# STATISTICAL ANALYSIS PLAN

Inno-GO-03

Open-Label, Multicenter Study of D07001-Softgel Capsules (Oral Gemcitabine Hydrochloride) in Subjects with Unresectable, Metastatic or Locally Advanced Gastrointestinal Cancer in Dose-Escalation Phase and in Subjects with Advanced Biliary Tract Cancer Following Primary Chemotherapy or Combined Chemoradiotherapy in Dose-Expansion Phase

**Version: Final 1.0**

**Date: 21/Jan/2019**

## REVISION HISTORY

| Version | Version Date | Author | Summary of Changes Made |
|---|---|---|---|
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# SIGNATURE PAGE – INNOPHARMAX INC.

## Declaration

The undersigned has/have reviewed and agree to the statistical analyses and procedures of this clinical study, as presented in this document.

| | |
|---|---|
| **Kelly Lin** | **Date (DD Mmm YY)** |
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## SIGNATURE PAGE – (CRO)

**Declaration**

The undersigned agree to the statistical analyses and procedures of this clinical study.

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# ABBREVIATION AND ACRONYM LIST

| Abbreviation / Acronym | Definition / Expansion |
|---|---|
| AE | Adverse event |
| ALT | Alanine transaminase |
| ALP | Alkaline phosphatase |
| ANC | Absolute neutrophil count |
| aPTT | Activated partial thromboplastin time |
| AST | Aspartate transaminase |
| ATC | Anatomical therapeutic chemical |
| AUC | Area under the concentration-time curve |
| $\%AUC_{extrapolated}$ | Percentage area under the plasma concentration-time curve extrapolated |
| $AUC_{(0\text{-}inf)}$ | AUC from time zero extrapolated to infinity |
| $AUC_{last}$ | AUC from time zero to the last quantifiable concentration |
| BOR | Best Overall Response |
| BLQ | Below the lower limit of quantification |
| BMI | Body Mass Index |
| Bpm | Beats per minute |
| BTC | Biliary tract cancer |
| BUN | Blood urea nitrogen |
| CA | Cancer antigen |
| CCRT | Combined chemoradiotherapy |
| CEA | Carcinoembryonic antigen |
| CI | Confidence interval |
| CL/F | Apparent clearance |
| CSP | Clinical Study Protocol |
| $C_{max}$ | Maximum observed concentration |
| $C_{min}$ | Minimum observed concentration in the dosing interval |
| $C_{trough}$ | Trough concentration |
| CR | Complete response |
| CS | Clinically significant |
| CSR | Clinical Study Report |

| Abbreviation / Acronym | Definition / Expansion |
|---|---|
| CTCAE | Common Terminology Criteria for Adverse Events |
| CV | Coefficient of variation |
| dFdC | Gemcitabine |
| dFdU | Difluorodeoxyuridine |
| DLT | Dose-limiting toxicity |
| DBP | Diastolic blood pressure |
| ECG | Electrocardiogram |
| ECOG | Eastern Cooperative Oncology Group |
| ENS | Enrolled set |
| EOT | End of treatment |
| gCV | geometric coefficient of variation |
| $\gamma$-GT | $\gamma$-glutamyl transpeptidase |
| GI | Gastrointestinal |
| HR | Heart rate |
| IMP | Investigational Medicinal Product |
| IV | Intravenous |
| IVRS | Interactive voice response system |
| LDH | Lactate dehydrogenase |
| LLOQ | Lower limit of quantification |
| MCH | Mean corpuscular hemoglobin |
| MCHC | Mean corpuscular hemoglobin concentration |
| MCV | Mean corpuscular volume |
| MedDRA | Medical Dictionary for Regulatory Activities |
| mITT | Modified Intent-to-Treat |
| MTD | Maximum tolerated dose |
| MUGA | Multigated acquisition |
| NCS | Not clinically significant |
| NK | Not known |
| ORR | Objective response rate |
| OS | Overall survival |
| PD | Progressive disease |
| PFS | Progression-free survival |

| Abbreviation / Acronym | Definition / Expansion |
|---|---|
| PK | Pharmacokinetic |
| PKS | Pharmacokinetic analysis set |
| PP | Per-Protocol |
| PR | Partial response |
| PS | Performance status |
| RBC | Red blood cell |
| RDI | Relative dose intensity |
| RECIST | Response Evaluation Criteria in Solid Tumors |
| SAE | Serious adverse event |
| SAF | Safety Analysis Set |
| SAP | Statistical Analysis Plan |
| SBP | Systolic blood pressure |
| SD | Standard deviation/ Stable disease |
| SE | Standard error of the mean |
| SOC | System Organ Class |
| $t_{½}$ | Apparent terminal elimination half-life |
| $t_{last}$ | Time of last quantifiable concentration |
| TEAE | Treatment-emergent adverse event |
| $t_{max}$ | Time corresponding to occurrence of $C_{max}$ |
| TTP | Time-to-progression |
| ULN | Upper limit of normal |
| VAS | Visual analogue scale |
| $V_z/F$ | Apparent volume of distribution |
| WBC | White blood cell |
| WHO-DD | World Health Organization - Drug Dictionary |
| $\lambda_z$ | Terminal elimination rate constant |

# STATISTICAL ANALYSIS PLAN

The Statistical Analysis Plan (SAP) details the statistical methodology to be used in analyzing study data and outlines the statistical programming specifications for the Tables, Listings and Figures (TLFs). It describes the variables and populations, anticipated data transformations and manipulations and other details of the analyses not provided in the Clinical Study Protocol (CSP).

The analyses described are based on the final CSP Version 4.0, dated 03 January 2018 The SAP will be finalized prior to database lock and describes the statistical analysis as it is foreseen when the study is being planned. If circumstances should arise during the study rendering this analysis inappropriate, or if improved methods of analysis should arise, updates to the analyses may be made. If after data base lock there are important changes in the data analysis relative to what is described in the final SAP, those new analysis methods and the reasons for such new analysis will be described in a separate SAP Addendum.

## 1. STUDY OBJECTIVES

This open-label, multicenter Phase 1b/2 study will be conducted in 2 parts: a dose-escalation phase (Part 1) and a dose-expansion phase (Part 2).

### 1.1 Primary Objectives

Part 1: Dose-Escalation Phase (Phase 1b)

- To assess the safety and tolerability of increasing doses of D07001-softgel in patients with unresectable locally advanced or metastatic gastrointestinal (GI) cancer

Part 2: Dose-Expansion Phase (Phase 2)

- To assess the safety and tolerability of D07001-softgel in patients who have achieved stable disease or better following first-line chemotherapy or combined chemoradiotherapy (CCRT) for unresectable metastatic or locally advanced biliary tract cancer (BTC)

### 1.2 Secondary Objectives

Part 1: Dose-Escalation Phase (Phase 1b)

- To evaluate the pharmacokinetic (PK) profile of D07001-softgel

Part 2: Dose-Expansion Phase (Phase 2)

- To assess the PK profile of D07001-softgel, including the effect of food

### 1.3 Exploratory Objectives

Part 1: Dose-Escalation Phase (Phase 1b)

- To evaluate the preliminary data on the efficacy of increasing doses of D07001-softgel
- To investigate the effect of increasing doses of D07001-softgel on additional parameters such as tumor markers
- To investigate the relationship between the efficacy, safety, and PK of D07001-softgel and pharmacogenomic, pharmacoproteomic, and cellular markers, including the levels of immune cells, circulating endothelial progenitor cells and circulating tumor cells

Part 2: Dose-Expansion Phase (Phase 2)

- To evaluate the efficacy of D07001-softgel, as assessed by progression-free survival (PFS), overall survival (OS), time to progression (TTP), and objective response rate (ORR; in patients with measurable disease at baseline only), in patients who have achieved stable disease or better following first-line chemotherapy or CCRT for unresectable metastatic or locally advanced BTC
- To investigate the effect of D07001-softgel on tumor markers
- To investigate the relationship between the efficacy, safety, and PK of D07001-softgel and pharmacogenomic, pharmacoproteomic, and cellular markers, including the levels of immune cells, circulating endothelial progenitor cells and circulating tumor cells

## 2. STUDY DESIGN

This open label, multicenter study will be conducted in 2 parts: a dose escalation phase (Part 1) and a dose expansion phase (Part 2).

In both Part 1 and Part 2, eligible patients will be assigned to receive oral D07001-softgel on Days 1, 3, 5, 8, 10, 12, 15, 17, and 19 of a 21 day cycle (9 doses per cycle). There will be no gap between the cycles, e.g., the

second cycle will commence immediately on the next day after Day 21 of the first cycle (Day 22 overall). Dosing on 2 consecutive days will not be allowed; there will be at least 1 day between 2 doses.

**Part 1: Dose Escalation Phase (Phase 1b)**

Part 1 of the study will follow a 3+3 dose escalation scheme at predefined dose levels. There will be sequential cohorts of 3 to 6 patients each with increasing doses of 40 mg, 60 mg, 80 mg, 120 mg, and 160 mg per cohort. There will be no intra patient dose escalation. Cycle 1 (21 days) is defined as the dose limiting toxicity (DLT) assessment period.

Each cohort will enroll 3 patients. If none of the 3 patients in the cohort experiences a DLT, the study may proceed with dose escalation to the next cohort. If 1 out of 3 patients experience a DLT, 3 additional patients will be entered into that cohort for a total of 6 patients. If none of the 3 additional patients in that cohort experiences a DLT, then the next ascending dose cohort may proceed. Dose escalation to a subsequent cohort will only proceed after assessment of safety and tolerability data (and raw PK data, if available) of the preceding cohort at a review meeting of the Safety Board. If ≥2 patients in a 3-6 patient cohort experience a DLT during Cycle 1, the maximum tolerated dose (MTD) is considered to have been exceeded and no additional patients will be treated at the current or higher doses. In this case, the Safety Board may decide to evaluate an intermediate dose level 20 mg lower than the dose level at which ≥2 patients in a cohort experienced a DLT. If an MTD is not identified following dose escalation to 160 mg, the intermediate dose level of 140 mg may also be evaluated. If an intermediate dose level is evaluated, up to 6 additional patients will be enrolled at that dose level.

Patients in Part 1 will continue treatment until withdrawal due to a DLT (Cycle 1 only), disease progression according to Response Evaluation Criteria in Solid Tumors version 1.1 (RECIST v1.1), withdrawn consent, or when another treatment discontinuation criterion is met.

PK samples will be obtained during Cycle 1. For Cycle 1 Day 1 and Day 15 visits, overnight fasting, except for water and medications are required.

Preliminary efficacy data will be obtained in Part 1. Tumor assessments by RECIST v1.1 will be conducted every 6 weeks relative to the first dose of study medication for all patients until disease progression, death, or withdrawal of consent. Disease progression will be based on the Investigator's evaluation of tumor assessments. Patients who are discontinued from study drug for a reason other than disease progression, death, or withdrawal of consent are to continue tumor assessments on the same schedule.

**Part 2: Dose Expansion Phase (Phase 2)**

The highest dose level of D07001-softgel tested at which <2 of 6 patients experience a DLT will be expanded in Part 2 of the study. In addition, because the highest dose level selected in Part 1 could lead to cumulative toxicity during treatment, the next lowest dose level below the highest evaluated in Part 1 at which <2 of 6 patients experienced a DLT will also be expanded for assessment in Part 2. If an MTD is not identified in Part 1 of the study, the 2 dose levels used in Part 2 will be 160 mg and 120 mg, or 160 mg and 140 mg if the intermediate dose of 140 mg has been evaluated in Part 1.

In Part 2 of the study, eligible patients will be randomized in a 1:1 ratio to receive D07001-softgel in an open label manner at 1 of the 2 dose levels selected for expansion. 20 patients will be enrolled to each dose expansion cohort. Patients will be treated until withdrawal from treatment due to disease progression according to RECIST v1.1, withdrawn consent, or when another treatment discontinuation criterion is met. Patients who are discontinued from study drug for reasons other than disease progression or toxicity in the first 2 cycles of Part 2 will be replaced.

As for Part 1, tumor assessments by RECIST v1.1 in Part 2 will be conducted every 6 weeks relative to the first dose of study medication for all patients until disease progression, death, or withdrawal of consent. Disease progression will be based on the Investigator's evaluation of tumor assessments. Patients who are discontinued from study drug for a reason other than disease progression, death, or withdrawal of consent are to continue tumor assessments on the same schedule.

PK samples will be obtained during Cycle 1. For Cycle 1 Day 1 visit, overnight fasting, except for water and medications are required. In addition, for all patients in the higher dose expansion cohort only, the PK of D07001-softgel will be evaluated after a high-fat breakfast or after overnight fasting. Patients will receive D07001-softgel on Cycle 1 Day 15 and Cycle 2 Day 1 in a high-fat fed or a fasting state. Patients will be randomized to the fed/fasted states in 1 of 2 sequences (Sequence 1: Cycle 1 Day 15 high fat, Cycle 2 Day 1 fasting; Sequence 2: Cycle 1 Day 15 fasting, Cycle 2 Day 1 high fat) with 10 patients per sequence in a cross over design (20 patients overall). PK samples will be taken over a period of 48 hours post-dose for the food effect evaluation in this dose expansion cohort.

