Statistical Analysis Plan
Study Part A

A multicenter open-label phase 1/1b study to evaluate the safety and preliminary efficacy of SO-C101 as monotherapy and in combination with pembrolizumab in patients with selected advanced/metastatic solid tumors.

Sponsor:	SOTIO Biotech AG
Study code:	SC103
EudraCT number:	2018-004334-15
VERSION:	Final 2.0
DATE:	30-SEP-2022

STATISTICAL ANALYSIS PLAN APPROVAL

We, the undersigned, confirm that we have read and are in agreement with the contents of this document.

NAME	[redacted]
JOB TITLE	
SIGNATURE	
DATE	
NAME	
JOB TITLE	
SIGNATURE	
DATE	
NAME	
JOB TITLE	
SIGNATURE	
DATE	
NAME	
JOB TITLE	
SIGNATURE	
DATE	

TABLE OF CONTENTS

ABBREVIATIONS

ADA	Anti-drug antibodies
AE	Adverse Event
ALP	Alkaline Phosphatase (ALP)
ALT	Alanine Transaminase
AST	Aspartate Transaminase
ATC	Anatomic, Therapeutic, Chemical (Classification System for Drugs)
AUC	Area under the plasma concentration-time curve
$AUC_{(0\text{-}inf)}$	Area under the plasma concentration-time curve from time zero to infinity
$AUC_{(0\text{-}t)}$	Area under the plasma concentration-time curve from time zero to time t
BLQ	Below Limit of Quantification
CBR	Clinical Benefit Rate
CD	Cluster of differentiation (cells)
CI	Confidence Interval
CK	Cytokines
CL	Apparent total body clearance of the drug from plasma
C_{max}	Maximum (or peak) serum concentration
CPI	Check Point Inhibitors
CRF	Case Report Form
CRO	Contract Research Organisation
CRP	C-Reactive Protein
CSR	Clinical Study Report
CV	Coefficient of Variation
DB	Database
DBL	Database lock
DEC	Dose Escalation Committee
DEM	Dose Escalation Meeting
DLT	Dose Limiting Toxicity
DOR	Duration of Response
ECG	Electro-cardiogram
ECOG	Eastern Cooperative Oncology Group
eCRF	Electronic Case Report Form
EOT	End of Treatment
FU	Follow-up
HLGT	High Group Level Term
HLT	High Level Term
IAP	Independent Advisory Panel
ICF	Informed Consent Form
ICH	International Conference of Harmonization
iCBR	(immune) Clinical Benefit Rate (based on response as per iRECIST)

iCPD	(immune) Confirmed Progression Disease (as per iRECIST)
iCR	(immune) Complete Response (as per iRECIST)
ID	(Patient) Identification Number
iDOR	(immune) Duration of Response (based on response as per iRECIST)
IMP	Investigational Medicinal Product
iORR	(immune) Overall Response Rate (based on response as per iRECIST)
iPFS	(immune) Progression Free Survival (as per iRECIST)
iPR	(immune) Partial Response (as per iRECIST)
iRECIST	(immune-based) Response Evaluation Criteria in Solid Tumors
iSD	(immune) Stable Disease (as per iRECIST)
ITT	Intent-To-Treat
iUPD	(immune) Unconfirmed Progression Disease (as per iRECIST)
IV	Intravenous
KM	Kaplan-Meier
LDH	Lactate Dehydrogenase
LLT	Lowest Level Term
Max	Maximum
MedDRA	Medical Dictionary for Regulatory Activities
Min	Minimum
MTD	Maximal Tolerated Dose
NA	Not Applicable, Not Available
NCI CTCAE	National Cancer Institute Common Terminology Criteria for Adverse Events
NK	Natural Killer (cell)
NKT	Natural killer T (cell)
ORR	Objective Response Rate
OS	Overall Survival
PBMC	Peripheral Blood Mononuclear Cell
PD	Pharmacodynamic
PK	Pharmacokinetic
PT	Preferred Term
Q1	Lower Quartile
Q3	Upper Quartile
QC	Quality Control
QT	QT interval
QTcF	Fridericia's correction of QT interval
R_{ac}	Accumulation ratio
RP2D	Recommended Phase 2 dose
SAE	Serious Adverse Event
SAF	Safety Set
SAP	Statistical Analysis Plan
SAS	Statistical Analysis Systems
SC	Subcutaneous
SOC	System Organ Class

StD	Standard Deviation
$t_{1/2}$	Elimination half-life (to be used in one-or noncompartmental model)
$t_{1/2\alpha}$	Initial or disposition half-life
TEAE	Treatment-emergent Adverse Events
TFLs	Tables, Figures and Listings
T_{max}	Time to reach maximum (peak) plasma concentration following drug administration
Treg	Regulatory T (cells)
ULN	Upper limit of Normal
V_d	Apparent volume of distribution
VS	Vital Signs
WHODrugD	World Health Organizations Drug Dictionary
λ_z	Termination elimination constant (symbol k_e is also used)

INTRODUCTION

Statistical evaluation of each SC103 study (AURELIO-03) part will be performed separately after lock of the relevant study part data in clinical database. This Statistical Analysis Plan (SAP) describes the statistical analyses and planned outputs for Study Part A. It includes definition of objectives and endpoints as per Study Protocol, the definition of analysis sets, and details needed for statistical programming. The SAP outlines the tables, listings and figures (TFLs) to be compiled in the Clinical Study Report (CSR).

This SAP does not include pharmacokinetic anal sis lan. SO (previously SO-C101, RLI-15) concentrations levels are measured by [redacted] who are also responsible for pharmacokinetic analysis and for writing pharmacokinetic analysis plan. This SAP does not include plan of statistical analysis to be performed on biomarkers collected from tumor tissue samples as collected data are limited and this analysis is intended to be fully exploratory.

This SAP is written according to the SC103 Study Protocol version 10.0 dated on 29-JUL-2021, current Mock Case Report Form (CRF), DEC charter version 4.0 dated on 26-MAR-2021, and IAP charter version 3.0 dated on 30-MAR-2021. The analyses and outputs closely follow the ICH guidelines for industry on topic E3 (Structure and Content of Clinical Study Reports) and E9 (Statistical Principles for Clinical Trials).

DOCUMENT HISTORY

Version	Date	Description of change	Performed by
Draft 0.1	05-APR-2019	First version of the document created.	[redacted]
Draft 0.2	28-MAY-2019	Update after review within statistical department.	
Draft 0.3	31-MAY-2020	Update after review of study team and update in line with Study Protocol version 6.1	
Draft 0.4	24-FEB-2021	Document changed to serve as SAP only for Part A, as the study parts will be analysed separately. Removing details about materials to be provided for for Dose Escalation Committee (DEC) and Independent Advisory Panel (IAP) as it is not relevant for the SAP. Simplification of document. Update of document template.	
Draft 0.5	25-MAR-2021	Further updates based on Stefano Ferrara feedback. Simplification of document and clarifications.	
Draft 0.6 and 0.7	21-JUL-2021	Additions on data handling and analyses for TEAEs. Other changes for PD/Cytokines and safety analyses. Review by Tereza Hrnčiarová.	
Draft 0.8	11-FEB-2022	Harmonization with protocol v10. Simplification of document. Slight modification on analyses for safety (labs, vital signs, figures, etc.). Slight modification on analyses for PD/Cytokines. Addition of efficacy analyses and figures.	
Draft 0.9	07-MAR-2022	Team review Implementation of feedback	
Final 1.0	26-JUL-2022	Implementation of minor changes and clarifying text Addition of outputs	
Final 2.0	30-SEP-2022	Implementation of following changes: - Day label from eCRF - Cross-over AEs should not be considered for AE episodes in Part A	

	- Correction of imputation of missing dates if start date is unknown - Clarified definition of efficacy population - Clarified CV definition - Clarified summary/listing of procedures - SOC added on PT standardization for certain AEs - Added ECG assessment selection in case of duplicates - Rules added for safety figures overtime where two or more values with same date (and same study day) - PK values BLQ are treated as 0 (aligned with PKAP) - Added spaghetti plot for efficacy figures - Clarified date to take when two dates are available for a single tumor assessment - Corrected duration of SD from start of study treatment - Clarified censoring for PFS and cross-overs - Added 2 cases of exclusion of PD data based on DRM - Changed major and minor protocol deviations to CSR Reportable and CSR not reportable - General formatting and text corrections

1 PLANNED CHANGES FROM STUDY PROTOCOL

In study protocol version 10.0, dated 29-JUL-2021, SO-C101 is specified in “Investigational medicinal products”. Throughout this SAP, SOT101 is used instead of SO-C101.

2 STUDY OBJECTIVES

2.1 PART A - SOT101 MONOTHERAPY

2.1.1 Primary objectives

- To assess the safety and tolerability of SOT101 given as monotherapy
- To determine the maximal tolerated dose (MTD) and/or recommended Phase 2 dose (RP2D) of SOT101 given as monotherapy

2.1.2 Secondary objectives

- To characterize the PK of SOT101
- To characterize the PD of SOT101 in peripheral blood
- To determine the preliminary efficacy of SOT101 monotherapy as measured by overall response rate (ORR), duration of response (DOR), clinical benefit rate (CBR), and progression-free survival (PFS) according to iRECIST
- To determine the immunogenicity of SOT101 given as monotherapy

According to iRECIST terminology responses assigned using iRECIST have a prefix of “i” (“i” stands for immune); therefore, abbreviations iORR, iDOR, iCBR, iPFS will be used afterwards.

2.1.3 Exploratory objectives

- To explore the mechanistic effects of SOT101 on selected immune cell populations in tumor tissue samples. Analysis of this exploratory objective is not described in this SAP, instead, a separate Biomarker analysis plan will be prepared.
- To assess overall survival (OS)

3 STUDY DESIGN

Study design is briefly described below. Full description of study design is included in the Study Protocol. The schedule of procedures and assessments is presented in the Study Protocol Table 9.6 to 9.17.

3.1 DEFINITION OF MTD/RP2D AND IMPLEMENTATION OF 3+3 DOSE ESCALATION DESIGN

MTD is defined as the dose level associated with ≥33% of DLT evaluable patients experiencing a DLT. If the MTD is reached, the RP2D will be conventionally defined as the dose level just below this non-tolerated dose level. If the MTD is not reached, the RP2D will be selected based on integrated evaluation of safety, tolerability, clinical benefit, PK and PD data, for all dose levels tested.

The 3+3 dose escalation design to identify MTD/RP2D includes the following steps for each dose level until MTD/RP2D is identified:

1. One patient will be enrolled and will receive the first four doses of SOT101 (day 1, day 2, day 8, and day 9). This patient will be observed for safety for 7 days after the fourth dose of SOT101, starting from day 9.
    - If there are no safety concerns at the end of these 7 days, second and third patients will be allowed to be dosed. The second and third patients will not be dosed on the same day.
    - Otherwise, dose escalation meeting (DEM) will be organized and DEC/IAP will decide next steps.
2. Next steps will depend on the occurrence of DLT within the DLT evaluation period of 21 days:
    - If **no DLT occurs** in 3 DLT evaluable patients, then next patient cohort treated with **higher dose level will start**.
    - If **one DLT occurs** in 3 DLT evaluable patients, then the cohort will be **extended to 6 DLT evaluable patients in total**.
        - If **one DLT occurs** in the 6 DLT evaluable patients, then the next patient cohort treated with **higher dose level start**.
        - If **≥2 DLT occur** in the 6 DLT evaluable patients, then MTD is identified and **enrolment/escalation is stopped**.
    - If **≥2 DLT occur** in 3 DLT evaluable patients, then MTD is identified **and enrolment/escalation is stopped**.

3.2 RANDOMIZATION AND BLINDING

Not applicable.

4 STUDY ENDPOINTS

4.1 DEMOGRAPHY AND BASELINE CHARACTERISTICS TO BE SUMMARIZED

The following baseline characteristics will be summarized in the tables:

- Demographic characteristics:
    - Age at informed consent (ICF) signature [years]
    - Age at informed consent (ICF) signature [years] according to: <18 years, >18 and ≤64 years, >64 and ≤84, >84 or older

  - Gender
  - Ethnicity
  - Race
- Baseline characteristics
  - Weight [kg]
  - Body Mass Index (derived)[kg/m^2]
- Disease history
  - Primary tumor location
  - Histological type
  - Cancer type (derived)
  - Time since diagnosis at ICF signature (derived) [years]
  - Time since latest radiological or clinical disease progression at ICF signature (derived) [weeks]
  - Number of lines of previous systemic anticancer therapy
  - Number of lines of previous systemic anticancer therapy categories: ≤ 2, > 2.
  - Previous treatment with check point inhibitors (CPI) (Yes/ No/ Unknown)
  - CPI Response (if CPI received) (Refractory/ Relapsed/ Unknown)
  - Prior anticancer non-systemic therapy (Yes/ No)
  - ECOG
  - ECOG categories: 0, > 0

4.2 ENDPOINTS

4.2.1 Primary endpoints

- Safety and tolerability of SOT101 as evaluated by the incidence of DLTs, incidence of SOT101-related adverse events (AEs), SAEs, AEs leading to premature discontinuation of SOT101, deaths, and clinical laboratory test abnormalities.
- Further, endpoints of the study are to determine MTD and the RP2D of SOT101 (as defined in the section 3.1).

4.2.2 Secondary endpoints

- PK of SOT101
- Immune response characterized by the changes in expression of immune markers in PBMCs
- iORR, iDOR, iCBR, and iPFS
- Detection of Anti-drug antibodies (ADA)

4.2.3 Exploratory endpoints

- Changes in the expression of immune biomarkers as compared to baseline in tumor tissue (analysis of this endpoint is not described in this SAP).
- OS at 6 months after the EOT visit.

5 COMMON DEFINITIONS

General and common definition relevant for statistical analysis/ Statistical Analysis Systems (SAS) programming are listed below. Definitions used only in analysis of a particular endpoint are included directly in analysis section.

5.1 TREATMENT CYCLE

Each treatment cycle in Part A should include 4 SOT101 administrations and should take 21 days as per Study Protocol. However, treatment interruptions and delays can occur. Therefore, the cycle number will be taken from the electronic CRF (eCRF) database.

The start of each cycle is defined by the date of the first SOT101 administration in the cycle.

The cycle lasts until Day 1 of the next cycle. The last cycle end is defined as Day 21 of the last cycle or end of the study participation (whatever occurs first).

For cross-over patients the number of cycles in Part A will end the day before combination treatment C1D1. Cycles for combination treatment will be counted from Cycle 1 in Part B.

5.2 LABELS USED IN SAP AND IN STATISTICAL OUTPUTS

EOT stands for end of treatment. FU stands for follow-up.

Cohort labels will include number of dose level (and dose administered µg/kg) as per Study Protocol. The label will be based on information recorded in eCRF in "Initial dose of SOT101 (ug/kg)".

- Example: 1 (1.5 µg/kg).

Individual time-points labels will be as follows:

- Screening
- Cycle X Day Y
    - Cycles will be identified by the number of the cycle as per eCRF data.
    - Days will be identified by the number of the day as per eCRF data.
- EOT
- EOT + X weeks, see below

The assignment to the time-point labels will be performed via SAS programming as follows:

- If Date of assessment – date of EOT ≤ 4+2 weeks then label = "EOT + 4 weeks"
- If 6 weeks < Date of assessment – date of EOT ≤ 8+2 then label = "EOT + 8 weeks"
- If 10 weeks < Date of assessment – date of EOT ≤ 12+2 then label = "EOT + 12 weeks", etc.

If two assessments are assigned to the same time-point label, the earliest assessment will be selected. In such case the tables or summaries will be contain a footnote specifying the case.

In the listings, the real post-treatment week (see section 6.2, rounded to one decimal) will be presented as well.

Timepoint labels used in the statistical outputs and derivations are described in the Appendix, Section 12.2.

5.3 BASELINE VALUES

5.3.1 Study baseline

Study baseline will be defined as the last non-missing measurement prior to the first SOT101 administration, unless specified otherwise.

5.3.2 Handling of missing data needed for baseline identification

The definitions above consider date and time of the assessment and SOT101 administration. If time is not known, then only dates will be used for identification of the baseline. Safety laboratory samples are supposed to be taken before study drug administration; therefore, if time of sample collection is not known and date is the same as date of administration then it will be considered as pre-dose sample.

Values which are identified as baseline via rule described in this paragraph will be flagged in the listings.

5.4 CODED TERMS AND DICTIONARIES USED

Data will be coded as described in the following table.

Table 3: Data to be coded

eCRF page name	Variable to be coded (Dictionary to be used for coding)
The previous therapies include the following pages:	
PRIOR ANTICANCER SYSTEMIC THERAPY	Medication (WHODD)
PRIOR ANTICANCER NON-SYSTEMIC THERAPY	Location and Surgery description (MedDRA)
Further, details about prior and concomitant medication/therapies will be collected on the following pages:	
MEDICATION DETAILS	Medication (WHODD)
NON-PHARMACOLOGICAL THERAPY DETAILS	Therapy (MedDRA)
NEW ANTICANCER SYSTEMIC THERAPY DETAILS	Medication (WHODD)
NEW ANTICANCER NON-SYSTEMIC THERAPY DETAILS	Location and Surgery description (MedDRA)
MEDICAL HISTORY DETAILS	Medical history term (MedDRA)
ADVERSE EVENT DETAILS	Adverse event term (MedDRA)
DEATH	Immediate cause of death and Underlying cause of death (MedDRA)

The coding will be performed directly in eCRF system. The terms will be coded with the most current version of Medical Dictionary for Regulatory Activities (MedDRA) and WHODD dictionaries at time of DB lock.

All MedDRA and WHODD levels listed below will be presented in the listings. Those used in the tables are underlined.

MedDRA coding levels will include:

- Preferred Term (PT)
- Lowest Level Term (LLT)
- High Level Term (HLT)
- High Group Level Term (HLGT)
- Primary System Organ Class (SOC)

WHODD coding will include the following Anatomic, Therapeutic, Chemical (ATC) levels:

- ATC Level 1: anatomical main group
- ATC Level 2: therapeutic subgroup
- ATC Level 3: pharmacological subgroup
- ATC Level 4: chemical subgroup

- WHODD preferred name

5.5 PREVIOUS/CONCOMITANT/POST-TREATMENT MEDICATIONS/ THERAPIES

The records of prior and concomitant medications will be classified as "Prior", "Concomitant" and "Post-treatment" according to the following definitions.

