Official Title: A Phase 3, Open-Label, Randomized, Active-Controlled, Multicenter Study to Evaluate the Efficacy and Safety of Pemigatinib Versus Gemcitabine Plus Cisplatin Chemotherapy in First-Line Treatment of Participants With Unresectable or Metastatic Cholangiocarcinoma With FGFR2 Rearrangement (FIGHT-302)

NCT Number: NCT03656536

Document Date: INCB 54828-302 Statistical Analysis Plan 10 JUN 2025

Statistical Analysis Plan

INCB 54828-302

A Phase 3, Open-Label, Randomized, Active-Controlled, Multicenter Study to Evaluate the Efficacy and Safety of Pemigatinib Versus Gemcitabine Plus Cisplatin Chemotherapy in First-Line Treatment of Participants With Unresectable or Metastatic Cholangiocarcinoma With FGFR2 Rearrangement (FIGHT-302)

IND Number:	[redacted]
EudraCT Number:	**2018-002894-23**
EU CT Number	**2024-513513-12-00**
Sponsor:	**Incyte Corporation** **1801 Augustine Cut-Off** **Wilmington, DE 19803**
Protocol Version:	**Protocol Amendment 7 dated 18 JUN 2024**
CRF Approval Date:	**29 MAY 2025**
SAP Version:	**Original**
SAP Author:	[redacted]**, Biostatistics** [redacted]**, Biostatistics**
Date of Plan:	**10 JUN 2025**

This study is being conducted in compliance with Good Clinical Practice, including the archiving of essential documents.

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LIST OF ABBREVIATIONS

Abbreviation	Term
AE	adverse event
APAC	Asia-Pacific
BSA	body surface area
CI	confidence interval
CR	complete response
CRF	Case Report Form
CTCAE	Common Terminology Criteria for Adverse Events
DCR	disease control rate
DMC	Data Monitoring Committee
DOR	duration of response
ECG	electrocardiogram
ECOG	Eastern Cooperative Oncology Group
eCRF	electronic Case Report Form
EORTC QLQ	European Organisation for Research and Treatment of Cancer Quality of Life Questionnaire
EU	European Union
FDA	Food and Drug Administration
FGFR	fibroblast growth factor receptor
FMI	Foundation Medicine Inc.
HR	hazard ratio
ICR	independent central reviewer
ITT	intent-to-treat
MedDRA	Medical Dictionary for Regulatory Activities
NA	North America
NCI	National Cancer Institute
NE	not evaluable
ORR	overall response rate
OS	overall survival
PD	progressive disease
PFS	progression-free survival
PP	per Protocol
PR	partial response
PT	preferred term
QoL	quality of life
QTcB	QT interval corrected using Bazett's formula

Abbreviation	Term
QTcF	QT interval corrected using Fridericia's formula
RECIST	Response Evaluation Criteria in Solid Tumors
ROW	rest of world
SAP	Statistical Analysis Plan
SD	stable disease
SOC	system organ class
TEAE	treatment-emergent adverse event
TNM	tumor, node, metastasis
WHO	World Health Organization

1. INTRODUCTION

This is a Phase 3, open-label, randomized, active-controlled study of pemigatinib versus gemcitabine plus cisplatin as first-line treatment of participants with unresectable and/or metastatic cholangiocarcinoma with FGFR2 rearrangement. Section 2 of the Protocol provides a detailed description of the investigational product, target patient population, rationale for doses and regimen to be examined, and potential risks and benefits of treatment with pemigatinib.

The purpose of this SAP is to provide details of the statistical analyses that have been outlined in the Study INCB54828-302 Protocol. The details of the analysis methodology of biomarkers and pharmacodynamics and results will appear in a separate report. Due to recruitment challenges, study enrollment was discontinued on 21 MAY 2024. Participants already enrolled will continue to receive study treatment and will be followed for a minimum of 12 months. As the study will not be completed as initially planned, the final analysis will be based on the actual number of PFS events observed at the time of database lock.

2. STUDY INFORMATION, OBJECTIVES, AND ENDPOINTS

2.1. Protocol and Case Report Form Version

This SAP is based on INCB 54828-302 Protocol Amendment 7 dated 18 JUN 2024 and CRFs approved 29 MAY 2025. Unless superseded by an amendment, this SAP will be effective for all subsequent Protocol amendments and eCRF versions.

2.2. Study Objectives and Endpoints

Table 1 presents the objectives and endpoints.

Table 1: Objectives and Endpoints

Objectives	Endpoints
Primary	
Evaluate the efficacy of pemigatinib versus gemcitabine plus cisplatin in the first-line treatment of participants with cholangiocarcinoma with FGFR2 rearrangement.	PFS: defined as the time from date of randomization until date of disease progression (according to RECIST v1.1 and assessed by an ICR) or death, whichever occurs first.
Secondary	
Evaluate the efficacy of pemigatinib versus gemcitabine plus cisplatin in the first-line treatment of participants with cholangiocarcinoma with FGFR2 rearrangement.	• ORR (CR + PR): defined as the proportion of participants with best overall response of CR or PR per RECIST v1.1 as assessed by an ICR. • OS: defined as the time from date of randomization until death due to any cause. • DOR: defined as the time from the date of the first assessment of CR or PR until the date of the first disease progression by an ICR per RECIST v1.1 or death, whichever occurs first. • DCR (CR + PR + SD): defined as the proportion of participants who achieved best overall response of CR, PR, or SD per RECIST v1.1 as assessed by an ICR.
Safety and tolerability of pemigatinib.	Occurrence of TEAEs and treatment-related AEs according to NCI CTCAE v5.0, physical findings, and vital sign, laboratory, and ECG changes.
Quality of Life impact.	QoL questionnaire data (EQ-5D, EORTC QLQ-30, and BIL-21).
[redacted]	

3. STUDY DESIGN

This is a Phase 3, open-label, randomized, active-controlled study of pemigatinib versus gemcitabine plus cisplatin as first-line treatment of participants with unresectable and/or metastatic cholangiocarcinoma with FGFR2 rearrangement. The study will enroll approximately 432 participants in a 1:1 randomization ratio stratified by receipt of 1 cycle of gemcitabine plus cisplatin for advanced cholangiocarcinoma prior to randomization (yes vs no), geographic region (Western [NA and EU] vs APAC vs ROW), and tumor burden (locally advanced vs distant metastasis) into 1 of the following 2 treatment groups:

- **Treatment Group A:** Pemigatinib (13.5 mg once daily) administered as continuous therapy schedule (a cycle is 3 weeks).
- **Treatment Group B:** Gemcitabine (1000 mg/m^2) and cisplatin (25 mg/m^2) administered as an intravenous infusion on Days 1 and 8 of every 3-week cycle for up to 8 cycles.

Full study drug administration information can be found in Section 6.1 of the Protocol.

Participant eligibility will be based on documented FGFR2 rearrangement from local and/or central (FMI) genomic testing; local testing performed using blood-based assays must be confirmed with tissue-based assays by a central laboratory; this can be done after enrollment. FGFR2 rearrangements may be classified as fusion, rearrangement, translocation, exon 18 truncation, exon 18 deletion, or fluorescence in situ hybridization–positive. If the participant is randomized using a local genomics assay (ie, other than FMI), the assay must be analytically validated (eg, Clinical Laboratory Improvement Amendments certified), and the genomics results should be confirmed by FMI but will not impact timing of randomization and/or starting treatment. If samples are negative for FGFR2 rearrangement by tests other than FMI, investigators are encouraged to submit samples for prescreening. FGFR2 rearrangements are complex molecular events, and many tests are not designed or optimized for detection of FGFR2 rearrangements and may result in false negative results.

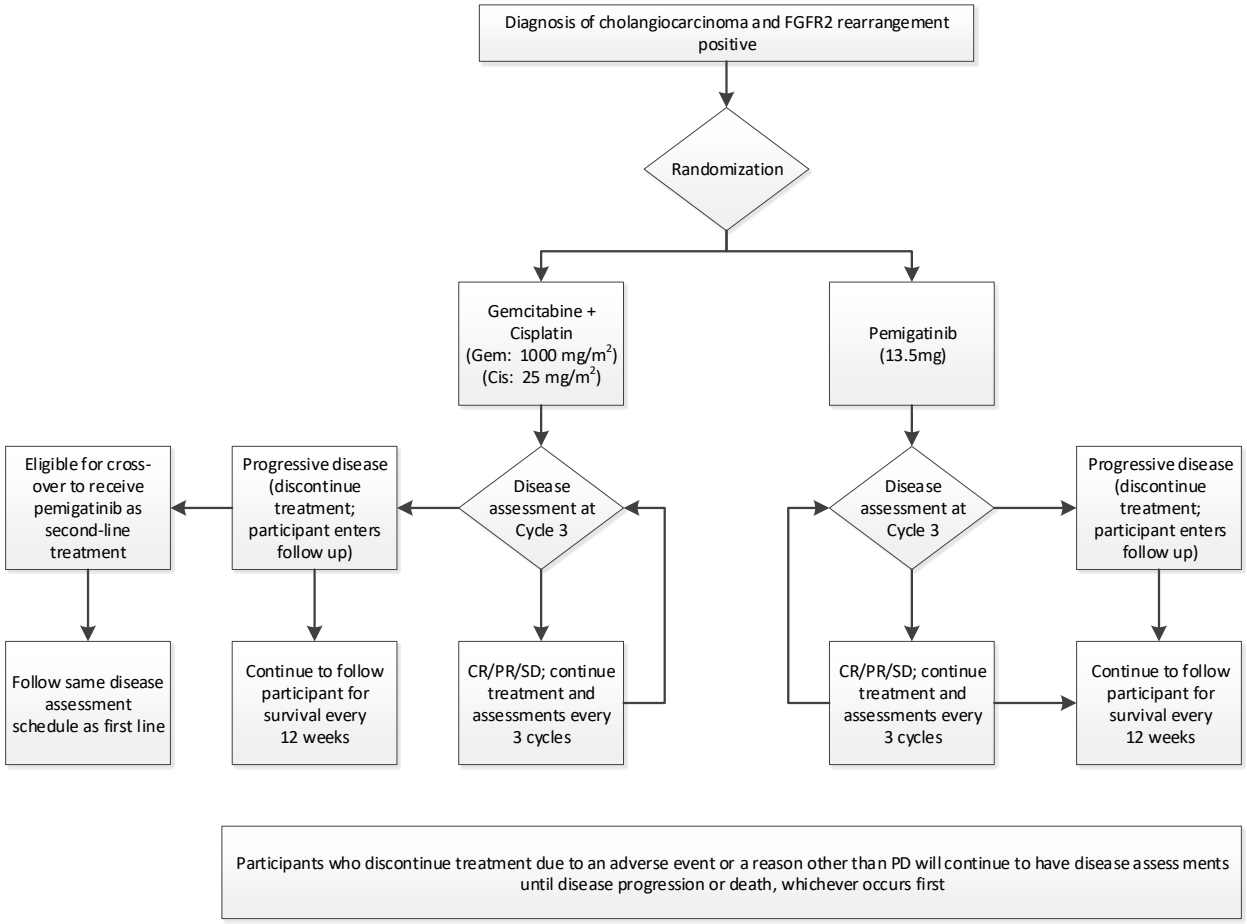
Previous therapies may include locoregional treatments and adjuvant or neoadjuvant treatments (at least 6 months prior to randomization) and, as of Protocol Amendment 6, no more than 1 cycle of gemcitabine plus cisplatin prior to randomization (< 28 days and ≥ 14 days prior to Cycle 1 Day 1).

Treatment will start on Cycle 1 Day 1. Participants will undergo regular safety assessments during treatment, as well as regular efficacy assessments. Participants will be allowed to continue administration in 3-week cycles of pemigatinib and up to 8 cycles of gemcitabine plus cisplatin (if 1 cycle was administered prior to randomization, the cycle total will include that cycle as well) until disease progression per RECIST v1.1 (Eisenhauer et al 2009) as assessed by an ICR or unacceptable toxicity is reported.

Participants who progress on gemcitabine plus cisplatin may be considered for crossover to pemigatinib as second-line treatment.

See Figure 1 for the study design.

Figure 1: Study Design Schema



3.1. Randomization

Participants will be randomized 1:1 between the 2 treatment groups and stratified by receipt of 1 cycle of gemcitabine plus cisplatin for advanced cholangiocarcinoma prior to randomization (yes vs no), geographic region (Western [NA and EU] vs APAC vs ROW), and tumor burden (locally advanced vs distant metastasis).

3.2. Control of Type I Error

The overall level of significance for the primary endpoint is 1-sided 0.025 with 0.0001 allocated for futility at interim and 0.0249 for primary endpoint at final analysis. The efficacy endpoints will be tested sequentially at 1-sided 0.0249 level for PFS, ORR, and OS. No other efficacy endpoints will be included in the alpha control.

The primary and key secondary efficacy endpoints will be tested in the following order:

1. The superiority of PFS will be tested at the 1-sided 0.0249 level at the final analysis.
2. If the test for PFS superiority is significant, ORR will be tested at the 1-sided 0.0249 level at the time when the PFS final analysis is conducted.

3. If the test for ORR superiority is significant, OS interim analysis will be performed at the time when the final PFS analysis is conducted. It is expected that about 240 deaths will be observed in the 2 combined treatment groups. Overall survival analysis will be conducted at nominal 1-sided alpha of 0.0089 according to the O'Brien-Fleming spending function (O'Brien and Fleming 1979). Final OS analysis will be conducted at the nominal 1-sided alpha of 0.0224 when approximately 322 deaths are observed in the combined treatment groups. The actual boundaries will be recalculated from the actual number of deaths at the time when final PFS analysis is conducted using the alpha spending function.

3.3. Sample Size Considerations

The sample size calculation is based on the primary endpoint PFS.

Based on available data from Study ABC-02 (Valle et al 2010), the median PFS in the gemcitabine plus cisplatin group is expected to be 8 months. It is expected that treatment with pemigatinib will result in a HR of 0.7 for PFS, which corresponds to an increase in median PFS of 3.4 months under the exponential model assumption.

Then, in order to ensure 90% power to test the null hypothesis: $PFS_{GroupA} \leq PFS_{GroupB}$ versus $PFS_{GroupA} > PFS_{GroupB}$, where Group A represents the pemigatinib group and Group B represents the gemcitabine plus cisplatin group. Assuming an HR of 0.7 for Group A, a total of 338 PFS events in the 2 combined treatment groups need to be observed. This calculation assumes analysis by a 1-sided log-rank test at the overall 0.025 level of significance, a futility interim analysis of PFS at 35% of the total events, and participants randomized to the 2 treatment groups in a 1:1 ratio. Assuming uniform accrual of the participants over a 36-month period, 10-month follow-up after the last participant is randomized, and a 5% lost to follow-up rate, a total of approximately 432 participants will need to be randomized to observe the targeted PFS events at about 46 months after the first participant randomized.

Based on available data from Lamarca et al (2020), the median OS for participants who take gemcitabine plus cisplatin is expected to be 15 months. Assuming 40% of participants who have treatment failure with gemcitabine plus cisplatin will cross over to the pemigatinib group and the expected median OS is around 10 months after crossover, it is estimated by simulation that the expected median OS in the gemcitabine plus cisplatin group is about 18 months.

It is calculated that a total of 322 deaths in the 2 combined treatment groups need to be observed to achieve 80% power to detect an HR of 0.73 (an increase of 6.7 months in median OS) using a 1-sided log-rank test at a 0.0249 overall significant level. Final OS analysis is expected to occur at approximately 61 months after the first participant is randomized.

3.4. Schedule of Assessments

Refer to Protocol Amendment 7 dated 18 JUN 2024 for a full description of all study procedures and assessment schedules for this study.

4. DATA HANDLING DEFINITIONS AND CONVENTIONS

4.1. Scheduled Study Evaluations and Study Periods

4.1.1. Day 1

For safety assessments, Day 1 is the date that the first dose of study drug (pemigatinib, gemcitabine, or cisplatin) is administered to the participants.

For efficacy assessments, Day 1 is the randomization date.

For randomized participants not treated with any study drug, Day 1 is defined as the day of randomization.

4.1.2. Study Day

If a visit/reporting date is on or after Day 1, then the study day at the visit/reporting date will be calculated as follows: Day # = (visit/reporting Date – Day 1 date) + 1.

If the visit/reporting date is before Day 1, then the study day at the visit/reporting date will be calculated as follows: Day # = visit/reporting Date – Day 1 date.

A study day of –1 indicates 1 day before Day 1.

4.1.3. Baseline Value

Baseline is the last nonmissing measurement obtained before the first administration of study drug, unless otherwise defined.

For randomized participants not treated with any study drug, baseline is defined as the last nonmissing assessment before randomization.

When scheduled and unscheduled assessments occur on the same day, and the time of the assessment or time of the first dose is not available, the following convention will be used to determine baseline:

- If both a scheduled and an unscheduled assessment are available on the day of the first dose and the time is missing, the scheduled assessment will be used as baseline.
- If all scheduled assessments are missing on the day of the first dose and an unscheduled assessment is available, the unscheduled assessment will be used as baseline.

4.1.4. Handling of Missing and Incomplete Dates

In general, values for missing date will not be handled unless the methods for handling missing dates are specified in this SAP. The original reported dates collected in the eCRF should be used for all relevant listings. The following rules will be used for handling partial dates for analyses requiring dates.

When calculating time since diagnosis of cholangiocarcinoma, partial cholangiocarcinoma diagnosis date will be handled as follows in the calculation:

- If only the day is missing, then the first day of the month will be used.
- If both the month and day are missing, then 01 JAN of the year will be used.
- Time since diagnosis will be missing if the diagnosis date is completely missing.

When the date of the last dose is used in deriving variables such as duration of treatment or TEAE flag, a missing or partial date of the last dose will be handled as follows:

- If only the day is missing, then the earlier date of the last day of the month or the date that the participant discontinued treatment will be used.
- Otherwise, the date that the participant discontinued treatment will be used as the date of the last dose.

For relevant efficacy endpoints, partial date of death date will be handled as follows in the calculation:

- If mmyyyy for the last known alive date = mmyyyy for the death date, then the death date will be set to the day after the last known alive date.
- If mmyyyy for the last known alive date < mmyyyy for the death date, then the death date will be set to the first day of the death month.
- Otherwise, the partial death date will not be imputed.

4.1.5. Cycle Length and Duration

Cycle 1 Day 1 is the day that the first dose of study drug is administered. Scheduled cycle length is 21 days. Actual Day 1 of subsequent cycles will correspond with the first day of administration of pemigatinib or gemcitabine plus cisplatin in that cycle.

4.2. Variable Definitions

4.2.1. Body Surface Area

Body surface area will be calculated if not reported on the eCRF. Body surface area will be calculated based on the Mosteller (1987) formula as follows: Body surface area (m^2) = $\{[\text{weight (kg)} \times \text{height (cm)}] / 3600\}^{½}$.

4.2.2. Prior and Concomitant Medications

Prior medication is defined as any nonstudy medication started before the first dose of pemigatinib or gemcitabine plus cisplatin.

Concomitant medication is defined as any nonstudy medication that is started accordingly:

- Before the date of first administration of study drug and is ongoing throughout the study or ends on/after the date of first study drug administration.
- On/after the date of first administration of study drug and is ongoing or ends during the course of study.

A prior medication could also be classified as "both prior and concomitant medication" if the end date is on or after first dose of study drug. In the listing, it will be indicated whether a medication is prior only, concomitant only, or both prior and concomitant.

For the purposes of analysis, all medications will be considered concomitant medications unless they can unequivocally be defined as not concomitant.

5. STATISTICAL METHODOLOGY

5.1. General Methodology

Unless otherwise noted, SAS® software (SAS Institute Inc, Cary, NC; v9 or later) will be used for the generation of all tables, graphs, and statistical analyses. Descriptive summaries for continuous variables will include but not be limited to the number of observations, mean, standard deviation, median, minimum, and maximum. Descriptive summaries for categorical variables will include the number and percentage of participants in each category.

Interim analyses are planned for this study as defined in Section 9.

5.2. Treatment Groups

This is a randomized, open-label, parallel treatment group design. Participants will be summarized by treatment groups. For subjects who cross over to pemigatinib from gemcitabine plus cisplatin, applicable efficacy and safety data will be summarized separately.

5.3. Analysis Populations

5.3.1. Intent-to-Treat Population

All participants who are randomized constitute the ITT Population. Treatment groups for this population will be defined according to the treatment assignment at the time of randomization.

The ITT Population will be used for the summary of demographics, baseline characteristics, participant disposition, and analyses of all efficacy data.

5.3.2. Per Protocol Population

The PP Population includes all ITT participants who are considered to be sufficiently compliant with the Protocol. This population includes all ITT participants who meet all major inclusion and no major exclusion criteria based on blinded review of clinical data.

The following procedures will be performed to identify participants who are to be excluded from the PP Population:

- Clinical review of Protocol deviations.
- Clinical review of concomitant medications as defined in Section 6.6 of the Protocol.
- Clinical review of the dose administration and drug accountability listing.

Participants being considered for exclusion from the PP Population will be determined by the clinical team before database lock. However, due to recruitment challenges, the study enrolled significantly fewer participants than planned. Thus the PP Population will not be defined.

The PP Population will be used in the supportive sensitivity analyses for efficacy endpoints.

5.3.3. Safety Population

The Safety Population includes all randomized participants who received at least 1 dose of study drug. Treatment groups for this population will be determined according to the actual treatment the participant received regardless of assigned study treatment.

All safety analyses will be conducted using the Safety Population.

5.3.4. Crossover-Evaluable Population

The Crossover-Evaluable Population includes all participants who received at least 1 dose of pemigatinib after crossover from the gemcitabine-plus-cisplatin group.

The Crossover-Evaluable Population will be used for the summary of demographics and baseline characteristics, as well as the analyses of efficacy and safety data collected after crossover to pemigatinib.

6. BASELINE, EXPOSURE, AND DISPOSITION

Appendix A provides a list of data displays.

6.1. Baseline and Demographics, Physical Characteristics, and Disease History

6.1.1. Demographics and Baseline Characteristics

The following demographics and baseline characteristics will be summarized for the ITT Population: age, sex, race, ethnicity, weight, height, body surface area, receipt of 1 cycle of gemcitabine plus cisplatin prior to randomization (yes vs no), geographic region (Western [NA and EU] vs APAC vs ROW), tumor burden (locally advanced vs distant metastasis), and baseline phosphate.

6.1.2. Disease History

Time since diagnosis, cholangiocarcinoma location, TNM classification, stage of disease at diagnosis, site of disease at study entry, as well as assessed PD-1status and CA19-9 status will be summarized for the ITT Population.

Time since diagnosis will be calculated as follows: Time since diagnosis (years) = ([date of randomization – date of diagnosis] + 1) / 365.25.

6.1.3. Prior Therapy

The number of participants who received prior systemic cancer therapy regimens will be summarized for the ITT Population. The component drugs of prior systemic therapy regimens will be coded using the WHO Drug Dictionary. Number and percentage of participants with each

drug will be summarized by WHO drug class and WHO drug term. Regimen name, component drugs, start and stop date, purpose of the regimen, best response, reason for discontinuation, and date of relapse/disease progression will be listed.

The number of participants who received prior radiation will be summarized for the ITT Population. Radiotherapy type, anatomical location of the administration, start and stop date, reason for regimen, total dose, number of fractions received, and best response will be listed.

The number of participants who had prior surgery or surgical procedure for the malignancies under study will be summarized for the ITT Population. Date and description of the surgery/procedure will be listed.

The number of participants who had prior locoregional therapy will be summarized for the ITT Population. Locoregional therapy name, start and stop date, any medication used, best response, reason for discontinuation, and date of relapse/disease progression will be listed.

6.1.4. Medical History

For participants in the ITT Population, medical history will be summarized by assigned treatment group. This summary will include the number and percentage of participants with significant medical history for each body system/organ class as documented in the eCRF.

6.1.5. Baseline Disease Characteristics

The following baseline disease characteristics will be summarized for the ITT Population: ECOG performance status.

6.2. Disposition of Participant

The number and percentage of participants randomized by country and/or site will be provided by treatment group.

The number and percentage of participants who were randomized, treated, ongoing with study treatment, completed study treatment before crossover (if applicable), discontinued study treatment with a primary reason for discontinuation, still in study, and withdrew from the study with a primary reason for withdrawal will be summarized for the ITT Population.

The number and percentage of participants who were treated, ongoing with study treatment, discontinued study treatment with a primary reason for discontinuation, still in study, and withdrew from the study with a primary reason for withdrawal will be summarized separately for the Crossover-Evaluable Population.

6.3. Protocol Deviations

Protocol deviations recorded on the eCRF will be summarized and listed for the ITT Population.

6.4. Exposure

For participants in the Safety Population, exposure to study drug will be summarized by treatment group descriptively as follows:

- **Number of cycles:** Number of cycles with a nonzero dose of study drug (pemigatinib, gemcitabine, or cisplatin).
- **Duration of treatment with study drug (days):**

  For pemigatinib: (date of last dose – date of first dose) + 1.

  For gemcitabine plus cisplatin: date of last dose + 6 – date of first dose +1 if last dose is at Day 1 of a cycle; date of last dose + 13 – date of first dose +1 if last dose is at Day 8 of a cycle.
- **Dose modifications:** Number of participants who had a study drug dose reduction or interruption will be summarized.
- **Average daily dose of pemigatinib (mg/day):** total actual pemigatinib dose taken (mg) / duration of treatment with pemigatinib (days).

  Total actual dose taken will be calculated based on the information entered in the Drug Accountability eCRF.

For gemcitabine and cisplatin, relative dose intensity will be summarized descriptively:

- **Relative dose intensity (%):** 100 × actual dose intensity / planned dose intensity.

  Planned dose intensity of study drug (mg/day): total planned study drug dose per cycle (mg) / planned duration of each dose

  Actual dose intensity(mg/day): total actual study drug dose taken (mg)/(duration of treatment with study drug (days))

For the Crossover-Evaluable Population, exposure to pemigatinib after crossover will be summarized separately.

6.5. Study Drug Compliance

For participants in the Safety Population and the Crossover-Evaluable Population, overall compliance (%) for pemigatinib will be calculated as:

Compliance (%) = 100 × [total dose actually taken] / [total prescribed dose].

The total prescribed dose is defined as the sum of the doses prescribed by the investigator accounting for dose modifications.

The total actual dose taken will be calculated based on information entered in the Drug Accountability eCRF. If there are dispensed drugs that have not been returned yet, the actual dose taken starting from the dispense date of the unreturned drug will be imputed by the dose taken as reported in the Dosing eCRF.

Compliance of pemigatinib will be summarized descriptively and listed.

6.6. Prior and Concomitant Medications

Prior and concomitant medications will be coded using the WHO Drug Dictionary. Number and percentage of participants in the ITT Population for each prior and concomitant medication will be summarized by WHO drug class and WHO drug term.

7. EFFICACY

Appendix A provides a list of data displays.

7.1. General Considerations

The efficacy endpoints will be analyzed by treatment group based on the ITT Population. Unless otherwise stated, the strata identified in the randomization process will be used in all efficacy analyses.

For the Crossover-Evaluable Population, efficacy data after crossover will be summarized separately if there are sufficient data and the analyses are needed.

7.2. Efficacy Hypotheses

The primary hypothesis is that pemigatinib will improve PFS compared with gemcitabine plus cisplatin in participants with cholangiocarcinoma.

Progression-free survival (Primary Endpoint): Administration of pemigatinib to participants with cholangiocarcinoma improves PFS compared with participants treated with gemcitabine plus cisplatin. Assume $S_1(t)$ is the survival function of pemigatinib and $S_2(t)$ is the survival function of gemcitabine plus cisplatin. The hypotheses of the study are:

- H_0 (null hypothesis): $S_1(t) = S_2(t)$
- H_A (alternative hypothesis): $S_1(t) > S_2(t)$

7.3. Analysis of the Primary Efficacy Parameter

7.3.1. Primary Efficacy Analysis

The primary endpoint of the study is PFS, defined as the time from the date of randomization until the earliest date of PD determined by ICR assessment of objective radiographic disease assessments per RECIST v1.1 or death due to any cause. Partial death dates will be handled using the rules described in Section 4.1.4. Participants without a PFS event at the time of analysis will be censored. Censoring for PFS will follow the algorithm outlined in Table 2, which is based on the FDA Guidance for Industry (FDA 2015, FDA 2018).

The primary analysis of PFS will be based on the ITT Population and will compare PFS difference between treatment groups using log-rank test stratified by receipt of 1 cycle of gemcitabine plus cisplatin for advanced cholangiocarcinoma prior to randomization, geographic region, and tumor burden. The strata identified in the randomization process will be used for the analysis.

The HR and its 95% CI will be estimated based on the stratified Cox regression model with receipt of 1 cycle of gemcitabine plus cisplatin for advanced cholangiocarcinoma prior to randomization, geographic region, and tumor burden as stratification factors using the Efron (1977) method accounting for ties in event times.

Kaplan-Meier curves for PFS will be presented by treatment groups. The Kaplan-Meier estimate of median PFS will be presented with the 95% CI. The 95% CI will be calculated using the generalization of the Brookmeyer and Crowley (1982) method with log-log transformation (Klein and Moeschberger 1997).

For participants in the Crossover-Evaluable Population, PFS is defined as the time from date of first dose of study drug after crossover to the earlier date of PD determined by ICR assessment of objective radiographic disease assessments per RECIST v1.1 or death due to any cause. The number of participants who progressed or died and the number of participants censored will be summarized. The Kaplan-Meier estimate of median PFS will be presented with the 95% CI. The 95% CI will be calculated using the generalization of the Brookmeyer and Crowley (1982) method with log-log transformation (Klein and Moeschberger 1997).

Table 2: Evaluation and Censoring of Progression-Free Survival

Situation	Outcome	Date of Progression or Censoring
No baseline tumor assessments	Censored	Date of randomization (date of first dose of study drug for crossover participants)
No valid postbaseline response assessments	Censored	Date of randomization (date of first dose of study drug for crossover participants)
Progression documented between scheduled response assessments	Progressed	Date of first overall response of PD
No progression	Censored	Date of last valid radiologic assessment (not NE and not missing)
Study discontinuation for undocumented progression	Censored	Date of last valid radiologic assessment (not NE and not missing)
Study discontinuation for toxicity or other reason	Censored	Date of last valid radiologic assessment (not NE and not missing)
New anticancer treatment started	Censored	Date of last valid radiologic assessment (not NE and not missing) on/before starting a new anticancer treatment
Death before first progressive response assessment	Progressed	Date of death
Death between adequate response assessments	Progressed	Date of death
Death or progression after 2 or more missed assessments	Censored	Date of last valid radiologic assessment (not NE and not missing)

7.3.2. Subgroup Analyses for Primary Endpoint

Subgroup analyses for the primary endpoint will be conducted for the ITT Population. Subgroups will be formed based on the following participant characteristics and baseline variables for those participants whose data are available:

- Age category (< 65 years vs 65 to < 75 years vs ≥ 75 years)
- Sex (female vs male)
- Receipt of 1 cycle of gemcitabine plus cisplatin prior to randomization (yes vs no)
- Geographic region (Western [NA and EU] vs APAC vs ROW)
- Tumor burden (locally advanced vs distant metastasis)

The PFS HR and the 95% CI will be estimated for subgroups and a forest plot of PFS will be provided.

7.3.3. Sensitivity and Supportive Analyses for Primary Endpoint

If a substantial number of participants have been randomized in the incorrect stratum, stratified log-rank test on PFS will be performed for the ITT Population based on the stratum identified in the clinical data as a sensitivity analysis to evaluate the robustness of the result.

7.4. Analysis of the Secondary Efficacy Parameters

Secondary efficacy analyses will be conducted for the ITT Population. Selected secondary efficacy analyses will also be conducted for the Crossover-Evaluable Population.

7.4.1. Overall Response Rate

Overall response rate is defined as the proportion of participants with best overall response of CR or PR per RECIST v1.1 as assessed by an ICR. Best overall response is the best response recorded postbaseline prior to and including the first PD, in the order of CR, PR, SD, PD, and NE. The best overall response will be determined from response assessments before or on the same day as new anticancer therapy. If any alternative cancer therapy is taken while on study, any subsequent assessments will be excluded from the best overall response determination.

In the case of SD, measurements must meet the SD criteria at least once after the date of randomization at a minimum interval of 42 days. Participants who do not meet this criterion will have best overall response of PD if the next available assessment indicates PD or NE if there is no additional assessment available. A best overall response of CR or PR must be confirmed, and the confirmation method is described in the ICR Charter. The ORR in the ITT Population will be presented by treatment groups along with exact 95% CIs. The ORR between treatment groups will be compared using the Cochran-Mantel-Haenszel test stratified by receipt of 1 cycle of gemcitabine plus cisplatin for advanced cholangiocarcinoma prior to randomization, geographic region, and tumor burden.

Overall response rate will also be summarized for the Crossover-Evaluable Population.

7.4.2. Overall Survival

Overall survival is defined as the time from date of randomization until death due to any cause, and will be analyzed for the ITT Population. Date of death will be determined using the Death Report and the Survival Follow-Up eCRFs. Participants who are lost to follow-up or still alive at the time of analysis will be right-censored at the earlier of the date the participant was last known alive and the clinical data cutoff date for the analysis. The last known alive date is defined as the later of the last study visit and the date the participant was last known alive from the Survival Follow-Up and Participant Status eCRFs. Partial death dates will be handled using the rules described in Section 4.1.4.

The log-rank test stratified by receipt of 1 cycle of gemcitabine plus cisplatin for advanced cholangiocarcinoma prior to randomization, geographic region, and tumor burden will be used to analyze the OS differences between treatment groups. The HR and 95% CI will be estimated based on the stratified Cox regression model with receipt of 1 cycle of gemcitabine plus cisplatin for advanced cholangiocarcinoma prior to randomization, geographic region, and tumor burden as stratification factors using the Efron (1977) method accounting for ties.

The rank-preserving structural failure time model may be applied as a sensitivity analysis for OS to minimize estimation bias in the presence of crossover.

7.4.3. Duration of Response

For objective responders, the DOR is defined as the time from the date of the first assessment of CR or PR until the date of the first PD assessed by an ICR per RECIST v1.1 or death, whichever occurs first. Partial death dates will be handled using the rules described in Section 4.1.4.

For participants in the ITT Population who achieve a response, the log-rank test stratified by receipt of 1 cycle of gemcitabine plus cisplatin for advanced cholangiocarcinoma prior to randomization, geographic region, and tumor burden will be used to analyze the differences of DOR between treatment groups. The HR and 95% CI will be estimated based on the stratified Cox regression model with receipt of 1 cycle of gemcitabine plus cisplatin for advanced cholangiocarcinoma prior to randomization, geographic region, and tumor burden as stratification factors using the Efron (1977) method accounting for ties.

For participants in the Crossover-Evaluable Population, DOR data will be analyzed by the Kaplan-Meier method. The total number of responders, the number of participants who had PD or died, and the number of participants censored will be summarized. The Kaplan-Meier estimate of median DOR will be presented with the 95% CI. The 95% CI will be calculated using the generalization of the Brookmeyer and Crowley (1982) method with log-log transformation (Klein and Moeschberger 1997).

Participants who are alive without disease progression before the time of analysis will be censored. Censoring of DOR will follow the same algorithm as the censoring of PFS.

7.4.4. Disease Control Rate

Disease control rate is defined as the proportion of participants who achieved best overall response of CR, PR, or SD per RECIST v1.1 as assessed by an ICR. Confirmation of CR and PR is required, and the confirmation method is documented in the ICR Charter. Participants who do

not have sufficient baseline or on-study response assessment information to be adequately assessed for response status will be included in the denominators in the calculation of DCR.

