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A Phase 2 Study of Futibatinib in Patients with Specific FGFR Aberrations

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This trial was conducted in accordance with the ethical principles of Good Clinical Practice (GCP), according to the International Conference on Harmonization (ICH) Harmonized Tripartite Guideline.

STATISTICAL ANALYSIS PLAN

Version 1.0

APPROVAL PAGE

A Phase 2 Study of Futibatinib in Patients with Specific FGFR Aberrations

Protocol TAS-120-202

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LIST OF ABBREVIATIONS AND DEFINITIONS OF TERMS

Abbreviation	Term
AE	Adverse event
AESI	Adverse event of special interest
ALT	Alanine aminotransferase
AST	Aspartate aminotransferase
ATC	Anatomical Therapeutic Chemical
CCA	Cholangiocarcinoma
Ccr	Calculated creatinine clearance
CCyR	Complete cytogenetic responses
CI	Confidence interval
CR	Complete response
CRi	Complete response with incomplete hematological recovery
CSR	Clinical study report
CT	Computed tomography
ctDNA	Circulating tumor DNA
DCR	Disease control rate
DOR	Duration of response
ECG	Electrocardiogram
ECOG	Eastern Cooperative Oncology Group
EFS	Event-free survival
EOT	End of treatment/end of therapy
FDA	Food and Drug Administration
FGF	Fibroblast growth factor
FGFR	Fibroblast growth factor receptor
GCP	Good clinical practice
GEJ	Gastro-esophageal junction
ICF	Informed consent form
IRC	Independent central review of radiologic images
MedDRA	Medical Dictionary for Regulatory Activities
MDS/MPN	Myelodysplastic/myeloproliferative neoplasms
MLN	Myeloid and lymphoid neoplasms
MRI	Magnetic resonance imaging
NCI-CTCAE	National Cancer Institute - Common Terminology Criteria for Adverse Events
ORR	Objective response rate

OS	Overall survival
PCyR	Partial cytogenetic responses
PD	Progressive disease
PET	Positron emission tomography
PFS	Progression-free survival
PK	Pharmacokinetics
PopPK	Population pharmacokinetics
PR	Partial response
PS	Performance status
PT	Preferred term
QD	Once daily
QTcB	QT interval corrected for heart rate using Bazett's formula
QTcF	QT interval corrected for heart rate using Fridericia's formula
RECIL	Response evaluation criteria in lymphoma
RECIST	Response Evaluation Criteria in Solid Tumors
RFS	Relapse-free survival
SAE	Serious adverse event
SAP	Statistical Analysis Plan
SD	Stable disease
SI	The International System of Units
SOC	System Organ Class
TEAE	Treatment-emergent adverse event
WHO	World Health Organization
WOCBP	Women of childbearing potential

1. INTRODUCTION

The purpose of this statistical analysis plan (SAP) is to describe the planned analyses and data displays to be included in the Clinical Study Report (CSR) for Protocol TAS-120-202.

Fibroblast growth factor receptor (*FGFR*) signaling plays a crucial role in cancer cell proliferation, migration, angiogenesis, and survival. Recent studies have uncovered increasing evidence that deregulated *FGFRs* can function as driving oncogenes in certain tumor types, maintaining the malignant properties of cancer cells. When *FGFRs* are amplified, rearranged, or undergo fusion, aberrant activation of downstream pathways results in mitogenic, mesenchymal, and antiapoptotic responses in cells.

Although *FGFR* rearrangements are rare, *FGFR2* fusions with multiple partners have been uncovered in many cancers, including cholangiocarcinoma (CCA), lung cancer, thyroid cancer, breast cancer, and prostate cancer (Wu et al. 2013; Gallo et al. 2015; Yoshihara et al. 2015). Of all the *FGFRs*, *FGFR2* shows the broadest range of fusion partners. Fusion genes have also been reported in bladder cancer and urothelial carcinoma (Williams et al. 2013; Loriot et al. 2019).

FGFR2 amplification has been described in 4-10% of gastric or gastroesophageal junction (GEJ) cancer, particularly the aggressive diffuse subtype (Deng et al. 2012; Kunii et al. 2008; Jung et al. 2012; Liu et al. 2014). Gastric and GEJ cancer is the fourth most common cancer and the second most common cause of cancer death (Jemal et al. 2010). In vitro, *FGFR2*-amplified gastric cancer cell lines have been shown to be selectively sensitive to the inhibitory effects of *FGFR* tyrosine kinase inhibitors (Kunii et al. 2008).

Myeloid and lymphoid neoplasms (MLNs) with abnormalities of the *FGFR1* gene have been recognized as a distinct disease group in the 2008 World Health Organization (WHO) classification of hematopoietic neoplasms (Bain et al. 2008). These MLNs are characterized by eosinophilia, lymphadenopathy, and a high incidence of T-cell non-Hodgkin lymphoma with progression to acute myeloid leukemia (MacDonald et al. 1995). This is a very rare disease, with fewer than 100 patients reported around the world (MacDonald et al. 2002; Jackson et al. 2010), and there is a marked absence of curative treatments for these patients.

This Phase 2 study will evaluate the efficacy and safety of futibatinib in patients with *FGFR* aberrations in 3 distinct cohorts. Patients will be enrolled into 1 of 3 cohorts: patients with advanced, metastatic, or locally-advanced solid tumors harboring *FGFR* rearrangements (excluding primary brain tumors and intrahepatic cholangiocarcinoma); patients with gastric or GEJ cancer harboring *FGFR2* amplification; and patients with MLNs harboring *FGFR1* rearrangements.

2. STUDY OBJECTIVES AND ENDPOINTS

2.1. Study Objectives

2.1.1. Cohorts A and B

2.1.1.1. Primary Objective

The primary objective in Cohorts A and B is to evaluate the objective response rate (ORR) in patients with solid tumors harboring *FGFR* rearrangements (Cohort A) or gastric cancer (including GEJ cancer) harboring *FGFR2* amplifications (Cohort B) based on independent central review of radiologic images (IRC).

2.1.1.2. Secondary Objectives

The secondary objectives in Cohorts A and B are the following:

- ORR based on Investigator,
- Disease control rate (DCR) based on IRC and Investigator,
- Duration of response (DOR) based on IRC and Investigator,
- Progression-free survival (PFS) based on IRC and Investigator,
- Overall survival (OS), and
- Safety and tolerability.

2.1.1.3. Exploratory Objectives

The exploratory objectives of this study are the following:

- To assess the possible impact of genetic alterations or other laboratory abnormalities on the efficacy of futibatinib. and
- To assess the population pharmacokinetics (PopPK) and exposure response.

2.1.2. Cohort C

2.1.2.1. Primary Objective

The primary objective in Cohort C is to evaluate complete response (CR) rate in patients with MLN harboring *FGFR1* rearrangements.

2.1.2.2. Secondary Objectives

The secondary objectives in Cohort C are the following:

- ORR,
- CR + complete response with incomplete hematological recovery (CRi) rate,
- Complete or partial cytogenetic responses (CCyR or PCyR) rate,
- Duration of CR,
- Duration of CR+CRi,

- DOR,
- Time-to-events (PFS, relapse-free survival [RFS], event-free survival [EFS], and OS), and
- Safety and tolerability.

2.1.2.3. Exploratory Objectives

The exploratory objectives in Cohort C are the following:

- To assess the pharmacodynamic effects of treatment with futibatinib,
- To assess the association of response and mechanisms of resistance in tumor tissue biopsies and/or blood, and
- To assess the PopPK and exposure response.

2.2. Study Endpoints

2.2.1. Cohorts A and B

2.2.1.1. Primary Endpoint

The definition of the primary endpoint is shown below:

- ORR is defined as the proportion of patients experiencing a best overall response of partial response (PR) or CR (per Response Evaluation Criteria in Solid Tumors, Version 1.1 [RECIST 1.1]), based on IRC.

2.2.1.2. Secondary Endpoints

The definition of the secondary endpoints is shown below:

- ORR is defined as the proportion of patients experiencing a best overall response of partial response of PR or CR (per RECIST 1.1), based on the opinion of the Investigator;
- DCR is defined as the proportion of patients experiencing a best overall response of stable disease (SD), PR, or CR (per RECIST 1.1), based on IRC and the opinion of the Investigator;
- DOR is defined as the time from the first documentation of response (CR or PR per RECIST 1.1 based on IRC and the opinion of the Investigator) to the first documentation of objective tumor progression or death due to any cause, whichever occurs first;
- PFS is defined as the time from first dose of study therapy to the date of death (any cause) or disease progression (based on IRC and the opinion of the Investigator), whichever occurs first;
- OS is defined as the time from the date of first dose to the death date; and
- Safety is based on reported AEs and on-study laboratory parameters, graded according to the National Cancer Institute—Common Terminology Criteria for Adverse Events, Version 5.0 (NCI-CTCAE V5.0).

2.2.1.3. Exploratory Endpoints

The definition of the exploratory endpoints is shown below:

- Assessment of pharmacodynamic effects will be analyzed from circulating tumor DNA (ctDNA), tumor biopsy, and/or plasma samples; and
- PopPK and exposure response will be analyzed from blood samples collected during treatment.

2.2.2. Cohort C

2.2.2.1. Primary Endpoint

The definition of the primary endpoint is shown below:

- CR rate is defined as the proportion of patients who achieved a CR.

Response will be determined based on disease presentation, and Investigators will assess response based on the Response Definition (Table 14). All the response assessments by Investigators will be adjudicated by a response adjudication committee.