The start of study treatment refers to the date of the first SOT101 administration.

The end of study treatment refers to the date of the last SOT101 administration.

"Concomitant" medication/therapy is any medication/therapy which was administered in the period starting with the start of study treatment (including) and lasts until the end of study treatment. The only exception will be medication/therapy which started on day of the end of study treatment: this medication will be classified as "Post-treatment".

"Prior" medication/therapy is any medication/therapy ended before the start of study treatment.

"Post-treatment" medication/therapy is any medication/therapy which started after or at the end of study treatment.

For records of medication/therapy with unknown and incomplete dates which cannot be identified according to definitions described above, the following rules will be applied:

- If end date of medication/therapy is completely unknown and the medication/therapy started after or at the end of study treatment, the medication/therapy will be counted as "Post-treatment". Otherwise (i.e., the medication/therapy started before the end of study treatment), the medication/therapy will be counted as "Concomitant".
- If start date of medication/therapy is completely unknown and the medication/therapy ended after or at start of study treatment, the medication/therapy will be counted as "Concomitant". Otherwise (i.e., the medication/therapy ended before the start of study treatment), the medication/therapy will be counted as "Prior".
- If start or end date is incomplete: the first possible start date (e.g., for xxDEC2019 this is 01DEC2019, for xxxxx2019 this is 01JAN2019) or last possible end date (e.g., for xxDEC2019 this is 31DEC2019, for xxxxx2019 this is 31DEC2019) will be derived. Classification "Prior", "Concomitant" and "Post-treatment" medication/therapy will be performed using these derived dates.
- If both end date and start date of medication/therapy are completely unknown, then it will be counted as "Concomitant".

5.6 ADVERSE EVENT (AE)

Detailed definition of AE and its classification is presented in the Study Protocol (See section 9.11.5.1).

Each increase or decrease of severity of AE will be collected as separate AE record on "ADVERSE EVENT DETAILS" eCRF page.

Raw data will be used to identify AE episodes as follows:

- Linked AE records by the investigator (i.e. AE record with an outcome of "Change in severity" in the eCRF) with the same MedDRA preferred term, where the start date of the subsequent AE record is equal to (or +1 day) end date of the previous AE record, will be identified as one AE (continuous) and each AE record will be assigned the same AE ID (equal to the AE ID of the first AE record in the episode).

In order to assign the TEAE status to AEs with the same AE ID (linked AE records), unaggregated data will be used. After the TEAE assignment, AE episodes with the same AE ID will be aggregated as per section 5.8. AE records belonging to cross-over (please refer to Section 5.9) will not be considered for aggregation purposes.

5.7 TREATMENT-EMERGENT ADVERSE EVENTS (TEAE)

According to the Study Protocol section 9.13.10.2 treatment-emergent AE is defined as an AE that

- emerges during treatment, having been absent at pretreatment (screening), or
- reemerges during treatment, having been present at pretreatment (screening), or
- worsens in severity during treatment relative to the pretreatment state.

The start of study treatment refers to the date of the first SOT101 administration.

Emerges or reemerges during treatment:

TEAEs are AEs with start date ≥ start of study treatment. Conditions when date/time is unknown or incomplete are defined below.

Worsening in severity:

When the AE belongs to an AE episode (as defined in section 5.6) where the first AE record is not TEAE, the subsequent AE record will be TEAE if:

- AE with start date ≥ start of study treatment, and
- Worsens in severity as compared to pretreatment state.

For adverse events with unknown or incomplete start date/time the following rules will be applied:

Incomplete date: when some information is available (e.g., month, year), but date is partially missing (e.g., missing day, month).

Unknown date/time: when no information is available and thus day, month and year are missing.

Unknown time for start or end of AE:

If time of AE start, or start of study treatment is unknown, the information will be derived only using dates – if AE start or end dates are unknown, conditions are defined below.

If start date is unknown and end date is known (and complete):

- If end date/time is < start of study treatment, the event will not be counted as TEAE.
- If end date/time is ≥ start of study treatment, the event will be counted as TEAE.

If start date is incomplete and end date is incomplete or unknown:

- last possible start date of AE (e.g., for xxDEC2019 this is 31DEC2019, for xxxxx2019 this is 31DEC2019) will be derived. If the last possible start date of AE ≥ start of study treatment the event will be counted as TEAE. Otherwise, if last possible start date of AE < start of study treatment, the event will not be counted as TEAE.

If start date is unknown and end date is incomplete:

- last possible end date of AE (e.g., for xxDEC2019 this is 31DEC2019, for xxxxx2019 this is 31DEC2019) will be derived. If the last possible end date of AE ≥ start of study treatment the event will be counted as TEAE. Otherwise, if last possible end date of AE < start of study treatment, the event will not be counted as TEAE.

Unknown date for start and end of AE:

- If both start date and end date are unknown, the event will be counted as TEAE.

5.8 AGGREGATION OF CONTINUOUS AE AND TEAE

In order to aggregate AE and/or TEAE episodes (in text below referred just as 'AE') that are continuous, the following will be applied:

- AE will be TEAE if any of all AE records belonging to the AE is TEAE (as defined in section 5.7).
- Start date/time of AE will be start date of the first AE record belonging to the AE. This date will be used to derive the Cycle as defined in sections 5.1 and 0, as well as the last dose level of SOT101 before the start of the AE.
- End date /time of AE will be end date of the last AE record belonging to the AE.
- Outcome of AE will be outcome of the last AE record belonging to the AE.
- Severity will be the highest grade out of all AE records belonging to the AE.
- AE will be serious if any of all AE records belonging to the AE is evaluated as serious.
- AE will be immune-related if any of all AE records belonging to the AE is evaluated as AE immune-related. Secondly, AE will be not immune-related if any of all AE records belonging to the AE is evaluated as AE not immune-related.
- AE will have suspected relationship to SOT101 if any of all AE records belonging to the AE is evaluated as to have suspected relationship to SOT101.
- Action taken to SOT101 will include all actions taken as per all AE records belonging to the AE.

The definition above will be used for tables. Clinical signs/symptoms of cytokine release syndrome will not be aggregated.

Listings will present all AE and TEAE (not aggregated) as defined in Section 8.7.2 and Section 8.7.3.

5.9 CROSS-OVER PATIENTS AND DATA HANDLING

The cross-over patients are patients who initiated SOT101 treatment in Study Part A and have signed informed consent to switch to combination treatment with Pembrolizumab, were confirmed by the Sponsor as eligible for combination treatment and received at least one dose of pembrolizumab after the switch.

As per eCRF completion guidelines in the cross-over part, the patient will start (again) from Cycle 1 with combination of SOT101 and pembrolizumab. Cross-over part starts with date of eligibility confirmation for cross-over to combination treatment (variable CR.CRELCDAT).

TEAEs that started before the first Pembrolizumab administration date (and time if available) for cross-over patients will be included into analysis of TEAEs in Part A.

Any other assessments, adverse events, medication and/or therapies that started in the cross-over part (at or after the first Pembrolizumab administration) will only be included in data listings where those assessments will be flagged.

6 GENERAL ALGORITHMS AND DERIVED VARIABLES

General and common algorithms to be used in SAS programming are listed below. Algorithms used only in analysis of particular endpoint are included directly in analysis section.

6.1 CONVERSION OF DAYS, MONTH, YEARS

Week will be counted as day/7. Planned to be used for presentation in listings where the value will be rounded for one decimal.

One year will be counted as 365.25 days.

One month will be counted as 365.25/12 days = 30.4375 days.

Number of calculated years and months will be used e.g. for calculation of age or survival time, rounding procedures are described in section 8.2.2.

6.2 TREATMENT/POST-TREATMENT DAY

Real treatment day will be calculated as date – date of the start of study treatment + 1. For dates before the start of study treatment, the treatment day will be negative and will be calculated as follows: start of study treatment – date.

Real post-treatment day will be calculated as date – date of the end of study treatment.

Real week, month and year will be converted from real day as defined in the section 6.1.

6.3 ALGORITHM FOR ALLOCATION OF DATA TO SCHEDULED VISITS/TIME-POINTS

The algorithms are described with definition of the time-point labels in Section 5.2.

6.4 APPLICATION OF CUT-OFF

No cut-off is planned to be applied for the final analysis.

7 ANALYSIS SETS

7.1 SAFETY SET (SAF)

The safety population will include all patients All patients exposed to SOT101 in Part A.

The SAF will be used for analysis of safety endpoints.

7.2 DLT-EVALUABLE PATIENTS

A patient evaluable for DLT will be a patient who has completed cycle 1 and received all planned treatments without any treatment delay or interruptions for any other reason than DLT: for Part A, received all 4 doses of SOT101 as planned. Patients who do not fulfil these criteria for any other reason than DLT should be replaced.

The DLT evaluable patients will be used for ongoing safety evaluation needed for decisions as per 3+3 dose escalation design.

7.3 PK/PD EVALUABLE

PK analysis set will include patients with evaluable PK profile.

PD analysis set will include patients with evaluable PD profile.

Evaluation of PK and PD are secondary objectives of Study Part A which is a dose-escalation study; limited number of patients is included in the individual dose levels and in RP2D level. This needs to be considered when interpreting the data. The PK/PD profile is further explored in Part D.

Protocol deviation related to PK and PD assessment and compliance with dosing schedule will be reviewed. Only patients which data would lead to biased conclusions or analysis interpretation will be excluded from the analysis sets.

The PK/PD analysis set will include patients in both PK analysis set, and PD analysis set. The PK/PD evaluable patients will be used for PK/PD analysis.

7.4 EFFICACY SET

All patients exposed to SOT101 (exposure for at least one treatment cycle) who had at least one evaluable tumor assessment per iRECIST after the initiation of SOT101 treatment.

Exposure for at least one treatment cycle is defined as 4 does of SOT101 (regardless of dose level) in Cycle 1, or if the patient is exposed to SOT101 (with any number of doses) in Cycle 1 and started Cycle 2.

AThe Efficacy set will be used for analysis of efficacy endpoints.

8 STATISTICAL METHODS AND DETERMINATION OF SAMPLE SIZE

This section describes the data analysis in detail (with exception of pharmacokinetic analysis which will is described in separate document attached). The statistical methods are planned in accordance with the Study Protocol (section 9.9) and in accordance with ICH Topic E9 Statistical Principles for Clinical Trials.

SAS version 9.4 or newer will be used for statistical programming.

8.1 SOURCE DATA TO BE USED FOR ANALYSIS

Data collected in clinical study database including MedDRA and WHODD coding will be used for analysis. Laboratory conversion factors will be taken from the internal IBMCD laboratory DB (as per Laboratory Data Unit Conversions standards).

Plasma concentration data and pharmacokinetic parameters will be provided by [redacted] n .sas7bdat format and will be directly used for analysis (will not be a part of clinical database). Dates and times of blood sampling in the datasets provided by [redacted] and those recorded in the clinical database will be reconciled as a part data management processes

Description of the provided datasets:

- pc_cnp_DDMMMYYYY.sas7bdat: dataset providing the PK concentrations overtime, per patient.
- pp_cnp_DDMMMYYYY.sas7bdat: dataset providing the calculated PK parameters, per patient.

Where n is the number of the cohort, p is the study part (e.g., ‘a’ for Part A), DDMMMYYYY is the date of transfer. Further details are specified in data transfer specification “SC103_Data Transfer Specification [redacted] 20Jul2021” dated 20-Jul-2021.

Anti-drug antibodies data will be provided b [redacted]

Description of the provided datasets:

- SC103ADASNAPSHO [redacted] DMMMYYYY.csv: provides per patient and overtime ADA positivity, titration, and NADA positivity. Where DDMMMYYYY is the date of transfer.

Further details are specified in data transfer specification "SC103_Data Transfer Specificatio [redacted] v5.0_20Jul2021" dated 20-Jul-2021.

Plasma concentration data and pharmacokinetic parameters will be provided by [redacted] Materials for DEC/IAP will be directly prepared by [redacted] Sotio will provide outputs for CSR.

Pharmacodynamic variables and cytokines levels will be provided by Central LAB [redacted] AS® v.9 transport files and will be directly used for analysis (will not be a part of clinical database). Dates and times of blood sampling in the datasets provided by [redacted] nd those recorded in the clinical database will be reconciled as a part data management processes

Description of the provided datasets:

- SC103SNAPSHO [redacted] DMMMYYYY.xpt: includes per patient and overtime the test results as per protocol. here DDMMMYYYY is the date of file transfer.

Further details are specified in data transmission agreement "SC103_Data Transmission Agreement [redacted] 15Jun2021" dated 15-Jun-2021.

8.2 GENERAL PRINCIPLES

The study includes Study Part A. Cross over patients to Part B will be included in the TFLs as described in section 5.9.

This is Phase I study with 3+3 dose escalation design with primary objective to determine MTD/RP2D. The analysis will be mainly descriptive. If appropriate regarding the number of patients (e.g., All cohorts pooled), the descriptive statistics will be presented with 95% confidence intervals. Descriptive statistics will include:

For categorical variables, standard set of summary statistics will be counts and percentages calculated from number of available observations. Number of available observations (and number of missing observations) will be presented as well. For baseline characteristics missing, not applicable/not available/not known will be counted as a category. The number of patients used for the percentages (denominator) is defined in each analysis section of this SAP.

For continuous variables, the following descriptive statistics will be presented: number of available observations (and number of missing observations), mean, standard deviation (StD), median, lower quartile (Q1), upper quartile (Q3), minimum (Min), and maximum (Max).

For time-to-event variables, Kaplan-Meier (KM) estimates of median, Q1 and Q3 will be presented. The number and percentage of patients with event and censored patients will be presented. KM curves will be provided as a part of descriptive analysis.

For pharmacokinetic parameters, the following descriptive statistics will be presented: number of available observations (and number of missing observations/ number of concentrations below limit of quantifications (BLQ)), arithmetic mean and geometric mean and their 95% confidence intervals, standard deviation (StD), StD of log-transformed data, median, inter-patients (between-patients, within-cycle) coefficient of variation, intra-patient (within-patient, between-cycles-days) coefficient of variation, minimum, and maximum. Coefficient of variation (CV) in % is computed as:

% CV = (StD x 100) / mean

8.2.1 Listings

Each listing will present the following variables/columns:

- Patient identification (ID), Cohort (dose level)
- If appropriate, analysis set relevant for particular listing

Listings will be sorted by ID and by chronological order of visits/assessments/events.

Dates will be presented in the listings in format YYMMDD10. (e.g., 2019-11-31). Partial dates as exported from the databased will be listed (e.g., 2019-11-UNK, 2019-UNK-UNK, UNK-UNK-UNK).

8.2.2 Rounding procedures

Percentages will be presented with one decimal place with exception of efficacy data where two decimal places will be presented.

Mean, median, Q1 and Q3 will be presented with one more decimal place and StD will be presented with two more decimal places than the original data used for calculation of the statistics

Other values such as temperature, number of weeks, coefficients of variation, etc. will be presented with one or two decimal places, according to the source data.

8.2.3 Unscheduled/ repeated assessments

Unscheduled/ repeated assessments which are performed in addition to those scheduled in the Study Protocol will not be used for analysis per time-point. Baseline values can include unscheduled/repeated assessment if they are the last before study drug administration (see section 5.3 for details).

8.2.4 Missing data

In general, missing data will not be imputed, i.e. complete case analyses will be performed. However, number of missing data is to be presented in descriptive statistics.

8.2.5 Methods for handling of incomplete/missing dates/ times

Methods for handling of incomplete and missing dates of medication/therapies and adverse events are presented in sections 5.5 and 5.7.

Similarly, methods for handling of incomplete and missing dates for Date of initial diagnosis are described in section 8.4.

8.2.6 Covariates and subgroups

The patients are planned to be analyzed by the cohorts (dose levels).

Subgroup analyses are not planned. No covariates to be used in analyses planned in this SAP.

8.2.7 Region/Country/Site analysis in multi-centric trial

Analysis by region, country or site is not planned.

8.2.8 Validation of statistical programming

Each SAS program will be validated by a second qualified SAS programmer to ensure a correct output and a correct presentation of the data. The validation process is documented in the validation sheet

(GCPS_DMF_033 A-C), which also prespecifies criteria for risk categorization of programs and the corresponding validation actions

Logs of all programs used for analysis and data preparation will be checked for errors and unexpected warnings. Any undocumented updating of raw study data in statistical programming instead of change in clinical DB (or source data) is not allowed.

8.3 DISPOSITION OF STUDY PATIENTS

Disposition of patients will be presented for Study Part A, for All cohorts pooled and by cohorts. Cases where patient signed the ICF (thus a Patient ID was assigned) for Part A but the patient was not treated due to safety concerns regarding previous patients (e.g., MTD reached) will not be included in the tables nor the listings: if applicable the patient signed a new ICF and a new Patient ID was assigned. These cases are recorded in the eCRF, in "Eligibility Verification" where the reason for Screen Failure is recorded as "Change of study part" (IE.IESFREA).

The following information will be presented in the table of patients' disposition:

No. of cohorts included (presented only for All cohorts pooled).

Count of the following groups of patients will be presented:

- Screened
    - Reason for screen failure with count and percentages* (from screened patients)
- Eligible (as per confirmation by the Sponsor)
- Treated

Count and percentages* of treated patients will be presented for the following groups of patients:

- DLT evaluable
- Ongoing patients (i.e., patients still in the study)
- Study discontinued patients
    - Reason for discontinuation with count and percentages* (from study discontinued patients)
- SOT101 discontinued patients
    - Reason for discontinuation with count and percentages* (from SOT101 discontinued patients)

*The percentages will be presented by cohort and for all cohorts pooled.

Formally, no EOT is performed for cross-over patients from Part A to Part B. Hence, the "discontinuation" of SOT101 monotherapy treatment in Part A for patients that cross-over to Part B will be shown as "Patient crossed-over to Part B".

Disposition of patients into analysis sets:

- Number of patients in analysis set (percentages calculated out of all treated patients), number of patients excluded from analysis set and reasons for exclusion from analysis sets (percentages calculated out of those patients excluded from analysis set).