Safety, tolerability, efficacy, and PK data will be compared between the 2 dose expansion cohorts to support selection of a recommended D07001-softgel dose for further clinical development as chemotherapy following primary chemotherapy or CCRT for unresectable metastatic or locally advanced BTC.

Patients in Part 1 and Part 2 who are continuing to derive clinical benefit from study drug at the time of study closure, as assessed by the Investigator, will be provided access to the study drug via a mechanism to be determined by the Sponsor.

Event Schedules for Part 1 and Part 2 are outlined in Table 5 and Table 6.

# 3. STUDY POPULATION

Part 1 of the study will identify dose-limiting toxicity (DLT) and establish the maximum tolerated dose (MTD), if any, of D07001-softgel in patients with unresectable locally advanced or metastatic GI cancer. There will be sequential cohorts of 3 to 6 patients each with increasing doses of 40 mg, 60 mg, 80 mg, 120 mg, and 160 mg per cohort. If an MTD is not identified following dose escalation to 160 mg, the intermediate dose level of 140 mg may also be evaluated.

In Part 2, 40 patients who have achieved stable disease or better following first-line chemotherapy or CCRT for unresectable metastatic or locally advanced BTC will be enrolled to receive D07001-softgel at the 2 dose levels selected in Part 1 (20 patients at each dose level). No more than 30% of patients enrolled in Part 2 will have received CCRT.

Detailed lists of inclusion and exclusion criteria are shown in Sections 4.1 and 4.2 of the CSP.

# 4. STATISTICAL BASIS FOR SAMPLE SIZE

No formal sample size calculations have been performed.

In Part 1 of the study, 3 to 6 patients will be enrolled to each of the predefined dose cohorts. If an intermediate dose level (140 mg) is to be investigated, another 3 to 6 patients will be enrolled to that cohort.

In Part 2, 40 patients will be enrolled to receive D07001-softgel at the 2 dose levels selected in Part 1.

# 5. RANDOMIZATION

No randomization will be performed in Part 1 of the study.

In Part 2, enrolled patients will be randomized in a 1:1 ratio to one of the 2 dose levels selected for expansion using a computer-generated block randomization scheme with stratification based on whether or not the patient received CCRT as first-line treatment. No more than 30% of patients enrolled in Part 2 will have received prior CCRT. In addition, patients randomized to the higher dose-expansion cohort in Part 2 will be randomized in a 1:1 ratio to 1 of the 2 sequences for the food-effect evaluation using a computer-generated block randomization

scheme. Computer-generated randomization will be performed centrally through an interactive voice response system (IVRS) service provider. The IVRS service provider will hold the randomization code throughout the conduct of the study.

# 6. STATISTICAL ANALYSIS CONVENTIONS

## 6.1 Analysis Variables

### 6.1.1 Demographic and Background Variables

The following demographic and anthropometric information will be recorded:

- Date of informed consent
- Inclusion/Exclusion criteria
- Medical history (including previous and current medical conditions and medications)
- Drug abuse and alcohol history
- Age
- Sex
- Ethnic
- Race
- Height (cm)
- Body weight (kg)
- Body mass index (BMI) calculated as [weight/height$^2$] (kg/m$^2$)
- Diagnosis

All medical history will be coded using Version **20.0 or higher** of the Medical Dictionary for Regulatory Activities (MedDRA).

### 6.1.2 Safety Variables

Safety will be assessed based on DLTs, adverse events (AEs), physical examination, vital signs, weight, BMI, Eastern Cooperative Oncology Group (ECOG) performance status (PS), electrocardiogram (ECG), and laboratory assessments (hematology, serum chemistry, coagulation parameters and urinalysis).

#### *6.1.2.1 Adverse Events*

An AE is any new, undesirable medical occurrence or change (worsening) of an existing condition in a subject that occurs from date of informed consent to 30-day follow up visit, whether or not considered to be product related. Therefore, AEs are treatment-emergent signs or symptoms. Elective hospitalizations for pre-treatment conditions (e.g., elective cosmetic procedures) and hospitalization to facilitate study assessments are not AEs. Abnormal laboratory values that are considered clinically significant should be reported as AEs. Disease progression as measured by tumor assessment should not be reported as an AE. Concomitant illness, which existed before entry into the study, will not be considered AEs unless they worsen during the treatment or safety follow-up period. Pre-existing conditions will be recorded on the CRF as medical history.

All AEs will be coded using the Version 20.0 or higher of the Medical Dictionary for Regulatory Activities (MedDRA).

Regarding DLT definition, in Part 1 of the study, any of the following AEs occurring during Cycle 1 will be classified as DLTs, if there is a reasonable possibility that it is related to the study drug:

- Hematologic:
    - Grade 4 neutropenia lasting >7 days
    - Febrile neutropenia (defined as neutropenia Grade ≥3 and a body temperature ≥38.3˚C)
    - Grade ≥3 neutropenic infection
    - Grade 4 anemia
    - Grade ≥3 thrombocytopenia with bleeding
    - Grade 4 thrombocytopenia
        - any platelet count <10,000/μL
        - platelet count 10,000-25,000/μL for >5 days

- Non-hematologic:
    - Grade ≥3 toxicities that are considered clinically significant, except those that have not been maximally treated (e.g., nausea, vomiting, diarrhea*) or can be easily treated (e.g., electrolyte abnormalities).

      [*Nausea, vomiting, and diarrhea: if Grade ≥3 toxicities persist for more than 48 h despite maximum treatment (loperamide, ondansetron, etc.), they will be considered DLTs]
- Delay by more than 7 days in receiving the next scheduled cycle due to persisting toxicities attributable to study drug.
- Failure to deliver at least 6 of the planned 9 doses during Cycle 1 due to treatment-related toxicities.
- Upon the second occurrence of a toxicity leading to a dose hold.

Any AEs with incomplete start and end dates/times will be shown in listing as follows:

- AEs with unknown start and/or end times (but where the date is known) will be shown as DDMMYYYY
- AEs with unknown start and/or dates will be shown as Unknown

Any AEs with incomplete start and end dates/times will be imputed as follows:

- Missing day and month
    - If the year of the incomplete start date is the same as the year of the date of the first dose of investigational product, then the day and month of the date of the first dose of investigational product will be assigned to the missing fields
    - If the year of the incomplete start date is before the year of the date of the first dose of investigational product, then December 31 will be assigned to the missing fields
    - If the year of the incomplete start date is after the year of the date of the first dose of investigational product, then 01 January will be assigned to the missing fields.
- Missing month only
    - The day will be treated as missing and both month and day will be replaced according to the above procedure.

- Missing day only
    - If the month and year of the incomplete start date are the same as the month and year of the date of the first dose of investigational product, then the day of the date of the first dose of investigational product will be assigned to the missing day
    - If either the year is before the year of the date of the first dose of investigational product or if both years are the same but the month is before the month of the date of the first dose of investigational product, then the last day of the month will be assigned to the missing day
    - If either the year is after the year of the date of the first dose of investigational product or if both years are the same but the month is after the month of the date of the first dose of investigational product, then the first day of the month will be assigned to the missing day.
- If the stop date is complete and the imputed start date is after the stop date, then the start date will be imputed using the stop date.

Adverse events will be regarded as Treatment Emergent Adverse Event (TEAE) if they started on or after the date and time of administration of the first dose of study drug, or if they were presented prior to the administration of the first dose of study drug and increased in severity during the study. Therefore, TEAE summaries will include all TEAEs starting on or after the day of the first intake of study treatment and starting no later than 30 days after the last study treatment date.

#### *6.1.2.2 Clinical Laboratory Tests*

Safety laboratory assessments in Part 1 and Part 2 will be assessed at screening; Day 1, Day 8, and Day 15 of cycles 1 and 2; Day 1 of cycle 3 onwards; EOT; and at the 30-day follow up visit. The following safety laboratory parameters will be measured:

- Hematology**:** RBCs, Hematocrit, Hemoglobin, MCH, MCHC, MCV, Platelets, WBCs (with differential), Neutrophils, Lymphocytes, Monocytes, Basophils, Eosinophils, ANC
- Serum chemistry: Albumin, Glucose, BUN, Bicarbonate, Creatinine, Total protein, Uric acid, Magnesium, Phosphorus, ALP, ALT, AST, Total bilirubin (direct and indirect), LDH, γ-GT, Electrolytes (sodium, potassium, chloride, calcium)
- Coagulation parameters: Prothrombin time, aPTT, Fibrinogen, D-dimer, INR
- Urinalysis: Bilirubin, Blood, Glucose, Ketones, Leukocytes, Epithelial cells, Casts, Crystals, Bacteria, Nitrite, pH, Protein, Specific gravity

Abbreviations: ALP=alkaline phosphatase; ALT=alanine aminotransferase; ANC=absolute neutrophil count; aPTT= activated partial thromboplastin time; AST=aspartate aminotransferase; ANC=absolute neutrophil count; BUN=blood urea nitrogen; γ-GT=γ-glutamyl transpeptidase; INR=international normalized ratio; LDH=lactate dehydrogenase; MCH=mean corpuscular hemoglobin; MCHC= mean corpuscular hemoglobin concentration; MCV=mean corpuscular volume; RBC=red blood cell; WBC=white blood cell.

#### *6.1.2.3 Vital Signs*

Vital signs assessments in Part 1 and Part 2 will be assessed at screening; Day 1, Day 8, and Day 15 of cycles 1 and 2; Day 1 of cycle 3 onwards; EOT; and at the 30-day follow up visit. The following vital signs measurements will be obtained:

- Sitting Systolic blood pressure (SBP) [mmHg]
- Sitting Diastolic blood pressure (DBP) [mmHg]
- Pulse rate (beats per minute [bpm])
- Respiratory rate (breaths per minute [brpm])
- Body temperature (oral) [℃]

#### *6.1.2.4 Electrocardiogram*

ECG assessments in Part 1 and Part 2 will be assessed at screening; Day 1, Day 8, and Day 15 of cycle 1; Day 1 of cycle 2; Day 1 of cycle 3 onwards; EOT; and at the 30-day follow up visit. The following 12-lead resting ECG parameters will be recorded:

- RR-interval (msec)
- PR-interval (msec)
- QRS-duration (msec)
- QT-interval (msec)
- QT-interval corrected (QTc) (msec)
- Heart rate (HR) (beats per minute [bpm])

The ECG will be evaluated by the Investigator as ‘Normal’, ‘Abnormal, NCS’ or ‘Abnormal, CS’.

#### *6.1.2.5 Echocardiogram/MUGA*

Echocardiogram/MUGA in Part 1 and Part 2 will be assessed at screening; Day1 of Cycles 3 and 5. The assessment will be evaluated by the Investigator as 'Normal', 'Abnormal, NCS' or 'Abnormal, CS'.

#### *6.1.2.6 Physical Examination*

A physical examination for Part 1 and Part 2 will be performed at screening; Day 1, Day 8, and Day 15 of cycles 1 and 2; Day 1 of cycle 3 onwards; EOT; and at the 30-day follow up visit.

The Physical Examination will be evaluated by the Investigator as 'Normal', 'Abnormal, NCS' or 'Abnormal, CS'.

All clinically significant treatment-emergent findings that were not present at baseline or described in the past medical history will be recorded as AEs.

#### *6.1.2.7 Pregnancy*

Serum pregnancy tests will be conducted at Screening and on Cycle 1 Day 1. Urine pregnancy tests will be conducted on Day 1 of all subsequent cycles, at the EOT visit, and at the 30-day safety follow-up visit.

#### *6.1.2.8 Prior and Concomitant Medication*

Prior and Concomitant medication will be coded using the World Health Organization-Drug Dictionary (WHO-DD) (Version **March 2017 or higher**) and will be classified by Anatomical Therapeutic Chemical (ATC) categories.

If the stop date is missing, ongoing or after the date and time of administration of the first dose of study drug, the medication will be considered as Concomitant medication. If the stop date is before the date and time of administration of the first dose of study drug, the medication will be considered as Prior medication.