2.2.2.2. Secondary Endpoints

The definition of the secondary endpoints is shown below:

- ORR is defined as the proportion of patients who achieved a CR, CRi, or PR;
- CR+CRi rate is defined as the proportion of patients who achieved a CR or CRi;
- CCyR rate is defined as the proportion of patients who achieved CCyR;
- PCyR rate is defined as the proportion of patients who achieved PCyR;
- Duration of CR is defined as the time from the first documentation of CR to the first documentation of objective tumor progression or death due to any cause, whichever occurs first;
- Duration of CR+CRi is defined as the time from the first documentation of CR or CRi to the first documentation of objective tumor progression or death due to any cause, whichever occurs first;
- DOR is defined as the time from the first documentation of CR, CRi, or PR to the first documentation of objective tumor progression or death due to any cause, whichever occurs first;
- PFS is defined as the time from first dose of study therapy to the date of death (any cause) or disease progression, whichever occurs first;
- RFS is defined as the time from the first documentation of CR to the first documentation of disease relapse or death due to any cause, whichever occurs first;
- Only for leukemia presentation, EFS is defined as the time from first dose of study therapy to treatment failure, disease relapse after CR, or patient death from any cause. Treatment failure for EFS is defined as PD in this study;
- OS is defined as the time from the date of first dose to the death date; and
- Safety is based on reported AEs and on-study laboratory parameters, graded according to the NCI CTCAE V5.0.

2.2.2.3. Exploratory Endpoints

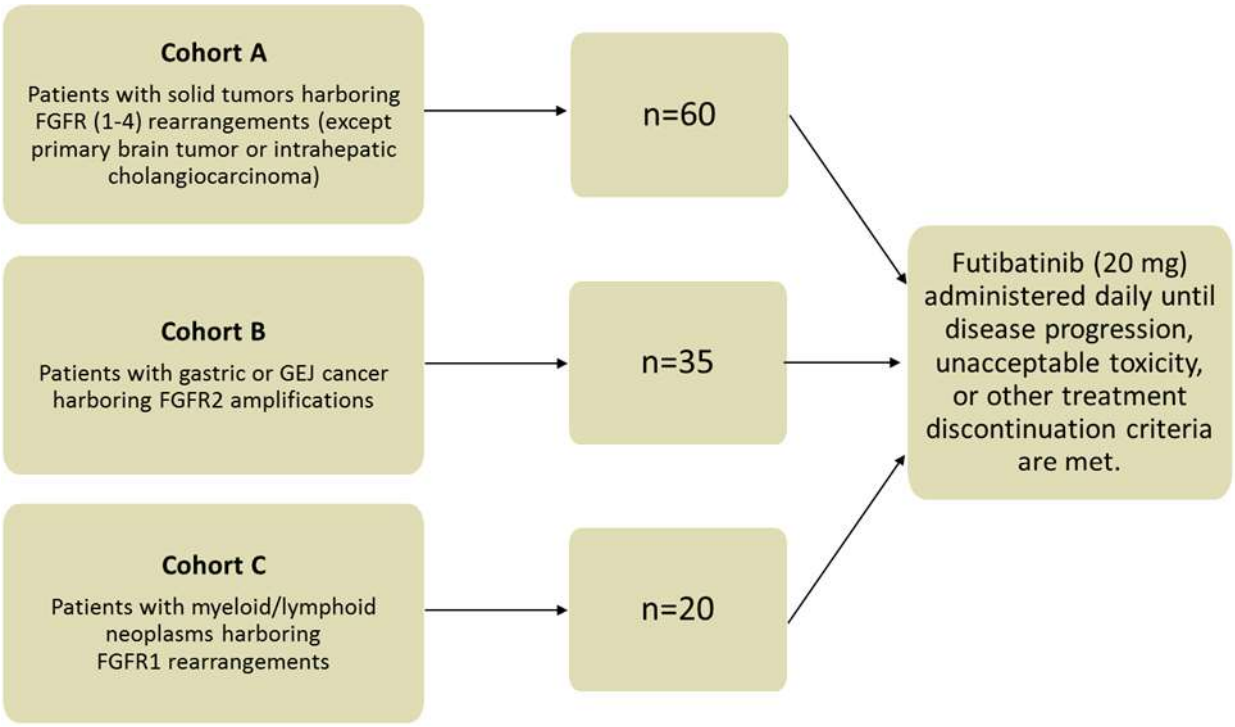
The definition of the exploratory endpoints is shown below:

- Changes in pharmacodynamic markers assessed in bone marrow tissue biopsies
- Exploratory association of tissue and/or blood markers with tumor efficacy endpoints and/or tumor resistance to futibatinib
- PopPK and exposure response analyzed from blood samples collected during treatment.

3. STUDY DESCRIPTION

3.1. Summary of Study Design

This study is an open-label, multinational, 3-arm Phase 2 study evaluating the efficacy, safety, tolerability, pharmacokinetics (PK), and pharmacodynamics of futibatinib in patients with *FGFR* aberrations. Eligible patients will be assigned to 1 of 3 treatment cohorts based on diagnosis and *FGFR* gene aberration status (Figure 1):



Abbreviations: FGFR=fibroblast growth factor receptor; n=number of patients planned; QD=daily

Figure 1: Study Design Flow Chart

Patients will receive futibatinib at an oral dose of 20 mg once a day on a continuous 28-day cycle.

Treatment will continue until disease progression, unacceptable toxicity, or any other of the criteria for treatment discontinuation is met. For patients who discontinue treatment for reasons other than disease progression, tumor assessments should be continued until disease progression is documented or until initiation of subsequent new anticancer therapy (whichever occurs first).

Patients will be followed for survival every 12 weeks (±2 weeks) until survival events (deaths) have been reported for 75% of enrolled patients, the patient withdraws consent, or the study is terminated early by the Sponsor.

Additional cohorts may be added in the future in the case of new emerging data. This change will be implemented through a protocol amendment which will describe the rationale for the addition(s).

Table 1. Schedule of Events (Cohorts A and B)

Evaluation	Screening (Within 28 days of 1st dose)	Treatment Period (1 cycle =28 days)						End of Treatment (+7 days)	Safety Follow-up 30 days after last dose (+7 days)	Survival Follow-up Period (every 12±2 weeks)	Notes
		Cycle 1				Cycle ≥2					
		D1 (±3 days)	D8 (±3 days)	D15 (±3 days)	D22 (±3 days)	D1 (±3 days)	End of Cycle (±7 days)				
Written informed consent	X										Written informed consent will be obtained prior to any study-related assessments or procedures.
Review eligibility criteria	X										
Demographics/medical history	X										
Review of baseline signs and symptoms	X										
Prior & concomitant medications, AE assessments	→	→	→	→	→	→	→	→	→		
Physical examination	X	X				X		X	X		Within 24 hours prior to dosing.
Vital signs	X	X				X		X	X		Heart rate, blood pressure, body temperature, and respiration rate.
Height and weight	X	X				X		X	X		Height at screening only.
ECOG performance status	X	X				X		X	X		Within 24 hours prior to dosing.
12-Lead electrocardiogram	X	X				X		X	X		
Hematology	X	X	X	X	X	X		X	X		Within 24 hours prior to dosing. More frequent assessments may be performed if clinically indicated
Coagulation	X	X				X		X	X		Within 24 hours prior to dosing.
Chemistry (serum or plasma)	X	X	X	X	X	X		X	X		Within 24 hours prior to dosing.

Evaluation	Screening (Within 28 days of 1st dose)	Treatment Period (1 cycle =28 days)						End of Treatment (+7 days)	Safety Follow-up 30 days after last dose (+7 days)	Survival Follow-up Period (every 12±2 weeks)	Notes
		Cycle 1				Cycle ≥2					
		D1 (±3 days)	D8 (±3 days)	D15 (±3 days)	D22 (±3 days)	D1 (±3 days)	End of Cycle (±7 days)				
Pregnancy test	X Within 7 days							X			Serum pregnancy test required for WOCBP. Additional testing may be required by local regulations.
Ophthalmological examination	X			See Note							Examination to be performed by an ophthalmologist or qualified delegate at screening, 4-6 weeks after first dose, and as indicated if symptoms or signs of mineral deposits.
PK blood sampling				See Note							Pre-dose (from -30 min to just before dose), 1 h±30 min post-dose, and 3 h±30 min post-dose
ctDNA blood samples	X							X			
Tumor tissue sample	X										Archival or fresh tumor biopsy
Tumor assessments (CT/MRI)	X						X	X	X	X	At baseline and the end of every 2 cycles ±7 days), or as clinically indicated, until radiologic PD or initiation of new anticancer therapy (whichever comes first). For patients who discontinue treatment for reasons other than radiographic disease progression, imaging will be performed at EOT, (if the prior scan was performed ≥9 weeks) and during Survival Follow-up until radiologic disease progression or initiation of new anticancer therapy (whichever occurs first) unless patient withdraws consent.
Survival status										X	For all patients, unless patient withdraws consent or the study is terminated early by the Sponsor.

