lymph node, in the opinion of the radiologist, is believed to be present and is faintly seen but too small to measure, a default value of 5 mm will be assigned. This default value is derived from the 5 mm CT slice thickness but will not be changed with varying CT slice thickness. Note: If the radiologist can provide an actual measure, that will be recorded, even if it is < 5 mm.

Target lesions that are biopsied or excised: In such situations, the sum of diameters of the remaining target lesions may not properly represent changes in disease burden. Imaging immediately before such surgical intervention is recommended if possible. After such an excision, unless the sum of diameters of the remaining target lesions has increased to such an extent that it has still increased by ≥20% from the nadir, consider all remaining lesions as nontarget lesions.

Lesions that split or coalesce on treatment: When non-nodal lesions "fragment", the longest diameters of the fragmented portions will be added together to calculate the target lesion sum.

Similarly, as lesions coalesce, a plane between them may be maintained that would aid in obtaining maximal diameter measurements of each individual lesion. If the lesions have truly coalesced such that they are no longer separable, the vector of the longest diameter in this instance will be the maximal longest diameter for the 'coalesced lesion'.

Evaluation of Nontarget Lesions:

While some nontarget lesions may be measurable, they need not be measured and instead will be assessed only qualitatively at the time points specified in the protocol.

CR: Disappearance of all nontarget lesions and normalization of any protocol-specified tumor marker level All non-malignant lymph nodes will be nonpathological in size (< 10 mm short axis).

Non-CR/Non-PD: Persistence of 1 or more nontarget lesion(s) and/or maintenance of tumor marker level above the normal limits.

PD: Unequivocal progression of the entire burden of existing nontarget lesions and/or the appearance of 1 or more new lesions is also considered progression.

When the participant also has measurable disease: In this setting, to achieve 'unequivocal progression' on the basis of the nontarget disease, there will be an overall level of substantial worsening in nontarget disease such that, even in the presence of SD or PR in target disease, the overall tumor burden has increased sufficiently to merit discontinuation of therapy. A modest "increase" in the size of 1 or more nontarget lesions is usually not sufficient to quality for unequivocal progression status. The designation of overall progression solely on the basis of change in nontarget disease in the face of SD or PR of target disease will therefore be extremely rare.

When the participant has only nonmeasurable disease: The same general concept applies here as noted above; however, in this instance there is no measurable disease assessment to factor into the interpretation of an increase in nonmeasurable disease burden. Because worsening in nontarget disease cannot be easily quantified, a useful test that can be applied when assessing participants for unequivocal progression is to be considered if the increase in overall disease burden based on the change in nonmeasurable disease is at least comparable in magnitude to the increase that would be required to declare PD for measurable disease: i.e. an increase in tumor burden representing an additional 73% increase in 'volume' (which is equivalent to a 20% increase diameter in a measurable lesion). Examples include an increase in a pleural effusion from "trace" to "large", an increase in lymphangitic disease from localized to widespread, or "sufficient to require a change in therapy". If "unequivocal progression" is seen, the participant will be considered to have had overall PD at that point. While it would be ideal to have objective criteria to apply to nonmeasurable disease, the very nature of that disease makes it impossible to do so; therefore, the increase will be substantial.

New Lesions:

The appearance of new malignant lesions denotes disease progression noting that the finding of a new lesion must be unequivocal: i.e. not attributable to differences in scanning technique, change

in imaging modality, or findings thought to represent something other than tumor (e.g. some 'new' bone lesions may be healing or flare of pre-existing lesions).

A lesion identified at a follow-up timepoint in an anatomical location that was not scanned at baseline is considered a new lesion and will indicate PD. An example of this is the participant who has visceral disease at baseline and while on study has a brain CT or MRI ordered which reveals metastases. The participant's brain metastases are considered to be evidence of PD even if the participant did not have brain imaging at baseline.

If a new lesion is equivocal, e.g. because of its small size, continued therapy and follow-up evaluation is required. If repeat scans confirm there is definitely a new lesion, then progression will be declared using the date of the initial scan as the date of progression.

New lesions on the basis of FDG-PET imaging can be identified according to the following algorithm:

a. Negative FDG-PET at baseline, with a positive FDG-PET at follow-up is a sign of PD based on a new lesion.

b. 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 PD. 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 PD 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 PD.