### 6.1.3 Pharmacokinetic Variables

The following PK parameters will be determined for gemcitabine (dFdC) and dFdU in plasma:

**Table 1 Pharmacokinetic Parameters For Part 1 Dose Escalation Phase - Cycle 1, Days 1, 2, 3, 8, 15, 16 and 17**

| Parameter | Definition |
|---|---|
| $C_{max}$ | Maximum observed concentration |
| $t_{max}$ | Time corresponding to occurrence of $C_{max}$ |
| $t_{½}$ | Apparent terminal elimination half life |
| $AUC_{(0-t)}$ | AUC from time zero to the last quantifiable concentration |
| $AUC_{(0-24)}$ | AUC from time zero to 24 hours post-dose |
| $AUC_{(0-48)}$ | AUC from time zero to 48 hours post-dose |
| $AUC_{(0-inf)}$ | AUC from time zero extrapolated to infinity |
| %AUCex | Percentage of $AUC_{(0-inf)}$ obtained by extrapolation |
| CL/F* | Apparent clearance following oral administration |
| $V_z$/F* | Apparent volume of distribution during terminal phase |
| $C_{trough}$ | Pre-dose concentration** |
| Rac($AUC_{(0-t)}$) | Accumulation Ratio, calculated as (Day 15 $AUC_{(0-t)}$ / Day 1 $AUC_{(0-t)}$) |
| Rac($AUC_{(0-24)}$) | Accumulation Ratio, calculated as (Day 15 $AUC_{(0-24)}$ / Day 1 $AUC_{(0-24)}$) |
| Rac($AUC_{(0-48)}$) | Accumulation Ratio, calculated as (Day 15 $AUC_{(0-48)}$ / Day 1 $AUC_{(0-48)}$) |
| Rac($AUC_{(0-inf)}$) | Accumulation Ratio, calculated as (Day 15 $AUC_{(0-inf)}$ / Day 1 $AUC_{(0-inf)}$) |
| Rac($C_{max}$) | Accumulation Ratio, calculated as (Day 15 $C_{max}$ / Day 1 $C_{max}$) |
| $MR(AUC_{(0-t)})_1$ | Metabolic Ratio for ($AUC_{(0-t)}$), calculated as Day 1 dFdC ($AUC_{(0-t)}$) / Day 1 dFdU ($AUC_{(0-t)}$) |
| $MR(AUC_{(0-24)})_1$ | Metabolic Ratio for ($AUC_{(0-24)}$), calculated as Day 1 dFdC ($AUC_{(0-24)}$) / Day 1 dFdU ($AUC_{(0-24)}$) |
| $MR(AUC_{(0-48)})_1$ | Metabolic Ratio for ($AUC_{(0-48)}$), calculated as Day 1 dFdC ($AUC_{(0-48)}$) / Day 1 dFdU ($AUC_{(0-48)}$) |
| $MR(AUC_{(0-inf)})_1$ | Metabolic Ratio for ($AUC_{(0-inf)}$), calculated as Day 1 dFdC ($AUC_{(0-inf)}$) / Day 1 dFdU ($AUC_{(0-inf)}$) |
| $MR(AUC_{(0-t)})_{15}$ | Metabolic Ratio for ($AUC_{(0-t)}$), calculated as Day 15 dFdC ($AUC_{(0-t)}$) / Day 15 dFdU ($AUC_{(0-t)}$) |
| $MR(AUC_{(0-24)})_{15}$ | Metabolic Ratio for ($AUC_{(0-24)}$), calculated as Day 15 dFdC ($AUC_{(0-24)}$) / Day 15 dFdU ($AUC_{(0-24)}$) |
| $MR(AUC_{(0-48)})_{15}$ | Metabolic Ratio for ($AUC_{(0-48)}$), calculated as Day 15 dFdC ($AUC_{(0-48)}$) / Day 15 dFdU ($AUC_{(0-48)}$) |
| $MR(AUC_{(0-inf)})_{15}$ | Metabolic Ratio for (AUC(0-inf)), calculated as Day 15 dFdC (AUC(0-inf)) / Day 15 dFdU (AUC(0-inf)) |

*dFdC only; all others for both dFdU and dFdC, or as defined.
** Pre-dose on Cycle 1 Day 1, 3, 8, 15 and 17

**Table 2 Pharmacokinetic Parameters for Part 2 Dose Expansion Phase - Cycle 1, Days 1, 2, 3, 8, 15, 16 and 17 and Cycle 2, Days 1, 2 and 3**

| Parameter | Definition |
|---|---|
| $C_{max}$ | Maximum observed concentration |
| $t_{max}$ | Time corresponding to occurrence of $C_{max}$ |
| $t_{½}$ | Apparent terminal elimination half life |
| $AUC_{(0-t)}$ | AUC from time zero to the last quantifiable concentration |
| $AUC_{(0-24)}$ | AUC from time zero to 24 hours post-dose |
| $AUC_{(0-48)}$ | AUC from time zero to 48 hours post-dose |
| $AUC_{(0-inf)}$ | AUC from time zero extrapolated to infinity |
| %AUCex | Percentage of $AUC_{(0-inf)}$ obtained by extrapolation |
| CL/F* | Apparent clearance following oral administration |
| $V_z/F$* | Apparent volume of distribution during terminal phase |
| $C_{trough}$ | Pre-dose concentration** |
| $Rac(AUC_{(0-t)})^{\#}$ | Accumulation Ratio, calculated as (Day 15 $AUC_{(0-t)}$ / Day 1 $AUC_{(0-t)}$) |
| $Rac(AUC_{(0-24)})^{\#}$ | Accumulation Ratio, calculated as (Day 15 $AUC_{(0-24)}$ / Day 1 $AUC_{(0-24)}$) |
| $Rac(AUC_{(0-48)})^{\#}$ | Accumulation Ratio, calculated as (Day 15 $AUC_{(0-48)}$ / Day 1 $AUC_{(0-48)}$) |
| $Rac(AUC_{(0-inf)})^{\#}$ | Accumulation Ratio, calculated as (Day 15 $AUC_{(0-inf)}$ / Day 1 $AUC_{(0-inf)}$) |
| $Rac(C_{max})^{\#}$ | Accumulation Ratio, calculated as (Day 15 $C_{max}$ / Day 1 $C_{max}$) |
| $MR(AUC_{(0-t)})_1^{\#}$ | Metabolic Ratio for ($AUC_{(0-t)}$), calculated as Day 1 dFdC ($AUC_{(0-t)}$) / Day 1 dFdU ($AUC_{(0-t)}$) |
| $MR(AUC_{(0-24)})_1^{\#}$ | Metabolic Ratio for ($AUC_{(0-24)}$), calculated as Day 1 dFdC ($AUC_{(0-24)}$) / Day 1 dFdU ($AUC_{(0-24)}$) |
| $MR(AUC_{(0-48)})_1^{\#}$ | Metabolic Ratio for ($AUC_{(0-48)}$), calculated as Day 1 dFdC ($AUC_{(0-48)}$) / Day 1 dFdU ($AUC_{(0-48)}$) |
| $MR(AUC_{(0-inf)})_1^{\#}$ | Metabolic Ratio for ($AUC_{(0-inf)}$), calculated as Day 1 dFdC ($AUC_{(0-inf)}$) / Day 1 dFdU ($AUC_{(0-inf)}$) |
| $MR(AUC_{(0-t)})_{15}^{\#}$ | Metabolic Ratio for ($AUC_{(0-t)}$), calculated as Day 15 dFdC ($AUC_{(0-t)}$) / Day 15 dFdU ($AUC_{(0-t)}$) |
| $MR(AUC_{(0-24)})_{15}^{\#}$ | Metabolic Ratio for ($AUC_{(0-24)}$), calculated as Day 15 dFdC ($AUC_{(0-24)}$) / Day 15 dFdU ($AUC_{(0-24)}$) |
| $MR(AUC_{(0-48)})_{15}^{\#}$ | Metabolic Ratio for ($AUC_{(0-48)}$), calculated as Day 15 dFdC ($AUC_{(0-48)}$) / Day 15 dFdU ($AUC_{(0-48)}$) |
| $MR(AUC(0-inf))_{15}^{\#}$ | Metabolic Ratio for (AUC(0-inf)), calculated as Day 15 dFdC (AUC(0-inf)) / Day 15 dFdU (AUC(0-inf)) |

*dFdC only; all others for both dFdU and dFdC, or as defined.

** Pre-dose on Cycle 1 Day 1, 3, 8, 15 and 17 and Cycle 2 Day 1 and 3.

# For Part 2, accumulation ratios for dFdC will be calculated for Day 15 relative to Day 1 for all AUC parameters and $C_{max}$. For the lower dose-expansion cohort in Part 2, the accumulation ratios for dFdU will be calculated for Day 15 relative to Day 1 for all AUC parameters and $C_{max}$, and the metabolic ratio will be calculated for dFdU for Days 1 and 15 for all AUC parameters.

#### *6.1.3.1 Pharmacokinetic Parameter Calculation Methods*

PK parameters will be calculated by non-compartmental analysis methods from the concentration-time data using WinNonlin (WNL) Professional (Version **6.3**) following these guidelines:

- Actual sampling times relative to dosing rather than nominal times will be used in the calculation of all derived PK parameters.
- There will be no imputation of missing data.
- All below the limit of quantification (BLQ) values pre-dose and in the absorption phase prior to the first quantifiable concentration will be substituted by zeros. Thereafter BLQ values between evaluable concentrations will be substituted by missing, before the calculation of the PK variables. Terminal BLQ values will be disregarded.
- For Day 1, all BLQ values pre-dose and in the absorption phase prior to the first quantifiable concentration will be substituted by zeros. For subsequent dosing days not separated by a washout, BLQ values pre-dose, in the absorption phase, and between evaluable concentrations will be substituted by missing, before the calculation of the PK variables. Terminal BLQ values will be disregarded.

PK parameters will be estimated according to the following guidelines:

- $C_{max}$ will be obtained directly from the concentration-time data.
- $t_{max}$ is the time at which $C_{max}$ is observed.
- $\lambda_Z$ will be estimated at terminal phase by linear regression after log-transformation of the concentrations:
  - Only those data points that are judged to describe the terminal log-linear decline will be used in the regression.
  - A minimum number of three data points in the terminal phase will be used in calculating $\lambda_z$ with the line of regression starting at any post-$C_{max}$ data point ($C_{max}$ should not be part of the regression slope) and including $C_{last}$, $t_{last}$.
  - The adjusted correlation coefficient ($R^2$ adjusted) in general should be greater than 0.90. Any value less than 0.90 may be used at the PK Scientist's best knowledge and judgment.
  - An appropriate number of decimal places should be used for $\lambda_z$ to enable the reported value of $t_{½}$ to be calculated.
- $t_{1/2}$ will be calculated as $\ln 2/\lambda_Z$.

- 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.
  - $AUC_{(0\text{-}t)} = \int_0^t C(t)dt$.
  - $AUC_{(0\text{-}inf)} = \int_0^t C(t)dt + \int_t^\infty C(t)dt = AUC_{(0\text{-}t)} + C_t/\lambda_z$.
  - $C_t$ is last observed quantifiable concentration.
- $\%AUC_{ex}$ will be calculated as $(1 - [AUC_{(0\text{-}t)}/AUC_{(0\text{-}inf)}]) \times 100$.
- CL/F will be calculated as dose/$AUC_{(0\text{-}inf)}$, parent drug only.
- $V_z/F$ will be calculated as $CL/F/\lambda_Z$, parent drug only.

The following PK parameters will also be derived using SAS (version x.x); (See Table 1 and Table 2 for more detail):

- $R_{ac}$ Accumulation ratio calculated as:
  $C_{max}$ (last dose interval)/ $C_{max}$ (first dose interval).
  $AUC_{(0\text{-}\tau),ss}$ (last dose interval)/ $AUC_{(0\text{-}\tau),ss}$ (first dose interval).
- MR Metabolite ratio calculated as AUC (parent)/ AUC (metabolite).

**Table 3 Summary of Required Pharmacokinetic Parameters for Dose Escalation Phase**

| | | DOSE ESCALATION | | | | | |
|---|---|---|---|---|---|---|---|
| | | dFdC | | | dFdU | | |
| | | Cycle 1 | | | Cycle 1 | | |
| | | Day 1 | Day 8 | Day 15 | Day 1 | Day 8 | Day 15 |
| $C_{max}$ | Maximum observed concentration | yes | N/A | yes | yes | N/A | yes |
| $C_{trough}$ | Pre-dose concentration | yes | yes | yes | yes | yes | yes |
| $t_{max}$ | Time corresponding to occurrence of $C_{max}$ | yes | N/A | yes | yes | N/A | yes |
| $t_{½}$ | Apparent terminal elimination half life | yes | N/A | yes | yes | N/A | yes |
| $AUC_{(0-t)}$ | AUC from time zero to the last quantifiable concentration | yes | N/A | yes | yes | N/A | yes |
| $AUC_{(0-24)}$ | AUC from time zero to 24 hours post-dose | yes | N/A | yes | yes | N/A | yes |
| $AUC_{(0-48)}$ | AUC from time zero to 48 hours post-dose | yes | N/A | yes | yes | N/A | yes |
| $AUC_{(0-inf)}$ | AUC from time zero extrapolated to infinity | yes | N/A | yes | yes | N/A | yes |
| %AUCex | Percentage of $AUC_{(0-inf)}$ obtained by extrapolation | yes | N/A | yes | yes | N/A | yes |
| CL/F | Apparent clearance following oral administration | yes | N/A | yes | no | N/A | no |
| $V_z/F$ | Apparent volume of distribution during terminal phase | yes | N/A | yes | no | N/A | no |
| Rac($AUC_{(0-t)}$) | Accumulation Ratio, calculated as (Day 15 $AUC_{(0-t)}$ / Day 1 $AUC_{(0-t)}$) | N/A | N/A | yes | N/A | N/A | yes |
| Rac($AUC_{(0-24)}$) | Accumulation Ratio, calculated as (Day 15 $AUC_{(0-24)}$ / Day 1 $AUC_{(0-24)}$) | N/A | N/A | yes | N/A | N/A | yes |