Protocol deviations will be summarized for SAF and for All cohorts pooled, as well as listed.

8.4 DESCRIPTION OF BASELINE PATIENTS' CHARACTERISTICS

Baseline characteristics and disease history information defined in section 4.1 will be summarized with descriptive statistics.

Cancer type will be medically reviewed prior to DBL and derived based on the list specified in Appendix (Section 12.3).

Body Mass Index will be calculated as weight in kg divided by height in m^2. Values will be rounded to one decimal.

Date of birth is not collected in the eCRF. Age at ICF signature in years as recorded in eCRF will be used. Then, time since diagnosis at ICF signature and time since latest radiological or clinical disease progression at ICF signature in years will be calculated as follows: date of ICF signature (at time of entering the study) – date of diagnosis/progression + 1 and transformed to years/weeks respectively as per section 6.1.

If Date of initial diagnosis is incomplete of partially missing, the following rules will be applied for imputation of dates:

- If day and month is missing, day will be imputed as 01 and month as 06.
- If only day is missing, day will be imputed as 01.
- If only month is missing, month will be imputed as 06.
- If year is missing or the date is completely unknown, no imputation will be performed.

Date of latest radiological or clinical disease progression will not be imputed regardless of unknown or partially missing dates.

Explanatory footnote will be presented in corresponding table and listing.

The baseline patients' characteristics will be analyzed using SAF and presented for All cohorts pooled, as well as by cohort. Percentages will be computed from the number of treated patients in All cohorts pooled and, in each cohort, respectively.

Medical history recorded in eCRF will be only listed.

8.5 MEDICATION/THERAPIES

Medication and therapies as specified in Table 3 will be presented by count and percentages of patients. Separate tables for prior, concomitant, and post-treatment medication/therapies (see section 5.5) will be presented. Prior, concomitant, and post-treatment medication/therapies will be flagged in the listings.

The tables will be generated using SAF and for All cohorts pooled. Percentages will be computed from the number of treated patients in All cohorts pooled for all cases: prior, concomitant, and post-treatment medication/therapies.

Prior, concomitant, and post-treatment procedures will also be listed.

8.6 EXPOSURE TO STUDY TREATMENTS

Duration of exposure to SOT101 will be calculated as: date of the last SOT101 administration - date of the first SOT101 administration + 1.

Descriptive statistics of duration of exposure to SOT101 will be presented in the table together with patient-years of exposure, analyzed as continuous variables.

Dose intensity will be calculated as follows, for each patient:

- Sum of (SOT101 administrations x dose level) / duration of exposure (in days)

Dose intensity will be summarized.

Additionally, to provide a dosing overview and a summary of changes from dosing (based on initial dose of SOT101 and actual dose of SOT101) the number of SOT101 administered doses will be analyzed descriptively as categorical variable.

Descriptive statistics for duration of exposure, dose intensity, and dosing overview will be provided for All cohorts pooled and by cohorts. Percentages will be computed from the number of treated patients in All cohorts pooled and, in each cohort, respectively. The tables will be generated using SAF.

Dose level, Dilution Fold, Total Volume Administered, Body Weight at Day 1 of each cycle, calculated Volume for Administration (as described in SC103_Instruction for handling of IMP and Trial Related Materials_v4.0_16Mar2021 (v4.0)) and compliance of dosing schedule for SOT101 with Study Protocol will be presented in Listings.

8.7 ANALYSES OF SAFETY

8.7.1 Summary of dose limiting toxicity events (DLTs) for determination of MTD/RP2D

AEs linked to DLTs will be summarized in frequency table as defined for summary table of TEAEs. Information in summary table will be completed by listing where information from dedicated DLT page in eCRF ("Dose Limiting Toxicity Details") will be merged in information recorded in "Adverse Event Details" eCRF page. Merging will be done on unaggregated data by Patient ID (AE.subnum, DLT.subnum) and AE number (AE.PAGESEQ, DLT.AENO).

8.7.2 Adverse events (AEs)

Details about AEs as collected on "Adverse Event Details" eCRF page will be used for analysis. Data collected on "Serious Adverse Event" eCRF page will be used for safety reporting in responsibility of pharmacovigilance department and will not be part of statistical outputs.

See section 5.8 for handling of AE records needed before programming of tables. All AE records will be presented in the listings without aggregation into AE episodes (derived number of episodes will indicate which AE records were aggregated for summaries).

8.7.3 Treatment-Emergent Adverse events (TEAEs)

TEAEs are defined in section 5.7 above. Note that as per Study Protocol AEs are collected in eCRF database until 90±2 days after last dose of SOT101.

Not TEAE will only be listed.

8.7.3.1 Grouping of TEAEs

For harmonization and safety data review purposes, the following grouping of Preferred Terms will be considered in the analysis and displayed as such in the tables. Listings of TEAEs will present the originally coded Preferred Term:

TEAE System Organ Class: Preferred Term	Preferred Term
Gastrointestinal disorders: Abdominal pain	Abdominal pain lower
	Abdominal pain upper
	Abdominal pain
Investigations: Blood bilirubin increased	Hyperbilirubinaemia
	Blood bilirubin increased

Investigations: Lymphocyte count decreased	Lymphopenia
	Lymphocyte count decreased
Investigations: Neutrophil count decreased	Neutropenia
	Neutrophil count decreased
Investigations: Platelet count decreased	Thrombocytopenia
	Platelet count decreased
General disorders and administration site conditions: Injection site reaction	Injection site reaction
	Injection site erythema Injection site rash Injection site pruritus Injection site induration Injection site inflammation Injection site oedema Injection site pain

8.7.3.2 General considerations for analysis of TEAEs

TEAEs will be displayed in frequency tables, presenting for all tables:

- Number of TEAEs and percentage of patients with at least one TEAE (TEAEs, n (%))
- Number of related TEAEs and percentage of patients with at least one related TEAE (related TEAEs, n (%))

Where percentages will be computed from the number of treated patients in All cohorts pooled and, in each cohort, respectively (unless stated otherwise, see below). Clinical sign/symptom of cytokine release syndrome (as per variable AE.AERELCRS) will be listed separately.

The following frequency tables will be generated for TEAEs, TESAEs:

- Summary table of TEAEs
- Frequencies of TEAEs by MedDRA preferred term (PT) and primary system organ class (SOC)

8.7.3.3 Summary tables of TEAEs

Summary table of TEAEs will present the frequencies of any TEAE and TEAEs by the following characteristics:

- Seriousness
- Outcome
- Severity (i.e., maximum severity reported for AE)
- Maximum severity per patient
- Severity of NCI CTCAE grade 3,4,5
- AE immune-related
- Action taken with SOT101

Frequencies by “Severity” AE and patient will be counted for each severity level which occurs (one patient can have several AEs with different severity). “Maximum severity per patient” will be calculated for each patient. Then, in frequency tables the patient will be counted only once (for the maximal severity) and only TEAEs with this maximal severity will be counted. Similarly, the worst action taken

will be considered, from best to worst: No action taken, Dose modified, Temporarily discontinued, Other (as temporarily discontinued + dose modified), Permanently discontinued.

Summary table of TEAEs will be presented for All cohorts pooled and by cohort. In addition, the summary table of TEAEs by cycle will be presented for All cohorts pooled and for the RP2D cohort, up to Cycle 3 and only for TEAEs with an NCI CTCAE grade > 2; when presenting by Cycle, the number of patients treated within that Cycle will be used for the calculation of percentages. The TEAE will be assigned to a Cycle if the onset is within that Cycle, or if the TEAE worsens within that Cycle. Frequency tables of TEAEs by MedDRA PT within SOC

Frequencies of TEAEs by MedDRA PT within SOC will present frequencies of any TEAE, by SOC and by PT within each SOC. The tables of the following groups of TEAEs will be provided:

- TEAEs
- TEAEs reported in ≥ 10% of patients
- Non-serious TEAEs reported in ≥5% of patients
- TESAEs
- Fatal TEAEs
- NCI CTCAE Grade 3, 4, 5 TEAEs
- Immune-related TEAEs
- TEAEs leading to SOT101 dose modification
- TEAEs leading to SOT101 temporary discontinuation
- TEAEs leading to SOT101 permanent discontinuation

Special cases regarding SOT101 Action Taken (e.g., Other, “free text” specified) will be reviewed before analysis and TEAEs will be counted as appropriate following the specification in other action taken: in general, certain keywords will be used to classify the TEAE into one pre-defined actions taken above (e.g., a keyword of “dose” in the free text would lead to a classification of dose modified as action taken, a keyword of “discontinuation” or “discontinued” in the free text would lead to a classification of temporary discontinuation).

Frequencies of TEAEs by MedDRA PT within SOC will be presented for All cohorts pooled and by cohort. In addition, when presenting by cohort, the last dose level of SOT101 before the start of the TEAE will also be presented.

Frequency table of TEAEs by MedDRA PT will be generated for All cohorts pooled. The table will be sorted by total number of patients with TEAE in descending order. Additionally, the proportion of patients with TEAE by MedDRA PT will also be presented graphically, by maximum grade and worse action taken.

Table of underlying causes of deaths by MedDRA PT and primary SOC will be generated for All cohorts pooled.

8.7.3.4 Listing of AEs

Listings of AEs will present the following information in addition to data collected on eCRF page “ADVERSE EVENT DETAILS”:

- Patient identification (ID), Study Part, Cohort (dose level), DLT evaluable (Yes/No)
- AE no. (derived as number of AE episode, see section 5.6, in chronological order of start date)
- TEAE (Yes/No) (derived)
- Cycle when AE started (derived)
- SOT101 Treatment Day when AE start (derived)

- Days* after the last SOT101 administration (derived)
- Last dose of SOT101 before AE start (derived)
- Total number of SOT101 administered before AE start**
- Duration of AE***
- MedDRA PT

* Days after last dose will be calculated as AE start date – administration date.

**If time of AE start is not recorded (or time of SO-C101 administration is not recorded), the information will be derived only using dates (i.e., date of last SOT101 administered before date of AE start, SOT101 doses administered before date of AE start). The administration of SOT101 at the same date as date of AE start will be indicated as "(+1)", e.g. 5 (+1). If AE start date (or SOT101 administration date) is unknown or incomplete, the derivation will not be performed.

***Duration of AE will be calculated as AE end date– AE start date + 1. If end date or start date is missing or incomplete, the derivation will not be performed.

8.7.4 Other safety assessments

Other safety data include ECG, vital signs, clinical laboratory, physical examination, and echocardiography.

Date of physical examination, date and results of echocardiography assessment will be only listed.

Absolute values of laboratory data (selected laboratory variables defined below), vital signs and QT/ QTcF (Fridericia's correction) will be summarized at individual time-points descriptively by cohort and all cohorts pooled. A more detailed overview will be provided with figures containing the profiles overtime, where the cohort (i.e., dose level) will be colored accordingly.

In all cases, tables and figures will present timepoints where at least 3 patients (or more) have data available at that timepoint.

8.7.4.1 ECG

In addition, analysis in line with ICH E14 guideline will be performed, i.e. number and percentage of patients who fit the criterial listed below will be presented in frequency table (All Cohort pooled and all time-point pooled).

- QTcF interval > 450
- QTcF interval > 480
- QTcF interval > 500
- QTcF interval increases from study baseline > 30
- QTcF interval increases from study baseline > 60
- Any criterion listed above met

QTcF levels which met the criteria above will be included in dedicated listing.

In case of any duplicated assessments, the assessment with the latest sequence (PAGESEQ in eCRF) will be selected.

8.7.4.2 Vital signs

In addition, the following will be provided:

- Mean profiles over time will be presented graphically by cohort and all cohorts pooled.

Vital signs will be analyzed irrespective of the position where the assessments were done.

8.7.4.3 Laboratory values

The selected laboratory variables: Total Bilirubin, Alanine Transaminase (ALT), Aspartate Transaminase (AST), Neutrophils, Platelets, Lymphocytes, Haemoglobin, C-reactive protein (CRP), Alkaline Phosphatase (ALP), Lactate Dehydrogenase (LDH).

Laboratory values will be converted to standard units: the conversion factors to SI units will be maintained in the lab repository database (IBMCD LAB). Changes will be audit trailed in the system. The conversion of laboratory results into SI units will be performed via SAS programming.

In addition, the following will be provided:

For selected laboratory variables not concerning liver enzymes (Neutrophils, Platelets, Lymphocytes, Haemoglobin, CRP, LDH):

- Mean profiles over time will be presented graphically by cohort and all cohorts pooled.

For selected laboratory variables concerning liver enzymes (Total Bilirubin, ALT, AST, ALP):

- Mean profiles over time will be presented graphically by cohort and all cohorts pooled.
- Patient profiles over time will be presented graphically for the RP2D and RP2D – 1 cohort, excluding the MTD.
- Maximal-levels per patient presented in figure with dose-level on X-axis.
- Maximal levels per patient will be also listed in dedicated listing.

For the profiles, if there are two or more values on the same day, the pre-dose value will be considered (as per protocol, safety laboratory measurements should be performed prior to dosing). If two or more pre-dose values, the one closest to the dosing will be selected for displaying purposes.

Hepatic function abnormality defined by an increase in AST and/or ALT to ≥ 3 × Upper limit of normal (ULN) concurrent with an increase in total bilirubin to ≥ 2 × ULN but without increase in alkaline phosphatase (i.e., alkaline phosphatase < 2 × ULN) meets the criteria for Hy's law and raises the concern for drug-induced liver injury when no other cause is identified. The summary of liver function tests will include the following categories, and the number and percentage of patients meeting Hy's Law at each scheduled visit during the on-treatment period will be summarized.

8.7.4.4 Prohibited medications

According to section 9.6.4.1 Prohibited medications in the Study Protocol medications which use is known to prolong QT/QTcF interval are prohibited. If such a prohibited medication is administered to the patients, then it will be taken into account in analysis of QT/ QTcF in the following way: patients with prohibited medications administered will be excluded from the analysis (tables) and further information will be provided: if the number of patients with prohibited medications administered is larger than 1, an extra table will be provided for the analysis of QT/QTcF including only these patients. Otherwise, a footnote specifying the case will be provided with the original table.

8.8 ANALYSES OF SOT101 CONCENTRATION DATA AND PK PARAMETERS

The PK analysis plan is provided by [redacted] nd attached to this SAP (section 12.1).

The following PK parameters will be calculated via non-compartmental model according to this plan:

- C_{max}
- T_{max}

- $t_{1/2,}$
- Termination elimination constant (λ_z)
- $t_{1/2\alpha}$ – distribution half-life (where possible)
- $AUC_{(0-6)}$, $AUC_{(0-t)}$, $AUC_{(0-24)}$, $AUC_{(0-inf)}$, same parameters per dose (AUC/D)
- CL - Clearance
- V_d - Volume of distribution
- R_{ac} - accumulation ratio over cohorts/dose levels

Concentration levels, C_{max}, T_{max} and $t_{1/2}$ will be analyzed descriptively by cohorts (dose administered). In addition, dose-normalized C_{max} (C_{max}/D) and T_{max} will be presented for all cohorts pooled. Mean concentration levels will be presented in figures with linear and semi-logarithmic scale (only for Cycle 1).

In line with Protocol Deviation Plan, PK samples taken out of schedule defined by the study protocol will be flagged in concentration listings and will not be a part of protocol deviation listing.

Dose proportionality analysis of AUC and C_{max} will be performed for exploratory purposes using standard "power-law model" according to approach describes by Brian Smith et al (200) which is concisely described in paper by Zhou et al (2006).

The "power-law model" is defined as follows:

$PK = c \cdot Dose^{\beta 1} \cdot e^{\varepsilon}$

Dose-proportionality implies that $\beta 1 = 1$.

After the logarithmic transformation, the "power-law model" can be expressed as:

$\log(PK) = \beta 0 + \beta 1 \cdot \log(Dose) + \varepsilon$

Dose-proportionality corresponds to $r^{\beta 1-1}=1$, where r=highest dose level/lowest dose level.

In order to conclude the dose-proportionality the following criterion has to be met:

$1 + (\log(\theta_L)/\log(r)) < 90\%$ CI of $\beta 1 < 1 + (\log(\theta_U)/\log(r))$.

The commonly used (θ_L, θ_U) will be (80%, 125%). If the SOT101 will be considered as highly variable drug (intra-patient variability >30%), then (77%, 130%) will be used as a margin.

PK samples are taken on cycle 1 day 1 for 24 hours after administration. Cycle 1 day 9, cycle 2 day 1 and 9 and cycle 3 day 1 are planned to be collected up to 6 hours from administration. All PK analyses will be conducted in PK/PD evaluable patients. Values below the BLQ will be treated as 0 when performing the analysis on a linear scale. On the logarithmic scale, these values will be disregarded.

Sensitivity analyses for hemolytic samples:

Any samples with presence of hemolysis will be flagged as follows: a keyword search (both in lower and upper case) of "Hemolytic", "Hemolysis" will be performed on concentration dataset, column PCREASND. Subsequently, a sensitivity on concentration levels and dose proportionality will be performed.

8.9 ANALYSES OF PHARMACODINAMIC MARKERS AND CYTOKINES

PD markers and cytokines levels will be provided by [redacted] nd will not be a part of eCRF database.

The PD marker of interest are as follows:

CD8 Panel
CD8+ Cells of CD3+ Cells (%)
CD8+ Cells of CD3+ Cells(%CD45+)
Ki-67+ Cells of CD8+ Cells (%)
Ki-67+ Cells of CD8+ Cells (%CD45+)
CD45RO+ CD45RA- (Memory) Cells of CD8+ Cells (%)
CD45RO+ CD45RA- (Memory) Cells of CD8+ Cells (%CD45+)
Ki-67+ Cells of CD8+CD45RO+ CD45RA- Cells (%)
Ki-67+ Cells of CD8+CD45RO+ CD45RA- Cells (%CD45+)
NKG2D+ Cells of CD8+ Cells (%)
NKG2D+ Cells of CD8+ Cells (MFI NKG2D)
NKG2D+ Cells of CD8+CD45RO+CD45RA- Cells (%)
NKG2D+ Cells of CD8+CD45RO+CD45RA- Cells (MFI NKG2D)
CD4+ Cells of CD3+ Cells (%)
CD4+ Cells of CD3+ Cells (%CD45+)
Ki-67+ Cells of CD4+ Cells (%)
Ki-67+ Cells of CD4+ Cells (%CD45+)

Natural killer cells (NK) Panel
CD25+Foxp3+ (Treg) Cells of CD4+ Cells (%)
CD25+Foxp3+ (Treg) Cells of CD4+ Cells (%CD45+)
Ki-67+ Cells of CD4+CD25+Foxp3+ (Treg) Cells (%)
Ki-67+ Cells of CD4+CD25+Foxp3+ (Treg) Cells (%CD45+)
CD3-CD56+ (NK) Cells of CD45+ Live Cells (%)
Ki-67+ Cells of CD3-CD56+ (NK) Cells (%)
Ki-67+ Cells of CD3-CD56+ (NK) Cells (%CD45+)
CD3+CD56+ (NKT) Cells of CD45+ Live Cells (%)
Ki-67+ Cells of CD3+CD56+ (NKT) Cells (%)
Ki-67+ Cells of CD3+CD56+ (NKT) Cells (%CD45+)
NKG2D+ Cells of CD3-CD56+ (NK) Cells (%)
NKG2D+ Cells of CD3-CD56+ (NK) Cells (MFI NKG2D)

Cytokines include the following variables:

Interleukin-2
Interleukin-4
Interleukin-6
Interleukin-8
Tumor Necrosis Factor Alpha
Interferon-gamma
Interleukin-1 beta
Interleukin-10
Interleukin-12p70

The eCRF Hematology data (specifically white blood cell count (WBC)) for each timepoint will be used to derive the Cell counts in 10^9/L. Once merged with the pharmacodynamic data by subject and timepoint, the following will be used as derivation:

- CD8+ Cells of CD3+ Cells (10^9/L) = CD8+ Cells of CD3+ Cells (%CD45+) x 0.01 x WBC
- Ki-67+ Cells of CD8+ Cells (10^9/L) = Ki-67+ Cells of CD8+ Cells (%CD45+) x 0.01 x WBC
- CD45RO+ CD45RA- (Memory) Cells of CD8+ Cells (10^9/L) = CD45RO+ CD45RA- (Memory) Cells of CD8+ Cells (%CD45+) x 0.01 x WBC
- CD4+ Cells of CD3+ Cells (10^9/L) = CD4+ Cells of CD3+ Cells (%CD45+) x 0.01 x WBC
- Ki-67+ Cells of CD4+ Cells (10^9/L) = Ki-67+ Cells of CD4+ Cells (%CD45+) x 0.01 x WBC

- CD25+Foxp3+ (Treg) Cells of CD4+ Cells (10^9/L) = CD25+Foxp3+ (Treg) Cells of CD4+ Cells (%CD45+) x 0.01 x WBC
- Ki-67+ Cells of CD4+CD25+Foxp3+ (Treg) Cells (10^9/L) = Ki-67+ Cells of CD4+CD25+Foxp3+ (Treg) Cells (%CD45+) x 0.01 x WBC
- CD3-CD56+ (NK) Cells of CD45+ Live Cells (10^9/L) = CD3-CD56+ (NK) Cells of CD45+ Live Cells (%) x 0.01 x WBC
- Ki-67+ Cells of CD3-CD56+ (NK) Cells (10^9/L) = Ki-67+ Cells of CD3-CD56+ (NK) Cells (%CD45+) x 0.01 x WBC
- CD3+CD56+ (NKT) Cells of CD45+ Live Cells (10^9/L) = CD3+CD56+ (NKT) Cells of CD45+ Live Cells (%) x 0.01 x WBC
- Ki-67+ Cells of CD3+CD56+ (NKT) Cells (10^9/L) = Ki-67+ Cells of CD3+CD56+ (NKT) Cells (%CD45+) x 0.01 x WBC

During the descriptive statistical analysis of PD markers and cytokines will be considered that the value can be below or above limits of quantification: the lower limit will be replaced by the actual value (e.g. “<0.5” should be considered as 0.5), similarly for the upper limit (e.g. “>20” should be considered as 20). In all cases, only Cycle 1 and Cycle 2 data will be used and analyzed to study the Pharmacodynamic activation. Only certain markers of interest will be included in the tables and figures, all markers will be listed.

The levels and fold increases will be analyzed descriptively at individual time-points by cohorts and all cohorts pooled. A more detailed overview will be provided with figures containing the profiles overtime, where the cohort (i.e., dose level) will be colored accordingly. A Boxplot for Cycle 1 Day 6 by dose level, and maximal levels of activation achieved by dose level (barplot), will be provided for selected PD markers:

- NK cells: Ki-67+ Cells of CD3-CD56+ (NK) Cells (%)
- NKT cells: Ki-67+ Cells of CD3+CD56+ (NKT) Cells (%)
- CD8+ T-cells: Ki-67+ Cells of CD8+ Cells (%)
- CD8+ Memory T cells: Ki-67+ Cells of CD8+CD45RO+ CD45RA- Cells (%)
- CD4+ T cells: Ki-67+ Cells of CD4+ Cells (%)
- T regs: Ki-67+ Cells of CD4+CD25+Foxp3+ (Treg) Cells (%)

The table summarizing the maximum levels of activation will contain the fold increase in cell counts (i.e., 10^9/L).

Additionally for cytokines, the mean fold increase overtime will also be plotted.

All PD analyses will be conducted on PK/PD evaluable patients.

Maximal levels of cytokines will also be listed.

8.10 ANALYSES OF EFFICACY

The efficacy population will be derived as follows: assuming at least one evaluable tumor assessment per iRECIST after the initiation of SOT101 treatment, a patient that receives 4 doses of SOT101 in cycle 1, will be included in the efficacy population; if a patient does not receive 4 doses of SOT101 in cycle 1 then the patient will be included in the efficacy population if monotherapy is not permanently discontinued in cycle 1 (i.e. patient starts cycle 2). The efficacy population will be used for the efficacy analyses.

Due to the lack of confirmation of progression (iCPD) and follow-up scans, any unconfirmed progression (iUPD) has been considered as progression if a discontinuation of any treatment is followed, and thus deviating from iRECIST guidelines.

Complete response (iCR), partial response (iPR), stable disease (iSD) and progression disease (iUPD and also after iCPD) will be identified according to iRECIST recorded to eCRF and cleaned via data management/medical review processes.

Tumor assessment data will be listed and disease response since the first SOT101 administration will be presented graphically per patient (swimmer plot). Additionally, tumor size evaluated via sum of diameters of target lesions will be presented graphically per patient (waterfall plot): the best change from baseline will be used. The change from baseline overtime will be graphically presented per patient as well (spaghetti plot).

If tumor assessment is performed after start of new anticancer therapy, it will be clearly indicated in the outputs. For tumor assessments with different dates (i.e. lesions are assessed at different dates), the earliest date will be used for efficacy derivations.

Overall response is defined as state when the patient achieves iPR or iCR. Clinical benefit is defined as state when patient achieves iSD, iPR, or iCR. iSD needs to last at least 6 weeks from the start of study treatment; if not, at least one follow-up scan assessed as iPR, iCR, or iSD is required to provide clinical benefit. Similarly, confirmation of iPR or iCR by a subsequent assessment of either iPR or iCR, at least 4 weeks apart, will be required to declare an overall response or clinical benefit.

Immune overall response rate (iORR) and Clinical benefit rate (iCBR):

- iORR will be defined as the proportion of patients with confirmed iPR or iCR, out of patients in efficacy population.
- iCBR will be defined as the proportion of patients with confirmed iPR, iCR, or iSD out of patients in efficacy population.

iORR and iCBR will be summarized for All cohorts pooled.

Progression free survival (iPFS):

iPFS is defined as the time from the first day of study treatment until the first date of iUPD (followed by iCPD, study treatment discontinuation or clinical progression) or death (whichever occurs earliest) and will be summarized using Kaplan-Meier estimates.

Patients with missing data or that start new anti-cancer therapy (other than palliative) will be censored at the date of the last evaluable tumor assessment. Pembrolizumab administration in cross-over to Part B will be considered as start of new anti-cancer therapy.

iPFS will be summarized and presented for All cohorts pooled.

Duration of response (iDoR):

iDoR is defined as the time since the first iPR or iCR until the first date of iUPD (followed by iCPD, study treatment discontinuation or clinical progression) or death (whichever occurs earliest) for patients with confirmed iPR or iCR. DoRwill be summarized using Kaplan-Meier estimates.

Patients with missing data or that start new anti-cancer therapy (other than palliative) will be censored at the date of the last evaluable tumor assessment. Pembrolizumab administration in cross-over to Part B will be considered as start of new anti-cancer therapy.

iDoR will be summarized and presented for All cohorts pooled.

Overall survival (OS):

OS is defined as the time from the first day of study treatment until the date of death and will be summarized using Kaplan-Meier estimates.

Patients with missing data will be censored at the last time known to be alive: apart from trial visits/survival status, information from AE, new anti-cancer therapy, and prior and concomitant medications data from eCRF will also be used to derive the alive status – the latest complete date will be selected.

OS will be summarized and presented for All cohorts pooled.

Duration of follow-up:

A reverse Kaplan-Meier analysis will be performed on OS to estimate the median follow-up incorporating censoring rules and flipping event/censored events.

8.11 OTHER ASSESSMENTS

8.11.1 ECOG performance status

ECOG performance status will be summarized for All cohorts pooled and listed.

8.11.2 Immunogenicity

ADA levels, titration, and Neutralizing ADA levels will be provided b [redacted] nd will not be a part of eCRF database. Levels and titration will be analyzed descriptively for co orts pooled and by cohorts for SAF population. The summary table will be completed with listing of positive results.

8.12 INTERIM ANALYSES

No interim analysis is planned.

8.13 DETERMINATION OF SAMPLE SIZE

According to Study Protocol section 9.13.11 the traditional 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 in a cohort. The estimated number of patients is 27-54 patients for Study Part A.

9 CONCLUSIONS BASED OF DATA REVIEW MEETING

From the statistical perspective the objectives of the meeting will be following:

- to agree on patients excluded from analysis sets and to agree on major protocol deviations/reportable protocol deviations
- to highlight any issue from statistical perspective and to decide the solution in joint decision.

The section below will state version of Protocol Deviation Plan valid at time of the data review meeting, refer to data review meeting minutes and summarize/ summarizes conclusion relevant to statistical analysis which were made during the data review meeting. All details are included in the corresponding section of the SAP. Slides of presentations used during the meeting are included and commented in the section below.

9.1 DATA REVIEW MEETING BEFORE ANALYSIS

The review has been performed under Protocol Deviation Plan version 1.0 dated 25 July 2022

No patients have been excluded from any of the populations. The following slides were presented during the data review meeting, conclusions are also summarized:

SC103_Data Review Meeting_20220718.p

The review of PK data includes derivation of sampling out of window according to Protocol v10 following the derivation: PK blood sampling out of window will be flagged in listing of concentration levels. Note referring to that listing (attached below) will be added to output of CSR reportable PDs. Several values have been assessed as unreliable in Pharmacokinetic concentrations, such values are not to be used for the calculation of PK parameters and descriptive analysis of PK concentrations. Hemolytic samples have been considered as reliable; however, a sensitivity analysis is included in this SAP.

SC103 DRM Part A Listing PK 09JUN202

Similarly, several values have been excluded from the review of Pharmacodynamic and Cytokine data, along with Immunogenicity, Tumor Biopsy, Genetic PBMC. Derivation of sampling out of window according to Protocol v10 following the derivation: sampling out of window will be flagged in listing of sampling dates and times. Note referring to that listing (attached below) will be added to output of CSR reportable PDs. Further derivation of rules for the exclusion of certain values in the analysis is described below.

SC103_ESP_DRM_PartA_G27JUN22_ESP1

Rules for exclusion of PBMC sample from the analysis (due to changes in dosing such as delays, dose modification, deviations, etc.) as follows.

Applicable to PBMC, all samples and all cycles:

- Any samples taken after a missed or delayed dose will be excluded within the cycle: for example, if C1D2 is not done then any day afterwards within the cycle should be excluded (C1D6, C1D8, ...). EXCEPT when that delay or deviation is shifting the CXD8 and CXD9 dosing to CXD9 and CXD10 dosing (consecutive)
- Any samples taken after a dose reduction or increase will be excluded
- Any dosing performed PRIOR to CXD8 (i.e., deviation) will lead to the exclusion of samples from CXD8 onwards within the cycle.
- Any sample taken with a deviation more than 1 day (>1 day) from the protocol schedule will be excluded

Furthermore, Cycle 1 Day 2 for patients SC103C101B008 and SC103C101B012 have been excluded from the analysis due to unreliable PK results, as concluded during the data review meeting.

The rules above will also be applied for Cytokines (CK). In addition, for CK, any sample taken outside of the protocol defined window will be excluded.

No data from other sampling (Immunogenicity, Tumor Biopsy, etc.) have been considered as unreliable and/or affected by deviations and no exclusion rules have been created.

10 LIST OF TABLES, FIGURES AND LISTINGS

The table hereunder presents preliminary list of content of tables, figures and listings which will be integrated in study report. The structure and numbering is proposed according the ICH guidelines - E3: Structure and Content of Clinical Study Reports.

10.1 SECTION 10 OF CSR (STUDY PATIENTS)

Selected tables from Section 14.1 of CSR (DEMOGRAPHIC DATA).

This section will cover the following:

- Summary of patient disposition
- Patient disposition by country
- Analysis populations
- Protocol deviations
- Summary of patient demographics and baseline characteristics
- Summary of disease history
- Summary of medical history
- Summary of prior, concomitant, and post-treatment therapies
- Exposure to study medication

10.2 SECTION 11 OF CSR (SAFETY AND PK/PD EVALUATIONS)

Selected tables from Section 14.3 (SAFETY DATA) and Section 14.2 (PK/PD DATA) of CSR.

This section will cover the following:

- DLTs
- Summary of TEAEs
- AE tables by PT within SOC
- Summary of causes of death

This section will cover also pharmacokinetic and pharmacodynamics evaluation.

10.3 SECTION 12 OF CSR (EFFICACY AND OTHER DATA)

Selected tables from Section 14.2 of CSR (EFFICACY AND OTHER DATA).

10.4 SECTION 13 OF CSR (DISCUSSION AND OVERALL CONCLUSIONS)

No tables are planned.

10.5 SECTION 14 OF CSR (TABLES, FIGURES AND GRAPHS REFERRED TO BUT NOT INCLUDED IN THE TEXT)

Output	Number	Title	Analysis Set
	Section 14.1	**Demographic data**	
		Patient disposition	
Table	14.1.1.1	Disposition of patients	All

Output	Number	Title	Analysis Set
Table	14.1.1.2	Disposition of patients by country	All
Table	14.1.1.3	Analysis populations and reasons for exclusion	All
Table	14.1.1.4	Reasons for discontinuation after treatment start	SAF
Table	14.1.1.5	Protocol deviations	SAF, Efficacy
		Baseline characteristics and disease history	
Table	14.1.2.1	Baseline characteristics	SAF, Efficacy, PK/PD
Table	14.1.2.2	Disease history	SAF, Efficacy, PK/PD
		Prior, concomitant, and post-treatment medication	
Table	14.1.3.1	Prior anticancer systemic therapy	SAF
Table	14.1.3.2	Prior anticancer non-systemic therapy	SAF
Table	14.1.3.3	Prior medication	SAF
Table	14.1.3.4	Prior non-pharmacological therapy	SAF
Table	14.1.3.5	Concomitant medication	SAF
Table	14.1.3.6	Concomitant non-pharmacological therapy	SAF
Table	14.1.3.7	Post-treatment medication	SAF
Table	14.1.3.8	Post-treatment non-pharmacological therapy	SAF
Table	14.1.3.9	New anticancer systemic therapy	SAF
Table	14.1.3.10	New anticancer non-systemic therapy	SAF
		Exposure	
Table	14.1.4.1	Exposure to study treatment	SAF
Table	14.1.4.2	SOT101 Dose intensity	SAF
Table	14.1.4.3	Dosing overview, summary of changes from dosing	SAF
	Section 14.2	**Efficacy and PK/PD evaluations**	
		Pharmacokinetics	
Table	14.2.1.1.1	SOT101 concentrations	PK/PD
Table	14.2.1.1.2	SOT101 concentrations	PK/PD (excluding hemolytic samples)
Table	14.2.1.2	SOT101 PK parameters	PK/PD

Output	Number	Title	Analysis Set
Figure	14.2.1.3	Patient profiles of SOT101 concentrations (linear and semi-logarithmic scale)	PK/PD
Figure	14.2.1.4.1	Mean SOT101 concentrations profiles (linear and semi-logarithmic scale)	PK/PD
Figure	14.2.1.4.2	Mean SOT101 concentrations profiles (linear and semi-logarithmic scale)	PK/PD (excluding hemolytic samples)
Table	14.2.1.5.1	Evaluation of dose proportionality	PK/PD
Table	14.2.1.5.2	Evaluation of dose proportionality	PK/PD (excluding hemolytic samples)
		Pharmacodynamics	
CD8+ T Cells			
Table	14.2.2.1	CD8+ Cells of CD3+ Cells (10^9/L): Values and fold increase	PK/PD
Table	14.2.2.2	CD8+ Cells of CD3+ Cells (%): Values and fold increase	PK/PD
Table	14.2.2.3	Ki-67+ Cells of CD8+ (%): Values and fold increase	PK/PD
Figure	14.2.2.4	Mean profiles of Ki-67+ Cells of CD8+ (%) by cohort and All cohorts pooled	PK/PD
CD8+ Memory T Cells			
Table	14.2.2.5	CD45RO+ CD45RA- (Memory) Cells of CD8+ Cells (10^9/L): Values and fold increase	PK/PD
Table	14.2.2.6	CD45RO+ CD45RA- (Memory) Cells of CD8+ Cells (%): Values and fold increase	PK/PD
Table	14.2.2.7	Ki-67+ Cells of CD8+CD45RO+ CD45RA- Cells (%): Values and fold increase	PK/PD
Figure	14.2.2.8	Mean profiles of Ki-67+ Cells of CD8+CD45RO+ CD45RA- Cells (%) by cohort and All cohorts pooled	PK/PD
NKG2D+ Cells (CD8)			
Table	14.2.2.9	NKG2D+ Cells of CD8+ Cells (%): Values and fold increase	PK/PD
Figure	14.2.2.10	Mean profiles of NKG2D+ Cells of CD8+ Cells (%) by cohort and All cohorts pooled	PK/PD
Table	14.2.2.11	NKG2D+ Cells of CD8+ Cells (MFI NKG2D): Values and fold increase	PK/PD

Output	Number	Title	Analysis Set
Figure	14.2.2.12	Mean profiles of NKG2D+ Cells of CD8+ Cells (MFI NKG2D) by cohort and All cohorts pooled	PK/PD
NKG2D+ Cells (CD8 Memory)			
Table	14.2.2.13	NKG2D+ Cells of CD8+ CD45RO+CD45RA- Cells (%): Values and fold increase	PK/PD
Figure	14.2.2.14	NKG2D+ Cells of CD8+ CD45RO+CD45RA- Cells (%) by cohort and All cohorts pooled	PK/PD
Table	14.2.2.15	NKG2D+ Cells of CD8+ CD45RO+CD45RA- Cells (MFI NKG2D): Values and fold increase	PK/PD
Figure	14.2.2.16	NKG2D+ Cells of CD8+ CD45RO+CD45RA- Cells (MFI NKG2D) by cohort and All cohorts pooled	PK/PD
CD4+ T Cells			
Table	14.2.2.17	CD4+ Cells of CD3+ Cells (10^9/L): Values and fold increase	PK/PD
Table	14.2.2.18	CD4+ Cells of CD3+ Cells (%): Values and fold increase	PK/PD
Table	14.2.2.19	Ki-67+ Cells of CD4+ Cells (%): Values and fold increase	PK/PD
Figure	14.2.2.20	Mean profiles of Ki-67+ Cells of CD4+ Cells (%) by cohort and All cohorts pooled	PK/PD
NK Cells			
Table	14.2.2.21	CD3-CD56+ (NK) Cells of CD45+ Live Cells (10^9/L): Values and fold increase	PK/PD
Table	14.2.2.22	CD3-CD56+ (NK) Cells of CD45+ Live Cells (%): Values and fold increase	PK/PD
Table	14.2.2.23	Ki-67+ Cells of CD3-CD56+ (%): Values and fold increase	PK/PD
Figure	14.2.2.24	Mean profiles of Ki-67+ Cells of CD3-CD56+ (%) by cohort and All cohorts pooled	PK/PD
Treg Cells			
Table	14.2.2.25	CD25+Foxp3+ (Treg) Cells of CD4+ Cells (10^9/L): Values and fold increase	PK/PD
Table	14.2.2.26	CD25+Foxp3+ (Treg) Cells of CD4+ Cells (%): Values and fold increase	PK/PD
Table	14.2.2.27	Ki-67+ Cells of CD4+CD25+Foxp3+ (Treg) Cells (%): Values and fold increase	PK/PD
Figure	14.2.2.28	Mean profiles of Ki-67+ Cells of CD4+CD25+Foxp3+ (Treg) Cells (%) by cohort and All cohorts pooled	PK/PD
NKT Cells			

Output	Number	Title	Analysis Set
Table	14.2.2.29	CD3+CD56+ (NKT) Cells of CD45+ Live Cells (10^9/L): Values and fold increase	PK/PD
Table	14.2.2.30	CD3+CD56+ (NKT) Cells of CD45+ Live Cells (%): Values and fold increase	PK/PD
Table	14.2.2.31	Ki-67+ Cells of CD3+CD56+ (NKT) Cells (%): Values and fold increase	PK/PD
Figure	14.2.2.32	Mean profiles of Ki-67+ Cells of CD3+CD56+ (NKT) Cells (%) by cohort and All cohorts pooled	PK/PD
NKG2D+ Cells (NK)			
Table	14.2.2.33	NKG2D+ Cells of CD3-CD56+ (NK) Cells (%): Values and fold increase	PK/PD
Figure	14.2.2.34	Mean profiles of NKG2D+ Cells of CD3-CD56+ (NK) Cells (%) by cohort and All cohorts pooled	PK/PD
Table	14.2.2.35	NKG2D+ Cells of CD3-CD56+ (NK) Cells (MFI NKG2D): Values and fold increase	PK/PD
Figure	14.2.2.36	Mean profiles of NKG2D+ Cells of CD3-CD56+ (NK) Cells (MFI NKG2D) by cohort and All cohorts pooled	PK/PD
Summary of pharmacodynamic activation			
Table	14.2.2.37	Overall activation levels (10^9/L) of selected PD markers in Cycle 1 Day 6	PK/PD
Table	14.2.2.38	Overall activation levels (%) of selected PD markers in Cycle 1 Day 6	PK/PD
Figure	14.2.2.39	Overall activation levels (%) of selected PD markers in Cycle 1 Day 6 (overview)	PK/PD
Figure	14.2.2.40	Overall activation levels (%) of selected PD markers in Cycle 1 Day 6 (specific)	PK/PD
Table	14.2.2.41	Maximum levels of fold increase in cell counts (10^9/L) for selected PD markers	PK/PD
Figure	14.2.2.42	Maximum levels of activation (%) for selected PD markers	PK/PD
		Immunocytokines	
Table	14.2.3.1	Interleukin-2: Values and fold increase	PK/PD
Figure	14.2.3.2	Mean profiles of Interleukin-2 by cohort and All cohorts pooled	PK/PD
Table	14.2.3.3	Interleukin-4: Values and fold increase	PK/PD
Figure	14.2.3.4	Mean profiles of Interleukin-4 by cohort and All cohorts pooled	PK/PD

Output	Number	Title	Analysis Set
Table	14.2.3.5	Interleukin-6: Values and fold increase	PK/PD
Figure	14.2.3.6	Mean profiles of Interleukin-6 by cohort and All cohorts pooled	PK/PD
Table	14.2.3.7	Interleukin-8: Values and fold increase	PK/PD
Figure	14.2.3.8	Mean profiles of Interleukin-8 by cohort and All cohorts pooled	PK/PD
Table	14.2.3.9	Tumor Necrosis Factor Alpha: Values and fold increase	PK/PD
Figure	14.2.3.10	Mean profiles of Tumor Necrosis Factor by cohort and All cohorts pooled	PK/PD
Table	14.2.3.11	Interferon-gamma: Values and fold increase	PK/PD
Figure	14.2.3.12	Mean profiles of Interferon-gamma by cohort and All cohorts pooled	PK/PD
Table	14.2.3.13	Interleukin-1 beta: Values and fold increase	PK/PD
Figure	14.2.3.14	Mean profiles of Interleukin-1 beta by cohort and All cohorts pooled	PK/PD
Table	14.2.3.15	Interleukin-10: Values and fold increase	PK/PD
Figure	14.2.3.16	Mean profiles of Interleukin-10 by cohort and All cohorts pooled	PK/PD
Table	14.2.3.17	Interleukin-12p70: Values and fold increase	PK/PD
Figure	14.2.3.18	Mean profiles of Interleukin-12p70 by cohort and All cohorts pooled	PK/PD
		Efficacy data	
Table	14.2.4.1	Duration of follow-up	SAF
Figure	14.2.4.2	Kaplan-Meier curve of duration of follow-up	SAF
Figure	14.2.4.3	Disease response since the first SOT101 administration per patient	SAF
Table	14.2.4.4	Tumor response (overall response rate and clinical benefit rate) as per iRECIST	Efficacy
Figure	14.2.4.5	Best change from baseline in tumor size per patient	Efficacy
Table	14.2.4.6	Duration of response as per iRECIST (iDoR)	Efficacy
Figure	14.2.4.7	Kaplan-Meier curve of iDoR as per iRECIST	Efficacy
Table	14.2.4.8	Progression free survival as per iRECIST (iPFS)	Efficacy
Figure	14.2.4.9	Kaplan-Meier curve of iPFS as per iRECIST	Efficacy
Table	14.2.4.10	Overall survival	Efficacy

Output	Number	Title	Analysis Set
Figure	14.2.4.11	Kaplan-Meier curve of overall survival	Efficacy
	Section 14.3	**Safety data**	
		DLT and TEAEs	
Table	14.3.1.1	Summary of dose limiting toxicity (DLT)	DLT evaluable
Table	14.3.2.1	Summary of Treatment-Emergent Adverse Events	SAF
Table	14.3.2.2	Summary of Treatment-Emergent Serious Adverse Events	SAF
Table	14.3.2.3	Summary of Treatment-Emergent Adverse Events by cycle	SAF
Table	14.3.2.4	Summary of Treatment-Emergent Serious Adverse Events by cycle	SAF
Table	14.3.3.1	Treatment-Emergent Adverse Events by MedDRA PT and primary SOC	SAF
Table	14.3.3.2	Treatment-Emergent Adverse Events by MedDRA PT and primary SOC reported in $\geq$10% of patients	SAF
Table	14.3.3.3	Non-serious Treatment-Emergent Adverse Events by MedDRA PT and primary SOC reported in $\geq$5% of patients	SAF
Table	14.3.3.4	Treatment-Emergent Adverse Events by MedDRA PT	SAF
Figure	14.3.3.5	Treatment-Emergent Adverse Events by MedDRA PT and Grade	SAF
Figure	14.3.3.6	Treatment-Emergent Adverse Events by MedDRA PT and Action Taken	SAF
Table	14.3.3.7	Treatment-Emergent Serious Adverse Events by MedDRA PT and primary SOC	SAF
Table	14.3.3.8	Fatal Treatment-Emergent Adverse Events by MedDRA PT and primary SOC	SAF
Table	14.3.3.9	Grade 3, 4, 5 Treatment-Emergent Adverse Events by MedDRA PT and primary SOC	SAF
Table	14.3.3.10	Immune-related Treatment-Emergent Adverse Events by MedDRA PT and primary SOC	SAF
Table	14.3.3.11	Treatment-Emergent Adverse Events leading to SOT101 dose modification by MedDRA PT and primary SOC	SAF
Table	14.3.3.12	Treatment-Emergent Adverse Events leading to SOT101 temporary discontinuation by MedDRA PT and primary SOC	SAF

Output	Number	Title	Analysis Set
Table	14.3.3.13	Treatment-Emergent Adverse Events leading to SOT101 permanent discontinuation by MedDRA PT and primary SOC	SAF
Table	14.3.3.14	Treatment Emergent Adverse Events symptoms of Cytokine release syndrome by MedDRA PT and primary SOC	
Table	14.3.4.1	Underlying causes of deaths by MedDRA PT and primary SOC	SAF
	Section 14.4	**Clinical Laboratory data**	
		Liver enzyme values	
Table	14.4.1.1	Total Bilirubin (µmol/L): Values, relative and absolute changes from baseline	SAF
Figure	14.4.1.2	Mean profile of Total Bilirubin (µmol/L) by cohort and All cohorts pooled	SAF
Figure	14.4.1.3	Patient profiles of Total Bilirubin (µmol/L) for RP2D and RP2D-1 cohorts (excluding the MTD)	SAF
Table	14.4.2.1	Alanine Transaminase (ALT) (µkat/L): Values, relative and absolute changes from baseline	SAF
Figure	14.4.2.2	Mean profile of Alanine Transaminase (ALT) (µkat/L) by cohort and All cohorts pooled	SAF
Figure	14.4.2.3	Patient profiles of Alanine Transaminase (ALT) (µkat/L) for RP2D and RP2D-1 cohorts (excluding the MTD)	SAF
Table	14.4.3.1	Aspartate Transaminase (AST) (µkat/L): Values, relative and absolute changes from baseline	SAF
Figure	14.4.3.2	Mean profile of Aspartate Transaminase (AST) (µkat/L) by cohort and All cohorts pooled	SAF
Figure	14.4.3.3	Patient profiles of Aspartate Transaminase (AST) (µkat/L) for RP2D and RP2D-1 cohorts (excluding the MTD)	SAF
Table	14.4.4.1	Alkaline Phosphatase (ALP) (µkat/L): Values, relative and absolute changes from baseline	SAF
Figure	14.4.4.2	Mean profiles of Alkaline Phosphatase (ALP) (µkat/L) by cohort and All cohorts pooled	SAF
Figure	14.4.4.3	Patient profiles of Alkaline Phosphatase (ALP) (µkat/L) for RP2D and RP2D-1 cohorts (excluding the MTD)	SAF
Table	14.4.4.4	Hepatic function (Hy's law)	SAF

Output	Number	Title	Analysis Set
Figure	14.4.4.5	Maximal levels per patient of Total Bilirubin (µmol/L), Alanine Transaminase (ALT) (µkat/L), Aspartate Transaminase (AST) (µkat/L), and Alkaline Phosphatase (ALP) (µkat/L) by cohort	SAF
		Other laboratory values	
Table	14.4.5.1	Haemoglobin (g/L): Values, relative and absolute changes from baseline	SAF
Figure	14.4.5.2	Mean profile of Haemoglobin (g/L) by cohort and All cohorts pooled	SAF
Table	14.4.6.1	Neutrophils (10E9/L): Values, relative and absolute changes from baseline	SAF
Figure	14.4.6.2	Mean profile of Neutrophils (10E9/L) by cohort and All cohorts pooled	SAF
Table	14.4.7.1	Neutrophils (%): Values and absolute changes from baseline	SAF
Figure	14.4.7.2	Mean profile of Neutrophils (%) by cohort and All cohorts pooled	SAF
Table	14.4.8.1	Lymphocytes (10E9/L): Values, relative and absolute changes from baseline	SAF
Figure	14.4.8.2	Mean profile of Lymphocytes (10E9/L) by cohort and All cohorts pooled	SAF
Table	14.4.9.1	Lymphocytes (%): Values and absolute changes from baseline	SAF
Figure	14.4.9.2	Mean profile of Lymphocytes (%) by cohort and All cohorts pooled	SAF
Table	14.4.10.1	Lactate Dehydrogenase (LDH) (ukat/L): Values, relative and absolute changes from baseline	SAF
Figure	14.4.10.2	Mean profile of Lactate Dehydrogenase (LDH) (ukat/L) by cohort and All cohorts pooled	SAF
Table	14.4.11.1	Platelet count (10E9/L): Values, relative and absolute changes from baseline	SAF
Figure	14.4.11.2	Mean profile of Platelet count (10E9/L) by cohort and All cohorts pooled	SAF
Table	14.4.12.1	C-reactive protein (CRP) (mg/L): Values, relative and absolute changes from baseline	SAF
Figure	14.4.12.2	Mean profile of C-reactive protein (CRP) (mg/L) by cohort and All cohorts pooled	SAF

Output	Number	Title	Analysis Set
	Section 14.5 Vital Signs		
Table	14.5.1.1	Systolic blood pressure (mmHg): Values and absolute changes from baseline	SAF
Figure	14.5.1.2	Mean profile of Systolic blood pressure (mmHg) by cohort and All cohorts pooled	SAF
Table	14.5.2.1	Diastolic blood pressure (mmHg): Values and absolute changes from baseline	SAF
Figure	14.5.2.2	Mean profile of Diastolic blood pressure (mmHg) by cohort and All cohorts pooled	SAF
Table	14.5.3.1	Heart rate (beats/min): Values and absolute changes from baseline	SAF
Figure	14.5.3.2	Mean profile of Heart rate (beats/min) by cohort and All cohorts pooled	SAF
Table	14.5.4.1	Respiratory rate (breaths/min): Values and absolute changes from baseline	SAF
Figure	14.5.4.2	Mean profile of Respiratory rate (breaths/min) by cohort and All cohorts pooled	SAF
Table	14.5.5.1	Body temperature (Celsius (°)): Values and absolute changes from baseline	SAF
Figure	14.5.5.2	Mean profile of Body temperature (Celsius (°)) by cohort and All cohorts pooled	SAF
	Section 14.6 ECG		
Table	14.6.1.1	QT [ms]: Values, relative and absolute changes from baseline	SAF
Table	14.6.2.1	QTcF [ms]: Values, relative and absolute changes from baseline	SAF
Figure	14.6.2.2	Mean profile of QTcF [ms] by cohort and All cohorts pooled	SAF
Table	14.6.3.1	QTcF [ms]: Frequency of Intervals	SAF
	Section 14.7 ECOG		
Table	14.7.1	ECOG performance status	SAF
	Section 14.8 Immunogenicity		
Table	14.8.1	Anti-drug Antibodies	SAF

Output	Number	Title	Analysis Set
Table	14.8.2	Titration of anti-drug Antibodies	SAF
Table	14.8.3	Neutralizing anti-drug Antibodies	SAF

10.6 APPENDIX 16.2 OF CSR (PATIENT DATA LISTINGS)

All patients included in clinical database will be listed (if not specified otherwise).