Disease control rate in the ITT Population will be presented along with exact 95% CIs. Disease control rate between treatment groups will be compared using the Cochran-Mantel-Haenszel test stratified by receipt of 1 cycle of gemcitabine plus cisplatin for advanced cholangiocarcinoma prior to randomization, geographic region, and tumor burden.

Disease control rate will also be summarized for the Crossover-Evaluable Population.

7.4.5. Quality-of-Life Questionnaires

The EORTC QLQ-C30 score for each of the 5 functional scales, 3 symptom scales, 1 global health status/QoL scale, and 6 single-item scales at each visit where the variable is measured, as well as change from baseline to each visit, will be summarized descriptively by treatment group for the ITT Population. The scores for each scale will be calculated based on responses from the 30 questions using the mapping of questions to scales presented in Table 3.

Table 3: European Organisation for Research and Treatment of Cancer Quality-of-Life Questionnaire–C30 Scales

Scale	Question(s)
Global health status/QoL	29, 30
Physical functioning	1-5
Role functioning	6, 7
Emotional functioning	21-24
Cognitive functioning	20, 25
Social functioning	26, 27
Fatigue	10, 12, 18
Nausea and vomiting	14, 15
Pain	9, 19
Dyspnea	8
Insomnia	11
Appetite loss	13
Constipation	16
Diarrhea	17
Financial difficulties	28

The raw score of each scale is the mean of the item values that contribute to the scale, and the standardized score is a linear transformation of the raw score so that the range is from 0 to 100. A higher standardized score represents a higher/better level of functioning/QoL or a higher/worse level of symptoms.

The raw score will be the mean of nonmissing item values if the number of missing item values is less than 50% of the items that contribute to the scale. Otherwise, the raw score will be considered as missing.

Let range be the difference between the possible maximum and minimum of a raw scale, which is 6 for Global Health Status/QoL and 3 for all other scales. The standardized score for functional scale will be calculated as follows:

$$(1-\frac{RawScore-1}{Range})\times 100$$

For all other scales, the standardized score will be calculated as follows:

$$(\frac{RawScore-1}{Range})\times 100$$

The EORTC QLQ-BIL21 score for each of the 5 multi-item scales and 3 single-item scales at each visit where the variable is measured, as well as change from baseline to each visit, will be summarized descriptively by treatment group for the ITT population. The scores for each scale will be calculated based on responses from the 21 questions using the mapping of questions to scales presented in Table 4.

Table 4: European Organisation for Research and Treatment of Cancer Quality-of-Life Questionnaire–BIL21 Scales

Scale	Question(s)
Eating	31-34
Jaundice	35-37
Tiredness	38-40
Pain	41-44
Anxiety	45-48
Treatment side effects	49
Drains	50
Weight loss	51

The raw score of each scale is the mean of the item values that contribute to the scale, and the standardized score is a linear transformation of the raw score so that the range is from 0 to 100. A higher standardized score represents a higher/worse level of symptoms.

The raw score will be the mean of nonmissing item values if the number of missing item values is less than 50% of the items that contribute to the scale. Otherwise, the raw score will be considered as missing.

Let range be the difference between the possible maximum and minimum of a raw scale, which is 3 for all scales. The standardized score will be calculated as follows:

$$(\frac{RawScore-1}{Range})\times 100$$

The EQ-5D (3L) is the descriptive system that comprises 5 dimensions: mobility, self-care, usual activities, pain/discomfort, and anxiety/depression. Each dimension has 3 levels: no problems, some problems, extreme problems. The answer for each of the 5 dimensions at each visit where the variable is measured will be summarized descriptively by treatment group in the ITT Population.

7.5. Analysis of Other Efficacy Parameters

7.5.1. Largest Percentage Reduction in Sum of Diameters of Target Lesions

For participants with measurable lesions at baseline, target lesion sizes will be measured by sum of diameters. The best percent change from baseline, defined as the largest decrease in target lesion size for each participant during the study, will be summarized by treatment groups in the ITT Population, and a waterfall plot of best percent change will be generated. The baseline is defined as the last nonmissing measurement obtained on or before the randomization date.

Per RECIST criteria, target lesions considered "too small to measure" will be assigned a default value of 5 mm for the purposes of this analysis. Likewise, target lesions identified as "not present" at postbaseline assessments will be assigned 0 mm for this analysis. In the event that a target lesion is unaccounted for in a particular postbaseline timepoint (ie, the assessment is missing or NE), then the overall sum of diameters for target lesions will not be evaluable for that postbaseline timepoint.

For Crossover-Evaluable Population, the baseline is defined as the last assessment obtained on or before the start date of pemigatinib after crossover. The best percent change from baseline in target lesions will also be summarized and plotted for the Crossover-Evaluable Population.

7.5.2. Investigator-Assessed Efficacy Parameters

Progression-free survival, ORR, DOR, and DCR based on review of scans by investigator per RECIST v1.1 will be analyzed for the ITT Population and the Crossover-Evaluable Population in a similar fashion as those parameters assessed by an ICR. Confirmation of CR and PR is not required.

7.5.3. Eastern Cooperative Oncology Group Performance Status

The ECOG performance status at scheduled assessment times will be summarized by treatment group for the ITT Population.

8. SAFETY AND TOLERABILITY

Appendix A provides a list of data displays.

8.1. General Considerations

Summary tables may be replaced with listings when appropriate. For instance, an AE frequency table may be replaced with a listing if it only contains a few unique PTs reported on relatively few participants.

All the safety analyses will be conducted for the Safety Population, and safety data will be summarized by treatment group up to the time before crossover for participants who cross over to the pemigatinib group. Separate analyses will be conducted for the Crossover-Evaluable Population, and only baseline and the assessments that occurred after the crossover will be summarized.

8.2. Adverse Events

8.2.1. Adverse Event Definitions

A TEAE for the Safety Population is any AE either reported for the first time or worsening of a pre-existing event after first dose of study drug until 30 days after the last dose of study drug for participants who do not cross over to pemigatinib. For participants who cross over to pemigatinib, the end date is 30 days after the last dose date of gemcitabine plus cisplatin or the day before the first dose of pemigatinib after crossover, whichever is first.

A TEAE for the Crossover-Evaluable Population is any AE either reported for the first time or worsening of a pre-existing event after first dose of pemigatinib after crossover and until 30 days after the last dose of pemigatinib.

Analysis of AEs (as discussed below) will be limited to TEAEs, but data listings will include all AEs regardless of their timing in relation to study drug administration. For purposes of analysis, all AEs will be considered TEAEs unless the AE can unequivocally be defined as not treatment-emergent.

Adverse events will be tabulated by MedDRA SOC and PT. Severity of AEs will be graded using the NCI CTCAE v5.0. The CTCAE reporting guidelines and grading details are available on the Cancer Therapy Evaluation Program website.

A grading (severity) scale is provided for each AE term. If the toxicity is not included in the CTCAE v5.0 criteria, it will be graded on a scale of 1 to 5 as follows: 1 = mild, 2 = moderate, 3 = severe, 4 = life-threatening, and 5 = fatal. All toxicities will be graded based on the worst level reached, not the level they may have reached if they had not been treated. When the intensity of an AE changes over time for a reporting period (eg, between visits), each change in intensity will be reported as an AE until the event resolves.

The subset of AEs considered by the investigator to be related to study drug will be considered to be treatment-related AEs. If the investigator does not specify the relationship of the AE to study drug, the AE will be considered to be treatment-related. The incidence of TEAEs, treatment-related TEAEs, and serious TEAEs will be tabulated.

8.2.2. Clinically Notable Adverse Events

Specific groupings of clinically notable AEs will be considered and the number of participants with at least 1 event within each grouping will be reported. Such groups consist of AEs for which there is a specific clinical interest in connection with the study drug or AEs that are similar in nature (although not identical). The groups are defined in Table 5. All clinically notable AEs are defined through reviewing PTs according to MedDRA v28.0.

Table 5: Clinically Notable Adverse Events Groupings

Categories	MedDRA Preferred Terms
Serous retinal detachment	Serous retinal detachment, detachment of macular retinal pigment epithelium, detachment of retinal pigment epithelium, retinal detachment, subretinal fluid, chorioretinopathy, retinal pigment epitheliopathy, chorioretinal disorder, retinopathy, maculopathy, retinal disorder, retinal thickening, chorioretinal folds, chorioretinal scar
Nail toxicity	Nail toxicity, nail bed tenderness, nail bed disorder, nail bed bleeding, nail disorder, nail discolouration, nail discomfort, nail dystrophy, nail hypertrophy, nail ridging, nail infection, onychalgia, onychoclasis, onycholysis, onychomadesis, onychomycosis, paronychia, fungal paronychia
Hyperphosphatemia	Hyperphosphataemia, blood phosphorus increased
Hypophosphatemia	Hypophosphataemia, blood phosphorus decreased
Dry eye	Dry eye, meibomian gland dysfunction, lacrimation increased, keratitis, punctate keratitis, pinguecula, pterygium
Eyelash changes	Eyelash changes, growth of eyelashes, trichiasis, trichomegaly
Vision blurred	Vision blurred, visual impairment, visual acuity reduced
Vitreous detachment	Vitreous detachment, vitreous floaters

8.2.3. Adverse Event Summaries

Adverse events will be summarized by treatment group for the Safety Population and for the Crossover-Evaluable Population.