| | | DOSE ESCALATION | | | | | |
|---|---|---|---|---|---|---|---|
| | | dFdC | | | dFdU | | |
| | | Cycle 1 | | | Cycle 1 | | |
| | | Day 1 | Day 8 | Day 15 | Day 1 | Day 8 | Day 15 |
| $Rac(AUC_{(0-48)})$ | Accumulation Ratio, calculated as (Day 15 $AUC_{(0-48)}$ / Day 1 $AUC_{(0-48)}$) | N/A | N/A | yes | N/A | N/A | yes |
| $Rac(AUC_{(0-inf)})$ | Accumulation Ratio, calculated as (Day 15 $AUC_{(0-inf)}$ / Day 1 $AUC_{(0-inf)}$) | N/A | N/A | yes | N/A | N/A | yes |
| $Rac(C_{max})$ | Accumulation Ratio, calculated as (Day 15 $C_{max}$ / Day 1 $C_{max}$) | N/A | N/A | yes | N/A | N/A | yes |
| $MR(AUC_{(0-t)})_1$ | Metabolic Ratio for ($AUC_{(0-t)}$), calculated as Day 1 dFdC ($AUC_{(0-t)}$) / Day 1 dFdU ($AUC_{(0-t)}$) | N/A | N/A | N/A | yes | N/A | N/A |
| $MR(AUC_{(0-24)})_1$ | Metabolic Ratio for ($AUC_{(0-24)}$), calculated as Day 1 dFdC ($AUC_{(0-24)}$) / Day 1 dFdU ($AUC_{(0-24)}$) | N/A | N/A | N/A | yes | N/A | N/A |
| $MR(AUC_{(0-48)})_1$ | Metabolic Ratio for ($AUC_{(0-48)}$), calculated as Day 1 dFdC ($AUC_{(0-48)}$) / Day 1 dFdU ($AUC_{(0-48)}$) | N/A | N/A | N/A | yes | N/A | N/A |
| $MR(AUC_{(0-inf)})_1$ | Metabolic Ratio for ($AUC_{(0-inf)}$), calculated as Day 1 dFdC ($AUC_{(0-inf)}$) / Day 1 dFdU ($AUC_{(0-inf)}$) | N/A | N/A | N/A | yes | N/A | N/A |
| $MR(AUC_{(0-t)})_{15}$ | Metabolic Ratio for ($AUC_{(0-t)}$), calculated as Day 15 dFdC ($AUC_{(0-t)}$) / Day 15 dFdU ($AUC_{(0-t)}$) | N/A | N/A | N/A | N/A | N/A | yes |
| $MR(AUC_{(0-24)})_{15}$ | Metabolic Ratio for ($AUC_{(0-24)}$), calculated as Day 15 dFdC ($AUC_{(0-24)}$) / Day 15 dFdU ($AUC_{(0-24)}$) | N/A | N/A | N/A | N/A | N/A | yes |
| $MR(AUC_{(0-48)})_{15}$ | Metabolic Ratio for ($AUC_{(0-48)}$), calculated as Day 15 dFdC ($AUC_{(0-48)}$) / Day 15 dFdU ($AUC_{(0-48)}$) | N/A | N/A | N/A | N/A | N/A | yes |
| $MR(AUC_{(0-inf)})_{15}$ | Metabolic Ratio for (AUC(0-inf)), calculated as Day 15 dFdC (AUC(0-inf)) / Day 15 dFdU (AUC(0-inf)) | N/A | N/A | N/A | N/A | N/A | yes |

**Table 4 Summary of Required Pharmacokinetic Parameters for Dose Expansion Phase**

| | | DOSE EXPANSION | | | | | | | |
|---|---|---|---|---|---|---|---|---|---|
| | | dFdC | | | | dFdU | | | |
| | | Cycle 1 | | | Cycle 2 | Cycle 1 | | | Cycle 2 |
| | | Day 1 | Day 8 | Day 15 | Day 1 | Day 1 | Day 8 | Day 15 | Day 1 |
| $C_{max}$ | Maximum observed concentration | yes | N/A | yes | yes | yes | N/A | yes | yes |
| $C_{trough}$ | Pre-dose concentration | yes | yes | yes | yes | yes | yes | yes | yes |
| $t_{max}$ | Time corresponding to occurrence of $C_{max}$ | yes | N/A | yes | yes | yes | N/A | yes | yes |
| $t_{½}$ | Apparent terminal elimination half life | yes | N/A | yes | yes | yes | N/A | yes | yes |
| $AUC_{(0-t)}$ | AUC from time zero to the last quantifiable concentration | yes | N/A | yes | yes | yes | N/A | yes | yes |
| $AUC_{(0-24)}$ | AUC from time zero to 24 hours post-dose | yes | N/A | yes | yes | yes | N/A | yes | yes |
| $AUC_{(0-48)}$ | AUC from time zero to 48 hours post-dose | yes | N/A | yes | yes | yes | N/A | yes | yes |
| $AUC_{(0-inf)}$ | AUC from time zero extrapolated to infinity | yes | N/A | yes | yes | yes | N/A | yes | yes |
| %AUCex | Percentage of $AUC_{(0-inf)}$ obtained by extrapolation | yes | N/A | yes | yes | yes | N/A | yes | yes |
| CL/F | Apparent clearance following oral administration | yes | N/A | yes | yes | no | N/A | no | no |
| $V_z/F$ | Apparent volume of distribution during terminal phase | yes | N/A | yes | yes | no | N/A | no | no |
| Rac($AUC_{(0-t)}$) | Accumulation Ratio, calculated as (Day 15 $AUC_{(0-t)}$ / Day 1 $AUC_{(0-t)}$) | N/A | N/A | yes | N/A | N/A | N/A | yes[#] | N/A |

| | | DOSE EXPANSION | | | | | | | |
|---|---|---|---|---|---|---|---|---|---|
| | | dFdC | | | | dFdU | | | |
| | | Cycle 1 | | | Cycle 2 | Cycle 1 | | | Cycle 2 |
| | | Day 1 | Day 8 | Day 15 | Day 1 | Day 1 | Day 8 | Day 15 | Day 1 |
| $Rac(AUC_{(0-24)})$ | Accumulation Ratio, calculated as (Day 15 $AUC_{(0-24)}$ / Day 1 $AUC_{(0-24)}$) | N/A | N/A | yes | N/A | N/A | N/A | yes[#] | N/A |
| $Rac(AUC_{(0-48)})$ | Accumulation Ratio, calculated as (Day 15 $AUC_{(0-48)}$ / Day 1 $AUC_{(0-48)}$) | N/A | N/A | yes | N/A | N/A | N/A | yes[#] | N/A |
| $Rac(AUC_{(0-inf)})$ | Accumulation Ratio, calculated as (Day 15 $AUC_{(0-inf)}$ / Day 1 $AUC_{(0-inf)}$) | N/A | N/A | yes | N/A | N/A | N/A | yes[#] | N/A |
| $Rac(C_{max})$ | Accumulation Ratio, calculated as (Day 15 $C_{max}$ / Day 1 $C_{max}$) | N/A | N/A | yes | N/A | N/A | N/A | yes[#] | N/A |
| $MR(AUC_{(0-t)})_1$ | Metabolic Ratio for ($AUC_{(0-t)}$), calculated as Day 1 dFdC ($AUC_{(0-t)}$) / Day 1 dFdU ($AUC_{(0-t)}$) | N/A | N/A | N/A | N/A | yes[#] | N/A | N/A | yes[#] |
| $MR(AUC_{(0-24)})_1$ | Metabolic Ratio for ($AUC_{(0-24)}$), calculated as Day 1 dFdC ($AUC_{(0-24)}$) / Day 1 dFdU ($AUC_{(0-24)}$) | N/A | N/A | N/A | N/A | yes[#] | N/A | N/A | yes[#] |
| $MR(AUC_{(0-48)})_1$ | Metabolic Ratio for ($AUC_{(0-48)}$), calculated as Day 1 dFdC ($AUC_{(0-48)}$) / Day 1 dFdU ($AUC_{(0-48)}$) | N/A | N/A | N/A | N/A | yes[#] | N/A | N/A | yes[#] |
| $MR(AUC_{(0-inf)})_1$ | Metabolic Ratio for ($AUC_{(0-inf)}$), calculated as Day 1 dFdC ($AUC_{(0-inf)}$) / Day 1 dFdU ($AUC_{(0-inf)}$) | N/A | N/A | N/A | N/A | yes[#] | N/A | N/A | yes[#] |
| $MR(AUC_{(0-t)})_{15}$ | Metabolic Ratio for ($AUC_{(0-t)}$), calculated as Day 15 dFdC ($AUC_{(0-t)}$) / Day 15 dFdU ($AUC_{(0-t)}$) | N/A | N/A | N/A | N/A | N/A | N/A | yes[#] | N/A |
| $MR(AUC_{(0-24)})_{15}$ | Metabolic Ratio for ($AUC_{(0-24)}$), calculated as Day 15 dFdC ($AUC_{(0-24)}$) / Day 15 dFdU ($AUC_{(0-24)}$) | N/A | N/A | N/A | N/A | N/A | N/A | yes[#] | N/A |

| | | DOSE EXPANSION | | | | | | | |
|---|---|---|---|---|---|---|---|---|---|
| | | dFdC | | | | dFdU | | | |
| | | Cycle 1 | | | Cycle 2 | Cycle 1 | | | Cycle 2 |
| | | Day 1 | Day 8 | Day 15 | Day 1 | Day 1 | Day 8 | Day 15 | Day 1 |
| $MR(AUC_{(0-48)})_{15}$ | Metabolic Ratio for ($AUC_{(0-48)}$), calculated as Day 15 dFdC ($AUC_{(0-48)}$) / Day 15 dFdU ($AUC_{(0-48)}$) | N/A | N/A | N/A | N/A | N/A | N/A | yes[#] | N/A |
| $MR(AUC_{(0-inf)})_{15}$ | Metabolic Ratio for ($AUC_{(0-inf)}$), calculated as Day 15 dFdC ($AUC_{(0-inf)}$) / Day 15 dFdU ($AUC_{(0-inf)}$) | N/A | N/A | N/A | N/A | N/A | N/A | yes[#] | N/A |

# For the lower dose-expansion cohort in Part 2.

### 6.1.4 Efficacy Variables

In Part 1 of the study, Tumor assessments by RECIST v1.1 will be conducted every 6 weeks relative to the first dose of study medication for all patients until disease progression, death, or withdrawal of consent. Disease progression will be based on the Investigator's evaluation of tumor assessments. Patients who are discontinued from study drug for a reason other than disease progression, death, or withdrawal of consent are to continue tumor assessments on the same schedule.

As for Part 1, tumor assessments by RECIST v1.1 in Part 2 will be conducted every 6 weeks relative to the first dose of study medication for all patients until disease progression, death, or withdrawal of consent. Disease progression will be based on the Investigator's evaluation of tumor assessments. Patients who are discontinued from study drug for a reason other than disease progression, death, or withdrawal of consent are to continue tumor assessments on the same schedule.

#### *6.1.4.1 Tumor assessments*

The classification of the objective tumor response is:

- Complete response (CR)
- Partial response (PR)
- Progressive disease (PD)
- Stable disease (SD)

Best overall response (BOR) will be assessed for patients with measurable disease at baseline. BOR is defined as a patient's best objective response since treatment started.

Patients with a best response of CR or PR will be classified as responders for the evaluation of the objective response rate (ORR). All other patients with measurable disease at baseline, including patients who do not have tumor response assessment due to rapid progression or toxicity, will be considered as non-responders and will be included in the denominator for the response rate.

#### *6.1.4.2 Other efficacy endpoints*

Besides ORR, the following exploratory efficacy endpoints will also be assessed in this study:

- PFS: The time from treatment assignment /randomization until PD or death.
- OS: The time from treatment assignment/randomization until death from any cause.
- TTP: The time from treatment assignment until PD.

### 6.1.5 Tumor Marker

Cancer antigen [CA]-19-9 and carcinoembryonic antigen [CEA] levels will be measured per the assessment schedules for Part 1 and Part 2.

### 6.1.6 Pharmacogenomic, Pharmacoproteomic, and Cellular Marker

Samples for pharmacogenomic, pharmacoproteomic and cellular markers will be collected if the patient provides additional consent.

Cellular markers will include the levels of immune cells, circulating endothelial progenitor cells and circulating tumor cells.

## 6.2 Analysis Populations

### 6.2.1 Enrolled Set

The Enrolled Set (ENS) will include all patients who provided informed consent.

### 6.2.2 Safety Analysis Set

The Safety Analysis Set (SAF) will include all patients who received at least 1 dose of D07001-softgel, classified by actual dose received.

### 6.2.3 Pharmacokinetic Set

The Pharmacokinetic Set (PKS) will include all patients in the SAF with evaluable PK data, and who have no major protocol deviations considered to impact the analysis of the PK data.

Data may be excluded from PK analysis (concentrations listed only) if any of the following criteria are fulfilled:

- Subject received a concomitant medication that could render the plasma concentration-time profile unreliable as judged by <insert name of roles/functions that will make the decision>
- The pre-dose concentration is greater than 5% of the corresponding $C_{max}$ in any given treatment period.
- Subject vomits within 2 x the reported median $t_{max}$ for the analyte.
- Subject has moderate or severe diarrhea within 2 x the reported median $t_{max}$ for the analyte.

Any data excluded will be reported in the CSR.

### 6.2.4 Efficacy Analysis Set

The following analysis sets will be defined only for Part 2 of the study.

#### *6.2.4.1 Modified Intent-to-Treat (mITT) Set*

mITT Set will include all randomized patients who received at least 1 dose of study drug and with at least 1 post-baseline disease assessment.

Note: Patients who do not meet eligibility criteria prior to randomization but are still randomized into the study will be excluded from the mITT Set.

#### *6.2.4.2 Per-Protocol (PP) Set*

PP Set will be a subset of the mITT Set that excludes patients who have major protocol deviations.

## 6.3 Statistical Analysis Methods

Data for patients in Part 1 and Part 2 will be analyzed separately.

### 6.3.1 Listings and Descriptive Statistics

All original and derived parameters as well as population characteristics will be listed and described using summary statistics. Frequency counts (number of patients [n] and percentages) will be made for each qualitative variable. Descriptive statistics (n, mean, standard deviation [SD], median, minimum and maximum) will be calculated for each quantitative variable (unless otherwise stated). Additional descriptive statistics will be reported for PK concentrations and parameters. All listings will include repeated and unscheduled measurements.

All descriptive statistics will be presented by dose level and study part. The baseline for all measurements (where applicable) will be the last pre-dose measurement.

All descriptive statistics will be presented by dose level for measurements obtained during the treatment period. Descriptive statistics for all data obtained at Screening and follow-up will be presented separately.

### 6.3.2 Statistical Significance Level

All statistical tests will be two-sided and will be performed at the 5% level of significance, unless otherwise stated.

### 6.3.3 Software

All statistical analyses will be performed using Statistical Analysis Software (SAS®) Version 9.2 or later. The PK analysis will be performed using WinNonlin Professional Software Version 6.3 or later.

### 6.3.4 Missing Data

Unless otherwise stated, there will be no special imputation of missing data.

### 6.3.5 Interim Analysis and Early Stopping Guidelines

Study enrollment may be suspended by the Safety Board if ≥2 patients in the 20 mg cohort (dose level -1) experience a DLT or upon the identification or discovery of an unexpected, significant, or unacceptable risk to the patients enrolled in the study.

A safety data review will be performed in the interim of the dose-expansion phase, i.e. when 10 patients in each of the 2 dose-expansion cohorts have completed at least 2 cycles of treatment.

### 6.3.6 Protocol Deviations

All protocol deviations will be recorded by the Investigator and will be listed by patient. All protocol deviations will be discussed between CRO (Medical Monitor, Data Manager, Biostatistician) and the Sponsor and classified as “minor” or “major”. Major protocol deviations will lead to the exclusion of a patient from the PP Set. Protocol Deviations will be assessed prior to database lock.

### 6.3.7 Disposition of Patients

Patients screened, randomized, treated with study drug and who have discontinued the treatment (i.e. end of treatment (EOT)) or discontinued the study (i.e. end of study (EOS)) will be presented by dose level and overall for each study part. If patients who discontinue from the treatment should, if possible, have an EOT visit. This visit should take place as soon as possible after the patient stops taking study drug or as soon as possible after it was learned that the patient will not be able to complete follow up. The reason for discontinuation from the treatment or study (EOT/ EOS) and for screen failure will also be summarized and listed by patient.

### 6.3.8 Demographic Data and Baseline Characteristics

All demographic data and baseline characteristics will be listed on the ENS and will be summarized using the SAF, PKS, mITT, and PP Sets.

### 6.3.9 Medical History

Medical history will be recorded at Screening. All of the medical history will be listed for each patient by dose level using the SAF. All of the medical history are also summarized and listed by SOC and PT terms.

### 6.3.10 Prior and Concomitant Medication

All prior medications will be coded using the WHO-DD and will be classified by ATC categories. All prior medications will be listed for each patient by dose level using the SAF. Frequency count and associated percentages of prior medications will be summarized by ATC Level 2, ATC Level 4 and Preferred Term.

All concomitant medications and therapeutic interventions (e.g., drug therapy, surgery, etc.) taken from screening and ongoing or those medications that started after first dosing start will be coded using the WHO-DD and will be classified by ATC categories.

All concomitant medications will be listed for each patient by dose level using the SAF. Frequency count and associated percentages of concomitant medications will be summarized by ATC Level 2, ATC Level 4 and Preferred Term.

### 6.3.11 Exposure to the Investigational Medicinal Product

Per ICH E3: When the dose received by each subject can vary, the actual dose received should be shown and individual subject's doses should be presented in a data listing.

The actual doses received will be presented in the Exposure to Investigational Medicinal Product listing for the SAF. Study dose administration will include dose reduction, hold and dose compliance. The patient’s drug compliance (i.e. amount used/amount expected to be used in interval between visits) will be recorded on the drug administration CRF.

Total actual dose of study drug, total treatment duration, actual treatment duration and Relative Dose Intensity (RDI) will be summarized by study part and dose level.

- Total treatment duration = last dose date - first dose date +1
- Actual treatment duration = total treatment duration, excluding dose interruptions and delay periods
- RDI (%) = percentage of the actual dose intensity delivered relative to the intended dose intensity

The number of treatment cycles, dose modification (reduction/ interruption/ delay), and drug compliance will also be summarized by study part and dose level.

### 6.3.12 Pharmacokinetic Concentrations and Variables

The analysis of the PK data will be based on the PKS.

Concentrations below the lower limit of quantification (LLOQ) will be indicated as BLQ in the listings.

Pharmacokinetic concentration data will be listed by patient including actual sampling times relative to dosing. Plasma concentrations will be summarized by study part and dose level. The following descriptive statistics will be presented for plasma concentrations obtained at each nominal time point: n, arithmetic mean, SD, coefficient of variation (CV%), geometric mean, geometric SD, geometric CV% (calculated as: gCV% =SQRT(es²-1)*100; where s is the standard deviation of the log-transformed values), median, minimum and maximum values.

Pharmacokinetic parameters will be listed by patient and summarized by study part and by dose level. Descriptive statistics for calculated PK parameters will include: n, arithmetic mean, SD, CV%, geometric mean, median, minimum and maximum values. For $t_{max}$, only median, minimum and maximum values will be presented. For each PK parameter, descriptive statistics will not be determined if fewer than three patients report a calculated result for a given parameter.

Individual plasma concentration versus actual times will be plotted by dose level for each analyte using linear and semi-logarithmic scales. Mean plasma concentrations versus nominal times will also be presented using linear and semi-logarithmic scales. All dose levels will be overlaid on the same plot.

#### *6.3.12.1 Handling of Values Below the Limit of Quantification (BLQ) in Concentration Summaries and Listings*

**Graphical presentation:**

For graphs of arithmetic means, all BLQ mean concentrations will be substituted by zeros. Graphs of geometric means include only time points with minimum concentration greater than zero. Any arithmetic mean that is BLQ will be excluded from log/linear presentation of arithmetic means. Any BLQ values prior to the last quantifiable concentration will be plotted at zero for individual linear/linear graphs and excluded from log/linear graphs. All BLQ values after the last quantifiable concentration will be excluded from individual linear/linear and log/linear graphs.

**Handling of values below the limit of quantification (BLQ) in listings and for the calculation of descriptive statistics at each time point:**

All concentrations below the limit of quantification (BLQ) or missing data will be labeled as such in the concentration data listings. Missing samples will be reported as no sample ("NS") and excluded from analysis.

Values that are BLQ will be substituted with zero for the calculation of descriptive statistics of concentration by time point and will be displayed as “not calculable” or NC if no descriptive statistics will be determined.

#### *6.3.12.2 Assessment of Food Effect*

For the food-effect evaluation in the higher dose-expansion cohort in Part 2, bioequivalence of the fed and fasted states will be evaluated for $AUC_{(0-t)}$ and $C_{max}$ (primary) and $AUC_{(0-inf)}$ (secondary), based on the 90% confidence interval (CI) using the PKS.

Individual PK parameter values will be used to fit a mixed linear model. Food-effect, sequence group and dosing period will be fixed effects while subject will be taken as random effect. The response variable ‘log_pkvar’ represents the natural log transformed $C_{max}$, $AUC_{(0-t)}$ or $AUC_{(0\ inf).}$ Food-effect can be estimated by the model. Ratio of Fed/Fasted can be obtained by the back log transformed of estimated difference.

The following SAS code will be used as reference:

```
PROC MIXED DATA=DATA;
  CLASS fed_status period sequence subject;
  MODEL log_pkvar = fed_status sequence period ;
  RAMDOM  subject (sequence);
    /*where "log_pkvar"= log transformed Cmax, AUC(0-t) and  AUC(0-inf)*/
       LSMEANS fed_status / CL ALPHA=0.05;
       ESTIMATE 'Fed versus Fasted’ food   1 -1   / CL ALPHA=0.1;
       ODS OUTPUT ESTIMATES=estim  LSMEANS=ls_means;
QUIT;
```

Before the data will be analyzed the fixed effect fed_status will be numerically coded; Fed=1 and Fasted=2. When the back-transformed estimated difference lies between 0.8 and 1.25 then then this suggests evidence of no effect of food.

#### *6.3.12.3 Assessment of Dose Proportionality*

Dose proportionality will be assessed for $C_{max}$, $C_{trough}$, $AUC_{(0-t)}$ and $AUC_{(0-inf)}$ using the PKS.

Individual concentration values will be used to perform a least-squares linear regression analysis, using the formula log_pkvar=A× log_dose + B, where 'log_pkvar' represents the natural log transformed $C_{max}$, $AUC_{(0-t)}$ or $AUC_{(0-inf)}$ and 'log_dose' represents the natural log transformed dose. An estimate of the slope of the regression line and corresponding 95% confidence interval (CI) will be obtained.

The following SAS code will be used:

```
PROC REG DATA=pkparam alpha=0.05;
        MODEL log_pkvar = log_dose / CLB;
RUN;
```

For each of the parameters $C_{max}$, $C_{trough}$, $AUC_{(0-t)}$ and $AUC_{(0-inf)}$ a plot of the log-transformed concentration against the log-transformed dose will be constructed including the fitted line from the linear regression and the line of unity.

### 6.3.13 Safety Analysis

The analysis of the safety variables will be based on the SAF.

#### *6.3.13.1 Adverse Events*

The following listings will be provided:

- All pre-treatment AEs and TEAEs
- TEAEs leading to study discontinuation
- TEAEs leading to treatment discontinuation
- TEAEs leading to dose modification (reduction/ interruption/ delay)
- TEAEs leading to death
- SAEs
- Patients experiencing toxicity Grade ≥3 according to CTCAE v4.03
- DLTs, MTD (Part 1 only)

The following information will be included in the AE listings: AE description, MedDRA PT, MedDRA SOC, Start date/time, End date/time/ongoing, Frequency, Serious AE (Yes/No), Severity, Causal relationship to IMP,

Action taken with study drug, Action taken to treat Adverse Event, Outcome, Seriousness, CTCAE Grade, Treatment emergent (Yes/No), Dose limiting toxicity event (Yes/No). The earliest date will be regarded as start date of the event and the latest date/time will be regarded as stop date of the event within the assigned study period.

Adverse events will be summarized on a per-subject basis and per-event. A per-subject basis means that even if a subject reported the same event repeatedly (i.e., events mapped to the same PT) during the study period, the event will be counted only once. A per-event basis the number of events will be reported.

Treatment-related TEAEs, severity of TEAEs, causality of TEAEs, TEAEs leading to dose reduction/interruption, , serious TEAEs , serious TEAEs with causality, TEAEs with Grade 3, DLTs will also be summarized. In the case of multiple occurrences of the same TEAEs (at the same SOC or PT level) in an individual subject, the AE with the strongest assessment of relationship to study and the AE with the worst severity will be reported.

#### *6.3.13.2 Clinical Safety Laboratory Tests (hematology, biochemistry, coagulation parameters and urinalysis)*

Laboratory values (hematology, biochemistry, coagulation parameters and urinalysis) will be listed by patient and study time point including changes from baseline (with the exception of urinalysis). The baseline for the laboratory values will be the last pre-dose measurement.

All values outside the clinical reference ranges will be flagged in the data listings. The abnormal values will be flagged with ‘L’ for values below the lower limit of the clinical reference range and ‘H’ for values above the upper limit of the clinical reference range and included in the listings. The Investigator will assess whether the values outside the clinical reference range are clinically significant and these will be reported as abnormal not clinically significant (NCS) or abnormal clinically significant (CS). Clinically significant laboratory values will be recorded by the Investigator as AEs.

For all hematology, biochemistry and coagulation data with numerical response, descriptive statistics will be presented by study part, dose level and time point (N, mean, SD, median, minimum, maximum). Summary tables will be provided for observed and changes from baseline values.

For all hematology, biochemistry, coagulation and urinalysis, shift tables for important qualitative items (number, % in each category) will be presented by study part, dose level and time point.