Table 2. Schedule of Events (Cohort C)

Evaluation	Screening (Within 28 days of 1st dose)	Treatment Period (1 cycle =28 days)						End of Treatment (+7 days)	Safety Follow-up 30 days after last dose (+7 days)	Survival Follow-up Period (every 12±2 weeks)	Notes
		Cycle 1				Cycle ≥2					
		D1 (±3 days)	D8 (±3 days)	D15 (±3 days)	D22 (±3 days)	D1 (±3 days)	End of Cycle (±7 days)				
Written informed consent	X										Written informed consent will be obtained prior to any study-related assessments or procedures.
Review eligibility criteria	X										
Demographics/medical history	X										
Review of baseline signs and symptoms	X										
Prior & concomitant medications, AE assessments	→										
Physical examination	X	X				X		X	X		Within 24 hours prior to dosing.
Vital signs	X	X				X		X	X		Heart rate, blood pressure, body temperature, and respiration rate.
Height and weight	X	X				X		X	X		Height at screening only.
ECOG performance status	X	X				X		X	X		Within 24 hours prior to dosing.
12-Lead electrocardiogram	X	X				X		X	X		
Hematology	X	X	X	X	X	X		X	X		Within 24 hours prior to dosing. More frequent assessments may be performed if clinically indicated
Coagulation	X	X				X		X	X		Within 24 hours prior to dosing.
Chemistry (serum or plasma)	X	X	X	X	X	X		X	X		Within 24 hours prior to dosing.
Pregnancy test	X Within 7 days							X			Serum pregnancy test required for WOCBP. Additional testing may be required by local regulations.

Evaluation	Screening (Within 28 days of 1st dose)	Treatment Period (1 cycle =28 days)						End of Treatment (+7 days)	Safety Follow-up 30 days after last dose (+7 days)	Survival Follow-up Period (every 12±2 weeks)	Notes
		Cycle 1				Cycle ≥2					
		D1 (±3 days)	D8 (±3 days)	D15 (±3 days)	D22 (±3 days)	D1 (±3 days)	End of Cycle (±7 days)				
Ophthalmological examination	X			See Note							Examination to be performed by an ophthalmologist or qualified delegate. At screening, 4-6 weeks after first dose, and as indicated if symptoms or signs of mineral deposits.
PK blood sampling				See Note							Pre-dose (from -30 min to just before dose), 1 h±30 min post-dose, and 3 h±30 min post-dose
ctDNA blood samples	X							X			
Tumor tissue sample	X										Archival or fresh tumor biopsy
CT/MRI	X						X	X	X	X	At baseline and the end of every 2 cycles ±7 days), or as clinically indicated, until radiologic PD or initiation of new anticancer therapy (whichever comes first). For patients who discontinue treatment for reasons other than radiographic disease progression, imaging will be performed at EOT, (if the prior scan was performed ≥9 weeks) and during Survival Follow-up until radiologic disease progression or initiation of new anticancer therapy (whichever occurs first) unless patient withdraws consent.
PET scan	X				See Note						PET scan to be performed at baseline then end of Cycle 1 if abnormal at baseline. Additional scans as required for response assessment.
Lymph node biopsy	X	See Note									Recommended at baseline if lymph node present at baseline and progression
Bone marrow biopsy	X	See Note									Biopsy to be performed at baseline and during treatment. Bone marrow biopsy should be performed in case of normalisation of peripheral

Evaluation	Screening (Within 28 days of 1st dose)	Treatment Period (1 cycle =28 days)						End of Treatment (+7 days)	Safety Follow-up 30 days after last dose (+7 days)	Survival Follow-up Period (every 12±2 weeks)	Notes
		Cycle 1				Cycle ≥2					
		D1 (±3 days)	D8 (±3 days)	D15 (±3 days)	D22 (±3 days)	D1 (±3 days)	End of Cycle (±7 days)				
											blood count. In absence of peripheral blood count normalisation, biopsy to be performed every 6 months. Additional biopsies to be performed as clinically indicated.
Survival status										X	For all patients, unless patient withdraws consent or the study is terminated early by the Sponsor.

3.2. Blinding/Unblinding

This is an open-label, non-randomized study. Blinding/unbinding is not applicable.

3.3. Determination of Sample Size

A total of approximately 115 patients will be enrolled in the study.

Approximately 60 patients with solid tumors harboring *FGFR* rearrangements will be enrolled in Cohort A. Sample size considerations (primary endpoint ORR) are based on a 2-stage Simon design (Simon, 1989), comparing a poor response of ≤ 10% vs a promising response of ≥ 25%, at a 5% 1-sided significance level and approximate 90% power.

- In Stage 1 (futility assessment), enrollment will include 35 patients and accrual will continue to Stage 2, if at least 4 (11.4%) of 35 patients respond (CR or PR).
- In Stage 2, if the Stage 1 futility boundary is exceeded, an additional 25 patients will be enrolled, for a total of approximately 60 patients. With a total of 60 patients, if the observed ORR is 30%, the 95% exact confidence interval (CI) is 18.9%, 43.2%.

Table 3: Observed ORR with Exact 95% CI (Cohort A)

ORR	95% Exact Confidence Interval
20%	[10.8% - 32.3%]
25%	[14.7% - 37.9%]
30%	[18.9% - 43.2%]

Approximately 35 patients with gastric or GEJ cancer harboring *FGFR2* amplification will be enrolled in Cohort B. Sample size considerations are based on differentiating a historical control ORR of 10% or less, with a target ORR of 35%. Assuming the true ORR is 35%, the cohort has approximately 96% power to reject the null hypothesis that the true ORR is ≤10%, considering a 2-sided alpha of 5%. With a sample size of 35, observing at least 8 responders will have a 95% CI lower bound excluding 10% (ORR of 23% with 95% CI [10.4% - 40.1%]).

Table 4: Observed ORR with Exact 95% CI (Cohort B)

ORR	95% Exact CI
23%	[10.4% - 40.1%]
29%	[14.6% - 46.3%]
37%	[21.5% - 55.1%]

Approximately 20 patients with MLNs harboring *FGFR1* rearrangements will be enrolled in Cohort C. Sample size considerations are based on differentiating a historical control CR rate of 10% or less, with a target CR rate of 50%. Assuming the true CR rate is 50%, the cohort has over 95% power to reject the null hypothesis that the true CR rate is ≤10%, considering a 2-sided alpha of 5%.

Observing at least 6 responders out of 20 treated patients will have a 95% CI lower bound excluding 10% (CR rate of 30% with 95% CI [11.9% - 54.3%]).

Table 5: Observed CR Rate with Exact 95% CI(Cohort C)

CR Rate	95% Exact Confidence Interval
30%	[11.9% - 54.3%]
40%	[19.1% - 64.0%]
50%	[27.2% - 72.8%]

3.4. Interim Analysis

The Sponsor will review the data at the time Cohort A has 35 evaluable patients for ORR to determine if that particular cohort should continue.

4. STUDY PERIODS AND POPULATIONS FOR ANALYSIS

4.1. Study Periods for Analyses

Study periods are defined in Table 6 and shown in Figure 2.

Table 6: Definition of Study Periods for Analysis

Period	Definition
Screening Period (Baseline)	The Screening Period is defined as the time from when the patient signs the Informed Consent Form (ICF) until the date of first dose of futibatinib.
Treatment Period	The treatment period is the time from first dose of futibatinib (Day 1) to the date of last dose of futibatinib.
Safety Assessment Period	The Safety Assessment Period begins at the time the ICF is signed and continues until at least 30 days after the last dose of futibatinib.
On-treatment Period (This period will be used for safety analyses)	On-treatment Period is the time from the first dose of futibatinib (Day 1) to 30 days after the last dose of futibatinib. Unless otherwise specified, the On-treatment Period will be the basis for safety analyses.

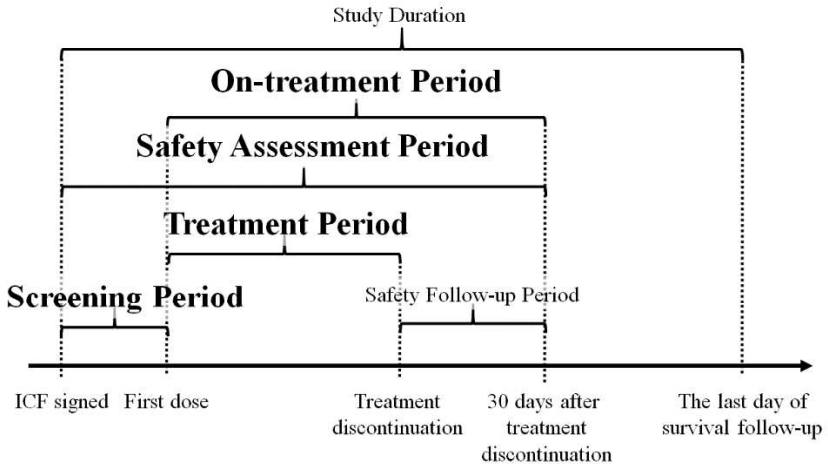


Figure 2: Study Periods for Analysis

4.2. Populations for Analysis

The analysis populations in the study are defined in Table 7.

Table 7: Definitions of Analysis Populations

Analysis Population	Definition
All Enrolled Population	All patients who signed the ICF in this study
All Treated Population/Full Analysis Set	All enrolled patients who received at least 1 dose of study drug
Pharmacodynamic/Biomarker Evaluable Set	All patients in the All Treated Population who have evaluable pharmacodynamic/biomarker data for analyses

As described in Section 5.5.1.1 and Section 5.5.1.2, DOR, duration of CR, duration of CR+CRi, RFS, and EFS will be analyzed using appropriate sub-populations of the All Treated Population.

4.3. Timing of Analysis

The Sponsor will review the data of Cohort A in order to determine if the Cohort A should continue or not when 35 patients (All Treated Population) in Cohort A have completed at least 6 months follow-up.

