Statistical Analysis Plan (SAP) - Part A

Protocol Title:	A multicentric phase 1/2 trial to evaluate the safety and efficacy of SOT102 as monotherapy and in combination with standard of care treatment in patients with gastric and pancreatic adenocarcinoma
Protocol Version No./Date:	Amendment 5/04-June-2024
CRF Version No./Date:	2.17/27-Oct-2024
SAP Version No./Date:	3.0/07-Feb-2025

1.0 Approvals

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2.0 Change History

Version/Date	Change Log
0.1	Created as new
0.2	Updated as per SOTIO and ICON reviews
0.3	Updated as per Sotio review
0.4	Updated as per Sotio review
1.0	Updated as per ICON review
1.1	Updated to add inferential PK analyses and changes from protocol amendment 2
1.2	Updated to reflect client comments, updated PKAP and ICON reviews
2.0	Prepared for sign off
2.1	Updated to reflect client comments and ICON reviews.
2.2	Updated for protocol versions 4 and 5; ICON review comments; Further updated for study early termination
2.3	Updated for changes to PK analysis
3.0	Version updated for signature

3.0 Table of Contents

4.0 Purpose

The Statistical Analysis Plan (SAP) describes the statistical methods to be used during the reporting and analyses of data collected under SOTIO Biotech a.s. Protocol SN201. In particular, this SAP is relevant to Part A segment of the protocol, which is dose finding of SOT102 in monotherapy.

5.0 Scope

The SAP outlines the following:

- Study objectives.
- Study design.
- Study endpoints.
- Applicable study definitions.
- Statistical methods.

6.0 Introduction

This SAP describes the statistical methods to be used during the analysis and reporting of data collected in the Part A segment for monotherapy treatment. Additional SAPs will be created for Parts B, C and D. The final analysis for Part A will occur prior to the final database lock for the study and Part A subject case report forms (CRFs) will be locked to data entry at this point.

This SAP should be read in conjunction with the study protocol and CRFs. This version of the plan has been developed using Protocol Amendment 5 dated 04 June 2024 and CRF version 2.17 dated 27 October 2024. Any further changes to the protocol or CRFs may necessitate updates to the SAP.

A stable draft SAP v1.0 was considered final for the purposes of programming activities and signed off prior to first patient in (FPI). The SAP will be updated and finalized prior to the effective database lock of Part A.

6.1 Changes from protocol

Given the small sample size in Part A, in section 12.7 Efficacy Analyses, Clopper-Pearson exact confidence intervals will be calculated instead of the Wald Confidence intervals specified in the protocol section 9.3.

7.0 Study Part A Objectives

7.1 Primary Objective

- To determine the maximum tolerated dose (MTD) and recommended phase 2 dose (RP2D) of SOT102 given as monotherapy

7.2 Secondary Objectives

- To assess the safety and tolerability of SOT102 in monotherapy.
- To characterize the pharmacokinetics (PK) of total SOT102, conjugated SOT102, [redacted].
- To explore evidence of SOT102 activity in monotherapy in individual patients.
- To explore whether patients develop any antibodies against SOT102.

8.0 Study Design

This study will assess the MTD and RP2D of SOT102 administered as monotherapy (Part A) and in combination with first-line standard of care (SoC) treatment (modified oxaliplatin + leucovorin + 5-fluorouracil containing chemotherapy regimen [mFOLFOX6] with nivolumab and nab-

paclitaxel/gemcitabine; (Part B) and efficacy of SOT102 administered as monotherapy (Part C) and in combination with first-line SoC treatment (Part D) in patients with advanced inoperable or metastatic gastric/gastroesophageal junction (GEJ) adenocarcinoma or inoperable or metastatic pancreatic adenocarcinoma.

In Part A, patients with advanced/metastatic gastric/GEJ adenocarcinoma or pancreatic adenocarcinoma will be treated with escalating doses of SOT102 given once every 14 days via the intravenous (IV) route over 45 (±15) minutes.

A starting dose of 0.032 mg/kg was selected in Part A of this study. If only grade ≤1 therapy-related toxicities are observed during cycle 1 in the first three patients at a given dose level, the dose will be increased by 100% for the next dose level. If grade ≥2 therapy-related toxicities are observed during cycle 1 in any patient at a particular dose level, the dose will be increased by de-escalating dose increases following a modified Fibonacci scheme. These adjustments of the planned dose levels and dose increments will be considered by the Dose Escalation Committee (DEC).

SOT102 monotherapy dose escalation will continue until dose-limiting toxicities (DLTs) are observed in ≥2 DLT-evaluable patients at a given dose level. The MTD will be declared as the highest dose level tested below that particular dose level. At least 6 DLT-evaluable patients will be included to assess the RP2D before the respective expansion Part C is initiated. Additional doses and schedules may be opened as required based on the MTD assessment results to define the dose and schedule of the RP2D.

The original intention of the trial was to investigate its objectives in two indications – gastric/GEJ cancer and pancreatic cancer. Following a reassessment of the benefit/risk ratio, it was decided by the sponsor to halt the clinical development in gastric/GEJ cancer and proceed only with pancreatic cancer. Per protocol amendment #4 subjects enrolled since the restart of the trial will receive premedication with corticosteroids (4 mg dexamethasone twice daily) the day before, the day of (at least one hour prior), and the day after each SOT102 administration.

Per protocol amendment #5, the study population was amended to patients with inoperable or metastatic pancreatic adenocarcinoma whose tumor expresses Claudin 18.2 (CLDN18.2). CLDN18.2, splice variant 2 of claudin 18, represents a potentially attractive tumor-associated antigen. SOT102 is an anti-body-drug conjugate targeting CLDN18.2. Subjects enrolled in the study after the restart are tested for CLDN18.2 positivity determined by immunohistochemistry assay.

As of December 2024, the study was terminated due to safety concerns.

8.1 Sample Size Considerations

In Part A, a 3+3 design dose escalation will be applied until the MTD is identified. Therefore, 3 to 6 DLT-evaluable patients per dose level will be included. Assuming 26 patients have been enrolled prior to Protocol Amendment 4 and expected enrollment upon trial restart of additional three patients at dose level 2, followed by two dose levels per 6 patients and additional patients for confirmation of RP2D (acknowledging that at least 6 DLT-evaluable patients will be included to assess the RP2D before the respective expansion parts C and D are initiated), the total number of assumed evaluable patients is 47. Assuming 8 patients needed for replacement, the estimated number of patients is 55.

8.2 Randomization

Random assignment is not being used in this study.

9.0 Study Endpoints

9.1 Endpoint Attributes

Objectives	Endpoints
Primary - Part A	Primary endpoint

• To determine the maximum tolerated dose (MTD) and recommended phase 2 dose (RP2D) of SOT102 given as monotherapy	• MTD is defined as the highest dose level tested below the dose level associated with ≥33% of DLT-evaluable patients experiencing a DLT. The RP2D will be selected based on integrated evaluation of the totality of clinical and preclinical data, for all dose levels tested.
Secondary	Secondary endpoints
• To assess the safety and tolerability of SOT102 in monotherapy • To characterize the pharmacokinetics (PK) of total SOT102, conjugated SOT102, [redacted] • To explore evidence of SOT102 activity in monotherapy in individual patients • To explore whether patients develop any antibodies against SOT102	• The occurrence of DLTs, occurrence of TEAEs, SOT102-related AEs, SAEs, AEs leading to premature discontinuation of SOT102, deaths, or clinical laboratory test abnormalities • PK of total SOT102, conjugated SOT102, [redacted] • Anecdotal tumor response per RECIST 1.1 by type and CLDN18.2 expression • The number of patients with detected antibodies against any part of SOT102

9.2 Population Sets

9.2.1 Screened Population

The screened population is defined as all patients who sign the initial study informed consent form.

9.2.2 Enrolled Population

The enrolled population is defined as all patients who sign the initial study informed consent form, and all eligibility criteria are met as confirmed by approver during screening assessments and recorded as enrolled on the Eligibility Criteria CRF page. This population will be used to describe patient disposition and protocol deviations and may include patients who do not receive SOT102 treatment.

9.2.3 Safety Population

The safety population is defined as all patients exposed to at least one dose of SOT102. All safety analyses will be performed on safety population with the exception of the DLT analysis which will be performed on the DLT-evaluable population.

9.2.4 Pharmacokinetic Evaluable Population

The Pharmacokinetic (PK) evaluable population consists of all patients exposed to at least one dose of SOT102 and who have at least one post-dose concentration measurement above the lower limit of quantitation (LLOQ) for total SOT102.

9.2.5 DLT-evaluable Population

The DLT evaluation period is 28 days counted from day 1 of cycle 1 of SOT102.

The DLT-evaluable patient will be:

- Patient who has received 2 doses of SOT102 per schedule (day 1 of cycle 1 and day 1 of cycle 2) with the maximum postponement of cycle 2 by 1 day (as agreed by the sponsor) and who completed the evaluation period of 28 days.
- Patient who experiences a treatment emergent adverse event at any time during the DLT evaluation period that meets the definition of a DLT.

Patients who do not fulfil the DLT evaluation criteria for any reason other than DLT will be replaced. This population will be used to assess DLT incidence and the estimate of MTD.

9.2.6 Efficacy Population

All patients exposed to at least one dose of SOT102 who had at least one evaluable tumor assessment per RECIST v1.1 after the initiation of SOT102 treatment. An evaluable tumor assessment is a post-baseline CT/MRI tumor assessment which is not NE (not evaluable).
This will be the main population for efficacy exploration.

10.0 Conventions and Derivations

10.1 Study Treatment

The study treatment defined for Part A are different dose levels of SOT102 as defined in the study protocol.

10.2 Baseline

Unless otherwise specified, baseline is defined as the last non-missing value prior to the first administration of SOT102 treatment.

10.3 Change from Baseline

Change from baseline (CFB) will be calculated as (post-baseline – baseline). CFB will be calculated for patients with both a baseline and post-baseline value as applicable.

10.4 Percentage Change from Baseline

Percentage CFB will be calculated as (CFB/baseline) *100, where applicable.

If a baseline value is 0 for a parameter, then percentage CFB will not be calculated for that parameter.

10.5 Definition of Study Day

All study days on or after the first administration of SOT102 treatment will be calculated as date of assessment minus date of first administration of SOT102 treatment + 1, i.e.,

- Date of assessment – date of first administration of SOT102 treatment + 1.

Study days that occur before the first administration of SOT102 treatment will be calculated as date of assessment minus date of first administration of SOT102 treatment, i.e.,

- Date of assessment – date of first administration of SOT102 treatment.

In cases of missing and/or incomplete dates, no study days will be calculated.