#### *6.3.13.3 Vital Signs, Weight, BMI and ECOG PS*

Vital signs, weight, BMI and ECOG PS data will be listed by patient including changes from baseline. The baseline for the vital signs measurements will be the last pre-dose measurement.

Descriptive statistics (n, mean, SD, median, minimum, maximum) for both observed values and changes from baseline will be presented by study part, dose level and time point.

ECOG PS shift tables for important qualitative items (number, % in each category) will be presented by study part, dose level and time point.

#### *6.3.13.4 Twelve-Lead Electrocardiogram*

All ECG parameters obtained from the ECG measurement will be listed by patient for each dose level and time point including changes from baseline. The baseline for the ECG measurements will be the last pre-dose measurement.

Descriptive statistics (n, mean, SD, median, minimum, maximum) for both observed values and changes from baseline will be presented by study part, dose level and time point.

The ECG will be summarized by the Investigator as 'Normal', 'Abnormal, NCS' or 'Abnormal, CS'.

Shift tables for important qualitative items (number, % in each category) will be presented by study part, dose level and time point.

#### *6.3.13.5 Echocardiogram/MUGA*

Echocardiogram/MUGA will be summarized by the Investigator as 'Normal', 'Abnormal, NCS' or 'Abnormal, CS'.

Shift tables for important qualitative items (number, % in each category) will be presented by study part, dose level and time point.

#### *6.3.13.6 Physical Examination and Pregnancy*

The results of the physical examination and pregnancy (only female) will be listed by patient and time point.

Physical examination will be summarized by the Investigator as 'Normal', 'Abnormal, NCS' or 'Abnormal, CS'.

Physical examination shift tables for important qualitative items (number, % in each category) will be presented by study part, dose level and time point.

### 6.3.14 Efficacy Analysis

The analysis of the efficacy variables will be based on the SAF in Part 1, and on mITT and PP Set in Part 2. The total duration of the study from the start of randomization to the analysis of PFS is expected to be 29 months (12 months of accrual + 17 months of the study duration for an individual patient).

Data for target lesions and the non-target lesions along with the tumor evaluation according to RECIST v1.1 will be listed and BOR will be listed by study part, dose level and visit. Summary table for ORR (number, % in all patients with measurable disease at baseline) will be presented with the corresponding exact 95% CI.

In Part 1, a by-patient listing will be generated for the survival outcomes. time-to-event estimates (including median event times and 95% CI) will be generated. PFS, OS and TTP will be estimated using Kaplan-Meier method and summarized. Kaplan-Meier plots will also be produced.

In Part 2, time-to-event estimates (including median event times and 95% CI) will be generated. PFS, OS and TTP will be estimated using Kaplan-Meier method and summarized. Kaplan-Meier plots will also be produced. If patients are excluded from the mITT Set, a sensitivity analysis will be performed by repeating the analyses without excluding patients from the mITT Set.

<u>PFS</u>

Time for PFS (Days) = event date (progression or death date) or censor date – date of first time taking study drugs

Censoring rules

- Without an event: Censored at the date of last valid tumor assessment; if no post-dosing tumor assessment, censored at the date of first dosing.

- With an event (progression or death): If an event occurs after 2 subsequent missed tumor assessments, censored at the date of last valid tumor assessment.

- Taking new anti-tumor treatment: censored at the last valid tumor assessment before taking new anti-tumor treatment.

OS

Time for OS (Days) = event date (death from any reason) or censor date – date of first time taking study drugs

Censoring rules

- Without an event: Censored at the date of last valid tumor assessment/ last survival confirmation date; if no post-dosing tumor assessment, censored at the date of first dosing.

TTP

Time for TTP (Days) = event date (progression) or censor date – date of first time taking study drugs

Censoring rules

- Without an event: Censored at the date of last valid tumor assessment; if no post-dosing tumor assessment, censored at the date of first dosing.

- With an event (progression): If an event occurs after 2 subsequent missed tumor assessments, censored at the date of last valid tumor assessment.

- Taking new anti-tumor treatment: censored at the last valid tumor assessment before taking new anti-tumor treatment.

### 6.3.15 Tumor Marker and Others

All tumor marker measured will be listed by patient for study part and each dose level. Descriptive statistics will also be presented.

Pharmacogenomic, pharmacoproteomic, and cellular markers (including the levels of immune cells, circulating endothelial progenitor cells and circulating tumor cells) obtained will be listed.

# 7. REFFRENCES

1. SAS® Version 9.2 of the SAS System for Personal Computers. Copyright © 2002-2003. SAS Institute Inc. SAS and all other SAS Institute Inc. product or service names are registered trademarks or trademarks of SAS Institute Inc., Cary, NC, USA.
2. WinNonlin Professional Software Version 6.3. http://www.pharsight.com
3. CPMP/EWP/QWP/1401/98 Rev. 1/ Corr, Guideline on the investigation of bioequivalence, London, 20 January 2010.

# 8. TABLES AND LISTINGS TO BE INCLUDED IN SETION 14 OF THE CLINICAL STUDY REPORT

**Subject Disposition**

**Table 14.1.1.1** Summary of Analysis Sets by Dose Level in Part 1 (Enrolled Set)

**Table 14.1.1.2** Summary of Analysis Sets by Dose Level in Part 2 (Enrolled Set)

**Table 14.1.2.1** Subject Disposition Details by Dose Level in Part 1 (Enrolled Set)

**Table 14.1.2.2** Subject Disposition Details by Dose Level in Part 2 (Enrolled Set)

**Baseline and Demographic Data**

**Table 14.1.3.1.1** Subject Demographics by Dose Level in Part 1 (Enrolled Set)

**Table 14.1.3.1.1** Subject Demographics by Dose Level in Part 2 (Enrolled Set )

**Table 14.1.3.2.1** Primary Diagnosis and Duration by Dose Level in Part 1 (Safety Analysis Set)

**Table 14.1.3.2.2** Primary Diagnosis and Duration by Dose Level in Part 2 (Safety Analysis Set)

**Medical History**

Table 14.1.4.1 Summary of Medical History by Dose Level in Part 1 (Safety Analysis Set)

Table 14.1.4.2 Summary of Medical History by Dose Level in Part 2 (Safety Analysis Set)

**Concomitant Medication**

**Table 14.1.5.1.1** Summary of Prior Medication by Dose Level in Part 1 (Safety Analysis Set)

**Table 14.1.5.1.2** Summary of Prior Medication by Dose Level in Part 2 (Safety Analysis Set)

**Table 14.1.5.2.1** Summary of Concomitant Medication by Dose Level in Part 1 (Safety Analysis Set)

**Table 14.1.5.2.2** Summary of Concomitant Medication by Dose Level in Part 2 (Safety Analysis Set)

**Efficacy Data**

**Safety Data**

**Table 14.3.1.1.1** Overview of Adverse Events by Dose Level in Part 1 (Safety Analysis Set)

**Table 14.3.1.1.2** Overview of Adverse Events by Dose Level in Part 2 (Safety Analysis Set)

**Table 14.3.1.2.1** Summary of Treatment-Emergent Adverse Event by Dose Level, System Organ Class and Preferred Term in Part 1 (Safety Analysis Set)

**Table 14.3.1.2.2** Summary of Treatment-Emergent Adverse Event by Dose Level, System Organ Class and Preferred Term in Part 2 (Safety Analysis Set)

**Table 14.3.1.3.1** Summary of Treatment Related Treatment-Emergent Adverse Event by Dose Level, System Organ Class and Preferred Term in Part 1 (Safety Analysis Set)

**Table 14.3.1.3.2** Summary of Treatment Related Treatment-Emergent Adverse Event by Dose Level, System Organ Class and Preferred Term in Part 2 (Safety Analysis Set)

**Table 14.3.1.4.1** Summary of Treatment-Emergent Adverse Event by Dose Level, System Organ Class, Preferred Term and Severity in Part 1 (Safety Analysis Set)

**Table 14.3.1.4.2** Summary of Treatment-Emergent Adverse Event leading to study discontinuation by Dose Level, System Organ Class, Preferred Term and Severity in Part 2 (Safety Analysis Set)

**Table 14.3.1.5.1** Summary of Treatment-Emergent Adverse Event by Dose Level, System Organ Class, Preferred Term and Causality in Part 1 (Safety Analysis Set)

**Table 14.3.1.5.2** Summary of Treatment-Emergent Adverse Event by Dose Level, System Organ Class, Preferred Term and Causality in Part 2 (Safety Analysis Set)

**Table 14.3.1.6.1** Summary of Treatment-Emergent Adverse Event leading to dose reductions by Dose Level, System Organ Class, Preferred Term in Part 1 (Safety Analysis Set)

**Table 14.3.1.6.2** Summary of Treatment-Emergent Adverse Event leading to dose reductions by Dose Level, System Organ Class, Preferred Term in Part 2 (Safety Analysis Set)

**Table 14.3.1.7.1** Summary of Treatment-Emergent Adverse Event leading to dose interruptions by Dose Level, System Organ Class, Preferred Term in Part 1 (Safety Analysis Set)

**Table 14.3.1.7.2** Summary of Treatment-Emergent Adverse Event leading to dose interruptions by Dose Level, System Organ Class, Preferred Term in Part 2 (Safety Analysis Set)

**Table 14.3.1.8.1** Summary of Serious Adverse Event by Dose Level, System Organ Class, Preferred Term in Part 1 (Safety Analysis Set)

**Table 14.3.1.8.2** Summary of Serious Adverse Event by Dose Level, System Organ Class, Preferred Term in Part 2 (Safety Analysis Set)

**Table 14.3.1.9.1** Summary of Serious Adverse Event by Dose Level, System Organ Class, Preferred Term and Causality in Part 1 (Safety Analysis Set)

**Table 14.3.1.9.2** Summary of Serious Adverse Event by Dose Level, System Organ Class, Preferred Term and Causality in Part 2 (Safety Analysis Set)

**Table 14.3.1.10.1** Summary of Treatment-Emergent Adverse Even by Dose Level, System Organ Class, Preferred Term and patients experiencing toxicity Grade ≥3 according to CTCAE v4.03 in Part 1 (Safety Analysis Set)

**Table 14.3.1.10.2** Summary of Treatment-Emergent Adverse Even by Dose Level, System Organ Class, Preferred Term and patients experiencing toxicity Grade ≥3 according to CTCAE v4.03 in Part 2 (Safety Analysis Set)

**Table 14.3.1.11** Summary of DLTs by Dose Level in Part 1 (Safety Analysis Set)

**Table 14.3.2.1.1** Hematology with N, mean, SD, median, minimum, maximum and change from baseline by Dose level in Part 1 (Safety Analysis Set)

**Table 14.3.2.1.2** Hematology with N, mean, SD, median, minimum, maximum and change from baseline by Dose level in Part 2 (Safety Analysis Set)

**Table 14.3.2.2.1** Biochemistry with N, mean, SD, median, minimum, maximum and change from baseline by Dose level in Part 2 (Safety Analysis Set)

**Table 14.3.2.2.2** Biochemistry with N, mean, SD, median, minimum, maximum and change from baseline by Dose level in Part 2 (Safety Analysis Set)

**Table 14.3.2.3.1** Coagulation with N, mean, SD, median, minimum, maximum and change from baseline by Dose level in Part 2 (Safety Analysis Set)

**Table 14.3.2.3.2** Coagulation with N, mean, SD, median, minimum, maximum and change from baseline by Dose level in Part 2 (Safety Analysis Set)

**Table 14.3.2.4.1** Summary of Shift in Hematology Results From Baseline to Post-Baseline by Dose level in Part 1 (Safety Analysis Set)

**Table 14.3.2.4.2** Summary of Shift in Hematology Results From Baseline to Post-Baseline by Dose level in Part 2 (Safety Analysis Set)

**Table 14.3.2.5.1** Summary of Shift in Biochemistry Results From Baseline to Post-Baseline by Dose level in Part 1 (Safety Analysis Set)

**Table 14.3.2.5.2** Summary of Shift in Biochemistry Results From Baseline to Post-Baseline by Dose level in Part 2 (Safety Analysis Set)

**Table 14.3.2.6.1** Summary of Shift in Coagulation Results From Baseline to Post-Baseline by Dose level in Part 1 (Safety Analysis Set)

**Table 14.3.2.6.2** Summary of Shift in Coagulation Results From Baseline to Post-Baseline by Dose level in Part 2 (Safety Analysis Set)

**Table 14.3.2.7.1** Summary of Shift in Urinalysis Results From Baseline to Post-Baseline by Dose level in Part 1 (Safety Analysis Set)

**Table 14.3.2.7.2** Summary of Shift in Urinalysis Results From Baseline to Post-Baseline by Dose level in Part 2 (Safety Analysis Set)

**Table 14.3.3.1.1** Vital Signs with N, mean, SD, median, minimum, maximum and change from baseline by Dose level in Part 1 (Safety Analysis Set)

**Table 14.3.3.1.2** Vital Signs with N, mean, SD, median, minimum, maximum and change from baseline by Dose level in Part 2 (Safety Analysis Set)

**Table 14.3.3.2.1** Weight with N, mean, SD, median, minimum, maximum and change from baseline by Dose level in Part 1 (Safety Analysis Set)