The final analysis will be performed when all patients either discontinue from the study or have sufficient follow-up (at least 6 months) from the first dosing date of futibatinib of the last enrolled patient, whichever comes first.

5. STATISTICAL ANALYSIS

5.1. General Methods

Other than exploratory biomarker data, which will be treated differently as explained above, all recorded data will be presented in listings. Data listings will be presented with patient ID and cohort.

Summary tables will be presented for each cohort.

The categorical data will be summarized using frequency counts and percentages of patients, unless otherwise specified.

The continuous data will be summarized using the number of non-missing observation (n), mean, standard deviation, median, minimum value, and maximum value, unless otherwise specified.

Prior anticancer therapy and concomitant medications will be coded with the WHO Drug Dictionary (the most up-to-date version at the time of analysis) and will be summarized by Anatomical Therapeutic Chemical (ATC) Classification level 2 (Therapeutic Main Group) and ATC level 4 (Chemical/Therapeutic Subgroup). Medications and therapies will be sorted in descending order of frequency of ATC level 2 and ATC level 4 within ATC level 2 in the total column. A patient will be counted only once within each level of summarization if the patient has taken a medication more than once. Agents and medications will be reported using the generic name.

For concomitant medications/therapy and adverse events (AEs), the cycle number is determined based on their start/onset dates. For other collected data, the cycle number is determined based on their visit dates. These data include a safety lab test, physical examination, vital signs, weight, ophthalmological exam, Eastern Cooperative Oncology Group (ECOG) performance status (PS), electrocardiogram (ECG), pregnancy test, and scheduled tumor assessment.

If there are multiple laboratory records for a scheduled visit, the one closest to the target date will be used for analysis. If there are two or more records with the same time period to the target date, the record with the latest database entry date will be used for analysis.

CIs for binomial proportions (eg, ORR and DCR) will be derived using the Clopper–Pearson method.

Time to event distribution (eg, PFS, OS, and DOR) will be estimated using the Kaplan–Meier method. The number of events and censorings will be reported. When appropriate, the median along with the corresponding log-log transformed 95% CI will be estimated. Survival rates at fixed time points will be derived from the Kaplan–Meier estimate and the corresponding CI will be derived based on the Greenwood formula for variance derivation and on log-log transformation applied on the survivor function S(t).

All the analyses for this study will be performed using SAS®, Version 9.3 or a higher version.

5.2. Study Conduct

5.2.1. Accrual

For All Enrolled Population, the number of patients accrued, will be summarized by country and investigational site for each cohort.

5.2.2. Protocol Deviations

For the All Enrolled Population, important protocol deviations will be summarized by category for each cohort. An important protocol deviation (ICH E3 Q&A [R1]) is defined as a subset of protocol deviations that may significantly impact the completeness, accuracy, and/or reliability of the study data or that may significantly affect the patient's rights, safety or well-being. These include important informed consent form (ICF) issues, inclusion/exclusion criteria not met, withdrawal criteria not followed; wrong treatment, incorrect dose/overdose based on protocol definitions, important deviations based on protocol design, and other important Good Clinical Practice (GCP) deviations.

According to US Food and Drug Administration (FDA)guidance on conduct of clinical trials of medical products during COVID-19 pandemic, updated on March 27, 2020, protocol deviations related to COVID-19 will be listed in the CSR (FDA, 2020).

5.3. Study Population

5.3.1. Patient Disposition

For All Treated Population, the number of patients in each patient disposition will be summarized for each cohort. The patient disposition table will include the number of patients treated at data cutoff, the number of patients with treatment ongoing at data cutoff, and the number of discontinued patients along with the reason for study discontinuation.

5.3.2. Demographic and Other Baseline Characteristics

For the All Treated Population, the following baseline characteristics will be summarized for each cohort.

For all cohorts:

- Age
- Age category (< 65, ≥65)
- Sex (Male, Female)
- Ethnicity (Hispanic/Latino, Not Hispanic/Latino, Unknown, Not collected)
- Race (Caucasian/White, Black or African American, Asian, American Indian or Alaska Native, Native Hawaiian or Other Pacific Islander, Not collected, Other)
- ECOG PS (0, 1)
- Baseline height
- Baseline weight

- Prior surgery (Yes, No)
- Prior radiotherapy (Yes, No)
- Prior systemic anticancer therapy (Yes, No)
- Number of prior lines of systemic therapy

For Cohort A:

- Primary cancer type
- Histology
- Any metastases (Yes, No)
- *FGFR* Receptor (*FGFR1*, *FGFR2*, *FGFR3*, *FGFR4*)
- *FGFR* Rearrangements including fusion
    - Rearrangement or fusion
    - Fusion partner

For Cohort B:

- Primary cancer type (Gastric, GEJ, Both)
- Location of Primary Tumor (Z-line, Cardia, Fundus, Body, Antrum, Pylorus, etc.)
- Histology (Papillary adenocarcinoma, Tubular adenocarcinoma, Mucinous adenocarcinoma, Signet-ring carcinoma, etc.)
- Histology subtype (Intestinal, Diffused, Mixed)
- Tumor grade (Well-, Moderately-, Poorly differentiated)
- Any metastases (Yes, No)
- *FGFR2* amplification as detected locally by FISH, PCR, NGS or IHC
- *FGFR2* copy number and/or FGFR2/CEN10 ratio

For Cohort C:

- MLN Characteristics (MLN only, Lymphoma presentation, Leukemia presentation)
- Eosinophilia (Yes, No)
- Thrombocytosis (Yes, No)
- Extramedullary disease (Yes, No)
- Blast Phase (Yes, No)
- Active CNS involvement related to primary disease (Yes, No)
- Palpable Splenomegaly (Yes, No)
- Palpable Hepatomegaly (Yes, No)
- Hematopoietic Stem Cell Transplantation (Yes, No)

- *FGFR1* rearrangements (including fusions)
    - Rearrangement or fusion
    - Fusion partner

5.3.3. Medical History

Medical history will be coded according to the Medical Dictionary for Regulatory Activities (MedDRA; the most up-to-date version at the time of analysis).

For the All Treated Population, medical history will be summarized by System Organ Class (SOC) and preferred term for each cohort.

5.3.4. Prior Anticancer Therapy

For the All Treated Population, the following analyses will be performed for each cohort:

- Prior anticancer surgery will be summarized. The number and percentage of patients with at least one anticancer surgery for primary disease will be presented. The type of surgery and the time from prior surgery to the first dosing date will be summarized.
- Prior radiation therapy for primary disease will be summarized. The number and percentage of patients with at least one prior radiation therapy for primary disease will be presented. The intent of the radiotherapy, site location of the radiotherapy, duration of the radiotherapy, and time from the end date of the radiation therapy to the first dosing date will be summarized.
- Prior anticancer therapy for primary disease will be summarized. The number and percentage of patients with at least one prior anticancer therapy for primary disease will be presented. The treatment type and therapy type will be summarized. The analysis described below will be repeated for each treatment type (Adjuvant, Neoadjuvant, Advanced/Metastatic disease, Maintenance therapy, or Other) in separate tables. The best response to therapy (CR, PR, SD, PD, or NE), the reason for the therapy discontinuation, duration of the anticancer therapy, and time from the end date of the anticancer therapy to the first dosing date will be summarized.

5.4. Concomitant Medication and Therapy

Medications taken on or after the first dose of study drug through 30 days after the last dose of study drug are considered concomitant medications and therapies. In addition, medications that started prior to the first dose of the study drug and continued into the treatment period are considered concomitant medications and therapies.

For the All Treated Population, the number and percentage of patients who received concomitant medications for management of hyperphosphatemia will be summarized by medication class and generic term for each cohort. The total duration of medications (excluding overlaps of duration) for management of hyperphosphatemia will also be summarized.

5.5. Efficacy Analyses

All efficacy analyses will be performed for each cohort using All Treated Population, unless otherwise specified.

5.5.1. Cohorts A and B

The description of each efficacy endpoint for Cohorts A and B is provided in Table 8.

Table 8: Efficacy Endpoint Definitions for Cohorts A and B

Endpoint	Definition
ORR	The proportion of patients experiencing a best overall response of PR or CR (per RECIST 1.1), based on IRC and Investigator assessment
DCR	The proportion of patients experiencing a best overall response of SD, PR, or CR (per RECIST 1.1), based on IRC and Investigator assessment
DOR	The time from the first documentation of response (CR or PR per RECIST 1.1 based on IRC and Investigator assessment) to the first documentation of objective tumor progression or death due to any cause, whichever occurs first
PFS	The time from first dose of study therapy to the date of death (any cause) or disease progression (based on IRC and Investigator assessment), whichever occurs first
OS	The time from the date of first dose to the death date

5.5.1.1. Primary Efficacy Analysis

ORR based on IRC will be calculated, and the 2-sided 95% CI will be derived by Clopper–Pearson method.

ORR will be calculated based on the best overall response recorded from the start of treatment until progression disease or start of subsequent new anticancer treatment. The overall response can be derived based on target lesion response, non-target lesion response and the emergence of a new lesion for patients with measurable disease at baseline.

The best objective response of CR and PR will be confirmed with at least 4 weeks intervals of two consecutive time points. A minimum of a 6-week interval between initial of treatment (first dose date) and tumor measurement is required for SD. If applicable, responses recorded after disease progression or initiation of new anticancer treatment will be excluded. The confirmation rule of the best overall response is shown in Table 9.