10.6 Study Phase

Phases of the study are defined as follows:

Screening: From the date of informed consent form signature to the day prior to the first infusion of SOT102

On-treatment (i.e., SOT102 Treatment period): From the day of the first infusion of SOT102 to 30 days after the last infusion of SOT102

Follow-up: Begins from the date of the last infusion of SOT102 + 31 days.

10.7 DLT Evaluation Period

Twenty-eight (28) days starting from Day 1 of Cycle 1 of SOT102 treatment

10.8 Cycle

Cycle number will be taken from the database. Unscheduled visits will be in listings only and identified with a numbering system that reflects the cycle they occur in by comparing the visit date against the scheduled visits and numbering in order of unscheduled visit e.g., Unscheduled Cycle 1 Day 1.01, Unscheduled Cycle 1 Day 8.01 etc. Unscheduled visits occurring on the same day as other visits (scheduled or otherwise) will be kept as separate records.

Tumor assessments are not performed regularly per cycle, these will be identified in the ADaM datasets by actual week of study by calculating (date of assessment – date of first infusion+1)/7 and rounding up.

10.9 Age group

Age at informed consent will be categorized as ≥ 18 years to ≤ 45 years, ≥ 46 years to ≤ 64 years, ≥65 years to ≤74 years, ≥75 years to ≤84 years, ≥85 years, with no rounding applied for assigning to categories, meaning patient will be in group ≥ 85 years once s/he has in the Demography CRF page age at least 85 or higher.

10.10 Time since Initial Diagnosis

The time since initial diagnosis will be calculated as date of first dose minus the date of initial diagnosis and converted to years. The date of initial diagnosis is from the Cancer History CRF page. Partial dates to be imputed as per section 10.16.2.

10.11 Number of previous lines of systemic therapy

The number of previous lines of systemic therapy is the maximum line of therapy recorded in previous anticancer systemic per patient from the Prior Systemic Anti-Cancer Therapy Regimen CRF page.

10.12 Prior and Concomitant Medications and Procedures

The medications that are taken prior to the first dose of SOT102 treatment and discontinued prior to the first dose of SOT102 treatment are defined as prior medications. Likewise, procedures occurring prior to the first dose of SOT102 treatment and discontinued prior to the first dose of SOT102 treatment will be defined as prior procedures.

The concomitant medications are defined as medications that have started at Day 1 or after Day1 or if they were started prior to first dose of SOT102 treatment but are ongoing at Day 1. Concomitant procedures are those that occur on or after Day 1 or if they were started prior to the first dose of SOT102 treatment but are ongoing at Day 1.

Refer to Section 10.16.1 below for how to handle partial or missing dates in the assessment of whether or not a treatment was taken prior to or concomitantly with the SOT102 treatment.

10.13 Derivation of Efficacy Variable

10.13.1 Tumor Response Endpoints

Tumor assessments will be performed by investigators and assessed per RECIST v1.1[1] for all tumor indications.

The RECIST v1.1 assessment has the following possible response categories (ordered from the best response to worst): complete response (CR), partial response (PR), stable disease (SD), progressive disease (PD), or NE.

10.13.2 Objective Response Rate and Tumor Burden

The objective response categorized in accordance with RECIST v1.1 is defined as the proportion of patients who achieved a confirmed CR or confirmed PR. The objective response rate (ORR) is calculated as the number of patients with objective response divided by the number of patients in the Efficacy population. Objective response should be confirmed by a repeat imaging assessment not earlier than 4 weeks (28 days) after the first CR or PR is observed.

Percentage CFB of Tumor burden will be summarized as the percent CFB in target lesions per time point.

It will be derived as:

- ((Sum of target lesions at post-baseline assessment – sum of target lesions at baseline)/sum of target lesions at baseline) x 100.

The maximum reduction in target lesions from baseline will be derived across all the post-baseline assessments until documented disease progression, as minimum of (Percentage CFB of Tumor Burden).

10.13.3 Best Overall Response

The best overall response is the best response recorded from the start of the treatment until disease progression/recurrence or death. The patient's best response assignment will depend on the achievement of both measurement and confirmation criteria.

A best response of CR or PR cannot be determined unless it is confirmed, no earlier than 4 weeks (28 days) from the time a response of CR or PR is first observed (SD does not require confirmation provided that observation of SD occurs at least 6 weeks (42 days) after the baseline scan).

10.14 Derivations for Exposure Variables

The planned dose level for SOT102 treatment will be recorded in the CRF at Screening. This is the dose level referred to wherever 'dose level' is referenced and is the starting dose level only, not accounting for changes.

The actual dose level for SOT102 treatment is calculated as actual dose administered/weight (mg/kg) as follows:

- Actual dose per cycle (mg/kg) = [(total dose planned) * (administered volume / total prepared infusion volume)] / pre-dose weight

The pre-dose weight of the patient recorded for that cycle will be used. If the pre-dose weight is not available for a particular cycle, the actual dose will not be calculated.

The duration of exposure will be calculated as the last dose date – the first dose date +1, converted to weeks.

10.15 Safety Variables

10.15.1 Dose-Limiting Toxicity

The DLTs are defined in Section 4.1.1.1 of the protocol. Toxicity will be assessed according to the National Cancer Institute (NCI) Common Terminology Criteria for Adverse Events, Version 5.0 (CTCAE v5.0; 27 November 2017). For analysis of DLT, the information of DLT collected on the Adverse Events CRF page will be used.

10.15.2 Treatment-emergent AEs

All AEs will be recorded in the database, but not all on-treatment events will be considered as treatment-emergent e.g., if they are an improvement of an existing condition. A treatment-emergent AE (TEAE) is defined as an AE that:

- emerges at SOT102 treatment start or afterwards, having been absent at the time of pre-treatment (screening), or
- re-emerges at SOT102 treatment start or afterwards, having been present at the time of pre-treatment (screening), or
- worsens in severity at SOT102 treatment start or afterwards relative to the pre-treatment state if the AE is continuous.

TEAEs will be identified as follows:

1. TEAE from start of treatment at Cycle 1 Day 1 to 30 days after final administration of SOT102.
2. TEAE within follow up period i.e., beyond 30 days after the final administration of SOT102 until disease progression (clinical progression or radiographic disease progression as recorded on the 'End of Treatment' eCRF page, or radiographical as recorded on the 'Disease Response' CRF page) or start of new anti-cancer therapy (defined as the earliest start date for subsequent systemic anti-cancer therapy recorded on the 'Systemic anti-cancer therapies' eCRF page).TEAEs will be combined for reporting.

10.16 Imputation of Missing Data

No further imputation of missing data except the cases below will be performed.

10.16.1 Imputation of Missing Dates on AEs or Concomitant Medications and Procedures

For the purposes of assigning AEs and concomitant medications/procedures to study periods the following algorithm will be used for missing or partial dates (AE start/stop dates and concomitant medication/procedure start/stop dates): The actual (non-imputed) value for date will be presented in all data listings and imputed dates will only be used for programming purposes, such as TEAE derivation.

Start date

If the start date is completely missing (i.e., the day, month, and year are all unknown), the start date will be set to the date of the first dose of study medication.

Missing day only

- If the month and year of the incomplete date are the same as the month and year of the **first dose date**, then the day of the **first dose date** will be assigned to the missing day.
- If either the year is before the year of the **first dose date** or if years are the same, but the month is before the month of the **first dose date**, then the last day of the month will be assigned to the missing day.
- If either the year is after the year of the **first dose date** or if both years are the same, but the month is after the month of the **first dose date**, then the first day of the month will be assigned to the missing day.

Missing month only

- The day will be treated as also missing and both month and day will be replaced according to the procedure below.

Missing day and month

- If the year of the incomplete date is the same as the year of the **first dose date**, then the day and month of the **first dose date** will be assigned to the missing fields.
- If the year of the incomplete date is not the same as the year of the **first dose date**, then January 1 will be assigned to the missing fields.

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.

Stop date

Missing day only

- If the month and year of the incomplete date are the same as the month and year of the **last visit date**, then the day of the **last visit date** will be assigned to the missing day.
- If either the year is before the year of the **last visit date** or if both years are the same, but the month is before the month of the **last visit date**, then the last day of the month will be assigned to the missing day.
- If either the year is after the year of the **last visit date** or if both years are the same, but the month is after the month of the **last visit date**, then the first day of the month will be assigned to the missing day.

Missing month only

- The day will be treated as missing and both month and day will be replaced according to the procedure below.

Missing day and month

- If the year of the incomplete date is the same as the year of the **last visit date**, then the day and month of the **last visit date** will be assigned to the missing fields.
- If the year of the incomplete date is before the year of the **last visit date**, then December 31st will be assigned to the missing fields.
- If the year of the incomplete date is after the year of the **last visit date**, then **January 1st** will be assigned to the missing fields.

Completely missing stop dates where a record is not ongoing, will not be imputed.

10.16.2 Imputation of Initial Diagnosis Date

The partial start date for initial diagnosis will be assigned to 15th day of the month (if only day is missing) or July 1st (if both month and day are missing). If imputation leads to a date of diagnosis after informed consent date, the date shall be imputed instead as the 1st of the month that informed consent occurred, or the last day of the previous month if informed consent occurred on the 1st. No imputation to be performed if year is missing.

10.16.3 Imputation of Laboratory Values with Character Symbol

Missing laboratory data will not be imputed. However, laboratory values of the form of "< x" (i.e., below the lower limit of quantification) or "> x" (i.e., above the upper limit of quantification) will be imputed as "x" for the purpose of calculation of summary statistics and comparing to normal ranges. These values will still be displayed as "< x" or "> x" in the listings.

10.16.4 Imputation of Pharmacokinetic Values with Character Symbol

Missing PK data will not be imputed. However, PK concentration or parameter values of the form of "< x" (i.e., below the lower limit of quantification) or "> x" (i.e., above the upper limit of quantification) will be

imputed as not available “NA” and excluded from summary tables. These values will still be displayed as “< x” in the listings.

10.17 Time Conversion

Time conversion will follow the rules described below:

- 1 week = 7 days,
- 1 month = 30.4375 days,
- 1 year = 365.25 days.

11.0 Interim Analyses

No interim analyses are planned in Part A of the study.

12.0 Statistical Methods

All data collected during this study will be displayed in data listings on the largest population for which data is available, unless otherwise specified. Data listings will be sorted by dose level and patient ID as a minimum, additional sorting variables will be specified as appropriate in the listing shell. Listings will include all relevant derived variables – those variables will be marked as “(derived)”. Where appropriate, a listing may also contain a flag for the related population: for safety data, if the patient is in the safety population; for efficacy outputs, if the patient is in the efficacy population; and for the DLTs, if the patient is DLT-evaluable. When listing options from the CRF in the case of ‘Other: Specify’, concatenate the specify text e.g. ‘Other: XXXXXXXXX’; in the case of missing end date due to an ongoing event, medication or procedure, the text ‘ongoing’ will be inserted in place of the end date.