Appendix 9 Protocol Amendment History

The information for the current amendment is on the title page.

Protocol Version 2.0 (17 December 2025)

Overall Rationale for the Amendment

The protocol was amended to clarify the wording regarding stratification according to geographical region. The original protocol (version 1.0) was not implemented or submitted to any health authority.

Section # and Name	Description of Change	Brief Rationale
1 Synopsis 1.1 Schema 4.1 Overall Design 4.2 Scientific Rationale for the Study Design 6.3.1 Study Intervention Assignment 9.1.3 Testing Strategy 9.4 Statistical Analyses	Clarification in the wording regarding stratification according to geographical region (i.e. from “Americas vs Europe vs APAC” to “North America, East Asia, and rest of the world”).	Clarification in the stratification by geographical region.

Appendix 10 Sponsor Signature Page

Study Title:	A randomized, open label, 3-arm Phase 3 study of precemtabart tocentecan with or without bevacizumab compared to trifluridine/tipiracil plus bevacizumab in participants with previously treated metastatic colorectal cancer (PROCEADE-CRC-03)
Regulatory Agency Identifying Numbers:	US FDA IND 156588 EU trial number: 2025-524648-37-00
Clinical Study Protocol Version:	23 February 2026 V3.0

I approve the design of the clinical study:

Electronically signed by: Camilo Moulin
Reason: approved
Date: Feb 24, 2026 14:10:42 GMT-3

24-Feb-2026

Signature Date of Signature

Name, Academic Degree:	Camilo Moulin, MD
Function/Title:	Medical Lead
Institution:	Ares Trading SA, an affiliate of Merck Healthcare KGaA
Address:	Route de Crassier 15, 1262 Eysins, Switzerland
General Merck Phone Number:	+41 (0) 58 432 3000
General Merck Fax Number:	Not applicable

Appendix 11 Coordinating Investigator Signature Page

Study Title:	A randomized, open label, 3-arm Phase 3 study of precemtabart tocentecan with or without bevacizumab compared to trifluridine/tipiracil plus bevacizumab in participants with previously treated metastatic colorectal cancer (PROCEADE-CRC-03)
Regulatory Agency Identifying Numbers:	US FDA IND 156588 EU trial number: 2025-524648-37-00
Clinical Study Protocol Version:	23 February 2026 V3.0

I approve the design of the clinical study, will comply with my responsibilities as coordinating Investigator for this study, and am responsible for the conduct of the study at this site and will conduct it per the clinical study protocol, any approved protocol amendments, ICH GCP (Topic E6) and all applicable Health Authority requirements and national laws.

Kanwal Raghav Electronically signed by: Kanwal Raghav
Reason: Coordinating PI
Date: Feb 25, 2026 08:33:31 CST

Signature

25-Feb-2026

Date of Signature

Name, academic degree:	Kanwal Raghav, MD, MBBS
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Appendix 12 Principal Investigator Signature Page

Study Title:	A randomized, open label, 3-arm Phase 3 study of precemtabart tocentecan with or without bevacizumab compared to trifluridine/tipiracil plus bevacizumab in participants with previously treated metastatic colorectal cancer (PROCEADE-CRC-03)
Regulatory Agency Identifying Numbers:	US FDA IND 156588 EU trial number: 2025-524648-37-00
Clinical Study Protocol Version:	23 February 2026 V3.0

I am responsible for the conduct of the study at this site and will conduct it per the clinical study protocol, any approved protocol amendments, ICH GCP (Topic E6) and all applicable Health Authority requirements and national laws.

I also understand that Health Authorities may require the Sponsors of clinical studies to obtain and supply details about ownership interests in the Sponsor or Investigational Medicinal Product and any other financial ties with the Sponsor. The Sponsor will use any such information solely for complying with the regulatory requirements. Therefore, I agree to supply the Sponsor with any necessary information regarding ownership interest and financial ties including those of my spouse and dependent children, and to provide updates as necessary to meet Health Authority requirements.

_____ _____

Signature Date of Signature

Name, academic degree:

Function/Title:

Institution:

Address:

Telephone number:

Fax number:

Email address: