STATISTICAL ANALYSIS PLAN

Study Protocol Number:	E7090-J081-101
Study Protocol Title:	A phase 1 study of E7090 in subjects with solid tumor
Date:	26 Nov 2021
Version:	Version 2.0

REVISION HISTORY

The table below describes revieions in version 2.0
Date: 26 Nov 2021

Section	Highlights of Major Changes/ Reason for Revision
5.5	Added the detail blood urine sampling schedules due to protocol amendment (version 4.0).
5.5.1	Added tables and figures of plasma concentrations by tumor type of Part 2 according to protocol amendment (version 7.0) and the assessment of dose proportionality using the power model.
5.5.2	Scatter plot for biomarker and dose levels was added.
5.6.2	Table for non-serious TEAEs were added.
5.6.2	Items in table for all death were updated.
5.6.6	A listing for potential Hy's cases were added.
13.2	Added the detail blood sampling schedule for pharmacokinetic assessments according to protocol.

1 TABLE OF CONTENTS

2 LIST OF ABBREVIATIONS AND DEFINITIONS OF TERMS

Abbreviation	Term
AE	adverse event
ATC	anatomical therapeutic chemical
AUC	area under the plasma concentration-time curve
BOR	best overall response
BLQ	below the limit of quantification
CC	cholangiocarcinoma
CI	confidence interval
CL	total clearance
CL_R	renal clearance
C_{max}	maximum observed concentration
CR	complete response
CRF	case report form
CSR	clinical study report
CTCAE	common toxicity criteria for adverse events
CV	coefficient variation
DCR	disease control rate
DLT	dose limiting toxicity
ECOG	Eastern Cooperative Oncology Group
FGF/FGFR	fibroblast growth factor/ fibroblast growth factor receptor
GC	gastric cancer
HPD	highest posterior density
LLT	lower level term
MedDRA	Medical Dictionary for Regulatory Activities
MTD	maximally tolerated dose
mTPI	modified toxicity probability interval
NE	not evaluable
ORR	objective response rate
OS	overall survival
PAVA	pooled adjacent violators algorithm
PD	pharmacodynamics
PD	progressive disease
PFS	progression free survival
PGx	pharmacogenomics

Abbreviation	Term
PK	pharmacokinetics
PR	partial response
PS	performance status
PT	preferred term
PTF	peak-trough fluctuation
QT	QT interval
RD	recommended dose
RECIST	response evaluation criteria in solid tumor
SAE	serious adverse event
SAP	statistical analysis plan
SD	stable disease
SI	système international
SOC	system organ class
SpO_2	percutaneous oxygen saturation
$t_{½}$	terminal elimination phase half-life
TEAE	treatment-emergent adverse event
TEMAV	treatment-emergent markedly abnormal laboratory value
TLG	tables, listings, and graphs
t_{max}	time at which the highest drug concentration occurs
UPM	unit probability mass
V_Z	volume of distribution at terminal phase
WHO DD	World Health Organization drug dictionary
λ_z	terminal phase rate constant

3 INTRODUCTION

The purpose of this statistical analysis plan (SAP) is to describe the procedures and the statistical methods that will be used to analyze and report results for Eisai Protocol E7090-J081-101. This document is based on Protocol version 9.0 (13th Jul 2018)

3.1 Study Objectives

3.1.1 Primary Objective

- To investigate the tolerability and safety of E7090 in subjects with advanced solid tumors.

3.1.2 Secondary Objectives

- To determine the maximally tolerated dose (MTD) of E7090. (Part 1)
- To establish the pharmacokinetics (PK) of E7090.
- To determine the recommended dose (RD) of E7090 in future studies.
- To assess the preliminary anti-tumor activity of E7090.

3.1.3 Exploratory Objectives

- To investigate the pharmacodynamics (PD) markers and pharmacogenomics (PGx) of E7090.
- To investigate the relationship among PK, PD markers and PGx of E7090.
- To assess the overall survival (OS) and progression-free survival (PFS) under administration of E7090. (Part 2)
- To analyze the metabolites of E7090 in plasma and urine. (Part 1)

3.2 Overall Study Design and Plan

3.2.1 Overall Study Design and Plan

This was a dose escalated, open-label Phase 1 study of E7090 in subjects with advanced solid tumors, for who it was deemed that standard treatments were not effective or there were not effective treatment. This study was conducted in 2 parts, shown in Figure 1: 1) Part 1 was the dose escalation portion of this study to assess dose limiting toxicity (DLT) and determine the MTD in subjects with solid tumors, and 2) Part 2 comprised cohort expansions to further characterize the safety and tolerability of E7090 and to assess preliminary efficacy of E7090 in subjects with gastric tumors with FGFR2 amplification or protein overexpression and cholangiocarcinoma with FGFR2 fusion. One or two doses for Part 2 might have been selected from the tested doses in Part 1 after evaluation of safety, efficacy, PK/PD and so on. The RD for future studies was estimated based on the data from Part 1 and Part 2. Selection of the dose for Part 2 and RD for future studies was agreed by investigators, sponsor, medical

monitor and independent medical adviser (if deemed necessary). This trial is single center for Part 1 and multicenter for Part 2.

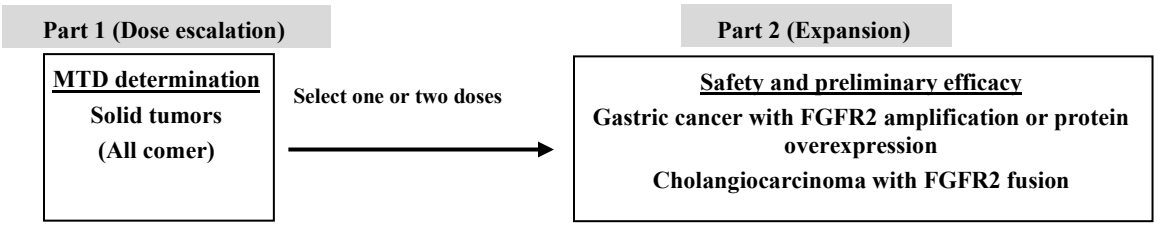


Figure 1 Overview of Study Design

3.2.2 Part 1

An overview of the study design for Part 1 is presented in Figure 2. Part 1 consisted of Pretreatment Period, Treatment Period, and Follow-up Period.

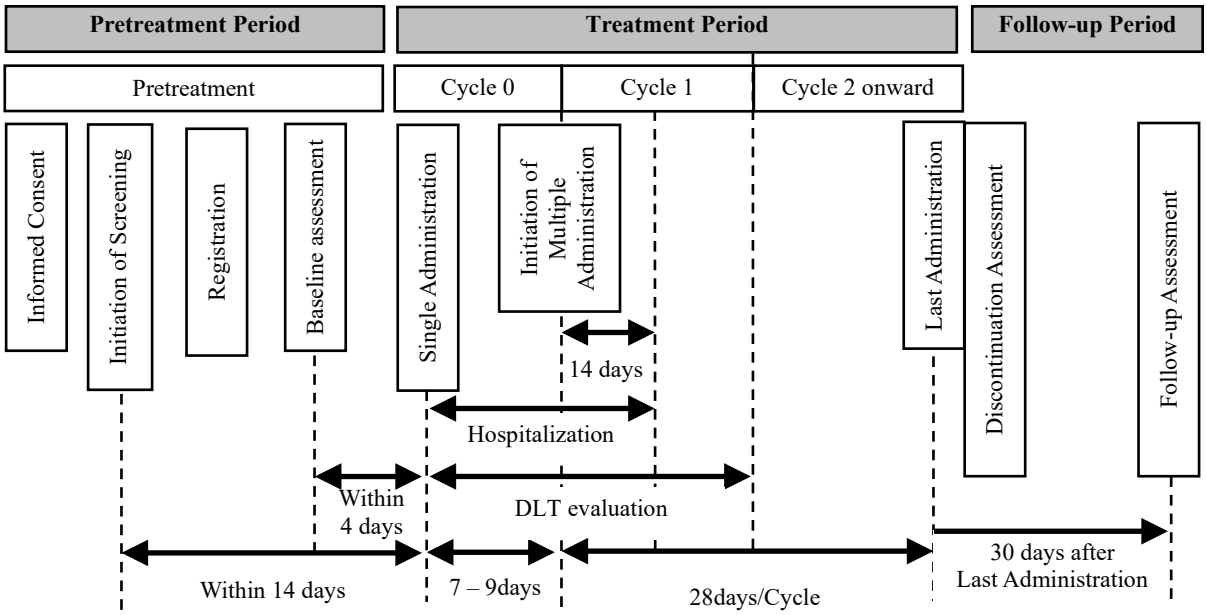


Figure 2 Overall Study design of Part 1

3.2.2.1 Pretreatment Period

The pretreatment period consisted of informed consent, screening, registration and baseline assessment. Informed consent was obtained after the study had been fully explained to each subject and before the conduct of any screening procedures or assessments. In screening assessment, it was confirmed that each subject fulfilled all the inclusion criteria and did not meet any exclusion criteria. Screening occurred within 14 days of the first dose of study drug. The subject confirmed eligibility in screening assessment was registered, and baseline assessment was performed within 4 days prior to first dose of study drug.

3.2.2.2 Treatment Period

The treatment period consisted of cycle 0, 1 and 2 onward. At cycle 0 day 1, the dose of each dose group was administrated singly to assess PK under single administration. Repeated dosing will be performed in Cycle 1 and onwards with 28 days as 1 cycle. Subjects were hospitalized from day 1 of Cycle 0 to morning of day 15 of Cycle 1. In cycle 0 and 1, DLT was evaluated. Subjects were allowed to continue administration of study drug unless the subject met the discontinuation criteria (Section 9.3.3.1 Criteria for Discontinuation in protocol).

3.2.2.3 Follow-up Period

The follow-up period consisted of discontinuation assessment and follow-up assessment. If the subject met the discontinuation criteria (Section 9.3.3.1 Criteria for Discontinuation in protocol ver. 1.0), administration of study drug was discontinued and discontinuation assessment was performed within 7 days after discontinuation form study drug. Also, the follow-up assessment was performed 30 (+7) days after the last administration of study drug.

3.2.2.4 Decision Rule for Dose Assignment

A modified toxicity probability interval (mTPI) design (Ji Y et al. 2010) was employed to assign dose. Each subject was assigned a dose of E7090 in accordance with the rules of the mTPI design based on a target dose-limiting toxicity (DLT) rate of 25% and the corresponding three toxicity probability intervals that are defined as 20 to 30% (proper dosing), 0 to 20% (under dosing), and 30 to 100% (over dosing). The entire dose assignment decision rule could be precalculated under the mTPI design and presented in two-way table (Table 1) as below.

Table 1 Decision Rule for Dose Assignment

		Number of Subjects Treated at the Current Dose				
		2	**4**	**6**	**8**	**10**
Number of Subjects with DLT's	**0**	**E**	**E**	**E**	**E**	**E**
	1	**D[a]**	**S**	**S**	**E**	**E**
	2	**D, U**	**D**	**S**	**S[b]**	**S**
	3		**D, U**	**D**	**S**	**S[b]**
	4		**D, U**	**D, U**	**D, U**	**S**
	5			**D, U**	**D, U**	**D, U**

E = Escalate to the next higher dose, **S** = Stay at the current dose, **D** = De-escalate to the next lower dose, **U** = Current dose is unacceptably toxic (i.e., Do not re-enter the current dose)
Target DLT rate at MTR = 25% and its equivalence toxicity interval = 20 to 30%, Cohort size = 2 subjects
Display for more than 10 subjects at the current dose is omitted
a: For initial dose level, subjects can be added
b: Subject registration can be stopped early.

Number of subjects for each tested dose level was two. Based on the number of subjects with DLTs in each dose level, dose assignment for next dose was determined according to the Table 1. However, if one out of two subjects developed DLT in initial dose level, subjects could be enrolled in the same dose level after discussion among the investigator, sponsor, and medical expert. In this case, an advice from independent medical adviser could be received. Subjects who could not be evaluable for DLT could be replaced within their dose level. Under the mTPI design, a Part 1 was terminated when the lowest dose had excessive DLT rate beyond the target DLT rate or a prespecified maximum sample size (i.e., approximately 20 subjects) was reached. However, the maximum sample size might have been adjusted if deemed necessary. If, in a certain dose, the probability that future registered subjects will also be assigned to that dose was predicted to be sufficiently high, subject registration could be stopped early. The details of the mTPI design were described under "5.3.6 Other Considerations". Figure 3 shows the process of dose assignment according to Table 1.

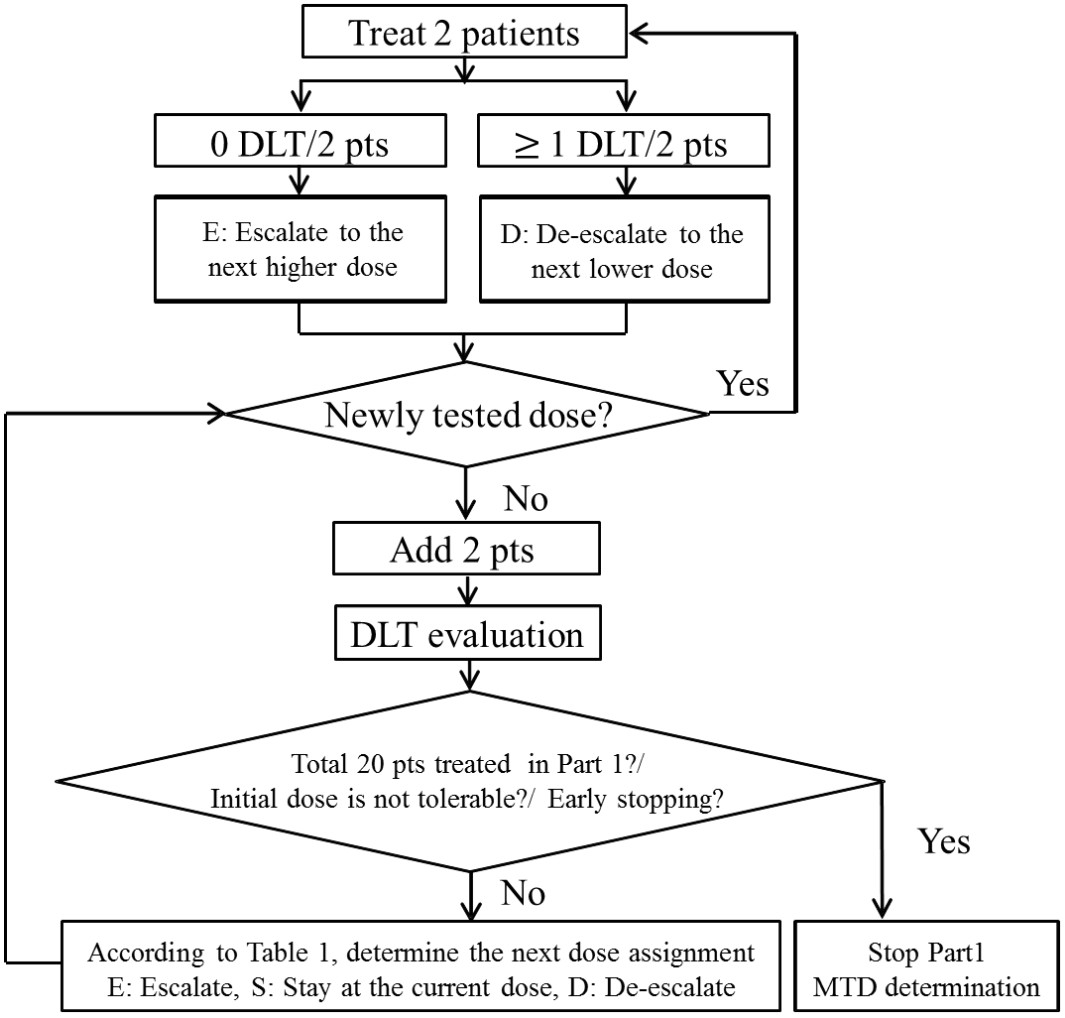


Figure 3 The Process of Dose Assignment

3.2.3 Part 2

An overview of the study design for Part 2 is presented in Figure 4. Part 2 consisted of Pretreatment Period, Treatment Period, and Follow-up Period.

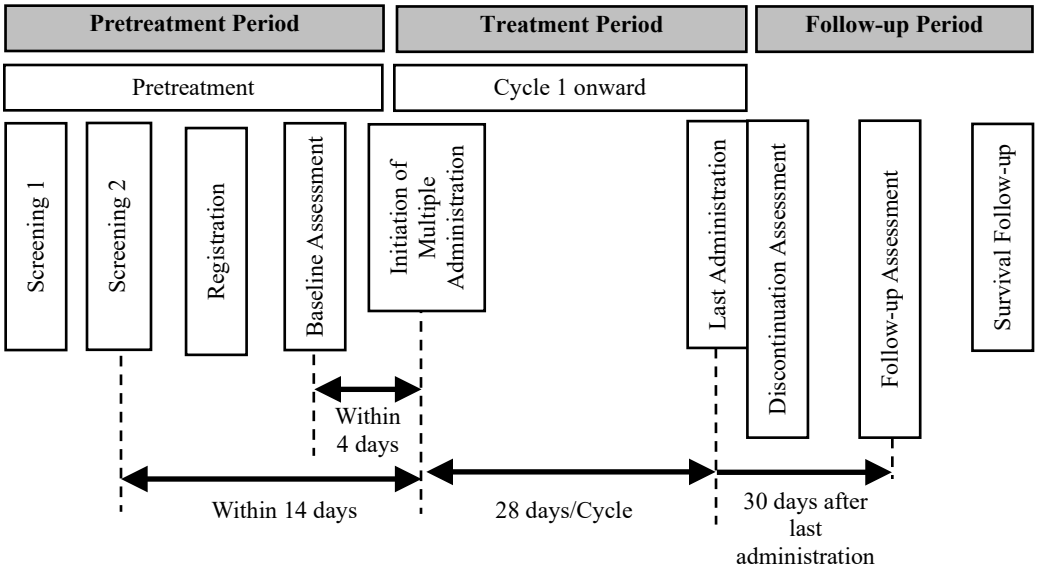


Figure 4 Overall Study design of Part 2

Following subjects were enrolled in Part 2.

- Gastric cancer with FGFR2 amplification or protein overexpression
- Cholangiocarcinoma with FGFR2 fusion

3.2.3.1 Pretreatment Period

Pretreatment period consisted of a Screen 1, Screen 2 and baseline test. Screen 1 was to confirm FGFR status and Screen 2 was to confirm other eligibility criteria. A separate study informed consent had to be signed prior to conducting screening procedures for Screen 1 and Screen 2. Screen 1 was for gastric cancer patients and cholangiocarcinoma patients who were previously determined to be FGFR2 amplification positive and FGFR2 fusion positive, respectively. Gastric cancer patients who were not previously determined to be FGFR2 amplification positive were also for Screen 1 if they had an available tumor sample. A fresh biopsy to obtain tumor sample for genetic screening was not permitted during Screen 1.

3.2.3.2 Treatment Period

The treatment period consisted of treatment cycles. The duration of each cycle was 28 days. The study treatment was continued unless subject met the discontinuation criteria (Section 9.3.3.1 Criteria for Discontinuation in protocol).

3.2.3.3 Follow-up Period

The follow-up period consisted of discontinuation assessment and follow-up assessment. If the subject met the discontinuation criteria (Section 9.3.3.1 Criteria for Discontinuation in protocol), administration of study drug was discontinued and discontinuation assessment was performed within 7 days after discontinuation form study drug. Also, the follow-up assessment was performed 30 days (+7 days) after the last administration of study drug. From the date of study drug discontinuation, the survival status was assessed every 12 weeks (±1 week). However, survival assessment might have been performed at unscheduled timing, if deemed necessary.

4 DETERMINATION OF SAMPLE SIZE

The primary objective of this study was to evaluate the tolerability and safety of E7090. The number of subjects in the Part 1 was approximately 20, based on the recommended sample size to reach MTD in mTPI design (Ji Y et al. 2013) assuming 9 dose levels to be tested and the cohort size of 2. The number of subjects might have been adjusted depending on the actual number of tested dose levels and evaluable subjects for DLT assessment, if deemed necessary.

The Part 2 by approximately 10 subjects in gastric cancer cohort, and 5–10 subjects in cholangiocarcinoma will allow for further evaluation of safety and preliminary anti-tumor activity. Sample size was also determined based on a feasibility.

5 STATISTICAL METHODS

5.1 Study Endpoints

5.1.1 Primary Endpoints

- DLTs (only Part 1)
- Safety endpoints (adverse events, clinical laboratory parameters, vital signs, weights, 12-lead ECG, ECOG-PS and ophthalmologic examination)

5.1.2 Secondary Endpoints

- PK parameters
- Efficacy endpoints (best overall response (BOR), ORR, disease control rate (DCR) and percent changes from baseline in the sum of the diameters of target lesions (if applicable)

5.1.3 Exploratory Endpoints

- PD marker
- PGx
- Efficacy endpoints (PFS and OS)

5.2 Study Subjects

5.2.1 Definitions of Analysis Sets

The DLT Analysis Set is the group of subjects in the Part 1 who completed Cycle 0 and Cycle 1 treatment of E7090 with at least 75% compliance and were evaluated for DLT, and those who developed DLT during Cycle 0 or Cycle 1. This will be the analysis set for MTD determination in the Part 1.

The Safety Analysis Set is the group of subjects who received at least 1 dose of E7090.

The Efficacy Analysis Set is the group of subjects who received at least 1 dose of E7090 and had both baseline and at least 1 post-baseline tumor assessments. This analysis set will also be used for interim evaluation in Part 2.

The PK Analysis Set is the group of subjects who received at least 1 dose of E7090 and had sufficient PK data to derive at least 1 PK parameter.

The PD and PGx Analysis Set is the group of subjects who received at least 1 dose of E7090 and had at least 1 PD or PGx data.

The number of subjects treated, the number and the percentage of subjects included in each analysis set will be presented for each dose group in Part 1, each cancer cohort in Part 2, total subjects of each part, and total subject in this study. Subject data listings will be provided.

5.2.2 Subject Disposition

Screening subjects table will include the number of subjects who are enrolled (i.e., subjects who signed informed consent), are eligible, failed screening, and the primary reason for screen failures. Subject disposition table will include the number of subjects who are treated/not treated, completed/discontinued the study, the primary reason, and other reason for the study discontinuation. Similarly, the number of subjects who completed/discontinued the study treatment, the primary reason, and, other reason for the study treatment discontinuation will also be summarized. The summarization will be performed on each dose group in Part 1, each cancer cohort in Part 2, total subjects of each part, and total subject in this study.

A subject who completed the study is defined as whose DLT assessment has been completed adequately in Part 1, and discontinuation or follow-up assessment has been done in Part 2. A subject who completed the study treatment is defined as who discontinued study treatment due to disease progression or study cut-off.

Subject data listings will be provided.

5.2.3 Protocol Deviations

Major protocol deviation criteria will be established and subjects with major protocol deviations will be identified and documented before the database lock. All protocol deviations identified according to study entry criteria and during treatment will not be included in TLGs, but presented in the clinical study report (CSR).

5.2.4 Demographic and Other Baseline Characteristics

Demographic and other baseline characteristics for the Safety Analysis Set will be summarized for each dose group in Part 1, each cancer cohort in Part 2, total subjects of each part, and total subject in this study using summary statistics. Continuous demographic and baseline variables include age, height and weight; categorical variables include sex, race, ethnicity, ECOG-PS, primary tumor, prior therapy (surgery, radiotherapy, anti-cancer therapy, and other therapies), use of contact lens, FGF/FGFR gene abnormality and the type (translocation, point mutation, amplification, overexpression and other). Subject data listings will be provided.

5.2.5 Prior and Concomitant Therapy

All investigator terms for medications recorded in the case report form (CRF) will be coded to an 11-digit code using the World Health Organization Drug Dictionary (WHO DD). The number (percentage) of subjects who took prior and concomitant medications will be summarized on the Safety Analysis Set for each dose group in Part 1, each cancer cohort in Part 2, total subjects of each part, and total subject in this study, Anatomical Therapeutic Chemical (ATC) class (anatomical class, pharmacological class, and pharmacological sub-class) and WHO DD preferred term. Prior medications are defined as medications that stopped before the first dose of study drug. Concomitant medications are defined as medications that (1) started before the first dose of study drug and were continuing at the time of the first dose of study drug, or (2) started on or after the date of the first dose of study drug up to 30 days after last dose (follow-up visit). Medications received after 30 days of last dose will be considered as post treatment medications. All medications will be presented in subject data listings.

5.2.6 Treatment Compliance

Subjects with treatment related protocol deviations will not be included in TLGs, but presented in CSR as provided in section “5.2.3 Protocol Deviations“.

5.3 Data Analysis General Considerations

5.3.1 Pooling of Centers

Subjects from all centers will be pooled for all analyses.

5.3.2 Adjustments for Covariates

No adjustment for covariates will be performed.

5.3.3 Multiple Comparisons/Multiplicity

No statistical comparison is planned in this study.

5.3.4 Examination of Subgroups

No subgroup analysis is planned in this study.

5.3.5 Handling of Missing Data, Dropouts, and Outliers

No imputation will be performed for missing data.

5.3.6 Other Considerations

mTPI Design

The mTPI design was employed to determine the MTD of E7090. The mTPI design used a Bayesian statistical framework and a beta/binomial hierarchic model to compute the posterior probabilities of three intervals that reflect the relative distance between the DLT rates of each dose level to the target DLT rate of 25%.

Decision rules for dose-finding were based on calculating the unit probability mass (UPM) of three intervals corresponding to 0 to 20% (under dosing), 20 to 30% (proper dosing) and 30 to 100% (over dosing) in terms of toxicity. The UPM for each interval was defined as the probability of the interval divided by the length of the interval, and the one with the largest UPM implied the decision for future dose level to be assigned, i.e., dose escalation (E), staying at the current dose (S), or dose de-escalation (D), respectively. This dose assignment rule minimizes the posterior expected penalty in the Bayes rule under a decision-theoretic framework with the equal prior expected penalties for E, S, and D. The entire dose assignment decision rule could be pre-calculated.

Determination of MTD

MTD will be determined when the initial dose level has a > 95% posterior probability of being DLT rate > 25% (i.e., unacceptable DLT rate beyond the target DLT rate) or a pre-specified maximum sample size of approximately 20 subjects is reached. However, the maximum sample size might have been adjusted depending on the actual number of tested dose levels and evaluable subjects for DLT assessment, if deemed necessary. Also, if the Bayesian predictive probability of being S was ≥ 80% with additional 10 subjects in a certain dose (i.e., the probability that future registered subjects will also be assigned to that dose was predicted to be sufficiently high), subject registration was stopped and MTD could be determined.

MTD will be defined as the dose with the smallest difference between the target DLT rate of 25% and an estimate of DLT rate at each dose among all the tested doses with ≤ 95% posterior probability of being DLT rate > 25%. The isotonically transformed posterior mean under the beta posterior distribution with non-informative beta prior distribution Beta (0.005, 0.005) will be used to determine the estimate of DLT rates at each dose. The pooled adjacent violators algorithm (PAVA) (Bartholomew, D, 1983) will be used to maintain monotonically increase of DLT rate with increasing dose level.

5.4 Efficacy Analyses

Efficacy analyses will be performed based on the Efficacy Analysis Set. For Part 2, each cancer cohort will be analyzed separately.

5.4.1 Primary Efficacy Analyses

Since this trial is phase 1, primary efficacy endpoint is not defined.

Part 1

Based on the tumor assessments according to response evaluation criteria in solid tumor (RECIST) 1.1, BOR will be summarized by each dose group and for total dose groups with the number of subject and percentage. BOR are complete response (CR), partial response (PR) stable disease (SD), progression of disease (PD) and not evaluable (NE). If a subject has a best overall response of non-CR/non-PD, the subject's best overall response will be grouped with the SD category. SD has to be achieved at ≥ 7 weeks after first dose. CR and PR do not have to be confirmed at ≥ 4 weeks later assessment.

Part 2

Besides the similar analyses for the Part 1, the number of subjects who archived objective response/disease control, their percentage (i.e. ORR, DCR) and their corresponding exact 2-sided 95% confidence intervals (CIs) will be calculated. ORR is defined as a proportion of subjects with BOR of CR or PR. DCR is defined as the proportion of subjects who with BOR of CR, PR, or SD.

Median, Q1, and Q3 for OS and PFS with their 95% CIs will be evaluated. The number (percentage) of subjects with event/censored will be summarized. The PFS rate and the OS rate with their 95% CIs at 6-month and 12-month will be calculated using Kaplan-Meier product limit estimates. Kaplan-Meier plots with the number of subjects at risk will be presented for PFS and OS.

PFS is defined as the time from the date of first dose to the date of first documented PD or death due to any cause (whichever occurs first). For subjects who do not have an event, PFS will be censored. Censoring rules for PFS are shown in Table 2.

PFS (days) = Date of first documented PD/ death/ Censored date – Date of first dose + 1.

Table 2 Censoring Rules for PFS

Situation	End Date	Censor/Event
Documented PD during the study	Date of the first assessment of the series of the tests that determined PD	Event[a]
Death during the study before PD	Date of death	Event[a]
No baseline or unreadable baseline tumor assessments	Date of first dose	Censor
Treatment discontinuation for other than PD or death, and no postb-aseline tumor assessments	Date of first dose	Censor
Treatment discontinuation for other than PD or death with post-baseline tumor assessments	Date of last adequate[b] tumor assessment	Censor
New anticancer treatment started prior to PD or death	Date of last adequate[b] tumor assessment prior to or on date of new treatment	Censor
PD or death after two or more missed tumor assessments[c]	Date of last adequate[b] tumor assessment before missed tumor assessment	Censor
Subjects still on study without PD or death as of data cut off	Date of last adequate[b] tumor assessment prior to or on date of data cut off	Censor

a: Earliest date among the two dates will be used in calculating the PFS.
b: Adequate tumor assessment is radiologic assessment of CR, PR, SD, non-CR/non-PD, or PD
c: Window of two or more missed tumor assessment is defined as duration between the last adequate tumor assessment and PD or death is ≥ 127 days, for scan schedule of every 8 weeks (±7 days)

OS is defined as the time from the date of first dose to the date of death from any cause. For subjects who do not die, OS will be censored. Censoring rules for OS are shown in Table 3.

OS (days) = Date of death/ Censored date – Date of first dose + 1.

Table 3 Censoring Rules for OS

Situation	End Date	Censor/Event
Death before or on data cut off	Date of death	Event
Death after data cut off	Date of data cut off	Censor
Subject still alive at data cut off	Date of data cut off	Censor
Subject lost to follow-up or withdraw of consent before data cut off	Data last known to be alive	Censor

If applicable, waterfall plot will be presented for the percent changes from baseline in the sum of the diameters of target lesions at post-baseline nadir.

If applicable, change in tumor marker will be plotted over time.

Subject data listings will be provided.

5.4.2 Secondary Efficacy Analyses

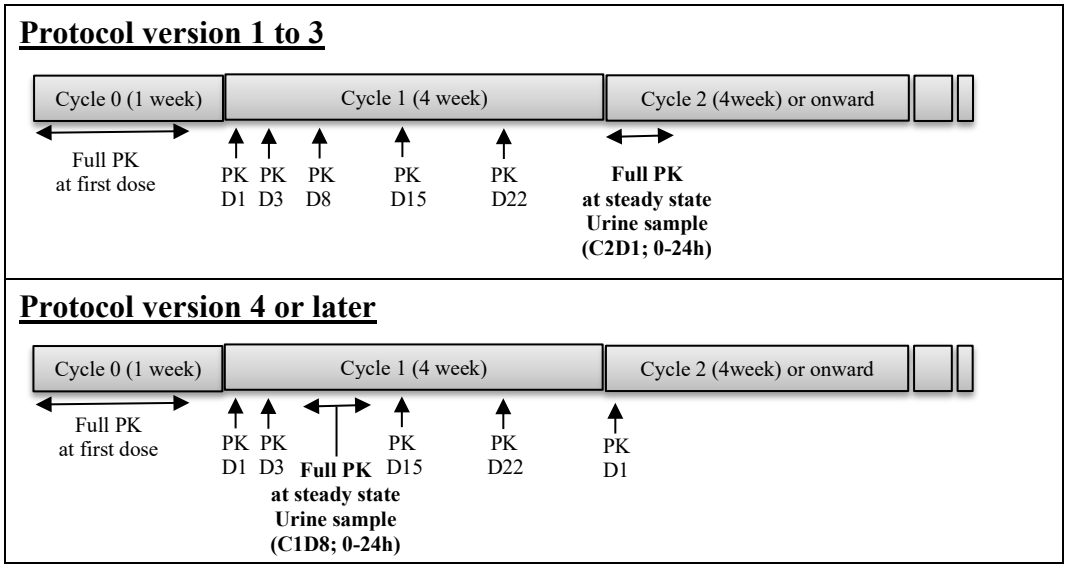
Not applicable.

5.4.3 Other Efficacy Analyses

Not applicable.

5.5 Pharmacokinetic, Pharmacodynamic, Pharmacogenomic, and Other Biomarker Analyses

The timepoints of blood and urine sampling for PK assessment were changed during Part 1 per Protocol version 4.0 as follows;



It was considered that the plasma concentrations would be reached steady state until Cycle 1 Day 8 (C1D8) based on the preliminary terminal half-life up to 30 mg dose, therefore PK and urine sampling at steady state was shifted from Cycle 2 Day 1(C2D1) to C1D8. Since both C2D1 data in lower dose cohort and C1D8 data in higher dose cohort are steady state, these data will be pooled for PK assessment at steady state.

The detail blood sampling schedule are shown in Appendix13.2.

5.5.1 Pharmacokinetic Analyses

The Safety Analysis Set will be used for individual E7090 plasma concentration, active metabolite (M2) plasma concentration and E7090 urine concentration listings. The PK Analysis Set will be used for summaries of E7090 plasma concentrations, M2 plasma concentrations, and E7090 urine concentrations and for summaries and listings of PK parameters.

The data in patient with dose-reduction/ interruption within 7 days[note] prior to steady state concentration measurement will not be included on calculation of summary statistics.

Note: It was considered that the plasma concentrations would be reached steady state until 8 days following once-daily administration, therefore the data in subject with dose-reduction/ interruption 8 days or earlier of steady state concentration measurement can be included.

5.5.1.1 Plasma Concentration Analysis

For each nominal time point, plasma concentrations for E7090 and M2 after study drug administration will be summarized by summary statistics (n, mean, SD, median, minimum

and maximum) by dose group. Handling of values below the limit of quantification (BLQ) is shown in Section 8.2.

<Tables>
(1) Individual and summary of plasma E7090 and M2 concentrations

a) Individual plasma concentrations will be presented by dose group and nominal time point in Part 1 followed by summary statistics.

b) Individual plasma concentrations will be presented by tumor type (total, gastric cancer, and cholangiocarcinoma) and nominal timepoint in Part 2 followed by summary statistics.

<Listings>
(1) Actual sampling time and plasma concentrations of E7090 and M2 for each subject will be listed.

5.5.1.2 Non-Compartmental Analysis

NON-COMPARTMENTAL ANALYSIS USING PLASMA CONCENTRATION-TIME DATA

Plasma concentrations of E7090 and M2 after study drug administration will be analyzed by non-compartmental methods. The following PK parameters will be calculated. Other PK parameters may be calculated as appropriate. To calculate PK parameters, actual sampling time will be used.

<PK parameters after first dose: Cycle 0 Day 1 in Part 1 and Cycle 1 Day 1 in Part 2>
(1) Maximum observed plasma concentration (C_{max})
(2) Time at which the highest drug concentration occurs (t_{max})
(3) Terminal phase rate constant (λ_z)
(4) Terminal phase half-life ($t_{½}$)
(5) Area under the plasma concentration-time curve
  1) AUC from zero (pre-dose) to time of last quantifiable concentration ($AUC_{(0\text{-}t)}$)
  2) AUC from zero (pre-dose) extrapolated to infinite time ($AUC_{(0\text{-}inf)}$)
  3) AUC from zero (pre-dose) to 24h ($AUC_{(0\text{-}24h)}$)
(6) Percentage of $AUC_{(0\text{-}inf)}$ by extrapolation ($\%AUC_{ex}$)
(7) Apparent clearance following oral administration (CL/F) (E7090 only)
(8) Apparent volume of distribution during the terminal phase (V_z/F) (E7090 only)
(9) Mean residence time (MRT)
(10) Metabolite to parent (M/P) ratio

<How to calculate PK parameters after first dose>
(1) C_{max} will be obtained directly from the concentration-time data.
(2) t_{max} is the time at which C_{max} is observed (actual time).
(3) λ_z will be estimated at terminal phase by linear regression of greater or equal 3 log-concentrations (excluding C_{max}) versus time data points.
(4) $t_{½}$ will be calculated as $\ln 2/\lambda_z$.
(5) AUC is calculated as follows;

The linear trapezoidal method will be employed for all incremental trapezoids arising from increasing concentrations and the logarithmic trapezoidal method will be used for those arising from decreasing concentrations.

1) $AUC_{(0\text{-}t)}=\int_0^t C(t)dt$

2) $AUC_{(0\text{-}inf)}=\int_0^t C(t)dt+\int_t^\infty C(t)dt = AUC_{(0\text{-}t)}+C_t/\lambda_z$

C_t is last observed concentration.

3) $AUC_{(0\text{-}24h)}=\int_0^{ti} C(t)dt$, where ti=24 hours

(6) $\%AUC_{ex}$ will be obtained as $\%AUC_{ex}=(1-AUC_{(0\text{-}t)}/AUC_{(0\text{-}inf)})\times 100$.

(7) CL/F will be calculated as amount of dose/$AUC_{(0\text{-}inf)}$.

(8) V_z/F will be calculated as $(CL/F)/\lambda_z$.

(9) MRT will be obtained as $MRT=S_1/S_0$. S_0 and S_1 will be obtained as;

$S_0=AUC_{(0\text{-}inf)}$

$S_1=AUMC=\int_0^t t\cdot C(t)dt+\int_t^\infty t\cdot C(t)dt = AUMC_{(0\text{-}t)}+t\cdot C_t/\lambda_z+C_t/\lambda_z^2$

(10) M/P ratio will be calculated as the PK parameter ($AUC_{(0\text{-}inf)}$) of M2 / the PK parameter of E7090 using the PK parameter normalized by molecular weight, where molecular weight of E7090 and M2 are 587.68 and 543.62, respectively.

<PK parameters after repeated doses at steady state: C2D1 or C1D8 in Part 1 and Part 2>

(1) Maximum observed plasma concentration at steady state ($C_{ss,max}$)

(2) Minimum observed plasma concentration at steady state ($C_{ss,min}$)

(3) Time at which the highest drug concentration occurs at steady state ($t_{max,ss}$)

(4) Area under the plasma concentration-time curve over the dosing interval ($AUC_{(0\text{-}\tau)}$)

(5) Average steady-state concentration ($C_{ss,av}$)

(6) Accumulation index

1) $R_{ac}(C_{max})$ based on C_{max}

2) R_{ac}(AUC) based on AUC

(7) Accumulation ratio reflecting time and concentration dependency (R_{ss})

(8) Peak-trough fluctuation（PTF）

(9) Metabolite to parent (M/P) ratio at steady state

<How to calculate PK parameters after repeated doses at steady state >

(1) $C_{ss,max}$ will be obtained directly from the concentration-time data.

(2) $C_{ss,min}$ will be obtained directly from the concentration-time data.

(3) $t_{max,ss}$ will use the time which observes $C_{ss,max}$ after dose at steady state as nominal time.

(4) AUC will be obtained from the following formulae. The linear trapezoidal method will be used at any time that the concentration data is increasing, and the logarithmic trapezoidal method will be used at any time that the concentration data is decreasing.

$AUC_{(0\text{-}\tau)}=\int_0^\tau C(t)dt$

τ represents the length of the dosing interval of multiple dose.

(5) $C_{ss,av}$ will be obtained as $AUC_{(0\text{-}\tau)}/\tau$.

(6) R_{ac} will be obtained as $R_{ac}(C_{max})=C_{ss,max}/C_{max}$, $R_{ac}(AUC)=AUC_{(0\text{-}\tau)}/AUC_{(0\text{-}24h)}$.

(7) R_{ss} will be obtained as $R_{ss}=AUC_{(0\text{-}\tau)}/AUC_{(0\text{-}inf)}$

(8) PTF will be obtained as $(C_{ss,max}-C_{ss,min})/C_{ss,av}\times 100$.
(9) M/P ratio at steady state will be calculated as the PK parameter ($AUC_{(0-\tau)}$) of M2 / the PK parameter of E7090 using the PK parameter normalized by molecular weight.

For each dose group, summary statistics will be tabulated for the PK parameters. General rules for presentation of PK parameters are shown in Section 8.2.6. The PK parameters in patient with dose-reduction/interruption within 7 days prior to steady state concentration measurement will not be included on calculation of summary statistics.

<Tables>
(1) Individual and summary of E7090 and M2 PK parameters
a) Individual E7090 and M2 PK parameters after first and repeated doses will be presented by dose group in Part 1 followed by summary statistics.

b) Individual E7090 and M2 PK parameters after first and repeated doses will be presented by tumor type (total, gastric cancer, and cholangiocarcinoma) and each cancer cohort in Part 2 followed by summary statistics.

<Listings>
(1) Individual E7090 and M2 PK parameters for plasma samples after first and repeated doses.

The number of time points used in calculation of λ_z, λ_z lower (earliest time) and λ_z upper (last time) will be shown in addition to other PK parameters.

URINE CONCENTRATIONS AND URINARY EXCRETION ANALYSIS

Following urinary excretion parameters by subject will be calculated from urine volume and urine E7090 concentration data between 0 to 24 h after repeated doses at steady state in Part 1. All of analysis will be performed at nominal times.

<Urine volume and urinary excretion parameters>
(1) Urine concentration
(2) Urine volume
(3) Excreted amount of E7090 in urine ($Ae_{(0-\tau)}$)
(4) Urinary excretion (%) of E7090 as a % of dose up to 24 h after repeated dose at steady state ($Fe_{(0-\tau)}$)
(5) Renal clearance (CL_R)

<How to calculate urinary excretion parameters>
(1) Urine concentrations for E7090 after study drug administration in Part 1 at steady state will be used.
(2) Urine volume will use the actual data for urine volume.
(3) $Ae_{(0-\tau)}$ will be obtained from the following formula.
$Ae_{(0-\tau)}$ = [urine volume during 0-24h interval collection] × [urine E7090 concentration during 0-24h interval collection]

(4) $Fe_{(0-\tau)}$ will be obtained as $Fe_{(0-\tau)} = (Ae_{(0-\tau)}/dose) \times 100$.
(5) CL_R will be obtained as $CL_R = Ae_{(0-\tau)}/AUC_{(0-\tau)}$.

For each dose group, summary statistics will be tabulated for the urinary excretion parameters. General rules for presentation of drug concentrations and urinary excretion parameters are shown in Section 8.2.6. The urinary excretion parameters in patient with dose-reduction/interruption will not be included on calculation of summary statistics.

<Tables>
(1) Individual and summary of urinary concentrations and excretion parameters

Individual urinary concentrations and excretion parameters will be presented by dose group, followed by summary statistics.

<Listings>
(1) Pharmacokinetic urine sampling, urine volume and concentrations of E7090 will be listed.
(2) Individual of urinary excretion parameters

Individual urinary excretion parameters will be presented.

5.5.1.3 Pharmacokinetic Data Figures

The following figures will be displayed.

(1) Linear and semi-log plots of mean E7090 plasma concentrations and M2 plasma concentrations in Part 1

a) The time after the dose of E7090 (nominal time) will be plotted on the X axis and mean plasma concentrations of E7090 of all dose groups with standard deviation will be plotted on the Y axis (linearly and logarithmically) by visit (first dose and repeated dose).

b) The time after the dose of E7090 (nominal time) will be plotted on the X axis and mean plasma concentrations of M2 of all dose groups with standard deviation will be plotted on the Y axis (linearly and logarithmically) by visit (first dose and repeated dose).

(2) Linear and semi-log plots of individual plasma drug concentration-time profiles by dose in Part 1

a) The time after the dose of E7090 (actual time) will be plotted on the X axis and individual plasma concentrations of E7090 will be plotted on the Y axis (linearly and logarithmically) by dose group and visit (first dose and repeated dose).

b) The time after the dose of E7090 (actual time) will be plotted on the X axis and individual plasma concentrations of M2 will be plotted on the Y axis (linearly and logarithmically) by dose group and visit (first dose and repeated dose).

(3) Linear and semi-log plots of mean plasma concentrations of E7090 and M2 at first dose

and steady state in Part 2

a) The time after the dose of E7090 (nominal time) will be plotted on the X axis and mean plasma concentrations of E7090 with standard deviation will be plotted on the Y axis (linearly and logarithmically) by tumor type (total, gastric cancer, and cholangiocarcinoma).

b) The time after the dose of E7090 (nominal time) will be plotted on the X axis and mean plasma concentrations of M2 with standard deviation will be plotted on the Y axis (linearly and logarithmically) by tumor type (total, gastric cancer, and cholangiocarcinoma).

(4) Linear and semi-log plots of plasma drug concentration-time profiles by individual subject in Part 2

a) The time after the dose of E7090 (actual time) will be plotted on the X axis and individual plasma concentrations of E7090 will be plotted on the Y axis (linearly and logarithmically) by each tumor type.

b) The time after the dose of E7090 (actual time) will be plotted on the X axis and individual plasma concentrations of M2 will be plotted on the Y axis (linearly and logarithmically) by each tumor type.

(5) The mean trough plasma concentrations of E7090 and M2 will be displayed using the nominal day in linear scale in Part 1. The timepoint for plot are referred to Appendix13.2.

(6) The individual trough plasma concentrations of E7090 and M2 will be displayed using the nominal day in linear scale in Part 1. The timepoint for plot are referred to Appendix13.2.

5.5.1.4 Evaluation of Dose-Proportionality in PK Parameters

The dose-proportionality for E7090 and M2 will be investigated visually using PK parameters in Part 1 obtained from non-compartmental analysis as follows.

(1) Doses will be plotted on the X axis and each parameter (C_{max}, $AUC_{(0-t)}$ and/or $AUC_{(0-inf)}$, $C_{ss,max}$ and $AUC_{(0-\tau)}$) will be plotted on the Y axis to display the data on all subjects.

(2) Doses will be plotted on X axis and each dose-normalized parameter (C_{max}, $AUC_{(0-t)}$ and/or $AUC_{(0-inf)}$, $C_{ss,max}$ and $AUC_{(0-\tau)}$) will be plotted on Y axis to display the data on all subjects.

(3) C_{max}, $AUC_{(0-t)}$, $AUC_{(0-inf)}$, $C_{ss,max}$ and $AUC_{(0-\tau)}$ of E7090 and M2 will be employed in assessing dose proportionality using the power model, assuming $AUC_{(0-t)} = a\ (dose)^{\beta}$, which is equivalent to the natural logarithm transformed model:
$\ln(AUC_{(0-t)}) = \ln(a) + \beta \ln(Dose) = \alpha + \beta \ln(Dose)$.
The linear regression model will be used to construct the 95% confidence interval for β.

The same analysis will be performed for C_{max}, $AUC_{(0\text{-}inf)}$, $C_{ss,max}$ and $AUC_{(0\text{-}\tau)}$.

The following two dose ranges are used to evaluate linearity: a) 1 to 180 mg, b) 30 to 140 mg.

5.5.2 Pharmacodynamic, Pharmacogenomic, and Other Biomarker Analyses

The PD and PGx Analysis Set will be used for PD and PGx biomarkers analyses of blood and tumor samples. The actual value and the percent change from baseline for the PD and PGx biomarkers will be summarized by each time point, dose group in each part using descriptive statistics. For Part 2, each cancer cohort will be analyzed separately.

The individual and mean plots with SD over time for the PD and PGx biomarkers (the actual value and the percent change from baseline) for each dose group in each part will be presented as appropriate. In addition, the relationship between the PD and PGx biomarker values (and/or percent change from base line) and plasma E7090 concentrations may be displayed in listings/plots as appropriate.

As for serum phosphate, FGF23, and 1,25 dihydroxy vitamin D, change from baseline of each marker at Cycle 1 Day 15 vs initial dose levels (mg) for each subject are presented in scatter plots. Subjects who did not have each marker results at both baseline and Cycle 1 Day 15 are excluded from the plots. Two scatter plots will be generated for each marker, one for subjects in Part 1, another for subjects in Part 1 and 2 total.

Also the exploratory and comprehensive biomarker analyses may be conducted as needed, however the exploratory results will not be included in the CSR as default.

Subject data listings (including subjects from whom available PD or PGx biomarker data without dose of E7090) will be provided.

5.6 Safety Analyses

DLT analyses will be performed on the DLT Analysis Set. The Safety Analysis Set will be used for all other safety analyses. Safety data, presented for each dose group in Part 1, each cancer cohort in Part 2, total subjects of each part, and total subject in this study, will be summarized on an “as treated” basis using summary statistics (e.g., n, mean, standard deviation, median, Q1, Q3, minimum, maximum for continuous variables; number [percentage] for categorical variables). Safety variables include treatment-emergent adverse events (TEAEs), clinical laboratory parameters, vital signs, weight, SpO_2, 12-lead ECG results, ECOG-PS and ophthalmologic examination. Study Day 1 for all safety analyses will be defined as the date of the first dose of study drug.

5.6.1 Extent of Exposure

The duration of treatment, number of subject weeks, total number of doses per subject, total doses per subject, dose intensity per subject, and relative dose intensity per subject will be summarized. The calculations are below:

- Duration of treatment (days) = Last dosing date – first dosing date + 1
- Number of subject weeks = Sum (Duration of treatment per subject) / 7
- Total number of doses = Sum of days with study drug dosing per subject
- Total doses (mg) = Sum of all the actual dose per subject
- Dose intensity (mg/days) = Total doses / Duration of treatment
- Relative dose intensity (%) = 100 × Dose intensity / defined starting dose for each dose group

Based on the actual dose records, the number (percentage) of subjects who experienced dose interruption, dose reduction will be provided. In addition, the time to first dose interruption and reduction will also be provided for subjects who experienced dose interruption and reduction.

Subject data listings will be provided.

5.6.2 Adverse Events

DLTs

The number (percentage) of subjects who experienced DLT will be summarized. DLT will be summarized by below criteria as well.

- Grade 4 neutropenia that persists for more than 7 days or febrile neutropenia
- Grade 4 thrombocytopenia or Grade 3 thrombocytopenia that requires blood transfusion
- Any Grade 3 or higher non-hematological toxicity with the exception of:
  - Abnormal clinical laboratory values with no clinical significance
  - Any events which can be managed and controlled to Grade 2 or less by maximal medical management.
- New ectopic de novo calcification with clinical significance confirmed by radiologic images.
- Hyperphosphatemia defined as follows
  - >7 mg/dl > 7 days despite phosphate lowering therapies
  - >9 mg/dl despite phosphate lowering therapies
- Totally, more than 7 days drug interruption during Cycle 0 and Cycle 1due to toxicity related to E7090.

As for the last bullet, even if total drug interruption duration is more than 7 days due to the other reason, that is not regarded as DLT and the subject will be excluded from DLT analysis set.

Adverse events (AE)

The AE verbatim descriptions (investigator terms from the CRF) will be classified into standardized medical terminology using the Medical Dictionary for Regulatory Activities (MedDRA). Adverse events will be coded to the MedDRA (Version 17.0 or higher) lower level term (LLT) closest to the verbatim term. The linked MedDRA preferred term (PT) and primary system organ class (SOC) will also be captured in the database.

A treatment-emergent adverse event (TEAE), defined in "8.1 General Data Handling", will be included in summary tables. All AEs, treatment emergent or otherwise, will be presented in subject data listings.

The incidence of TEAEs will be reported as the number (percentage) of subjects with TEAEs by MedDRA SOC and PT. A subject will be counted only once within a SOC and PT, even if the subject experienced more than 1 TEAE within a specific SOC and PT. The number (percentage) of subjects with TEAEs will also be summarized by highest grade according to common toxicity criteria for adverse events (CTCAE) ver. 4.03.

The number (percentage) of subjects with treatment-related TEAEs will be summarized by MedDRA SOC and PT. Treatment-related TEAEs include those events considered by the investigator to be related to study treatment. The number (percentage) of subjects with treatment-related TEAEs will also be summarized by highest CTCAE grade.

The number (percentage) of subjects with TEAEs / treatment-related TEAEs with CTCAE grade 3 or above will be summarized by MedDRA SOC and PT. All AEs with CTCAE grade 3 or above will be presented in subject data listings.

The number (percentage) of subjects with DLTs will be summarized by MedDRA SOC and PT. All DLTs will be presented in subject data listings.

The number (percentage) of subjects with TEAEs leading to death will be summarized by MedDRA SOC and PT. A subject data listing of all AEs leading to death will be provided.

The number (percentage) of subjects with treatment-emergent serious adverse events (SAEs) will be summarized by MedDRA SOC and PT. The number (percentage) of subjects with treatment-emergent non-serious adverse events will also be summarized by MedDRA SOC and PT. A subject data listing of all SAEs will be provided.

The number (percentage) of subjects with TEAEs / treatment-related TEAEs leading to discontinuation from study treatment, dose reduction and dose interruption will be summarized by MedDRA SOC and PT. A subject data listing of all AEs leading to discontinuation from study treatment, dose reduction and dose interruption will be provided.

An overview table, including the incidence of and the number of subjects with TEAEs, treatment-related TEAEs, TEAEs with CTCAE grade 3 or above, treatment-emergent SAEs, deaths, and those TEAEs leading to treatment discontinuation, dose reduction, or dose interruption, and corresponding treatment-related TEAEs in above categories will be provided.

All deaths within 30 days of last dose and deaths >30 days of last dose will also be summarized. The AEs leading to death will also be summarized by its reason (due to disease progression, not due to disease progression) from AE form of CRF in same table. A subject data listing of all deaths will be provided for all treated subjects.

5.6.3 Laboratory Values

Laboratory results will be summarized using Système International (SI) units. For all quantitative parameters listed in protocol Section 9.5.1.5.3, the actual value and the change from baseline to each post-baseline time point will be summarized by time point using summary statistics. Qualitative parameters will be summarized by number and percentage of subjects, and changes from baseline to each post-baseline time point will be reported using shift tables. Percentages will be based on the number of subjects with both nonmissing baseline and relevant post-baseline results.

Laboratory parameters that are graded in CTCAE ver. 4.03 will be summarized by CTCAE grade at each time point and by highest post-baseline CTCAE grade, and changes from CTCAE grade at baseline to each post-baseline time point will be reported using shift tables.

Laboratory test results will be assigned a low/normal/high (LNH) classification according to whether the value is below (L), within (N), or above (H) the laboratory parameter's reference range. The result of LHN classification will be provided in a subject data listing.

For each item, spaghetti plots of individual laboratory values over time will be displayed.

CTCAE ver. 4.03 will be used to identify subjects with Treatment-emergent markedly abnormal laboratory value (TEMAV). TEMAV is defined as a value with post-baseline value of grade 2 or higher with a grade increase from baseline (i.e., Increasing grade 0 to 2 or higher, grade 1 to 2 or higher, grade 2 to 3 or higher, grade 3 to 4 or 5, grade 4 to 5). The number (percentage) of subjects with TEMAV (markedly abnormal high/low) at least one time will be summarized. When displaying the incidence of TEMAVs, each subject will be counted once in the laboratory parameter high and in the laboratory parameter low categories, as applicable.

5.6.4 Vital Signs

Summary statistics for vital signs parameters (diastolic and systolic blood pressure, pulse, respiration rate and temperature), weight and SpO_2 and changes from baseline will be presented by time point.

For each item, spaghetti plots of individual laboratory values over time will be displayed.

Subject data listings will be provided.

5.6.5 Electrocardiograms

The results of ECG assessments performed at each time point will be evaluated. Summary statistics for ECG parameters (Heart Rate, RR, PR, QRS, QT, QTcB and QTcF) and changes from baseline will be presented by time point.

Shift tables will present changes from baseline in ECG interpretation (categorized as normal; abnormal, not clinically significant; and abnormal, clinically significant) to each time point.

In addition, the number (percentage) of subjects who met below criteria at least once in QTcF:

Absolute QTcF interval prolongation:

- QTcF interval >450 ms
- QTcF interval >480 ms
- QTcF interval >500 ms

Change from baseline in QTcF interval:

- QTcF interval increases from baseline >30 ms
- QTcF interval increases from baseline >60 ms

Subject data listings will be provided.

5.6.6 Other Safety Analyses

ECOG-PS

ECOG-PS will be summarized by scale at each time point and by highest post-baseline scale. Spaghetti plots of individual laboratory values over time will be displayed.

Subject data listings will be provided.

Ophthalmologic examination

Summary statistics for ophthalmologic examination results (corrected visual acuity and thickness of corneal epithelium [right and left]) and changes from baseline will be presented by each time point.

Subject data listings will be provided.

Potential Hy's cases

A subject data listing for potential subjects who meet Hy's law criteria will be presented. Potential subjects meeting Hy's law criteria are those who meets following definition at same timepoint:

Elevated AST or ALT lab value that is greater than or equal to 3X the upper limit of normal

AND

Elevated total bilirubin lab value that is greater than or equal to 2X the upper limit of normal

AND

Alkaline phosphatase lab value that is less than 2X the upper limit of normal.

5.7 Other Analyses

Not applicable.

5.8 Exploratory Analyses

No exploratory analyses are planned for this study.

6 INTERIM ANALYSES

No formal interim analysis will be conducted in this study.

Interim evaluation for efficacy will be conducted in gastric cancer cohort of Part 2. If no patient having BOR of CR or PR is observed in 5 subjects evaluated, the cohort can stop further enrollment. Follow-up duration of the subject with SD will be discussed with sponsor.

These criteria are based on posterior probability of Bayesian statistics. Non-informative beta prior distribution Beta (1, 1) was used. Above criterion is corresponding the case where the probability of ORR $\geq$ 40% is less than 10%. If necessary, interim evaluation and termination of enrollment can be judged with other number of patients evaluated using same stop criterion as above. The threshold of ORR (40%) was set as a promising effect size considering the mechanism of action of this study drug.

7 CHANGES IN THE PLANNED ANALYSES

There are additions from protocol as below:

- The analysis for dose interruption and dose reduction were added.
- The analysis for TEAEs and treatment-related TEAEs with CTCAE grade 3 or above, DLTs, non-serious TEAEs, treatment-related serious TEAEs, and treatment-related TEAEs leading to death were added.

- An overview table of TEAEs was added.
- The analysis for all deaths was added.
- The analysis for TEMAV was added.
- Spaghetti plots of laboratory values, vital signs, and ECOG-PS were added.
- The analysis for corrected visual acuity was added

8 DEFINITIONS AND CONVENTIONS FOR DATA HANDLING

The data will be handled as follows. The sponsor will determine how to handle all data prior to data base lock.

8.1 General Data Handling

Baseline

Baseline is defined as the last non-missing value observed prior to the first dose of study drug for a given parameter.

Change from Baseline, Percent Change from Baseline

Change from baseline is defined as post-baseline value minus baseline value.
Percent change from baseline is defined as follows:

% Change from baseline = (Change from baseline/Baseline)*100%

For any Baseline value of 0, the subject's corresponding percent change from baseline will not be included in the summary statistics table.

Handling of Missing data

Refer "5.3.5 Handling of Missing Data, Dropouts, and Outliers".

Handling of multiple data

The analysis window for safety analysis is based on the visits recorded in CRF. In the calculation of descriptive statistics for safety parameters (e.g., laboratory values and vital signs, etc.) per scheduled visit, and change from baseline per visit, if multiple observations fall in the same scheduled visit, the first record will be used for summary tables. Other safety analyses (e.g., worst grade laboratory results) will include all observations until the date of 30 days following the last dose of study drug.

Treatment-emergent adverse event

A TEAE is defined as an AE that emerged during treatment, having been absent at pretreatment or

- Reemerged during treatment, having been present at pretreatment but stopped before treatment, or
- Worsened in severity during treatment relative to the pretreatment state, when the AE was continuous.

All the adverse events will be considered as TEAE if the AE onset date was on or after the first dose of study drug up to 30 days after last dose.

8.2 Pharmacokinetic Data Handling

8.2.1 Lower Limit of Quantification of E7090 in Plasma and Urine

The LLOQ of E7090 in plasma and urine is 1.00 ng/mL. (1 and 2 mg cohort)

The LLOQ of E7090 in plasma and urine is 0.250 ng/mL. (≥ 4 mg cohort)

The LLOQ of M2 in plasma is 0.500 ng/mL. (≥ 4 mg cohort) BLQ Handling for Calculation of PK Parameters

While calculating PK parameters in WinNonlin, BLQ values will be handled according to 302-104.01-MNL, for non-compartmental pharmacokinetic analysis. BLQ Handling for Developing Concentration-Time Profiles

When developing individual concentration-time profiles, BLQ values will be handled according to 302-104.01-MNL for non-compartmental pharmacokinetic analysis.

8.2.2 BLQ Handling for Developing Tables

When developing individual concentration-time profiles, BLQ values will be handled according to 302-104.01-MNL for non-compartmental pharmacokinetic analysis. Handling of Anomalous Concentration Values

The handling of anomalous concentration values will follow the guidance in the SWP for non-compartmental pharmacokinetic analysis (302-104.01-MNL). General Rules for Presentation of Drug Concentrations and PK Parameters

When presenting individual/raw (raw, hereafter) values and summary statistics, the following rule will be applied: for drug concentrations and concentration-dependent pharmacokinetic parameters, all summary statistics (mean, median, geometric mean, SD and coefficient variation (CV)) will have 3 significant digits. For t_{max} and $t_{ss,max}$, raw values are shown in fixed 2 decimal places and their median has fixed 2 decimal places.

Typical variable	Unit	N	Digit rule	Raw Minimum	Mean Median	SD	Geometric Mean	CV (%)

				Maximum				
E7090 concentration	ng/mL	X	Significant digits	3	3	3	-	-
Urine Volume	mL	X	Fixed decimal places	0	0	0	-	-
C_{max}, $C_{ss,max}$, $C_{ss,min}$, $C_{ss,av}$	ng/mL	X	Significant digits	3	3	3	3	3
t_{max}, $t_{ss,max}$ *	h	X	Fixed decimal places	2	2	-	-	-
λ_z	1/h	X	Significant digits	3	3	3	3	3
$t_{½}$, $t_{½,ss}$	h	X	Significant digits	3	3	3	3	3
$AUC_{(0-t)}$ $AUC_{(0-inf)}$ $AUC_{(0-24h)}$ $AUC_{(0-\tau)}$	ng•h/mL	X	Significant digits	3	3	3	3	3
$\%AUC_{ex}$	%	X	Significant digits	3	3	3	3	3
CL/F CL_R	L/h	X	Significant digits	3	3	3	3	3
V_z/F	L	X	Significant digits	3	3	3	3	3
R_{ac}, R_{ss}	-	X	Significant digits	3	3	3	3	3
PTF	%	X	Significant digits	3	3	3	3	3
MRT	h	X	Significant digits	3	3	3	3	3
$Ae_{(0-\tau)}$	mg	X	Significant digits	3	3	3	3	3
$Fe_{(0-\tau)}$	%	X	Significant digits	3	3	3	3	3
MP ratio	%	X	Significant digits	3	3	3	3	3

*: Mean, SD, geometric mean and CV will not be calculated for t_{max} and $t_{ss,max}$.
CV(%)= sqrt(exp[SD**2 of log transformed data]-1)*100

NOTE: The following parameters are reported in the CSR, but appear in Listings only. They are important information to confirm that individual $t_{½}$ is appropriately derived and allow those PK parameters to be reproduced when necessary.

a) Time points used for estimation of λ_z (lower and upper)
b) Number of the time points used for λ_z
c) Adjusted R^2 (R^2adj)

In Listings, a) are shown in same digits as actual sampling time after dosing used for calculation of PK parameters. For b), integer number is used in Listings. For c), significant digits (3) are used in Listings.

9 PROGRAMMING SPECIFICATIONS

The rules for programming derivations and dataset specifications are provided in separate documents.

10 STATISTICAL SOFTWARE

All statistical Analyses will be conducted by Eisai / Takumi Information Technology, using validated standard programs or double programming. For analyses needed in data review, single programming will be used.

All statistical analyses will be performed using SAS (version 9.2 or later), WinNonlin (Professional version 6.2.1 or newer), Pharsight Knowledgebase Server (version 4.02 or newer), Microsoft Excel (97 or newer) and S-PLUS (6.1J or newer for Windows). As necessary, other validated statistical software will also be used.

11 MOCK TABLES, LISTINGS, AND GRAPHS

The study TLG shells will be provided in a separate document, which will show the content and format of all tables, listings, and graphs in detail.

12 REFERENCES

Bartholomew, D. Isotonic inference. In: Samuel K, Norman LJ, editors. Encyclopedia of Statistical Science volume 4, New York: Wiley-Interscience. 1983;260-5.

Ji Y, Liu P, Li Y, Bekele BN. A modified toxicity probability interval method for dose-finding trials. Clin Trials. 2010;7:653-63.

Ji Y, Wang, S. Modified Toxicity Probability Interval Design: A Safer and More Reliable Method Than the3 + 3 Design for Practical Phase I Trials. J Clin Oncol. 2013;31:1785-91.

13 APPENDICES

13.1 National Institute for Health: Common Terminology Criteria for Adverse Events (CTCAE) Version 4.03

National Cancer Institute (NCI) Cancer therapy evaluation program Common Terminology Criteria for Adverse Events (CTCAE) version 4.0 May 2009 (v4.03 June 2010) is available online at:

http://evs.nci.nih.gov/ftp1/CTCAE/CTCAE_4.03_2010-06-14_QuickReference_5x7.pdf

CTCAE grades for selected laboratory parameters are listed in the table below, where ULN is the upper limit of normal and LLN is the lower limit of normal.