Listing Number	Title
Section 16.2.1	**Discontinued patients**
16.2.1.1	Study dates and patients' discontinuation overview in treated patients
16.2.1.2	Screening failures and withdrawals prior study treatment start
16.2.1.3	Cross-over from Part A to combination therapy with Pembrolizumab
Section 16.2.2	**Protocol Deviations**
16.2.2.1	CSR reportable protocol deviations
16.2.2.2	CSR not reportable protocol deviations
16.2.2.3	Eligibility criteria and eligibility verification
16.2.2.4	Protocol deviations related to COVID-19
Section 16.2.3	**Patients excluded from efficacy analysis**
16.2.3.1	Disposition of patients to analysis sets and reasons for exclusion
Section 16.2.4	**Demographic data**
16.2.4.1	Informed consent signatures
16.2.4.2	Demographic data, patients' characteristics and disease history details
16.2.4.3	Medical history
16.2.4.4	Medical history – MedDRA coding details
16.2.4.5	Previous medication
16.2.4.6	Prior medication (including WHODD coding)
16.2.4.7	Prior anticancer systemic therapy (including WHODD coding)
16.2.4.8	Prior anticancer non-systemic therapy (including MedDRA coding)
16.2.4.9	Concomitant medication
16.2.4.10	Concomitant medication (including WHODD coding)
16.2.4.11	Post-treatment medication
16.2.4.12	Post-treatment medication (including WHODD coding)
16.2.4.13	Prior non-pharmacological therapy (including MedDRA coding)
16.2.4.14	Concomitant non-pharmacological therapy (including MedDRA coding)
16.2.4.15	Post-treatment non-pharmacological therapy (including MedDRA coding)

Listing Number	Title
16.2.4.16	New anticancer systemic therapy (including WHODD coding)
16.2.4.17	New anticancer non-systemic therapy (including MedDRA coding)
Section 16.2.5	**Compliance and drug concentration data**
16.2.5.1	Exposure to SOT101
16.2.5.2	SOT101 Dose intensity
16.2.5.3	Body weight and compliance of study drug administration with Study Protocol
16.2.5.4	SOT101 concentration levels
16.2.5.5	SOT101 pharmacokinetic parameters
Section 16.2.6	**Individual efficacy response and pharmacodynamics data**
16.2.6.1	Tumor assessment
16.2.6.2	Disease response
16.2.6.3	Clinical progression
16.2.6.4	Pharmacodynamics markers and cytokine levels
16.2.6.5	Maximal levels of Cytokines
Section 16.2.7	**Adverse events listings**
16.2.7.1	Listing of DLT events
16.2.7.2	All treatment-emergent AEs
16.2.7.3	All treatment-emergent SAEs
16.2.7.4	Treatment-emergent AEs recorded in detailed description of dose limiting toxicities
16.2.7.5	All adverse events leading to death
16.2.7.6	Causes of death including MedDRA coding details
16.2.7.7	Treatment-emergent AEs leading to permanent discontinuation of SOT101
16.2.7.8	Treatment-emergent AEs leading to permanent discontinuation of pembrolizumab
16.2.7.9	Treatment-emergent AEs with suspected causal relationship with SOT101
16.2.7.10	Treatment-emergent AEs with suspected causal relationship with pembrolizumab
16.2.7.11	Treatment-emergent AE immune-related
16.2.7.12	Treatment-emergent clinical signs/symptoms of cytokine release syndrome
16.2.7.13	Adverse events started before the first study drug administration
16.2.7.14	Adverse events with missing or partial start date
16.2.7.15	Adverse events – MedDRA coding details

Listing Number	Title
Section 16.2.8	**Listing of individual laboratory measurements**
16.2.8.1	Hematology
16.2.8.2	Biochemistry
16.2.8.3	Coagulation
16.2.8.4	Urinalysis
16.2.8.5	Maximal levels of selected laboratory variables
16.2.8.6	Creatinine clearance levels
16.2.8.7	Thyroid function tests (TSH, free T3, free T4)
16.2.8.8	Cardiac troponin-T test
16.2.8.9	C-reactive protein (CRP) levels
16.2.8.10	Glycated hemoglobin (HbA1c)
16.2.8.11	24-hour urine protein test
16.2.8.12	Pregnancy test
16.2.8.13	Serology (HIV, hepatitis B and C tests)
16.2.8.14	Listing of abnormal laboratory results
Section 16.2.9	**Other safety data**
16.2.9.1	Vital signs
16.2.9.2	ECG results
16.2.9.3	Echocardiography results
16.2.9.4	Date of physical examination
Section 16.2.10	**Other data**
16.2.10.1	ECOG performance score
16.2.10.2	Immunogenicity

11 LAYOUT REQUIREMENTS OF TFLs

No layout requirements specified by the sponsor.

12 APPENDICES

12.1 PHARMACOKINETIC ANALYSIS PLAN

N-A-PH1-19-027_SC 103_Pharmacokineti

12.2 TIMEPOINT LABELS SPECIFICATIONS

For vital signs: Pre-dose, 15 min, 30 min, 1 h, 2 h, 3 h, 4 h, 5 h, 6 h, 7 h, 8 h will be used as per eCRF records. In the listings also real time since SOT101 administration will be presented. In the Follow-up period (Follow-up) the timepoints will be presented as EOT + X weeks as defined in the Study Protocol.

For electrocardiogram (ECG): Pre-dose, 2 h will be used as per eCRF records. In the listings also real time since SOT101 administration will be presented. At EOT visit, the timepoint will be presented as EOT as defined in the Study Protocol.

For PK and Cytokine blood sampling: Pre-dose, 30 min, 1 h, 2 h, 4h, 6h, 8 h, 24 h will be used as per eCRF records. In the listings also real time since SOT101 administration will be presented.

For safety laboratory: as per standard medical practice the safety laboratory should be performed before the dosing then the label will be Cycle X Day Y – Pre-dose; otherwise, just Cycle X Day Y will be presented except in EOT visit which will be presented as EOT as defined in the Study Protocol.

Other assessments (Physical examination, body weight and Eastern Cooperative Oncology Group (ECOG) performance status) will be presented using the Cycle X Day Y label, except in the Follow-up period (Follow-up) where the label will be EOT + X weeks as defined in the Study Protocol.

In the listings, "^{UNS}" will be added into assessments performed in addition to assessment planned in the Study Protocol, for example Screening^{UNS} for some not required at screening by the Study Protocol or repeated assessment at screening, Follow-up ^{UNS} for hematologic assessment or Cycle 1 Day 9^{UNS} for coagulation assessment or Cycle 1 Day 12^{UNS}.

Time-points labels of tumor assessment: Tumor assessment will be recorded into eCRF as repeated pages and will be analyzed as iORR, iCBR, and time to event data. Therefore, time-point labels for tables will not be needed. In the listings the assessments will be identified by date, real treatment week (as defined in section 6.2, rounded to one decimal), and period label ("Cycle X" derived as defined below) or "Follow-up".

Cycle derivation:

- For each cycle will be identified Day 1 (as per eCRF records) and end of cycle as defined in section 5.1.
- Then, it will be identified which cycle the assessment date belongs to.

Time-points labels for survival follow-up information: The similar approach as for tumor assessment will be applied. Time-point labels for tables will not be needed. In the listings the information will be identified by date, real treatment week, and label "Follow-up".

Time-point labels used in tables of adverse events:

The tables of adverse events will present summary of treatment-emergent adverse events (TEAEs) recorded during the study and TEAEs depending on the time period:

- Cycle X: the time-point label will indicate treatment cycle when the adverse event (AE) started
- After last: the time-point label will indicate AEs started after end of last cycle

See treatment cycle definition in the section 5.1 above. Treatment cycle when TEAE started will only be derived for AEs with complete (and non-missing) start dates.

12.3 CANCER TYPE DERIVATION

Histological type	Primary tumor location	Cancer type (long name)	Cancer type (short name)
ADENOCARCINOMA	Stomach	Gastric	Gastric
serous papillary adenocarcinoma	Ovarian	Ovarian	Ovarian
Adenocarcinoma	Other: Gastro-esophageal tumor	Gastro-esophageal	Gastro-esoph.
Clear cell carcinoma	Ovarian	Ovarian	Ovarian
Adenocarcinoma	Other: Gastro-esophageal tumor	Gastro-esophageal	Gastro-esoph.
Clear cell carcinoma	Kidney	Kidney	Kidney
MELANOMA	Skin	Melanoma skin	Melanoma
Adenocarcinoma	Biliary tract	Biliary tract	Biliary tract
Merkel cell carcinoma	Other: no primary found	Merkel cell	Merkel cell
ADENOCARCINOMA	Cervix uteri	Cervix uteri	Cervix uteri
epidermoid carcinoma	Anus	Anal epidermoid	Anal
urothelial bladder carcinoma	Bladder	Bladder urothelial	Bladder
Intrahepatic cholangiocarcinoma	Biliary tract	Biliary tract	Biliary tract
squamous cell carcinoma	Skin	Skin SCC	Skin SCC
urothelial bladder carcinoma	Bladder	Bladder urothelial	Bladder
Clear-cell carcinoma	Kidney	Kidney	Kidney
merkel cell carcinoma	Other: LEFT TIBIAL CREST	Merkell cell	Merkell cell
Papillar	Kidney	Kidney	Kidney
Non Squamous cell carcinoma	Lung	NSCLC	NSCLC

Mucinous carcinoma of the ovary	Ovarian	Ovarian	Ovarian
adenocarcinom biliar	Biliary tract	Biliary tract	Biliary tract
squamous cell carcinoma	Other: Tonsil	Tonsil SCC	Tonsil SCC
papillar carcinoma	Bladder	Bladder urothelial	Bladder
Colangiocarcinoma	Biliary tract	Biliary tract	Biliary tract
Thymic Carcinoma	Thymus	Thymus	Thymus
folicular carcinoma	Thyroid gland	Thyroid follicular	Thyroid
squamous cell carcinoma of the internal canthus of the left eye	Other: squamous cell carcinoma of the internal canthus of the left eye	Eye canthus SCC	Eye canthus SCC
non-keratinizing differentiated squamous cell carcinoma , Induced HPV16	Other: tonsil	Tonsil SCC	Tonsil SCC
Non-small cell lung cancer (Adenocarcinoma)	Lung	NSCLC	NSCLC
Merkel cell carcinoma	Skin	Merkel cell	Merkel cell

13 REFERENCES

[1] Seymour L, Bogaerts J, Perrone A, Ford R, Schwartz LH, Mandrekar S, Lin NU, Litière S, Dancey J, Chen A, Hodi FS, Therasse P, Hoekstra OS, Shankar LK, Wolchok JD, Ballinger M, Caramella C, de Vries EGE, group Rw. iRECIST: guidelines for response criteria for use in trials testing immunotherapeutics. The Lancet Oncology. 2017;18(3):e143-e152. ICH guidelines - E9: Statistical Principles for Clinical Trials, Adopted in EU by CPMP, March 1998, issued as CPMP/ICH/363/96

[2] ICH guidelines - E3: Structure and Content of Clinical Study Reports, Adopted in EU by CPMP, December 95, issued as CPMP/ICH/137/95

[3] U.S. Food and Drug Administration. E14 clinical evaluation of QT/QTc interval prolongation and proarrhythmic potential for non-antiarrhythmic drugs: Guidance for industry. 2018; https://www.fda.gov/downloads/Drugs/GuidanceComplianceRegulatoryInformation/Guidances/ucm073153.pdf. Accessed October 22, 2018.

[4] Smith BP, Vandenhende FR, deSante KA, et al (2000)., Confidence Interval Criteria for Assessment of Dose proportionality. Pharmaceutical Research, 17:1278-1283.

[5] Zhou, J., J. Li, and B. Coate. 2006. Empirical Power Estimation for Phase I Dose Proportionality Studies Based on Power-Law Model Using Confidence Interval Criteria. In SUGI 31, San Francisco, California.

[6] SAS 9.4; 2008 by SAS Institute Inc., Cary, NC, USA; OnLine Doc.

Statistical Analysis Plan
Study Part A1

A multicenter open-label phase 1/1b study to evaluate the safety and preliminary efficacy of SO-C101 as monotherapy and in combination with pembrolizumab in patients with selected advanced/metastatic solid tumors.

Sponsor:	SOTIO Biotech AG
Study code:	SC103
EudraCT number:	2018-004334-15
VERSION:	Final 1.0
DATE:	09-MAR-2023

STATISTICAL ANALYSIS PLAN APPROVAL

We, the undersigned, confirm that we have read and are in agreement with the contents of this document.

NAME	[redacted]
JOB TITLE	
SIGNATURE	
DATE	
NAME	
JOB TITLE	
SIGNATURE	
DATE	
NAME	
JOB TITLE	
SIGNATURE	
DATE	
NAME	
JOB TITLE	
SIGNATURE	
DATE	

TABLE OF CONTENTS

ABBREVIATIONS

ADA	Anti-drug antibodies
AE	Adverse Event
ALP	Alkaline Phosphatase (ALP)
ALT	Alanine Transaminase
AST	Aspartate Transaminase
ATC	Anatomic, Therapeutic, Chemical (Classification System for Drugs)
AUC	Area under the plasma concentration-time curve
$AUC_{(0\text{-}inf)}$	Area under the plasma concentration-time curve from time zero to infinity
$AUC_{(0\text{-}t)}$	Area under the plasma concentration-time curve from time zero to time t
BLQ	Below Limit of Quantification
CBR	Clinical Benefit Rate
CD	Cluster of differentiation (cells)
CI	Confidence Interval
CK	Cytokines
CL	Apparent total body clearance of the drug from plasma
C_{max}	Maximum (or peak) serum concentration
CPI	Check Point Inhibitors
CRF	Case Report Form
CRO	Contract Research Organisation
CRP	C-Reactive Protein
CSR	Clinical Study Report
CV	Coefficient of Variation
DB	Database
DBL	Database lock
DEC	Dose Escalation Committee
DEM	Dose Escalation Meeting
DLT	Dose Limiting Toxicity
DOR	Duration of Response
ECG	Electro-cardiogram
ECOG	Eastern Cooperative Oncology Group
eCRF	Electronic Case Report Form
EOT	End of Treatment
FU	Follow-up
HLGT	High Group Level Term
HLT	High Level Term
IAP	Independent Advisory Panel
ICF	Informed Consent Form
ICH	International Conference of Harmonization
iCBR	(immune) Clinical Benefit Rate (based on response as per iRECIST)

iCPD	(immune) Confirmed Progression Disease (as per iRECIST)
iCR	(immune) Complete Response (as per iRECIST)
ID	(Patient) Identification Number
iDOR	(immune) Duration of Response (based on response as per iRECIST)
IMP	Investigational Medicinal Product
iORR	(immune) Overall Response Rate (based on response as per iRECIST)
iPFS	(immune) Progression Free Survival (as per iRECIST)
iPR	(immune) Partial Response (as per iRECIST)
iRECIST	(immune-based) Response Evaluation Criteria in Solid Tumors
iSD	(immune) Stable Disease (as per iRECIST)
ITT	Intent-To-Treat
iUPD	(immune) Unconfirmed Progression Disease (as per iRECIST)
IV	Intravenous
KM	Kaplan-Meier
LDH	Lactate Dehydrogenase
LLT	Lowest Level Term
Max	Maximum
MedDRA	Medical Dictionary for Regulatory Activities
Min	Minimum
MTD	Maximal Tolerated Dose
NA	Not Applicable, Not Available
NCI CTCAE	National Cancer Institute Common Terminology Criteria for Adverse Events
NK	Natural Killer (cell)
NKT	Natural killer T (cell)
ORR	Objective Response Rate
OS	Overall Survival
PBMC	Peripheral Blood Mononuclear Cell
PD	Pharmacodynamic
PK	Pharmacokinetic
PT	Preferred Term
Q1	Lower Quartile
Q3	Upper Quartile
QC	Quality Control
QT	QT interval
QTcF	Fridericia's correction of QT interval
R_{ac}	Accumulation ratio
RP2D	Recommended Phase 2 dose
SAE	Serious Adverse Event
SAF	Safety Set
SAP	Statistical Analysis Plan
SAS	Statistical Analysis Systems
SC	Subcutaneous
SOC	System Organ Class

StD	Standard Deviation
$t_{1/2}$	Elimination half-life (to be used in one-or noncompartmental model)
$t_{1/2\alpha}$	Initial or disposition half-life
TEAE	Treatment-emergent Adverse Events
TFLs	Tables, Figures and Listings
T_{max}	Time to reach maximum (peak) plasma concentration following drug administration
Treg	Regulatory T (cells)
ULN	Upper limit of Normal
V_d	Apparent volume of distribution
VS	Vital Signs
WHODrugD	World Health Organizations Drug Dictionary
λ_z	Termination elimination constant (symbol k_e is also used)

INTRODUCTION

Statistical evaluation of each SC103 study (AURELIO-03) part will be performed separately after lock of the relevant study part data in clinical database. This Statistical Analysis Plan (SAP) describes the statistical analyses and planned outputs for Study Part A1. It includes definition of objectives and endpoints as per Study Protocol, the definition of analysis sets, and details needed for statistical programming. The SAP outlines the tables, listings and figures (TFLs) to be compiled in the Clinical Study Report (CSR).

This SAP does not include pharmacokinetic analysis plan. SOT101 (previously SO-C101, RLI-15; INN nanrilkefusp alfa) concentrations levels are measured by [redacted] ho are also responsible for pharmacokinetic analysis and for writing pharmacokinetic analysis plan. This SAP does not include plan of statistical analysis to be performed on biomarkers collected from tumor tissue samples as collected data are limited and this analysis is intended to be fully exploratory.

This SAP is written according to the SC103 Study Protocol version 10.0 dated on 29-JUL-2021, current Mock Case Report Form (CRF), DEC charter version 4.0 dated on 26-MAR-2021, and IAP charter version 3.0 dated on 30-MAR-2021. The analyses and outputs closely follow the ICH guidelines for industry on topic E3 (Structure and Content of Clinical Study Reports) and E9 (Statistical Principles for Clinical Trials).

DOCUMENT HISTORY

Version	Date	Description of change	Performed b
Draft 0.1	17-FEB-2023	First version of the document created based on Part A SAP.	[redacted]
Draft 0.2	09-MAR-2023	Minor edits for Part A1 adaptation and minor corrections throughout the text after review by Medical Writer, CRO Statistician, and Medical Director.	
Final 1.0	09-MAR-2023	Final version	

1 PLANNED CHANGES FROM STUDY PROTOCOL

In study protocol version 10.0, dated 29-JUL-2021, SO-C101 is specified in “Investigational medicinal products”. Throughout this SAP, SOT101 is used instead of SO-C101.

2 STUDY OBJECTIVES

2.1 PART A1 - SOT101 MONOTHERAPY, DOSING SCHEDULE 2

2.1.1 Primary objectives

- To assess the safety and tolerability of SOT101 given as monotherapy
- To determine the maximal tolerated dose (MTD) and/or recommended Phase 2 dose (RP2D) of SOT101 given as monotherapy

2.1.2 Secondary objectives

- To characterize the PK of SOT101
- To characterize the PD of SOT101 in peripheral blood
- To determine the preliminary efficacy of SOT101 monotherapy as measured by overall response rate (ORR), duration of response (DOR), clinical benefit rate (CBR), and progression-free survival (PFS) according to iRECIST
- To determine the immunogenicity of SOT101 given as monotherapy

According to iRECIST terminology, responses assigned using iRECIST have a prefix of “i” (“i” stands for immune); therefore, abbreviations iORR, iDOR, iCBR, iPFS will be used afterwards.