Table 9: Confirmation Rules for Overall Response of PR and CR

Earlier Response (to be confirmed)	Later Response (confirmation)	Confirmed Response
CR	CR [a]	CR
CR	Not CR or missing [b]	SD
PR	CR or PR [a]	PR
PR	SD or PD or missing [b]	SD
PR	SD and then PR (only one SD in between) [a]	PR

Earlier Response (to be confirmed)	Later Response (confirmation)	Confirmed Response
SD	n/a – no confirmation needed [b]	SD
PD	n/a – no confirmation needed	PD

[a:] A minimum of 4-week interval between two tumor measurements is required to confirm PR or CR.
[b:] A minimum of 6-week interval between initial of treatment (first dose date) and tumor measurement is required for SD

5.5.1.2. Secondary Efficacy Analyses

- ORR based on Investigator assessment will be calculated and the 2-sided 95% CI will be derived by the Clopper–Pearson method. The confirmation rule of CR and PR is the same as the primary endpoint.
- DCR based on IRC and Investigator assessment will be calculated and the 2-sided 95% CI will be derived by the Clopper–Pearson method. The confirmation rule of CR and PR is the same as the primary endpoint. A minimum of a 6-week interval is required between the first dosing date and the first SD.
- PFS based on IRC and Investigator assessment will be estimated using the Kaplan–Meier method. Patients who did not progress or die will be censored on the date of their last tumor assessment. Patients who did not have any post-baseline assessments will be censored on the first dosing date. Patients who started any subsequent anti-cancer therapy without a prior reported progression will be censored at the last tumor assessment prior to initiation of the subsequent anti-cancer therapy. The censoring rule for PFS is in Table 10.
- Overall survival will be estimated using the Kaplan–Meier method. In the absence of confirmation of death or for patients who are alive as of the OS cut-off date, survival time will be censored at the last known date that the patient was alive. The censoring rule for OS is in Table 11.
- DOR based on IRC and Investigator assessment will be evaluated only in patients with an objective response of CR or PR. The starting time point is the first documentation of response (CR or PR). DOR will be estimated using the Kaplan–Meier method. Patients who are alive and progression-free as of the data cut-off date will be censored at their last evaluable tumor response assessment. Patients who start subsequent anticancer therapy without a prior reported progression will be censored at the last tumor assessments prior to initiation of the subsequent anticancer therapy. The censoring rule for DOR is described in Table 12.

Table 10: Censoring Rules for Progression-Free Survival (PFS)

No.	Situation	End Date	Outcome
1	Documented PD between scheduled visits	Date of the first assessment that determined PD	PFS event
2	Death during the study with no prior PD	Date of death	PFS event
3	Patients still on treatment without PD as of data cut-off [a]	Date of the last tumor assessment [b]	Censored

No.	Situation	End Date	Outcome
4	Treatment discontinuation for reasons other than PD or death, and no post baseline tumor assessments	Date of the first dose	Censored
5	Treatment discontinuation for reasons other than PD or death with post baseline tumor assessments	Date of the last tumor assessment	Censored
6	New anticancer treatment started	Date of the last tumor assessment before start of new treatment	Censored
7	Death or PD after two or more missed tumor assessments [c]	Date of the last tumor assessment before missed assessments	Censored
8	No baseline or unreadable baseline assessment but readable post baseline assessments	Date of the first dose	Censored

[a.] This refers to patients who were still receiving study treatment at time of data cutoff.
[b.] For PFS analysis, the date of last tumor assessment refers to the date of last adequate tumor assessment.
[c.] Two or more missed tumor assessments is defined as having either one of the following two durations being longer than 126 days (= (28 [days/cycle] x 2 [cycles] + 7 [days]) x 2):
Duration between two consecutive tumor assessments
Duration between the last tumor assessment and death or PD

Table 11: Censoring Rules for Overall Survival (OS)

No.	Situation	End Date
1	Death before cut-off	Date of death
2	Death after data cut-off	Date of data cut-off
3	Patient still alive at data cut-off	Date of data cut-off
5	Patient discontinued treatment due to any reason before data cut-off	Date last known to be alive

Table 12: Censoring Rules for Duration of Response (DOR)

No.	Situation	End Date	Outcome
1	Documented PD between scheduled visits	Date of the first assessment that determined PD	DOR event
2	Death during the study with no prior PD	Date of death	DOR event
3	Patients still on treatment without PD as of data cut-off [a]	Date of the last tumor assessment [b]	Censored
4	Treatment discontinuation for reasons other than PD or death	Date of the last tumor assessment	Censored

No.	Situation	End Date	Outcome
5	New anticancer treatment started	Date of the last tumor assessment before start of new treatment	Censored
6	Death or PD after two or more missed tumor assessments [c]	Date of the last tumor assessment before missed assessments	Censored

[a.] This refers to patients who were still receiving study treatment at time of data cutoff.
[b.] For DOR, the date of last tumor assessment refers to the date of last adequate tumor assessment.
[c.] Two or more missed tumor assessments is defined as having either one of the following two durations being longer than 126 days (= (28 [days/cycle] x 2 [cycles] + 7 [days]) x 2):
Duration between two consecutive tumor assessments
Duration between the last tumor assessment and death or PD

5.5.2. Cohort C

The description of each efficacy endpoint for Cohort C is provided in Table 13 .

Table 13: Efficacy Endpoint Definitions for Cohort C

Endpoint	Definition
CR rate	The proportion of patients who achieved a CR per the Response Definition (Table 14)
ORR	The proportion of patients who achieved a CR, CRi, or PR
CR+CRi rate	The proportion of patients who achieved a CR or CRi
CCyR rate	The proportion of patients who achieved CCyR
PCyR rate	The proportion of patients who achieved PCyR
Duration of CR	The time from the first documentation of CR to the first documentation of objective tumor progression or death due to any cause, whichever occurs first
Duration of CR+CRi	The time from the first documentation of CR or CRi to the first documentation of objective tumor progression or death due to any cause, whichever occurs first
DOR	The time from the first documentation of CR, CRi, or PR to the first documentation of objective tumor progression or death due to any cause, whichever occurs first
PFS	The time from first dose of study therapy to the date of death (any cause) or disease progression, whichever occurs first
RFS	The time from the first documentation of CR to the first documentation of disease relapse or death due to any cause, whichever occurs first
EFS	The time from first dose of study therapy to treatment failure (defined as PD in this study), disease relapse after CR, or patient death from any cause
OS	The time from the date of first dose to the death date

5.5.2.1. Primary Efficacy Analysis

CR rate will be calculated and the 2-sided 95% CI will be derived by Clopper–Pearson method.

The confirmation of the best objective response of CR with at least 4 weeks interval of two consecutive time points is not required; however, CR must be confirmed by a minimum of 2 bone marrow assessments when the first response assessment shows marrow fibrosis. If applicable, responses recorded after disease progression or initiation of new anticancer treatment will be excluded.

Response will be determined based on disease presentation, and Investigators will assess response based on the Response Definition described in Table 14. All the response assessments by Investigators will be adjudicated by a response adjudication committee.

Table 14: Response Definitions for Cohort C

MLN Characteristic	MLN Only	Lymphoma Presentation	Leukemia Presentation
Response Criteria	**Savona 2015[a]**	**Younes 2017[b]**	**Cheson 2003[c]**
Complete response (CR)	Must fulfill all criteria defined for CR	Must fulfill all criteria defined for CR	Must fulfill all criteria defined for morphologic complete response CR does not include: • morphologic leukemia-free state • complete response with incomplete hematological recovery (CRi), or cytologic complete response (CRc)
Partial response (PR)	Must fulfill all criteria defined for PR	Must fulfill all criteria defined for PR	Must fulfill all criteria defined for partial remission
Complete response with incomplete blood count recovery (CRi)	N/A	N/A	Must fulfill all criteria defined for CRi
Complete cytogenetic response (CCyR)	Resolution of previously present chromosomal abnormality known to be associated with MLN (eg. 8p11 translocation)	Must fulfill all criteria defined for CCyR	Must fulfill all criteria defined for cytogenetic complete response (CRc) and CCyR

[a] Savona, et al. An international consortium proposal of uniform response criteria for myelodysplastic/myeloproliferative neoplasms (MDS/MPN) in adults. Blood. 2015.
[b] Younes, et al. International Working Group consensus response evaluation criteria in lymphoma (RECIL 2017). Ann Oncol. 2017.
[c] Cheson, et al. Revised recommendations of the International Working Group for Diagnosis, Standardization of Response Criteria, Treatment Outcomes, and Reporting Standards for Therapeutic Trials in Acute Myeloid Leukemia. J Clin Oncol. 2003.