Lab Parameter	**NCI Common Terminology Criteria for Adverse Events (CTCAE) - SI Units**				
	Grade 1	**Grade 2**	**Grade 3**	**Grade 4**	**Grade 5**
Hematology					
Hemoglobin (low)	100 - <LLN (g/L)	80 - <100 (g/L)	<80 (g/L)	__	Death
Hemoglobin (high)	Increase in >0 - 20 g/L above ULN (i.e., Increase in >0 - 2 gm/dL above ULN) or above baseline if baseline is above ULN	Increase in >20 - 40 g/L above ULN (i.e., Increase in >2 - 4 gm/dL above ULN) or above baseline if baseline is above ULN	Increase in >40 g/L above ULN (i.e., Increase in >4 gm/dL above ULN) or above baseline if baseline is above ULN	__	__
Platelet Count (PLT) (low)	75 - <LLN (x 10^9/L)	50 - <75 (x 10^9/L)	25 - <50 (x 10^9/L)	<25 (x 10^9/L)	__
White Blood Cell Count (WBC) (low)	3 - <LLN (x 10^9/L)	2 - <3 (x 10^9/L)	1 - <2 (x 10^9/L)	<1 (x 10^9/L)	__
White Blood Cell Count (WBC) (high)	__	__	>100 x 10^9/L (i.e., >100,000/mm^3)	__	Death
Lymphocytes (low)	0.8 - <LLN (x 10^9/L)	0.5 - <0.8 (x 10^9/L)	0.2 - <0.5 (x 10^9/L)	<0.2 (x 10^9/L)	__
Lymphocytes (high)	__	>4 - 20 (x 10^9/L) (i.e., >4,000 - 20,000/mm^3)	>20 (x 10^9/L) (i.e., > 20,000/mm^3)	__	__
Neutrophils (low)	1.5 - <LLN (x 10^9/L)	1 - <1.5 (x 10^9/L)	0.5 - <1 (x 10^9/L)	<0.5 (x 10^9/L)	__

Lab Parameter	NCI Common Terminology Criteria for Adverse Events (CTCAE) - SI Units				
	Grade 1	**Grade 2**	**Grade 3**	**Grade 4**	**Grade 5**
Blood Coagulation					
INR (high)	>1 - 1.5 x ULN	>1.5 - 2.5 x ULN	>2.5 x ULN	__	__
Activated partial thromboplastin time prolonged (high)	>1 - 1.5 x ULN	>1.5 - 2.5 x ULN	>2.5 x ULN	__	__
Blood Chemistry					
Albumin (low)	30 - <LLN (g/L)	20 - <30 (g/L)	<20 (g/L)	__	Death
Alkaline Phosphatase (ALP) (high)	>ULN - 2.5 x ULN	>2.5 - 5.0 x ULN	>5.0 - 20.0 x ULN	>20.0 x ULN	__
ALT (SGPT) (high)	>ULN - 3 x ULN	>3 - 5.0 x ULN	>5.0 - 20.0 x ULN	>20.0 x ULN	__
AST (SGOT) (high)	>ULN - 3 x ULN	>3 - 5.0 x ULN	>5.0 - 20.0 x ULN	>20.0 x ULN	__
Total Bilirubin (high)	>ULN – 1.5 x ULN	>1.5 – 3.0 x ULN	>3.0 – 10.0 x ULN	>10.0 x ULN	__
Calcium, serum-low (hypocalcemia)	2.0 - <LLN (mmol/L) (i.e., 8.0 mg/dL - <LLN) *	1.75 - <2 (mmol/L) (i.e., 7.0 - <8.0 mg/dL) *	1.5 - <1.75 (mmol/L) (i.e., 6.0 - <7.0 mg/dL) *	<1.5 (mmol/L) (i.e., <6.0 mg/dL) *	Death
Calcium, serum-high (hypercalcemia)	>ULN – 2.9 (mmol/L) (i.e., >ULN – 11.5 mg/dL) *	>2.9 – 3.1 (mmol/L) (i.e., >11.5 – 12.5 mg/dL) *	>3.1 – 3.4 (mmol/L) (i.e., >12.5 – 13.5 mg/dL) *	>3.4 (mmol/L) (i.e., >13.5 mg/dL) *	Death
Cholesterol (high)	>ULN -7.75 mmol/L	>7.75 -10.34 mmol/L	>10.34 -12.92 mmol/L	>12.92 mmol/L	__
CPK (high)	>ULN – 2.5 x ULN	>2.5 x ULN – 5 x ULN	>5 x ULN – 10 x ULN	>10 x ULN	__
Creatinine (high)	>1 – 1.5 x baseline; >ULN – 1.5 x ULN	>1.5 – 3.0 x baseline; >1.5 – 3.0 x ULN	>3.0 x baseline; >3.0 – 6.0 x ULN	>6.0 x ULN	__
GGT (gamma-glutamyltransferase) (high)	>ULN – 2.5 x ULN	>2.5 x ULN – 5.0 x ULN	>5.0 x ULN – 20.0 x ULN	>20.0 x ULN	__

Lab Parameter	NCI Common Terminology Criteria for Adverse Events (CTCAE) - SI Units				
	Grade 1	**Grade 2**	**Grade 3**	**Grade 4**	**Grade 5**
Glucose, serum-low (hypoglycemia)	3 - <LLN (mmol/L)	2.2 - <3 (mmol/L)	1.7 - <2.2 (mmol/L)	<1.7 (mmol/L)	Death
Glucose, serum-high (hyperglycemia)	ULN – 8.9 (mmol/L)	>8.9 – 13.9 (mmol/L)	>13.9 – 27.8 (mmol/L)	>27.8 (mmol/L)	Death
Lipase (high)	>ULN – 1.5 x ULN	>1.5 – 2.0 x ULN	>2.0 – 5.0 x ULN	>5.0 x ULN	__
Magnesium (low)	<LLN – 0.5 (mmol/L)	<0.5 – 0.4 (mmol/L)	<0.4 – 0.3 (mmol/L)	<0.3 (mmol/L)	Death
Magnesium (high)	>ULN – 1.23 (mmol/L)	__	>1.23 – 3.30 (mmol/L)	>3.30 (mmol/L)	Death
Triglyceride (hypertriglyceridemia) (high)	1.71 – 3.42 (mmol/L)	>3.42 – 5.7 (mmol/L)	>5.7 – 11.4 (mmol/L)	>11.4 (mmol/L)	Death
Phosphate, serum-low (hypophosphatemia)	0.8 - <LLN (mmol/L)	0.6 - <0.8 (mmol/L)	0.3 - <0.6 (mmol/L)	<0.3 (mmol/L)	Death
Potassium, serum-low (hypokalemia)	3.0 - <LLN (mmol/L)	__	2.5 - <3.0 (mmol/L)	<2.5 (mmol/L)	Death
Potassium, serum-high (hyperkalemia)	>ULN – 5.5 (mmol/L)	>5.5 – 6.0 (mmol/L)	>6.0 – 7.0 (mmol/L)	>7.0 (mmol/L)	Death
Uric Acid (hyperuricemia) (high)	>ULN – 590 (umol/L)	__	__	>590 (umol/L)	__
Sodium, serum-low (hyponatremia)	130 - <LLN (mmol/L)	__	120 - <130 (mmol/L)	<120 (mmol/L)	Death
Sodium, serum-high (hypernatremia)	>ULN - 150 (mmol/L)	>150 - 155 (mmol/L)	>155 - 160 (mmol/L)	>160 (mmol/L)	Death
Urinalysis					

Lab Parameter	NCI Common Terminology Criteria for Adverse Events (CTCAE) - SI Units				
	Grade 1	**Grade 2**	**Grade 3**	**Grade 4**	**Grade 5**
Proteinuria (high)	1+ proteinuria; urinary protein <1.0 g/24 hrs	>1+ proteinuria; urinary protein 1.0 - 3.4 g/24 hrs	urinary protein >=3.5 g/24 hrs	__	__

* Corrected serum calcium by albumin should be referred. If serum albumin is <4.0 g/dL, the corrected calcium will be calculated using the following formula: Corrected calcium (mg/dL) = Total calcium (mg/dL) – 0.8 x [Albumin (g/dL) – 4]

13.2 Blood Sampling Schedule for Pharmacokinetic Assessments in Part 1.

Cycle	Day	Protocol version1 to 3 timepoint	Protocol version 4 or later Timepoint
Cycle 0	Day 1	Predose	Predose
		30 minutes postdose	30 minutes postdose
		1 hour postdose	1 hour postdose
		2 hour postdose	2 hour postdose
		3 hour postdose	3 hour postdose
		5 hour postdose	5 hour postdose
		10 hour postdose	10 hour postdose
	Day 2	24 hour postdose	24 hour postdose
	Day 3	48 hour postdose	48 hour postdose
	Day 4	72 hour postdose	72 hour postdose
Cycle 1	Day 1	Predose [a)]	Predose [a)]
	Day 3	Predose [a)]	Predose [a)]
	Day 8	Predose [a)]	Predose [a)]
			30 minutes postdose
			1 hour postdose
			2 hour postdose
			3 hour postdose
			5 hour postdose
			10 hour postdose
	Day 9	—	Predose [a)]
	Day 15	Predose [a)]	Predose [a)]
	Day 22	Predose [a)]	Predose [a)]
Cycle 2	Day 1	Predose [a)]	Predose [a)]
		30 minutes postdose	—
		1 hour postdose	—
		2 hour postdose	—
		3 hour postdose	—
		5 hour postdose	—
		10 hour postdose	—
	Day 2	Predose	—
Cycle 3 or onward	Day 1	Predose	Predose

a) timepoints for a plot of trough plasma concentrations

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