**Table 14.3.3.2.2** Weight Signs with N, mean, SD, median, minimum, maximum and change from baseline by Dose level in Part 2 (Safety Analysis Set)

**Table 14.3.3.3.1** BMI with N, mean, SD, median, minimum, maximum and change from baseline by

**Table 14.3.6.1.1** Summary of Physical Examination by Dose level in Part 1 (Safety Analysis Set)

**Table 14.3.6.1.2** Summary of Physical Examination by Dose level in Part 2 (Safety Analysis Set)

**Table 14.3.6.2.1** Physical Examination shift table by Dose level in Part 1 (Safety Analysis Set)

**Table 14.3.6.2.2** Physical Examination shift table by Dose level in Part 2 (Safety Analysis Set)

**Exposure**

**Table 14.4.1.1.1** Summary of Study Drug Exposure by Dose Level in Part 1 (Safety Analysis Set)

**Table 14.4.1.1.2** Summary of Study Drug Exposure by Dose Level in Part 2 (Safety Analysis Set)

**Table 14.4.1.2.1** Summary of Study Drug Modifications by Dose Level in Part 1 (Safety Analysis Set)

**Table 14.4.1.2.2** Summary of Study Drug Modifications by Dose Level in Part 2 (Safety Analysis Set)

**Table 14.4.1.3.1** Summary of Study Drug Compliance by Dose Level in Part 1 (Safety Analysis Set)

**Table 14.4.1.3.2** Summary of Study Drug Compliance by Dose Level in Part (Safety Analysis Set)

**Pharmacokinetic Data**

**Table 14.4.2.1.1** Summary of Plasma Concentrations of dFdC versus Nominal Sampling Times by Dose Level in Part 1 (Pharmacokinetic Set)

**Table 14.4.2.1.2** Summary of Plasma Concentrations of dFdC versus Nominal Sampling Times by Dose Level in Part 2 (Pharmacokinetic Set)

**Table 14.4.2.2.1** Summary of Plasma Concentrations of dFdU versus Nominal Sampling Times by Dose Level in Part 1 (Pharmacokinetic Set)

**Table 14.4.2.2.2** Summary of Plasma Concentrations of dFdU versus Nominal Sampling Times by Dose Level in Part 2 (Pharmacokinetic Set)

**Table 14.4.2.3.1** Summary of Pharmacokinetic Parameters of dFdC by Dose Level in Part 1 (Pharmacokinetic Set)

**Table 14.6.2** Summary of Protocol Deviation by Dose Level in Part 2 (Safety Analysis Set)

# 9. FIGURES

**Figure 14.2.1.1** Kaplan-Meier Plot for PFS in Part 1 (Safety Analysis Se)

**Figure 14.2.1.2** Kaplan-Meier Plot for PFS in Part 2 (Modified Intent-to-Treat Set)

**Figure 14.2.1.3** Kaplan-Meier Plot for PFS in Part 2 (Per-Protocol Set)

**Figure 14.2.1.4** Kaplan-Meier Plot for PFS in Part 2 (Safety Analysis Set)

**Figure 14.2.2.1** Kaplan-Meier Plot for OS in Part 1 (Safety Analysis Set)

**Figure 14.2.2.2** Kaplan-Meier Plot for OS in Part 2 (Modified Intent-to-Treat Set)

**Figure 14.2.2.3** Kaplan-Meier Plot for OS in Part 2 (Per-Protocol Set)

**Figure 14.2.2.4** Kaplan-Meier Plot for OS in Part 2 (Safety Analysis Set)

**Figure 14.2.3.1** Kaplan-Meier Plot for TTP in Part 1 (Safety Analysis Set)

**Figure 14.2.3.2** Kaplan-Meier Plot for TTP in Part 2 (Modified Intent-to-Treat Set)

**Figure 14.2.3.3** Kaplan-Meier Plot for TTP in Part 2 (Per-Protocol Set)

**Figure 14.2.3.4** Kaplan-Meier Plot for TTP in Part 2 (Safety Analysis Set)

**Figure 14.4.1.1** Subject Profiles for dFdC Plasma Concentration Time Data (Linear Scale) (Pharmacokinetic Set)

**Figure 14.4.1.2** Subject Profiles for dFdU Plasma Concentration Time Data (Linear Scale) (Pharmacokinetic Set)

**Figure 14.4.1.3** Subject Profiles for dFdC Plasma Concentration Time Data (Semi-logarithmic Scale) (Pharmacokinetic Set)

**Figure 14.4.1.4** Subject Profiles for dFdU Plasma Concentration Time Data (Semi-logarithmic Scale) (Pharmacokinetic Set)

**Figure 14.4.2.1** Mean (± Standard Deviation) Profiles for dFdC Plasma Concentration Time Data in

Part 1 (Linear Scale) (Pharmacokinetic Set)

**Figure 14.4.2.2** Mean (± Standard Deviation) Profiles for dFdC Plasma Concentration Time Data in Part 2 (Linear Scale) (Pharmacokinetic Set)

**Figure 14.4.2.3** Mean (± Standard Deviation) Profiles for dFdC Plasma Concentration Time Data in Part 1 (Semi-logarithmic Scale) (Pharmacokinetic Set)

**Figure 14.4.2.4** Mean (± Standard Deviation) Profiles for dFdC Plasma Concentration Time Data in Part 2 (Semi-logarithmic Scale) (Pharmacokinetic Set)

**Figure 14.4.3.1** Mean (± Standard Deviation) Profiles for dFdU Plasma Concentration Time Data in Part 1 (Linear Scale) (Pharmacokinetic Set)

**Figure 14.4.3.2** Mean (± Standard Deviation) Profiles for dFdU Plasma Concentration Time Data in Part 2 (Linear Scale) (Pharmacokinetic Set)

**Figure 14.4.3.3** Mean (± Standard Deviation) Profiles for dFdU Plasma Concentration Time Data in Part 1 (Semi-logarithmic Scale) (Pharmacokinetic Set)

**Figure 14.4.3.4** Mean (± Standard Deviation) Profiles for dFdU Plasma Concentration Time Data in Part 2 (Semi-logarithmic Scale) (Pharmacokinetic Set)

**Figure 14.4.4.1** Assessment of dFdC Dose Proportionality in Part 1 (Pharmacokinetic Set)

**Figure 14.4.4.2** Assessment of dFdC Dose Proportionality in Part 2 (Pharmacokinetic Set)

**Figure 14.4.4.3** Assessment of dFdU Dose Proportionality in Part 1 (Pharmacokinetic Set)

**Figure 14.4.4.4** Assessment of dFdU Dose Proportionality in Part 2 (Pharmacokinetic Set)

# 10. LISTINGS TO BE INCLUDED IN SECTION 16 OF THE CLINICAL STUDY REPORT

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**Listing 16.2.1.1.1** Disposition of the Patients in Part 1 (Enrolled Set)

**Listing 16.2.1.1.2** Disposition of the Patients in Part 2 (Enrolled Set)

**Listing 16.2.1.2.1** Failed Inclusion and Exclusion Criteria in Part 1 (Enrolled Set)

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**Listing 16.2.1.3.1** Discontinued patients in Part 1 (Safety Analysis Set)

**Listing 16.2.1.3.2** Discontinued patients in Part 2 (Safety Analysis Set)

**Listing 16.2.2.1** Protocol Deviations in Part 1 (Safety Analysis Set)

**Listing 16.2.2.2** Protocol Deviations in Part 2 (Safety Analysis Set)

**Baseline and Demographic Data**

**Listing 16.2.4.1.1** Subject Demographics and Baseline Characteristics in Part 1 (Safety Analysis Set )

**Listing 16.2.4.1.2** Subject Demographics and Baseline Characteristics in Part 2 (Safety Analysis Set )

**Listing 16.2.4.2.1** Medical History in Part 1 (Safety Analysis Set )

**Listing 16.2.4.2.2** Medical History in Part 2 (Safety Analysis Set )

**Listing 16.2.4.3.1** Primary Diagnosis and Duration in Part 1 (Safety Analysis Set )

**Listing 16.2.4.3.2** Primary Diagnosis and Duration in Part 2 (Safety Analysis Set )

**Listing 16.2.4.4.1** Substance use - drugs in Part 1 (Safety Analysis Set )

**Listing 16.2.4.4.2** Substance use - drugs in Part 2 (Safety Analysis Set )

**Concomitant Medication**

**Listing 16.2.4.5.1** Prior Medication in Part 1 (Safety Analysis Set )

**Listing 16.2.4.5.2** Prior Medication in Part 2 (Safety Analysis Set )

**Listing 16.2.4.6.1** Concomitant Medication in Part 1 (Safety Analysis Set)

**Listing 16.2.4.6.2** Concomitant Medication in Part 2 (Safety Analysis Set)

**Exposure**

**Listing 16.2.5.1.1** Study Drug Administration in Part 1 (Safety Analysis Set)

**Listing 16.2.5.1.2** Study Drug Administration in Part 2 (Safety Analysis Set)

**Listing 16.2.5.2.1** Listing of Derived Study Drug Administration in Part 1 (Safety Analysis Set)

**Listing 16.2.5.2.2** Listing of Derived Study Drug Administration in Part 2 (Safety Analysis Set)

**Pharmacokinetic Data**

**Listing 16.2.5.3.1** Individual Blood Sampling Times in Part 1 (Pharmacokinetic Set)

**Listing 16.2.5.3.2** Individual Blood Sampling Times in Part 2 (Pharmacokinetic Set)

**Listing 16.2.5.4.1** Individual Plasma Concentrations of dFdC in Part 1 (Pharmacokinetic Set)

**Listing 16.2.5.4.2** Individual Plasma Concentrations of dFdC in Part 2 (Pharmacokinetic Set)

**Listing 16.2.5.5.1** Individual Plasma Concentrations of dFdU in Part 1 (Pharmacokinetic Set)

**Listing 16.2.5.5.2** Individual Plasma Concentrations of dFdU in Part 2 (Pharmacokinetic Set)

**Listing 16.2.5.6.1** Pharmacokinetic Parameters of dFdC (Pharmacokinetic Set)

**Listing 16.2.5.6.2** Pharmacokinetic Parameters of dFdU (Pharmacokinetic Set)

**Efficacy Data**

**Listing 16.2.6.1.1** Tumor Assessment – Target Lesions and Clinical Overall Visit Response in Part 1 (Safety Analysis Set)

**Listing 16.2.6.1.2** Tumor Assessment – Target Lesions and Clinical Overall Visit Response in Part 2 (Safety Analysis Set)

**Listing 16.2.6.2.1** Tumor Assessment – Non-Target Lesions in Part 1(Safety Analysis Set)

**Listing 16.2.6.2.2** Tumor Assessment – Non-Target Lesions in Part 2(Safety Analysis Set)

**Listing 16.2.6.3.1** Tumor Assessment – New Lesions in Part 1(Safety Analysis Set)

**Listing 16.2.6.3.2** Tumor Assessment – New Lesions (Safety Analysis Set)

**Listing 16.2.6.4.1** Best Overall Response and ORR in Part 1(Safety Analysis Set)

**Listing 16.2.6.4.2** Best Overall Response and ORR in Part 2(Safety Analysis Set)

**Listing 16.2.6.5.1** PFS, OS and TTP in Part 1 (Safety Analysis Set)

**Listing 16.2.6.5.2** PFS, OS and TTP in Part 2 (Safety Analysis Set)

**Safety Variables**

**Listing 16.2.7.1.1** All Adverse Events in Part 1 (Safety Analysis Set)

**Listing 16.2.7.1.2** All Adverse Events in Part 2 (Safety Analysis Set)

**Listing 16.2.7.2.1** All Serious Adverse Events in Part 1 (Safety Analysis Set)

**Listing 16.2.7.2.2** All Serious Adverse Events in Part 2 (Safety Analysis Set)

**Listing 16.2.7.3.1** Treatment-Emergent Adverse Event leading to study discontinuation in Part 1 (Safety Analysis Set)

**Listing 16.2.7.3.2** Treatment-Emergent Adverse Event leading to study discontinuation in Part 2 (Safety Analysis Set)

**Listing 16.2.7.4.1** Treatment-Emergent Adverse Event leading to treatment discontinuation in Part 1 (Safety Analysis Set)

**Listing 16.2.7.4.2** Treatment-Emergent Adverse Event leading to treatment discontinuation in Part 2 (Safety Analysis Set)

**Listing 16.2.7.5.1** Treatment-Emergent Adverse Event leading to dose modification (reduction/interruption/delay) in Part 1 (Safety Analysis Set)

**Listing 16.2.7.5.2** Treatment-Emergent Adverse Event leading to dose modification (reduction/interruption/delay) in Part 2 (Safety Analysis Set)