An overall summary of AEs by treatment group will include the following:

- Number (%) of participants who had any TEAEs
- Number (%) of participants who had any Grade 3 or higher TEAEs
- Number (%) of participants who had any serious TEAEs
- Number (%) of participants who had any TEAEs related to study drug
- Number (%) of participants who had any fatal TEAEs
- Number (%) of participants who had any TEAEs leading to dose interruption of study drug
- Number (%) of participants who had any TEAEs leading to dose reduction of study drug
- Number (%) of participants who had any TEAEs leading to discontinuation of study drug

The following summaries will be produced by MedDRA term:

- Summary of TEAEs by MedDRA SOC and PT
- Summary of TEAEs by MedDRA PT in decreasing order of frequency
- Summary of TEAEs by MedDRA SOC, PT, and maximum severity
- Summary of TEAEs by MedDRA SOC, PT, and CTCAE grade category
- Summary of Grade 3 or higher TEAEs by MedDRA SOC and PT
- Summary of Grade 3 or higher TEAEs by MedDRA PT in decreasing order of frequency
- Summary of serious TEAEs by MedDRA SOC and PT
- Summary of serious TEAEs by MedDRA PT in decreasing order of frequency
- Summary of treatment-related TEAEs by MedDRA SOC and PT
- Summary of treatment-related TEAEs by MedDRA PT in decreasing order of frequency
- Summary of Grade 3 or higher treatment-related TEAEs by MedDRA SOC and PT
- Summary of treatment-related serious TEAEs by MedDRA SOC and PT
- Summary of TEAEs with a fatal outcome by MedDRA SOC and PT
- Summary of TEAEs leading to study drug dose interruption by MedDRA SOC and PT
- Summary of TEAEs leading to study drug dose reduction by MedDRA SOC and PT
- Summary of TEAEs leading to discontinuation of study drug by MedDRA SOC and PT
- Summary of sponsor-defined clinically notable TEAEs by category and MedDRA PT
- Summary of Grade 3 or higher sponsor-defined clinically notable TEAEs by category and MedDRA PT
- Summary of serious sponsor-defined clinically notable TEAEs by category and MedDRA PT
- Summary of sponsor-defined clinically notable TEAEs leading to study drug dose reduction by category and MedDRA PT
- Summary of sponsor-defined clinically notable TEAEs leading to study drug dose interruption by category and MedDRA PT
- Summary of sponsor-defined clinically notable TEAEs leading to discontinuation of study drug by category and MedDRA PT

8.3. Clinical Laboratory Tests

8.3.1. Laboratory Value Definitions

Laboratory values and change from baseline values will be summarized descriptively by visit for numeric laboratory parameters. Baseline will be determined according to Section 4.1.3. If there are multiple values that meet the criteria for baseline, additional rules may be provided after consultation with the medical monitor to delineate which value will be defined as baseline.

Laboratory test values outside the normal range will be assessed for severity based on the numerical component of CTCAE v5.0.

8.3.2. Laboratory Value Summaries

All test results and associated normal ranges from local laboratories will be converted to SI units.

For numeric laboratory values, baseline value, postbaseline value, change from baseline, and percent change from baseline will be summarized descriptively by visit. The number and percentage of participants with the laboratory values being low, normal, and high will be summarized by visit. In addition, mean change from baseline will be plotted over time for selected laboratory parameters, including, but not limited to, phosphate, calcium, creatinine, sodium, and parathyroid hormone.

Severity grades will be assigned to laboratory test values based on the numerical component of CTCAE v5.0. Shift tables will be presented showing change in CTCAE grade from baseline to worst grade postbaseline. Separate summaries for abnormally high and abnormally low laboratory values will be provided when the laboratory parameter has both high and low grading criteria. The denominator for the percentage calculation will be the number of participants in the baseline category. The number of participants who had worsening of laboratory abnormalities will be summarized by maximum severity.

8.3.3. Potential Drug-Induced Liver Injury Events

The participants with elevated alanine aminotransferase or aspartate aminotransferase $\geq 3 \times$ upper limit of normal range and alkaline phosphatase $\leq 2 \times$ upper limit of normal range accompanied by total bilirubin $> 2 \times$ upper limit of normal range at the same visit will be listed by treatment group.

8.4. Vital Signs

Values at each scheduled visit and the change and percentage change from baseline for vital signs, including weight, systolic blood pressure, diastolic blood pressure, pulse, temperature, and respiratory rate, will be summarized descriptively.

Criteria for clinically notable vital sign abnormalities are defined in Table 6. The abnormal values for participants exhibiting clinically notable vital sign abnormalities will be listed along with their treatment group. Alert vital signs are defined as an absolute value outside the defined range and percentage change from baseline greater than 25%. Note that the definition of alert vital signs does not apply for body temperature and weight. The abnormal values for participants exhibiting alert vital sign abnormalities will be listed.

Table 6: Criteria for Clinically Notable Vital Sign Abnormalities

Parameter	High Threshold	Low Threshold
Systolic blood pressure	> 155 mmHg	< 85 mmHg
Diastolic blood pressure	> 100 mmHg	< 40 mmHg
Pulse	> 100 bpm	< 45 bpm
Temperature	> 38°C	< 35.5°C
Respiratory rate	> 24 breaths/min	< 8 breaths/min

8.5. Electrocardiograms

Twelve-lead ECGs including PR, QT, QRS, and QTcF intervals as well as heart rate will be obtained for each participant during the study. Values at each scheduled visit and change and percentage change from baseline will be summarized for each ECG parameter. Baseline will be determined as the average of all nonmissing values before the first administration of study drug.

Criteria for clinically notable ECG abnormalities are defined in Table 7. Electrocardiogram values will also be considered abnormal if the absolute percentage change from baseline is more than 25% (30% QRS interval). Participants exhibiting ECG abnormalities will be listed with study visit and assigned treatment group. Abnormal values for participants with alert ECG values, defined as both the absolute value and the percentage change from baseline being outside defined ranges, will be identified and listed. The number of participants with clinically significant ECG abnormalities will be summarized. Outliers of QT, QTcB, and QTcF values, defined as absolute values > 450 ms, > 500 ms, or change from baseline > 30 ms, will be summarized.

Table 7: Criteria for Clinically Notable Electrocardiogram Abnormalities

Parameter	High Threshold	Low Threshold
PR	> 220 ms	< 75 ms
HR	> 100 bpm	< 45 bpm
QT	> 500 ms	< 300 ms
QRS	> 120 ms	< 50 ms
QTcF, QTcB	> 450 ms	< 295 ms

9. INTERIM ANALYSES

An interim analysis is no longer applicable due to early discontinuation of enrollment for the study.

Preplanned analyses of safety will be provided to an independent DMC as specified in the DMC Charter. The DMC will review safety data of the ongoing study at regular intervals as specified in the DMC Charter. Such safety will be summarized by treatment group. The process by which the DMC will make recommendations and decisions will be documented in the DMC Charter.

10. CHANGES AND MODIFICATIONS TO THE ANALYSIS PLAN

All versions of the SAP are listed in Table 8.

Table 8: Statistical Analysis Plan Versions

SAP Version	Date
Original	10 JUN 2025

10.1. Changes to Protocol-Defined Analyses

Interim analyses have been removed as study enrollment was stopped before the planned timing for interim analysis was reached. In addition, the final analysis will be based on the actual number of PFS events observed at the time of database lock.

10.2. Changes to the Statistical Analysis Plan

Not applicable.

11. REFERENCES

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APPENDIX A. PLANNED TABLES, FIGURES, AND LISTINGS

This appendix provides a list of the planned tables, figures, and listings for the Clinical Study Report. Shells are provided in a separate document for tables that are not in the Standard Safety Tables v2.2.

The lists of tables, figures, and listings are to be used as guidelines. Modifications of the lists that do not otherwise affect the nature of the analysis will not warrant an amendment to the SAP.