5.5.2.2. Secondary Efficacy Analyses

- ORR, CR+CRi rate (if applicable in leukemia presentation), CCyR rate, and PCyR rate will be calculated and the 2-sided 95% CI will be derived by Clopper–Pearson method. Note that the ORR in Cohort C is defined as the proportion of patients who achieved a CR, CRi, or PR.
- PFS will be estimated using the Kaplan–Meier method. Patients who did not progress or die will be censored on the date of their last response assessment. Patients who did not have any post-baseline assessments will be censored on the first dosing date. Patients who started any subsequent anti-cancer therapy without a prior reported progression will be censored at the last response assessment prior to initiation of the subsequent anti-cancer therapy. The censoring rule for PFS is in Table 10.
- Overall survival will be estimated using the Kaplan–Meier method. In the absence of confirmation of death or for patients who are alive as of the OS cut-off date, survival time will be censored at the last known date that the patient was alive. The censoring rule for OS is in Table 11.
- DOR will be evaluated only in patients with an objective response of CR, PR, or CRi (if applicable in leukemia presentation). Duration of CR will be evaluated only in patients with an objective response of CR. Duration of CR+CRi will be evaluated only in patients with an objective response of CR or CRi (if applicable in leukemia presentation). DOR is defined as the time from the first documentation of CR, CRi, or PR to the first documentation of objective tumor progression or death due to any cause, whichever occurs first. Duration of CR (CR+CRi) is defined as the time from the first documentation of CR (CR or CRi) to the first documentation of objective tumor progression or death due to any cause, whichever occurs first. DOR, duration of CR, and duration of CR+CRi will be estimated using the Kaplan–Meier method. Patients who are alive and progression/relapse-free as of the data cut-off date will be censored at their last evaluable tumor response assessment prior to initiation of any new anticancer treatment. Patients who start subsequent anticancer therapy without a prior reported progression/relapse will be censored at the last response assessments prior to initiation of the subsequent anticancer therapy. The censoring rule for DOR is in Table 12, and that for duration of CR and for duration of CR+CRi is in Table 15.
- RFS will be evaluated only in patients with an objective response of CR. RFS will be estimated using the Kaplan–Meier method. RFS is measured from the first date of achieving CR until the first date of disease relapse or death from any cause, whichever occurs first. Patients who die without a reported disease relapse will be considered to have relapsed on the date of their death. Patients who did not relapse or die will be censored on the date of their last response assessment. Patients who started any subsequent anti-cancer therapy without a prior reported relapse will be censored at the last response assessment prior to initiation of the subsequent anti-cancer therapy. The censoring rule for RFS is in Table 16.
- EFS will be estimated only in patients with leukemia presentation. EFS will be estimated using the Kaplan–Meier method. EFS is defined as the time from the first dose of study therapy to treatment failure, relapse after CR (if applicable), or death

from any cause, whichever occurs first. Treatment failure for EFS is defined as PD in this study. If the patient does not achieve a CR, EFS is defined as the point of treatment failure (PD) or death, whichever comes first. For a patient with none of these events before the end of the study follow-up, observation of EFS is censored at the date of the last contact prior to the analysis cut-off date. The censoring rule for EFS is described in Table 17. Note that the start date of EFS is the same regardless of achieving a CR.

Table 15: Censoring Rules for Duration of CR and Duration of CR+CRi

No.	Situation	End Date	Outcome
1	Disease relapse between scheduled visits	Date of the first assessment that determined disease relapse	Event
2	Death during the study with no prior disease relapse	Date of death	Event
3	Patients still on treatment without disease relapse as of data cut-off [a]	Date of the last response assessment [b]	Censored
4	Treatment discontinuation for reasons other than disease relapse or death	Date of the last response assessment	Censored
5	New anticancer treatment started	Date of the last response assessment before start of new treatment	Censored
6	Death or disease relapse after two or more missed response assessments [c]	Date of the last response assessment before missed assessments	Censored

[a]This refers to patients who were still receiving study treatment at time of data cutoff.
[b]For duration of CR and duration of CR+CRi, the date of last response assessment refers to the date of last adequate response assessment.
[c]Two or more missed response assessments is defined as having either one of the following two durations being longer than 126 days (= (28 [days/cycle] x 2 [cycles] + 7 [days]) x 2):
Duration between two consecutive response assessments
Duration between the last response assessment and death or disease relapse

Table 16: Censoring Rules for Relapse-free Survival (RFS)

No.	Situation	Event or Censoring Date	Outcome
1	Disease relapse between scheduled visits	Date of the first assessment that determined disease relapse	Event
2	Death during the study with no prior disease relapse	Date of death	Event
3	Patients still on treatment without disease relapse as of data cut-off [a]	Date of the last response assessment [b]	Censored
4	Treatment discontinuation for reasons other than disease relapse or death	Date of the last response assessment	Censored
5	New anticancer treatment started	Date of the last response assessment before start of new treatment	Censored
6	Death or disease relapse after two or more missed response assessments [c]	Date of the last response assessment before start of new treatment	Censored

[a] This refers to patients who were still receiving study treatment at time of data cutoff.
[b] For RFS, the date of last response assessment refers to the date of last adequate response assessment.
[c]Two or more missed response assessments is defined as having either one of the following two durations being longer than 126 days (= (28 [days/cycle] x 2 [cycles] + 7 [days]) x 2):
Duration between two consecutive response assessments
Duration between the last response assessment and death or disease relapse

Table 17: Censoring Rules for Event-Free Survival (EFS)

No.	Situation	Event or Censoring Date	Outcome
If a patient achieved a CR at the analysis, the following rules (No. 1 to 6) will be applied.			
1	Disease relapse between scheduled visits	Date of the first assessment that determined disease relapse	Event
2	Death during the study with no prior disease relapse	Date of death	Event
3	Patients still on treatment without disease relapse as of data cut-off [a]	Date of the last response assessment [b]	Censored
4	Treatment discontinuation for reasons other than disease relapse or death	Date of the last response assessment	Censored
5	New anticancer treatment started	Date of the last response assessment before start of new treatment	Censored

No.	Situation	Event or Censoring Date	Outcome
6	Death or disease relapse after two or more missed response assessments [c]	Date of the last response assessment before start of new treatment	Censored
If a patient did not achieve a CR at the analysis, the following rules (No. 7 to 11) will be applied.			
7	Documented PD between scheduled visits	Date of the first assessment that determined PD	Event
8	Death during the study with no prior PD	Date of death	Event
9	Patients still on treatment without PD as of data cut-off [a]	Date of the last contact	Censored
10	Treatment discontinuation for reasons other than PD or death, and no post baseline response assessments	Date of the first dose	Censored
11	Treatment discontinuation for reasons other than PD or death with post baseline response assessments	Date of the last contact	Censored
12	New anticancer treatment started	Date of the last contact	Censored
13	Death or PD after two or more missed response assessments [c]	Date of the last contact	Censored
14	No baseline or unreadable baseline assessment but readable post baseline assessments	Date of the first dose	Censored

[a.] This refers to patients who were still receiving study treatment at time of data cutoff.
[b.] For EFS, the date of last response assessment refers to the date of last adequate response assessment.
[c.] Two or more missed response assessments is defined as having either one of the following two durations being longer than 126 days (= (28 [days/cycle] x 2 [cycles] + 7 [days]) x 2):
Duration between two consecutive response assessments
Duration between the last response assessment and death or disease relapse

5.6. Safety Analyses

All safety analyses will be performed for each cohort using the All Treated Population, unless otherwise specified.

5.6.1. Extent of Exposure

5.6.1.1. Administration of Study Drug

The following parameters will be summarized:

- Duration of treatment
- Number of cycles treated
- Number of doses received
- Cumulative dose
- Relative dose intensity

Duration of treatment (days) will be calculated as follows: 1) calculate the date of the last dose – date of first dose + 1 for each treated cycle; 2) sum up across all treated cycles.

Cumulative dose is the sum of the doses administered to a subject during the treatment period.

Relative dose intensity will be calculated as cumulative dose (dose received) divided by dose planned (taking the dosing cycle into consideration)

A by-patient listing of dosing of study drug and listing of batch number will be also provided.

5.6.1.2. Modification of Study Drug

The number and percentage of patients with at least one dose interruption along with reason for the interruptions will be summarized.

The number and percentage of subjects with at least one dose reduction and reason for the dose reduction will be summarized.

The number and percentage of subjects with at least one dose discontinuation and reason for the dose discontinuation will be summarized.

By-patient listings of dose interruption, dose reduction, and dose discontinuation will be also provided.

5.6.2. Adverse Events

5.6.2.1. Deaths

On-treatment deaths and reasons for death will be summarized.

A by-patient listing of all deaths occurring during screening, on treatment, 30-day safety follow-up, or survival follow-up periods will be provided.

5.6.2.2. Adverse Events

An AE is any untoward medical condition that occurs in patients while participating in this clinical trial. AEs will be coded according to the MedDRA (the most up-to-date version at the time of analysis) terminology and the severity of the toxicities will be graded according to NCI CTCAE Version 5.0, where applicable.

A treatment-emergent AE (TEAE) is defined as an AE that is starting or worsening at the time of or after the first dose of study drug administration and within 30 days after the last dose of study drug, and does not necessarily have a causal relationship to the use of the study drug.

In this study, only TEAEs will be summarized. Note that all collected AEs, including TEAEs, will be presented in listings as described in Section 5.1.

The following summary tables will be generated:

1. Summary of AEs with the number and percentage of patients reporting AEs, serious AEs, grade ≥ 3 AEs, AEs leading to study drug discontinuation, interruption and dose reduction, and AEs with the outcome of death.
2. Summary of treatment-related AEs with the number and percentage of patients reporting AEs, serious AEs, grade ≥ 3 AEs, AEs leading to study drug discontinuation, interruption and dose reduction, and AEs with outcome of deaths.
3. Summary of AEs by worst CTC Grade (grade 1, 2, 3, 4, 5, any grade, Grade ≥ 3) presented by SOC and Preferred Term (PT).
4. Summary of TEAEs by worst CTC grade (Grade 1, 2, 3, 4, 5, any grade, Grade ≥ 3) presented by SOC and PT.
5. Grade ≥ 3 AEs by worst CTC Grade (grade 3, 4, 5, 3-5) presented by SOC and PT.
6. Grade ≥ 3 TEAEs by worst CTC Grade (grade 3, 4, 5, 3-5) presented by SOC and PT.
7. Summary of AEs leading to death by SOC and PT.
8. Summary of the most common AEs (≥10% incidence) and median time to first AE by SOC and PT.