**Listing 16.2.7.6.1** Treatment-Emergent Adverse Event leading to death in Part 1 (Safety Analysis Set)

**Listing 16.2.7.6.2** Treatment-Emergent Adverse Event leading to death in Part 2 (Safety Analysis Set)

**Listing 16.2.7.7.1** Treatment-Emergent Adverse Event with Grade≥ 3 in Part 1(Safety Analysis Set)

**Listing 16.2.7.7.2** Treatment-Emergent Adverse Event with Grade≥ 3 in Part 2(Safety Analysis Set)

**Listing 16.2.7.8.1** Patients experiencing toxicity Grade ≥3 according to CTCAE v4.03 in Part 1 (Safety Analysis Set)

**Listing 16.2.7.8.2** Patients experiencing toxicity Grade ≥3 according to CTCAE v4.03 in Part 2 (Safety Analysis Set)

**Listing 16.2.7.8.2** DLTs in Part 2 (Safety Analysis Set)

**Listing 16.2.8.1.1** Biochemistry Laboratory Values in Part 1 (Safety Analysis Set)

**Listing 16.2.8.1.2** Biochemistry Laboratory Values in Part 2(Safety Analysis Set)

**Listing 16.2.8.2.1** Hematology Laboratory Values in Part 1 (Safety Analysis Set)

**Listing 16.2.8.2.2** Hematology Laboratory Values in Part 2 (Safety Analysis Set)

**Listing 16.2.8.3.1** Coagulation Laboratory Values in Part 1 (Safety Analysis Set)

**Listing 16.2.8.3.2** Coagulation Laboratory Values in Part 2 (Safety Analysis Set)

**Listing 16.2.8.4.1** Urinalysis Laboratory Values in Part 1 (Safety Analysis Set)

**Listing 16.2.8.4.2** Urinalysis Laboratory Values in Part 2 (Safety Analysis Set)

**Listing 16.2.9.1.1** Vital Signs in Part 1 (Safety Analysis Set)

**Listing 16.2.9.1.2** Vital Signs in Part 2 (Safety Analysis Set)

**Listing 16.2.9.2.1** Body Height, Weight and BMI in Part 1 (Safety Analysis Set)

**Listing 16.2.9.2.2** Body Height, Weight and BMI in Part 2 (Safety Analysis Set)

**Listing 16.2.9.3.1** ECOG PS in Part 1 (Safety Analysis Set)

**Listing 16.2.9.3.2** ECOG PS in Part 2 (Safety Analysis Set)

**Listing 16.2.10.1** Twelve-Lead Electrocardiogram in Part 1 (Safety Analysis Set)

**Listing 16.2.10.2** Twelve-Lead Electrocardiogram in Part 2 (Safety Analysis Set)

**Listing 16.2.11.1** Echocardiogram /MUGA in Part 1 (Safety Analysis Set)

**Listing 16.2.11.2** Echocardiogram /MUGA in Part 2 (Safety Analysis Set)

**Listing 16.2.12.1.1** Physical Examination in Part 1 (Safety Analysis Set)

**Listing 16.2.12.1.2** Physical Examination in Part 2 (Safety Analysis Set)

**Listing 16.2.12.2.1** Pregnancy Test in Part 1 (Safety Analysis Set)

**Listing 16.2.12.2.2** Pregnancy Test in Part 2 (Safety Analysis Set)

# 11. DOCUMENTATION OF STATISTICAL METHODS

# 12. EVENT SCHEDULES

## Table 5 Part 1 Event Schedule (Dose Escalation)

| | SV | Cycle 1[a] | | | | | | | Cycle 2 | | | Cycle 3 onwards[b] | EOT[c] | 30-day FU | FU for OS |
|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|
| | D -28 to 0 | D1 | D2 | D3 | D8 | D15 | D16 | D17 | D1 (±1d) | D8 (±1d) | D15 (±1d) | D1 (±1d) | (±3d) | (±3d) | (±3d) |
| Informed consent | X | | | | | | | | | | | | | | |
| Inclusion/Exclusion criteria | X | X | | | | | | | | | | | | | |
| Medical history | X | | | | | | | | | | | | | | |
| Demographics | X | | | | | | | | | | | | | | |
| Prior medication | X | | | | | | | | | | | | | | |
| Concomitant medication | X | X | X | X | X | X | X | X | X | X | X | X | X | X | |
| Height | X | | | | | | | | | | | | | | |
| Weight | X | X | | | X | X | | | X | X | X | X | X | X | |
| Physical examination | X | X | | | X | X | | | X | X | X | X | X | X | |
| Vital signs | X | X | | | X | X | | | X | X | X | X | X | X | |
| ECG | X | X | | | X | X | | | X | | | X | X | X | |
| Echocardiogram or MUGA | X | | | | | | | | | | | X[d] | | | |
| ECOG PS | X | X | | | X | X | | | X | X | X | X | X | X | |
| Pregnancy test[e] | X | X | | | | | | | X | | | X | X | X | |
| Hematology, serum chemistry, coagulation parameters[f] | X | X[g] | | | X | X | | | X | X | X | X | X | X | |
| Urinalysis | X | X[g] | | | X | X | | | X | | | X | X | X | |
| Tumor markers | X | X[g] | | | | | | | X | | | X | X | | |
| AE/SAE[f] | X | X | X | X | X | X | X | X | X | X | X | X | X | X | |
| Study drug administration[h] | | X | | X | X | X | | X | X | X | X | X | | | |
| Dispense study drug | | X | | | | | | | X | | | X | | | |
| Provide/review diary | | X | | | | | | | X | | | X | X | | |
| PK sampling[i] | | X | X | X | X | X | X | X | | | | | | | |
| Tumor assessment | X | | | | | | | | | | | X[j] | | | |

| | | | | | | | | | | | | | | | |
|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|
| (RECIST v1.1) | | | | | | | | | | | | | | | |
| Contact of patient by site | | | | | | | | | | | | | | | X[k] |
| Biomarker sample | X[l] | | | | | | | | | | | X | X | | |

Abbreviations: AE=adverse event; D/d=day; ECG=electrocardiogram; ECOG= Eastern Cooperative Oncology Group; EOT=end of treatment; FU=follow up; MUGA=multigated acquisition; OS=overall survival; PK=pharmacokinetic; PS=performance status; RECIST=Response Evaluation Criteria in Solid Tumors; SAE=serious adverse event; SV=Screening Visit; v=version.

a. Only the days on which the patient will visit the study site are displayed in this table.
b. Patients will receive D07001-softgel until withdrawal due to a DLT, disease progression according to RECIST v1.1, withdrawn consent, or when another treatment discontinuation criterion is met.
c. Patients who are discontinued from study drug for a reason other than disease progression, death, or withdrawal of consent are to continue tumor assessments on the same schedule.
d. Cycles 3 and 5 only.
e. In women of childbearing potential only. A serum pregnancy test will be done at Screening and on Cycle 1 Day 1. A urine pregnancy test will be done on Day 1 of each subsequent cycle, at the EOT visit, and at the safety follow-up visit.
f. Abnormal liver function test values and AEs will be followed as indicated until resolution or return to baseline.
g. To be repeated only if screening was more than 7 calendar days prior.
h. Patients will receive study drug in the fasted state on Days 1, 3, 5, 8, 10, 12, 15, 17, and 19 of each cycle. During Cycle 1, patients may take study drug at home on Days 5, 10, 12, and 19. During Cycle 2, patients may take study drug at home on Days 3, 5, 10, 12, 17, and 19. From Cycle 3 onwards, patients may take study drug at home on all dosing days except for Day 1 of each cycle. Dosing on 2 consecutive days will not be allowed; there will be at least 1 day between 2 doses.
i. For PK sampling, there may be a time window of within 30 minutes before the study drug administration for the pre-dose time point, ±5 minutes for time points up to 4 hours of study drug administration, ±15 minutes for time points after 4 hours of study drug administration, and ±60 minutes for the time points on return visits.
j. Tumor assessment will be performed within 0-7 calendar days before the start of every odd-numbered cycle, starting from 0-7 calendar days before the start of Cycle 3.
k. Every 6 weeks.
l. Samples for pharmacogenomic, pharmacoproteomic and cellular analysis will be collected if the patient provides additional consent.

**Table 6 Part 2 Event Schedule (Dose Expansion)**

| | SV | Cycle 1[a] | | | | | | | Cycle 2 | | | | | Cycle 3 onwards[b] | EOT[c] | 30-day FU | FU for OS |
|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|
| | D -28 to 0 | D1 | D2 | D3 | D8 | D 15 | D 16 | D 17 | D1 (±1d) | D2[d] (±1d) | D3[d] (±1d) | D8 (±1d) | D15 (±1d) | D1 (±1d) | (±3d) | (±3d) | (±3d) |
| Informed consent | X | | | | | | | | | | | | | | | | |
| Inclusion/Exclusion criteria | X | X | | | | | | | | | | | | | | | |
| Medical history | X | | | | | | | | | | | | | | | | |
| Demographics | X | | | | | | | | | | | | | | | | |
| Prior medication | X | | | | | | | | | | | | | | | | |
| Concomitant medication | X | X | X | X | X | X | X | X | X | X[d] | X[d] | X | X | X | X | X | |
| Height | X | | | | | | | | | | | | | | | | |
| Weight | X | X | | | X | X | | | X | | | X | X | X | X | X | |
| Physical examination | X | X | | | X | X | | | X | | | X | X | X | X | X | |
| Vital signs | X | X | | | X | X | | | X | | | X | X | X | X | X | |
| ECG | X | X | | | X | X | | | X | | | | | X | X | X | |
| Echocardiogram or MUGA | X | | | | | | | | | | | | | X[e] | | | |
| ECOG PS | X | X | | | X | X | | | X | | | X | X | X | X | X | |
| Pregnancy test[f] | X | X | | | | | | | X | | | | | X | X | X | |
| Hematology, serum chemistry, coagulation parameters[g] | X | X[h] | | | X | X | | | X | | | X | X | X | X | X | |
| Urinalysis | X | X[h] | | | X | X | | | X | | | | | X | X | X | |
| Tumor markers | X | X[h] | | | | | | | X | | | | | X | X | | |
| AE/SAE[g] | X | X | X | X | X | X | X | X | X | X[d] | X[d] | X | X | X | X | X | |
| Study drug administration[i] | | X | | X | X | X | | X | X | | X[d] | X | X | X | | | |
| Dispense study drug | | X | | | | | | | X | | | | | X | | | |
| Provide/review diary | | X | | | | | | | X | | | | | X | X | | |
| PK sampling[j] | | X | X | X | X | X | X | X | X[d] | X[d] | X[d] | | | | | | |
| Tumor assessment (RECIST v1.1) | X | | | | | | | | | | | | | X[k] | | | |
| Contact of patient by site | | | | | | | | | | | | | | | | | X[l] |

| | | | | | | | | | | | | | | | | | |
|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|
| Biomarker sample | X[m] | | | | | | | | | | | | | X | X | | |

Abbreviations: AE=adverse event; D/d=day; ECG=electrocardiogram; ECOG= Eastern Cooperative Oncology Group; EOT=end of treatment; FU=follow up; MUGA=multigated acquisition; OS=overall survival; PK=pharmacokinetic; PS=performance status; RECIST=Response Evaluation Criteria in Solid Tumors; SAE=serious adverse event; SV=Screening Visit; v=version.

a. Only the days on which the patient will visit the study site are displayed in this table.
b. Patients will receive D07001-softgel until withdrawal due to disease progression according to RECIST v1.1, withdrawn consent, or when another treatment discontinuation criterion is met.
c. Patients who are discontinued from study drug for a reason other than disease progression, death, or withdrawal of consent are to continue tumor assessments on the same schedule.
d. Patients in food-effect cohort only. Patients who are not in the food-effect cohort will not attend the study site on Cycle 2 Days 2 and 3, and so may take the study drug at home on Cycle 2 Day 3.
e. Cycles 3 and 5 only.
f. In women of childbearing potential only. A serum pregnancy test will be done at Screening and on Cycle 1 Day 1. A urine pregnancy test will be done on Day 1 of each subsequent cycle, at the EOT visit, and at the safety follow-up visit.
g. Abnormal liver function test values and AEs will be followed as indicated until resolution or return to baseline.
h. To be repeated only if screening was more than 7 calendar days prior.
i. Patients will receive study drug in the fasted state on Days 1, 3, 5, 8, 10, 12, 15, 17, and 19 of each cycle, besides who was randomized to the high-fat fed in Cycle 1 Day 15 or Cycle 2 Day 1. During Cycle 1, patients may take study drug at home on Days 5, 10, 12, and 19. During Cycle 2, patients in the lower dose-expansion cohort may take study drug at home on Days 3, 5, 10, 12, 17, and 19; patients in the higher dose-expansion cohort (food-effect cohort) may take study drug at home on Days 5, 10, 12, 17, and 19. From Cycle 3 onwards, patients may take study drug at home on all dosing days except for Day 1 of each cycle. Dosing on 2 consecutive days will not be allowed; there will be at least 1 day between 2 doses.
j. For PK sampling, there may be a time window of within 30 minutes before the study drug administration for the pre-dose time point, ±5 minutes for time points up to 4 hours of study drug administration, ±15 minutes for time points after 4 hours of study drug administration, and ±60 minutes for the time points on return visits.
k. Tumor assessment will be performed within 0-7 calendar days before the start of every odd-numbered cycle, starting from 0-7 calendar days before the start of Cycle 3.
l. Every 6 weeks.
m. Samples for pharmacogenomic, pharmacoproteomic and cellular analysis will be collected if the patient provides additional consent.