Tables

Table No.	Title	Population	Standard
Baseline and Demographic Characteristics			
1.1.1	Analysis Populations	ITT	X
1.1.2.1	Summary of Participant Disposition	ITT	X
1.1.2.2	Summary of Participant Disposition	Crossover-Evaluable	X
1.1.3.1	Summary of Number of Participants Enrolled by Country and Site	ITT	X
1.1.3.2	Summary of Number of Participants Enrolled by Country and Site	Crossover-Evaluable	X
1.1.4.1	Summary of Protocol Deviations	ITT	X
1.2.1.1	Summary of Demographics and Baseline Characteristics	ITT	X
1.3.1	Summary of Disease History	ITT	X
1.3.2	Summary of Prior Cancer Therapy	ITT	X
1.4.1	Summary of Prior Medications	ITT	X
1.4.2	Summary of Concomitant Medications	ITT	X
1.5.1	Summary of General Medical History	ITT	X
Efficacy			
2.1.1.1	Summary of Progression-Free Survival (Assessed by Independent Reviewer)	ITT	
2.1.1.2	Summary of Progression-Free Survival (Assessed by Independent Reviewer)	Crossover-Evaluable	
2.1.2.1	Summary of Progression-Free Survival (Assessed by Investigator)	ITT	
2.1.2.2	Summary of Progression-Free Survival (Assessed by Investigator)	Crossover-Evaluable	
2.1.3.1	Summary of Progression-Free Survival - Based on Actual Stratification Factors (Assessed by Independent Reviewer)	ITT	
2.1.3.2	Summary of Progression-Free Survival - Based on Actual Stratification Factors (Assessed by Investigator)	ITT	
2.1.4.1	Subgroup Analysis of Progression-Free Survival (Assessed by Independent Reviewer)	ITT	
2.1.4.2	Subgroup Analysis of Progression-Free Survival (Assessed by Investigator)	ITT	
2.2.1.1.1	Summary of Best Overall Response and Objective Response Rate (Assessed by Independent Reviewer - Response Confirmed)	ITT	
2.2.1.1.2	Summary of Best Overall Response and Objective Response Rate (Assessed by Independent Reviewer - Response Confirmed)	Crossover-Evaluable	

Table No.	Title	Population	Standard
2.2.1.2.1	Summary of Best Overall Response and Objective Response Rate (Assessed by Independent Reviewer - Response Unconfirmed)	ITT	
2.2.1.2.2	Summary of Best Overall Response and Objective Response Rate (Assessed by Independent Reviewer - Response Unconfirmed)	Crossover-Evaluable	
2.2.1.3.1	Summary of Best Overall Response and Objective Response Rate (Assessed by Investigator - Response Unconfirmed)	ITT	
2.2.1.3.2	Summary of Best Overall Response and Objective Response Rate (Assessed by Investigator - Response Unconfirmed)	Crossover-Evaluable	
2.2.2	Summary of Overall Survival	ITT	
2.2.3.1.1	Summary of Duration of Response (Assessed by Independent Reviewer - Response Confirmed)	ITT	
2.2.3.1.2	Summary of Duration of Response (Assessed by Independent Reviewer - Response Confirmed)	Crossover-Evaluable	
2.2.3.2.1	Summary of Duration of Response (Assessed by Independent Reviewer - Response Unconfirmed)	ITT	
2.2.3.2.2	Summary of Duration of Response (Assessed by Independent Reviewer - Response Unconfirmed)	Crossover-Evaluable	
2.2.3.3.1	Summary of Duration of Response (Assessed by Investigator - Response Unconfirmed)	ITT	
2.2.3.3.2	Summary of Duration of Response (Assessed by Investigator - Response Unconfirmed)	Crossover-Evaluable	
2.2.4.1.1	Summary of Disease Control Rate (Assessed by Independent Reviewer - Response Confirmed)	ITT	
2.2.4.1.2	Summary of Disease Control Rate (Assessed by Independent Reviewer - Response Confirmed)	Crossover-Evaluable	
2.2.4.2.1	Summary of Disease Control Rate (Assessed by Independent Reviewer - Response Unconfirmed)	ITT	
2.2.4.2.2	Summary of Disease Control Rate (Assessed by Independent Reviewer - Response Unconfirmed)	Crossover-Evaluable	
2.2.4.3.1	Summary of Disease Control Rate (Assessed by Investigator - Response Unconfirmed)	ITT	
2.2.4.3.2	Summary of Disease Control Rate (Assessed by Investigator - Response Unconfirmed)	Crossover-Evaluable	
2.2.5.1.1	Summary of Best Change in Target Lesion Size (Assessed by Independent Reviewer)	ITT	
2.2.5.1.2	Summary of Best Change in Target Lesion Size (Assessed by Independent Reviewer)	Crossover-Evaluable	
2.2.5.2.1	Summary of Best Change in Target Lesion Size (Assessed by Investigator)	ITT	
2.2.5.2.2	Summary of Best Change in Target Lesion Size (Assessed by Investigator)	Crossover-Evaluable	
2.2.6	Summary of EORTC QLQ-C30 Score	ITT	
2.2.7	Summary of EORTC QLQ-BIL21 Score	ITT	
2.2.8	Summary of EQ-5D (3L) Questionnaire	ITT	
2.2.9	Summary of ECOG Status	ITT	

Table No.	Title	Population	Standard
Safety			
3.1.1.1	Summary of Study Drug Exposure	Safety	X
3.1.1.2	Summary of Study Drug Exposure	Crossover-Evaluable	X
3.1.2.1	Summary of Study Drug Compliance	Safety	X
3.1.2.2	Summary of Study Drug Compliance	Crossover-Evaluable	X
3.1.3.1	Summary of Dose Modifications	Safety	X
3.1.3.2	Summary of Dose Modifications	Crossover-Evaluable	X
3.2.1.1	Overall Summary of Treatment-Emergent Adverse Events	Safety	X
3.2.1.2	Overall Summary of Treatment-Emergent Adverse Events	Crossover-Evaluable	X
3.2.2.1	Summary of Treatment-Emergent Adverse Events by MedDRA System Organ Class and Preferred Term	Safety	X
3.2.2.2	Summary of Treatment-Emergent Adverse Events by MedDRA System Organ Class and Preferred Term	Crossover-Evaluable	X
3.2.3.1	Summary of Treatment-Emergent Adverse Events by MedDRA Preferred Term in Decreasing Order of Frequency	Safety	X
3.2.3.2	Summary of Treatment-Emergent Adverse Events by MedDRA Preferred Term in Decreasing Order of Frequency	Crossover-Evaluable	X
3.2.4.1	Summary of Treatment-Emergent Adverse Events by MedDRA System Organ Class, Preferred Term, and Maximum Severity	Safety	X
3.2.4.2	Summary of Treatment-Emergent Adverse Events by MedDRA System Organ Class, Preferred Term, and Maximum Severity	Crossover-Evaluable	X
3.2.5.1	Summary of Treatment-Emergent Adverse Events by MedDRA System Organ Class, Preferred Term, and CTCAE Grade Category	Safety	X
3.2.5.2	Summary of Treatment-Emergent Adverse Events by MedDRA System Organ Class, Preferred Term, and CTCAE Grade Category	Crossover-Evaluable	X
3.2.6.1	Summary of Grade 3 or Higher Treatment-Emergent Adverse Events by MedDRA System Organ Class and Preferred Term	Safety	X
3.2.6.2	Summary of Grade 3 or Higher Treatment-Emergent Adverse Events by MedDRA System Organ Class and Preferred Term	Crossover-Evaluable	X
3.2.7.1	Summary of Grade 3 or Higher Treatment-Emergent Adverse Events by MedDRA Preferred Term in Decreasing Order of Frequency	Safety	X
3.2.7.2	Summary of Grade 3 or Higher Treatment-Emergent Adverse Events by MedDRA Preferred Term in Decreasing Order of Frequency	Crossover-Evaluable	X
3.2.8.1	Summary of Serious Treatment-Emergent Adverse Events by MedDRA System Organ Class and Preferred Term	Safety	X
3.2.8.2	Summary of Serious Treatment-Emergent Adverse Events by MedDRA System Organ Class and Preferred Term	Crossover-Evaluable	X
3.2.9.1	Summary of Serious Treatment-Emergent Adverse Events by MedDRA Preferred Term in Decreasing Order of Frequency	Safety	X
3.2.9.2	Summary of Serious Treatment-Emergent Adverse Events by MedDRA Preferred Term in Decreasing Order of Frequency	Crossover-Evaluable	X
3.2.10.1	Summary of Treatment-Related Treatment-Emergent Adverse Events by MedDRA System Organ Class and Preferred Term	Safety	X
3.2.10.2	Summary of Treatment-Related Treatment-Emergent Adverse Events by MedDRA System Organ Class and Preferred Term	Crossover-Evaluable	X