5.6.2.3. Adverse Events Leading to Discontinuation of Study Drug

AEs leading to discontinuation will be summarized:

- Summary of AEs leading to discontinuation of study drug by worst CTC Grade (grade 1, 2, 3, 4, 5, any grade, Grade ≥ 3) presented by SOC and PT
- Summary of TEAEs leading to discontinuation of study drug by worst CTC grade (Grade 1, 2, 3, 4, 5, any grade, Grade ≥ 3) presented by SOC and PT

A by-patient listing of AEs leading to discontinuation of study drug will also be provided.

5.6.2.4. Adverse Events Leading to Dose Modification of Study Drug

AEs leading to dose modification (including dose interruption and reduction) of study drug will be summarized:

- Summary of AEs leading to dose modification of study drug by worst CTC Grade (grade 1, 2, 3, 4, 5, any grade, Grade ≥ 3) presented by SOC and PT
- Summary of TEAEs leading to dose modification of study drug by worst CTC grade (Grade 1, 2, 3, 4, 5, any grade, Grade ≥ 3) presented by SOC and PT

A by-patient listing of AEs leading to dose modification of the study drug will also be provided.

5.6.2.5. Serious Adverse Events

Serious adverse events (SAEs) will be summarized:

- Summary of SAEs by worst CTC Grade (grade 1, 2, 3, 4, 5, any grade, Grade ≥ 3) presented by SOC and PT
- Summary of treatment-related SAEs by worst CTC Grade (grade 1, 2, 3, 4, 5, any grade, Grade ≥ 3) presented by SOC and PT

A by-patient listing of SAEs will also be provided.

5.6.2.6. Adverse Events of Special Interest

Incidence

Adverse events of special interest (AESIs) will be summarized:

- Summary of AESIs with the number and percentage of patients reporting AESIs, serious AESIs, grade ≥ 3 AESIs, AESIs leading to study drug discontinuation, interruption and dose reduction, and AESIs with the outcome of death.
- Summary of AESIs by worst CTC grade (grade 1, 2, 3, 4, 5, any grade, Grade ≥ 3) presented by category or subcategory / PT

A by-patient listing of AESI will also be provided.

Time to Onset

Time-to-onset of selected AESI (eg,hyperphosphatemia) will be graphically displayed using the Kaplan-Meier technique.

- Time-to-onset of any grade AESI
- Time-to-onset of Grade ≥3 AESI

The derivation of time-to-onset of AESI is detailed in Section 7.4.

Time to Resolution

Time-to-resolution of selected AESI (eg, hyperphosphatemia) will be summarized.

- Time-to-resolution of Grade ≥3 AESI

The following summary statistics will be reported: percentage of subjects who experienced the specific events, percentage of subjects with resolution of the AESI (clustered), median, 1st quartile and 2nd quartile of time-to-resolution along with 95% CI (derived from Kaplan-Meier estimation) and ranges.

Time-to-resolution of Grade ≥3 AESI (eg, hyperphosphatemia) will be graphically displayed using the Kaplan-Meier technique.

Time-to-resolution analyses are restricted to patients who experienced the specific events. Collapsing selected AE and derivation of time-to-resolution of AESI is detailed in Section 7.5.

5.6.2.7. Multiple Events

The following summary tables will be provided:

- A table showing the total number and rate (exposure adjusted) of occurrences for all AEs by SOC and PT
- A table showing the total number and rate (exposure adjusted) of occurrences for AESI by category / subcategory

The exposure adjusted incidence rate per X patient time is calculated as X×Y× (total number of unique AEs) / (total exposure time), where:

- X = user-specified time factor, X= 1000 or 100
- Y = 365.25 for years or Y = 30.4375 for months

For example, Incidence rate per 100 person-years of exposure (IR/100 P-Y) is calculated as 100 x 362.5 x (total number of unique AE count) / (total exposure time in days).

Unique instances of all AEs (that is, after duplicates have been eliminated and overlapping and contiguous occurrences of the same event (same PT) have been collapsed) will be summarized (0 event, 1 event, 2-3 events, ≥ 4 events) by PT. Unique instances of AESI will be summarized (0 event, 1 event, 2-3 events, ≥ 4 events) by category/subcategory.

Unique instances of all AEs will be listed.

The algorithm of collapsing selected AE records is detailed in Section 7.5.

5.6.3. Clinical Laboratory Evaluations

Clinical laboratory results will be summarized using SI units. Laboratory measurements will be summarized for each parameter. Descriptive statistics (n, mean, standard deviation, median, minimum and maximum) will be presented for clinical chemistry, hematology, and coagulation parameters at each scheduled visit. Change from baseline will be summarized in a similar manner.

Laboratory test results will be graded by NCI CTCAE (Version 5.0). Shift tables will be presented for each laboratory parameter to display the shift from baseline grade to the worst post-baseline grade. Summary tables will be provided presenting the number and percentage of patients for each laboratory test by baseline grade and worst post-baseline grade. All post-baseline assessments (including unscheduled visits) will be used to determine the worst post-baseline grade. Time to maximum Grade 3/4 and time to resolution (return to grade <=2 or baseline grade or below) may be summarized as appropriate.

All clinical laboratory data will be presented in by-patient listings.

The laboratory tests of hematology, coagulation, serum chemistry are listed in Table 18 .

Table 18: Laboratory Tests

Assessment	Test Items
Hematology and Coagulation	Red blood cell count, hemoglobin, hematocrit, platelets, white blood cell count with differential (absolute neutrophil count, lymphocytes, monocytes, eosinophils, basophils), Prothrombin time-international normalized ratio, Activated partial thromboplastin time, fibrinogen
Chemistry (Serum or plasma)	AST, ALT, alkaline phosphatase, total bilirubin, direct bilirubin, albumin, lactate dehydrogenase, inorganic phosphorus, triglyceride, total cholesterol, creatinine, urea or blood urea nitrogen, sodium, potassium, chloride, calcium (corrected value), magnesium, blood glucose, creatinine clearance (if there is a measured value, use the measured value)

For a calculated creatinine clearance (Ccr) value, use the Cockcroft-Gault formula:
Male Ccr (mL/min) = weight (kg)×(140-age(years))/[72×serum creatinine (mg/dL)]
Female Ccr (mL/min) = male Ccr×0.85

5.6.4. Ophthalmological Examination

An ophthalmological examination is performed at Screening (within 28 days prior to TAS-120 administration on Day 1 of Cycle 1) and 4-6 weeks after starting treatment with TAS-120. The ophthalmological examination encompasses external ocular examination, slit lamp biomicroscopy, and dilated ophthalmoscopy. The results of each test, including ad-hoc examinations, will be summarized by scheduled time point. All ophthalmological examination results will be listed in by-patient listings.

5.6.5. Vital Signs and Weight

Vital sign measurements include systolic blood pressure, diastolic blood pressure, pulse rate, respiration rate, and body temperature. Each vital sign parameter will be summarized with descriptive statistics by scheduled time point. Change from baseline will be summarized in a similar manner.

Weight at each scheduled time point and change from baseline will be summarized with descriptive statistics by scheduled time point. Weight will be displayed in kilograms. Height, collected only at baseline, will be displayed in centimeters. Body temperature will be displayed in Celsius.

All vital sign data will be presented in by-patient listings.

5.6.6. Electrocardiograms

ECG measurements include HR, RR interval, QT interval and its Fridericia's correction and Bazett's correction, and clinically abnormal findings. QTcF (Fridericia's correction) is calculated as $QT/RR^{0.33}$. QTcB (Bazett's correction) is calculated as $QT/RR^{0.5}$. Each ECG parameter will be summarized with descriptive statistics by scheduled time point. Changes from baseline will be summarized in a similar manner.

Shift tables will present changes from baseline in ECG interpretation (categorized as normal, abnormal not clinically significant, abnormal clinically significant) to the worst post-baseline result.

In addition, the number and percentage of patients with at least one post-baseline abnormal ECG result in QTcF during on-treatment period will be summarized. Clinically abnormal ECG results in QTcF will be categorized as follows:

Absolute QTcF interval prolongation:

- QTc interval <= 470 ms
- QTc interval >470 - 480 ms (with baseline QTc interval ≤ 470)
- QTc interval > 480 - 500 ms (with baseline QTc interval ≤ 480)
- QTc interval > 500 ms (with baseline QTc interval ≤ 500)

Change from baseline in QTcF interval:

- QTC interval increases from baseline <= 30 ms
- QTC interval increases from baseline 30 - 60 ms
- QTC interval increases from baseline > 60 ms

All ECG data will be presented in by-patient listings.

5.6.7. Physical Examination

The physical examination will be performed during the Screening period, on Day 1 of each cycle of the Treatment Period, at the End of Treatment, and at 30-day Safety Follow-up.

The physical examination data will be presented in by-patient listings.

5.6.8. ECOG Performance Status

The ECOG PS score will be obtained during the Screening period, on Day 1 of each cycle of Treatment Period, at the End of Treatment, and at 30-day Safety Follow-up. The ECOG PS scores and the grades from 0 to 5 are described in Table 19 :

Table 19: Grade Categories of Eastern Cooperative Oncology Group Score

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

The ECOG performance status score will be summarized with descriptive statistics by scheduled time point. A shift table will be presented to display the shift from baseline grade to the worst post-baseline grade.