Descriptive statistics (number of observations [n], mean, median, standard deviations [STD], minimum, Q1, Q3 [or interquartile range as indicated below], and maximum values) for continuous variables will be presented. Mean, median, Q1 and Q3 will be presented to 1 decimal more than original data. STD will be presented to 2 decimals more than original data. Minimum and maximum will match the decimal points in the original data. For categorical variables, summary measures will include the frequency and percentage (with 1 decimal place) of patients in each category. Percentages will not be displayed for zero counts.

The summary tables will be presented by dose level and all dose levels combined.

The analyses will be descriptive, no formal testing of statistical hypotheses is planned.

All data summaries and tabulations will be prepared with SAS® Version 9.4 or higher.

12.1 Patient Disposition

The number and percentage of patients screened (Informed Consent Form signed), enrolled, and treated in the study will be presented.

The number and percentage of patients and each population to which they belong will be presented.

The number of patients screened, enrolled, and treated by country and site will be presented.

Disposition will be summarized descriptively for all enrolled population by dose level and all dose levels combined. Total number of screen failures will be summarized, together with the number and percentage of patients who discontinued from the study and a breakdown of the corresponding reasons for discontinuation (the percentages are calculated from enrolled population), and the number and percentage of patients who discontinued SOT102 treatment with the corresponding reasons.

12.2 Demographic and Baseline Characteristics

Demographic and baseline characteristics data will be summarized descriptively by dose level and all dose levels combined for the Safety population. The demographic and disease history summaries will be repeated for the Efficacy population.

12.2.1 Demographics

Demographic characteristics will be summarized using the following information from the Demographics CRF page: sex, ethnicity, race, age at informed consent and age group. From other CRF pages, also baseline weight (kg), baseline height (m), baseline body surface area [BSA] (m2), and baseline Eastern Cooperative Oncology Group (ECOG) status will be summarized.

12.2.2 Primary Disease History

Primary disease history will be listed and summarized by dose level using the information from the Cancer History CRF page. Variables to be summarized include location of primary tumor, time since initial diagnosis, stage of disease at diagnosis, HER2 status. The number of previous lines of systemic therapy will be summarized.

Prior mutations and other genetic analysis data will be listed only.

12.3 Prior Therapy for Primary Diagnosis

A tabulation of prior systemic therapies coded according to WHODrug (v Global B3 Sep 2019 or later) will be presented for the Safety and Efficacy populations. Prior anti-cancer therapies will be tabulated and categorized by medication group (ATC level 2) and subgroup (ATC level 4) using counts and percentages.

A tabulation of non-systemic anti-cancer therapies coded according to MedDRA (version 25 or later) will be presented for the Safety and Efficacy populations. Prior non-systemic anti-cancer therapies will be tabulated and categorized by System Organ Class and Preferred Term using counts and percentages. Prior radiotherapy will not be coded, and the verbatim terms will be listed only.

Systemic and non-systemic anti-cancer therapies will be presented separately.

Full details of prior systemic and non-systemic anti-cancer therapies will be listed only.

12.4 Medical History

Medical history will be coded according to Medical Dictionary for Regulatory Activities (MedDRA, Version 25 or later).

Medical history will be tabulated by system organ class (SOC) and preferred term (PT) using counts and percentages.

12.5 Treatments

12.5.1 Exposure to SOT102

Descriptive statistics will be provided by dose level and all dose levels combined on the Safety and Efficacy populations for the duration of exposure (weeks) and the total number of doses administered.

The total number of doses administered will be summarized both as a continuous and categorical variable.

The number and percentage of patients with missing doses, at least one dose adjusted, at least one dose interruption, and reasons for missing dosing, dose adjustment and interruption will be presented on the Safety population.

A summary of dose levels and actual dose levels administered will be presented by the number of doses administered and number of patients dosed. Further information regarding patients' dosing regimens, including total dose, dosing form, over/under-dosing, and dose changes and interruptions will be listed.

12.5.2 Prior and Concomitant Medications and Procedures

Medications received priorly and concomitantly with study drug, categorized by medication group (ATC level 2) and subgroup (ATC level 4) according to WHODrug, will be summarized by dose level for the Safety population.

Prior and concomitant procedures will be coded according to MedDRA summarized by System Organ Class and Preferred Term.

Prior and concomitant medications and procedures will be tabulated separately using counts and percentages to display the number and percentage of patients using at least one medication.

Full details of medications and procedures will be presented in the listings only.

12.5.3 Premedications

Patients enrolled from Protocol Amendment v4 onwards will be premedicated with dexamethasone. Dexamethasone administration will be listed only.

12.6 Protocol Deviations

Protocol deviations will be documented by category (as per the latest study Protocol Deviation Guidance document). All deviations will be reviewed, categorized, designated important or not important, and finalized prior to database lock of Part A. Important protocol deviations will be defined as those potentially impacting safety or efficacy assessments and analyses. Additional details of what will be considered important protocol deviation can be found in the Protocol Deviation Guidance document.

Important protocol deviations for patients in the Enrolled population will be summarized by category. All protocol deviations will be listed only.

Any COVID-19-specific protocol deviations will be listed separately.

12.7 Efficacy Analyses

All efficacy analyses will be performed for the Efficacy population.

12.7.1 Objective Disease Response

Descriptive statistics (frequency and percentage) for ORR, for best confirmed overall response, and the two-sided 95% Clopper-Pearson confidence interval[(2)] for the ORR will be presented. ORR will be summarized for all dose levels combined only. Best confirmed overall response will be summarized by dose level and all dose levels combined.

Analysis by claudin 18.2 expression will be considered exploratory and may be performed after sponsor assessment of available data.

12.7.2 Tumor Burden

A waterfall plot of maximum percent reduction in the sum of diameter of target lesions from baseline will be created. This plot will display the best percentage CFB in the sum of the diameter of all target lesions for each patient. The bar for each patient will be colored by their dose level.

A spaghetti plot of percent reduction in the sum of target lesions from baseline will be created to plot the change in tumor burden over time for each patient. The time will be calculated from the treatment initiation (first dose of treatment). RECIST assessments contributing towards a particular visit may be performed on different dates and the latest date of the scan dates of the component from the CRF will be used as the assessment time. The colors of the lines will be based on the patient's dose level.

12.8 Safety Analyses

AEs will be graded according to the NCI CTCAE Version 5.0.

All safety analyses will be summarized by dose level and all dose levels combined. Safety analyses will be performed in the Safety population unless other specified.

12.8.1 Adverse Events

AEs will be coded according to MedDRA (Version 25.0 or later) by SOC, PT, and severity grade using NCI CTCAE Version 5.0.

Linked AEs will be identified via the AE ID recorded as change in severity of an existing AE on the AE CRF page. Multiple AE records with differing attributes can comprise a single linked AE occurrence. Linked AEs will be selected for analysis in tables based on their worst-case scenario attribute e.g., maximum CTCAE grade, causal relationship, seriousness, treatment emergence and action taken out of all records.

The ordering (the worst to best) for the following characteristics will be applied:

- Relationship: suspected, not suspected.
- Toxicity Grade: Grade 5 to Grade 1.

AE records within a linked AE can be given different treatment-emergence status. Treatment emergence for linked AEs will be established as those records in the linked AE with a worsening of severity from the preceding record.

12.8.1.1 Treatment-emergent AEs

An overall summary of event incidence will be presented, displaying the number of events and number of patients with events for the following: TEAEs; Grade 3 or Greater TEAEs and SOT102 related TEAEs; Serious TEAEs and SOT102 related SAEs; Fatal TEAEs, TEAEs and related TEAEs leading to discontinuation of SOT102; Immune related TEAEs; TEAES leading to reduction of SOT102 and interruption of SOT102; DLTs.

A breakdown of the number and percentage of patients reporting each AE categorized by SOC and PT will be presented. Note that the counts will be presented by patient, rather than event, and patients are only counted once within each SOC or PT if an AE was reported more than once. Selected tables will include the number of events (the linked AEs, if applicable) alongside the patient count. ‘Treatment-related’ AEs refers to those AEs with relationship of ‘Suspected’ reported for treatment. The following summaries of TEAEs will be presented by SOC and PT:

- Patients reporting DLTs in DLT-evaluable population,
- Patients reporting at least one TEAE),
- Patients reporting at least one treatment-related TEAE,
- Patients reporting at least one CTCAE grade 3 or greater TEAE,
- Patients reporting at least one CTCAE grade 3 or greater treatment-related TEAE,
- Patients who permanently discontinued study drug due to a TEAE,
- Patients who permanently discontinued study drug due to a treatment-related TEAE,
- Patients with TEAEs leading to dose reduction or interruption,
- Patients with treatment related TEAEs leading to dose reduction or interruption.

The following summaries will be presented by PT in descending order of frequency:

- Patients reporting at least one TEAE for PTs occurring in at least 10% of patients,

- Patients reporting at least one CTCAE grade 3 or greater TEAE for PTs occurring in at least 5% of patients,
- Patients reporting at least one non-serious TEAE for PTs occurring in at least 5% of patients.

The percentage for the thresholds mentioned above will be counted from all patients in the safety population, not distinguishing dose levels.

The following summaries will be presented by SOC, PT, and maximum CTCAE grade:

- Patients reporting at least one TEAE,
- Patients reporting at least one treatment-related TEAE

Additionally, the following summary will be presented for all subjects by SOC and PT, along with the highest reported CTCAE grade per PT:

- Non-serious TEAEs related to SOT102.

The following listings will be produced separately on the Safety Population unless otherwise specified:

- All AEs (Screened population and including Enrolled and Safety population flags, and TEAE flag),
- Dose-limiting toxicities (including DLT-evaluable population flag),
- AEs leading to death (On Screened population and including Enrolled and Safety population flags),
- Treatment-emergent SAEs,
- TEAEs leading to discontinuation of SOT102,
- TEAEs leading to dose reduction or interruption of SOT102,
- Non-treatment-emergent AEs (On Screened population and including Enrolled and Safety population flags).
- All AEs related to SOT102 reported after 30 days (including TEAE flag).

12.8.2 Serious AEs and Deaths

The following summaries of SAEs, including AEs that lead to death, will be presented by SOC and PT:

- Patients with at least one SAE,
- Patients with at least one treatment-related SAE,
- Patients with a TEAE leading to death,
- Patients with a treatment-related TEAE leading to death.

12.8.3 Laboratory Data

12.8.3.1 Laboratory Parameters

Quantitative data will be summarized by dose level and all dose levels combined using descriptive statistics of actual values and CFBs for each scheduled visit over the course of the study. All laboratory data will be summarized in International System units. The laboratory data will be presented by visit for all timepoints with at least two subjects present in a dose level.

The actual values for each scheduled visit over the course of the study for selected laboratory parameters will be plotted at each collected time point by line-plot. Each line will show one patient, one figure will represent all patients from one dose level. The timepoint will be calculated from the first dose of treatment as Day 1 and pre-baseline measurements will be included as negative days. Unscheduled visits will be included into the plots only. The selected laboratory parameters are Leukocytes, Hemoglobin, Platelets,

Neutrophils, Albumin, Sodium, ALT, ALP, AST, Bilirubin, Potassium, Magnesium, Calcium and Creatinine clearance.

Laboratory values out of local normal ranges will be presented in separate listings.

Categorical laboratory parameters will be provided in listings only.

12.8.3.2 Hy's Law

Hepatic function abnormality will be defined by an increase in AST and/or ALT to ≥ 3 × ULN and/or an increase in total bilirubin to ≥2 × ULN but without increase in ALP (i.e., ALP < 2 × ULN).

Summary of liver function tests will include the number and percentage of patients meeting Hy's Law at each scheduled visit.

12.8.4 Vital Signs

The following vital signs will be summarized: heart rate (beats/min), systolic blood pressure (SBP; mmHg), diastolic blood pressure (DBP; mmHg), body temperature (C), and weight (kg).

Vital signs will be summarized descriptively at each study timepoint where they are collected, separately for each dose level and all dose levels combined. CFB values will be summarized for the post-baseline time points. Sa02 monitoring data will be listed only.

12.8.5 Physical Examinations, ECGs, and Other Observations Related to Safety

Additional safety assessments include physical examinations, ECOG evaluation, ECG measurements, left ventricular ejection fraction (LVEF), esophagogastroduodenoscopy, HIV/HBV monitoring, and pregnancy test. Summaries of selected safety assessments will be tabulated by dose level and overall and at each assessment timepoint. All data will be listed.

12.8.5.1 Physical Examination

Physical examination data will be listed only.

12.8.5.2 ECOG Performance Status

A tabulation of ECOG performance status by timepoint will be provided separately for each dose level and all dose levels combined, including the number and percentage of patients reporting each ECOG category at each scheduled time point.

12.8.5.3 Electrocardiogram

A summary of ECG parameters including heart rate (beats/min), QT interval (msec), QTcF (msec), and RR interval (msec) and CFB (for only QTcF) will be presented, separately for each dose level and all dose levels combined for each planned visit as well as the minimum, maximum, and last post-baseline observation.

Summaries will be generated for patients based on International Council for Harmonisation (ICH) E14 category, with QTcF increased to value > 450 and ≤ 480 msec, > 480 and ≤ 500 msec, and value > 500 msec, and patients with CFB in QTcF increased to > 30 to ≤ 60 msec, and > 60 msec at each timepoint.

12.8.5.4 Left Ventricular Ejection Fraction

LVEF data will be summarized. Observed values and CFBs will be presented for each planned visit. Additionally, patients will be summarized using the following categories at each timepoint:

- Decrease from baseline of ≥ 10% and < 20%; and absolute post-baseline value 40-50%.
- Decrease from baseline of ≥ 20% and absolute post-baseline value 20% to 40%.

- Absolute post-baseline value < 20%.

12.8.5.5 Esophagogastroduodenoscopy

Esophagogastroduodenoscopy data will be listed only.

12.8.5.6 HIV/HBV Monitoring

HIV/HBV monitoring data will be listed only by cohort.

12.8.5.7 Pregnancy Test

Pregnancy testing data will be listed only.

12.8.5.8 Death Report

Death report data will be listed for the Screened population. Primary and secondary causes of death will be summarized using a combination of coded terms (MedDRA coded PT and SOC terms) and the CRF responses.

12.9 Plasma PK Summaries

All PK Analyses will be performed using the PK population.

Descriptive statistics (number of patients, mean, geometric mean, standard deviation (SD), coefficient of variation [%CV], geometric CV, median, min, and max) will be used to summarize each analyte's [total SOT102 and conjugated SOT102] plasma concentrations descriptively by timepoint and actual dose level received at each PK timepoint. All concentrations data will be listed by planned dose level and nominal timepoints (cycles will not be pooled), with the actual dose level received at each timepoint presented at record level. Patient profiles of plasma concentration will be presented graphically with subjects from a planned dose level presented side by side on one page. Mean concentrations over time per planned dose level will also be presented, in linear and semi-logarithmic scale.

The following rules apply:

- If there are less than 3 quantifiable values in a data series, only the minimum, maximum and n will be presented. The other summary statistics will be denoted as not calculated (NC).
- If any of the values at a certain timepoint are BLQ, the geometric mean and geometric coefficient of variation (CV) will be denoted as NC.

PK Parameters will be calculated by Quinta and details can be found in the Part A PK analysis plan.

The same list of descriptive statistics as for the plasma concentrations will be provided.

Pharmacokinetic parameters will be listed, and tabulated/ summarized by dose level and cycle.

An exploratory assessment of dose proportionality will be presented. The plasma PK parameters C_{max}, $AUC_{0\text{-last}}$, and $AUC_{0\text{-inf}}$ for total SOT102, and conjugated SOT102 will be compared across each dose level to assess dose proportionality (i.e., proportionality of a change in systemic exposure with a change in dose). Statistical analyses will be done using a power model

$$parameter_{ij} = \exp(\alpha)\cdot(Dose_{ij})^{\beta}\cdot\exp(C_j)\cdot\exp(\varepsilon_{ij}),$$

with the following general form after linearization by natural logarithm (ln-transformation)

$$\ln(parameter_{ij}) = \alpha + \beta\cdot\ln(Dose_{ij}) + C_j + \varepsilon_{ij},$$

where ($parameter_{ij}$) is the PK parameter value for subject i at cycle j; α is the y-intercept, β is the slope (a measure of dose proportionality between Dose and PK parameter value), C_j is the cycle j and ε_{ij} is the error term. Modelling will be performed using a linear mixed effects model with unstructured covariance matrix, with above mentioned parameters fitted as fixed effects, and with subject slope and intercept fitted as random effects.

The estimates of α and β will be reported, along with 90% confidence intervals (CIs) for β for each PK parameter. If the 90% CIs of the slope of the C_{max} and AUCs contain 1, then dose proportionality is indicated.

12.10 Immunogenicity

The presence or absence of anti-drug antibodies will be summarized by dose level, all dose levels combined and timepoint. Presence will be inferred by the result 'POSITIVE CANDIDATE' at screening, or 'POSITIVE' at post-baseline assessments. Immunogenicity data will be listed. Further exploration of ADA impact on PK may be performed post-hoc if the dose relationship appears normal from interim PK analyses; in such a case it may be considered to run an analysis pooled across doses using dose-normalized PK parameters to assess the impact of ADAs.

13.0 References

1. Eisenhauer EA, Therasse P, Bogaerts J, Schwartz LH, Sargent D, Ford R, et al. New response evaluation criteria in solid tumours: revised RECIST guideline (version 1.1). European Journal of Cancer. 2009;45(2):228-47.
2. Clopper C, Pearson ES. The use of confidence or fiducial limits illustrated in the case of the binomial. Biometrika. 1934;26:404-13.

14.0 Glossary of Abbreviations

Glossary of Abbreviations:	
AE	Adverse event
ALP	Alkaline phosphatase
ALT	Alanine transaminase
AST	Aspartate transaminase
ATC	Anatomic Therapeutic Classification
AUC	Area Under the Curve
BLQ	Below the Limit of Quantification
BMI	Body Mass Index
BOR	Best Overall Response
BSA	Body Surface Area
CFB	Change from baseline
CLDN18.2	Claudin 18 splice variant 2
CR	Complete Response
CRF	Case Report Form
CSR	Clinical Study Report
CT	Computed Tomography
CV	Coefficient of variation
DBP	Diastolic blood pressure
DEC	Dose Escalation Committee
DLT	Dose-limiting toxicity
ECG	Electrocardiogram
ECOG	Eastern Cooperative Oncology Group
EDA	Ethylene diamine
FPI	first patient in
GEJ	Gastroesophageal junction
HBV	Hepatitis B Virus
HER2	Human epidermal growth factor receptor 2
HIV	Human Immunodeficiency Virus
ICH	International Council for Harmonisation
INR	International normalized ratio
IV	Intravenous

LLOQ	lower limit of quantitation
LVEF	Left ventricular ejection fraction
MedDRA	Medical Dictionary for Regulatory Activities
mFOLFOX6	Modified oxaliplatin + leucovorin + 5-fluorouracil containing chemotherapy regimen
MRI	Magnetic Resonance Imaging
MTD	Maximum tolerated dose
NA	Not Available
NCI CTCAE	National Cancer Institute Common Terminology Criteria for Adverse Events
ORR	Objective Response Rate
NE	Not Evaluable
PK	Pharmacokinetics
PT	Preferred term
PD	Progressive Disease
PR	Partial response
PK	Pharmacokinetic
Q1	1st Quartile
Q3	3rd Quartile
RECIST	Response Evaluation Criteria in Solid Tumors
RP2D	Recommended phase 2 dose
SAP	Statistical Analysis Plan
SAE	Serious Adverse Event
SBP	Systolic Blood pressure
SD	stable disease
SoC	Standard of care
SOT102	CLDN18.2-specific monoclonal antibody SOT102.1 conjugated to [redacted]
TEAE	Treatment-emergent adverse event
STD	Standard Deviation
ULN	Upper limits of normal
WHO	World Health Organization

Statistical Analysis Plan (SAP) - Part B

Protocol Title:	A multicentric phase 1/2 trial to evaluate the safety and efficacy of SOT102 as monotherapy and in combination with standard of care treatment in patients with gastric and pancreatic adenocarcinoma
Protocol Version No./Date:	Amendment 3/17-April-2023
CRF Version No./Date:	1.28/07-Dec-2022
SAP Version No./Date:	2.0/10-Feb-2025

1.0 Approvals

Sponsor	
Sponsor Name:	SOTIO Biotech a.s.
Representative/ Title:	[redacted] / Senior Statistician
Signature /Date:	Signed by: [redacted] Signer Name: [redacted] Signing Reason: I approve this document Signing Time: 11-Feb-2025 | 07:16:14 GMT 97516DB6DB0F45E3B304EA94FACDBC2C
ICON	
Biostatistician / Title:	[redacted] / Senior Principal Biostatistician
Signature /Date:	Signed by: [redacted] Signer Name: [redacted] Signing Reason: I approve this document Signing Time: 10-Feb-2025 | 18:25:44 GMT A27576F2CC634C6F8CA561D5FECF1CD4

2.0 Change History

Version/Date	Change Log
0.1	Created as new
0.2	Updated per Client and Internal review comments
0.3	Updated per Client and Internal review comments
0.4/1.0	Updated as per Sponsor responses to questions
1.1	Updated for protocol amendments 3, 4, and 5 as well as for study early termination
2.0	Updated for sponsor comments to remove references to protocol amendments 4 & 5

3.0 Table of Contents

4.0 Purpose

The Statistical Analysis Plan (SAP) describes the statistical methods to be used during the reporting and analyses of data collected under SOTIO Biotech a.s. Protocol SN201. In particular, this SAP is relevant to Part B segment of the protocol, which is dose finding of SOT102 in combination with Standard of care (SoC).

5.0 Scope

The SAP outlines the following:

- Study objectives.
- Study design.
- Study endpoints.
- Applicable study definitions.
- Statistical methods.

6.0 Introduction

This SAP describes the statistical methods to be used during the analysis and reporting of data collected in the Part B segment for combination treatment. Additional SAPs will be created for Parts C and D, along with the Part A SAP already created. The final analysis for Part B will occur prior to the final database lock for the study and Part B subject case report forms (CRFs) will be locked to data entry at this point.

This SAP should be read in conjunction with the study protocol and CRFs. This version of the plan has been developed using protocol Amendment 3 dated 27 April 2023 and CRF version 1.28 dated 07 December 2022. Any further changes to the protocol or CRFs may necessitate updates to the SAP.

A stable draft SAP v1.0 was considered final for the purposes of programming activities and signed off prior to first patient in (FPI). The SAP will be updated and finalized prior to the effective database lock of Part B.

6.1 Changes from protocol

Given the small sample size in Part B, in section 12.7 Efficacy Analyses, Clopper-Pearson exact confidence intervals will be calculated instead of the Wald confidence intervals specified in the protocol section 9.3.

7.0 Study Part B Objectives

7.1 Primary Objective

- To determine the maximum tolerated dose (MTD) and recommended phase 2 dose (RP2D) of SOT102 in combination with first-line standard of care (SoC) treatment.

7.2 Secondary Objectives

- To assess the safety and tolerability of SOT102 given in combination with first-line SoC treatment.
- To characterize the pharmacokinetics (PK) of total SOT102, conjugated SOT102 [redacted]
- To explore evidence of SOT102 activity in combination with first-line SoC treatment in individual patients.
- To explore whether patients develop any antibodies against SOT102.

8.0 Study Design

This study will assess the MTD and RP2D of SOT102 administered as monotherapy (Part A) and in combination with first-line standard of care (SoC) treatment (modified oxaliplatin + leucovorin + 5-fluorouracil containing chemotherapy regimen [mFOLFOX6] with nivolumab and nab-paclitaxel/gemcitabine; (Part B) and efficacy of SOT102 administered as monotherapy (Part C) and in combination with first-line SoC treatment (Part D) in patients with advanced inoperable or metastatic gastric/gastroesophageal junction (GEJ) adenocarcinoma or inoperable or metastatic pancreatic adenocarcinoma.

Part B will consist of two patient cohorts; Gastric B and Pancreatic B. In each cohort, patients with advanced/metastatic gastric/GEJ or pancreatic adenocarcinoma will be treated with escalating doses of SOT102 given once every 14 days via the intravenous (IV) route over 45 (±15) minutes, in combination with SoC treatment specific for each cohort.

In Gastric B cohort, SoC includes Nivolumab (240 mg) given as a 30 minutes infusion followed by oxaliplatin (85 mg/m^2) given as a 2-hour infusion and leucovorin (400 mg/m^2) given as a 30-minute infusion, followed by a 5-FU bolus of 400 mg/m^2 followed by 2400 mg/m^2 5-FU given as a 46-hour continuous infusion (mFOLFOX6). This treatment will be repeated every 14 days.

In Pancreatic B cohort, SoC is Nab-paclitaxel (125 mg/m^2), given as a 30- to 40-minute infusion followed by gemcitabine (1000 mg/m^2) given as a 30-minute infusion on days 1, 8, and 15. This treatment will be repeated every 28 days.

SOT102 will be administered first and upon completion of the SOT102 infusion, patients will be observed for any acute side effects for 120 minutes. After the observation period, first-line SoC treatment will be administered.

Part B will start once monotherapy SOT102 dose level 3 in Part A is successfully completed and is safe. The starting dose of SOT102 in Part B will be Part A dose level 1. If an MTD in Part A is reached before dose level 3, then the starting dose of SOT102 in Part B will be decided based on review of all available safety/PK data.

The Part B SOT102 dose levels will stay within the safe dose levels of SOT102 monotherapy from Part A. Under no circumstances will the Part B SOT102 dose levels exceed the highest dose deemed safe in Part A.

Dose escalation will follow a modified Fibonacci scheme. Adjustments of the planned dose levels and dose increments will be considered by the Dose Escalation Committee (DEC).

SOT102 dose escalation in combination with the first-line SoC treatment will continue until DLTs are observed in ≥2 DLT-evaluable patients at a given dose level. The MTD will be declared as the dose level below that particular dose level. Based on the MTD assessment results, additional doses and schedules may be opened as required to define the dose and schedule of RP2D.

Patients will be monitored at the same visits and assessments as specified in Part A (for 30 days after the last dose of SOT102 and every 6 weeks [±2 weeks] until disease progression or start of new anti-cancer therapy) during the combination treatment with SOT102. Any late toxicities will be considered in the determination of the MTD/RP2D and dose schedules for Part B.

As of December 2024, the study was terminated due to safety concerns prior to any Part B subjects being enrolled under the protocol amendments 4 and 5, so for this study part protocol amendment version 3 is being followed.

8.1 Sample Size Considerations

In Part B, a 3+3 design dose escalation will be applied until the MTD is identified. Therefore, 3 to 6 DLT-evaluable patients per dose level will be included. Assuming 2 dose levels per 3 patients, 2 dose levels per 6 patients and 6 additional patients for confirmation of RP2D (acknowledging that at least 6 DLT-evaluable patients will be included to assess the RP2D before the respective expansion Parts C and D are initiated),

the total number of assumed evaluable patients is 24. Assuming 8 patients needed for replacement, the estimated number of patients per cohort is 32. The total estimated number of patients in Part B is 64.

8.2 Randomization

Random assignment is not being used in this study.

9.0 Study Endpoints

9.1 Endpoint Attributes

Objectives	Endpoints
Primary - Part B	Primary endpoint
• To determine the maximum tolerated dose (MTD) and recommended phase 2 dose (RP2D) of SOT102 in combination with first-line standard of care (SoC) treatment.	• MTD is defined as the highest dose level tested below the dose level associated with ≥33% of DLT-evaluable patients experiencing a DLT. The RP2D will be selected based on integrated evaluation of the totality of clinical and preclinical data, for all dose levels tested.
Secondary	Secondary endpoints
• To assess the safety and tolerability of SOT102 in combination with first-line SoC treatment • To characterize the pharmacokinetics (PK) of total SOT102, conjugated SOT102, [redacted] • To explore evidence of SOT102 activity in combination with first-line SoC treatment in individual patients • To explore whether patients develop any antibodies against SOT102	• The occurrence of DLTs, occurrence of TEAEs, SOT102-related AEs, SAEs, AEs leading to premature discontinuation of SOT102, deaths, or clinical laboratory test abnormalities • PK of total SOT102, conjugated SOT102, [redacted] • Anecdotal tumor response per RECIST 1.1 by type and CLDN18.2 expression • The number of patients with detected antibodies against any part of SOT102

9.2 Population Sets

9.2.1 Screened Population

The screened population is defined as all patients who sign the initial study informed consent form.

9.2.2 Enrolled Population

The enrolled population is defined as all patients who sign the initial study informed consent form, and all eligibility criteria are met as confirmed by approver during screening assessments and recorded as enrolled on the Eligibility Criteria CRF page. This population will be used to describe patient disposition and protocol deviations and may include patients who do not receive SOT102 treatment.

9.2.3 Safety Population

The safety population is defined as all patients exposed to at least one dose of SOT102. All safety analyses will be performed on safety population with the exception of the DLT analysis which will be performed on the DLT-evaluable population.

9.2.4 Pharmacokinetic Evaluable Population

The Pharmacokinetic (PK) evaluable population consists of all patients exposed to at least one dose of SOT102 and who have at least one post-dose concentration measurement above the lower limit of quantitation (LLOQ) for total SOT102.

9.2.5 DLT-evaluable Population

The DLT evaluation period is 28 days counted from day 1 of cycle 1 of SOT102.

The DLT-evaluable patient will be:

- Patient who has received 2 doses of SOT102 per schedule (day 1 of cycle 1 and day 1 of cycle 2) with the maximum postponement of cycle 2 by 1 day (as agreed by the sponsor) and who completed the evaluation period of 28 days.
- Gastric B patients who have received 2 doses of SoC per schedule (day 1 of cycle 1 and day 1 of cycle 2)
- Pancreatic B patients who have received three doses of SoC (days 1, 8 and 15 of cycle 1).
- Patient who experiences a treatment emergent adverse event at any time during the DLT evaluation period that meets the definition of a DLT.

Complete doses of all elements of SoC should be administered for DLT evaluability. Patients who do not fulfill the DLT evaluation criteria for any reason other than DLT will be replaced. This population will be used to assess DLT incidence and the estimate of MTD.

9.2.6 Efficacy Population

All patients exposed to at least one dose of SOT102 who had at least one evaluable tumor assessment per RECIST v1.1 after the initiation of SOT102 treatment. An evaluable tumor assessment is a post-baseline CT/MRI tumor assessment which is not NE (not evaluable).
This will be the main population for efficacy exploration.

10.0 Conventions and Derivations

10.1 Study Treatment

The study treatment defined for Part B are different dose levels of SOT102, as defined in the study protocol, combined with SoC. The starting dose of Part B will be dose level 1 of Part A. The Part B SOT102 dose levels will stay within the safe dose levels of SOT102 monotherapy from Part A. Under no circumstances will the Part B SOT102 dose levels exceed the highest dose deemed safe in Part A.

10.2 Baseline

Unless otherwise specified, baseline is defined as the last non-missing value prior to the first administration of SOT102 treatment.

10.3 Change from Baseline

Change from baseline (CFB) will be calculated as (post-baseline – baseline). CFB will be calculated for patients with both a baseline and post-baseline value as applicable.

10.4 Percentage Change from Baseline

Percentage CFB will be calculated as (CFB/baseline) *100, where applicable.

If a baseline value is 0 for a parameter, then percentage CFB will not be calculated for that parameter.

10.5 Definition of Study Day

All study days on or after the first administration of SOT102 treatment will be calculated as date of assessment minus date of first administration of SOT102 treatment + 1, i.e.,

- Date of assessment – date of first administration of SOT102 treatment + 1.

Study days that occur before the first administration of SOT102 treatment will be calculated as date of assessment minus date of first administration of SOT102 treatment, i.e.,

- Date of assessment – date of first administration of SOT102 treatment.

In cases of missing and/or incomplete dates, no study days will be calculated.

10.6 Study Phase

Phases of the study are defined as follows:

Screening: From the date of informed consent form signature to the day prior to the first infusion of SOT102

On-treatment (i.e., SOT102 Treatment with combination therapy of SoC period): From the day of the first infusion of SOT102 to 30 days after the last infusion of SOT102.

Follow-up: Begins from the date of the last infusion of SOT102 +31 days.

10.7 DLT Evaluation Period

Twenty-eight (28) days starting from Day 1 of Cycle 1 of SOT102 treatment.

10.8 Cycle

Cycle number will be taken from the database. Unscheduled visits will be in listings only and identified with a numbering system that reflects the cycle they occur in by comparing the visit date against the scheduled visits and numbering in order of unscheduled visit, e.g., Unscheduled Cycle 1 Day 1.01, Unscheduled Cycle 1 Day 8.01 etc. Unscheduled visits occurring on the same day as other visits (scheduled or otherwise) will be kept as separate records.

Tumor assessments are not performed regularly per cycle, these will be identified in the ADaM datasets by actual week of study by calculating (date of assessment – date of first infusion + 1)/7 and rounding up.

10.9 Age group

Age at informed consent will be categorized as ≥ 18 years to ≤ 45 years, ≥ 46 years to ≤ 64 years, ≥ 65 years to ≤ 74 years, ≥ 75 years to ≤ 84 years, ≥ 85 years, with no rounding applied for assigning to categories, meaning patient will be in group ≥ 85 years once s/he has in the Demography CRF page age at least 85 or higher.

10.10 Time since Initial Diagnosis

The time since initial diagnosis will be calculated as date of first dose minus the date of initial diagnosis and converted to years. The date of initial diagnosis is from the Cancer History CRF page. Partial dates to be imputed as per section 10.16.2.

10.11 Number of previous lines of systemic therapy

The number of previous lines of systemic therapy is the maximum line of therapy in the adjuvant or neoadjuvant setting recorded per patient from the Prior Systemic Anti-Cancer Therapy Regimen CRF page.

10.12 Prior and Concomitant Medications and Procedures

The medications that are taken prior to the first dose of SOT102 treatment and discontinued prior to the first dose of SOT102 treatment are defined as prior medications. Likewise, procedures occurring prior to the first dose of SOT102 treatment and discontinued prior to the first dose of SOT102 treatment will be defined as prior procedures.

The concomitant medications are defined as medications that have started at Day 1 or after Day1 or if they were started prior to first dose of SOT102 treatment but are ongoing at Day 1. Concomitant procedures are those that occur on or after Day 1 or if they were started prior to the first dose of SOT102 treatment but are ongoing at Day 1.

Refer to Section 10.16 below for how to handle partial or missing dates in the assessment of whether or not a treatment was taken prior to or concomitantly with the SOT102 treatment.

10.13 Derivation of Efficacy Variable

10.13.1 Tumor Response Endpoints

Tumor assessments will be performed by investigators and assessed per RECIST v1.1[1] for all tumor indications.

The RECIST v1.1 assessment has the following possible response categories (ordered from the best response to worst): complete response (CR), partial response (PR), stable disease (SD), progressive disease (PD), or NE.

10.13.2 Objective Response Rate and Tumor Burden

The objective response categorized in accordance with RECIST v1.1 is defined as the proportion of patients who achieved a confirmed CR or confirmed PR. The objective response rate (ORR) is calculated as the number of patients with objective response divided by the number of patients in the Efficacy population. Objective response should be confirmed by a repeat imaging assessment not earlier than 4 weeks (28 days) after the first CR or PR is observed.

Percentage CFB of Tumor burden will be summarized as the percent CFB in target lesions per time point.

It will be derived as:

- ((Sum of target lesions at post-baseline assessment – sum of target lesions at baseline)/sum of target lesions at baseline) x 100.

The maximum reduction in target lesions from baseline will be derived across all the post-baseline assessments until documented disease progression, as minimum of (Percentage CFB of Tumor Burden).

10.13.3 Best Overall Response

The best overall response is the best response recorded from the start of the treatment until disease progression/recurrence or death. The patient's best response assignment will depend on the achievement of both measurement and confirmation criteria.

A best response of CR or PR cannot be determined unless it is confirmed, no earlier than 4 weeks (28 days) from the time a response of CR or PR is first observed (SD does not require confirmation if observation of SD occurs at least 6 weeks (42 days) after the baseline scan).

10.14 Derivations for Exposure Variables

The planned dose level for SOT102 treatment will be recorded in the CRF at Screening. This is the dose level referred to wherever 'dose level' is referenced and is the starting dose level only, not accounting for changes.

The actual dose level for SOT102 treatment is calculated as actual dose administered/weight (mg/kg) as follows:

- Actual dose per cycle (mg/kg) = [(total dose planned) * (administered volume / total prepared infusion volume)] / pre-dose weight

The pre-dose weight of the patient recorded for that cycle will be used. If the pre-dose weight is not available for a particular cycle, the actual dose will not be calculated.

The duration of exposure to SOT102 will be calculated as the last dose date – the first dose date +1, converted to weeks.

The duration of exposure to SoC will be calculated as the last dose date – the first dose date +1, converted to weeks. No other derivations will be performed for exposure to SoC therapies.

10.15 Safety Variables

10.15.1 Dose-Limiting Toxicity

The DLTs are defined in Section 4.1.1.1 of the protocol. Toxicity will be assessed according to the National Cancer Institute (NCI) Common Terminology Criteria for Adverse Events, Version 5.0 (CTCAE v5.0; 27 November 2017). For analysis of DLT, the information of DLT collected on the Adverse Events CRF page will be used.

10.15.2 Treatment-emergent AEs

All AEs will be recorded in the database but not all on-treatment events will be considered as treatment-emergent e.g., if they are an improvement of an existing condition. A treatment-emergent AE (TEAE) is defined as an AE that:

- emerges at SOT102 treatment start or afterwards, having been absent at the time of pre-treatment (screening), or
- re-emerges at SOT102 treatment start or afterwards, having been present at the time of pre-treatment (screening), or
- worsens in severity at SOT102 treatment start or afterwards relative to the pre-treatment state if the AE is continuous.

TEAEs will be identified as follows:

1. TEAE from start of treatment at Cycle 1 Day 1 to 30 days after final administration of SOT102.
2. TEAE within follow up period, i.e., beyond 30 days after the final administration of SOT102 until disease progression (clinical progression or radiographic disease progression as recorded on the ‘End of Treatment’ eCRF page, or radiographical as recorded on the ‘Disease Response’ CRF page) or start of new anti-cancer therapy (defined as the earliest start date for subsequent systemic anti-cancer therapy recorded on the ‘Systemic anti-cancer therapies’ eCRF page).

TEAEs will be combined for reporting.

10.16 Imputation of Missing Data

No further imputation of missing data except the cases below will be performed.

10.16.1 Imputation of Missing Dates on AEs or Concomitant Medications and Procedures

For the purposes of assigning AEs and concomitant medications/procedures to study periods the following algorithm will be used for missing or partial dates (AE start/stop dates and concomitant medication/procedure start/stop dates): The actual (non-imputed) value for date will be presented in all data listings and imputed dates will only be used for programming purposes, such as TEAE derivation.

Start date

If the start date is completely missing (i.e., the day, month, and year are all unknown) the start date will be set to the date of the first dose of SOT102.

Missing day only

- If the month and year of the incomplete date are the same as the month and year of the **first dose date**, then the day of the **first dose date** will be assigned to the missing day.
- If either the year is before the year of the **first dose date** or if years are the same, but the month is before the month of the **first dose date**, then the last day of the month will be assigned to the missing day.
- If either the year is after the year of the **first dose date** or if both years are the same, but the month is after the month of the **first dose date**, then the first day of the month will be assigned to the missing day.

Missing month only

- The day will be treated as also missing and both month and day will be replaced according to the procedure below.

Missing day and month

- If the year of the incomplete date is the same as the year of the **first dose date**, then the day and month of the **first dose date** will be assigned to the missing fields.
- If the year of the incomplete date is not the same as the year of the **first dose date**, then January 1 will be assigned to the missing fields.

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.

Stop date

Missing day only

- If the month and year of the incomplete date are the same as the month and year of the **last visit date**, then the day of the **last visit date** will be assigned to the missing day.
- If either the year is before the year of the **last visit date** or if both years are the same, but the month is before the month of the **last visit date**, then the last day of the month will be assigned to the missing day.
- If either the year is after the year of the **last visit date** or if both years are the same, but the month is after the month of the **last visit date**, then the first day of the month will be assigned to the missing day.

Missing month only

- The day will be treated as missing and both month and day will be replaced according to the procedure below.

Missing day and month

- If the year of the incomplete date is the same as the year of the **last visit date**, then the day and month of the **last visit date** will be assigned to the missing fields.
- If the year of the incomplete date is before the year of the **last visit date**, then December 31st will be assigned to the missing fields.
- If the year of the incomplete date is after the year of the **last visit date**, then **January 1st** will be assigned to the missing fields.

Completely missing stop dates where a record is not ongoing, will not be imputed.

10.16.2 Imputation of Initial Diagnosis Date

The partial start date for initial diagnosis will be assigned to 15th day of the month (if only day is missing) or July 1st (if both month and day are missing). If imputation leads to a date of diagnosis after informed consent date, the date shall be imputed instead as the 1st of the month that informed consent occurred, or the last day of the previous month if informed consent occurred on the 1st. No imputation to be performed if year is missing.

10.16.3 Imputation of Laboratory Values with Character Symbol

Missing laboratory data will not be imputed. However, laboratory values of the form of "< x" (i.e., below the lower limit of quantification) or "> x" (i.e., above the upper limit of quantification) will be imputed as "x" for the purpose of calculation of summary statistics and comparing to normal ranges. These values will still be displayed as "< x" or "> x" in the listings.

10.16.4 Imputation of Pharmacokinetic Values with Character Symbol

Missing PK data will not be imputed. However, PK concentration or parameter values of the form of "< x" (i.e., below the lower limit of quantification) or "> x" (i.e., above the upper limit of quantification) will be imputed as not available "NA" and excluded from summary tables. These values will still be displayed as "< x" in the listings.

10.17 Time Conversion

Time conversion will follow the rules described below:

- 1 week = 7 days,
- 1 month = 30.4375 days,
- 1 year = 365.25 days.

11.0 Interim Analyses

No interim analyses are planned in Part B of the study.

12.0 Statistical Methods

All data collected during this study will be displayed in data listings on the largest population for which data is available, unless otherwise specified. Data listings will be sorted by cohort, dose level and patient ID as a minimum, additional sorting variables will be specified as appropriate in the listing shell. Listings will include all relevant derived variables – those variables will be marked as "(derived)". Where appropriate, a listing may also contain a flag for the related population: for safety data, if the patient is in the safety population; for efficacy outputs, if the patient is in the efficacy population; and for the DLTs, if the patient is DLT-evaluable. When listing options from the CRF in the case of 'Other: Specify', concatenate the specify text e.g. 'Other: XXXXXXXXX'; in the case of missing end date due to an ongoing event, medication or procedure, the text 'ongoing' will be inserted in place of the end date.

Descriptive statistics (number of observations [n], mean, median, standard deviations [STD], minimum, Q1, Q3 [or interquartile range as indicated below], and maximum values) for continuous variables will be presented. Mean, median, Q1 and Q3 will be presented to 1 decimal more than original data. STD will be presented to 2 decimals more than original data. Minimum and maximum will match the decimal points in the original data. For categorical variables, summary measures will include the frequency and percentage (with 1 decimal place) of patients in each category. Percentages will not be displayed for zero counts.

The summary tables will be split by cohort (Gastric B Cohort and Pancreatic B Cohort), presented by dose level and all dose levels combined.

The analyses will be descriptive, no formal testing of statistical hypotheses is planned.

All data summaries and tabulations will be prepared with SAS® Version 9.4 or higher.

This SAP describes the planned analysis for the Part B, however, due to the early termination of the study with only four subjects treated in Part B, a Summary of Results will be produced instead of the planned CSR. Minimal tables and listings will be created and for summaries the gastric and pancreatic subjects will be combined in the same table.

12.1 Patient Disposition

The number and percentage of patients screened (Informed Consent Form signed), enrolled, and treated in the study will be presented by cohort.

The number and percentage of patients and each population to which they belong will be presented by cohort.

The number of patients screened, enrolled, and treated by country and site will be presented.

Disposition will be summarized descriptively for all enrolled population separately for each cohort, by dose level and all dose levels combined. Total number of screen failures will be summarized, together with the:

- number and percentage of patients who discontinued from the study and a breakdown of the corresponding reasons for discontinuation (the percentages are calculated from enrolled population),
- number and percentage of patients who discontinued SOT102 with combination therapy of SoC with the corresponding reasons.
- Number and percentage of patients discontinuing SOT102 but remaining on SoC, and vice versa.

12.2 Demographic and Baseline Characteristics

Demographic and baseline characteristics data will be summarized descriptively for each cohort by dose level and all dose levels combined for the Safety population. The demographic and disease history summaries will be repeated for the Efficacy population.

12.2.1 Demographics

Demographic characteristics will be summarized by cohort and dose level using the following information from the Demographics CRF page: sex, ethnicity, race, age at informed consent and age group. From other CRF pages, also baseline weight (kg), baseline height (m), baseline body surface area [BSA] (m2) and baseline Eastern Cooperative Oncology Group (ECOG) status will be summarized.

12.2.2 Primary Disease History

Primary disease history will be listed by cohort and dose level and summarized using the information from the Cancer History CRF page. Variables to be summarized include location of primary tumor, time since initial diagnosis, stage of disease at diagnosis, and Human Epidermal Growth Factor Receptor 2 (HER2) status. The number of previous lines of systemic therapy will be summarized. Lauren's classification and HER2 status are only summarized for the Gastric Cohort.

Prior mutations and other genetic analysis data will be listed only by cohort.

12.3 Prior Therapy for Primary Diagnosis

A tabulation of prior systemic therapies coded according to WHODrug (v Global B3 Sep 2019 or later) will be presented separately for each cohort for the Safety and Efficacy populations. Prior anti-cancer therapies will be tabulated and categorized separately for each cohort by medication group (ATC level 2) and subgroup (ATC level 4) using counts and percentages.

A tabulation of non-systemic anti-cancer therapies coded according to MedDRA (version 25 or later) will be presented separately for each cohort for the Safety and Efficacy populations. Prior non-systemic anti-cancer therapies will be tabulated separately for each cohort and categorized by System Organ Class and Preferred Term using counts and percentages. Prior radiotherapy will not be coded, and the verbatim terms will be listed only by cohort.

Systemic and non-systemic anti-cancer therapies will be presented separately for each cohort.

Full details of prior systemic and non-systemic anti-cancer therapies will be listed only by cohort.

12.4 Medical History

Medical history will be coded according to Medical Dictionary for Regulatory Activities (MedDRA, Version 25 or later).

Medical history will be tabulated by system organ class (SOC) and preferred term (PT) using counts and percentages separately for each cohort.

12.5 Treatments

12.5.1 Exposure to SOT102

Descriptive statistics will be provided separately for each cohort by dose and also by dose overall both cohorts, on the Safety and Efficacy populations for the duration of exposure (weeks) and the total number of doses administered.

The total number of doses administered will be summarized both as a continuous and categorical variable, separately for each cohort.

Number and percentage of patients with missed doses, at least one dose adjusted, at least one dose interruption, and reasons for missed dosing, dose adjustment and interruption will be presented on the Safety population.

A summary of dose levels and actual dose levels administered within each cohort will be presented by the number of doses administered and number of patients dosed. Further information regarding patients' dosing regimens, including total dose, dosing form, and dose changes and interruptions will be listed.

12.5.2 Exposure to SoC

Descriptive statistics will be provided separately for each cohort and dose level on the Safety and Efficacy populations for the duration of exposure of SoC (weeks) and the total number of doses administered for each therapy of the SoC.

The total number of doses administered of each therapy will be summarized both as a continuous and categorical variable, separately for each cohort, dose level, and therapy; the reasons for missing doses will be summarized.

Further information regarding patients' dosing regimens, including total dose administered, lot number, and start and end time of administration will be listed only.

12.5.3 Prior and Concomitant Medications and Procedures

Medications received priorly and concomitantly with study drug, categorized by medication group (ATC level 2) and subgroup (ATC level 4) according to WHODrug, will be summarized for the Safety population separately for each cohort.

Prior and concomitant procedures will be coded according to MedDRA summarized by System Organ Class and Preferred Term.

Prior and concomitant medications and procedures will be tabulated separately for each cohort using counts and percentages to display the number and percentage of patients using at least one medication.

Full detail of medications and procedures will be presented in listings only by cohort.

12.6 Protocol Deviations

Protocol deviations will be documented by category (as per the latest study Protocol Deviation Guidance document). All deviations will be reviewed, categorized, designated important or not important, and finalized prior to database lock of Part B. Important protocol deviations will be defined as those potentially impacting safety or efficacy assessments and analyses. Additional details of what will be considered important protocol deviation can be found in the Protocol Deviation Guidance document.

Important protocol deviations for patients in the Enrolled population will be summarized by category separately for each cohort and over all Part B patients. All protocol deviations will be listed only by cohort.

Any COVID-19-specific protocol deviations will be listed separately by cohort.

12.7 Efficacy Analyses

All efficacy analyses will be performed for the Efficacy population.

12.7.1 Objective Disease Response

Descriptive statistics (frequency and percentage) for ORR, for best confirmed overall response, and the two-sided 95% Clopper-Pearson confidence interval[(2)] for the ORR will be presented separately for each cohort. ORR will be summarized for all dose levels combined only. The best confirmed overall response will be summarized separately for each cohort by dose level and all dose levels combined.

Analysis by claudin 18.2 expression will be considered exploratory and may be performed after sponsor assessment of available data. For the Gastric cohort a subgroup analysis by gastrectomy status will be performed. Gastrectomy status will be identified from presence or absence of gastrectomy recorded on the Prior Anti-cancer Surgery CRF page.

12.7.2 Tumor Burden

A waterfall plot of maximum percent reduction in the sum of diameter of target lesions from baseline will be created separately for each cohort. This plot will display the best percentage CFB in the sum of the diameter of all target lesions for each patient. The bar for each patient will be colored by their dose level.

A spaghetti plot of percent reduction in the sum of target lesions from baseline will be created separately for each cohort to plot the change in tumor burden over time for each patient. The time will be calculated from the treatment initiation (first dose of treatment). RECIST assessments contributing towards a particular visit may be performed on different dates and the latest date of the scan dates of the component from the CRF will be used as the assessment time. The colors of the lines will be based on the patient's dose level.

12.8 Safety Analyses

AEs will be graded according to the NCI CTCAE Version 5.0.

All safety analyses will be summarized separately for each cohort by dose level and all dose levels combined. Selected analyses will be performed for all Part B patients combined. Safety analyses will be performed in the Safety population unless other specified.

12.8.1 Adverse Events

AEs will be coded according to MedDRA (Version 25.0 or later) by SOC, PT, and severity grade using NCI CTCAE Version 5.0.

Linked AEs will be identified via the AE ID recorded as change in severity of an existing AE on the AE CRF page. Multiple AE records with differing attributes can comprise a single linked AE occurrence. Linked AEs will be selected for analysis in tables based on their worst-case scenario attribute e.g.,

maximum CTCAE grade, causal relationship, seriousness, treatment emergence and action taken out of all records.

The ordering (the worst to best) for the following characteristics will be applied:

- Relationship to SOT102: suspected, not suspected.
- Relationship to SoC: suspected, not suspected.
- Toxicity Grade: Grade 5 to Grade 1.

AE records within a linked AE can be given different treatment-emergence status. Treatment emergence for linked AEs will be established as those records in the linked AE with a worsening of severity from the preceding record.

12.8.1.1 Treatment-emergent AEs

An overall summary of event incidence will be presented, displaying the number of events and number of patients with events for the following; TEAEs; Grade 3 or Greater TEAEs and SOT102 or SoC related TEAEs; Serious TEAEs and SOT102 or SoC related SAEs; Fatal TEAEs, TEAEs and related TEAEs leading to discontinuation of SOT102 or SoC; Immune related TEAEs; TEAES leading to reduction of SOT102 or SoC and interruption of SOT102 or SoC; DLTs.