Table No.	Title	Population	Standard
3.2.11.1	Summary of Treatment-Related Treatment-Emergent Adverse Events by MedDRA Preferred Term in Decreasing Order of Frequency	Safety	X
3.2.11.2	Summary of Treatment-Related Treatment-Emergent Adverse Events by MedDRA Preferred Term in Decreasing Order of Frequency	Crossover-Evaluable	X
3.2.12.1	Summary of Grade 3 or Higher Treatment-Related Treatment-Emergent Adverse Events by MedDRA System Organ Class and Preferred Term	Safety	X
3.2.12.2	Summary of Grade 3 or Higher Treatment-Related Treatment-Emergent Adverse Events by MedDRA System Organ Class and Preferred Term	Crossover-Evaluable	X
3.2.13.1	Summary of Treatment-Related Serious Treatment-Emergent Adverse Events by MedDRA System Organ Class and Preferred Term	Safety	X
3.2.13.2	Summary of Treatment-Related Serious Treatment-Emergent Adverse Events by MedDRA System Organ Class and Preferred Term	Crossover-Evaluable	X
3.2.14.1	Summary of Treatment-Emergent Adverse Events with a Fatal Outcome by MedDRA System Organ Class and Preferred Term	Safety	X
3.2.14.2	Summary of Treatment-Emergent Adverse Events with a Fatal Outcome by MedDRA System Organ Class and Preferred Term	Crossover-Evaluable	X
3.2.15.1	Summary of Treatment-Emergent Adverse Events Leading to Study Drug Dose Interruption by MedDRA System Organ Class and Preferred Term	Safety	X
3.2.15.2	Summary of Treatment-Emergent Adverse Events Leading to Study Drug Dose Interruption by MedDRA System Organ Class and Preferred Term	Crossover-Evaluable	X
3.2.16.1	Summary of Treatment-Emergent Adverse Events Leading to Study Drug Dose Reduction by MedDRA System Organ Class and Preferred Term	Safety	X
3.2.16.2	Summary of Treatment-Emergent Adverse Events Leading to Study Drug Dose Reduction by MedDRA System Organ Class and Preferred Term	Crossover-Evaluable	X
3.2.17.1	Summary of Treatment-Emergent Adverse Events Leading to Discontinuation of Study Drug by MedDRA System Organ Class and Preferred Term	Safety	X
3.2.17.2	Summary of Treatment-Emergent Adverse Events Leading to Discontinuation of Study Drug by MedDRA System Organ Class and Preferred Term	Crossover-Evaluable	X
3.2.18.1	Summary of Sponsor-Defined Clinically Notable Treatment-Emergent Adverse Events by Category and MedDRA Preferred Term	Safety	X
3.2.18.2	Summary of Sponsor-Defined Clinically Notable Treatment-Emergent Adverse Events by Category and MedDRA Preferred Term	Crossover-Evaluable	X
3.2.19.1	Summary of Grade 3 or Higher Sponsor-Defined Clinically Notable Treatment-Emergent Adverse Events by Category and MedDRA Preferred Term	Safety	X
3.2.19.2	Summary of Grade 3 or Higher Sponsor-Defined Clinically Notable Treatment-Emergent Adverse Events by Category and MedDRA Preferred Term	Crossover-Evaluable	X
3.2.20.1	Summary of Serious Sponsor-Defined Clinically Notable Treatment-Emergent Adverse Events by Category and MedDRA Preferred Term	Safety	X

Table No.	Title	Population	Standard
3.2.20.2	Summary of Serious Sponsor-Defined Clinically Notable Treatment-Emergent Adverse Events by Category and MedDRA Preferred Term	Crossover-Evaluable	X
3.2.21.1	Summary of Sponsor-Defined Clinically Notable Treatment-Emergent Adverse Events Leading to Study Drug Dose Reduction by Category and MedDRA Preferred Term	Safety	X
3.2.21.1.2	Summary of Sponsor-Defined Clinically Notable Treatment-Emergent Adverse Events Leading to Study Drug Dose Reduction by Category and MedDRA Preferred Term	Crossover-Evaluable	X
3.2.22.1	Summary of Sponsor-Defined Clinically Notable Treatment-Emergent Adverse Events Leading to Study Drug Dose Interruption by Category and MedDRA Preferred Term	Safety	X
3.2.22.2	Summary of Sponsor-Defined Clinically Notable Treatment-Emergent Adverse Events Leading to Study Drug Dose Interruption by Category and MedDRA Preferred Term	Crossover-Evaluable	X
3.2.23.1	Summary of Sponsor-Defined Clinically Notable Treatment-Emergent Adverse Events Leading to Discontinuation of Study Drug by Category and MedDRA Preferred Term	Safety	X
3.2.23.2	Summary of Sponsor-Defined Clinically Notable Treatment-Emergent Adverse Events Leading to Discontinuation of Study Drug by Category and MedDRA Preferred Term	Crossover-Evaluable	X
3.3.1.1.1	Summary of Laboratory Values - Hematology	Safety	X
3.3.1.1.2	Summary of Laboratory Values - Hematology	Crossover-Evaluable	X
3.3.1.2.1	Summary of Laboratory Values - Chemistry	Safety	X
3.3.1.2.2	Summary of Laboratory Values - Chemistry	Crossover-Evaluable	X
3.3.1.3.1	Summary of Laboratory Values - Coagulation	Safety	X
3.3.1.3.2	Summary of Laboratory Values - Coagulation	Crossover-Evaluable	X
3.3.1.4.1	Summary of Laboratory Values - Urinalysis	Safety	X
3.3.1.4.2	Summary of Laboratory Values - Urinalysis	Crossover-Evaluable	X
3.3.2.1.1	Shift Summary of Hematology Laboratory Values in CTCAE Grade - to the Worst Abnormal Value	Safety	X
3.3.2.1.2	Shift Summary of Hematology Laboratory Values in CTCAE Grade - to the Worst Abnormal Value	Crossover-Evaluable	X
3.3.2.2.1	Shift Summary of Chemistry Laboratory Values in CTCAE Grade - to the Worst Abnormal Value	Safety	X
3.3.2.2.2	Shift Summary of Chemistry Laboratory Values in CTCAE Grade - to the Worst Abnormal Value	Crossover-Evaluable	X
3.3.2.3.1	Shift Summary of Coagulation Laboratory Values in CTCAE Grade - to the Worst Abnormal Value	Safety	X
3.3.2.3.2	Shift Summary of Coagulation Laboratory Values in CTCAE Grade - to the Worst Abnormal Value	Crossover-Evaluable	X
3.3.3.1.1	Treatment-Emergent Worsening of Laboratory Abnormalities - Hematology	Safety	X
3.3.3.1.2	Treatment-Emergent Worsening of Laboratory Abnormalities - Hematology	Crossover-Evaluable	X

Table No.	Title	Population	Standard
3.3.3.2.1	Treatment-Emergent Worsening of Laboratory Abnormalities - Chemistry	Safety	X
3.3.3.2.2	Treatment-Emergent Worsening of Laboratory Abnormalities - Chemistry	Crossover-Evaluable	X
3.3.3.3.1	Treatment-Emergent Worsening of Laboratory Abnormalities - Coagulation	Safety	X
3.3.3.3.2	Treatment-Emergent Worsening of Laboratory Abnormalities - Coagulation	Crossover-Evaluable	X
3.4.1.1	Summary of Systolic Blood Pressure (mmHg)	Safety	X
3.4.1.2	Summary of Systolic Blood Pressure (mmHg)	Crossover-Evaluable	X
3.4.2.1	Summary of Diastolic Blood Pressure (mmHg)	Safety	X
3.4.2.2	Summary of Diastolic Blood Pressure (mmHg)	Crossover-Evaluable	X
3.4.3.1	Summary of Pulse (bpm)	Safety	X
3.4.3.2	Summary of Pulse (bpm)	Crossover-Evaluable	X
3.4.4.1	Summary of Respiratory Rate (breaths/min)	Safety	X
3.4.4.2	Summary of Respiratory Rate (breaths/min)	Crossover-Evaluable	X
3.4.5.1	Summary of Body Temperature (ºC)	Safety	X
3.4.5.2	Summary of Body Temperature (ºC)	Crossover-Evaluable	X
3.4.6.1	Summary of Weight (kg)	Safety	X
3.4.6.2	Summary of Weight (kg)	Crossover-Evaluable	X
3.5.1.1	Summary of PR Interval (ms) From 12-Lead ECG	Safety	X
3.5.1.2	Summary of PR Interval (ms) From 12-Lead ECG	Crossover-Evaluable	X
3.5.2.1	Summary of QRS Interval (ms) From 12-Lead ECG	Safety	X
3.5.2.2	Summary of QRS Interval (ms) From 12-Lead ECG	Crossover-Evaluable	X
3.5.3.1	Summary of QT Interval (ms) From 12-Lead ECG	Safety	X
3.5.3.2	Summary of QT Interval (ms) From 12-Lead ECG	Crossover-Evaluable	X
3.5.4.1	Summary of QTcF Interval (ms) From 12-Lead ECG	Safety	X
3.5.4.2	Summary of QTcF Interval (ms) From 12-Lead ECG	Crossover-Evaluable	X
3.5.5.1	Summary of Heart Rate (bpm) From 12-Lead ECG	Safety	X
3.5.5.2	Summary of Heart Rate (bpm) From 12-Lead ECG	Crossover-Evaluable	X
3.5.6.1	Summary of Outliers of QT, QTcB, and QTcF Interval Values (ms) From 12-Lead ECG	Safety	X
3.5.6.2	Summary of Outliers of QT, QTcB, and QTcF Interval Values (ms) From 12-Lead ECG	Crossover-Evaluable	X
3.5.7.1	Summary of Clinically Significant ECG Abnormalities	Safety	X
3.5.7.2	Summary of Clinically Significant ECG Abnormalities	Crossover-Evaluable	X

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Figure No.	Title	Population
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4.1.1.2	Kaplan-Meier Estimates of Progression-Free Survival	Crossover-Evaluable
4.1.2	Forest Plot of Progression-Free Survival by Subgroups	ITT
4.1.3.1	Kaplan-Meier Estimates of Duration of Response	ITT
4.1.3.2	Kaplan-Meier Estimates of Duration of Response	Crossover-Evaluable
4.2.1	Kaplan-Meier Estimates of Overall Survival	ITT
4.3.1.1	Waterfall Plot of Best Percent Change in Sum of Target Lesions	ITT
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4.6.1	Line Graph of Selected Laboratory Values by Study Visit	Safety

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