2.1.3 Exploratory objectives

- To explore the mechanistic effects of SOT101 on selected immune cell populations in tumor tissue samples. Analysis of this exploratory objective is not described in this SAP, instead, a separate Biomarker analysis plan will be prepared.
- To assess overall survival (OS)

3 STUDY DESIGN

Study design is briefly described below. Full description of study design is included in the Study Protocol. The schedule of procedures and assessments is presented in the Study Protocol Table 9.6 to 9.17.

3.1 DEFINITION OF MTD/RP2D AND IMPLEMENTATION OF 3+3 DOSE ESCALATION DESIGN

Part A1 will start with the starting daily dose at 1 dose level below the RP2D identified in Part A (which will be split into two identical [50%:50%] daily doses) until the MTD and/or RP2D of SOT101 monotherapy given as per dosing schedule 2 is defined.

MTD is defined as the dose level associated with ≥33% of DLT evaluable patients experiencing a DLT. If the MTD is reached, the RP2D will be conventionally defined as the dose level just below this non-tolerated dose level. If the MTD is not reached, the RP2D will be selected based on integrated evaluation of safety, tolerability, clinical benefit, PK and PD data, for all dose levels tested.

The 3+3 dose escalation design to identify MTD/RP2D includes the following steps for each dose level until MTD/RP2D is identified:

1. One patient will be enrolled and will receive the first eight doses of SOT101 (2 on day 1, 2 on day 2, 2 on day 8, and 2 on day 9). This patient will be observed for safety for 7 days after the eighth dose of SOT101, starting from day 9.
    - If there are no safety concerns at the end of these 7 days, second and third patients will be allowed to be dosed. The second and third patients will not be dosed on the same day.
    - Otherwise, dose escalation meeting (DEM) will be organized and DEC/IAP will decide next steps.
2. Next steps will depend on the occurrence of DLT within the DLT evaluation period of 21 days:
    - If **no DLT occurs** in 3 DLT evaluable patients, then next patient cohort treated with **higher dose level will start**.
    - If **one DLT occurs** in 3 DLT evaluable patients, then the cohort will be **extended to 6 DLT evaluable patients in total**.
        - If **one DLT occurs** in the 6 DLT evaluable patients, then the next patient cohort treated with **higher dose level start**.
        - If **≥2 DLTs occur** in the 6 DLT evaluable patients, then MTD is identified and **enrolment/escalation is stopped**.
    - If **≥2 DLTs occur** in 3 DLT evaluable patients, then MTD is identified **and enrolment/escalation is stopped**.

3.2 RANDOMIZATION AND BLINDING

Not applicable.

4 STUDY ENDPOINTS

4.1 DEMOGRAPHY AND BASELINE CHARACTERISTICS TO BE SUMMARIZED

The following baseline characteristics will be summarized in the tables:

- Demographic characteristics:

- Age at informed consent (ICF) signature [years]
- Age at informed consent (ICF) signature [years] according to: <18 years, >18 and ≤64 years, >64 and ≤84, >84 or older
- Gender
- Ethnicity
- Race

- Baseline characteristics
  - Weight [kg]
  - Body Mass Index (derived)[kg/m^2]
- Disease history
  - Primary tumor location
  - Histological type
  - Cancer type (derived)
  - Time since diagnosis at ICF signature (derived) [years]
  - Time since latest radiological or clinical disease progression at ICF signature (derived) [weeks]
  - Number of lines of previous systemic anticancer therapy
  - Number of lines of previous systemic anticancer therapy categories: ≤ 2, > 2.
  - Previous treatment with check point inhibitors (CPI) (Yes/ No/ Unknown)
  - CPI Response (if CPI received) (Refractory/ Relapsed/ Unknown)
  - Prior anticancer non-systemic therapy (Yes/ No)
  - ECOG
  - ECOG categories: 0, > 0

4.2 ENDPOINTS

4.2.1 Primary endpoints

- Safety and tolerability of SOT101 as evaluated by the incidence of DLTs, incidence of SOT101-related adverse events (AEs), SAEs, AEs leading to premature discontinuation of SOT101, deaths, and clinical laboratory test abnormalities.
- Further, endpoints of the study are to determine MTD and the RP2D of SOT101 (as defined in the section 3.1).

4.2.2 Secondary endpoints

- PK of SOT101
- Immune response characterized by the changes in expression of immune markers in PBMCs
- iORR, iDOR, iCBR, and iPFS
- Detection of Anti-drug antibodies (ADA)

4.2.3 Exploratory endpoints

- Changes in the expression of immune biomarkers as compared to baseline in tumor tissue (analysis of this endpoint is not described in this SAP).
- OS at 6 months after the EOT visit.

5 COMMON DEFINITIONS

General and common definition relevant for statistical analysis/ Statistical Analysis Systems (SAS) programming are listed below. Definitions used only in analysis of a particular endpoint are included directly in analysis section.

5.1 TREATMENT CYCLE

Each treatment cycle in Part A1 should include 8 SOT101 administrations and should take 21 days as per Study Protocol. However, treatment interruptions and delays can occur. Therefore, the cycle number will be taken from the electronic CRF (eCRF) database.

The start of each cycle is defined by the date of the first SOT101 administration in the cycle.

The cycle lasts until Day 1 of the next cycle. The last cycle end is defined as Day 21 of the last cycle or end of the study participation (whatever occurs first).

5.2 LABELS USED IN SAP AND IN STATISTICAL OUTPUTS

EOT stands for end of treatment. FU stands for follow-up.

Cohort labels will include number of dose level (and dose administered µg/kg) as per Study Protocol. The label will be based on information recorded in eCRF in "Initial dose of SOT101 (ug/kg)".

- Example: 1 (4.5 µg/kg).

Individual time-points labels will be as follows:

- Screening
- Cycle X Day Y
    - Cycles will be identified by the number of the cycle as per eCRF data.
    - Days will be identified by the number of the day as per eCRF data.
- EOT
- EOT + X weeks, see below

The assignment to the time-point labels will be performed via SAS programming as follows:

- If Date of assessment – date of EOT ≤ 4+2 weeks then label = "EOT + 4 weeks"
- If 6 weeks < Date of assessment – date of EOT ≤ 8+2 then label = "EOT + 8 weeks"
- If 10 weeks < Date of assessment – date of EOT ≤ 12+2 then label = "EOT + 12 weeks", etc.

If two assessments are assigned to the same time-point label, the earliest assessment will be selected. In such case the tables or summaries will be contain a footnote specifying the case.

In the listings, the real post-treatment week (see section 6.2, rounded to one decimal) will be presented as well.

Timepoint labels used in the statistical outputs and derivations are described in the Appendix, Section 12.2.

5.3 BASELINE VALUES

5.3.1 Study baseline

Study baseline will be defined as the last non-missing measurement prior to the first SOT101 administration, unless specified otherwise.

5.3.2 Handling of missing data needed for baseline identification

The definitions above consider date and time of the assessment and SOT101 administration. If time is not known, then only dates will be used for identification of the baseline. Safety laboratory samples are supposed to be taken before study drug administration; therefore, if time of sample collection is not known and date is the same as date of administration then it will be considered as pre-dose sample.

Values which are identified as baseline via rule described in this paragraph will be flagged in the listings.

5.4 CODED TERMS AND DICTIONARIES USED

Data will be coded as described in the following table.

Table 3: Data to be coded

eCRF page name	Variable to be coded (Dictionary to be used for coding)
The previous therapies include the following pages:	
PRIOR ANTICANCER SYSTEMIC THERAPY	Medication (WHODD)
PRIOR ANTICANCER NON-SYSTEMIC THERAPY	Location and Surgery description (MedDRA)
Further, details about prior and concomitant medication/therapies will be collected on the following pages:	
MEDICATION DETAILS	Medication (WHODD)
NON-PHARMACOLOGICAL THERAPY DETAILS	Therapy (MedDRA)
NEW ANTICANCER SYSTEMIC THERAPY DETAILS	Medication (WHODD)
NEW ANTICANCER NON-SYSTEMIC THERAPY DETAILS	Location and Surgery description (MedDRA)
MEDICAL HISTORY DETAILS	Medical history term (MedDRA)
ADVERSE EVENT DETAILS	Adverse event term (MedDRA)
DEATH	Immediate cause of death and Underlying cause of death (MedDRA)

The coding will be performed directly in eCRF system. The terms will be coded with the most current version of Medical Dictionary for Regulatory Activities (MedDRA) and WHODD dictionaries at time of DB lock.

All MedDRA and WHODD levels listed below will be presented in the listings. Those used in the tables are underlined.

MedDRA coding levels will include:

- Preferred Term (PT)
- Lowest Level Term (LLT)
- High Level Term (HLT)
- High Group Level Term (HLGT)
- Primary System Organ Class (SOC)

WHODD coding will include the following Anatomic, Therapeutic, Chemical (ATC) levels:

- ATC Level 1: anatomical main group
- ATC Level 2: therapeutic subgroup
- ATC Level 3: pharmacological subgroup

- ATC Level 4: chemical subgroup
- WHODD preferred name

5.5 PREVIOUS/CONCOMITANT/POST-TREATMENT MEDICATIONS/ THERAPIES

The records of prior and concomitant medications will be classified as "Prior", "Concomitant" and "Post-treatment" according to the following definitions.

The start of study treatment refers to the date of the first SOT101 administration.

The end of study treatment refers to the date of the last SOT101 administration.

"Concomitant" medication/therapy is any medication/therapy which was administered in the period starting with the start of study treatment (including) and lasts until the end of study treatment. The only exception will be medication/therapy which started on day of the end of study treatment: this medication will be classified as "Post-treatment".

"Prior" medication/therapy is any medication/therapy ended before the start of study treatment.

"Post-treatment" medication/therapy is any medication/therapy which started after or at the end of study treatment.

For records of medication/therapy with unknown and incomplete dates which cannot be identified according to definitions described above, the following rules will be applied:

- If end date of medication/therapy is completely unknown and the medication/therapy started after or at the end of study treatment, the medication/therapy will be counted as "Post-treatment". Otherwise (i.e., the medication/therapy started before the end of study treatment), the medication/therapy will be counted as "Concomitant".
- If start date of medication/therapy is completely unknown and the medication/therapy ended after or at start of study treatment, the medication/therapy will be counted as "Concomitant". Otherwise (i.e., the medication/therapy ended before the start of study treatment), the medication/therapy will be counted as "Prior".
- If start or end date is incomplete: the first possible start date (e.g., for xxDEC2019 this is 01DEC2019, for xxxxx2019 this is 01JAN2019) or last possible end date (e.g., for xxDEC2019 this is 31DEC2019, for xxxxx2019 this is 31DEC2019) will be derived. Classification "Prior", "Concomitant" and "Post-treatment" medication/therapy will be performed using these derived dates.
- If both end date and start date of medication/therapy are completely unknown, then it will be counted as "Concomitant".

5.6 ADVERSE EVENT (AE)

Detailed definition of AE and its classification is presented in the Study Protocol (See section 9.11.5.1).

Each increase or decrease of severity of AE will be collected as separate AE record on "ADVERSE EVENT DETAILS" eCRF page.

Raw data will be used to identify AE episodes as follows:

- Linked AE records by the investigator (i.e. AE record with an outcome of "Change in severity" in the eCRF) with the same MedDRA preferred term, where the start date of the subsequent AE record is equal to (or +1 day) end date of the previous AE record, will be identified as one

AE (continuous) and each AE record will be assigned the same AE ID (equal to the AE ID of the first AE record in the episode).

In order to assign the TEAE status to AEs with the same AE ID (linked AE records), unaggregated data will be used. After the TEAE assignment, AE episodes with the same AE ID will be aggregated as per section 5.8.

5.7 TREATMENT-EMERGENT ADVERSE EVENTS (TEAE)

According to the Study Protocol section 9.13.10.2 treatment-emergent AE is defined as an AE that

- emerges during treatment, having been absent at pretreatment (screening), or
- reemerges during treatment, having been present at pretreatment (screening), or
- worsens in severity during treatment relative to the pretreatment state.

The start of study treatment refers to the date of the first SOT101 administration.

Emerges or reemerges during treatment:

TEAEs are AEs with start date ≥ start of study treatment. Conditions when date/time is unknown or incomplete are defined below.

Worsening in severity:

When the AE belongs to an AE episode (as defined in section 5.6) where the first AE record is not TEAE, the subsequent AE record will be TEAE if:

- AE with start date ≥ start of study treatment, and
- Worsens in severity as compared to pretreatment state.

For adverse events with unknown or incomplete start date/time the following rules will be applied:

Incomplete date: when some information is available (e.g., month, year), but date is partially missing (e.g., missing day, month).

Unknown date/time: when no information is available and thus day, month and year are missing.

Unknown time for start or end of AE:

If time of AE start, or start of study treatment is unknown, the information will be derived only using dates – if AE start or end dates are unknown, conditions are defined below.

If start date is unknown and end date is known (and complete):

- If end date/time is < start of study treatment, the event will not be counted as TEAE.
- If end date/time is ≥ start of study treatment, the event will be counted as TEAE.

If start date is incomplete and end date is incomplete or unknown:

- last possible start date of AE (e.g., for xxDEC2019 this is 31DEC2019, for xxxxx2019 this is 31DEC2019) will be derived. If the last possible start date of AE ≥ start of study treatment the event will be counted as TEAE. Otherwise, if last possible start date of AE < start of study treatment, the event will not be counted as TEAE.

If start date is unknown and end date is incomplete:

- last possible end date of AE (e.g., for xxDEC2019 this is 31DEC2019, for xxxxx2019 this is 31DEC2019) will be derived. If the last possible end date of AE ≥ start of study treatment the

event will be counted as TEAE. Otherwise, if last possible end date of AE < start of study treatment, the event will not be counted as TEAE.

Unknown date for start and end of AE:

- If both start date and end date are unknown, the event will be counted as TEAE.

5.8 AGGREGATION OF CONTINUOUS AE AND TEAE

In order to aggregate AE and/or TEAE episodes (in text below referred just as 'AE') that are continuous, the following will be applied:

- AE will be TEAE if any of all AE records belonging to the AE is TEAE (as defined in section 5.7).
- Start date/time of AE will be start date of the first AE record belonging to the AE. This date will be used to derive the Cycle as defined in sections 5.1 and 5.2, as well as the last dose level of SOT101 before the start of the AE.
- End date /time of AE will be end date of the last AE record belonging to the AE.
- Outcome of AE will be outcome of the last AE record belonging to the AE.
- Severity will be the highest grade out of all AE records belonging to the AE.
- AE will be serious if any of all AE records belonging to the AE is evaluated as serious.
- AE will be immune-related if any of all AE records belonging to the AE is evaluated as AE immune-related. Secondly, AE will be not immune-related if any of all AE records belonging to the AE is evaluated as AE not immune-related.
- AE will have suspected relationship to SOT101 if any of all AE records belonging to the AE is evaluated as to have suspected relationship to SOT101.
- Action taken to SOT101 will include all actions taken as per all AE records belonging to the AE.

The definition above will be used for tables. Clinical signs/symptoms of cytokine release syndrome will not be aggregated.

Listings will present all AE and TEAE (not aggregated) as defined in Section 8.7.2 and Section 8.7.3.

5.9 CROSS-OVER PATIENTS AND DATA HANDLING

Cross-over to other Parts from Part A1 did not occur.

6 GENERAL ALGORITHMS AND DERIVED VARIABLES

General and common algorithms to be used in SAS programming are listed below. Algorithms used only in analysis of particular endpoint are included directly in analysis section.

6.1 CONVERSION OF DAYS, MONTH, YEARS

Week will be counted as day/7. Planned to be used for presentation in listings where the value will be rounded for one decimal.

One year will be counted as 365.25 days.

One month will be counted as 365.25/12 days = 30.4375 days.

Number of calculated years and months will be used e.g. for calculation of age or survival time, rounding procedures are described in section 8.2.2.

6.2 TREATMENT/POST-TREATMENT DAY

Real treatment day will be calculated as date – date of the start of study treatment + 1. For dates before the start of study treatment, the treatment day will be negative and will be calculated as follows: start of study treatment – date.

Real post-treatment day will be calculated as date – date of the end of study treatment.

Real week, month and year will be converted from real day as defined in the section 6.1.

6.3 ALGORITHM FOR ALLOCATION OF DATA TO SCHEDULED VISITS/TIME-POINTS

The algorithms are described with definition of the time-point labels in Section 5.2.

6.4 APPLICATION OF CUT-OFF

No cut-off is planned to be applied for the final analysis.

7 ANALYSIS SETS

7.1 SAFETY SET (SAF)

The safety population will include all patients All patients exposed to SOT101 in Part A1.

The SAF will be used for analysis of safety endpoints.

7.2 DLT-EVALUABLE PATIENTS

A patient evaluable for DLT will be a patient who has completed cycle 1 and received all planned treatments without any treatment delay or interruptions for any other reason than DLT: for Part A1, received all 8 doses of SOT101 as planned. Patients who do not fulfil these criteria for any other reason than DLT should be replaced.

The DLT evaluable patients will be used for ongoing safety evaluation needed for decisions as per 3+3 dose escalation design.

7.3 PK/PD EVALUABLE

PK analysis set will include patients with evaluable PK profile.

PD analysis set will include patients with evaluable PD profile.

Evaluation of PK and PD are secondary objectives of Study Part A1 which is a dose-escalation study; limited number of patients is included in the individual dose levels and in RP2D level. This needs to be considered when interpreting the data. The PK/PD profile is further explored in Part D.

Protocol deviation related to PK and PD assessment and compliance with dosing schedule will be reviewed. Only patients which data would lead to biased conclusions or analysis interpretation will be excluded from the analysis sets.

The PK/PD analysis set will include patients in both PK analysis set, and PD analysis set. The PK/PD evaluable patients will be used for PK/PD analysis.

7.4 EFFICACY SET

All patients exposed to SOT101 (exposure for at least one treatment cycle) who had at least one evaluable tumor assessment per iRECIST after the initiation of SOT101 treatment.

Exposure for at least one treatment cycle is defined as 8 doses of SOT101 (regardless of dose level) in Cycle 1, or if the patient is exposed to SOT101 (with any number of doses) in Cycle 1 and started Cycle 2.

The Efficacy set will be used for analysis of efficacy endpoints.