A breakdown of the number and percentage of patients reporting each AE categorized by SOC and PT will be presented separately for each cohort. Note that the counts will be presented by patient, rather than event, and patients are only counted once within each SOC or PT if an AE was reported more than once. Selected tables will include the number of events (the linked AEs, if applicable) alongside the patient count. 'Treatment-related' AEs refers to those AEs with relationship of 'Suspected' reported for either SOT102, SoC, or both. The following summaries of TEAEs will be presented separately for each cohort by SOC and PT:

- Patients reporting DLTs in DLT-evaluable population,
- Patients reporting at least one TEAE (also summarized for all patients),
- Patients reporting at least one SOT102-related TEAE (also summarized for all patients),
- Patients reporting at least one SoC-related TEAE (also summarized for all patients),
- Patients reporting at least one treatment-related TEAE,
- Patients reporting at least one CTCAE grade 3 or greater TEAE,
- Patients reporting at least one CTCAE grade 3 or greater SOT102-related TEAE,
- Patients reporting at least one CTCAE grade 3 or greater SoC-related TEAE,
- Patients reporting at least one CTCAE grade 3 or greater treatment-related TEAE,
- Patients who permanently discontinued SOT102 due to a TEAE,
- Patients who permanently discontinued SoC due to a TEAE,
- Patients who permanently discontinued Treatment due to a TEAE,
- Patients who permanently discontinued SOT102 due to a treatment related TEAE (also summarized for all patients), Patients who permanently discontinued SoC due to a treatment related TEAE (also summarized for all patients),
- Patients who permanently discontinued treatment due to a treatment related TEAE,
- Patients with TEAEs leading to dose reduction or interruption,
- Patients with SOT102 related TEAEs leading to dose reduction or interruption,

- Patients with SoC related TEAEs leading to dose reduction or interruption,
- Patients with treatment related TEAEs leading to dose reduction or interruption.

The following summaries will be presented separately for each cohort by PT in descending order of frequency:

- Patients reporting at least one TEAE for PTs occurring in at least 10% of patients,
- Patients reporting at least one CTCAE grade 3 or greater TEAE for PTs occurring in at least 5% of patients,
- Patients reporting at least one non-serious TEAE for PTs occurring in at least 5% of patients.

The percentage for the thresholds mentioned above will be counted from all patients in safety population by cohort, not distinguishing dose levels.

The following summaries will be presented separately for each cohort by SOC, PT, and maximum CTCAE grade:

- Patients reporting at least one TEAE,
- Patients reporting at least one SOT102-related TEAE (also summarized for all patients)
- Patients reporting at least one SoC-related TEAE (also summarized for all patients),

Additionally, the following summary will be presented separately for each cohort by SOC and PT, along with the highest reported CTCAE grade per PT:

- Non-serious TEAEs related to SOT102.

The following listings will be produced separately on the Safety Population by cohort unless otherwise specified:

- All AEs (Screened population and including Enrolled and Safety population flags, and TEAE flag),
- Dose-limiting toxicities (including DLT-evaluable population flag),
- AEs leading to death (On Screened population and including Enrolled and Safety population flags),
- Treatment-emergent SAEs,
- TEAEs leading to discontinuation of SOT102,
- TEAEs leading to discontinuation of SoC,
- TEAEs leading to dose reduction or interruption of SOT102,
- TEAEs leading to dose reduction or interruption of SoC,
- Non-treatment-emergent AEs (On Screened population and including Enrolled and Safety population flags),
- All AEs related to SOT102 reported after 30 days (including TEAE flag).

12.8.2 Serious AEs and Deaths

The following summaries of SAEs, including AEs that lead to death, will be presented separately for each cohort and as a total summary by SOC and PT:

- Patients with at least one SAE,
- Patients with at least one SOT102-related SAE,
- Patients with at least one SoC-related SAE,
- Patients with at least one treatment related SAE,

- Patients with a TEAE leading to death,
- Patients with a SOT102-related TEAE leading to death,
- Patients with a SoC-related TEAE leading to death,
- Patients with treatment related TEAE leading to death.

12.8.3 Laboratory Data

12.8.3.1 Laboratory Parameters

Quantitative data will be summarized separately for each cohort and dose level, using descriptive statistics of actual values and CFBs for each scheduled visit over the course of the study. All laboratory data will be summarized in International System units. The laboratory data will be presented separately for each cohort and dose level by visit for all timepoints with at least two subjects present in a dose level.

The actual values for each scheduled visit over the course of the study for selected laboratory parameters will be plotted separately for each cohort at each collected time point by line-plot. Each line will show one patient, one figure will represent all patients from one dose level. The timepoint will be calculated from the first dose of treatment as Day 1, and pre-baseline measurements will be included as negative days. Unscheduled visits will be included into the plots only. The selected laboratory parameters are Leukocytes, Hemoglobin, Platelets, Neutrophils, Albumin, Sodium, ALT, ALP, AST, Bilirubin, Potassium, Magnesium, Calcium and Creatinine clearance.

Laboratory values out of local normal ranges will be presented in separate listings by cohort.

Categorical laboratory parameters will be provided in listings only by cohort.

12.8.3.2 Hy's Law

Hepatic function abnormality will be defined by an increase in AST and/or ALT to ≥ 3 × ULN and/or an increase in total bilirubin to ≥ 2 × ULN but without increase in ALP (i.e., ALP < 2 × ULN).

Summary of liver function tests will include the number and percentage of patients meeting Hy's Law at each scheduled visit and will be presented separately for each cohort.

12.8.4 Vital Signs

The following vital signs will be summarized: heart rate (beats/min), systolic blood pressure (SBP; mmHg), diastolic blood pressure (DBP; mmHg), body temperature (C), and weight (kg).

Vital signs will be summarized descriptively at each study timepoint where they are collected, separately for each cohort and dose level. CFB values will be summarized for the post-baseline time points. Sa02 monitoring data will be listed only.

12.8.5 Physical Examinations, ECGs, and Other Observations Related to Safety

Additional safety assessments include physical examinations, ECOG evaluation, ECG measurements, left ventricular ejection fraction (LVEF), esophagogastroduodenoscopy, HIV/HBV monitoring, and pregnancy test. Summaries of selected safety assessments will be separately tabulated for each cohort by dose level and overall and at each assessment timepoint. All data will be listed.

12.8.5.1 Physical Examination

Physical examination data will be listed only by cohort.

12.8.5.2 ECOG Performance Status

A tabulation of ECOG performance status by timepoint will be provided separately for each cohort and dose level, including the number and percentage of patients reporting each ECOG category at each scheduled time point.

12.8.5.3 Electrocardiogram

A summary of ECG parameters including heart rate (beats/min), QT interval (msec), QTcF (msec), and RR interval (msec) and CFB (for only QTcF) will be presented, separately for each cohort, and dose level for each planned visit as well as the minimum, maximum, and last post-baseline observation.

Summaries will be generated for patients based on International Council for Harmonisation (ICH) E14 category, with QTcF increased to value > 450 and ≤ 480 msec, > 480 and ≤ 500 msec, and value > 500 msec, and patients with CFB in QTcF increased to > 30 to ≤ 60 msec, and > 60 msec at each timepoint.

12.8.5.4 Left Ventricular Ejection Fraction

LVEF data will be summarized separately for each cohort. Observed values and CFBs will be presented for each planned visit. Additionally, patients will be summarized using the following categories at each timepoint:

- Decrease from baseline of ≥ 10% and < 20%; and absolute post-baseline value 40-50%.
- Decrease from baseline of ≥ 20% and absolute post-baseline value 20% to 40%.
- Absolute post-baseline value < 20%.

12.8.5.5 Esophagogastroduodenoscopy

Esophagogastroduodenoscopy data will be listed only by cohort.

12.8.5.6 HIV/HBV Monitoring

HIV/HBV monitoring data will be listed only by cohort.

12.8.5.7 Pregnancy Test

Pregnancy testing data will be listed only by cohort.

12.8.5.8 Death Report

Death report data will be listed for the Screened population by cohort. Primary and secondary causes of death will be summarized using a combination of coded terms (MedDRA coded PT and SOC terms) and the CRF responses.

12.9 Plasma PK Summaries

Due to the early termination of the trial, no PK analyses will be performed for Part B.

12.10 Immunogenicity

The presence or absence of anti-drug antibodies will be summarized by cohort, dose level, and timepoint. Presence will be inferred by the result ‘POSITIVE CANDIDATE’ at screening, or ‘POSITIVE’ at post-baseline assessments. Immunogenicity data will be listed. Further exploration of ADA impact on PK may be performed post-hoc if the dose relationship appears normal from interim PK analyses; in such a case it may be considered to run an analysis pooled across doses using dose-normalized PK parameters to assess the impact of ADAs.

13.0 References

1. Eisenhauer EA, Therasse P, Bogaerts J, Schwartz LH, Sargent D, Ford R, et al. New response evaluation criteria in solid tumours: revised RECIST guideline (version 1.1). European Journal of Cancer. 2009;45(2):228-47.
2. Clopper C, Pearson ES. The use of confidence or fiducial limits illustrated in the case of the binomial. Biometrika. 1934;26:404-13.

14.0 Glossary of Abbreviations

Glossary of Abbreviations:	
AE	Adverse event
ALP	Alkaline phosphatase
ALT	Alanine transaminase
AST	Aspartate transaminase
ATC	Anatomic Therapeutic Classification
BLQ	Below the Limit of Quantification
BMI	Body Mass Index
BOR	Best Overall Response
BSA	Body Surface Area
CFB	Change from baseline
CLDN18.2	Claudin 18 splice variant 2
CR	Complete Response
CRF	Case Report Form
CSR	Clinical Study Report
CT	Computed Tomography
DEC	Dose Escalation Committee
DLT	Dose-limiting toxicity
ECG	Electrocardiogram
ECOG	Eastern Cooperative Oncology Group
EDA	Ethylene diamine
FPI	First Patient In
GEJ	Gastroesophageal junction
HBV	Hepatitis B Virus
HER2	Human Epidermal Growth Factor Receptor 2
HIV	Human Immunodeficiency Virus
ICH	International Council for Harmonisation
INR	International normalized ratio
IV	Intravenous
LLOQ	lower limit of quantitation
LVEF	Left ventricular ejection fraction
MedDRA	Medical Dictionary for Regulatory Activities

mFOLFOX6	Modified oxaliplatin + leucovorin + 5-fluorouracil containing chemotherapy regimen
MRI	Magnetic Resonance Imaging
MTD	Maximum tolerated dose
NA	Not Available
NCI CTCAE	National Cancer Institute Common Terminology Criteria for Adverse Events
ORR	Objective Response Rate
NE	Not Evaluable
PK	Pharmacokinetics
PT	Preferred term
PD	Progressive Disease
PR	Partial response
PK	Pharmacokinetic
Q1	1st Quartile
Q3	3rd Quartile
RECIST	Response Evaluation Criteria in Solid Tumors
RP2D	Recommended phase 2 dose
SAP	Statistical Analysis Plan
SAE	Serious Adverse Event
SBP	Systolic Blood pressure
SD	stable disease
SoC	Standard of care
SOC	System Organ Class
SOT102	CLDN18.2-specific monoclonal antibody SOT102.1 conjugated to [redacted]
STD	Standard Deviation
TEAE	Treatment-emergent adverse event
ULN	Upper limits of normal
WHO	World Health Organization