5.6.9. Pregnancy Test

If the patient is female and of childbearing potential, a serum or urine β-HCG pregnancy test will be performed during Screening Period and at the End of Treatment. Pregnancy test result will be presented in by-patient listing.

5.7. Pharmacokinetic Analyses

Blood samples will be collected for PopPK analysis, including estimation of steady-state exposure such as area under the curve. The samples will be used to determine concentrations of futibatinib in plasma. Detailed analytical procedures will be described in the independent SAP for PopPK.

The listing of futibatinib plasma concentration will be provided.

5.8. Pharmacodynamic/Biomarker Analyses

Biomarkers, including *FGFR* and, possibly, other genetic variants other than those which were listed above as criteria for eligibility, will be investigated on exploratory basis and will not be listed in this formal SAP.

5.9. Interim Analyses

The interim analysis will be performed in Cohort A at the time when there are 35 response evaluable patients in the cohort in order to determine if the cohort should continue. During interim analysis, the Sponsor will review the data and perform statistical analyses on the primary efficacy endpoint.

Because Cohort A is based on a 2-stage Simon design, the overall type I error is controlled for the interim analysis. There is no need for type I error adjustment or sample size adjustment. Because this is open label study, there is no blinding/unblinding. Therefore there is no need for maintaining blinding during the interim analysis.

5.10. Other Analyses

Assessments that were not completed or missed due to COVID-19 will be listed per visit.

6. CHANGES IN PLANNED ANALYSIS

There have been no changes to the initially planned analyses as of the finalization of this SAP.

7. DEFINITIONS AND CONVENTIONS FOR DATA HANDLING

7.1. Baseline Period

Baseline evaluations or events will be defined as evaluations or events that occur before the date and time of the first dose of study drug.

If the onset time of event or evaluation time or dosing time is missing or not collected, the following definitions will apply:

- Pre-treatment AEs will be defined as AEs with an onset date prior to but not including the day of the first dose of study drug
- Baseline evaluations (laboratory tests, ECOG PS and vital signs) will be defined as evaluations with a date on or prior to the day of first dose of study drug (for ECG, assessments on the day of first dose of study drug will not be included in baseline evaluation)

If there are multiple valid assessments, the assessment that is closest to the day (and time if collected) of the first dose of study drug will be used as the baseline in the analyses. If multiple assessments are collected on the same date (and time, if collected), the assessment with the latest database entry date (and time, if collected) will be considered as baseline.

7.2. Post-Baseline Period

To allow differentiation as to which study period an AE occurred, three categories are defined based upon onset date. AEs that have onset dates prior to the first dose of study drug are considered "prior." AEs with onset dates on or after the first dose of study drug and within 30 days following the last dose of study drug are considered "on-treatment" or equivalently "treatment emergent.". Events with onset dates more than 30 days after the last dose of study drug are considered "post-treatment." No "subtracting rule" will be applied when an AE occurs both pre-treatment and post-treatment with the same preferred term and grade. AE summary tables will be based on on-treatment AEs only. AEs with onset dates prior to the first dose of study drug as well as those after the last dose of study drug +30 days will be identified in the data listings.

7.3. AESI Definition and Conventions

The AESI consist of a list of preferred terms grouped by specific category (for example, pulmonary events, gastrointestinal events categories) and/or by subcategory (for example, diabetes). These categories and subcategories are defined based on MedDRA, and the list that is most current at the time of analysis will be used. Also, changes may be made to this list with each new version of MedDRA.

7.4. Time-to-Onset Definition

Time-to-onset of AESI (any grade) for a specific category (for example, pulmonary events, gastrointestinal events) is defined as the time between the day of the first dose of study drug and the onset date of the earliest AESI (of any grade) in this category.

If the patient did not experience an AESI (of any grade) in the category, time-to-onset will be censored at the maximum follow-up time of that patient (that is, for patients without an event,

time-to-onset will be censored at last dosing date +30 days if patients are off treatment and followed for at least 30 days, otherwise it will be censored at the last known alive date.). If patients experience AESI for a specific category but with event start date after the last dosing date +30 days, time-to-onset will be censored at last dosing date +30 days. The resulting Kaplan–Meier plot will represent the cumulative rate of the AESI (any grade) in the category over time.

Time-to-onset of AESI (Grade 3-5) for a specific category is defined similarly but restricted to Grade 3-5 AESI.

Time-to-onset of drug-related (Grade 3-5 or any grade) AESI for a specific category is defined similarly but restricted to drug-related AESIs.

Time-to-onset for a specific subcategory is defined similarly but restricted to events in this subcategory.

7.5. Time-to-Resolution Definition

In order to derive the time-to-resolution, overlapping or contiguous AESIs within a specific category will be collapsed into what will be termed "clustered" AESIs. For example, if a patient (without pre-treatment AE) experienced an AE from 01 January to 05 January, another AE (with different PT but within same category) from 06 January to 11 January, and the same AE from 10 January to 12 January, these will be collapsed into one clustered AESI from 01 January (onset date) to 12 January (resolution date). Table 20 summarizes key derivation steps for each type of clustered select AEs.

Time-to-resolution of AESI (any grade) for a specific category is defined as the longest time from onset to complete resolution or improvement to the grade at baseline among all AESI clusters in this category experienced by patients. Events which worsened into Grade 5 events (death) or have a resolution date equal to the date of death are considered unresolved. If a clustered AESI is considered to unresolved, the resolution date will be censored to the last known date that the patient was alive. Improvement to the grade at baseline implies that all different AE events in the clustered AESI should at least have improved to the corresponding (that is, with same preferred term) baseline grade (or improve to a lower grade). Time-to-resolution is defined only for patients who experienced at least one AESI in the specific category.

The time-to-resolution of AESI (Grade 3-5) for a specific category is defined similarly, with an onset date corresponding to a Grade 3-5 AESI.

Time-to-resolution of drug-related AESI (any grade or Grade 3-5) is defined similarly but restricted to drug-related AESIs.

Time-to-resolution for a specific subcategory is defined similarly but restricted to events of this subcategory.

Table 20: Derivation of Clustered AESIs

Type of clustered select AE	Derivation
Any grade	Collapse any on-treatment AESI from the same category

Type of clustered select AE	Derivation
Drug-related of any grade	Collapse any on-treatment drug-related AESI from the same category
Grade 3-5	Collapse any on-treatment AESI from the same category. Resolution will be based on the onset date of the earliest Grade 3-5 records (clusters with only Grade 1-2 should not be selected)
Drug-related of Grade 3-5	Collapse any on-treatment drug-related AESI from the same category. Resolution will be based on the onset date of the earliest Grade 3-5 record (clusters with only Grade 1-2 should not be selected)

Abbreviations: AE=adverse event; AESI=adverse event of special interest.

The algorithm for collapsing selected AE records is using the following conventions. For each patient and specified category, the corresponding AE records will be collapsed when:

- Multiple AE records have the same onset date.
- The onset date of an event record is either the same day or 1 day later than the resolution date of a preceding event record (contiguous events).
- The onset date of an event record is after the onset date and prior to or on the resolution date of a preceding event record (overlapping events).

7.6. Other Data Handling Rules

Missing data will not be imputed in listings. The listings will only present the data recorded on the original Case Report Form.

If an AE has a completely missing onset date, then the AE will be considered a TEAE. A medication with a completely missing start date is considered a prior medication. A medication with a completely missing stop date is considered a concomitant medication.

If an AE or a medication has a partial missing start date or stop date, the following rules will be used to determine whether it is a TEAE, or a prior or concomitant medication.

Table 21: Partial Date Imputation Rule for TEAE or Medication

Partial Missing Start or Stop Date	Derived Start Date	Imputed Stop Date
Missing month and day, and the year is present	January 1 of that year or first dose date if the year is the same as the year of first dose date	December 31 of that year
Missing day, but year and month are present	First day of that month or first dose date if the year and month are the same as the year and month of first dose date	Last day of that month
Missing month, but year and day are present	Missing month derived as January or same as first dose month if the year is same as the year of first dose.	Missing month imputed as December

A date with a missing year will be considered as a completely missing date, and no imputation rule will be applied.

The rules described in Table 21 is also used for determining the cycle of AE and concomitant medication. The derived date is used for determining TEAEs, the cycle of AE, and concomitant medication.

For medical history, pre-study surgery, prior radiotherapy, and prior systemic anticancer therapies, a partial missing start date will be imputed as below:

1. Missing year :no imputation, date left missing

2. Missing day and month : January 1 will be assigned to the missing fields.
3. Missing month only: Treat day as missing and replace both month and day with January 1.
4. Missing day only: Assign the first day of the month to the missing day.

Note: Additional rules for prior systemic anticancer therapies may apply as they pertain to checking for protocol violations

For medical history, pre-study surgery, prior radiotherapy, and prior systemic anticancer therapies, a partially missing stop date will be imputed as below:

1. Missing year : no imputation, date left missing
2. Month is missing and year is prior to year of first dose of study drug:impute 'December'.
3. Month is missing and year is the same as the year of the first dose of study drug: impute same month as in first dose date of study drug.
4. Day is missing: impute 'last day of that month'. If results in a date ≥ the date of the first dose of study drug impute day as the day prior to date of first dose of study drug.

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