8 STATISTICAL METHODS AND DETERMINATION OF SAMPLE SIZE

This section describes the data analysis in detail (with exception of pharmacokinetic analysis which will is described in separate document attached). The statistical methods are planned in accordance with the Study Protocol (section 9.9) and in accordance with ICH Topic E9 Statistical Principles for Clinical Trials.

SAS version 9.4 or newer will be used for statistical programming.

8.1 SOURCE DATA TO BE USED FOR ANALYSIS

Data collected in clinical study database including MedDRA and WHODD coding will be used for analysis. Laboratory conversion factors will be taken from the internal IBMCD laboratory DB (as per Laboratory Data Unit Conversions standards).

Plasma concentration data and pharmacokinetic parameters will be provided by [redacted] n .sas7bdat format and will be directly used for analysis (will not be a part o c n ca a a ase . Dates and times of blood sampling in the datasets provided b [redacted] nd those recorded in the clinical database will be reconciled as a part data management processes

Description of the provided datasets:

- pc_cnp_DDMMMYYYY.sas7bdat: dataset providing the PK concentrations overtime, per patient.
- pp_cnp_DDMMMYYYY.sas7bdat: dataset providing the calculated PK parameters, per patient.

Where n is the number of the cohort, p is the study part (e.g., 'a1' for Part A1), DDMMMYYYY is the date of transfer. Further details are specified in data transfer specification "SC103_Data Transfer Specification [redacted] 20Jul2021" dated 20-Jul-2021.

Anti-drug antibodies data will be provided b [redacted]

Description of the provided datasets:

- SC103ADASNAPSHO [redacted] DMMMYYYY.csv: provides per patient and overtime ADA positivity, titration, and NADA positivity. Where DDMMMYYYY is the date of transfer.

Further details are specified in data transfer specification "SC103_Data Transfer Specification [redacted] v5.0_20Jul2021" dated 20-Jul-2021.

Plasma concentration data and pharmacokinetic parameters will be provided by [redacted] Materials for DEC/IAP will be directly prepared by [redacted] o o w provide outputs for CSR.

Pharmacodynamic variables and cytokines levels will be provided by Central LA [redacted] SAS® v.9 transport files and will be directly used for analysis (wil[redacted] art of clinical database). Dates and times of blood sampling in the datasets provided by [redacted] and those recorded in the clinical database will be reconciled as a part data management processes

Description of the provided datasets:

- SC103SNAPSHO [redacted] DMMMYYYY.xpt: includes per patient and overtime the test results as per protocol. Where DDMMMYYYY is the date of file transfer.

Further details are specified in data transmission agreement "SC103_Data Transmission Agreement [redacted] 15Jun2021" dated 15-Jun-2021.

8.2 GENERAL PRINCIPLES

The study includes Study Part A1.

This is a Phase I study with 3+3 dose escalation design with primary objective to determine MTD/RP2D. The analysis will be mainly descriptive. If appropriate regarding the number of patients (e.g., All cohorts pooled), the descriptive statistics will be presented with 95% confidence intervals. Descriptive statistics will include:

For categorical variables, standard set of summary statistics will be counts and percentages calculated from number of available observations. Number of available observations (and number of missing observations) will be presented as well. For baseline characteristics missing, not applicable/not available/not known will be counted as a category. The number of patients used for the percentages (denominator) is defined in each analysis section of this SAP.

For continuous variables, the following descriptive statistics will be presented: number of available observations (and number of missing observations), mean, standard deviation (StD), median, lower quartile (Q1), upper quartile (Q3), minimum (Min), and maximum (Max).

For time-to-event variables, Kaplan-Meier (KM) estimates of median, Q1 and Q3 will be presented. The number and percentage of patients with event and censored patients will be presented. KM curves will be provided as a part of descriptive analysis.

For pharmacokinetic parameters, the following descriptive statistics will be presented: number of available observations (and number of missing observations/ number of concentrations below limit of quantifications (BLQ)), arithmetic mean and geometric mean and their 95% confidence intervals, standard deviation (StD), StD of log-transformed data, median, inter-patients (between-patients, within-cycle) coefficient of variation, intra-patient (within-patient, between-cycles-days) coefficient of variation, minimum, and maximum. Coefficient of variation (CV) in % is computed as:

% CV = (StD x 100) / mean

8.2.1 Listings

Each listing will present the following variables/columns:

- Patient identification (ID), Cohort (dose level)
- If appropriate, analysis set relevant for particular listing

Listings will be sorted by ID and by chronological order of visits/assessments/events.

Dates will be presented in the listings in format YYMMDD10. (e.g., 2019-11-31). Partial dates as exported from the database will be listed (e.g., 2019-11-UNK, 2019-UNK-UNK, UNK-UNK-UNK).

8.2.2 Rounding procedures

Percentages will be presented with one decimal place with exception of efficacy data where two decimal places will be presented.

Mean, median, Q1 and Q3 will be presented with one more decimal place and StD will be presented with two more decimal places than the original data used for calculation of the statistics. The maximum number of decimal places will be up to three.

Other values such as temperature, number of weeks, coefficients of variation, etc. will be presented with one or two decimal places, according to the source data.

8.2.3 Unscheduled/ repeated assessments

Unscheduled/ repeated assessments which are performed in addition to those scheduled in the Study Protocol will not be used for analysis per time-point. Baseline values can include unscheduled/repeated assessment if they are the last before study drug administration (see section 5.3 for details).

8.2.4 Missing data

In general, missing data will not be imputed, i.e. complete case analyses will be performed. However, number of missing data is to be presented in descriptive statistics.

8.2.5 Methods for handling of incomplete/missing dates/ times

Methods for handling of incomplete and missing dates of medication/therapies and adverse events are presented in sections 5.5 and 5.7.

Similarly, methods for handling of incomplete and missing dates for Date of initial diagnosis are described in section 8.4.

8.2.6 Covariates and subgroups

The patients are planned to be analyzed by the cohorts (dose levels).

Subgroup analyses are not planned. No covariates to be used in analyses planned in this SAP.

8.2.7 Region/Country/Site analysis in multi-centric trial

Analysis by region, country or site is not planned.

8.2.8 Validation of statistical programming

Each SAS program will be validated by a second qualified SAS programmer to ensure a correct output and a correct presentation of the data. The validation process is documented in the validation sheet (GCPS_DMF_033 A-C), which also prespecifies criteria for risk categorization of programs and the corresponding validation actions.

Logs of all programs used for analysis and data preparation will be checked for errors and unexpected warnings. Any undocumented updating of raw study data in statistical programming instead of change in clinical DB (or source data) is not allowed.

8.3 DISPOSITION OF STUDY PATIENTS

Disposition of patients will be presented for Study Part A1, for All cohorts pooled and by cohorts. Cases where patient signed the ICF (thus a Patient ID was assigned) for Part A1 but the patient was not treated due to safety concerns regarding previous patients (e.g., MTD reached) will not be included in the tables nor the listings: if applicable the patient signed a new ICF and a new Patient ID was assigned. These cases are recorded in the eCRF, in "Eligibility Verification" where the reason for Screen Failure is recorded as "Change of study part" (IE.IESFREA).

The following information will be presented in the table of patients' disposition:

No. of cohorts included (presented only for All cohorts pooled).

Count of the following groups of patients will be presented:

- Screened
  - Reason for screen failure with count and percentages* (from screened patients)
- Eligible (as per confirmation by the Sponsor)
- Treated

Count and percentages* of treated patients will be presented for the following groups of patients:

- DLT evaluable
- Ongoing patients (i.e., patients still in the study)
- Study discontinued patients
  - Reason for discontinuation with count and percentages* (from study discontinued patients)
- SOT101 discontinued patients
  - Reason for discontinuation with count and percentages* (from SOT101 discontinued patients)

*The percentages will be presented by cohort and for all cohorts pooled.

Disposition of patients into analysis sets:

- Number of patients in analysis set (percentages calculated out of all treated patients), number of patients excluded from analysis set and reasons for exclusion from analysis sets (percentages calculated out of those patients excluded from analysis set).

Protocol deviations will be summarized for SAF and for All cohorts pooled, as well as listed.

8.4 DESCRIPTION OF BASELINE PATIENTS' CHARACTERISTICS

Baseline characteristics and disease history information defined in section 4.1 will be summarized with descriptive statistics.

Cancer type will be medically reviewed prior to DBL and derived based on the list specified in Appendix (Section 12.3).

Body Mass Index will be calculated as weight in kg divided by height in m^2. Values will be rounded to one decimal.

Date of birth is not collected in the eCRF. Age at ICF signature in years as recorded in eCRF will be used. Then, time since diagnosis at ICF signature and time since latest radiological or clinical disease progression at ICF signature in years will be calculated as follows: date of ICF signature (at time of

entering the study) – date of diagnosis/progression + 1 and transformed to years/weeks respectively as per section 6.1.

If Date of initial diagnosis is incomplete of partially missing, the following rules will be applied for imputation of dates:

- If day and month is missing, day will be imputed as 01 and month as 06.
- If only day is missing, day will be imputed as 01.
- If only month is missing, month will be imputed as 06.
- If year is missing or the date is completely unknown, no imputation will be performed.

Date of latest radiological or clinical disease progression will not be imputed regardless of unknown or partially missing dates.

Explanatory footnote will be presented in corresponding table and listing.

The baseline patients' characteristics will be analyzed using SAF and presented for All cohorts pooled, as well as by cohort. Percentages will be computed from the number of treated patients in All cohorts pooled and, in each cohort, respectively.

Medical history recorded in eCRF will be only listed.

8.5 MEDICATION/THERAPIES

Medication and therapies as specified in Table 3 will be presented by count and percentages of patients. Separate tables for prior, concomitant, and post-treatment medication/therapies (see section 5.5) will be presented. Prior, concomitant, and post-treatment medication/therapies will be flagged in the listings.

The tables will be generated using SAF and for All cohorts pooled. Percentages will be computed from the number of treated patients in All cohorts pooled for all cases: prior, concomitant, and post-treatment medication/therapies.

Prior, concomitant, and post-treatment procedures will also be listed.

8.6 EXPOSURE TO STUDY TREATMENTS

Duration of exposure to SOT101 will be calculated as: date of the last SOT101 administration - date of the first SOT101 administration + 1.

Descriptive statistics of duration of exposure to SOT101 will be presented in the table together with patient-years of exposure, analyzed as continuous variables.

Dose intensity will be calculated as follows, for each patient:

- Sum of (SOT101 administrations x dose level) / duration of exposure (in days)

Dose intensity will be summarized.

Additionally, to provide a dosing overview and a summary of changes from dosing (based on initial dose of SOT101 and actual dose of SOT101) the number of SOT101 administered doses will be analyzed descriptively as categorical variable.

Descriptive statistics for duration of exposure, dose intensity, and dosing overview will be provided for All cohorts pooled and by cohorts. Percentages will be computed from the number of treated patients in All cohorts pooled and, in each cohort, respectively. The tables will be generated using SAF.

Dose level, Dilution Fold, Total Volume Administered, Body Weight at Day 1 of each cycle, calculated Volume for Administration (as described in SC103_Instruction for handling of IMP and Trial Related Materials_v4.0_16Mar2021 (v4.0)) and compliance of dosing schedule for SOT101 with Study Protocol will be presented in Listings.

8.7 ANALYSES OF SAFETY

8.7.1 Summary of dose limiting toxicity events (DLTs) for determination of MTD/RP2D

AEs linked to DLTs will be summarized in frequency table as defined for summary table of TEAEs. Information in summary table will be completed by listing where information from dedicated DLT page in eCRF ("Dose Limiting Toxicity Details") will be merged in information recorded in "Adverse Event Details" eCRF page. Merging will be done on unaggregated data by Patient ID (AE.subnum, DLT.subnum) and AE number (AE.PAGESEQ, DLT.AENO).

8.7.2 Adverse events (AEs)

Details about AEs as collected on "Adverse Event Details" eCRF page will be used for analysis. Data collected on "Serious Adverse Event" eCRF page will be used for safety reporting in responsibility of pharmacovigilance department and will not be part of statistical outputs.

See section 5.8 for handling of AE records needed before programming of tables. All AE records will be presented in the listings without aggregation into AE episodes (derived number of episodes will indicate which AE records were aggregated for summaries).

8.7.3 Treatment-Emergent Adverse events (TEAEs)

TEAEs are defined in section 5.7 above. Note that as per Study Protocol AEs are collected in eCRF database until 90±2 days after last dose of SOT101.

Not TEAE will only be listed.

8.7.3.1 Grouping of TEAEs

For harmonization and safety data review purposes, the following grouping of Preferred Terms will be considered in the analysis and displayed as such in the tables. Listings of TEAEs will present the originally coded Preferred Term:

TEAE System Organ Class: Preferred Term	Preferred Term
Gastrointestinal disorders: Abdominal pain	Abdominal pain lower
	Abdominal pain upper
	Abdominal pain
Investigations: Blood bilirubin increased	Hyperbilirubinaemia
	Blood bilirubin increased
Investigations: Lymphocyte count decreased	Lymphopenia
	Lymphocyte count decreased
Investigations: Neutrophil count decreased	Neutropenia
	Neutrophil count decreased
Investigations: Platelet count decreased	Thrombocytopenia
	Platelet count decreased

General disorders and administration site conditions: Injection site reaction	Injection site reaction Injection site erythema Injection site rash Injection site pruritus Injection site induration Injection site inflammation Injection site oedema Injection site pain

8.7.3.2 General considerations for analysis of TEAEs

TEAEs will be displayed in frequency tables, presenting for all tables:

- Number of TEAEs and percentage of patients with at least one TEAE (TEAEs, n (%))
- Number of related TEAEs and percentage of patients with at least one related TEAE (related TEAEs, n (%))

Where percentages will be computed from the number of treated patients in All cohorts pooled and, in each cohort, respectively (unless stated otherwise, see below). Clinical sign/symptom of cytokine release syndrome (as per variable AE.AERELCRS) will be listed separately.

The following frequency tables will be generated for TEAEs, TESAEs:

- Summary table of TEAEs
- Frequencies of TEAEs by MedDRA preferred term (PT) and primary system organ class (SOC)

8.7.3.3 Summary tables of TEAEs

Summary table of TEAEs will present the frequencies of any TEAE and TEAEs by the following characteristics:

- Seriousness
- Outcome
- Severity (i.e., maximum severity reported for AE)
- Maximum severity per patient
- Severity of NCI CTCAE grade 3,4,5
- AE immune-related
- Action taken with SOT101

Frequencies by “Severity” AE and patient will be counted for each severity level which occurs (one patient can have several AEs with different severity). “Maximum severity per patient” will be calculated for each patient. Then, in frequency tables the patient will be counted only once (for the maximal severity) and only TEAEs with this maximal severity will be counted. Similarly, the worst action taken will be considered, from best to worst: No action taken, Dose modified, Temporarily discontinued, Other (as temporarily discontinued + dose modified), Permanently discontinued.

Summary table of TEAEs will be presented for All cohorts pooled and by cohort. In addition, the summary table of TEAEs by cycle will be presented for All cohorts pooled and for the RP2D cohort, up to Cycle 3 and only for TEAEs with an NCI CTCAE grade > 2; when presenting by Cycle, the number of patients treated within that Cycle will be used for the calculation of percentages. The TEAE will be assigned to a Cycle if the onset is within that Cycle, or if the TEAE worsens (relative to pretreatment state) within that Cycle. Frequency tables of TEAEs by MedDRA PT within SOC

Frequencies of TEAEs by MedDRA PT within SOC will present frequencies of any TEAE, by SOC and by PT within each SOC. The tables of the following groups of TEAEs will be provided:

- TEAEs
- TEAEs reported in ≥ 10% of patients
- Non-serious TEAEs reported in ≥5% of patients
- TESAEs
- Fatal TEAEs
- NCI CTCAE Grade 3, 4, 5 TEAEs
- Immune-related TEAEs
- TEAEs leading to SOT101 dose modification
- TEAEs leading to SOT101 temporary discontinuation
- TEAEs leading to SOT101 permanent discontinuation

Special cases regarding SOT101 Action Taken (e.g., Other, "free text" specified) will be reviewed before analysis and TEAEs will be counted as appropriate following the specification in other action taken: in general, certain keywords will be used to classify the TEAE into one pre-defined actions taken above (e.g., a keyword of "dose" in the free text would lead to a classification of dose modified as action taken, a keyword of "discontinuation" or "discontinued" in the free text would lead to a classification of temporary discontinuation).

Frequencies of TEAEs by MedDRA PT within SOC will be presented for All cohorts pooled and by cohort.

Frequency table of TEAEs by MedDRA PT will be generated for All cohorts pooled. The table will be sorted by total number of patients with TEAE in descending order. Additionally, the proportion of patients with TEAE by MedDRA PT will also be presented graphically, by maximum grade and worse action taken.

Table of underlying causes of deaths by MedDRA PT and primary SOC will be generated for All cohorts pooled.

8.7.3.4 Listing of AEs

Listings of AEs will present the following information in addition to data collected on eCRF page "ADVERSE EVENT DETAILS":

- Patient identification (ID), Study Part, Cohort (dose level), DLT evaluable (Yes/No)
- AE no. (derived as number of AE episode, see section 5.6, in chronological order of start date)
- TEAE (Yes/No) (derived)
- Cycle when AE started (derived)
- SOT101 Treatment Day when AE start (derived)
- Days* after the last SOT101 administration (derived)
- Last dose of SOT101 before AE start (derived)
- Total number of SOT101 administered before AE start**
- Duration of AE***
- MedDRA PT

* Days after last dose will be calculated as AE start date – administration date.

**If time of AE start is not recorded (or time of SOT101 administration is not recorded), the information will be derived only using dates (i.e., date of last SOT101 administered before date of AE start, SOT101 doses administered before date of AE start). The administration of SOT101 at the same

date as date of AE start will be indicated as "(+1)", e.g. 5 (+1). If AE start date (or SOT101 administration date) is unknown or incomplete, the derivation will not be performed.

***Duration of AE will be calculated as AE end date– AE start date + 1. If end date or start date is missing or incomplete, the derivation will not be performed.

8.7.4 Other safety assessments

Other safety data include ECG, vital signs, clinical laboratory, physical examination, and echocardiography.

Date of physical examination, date and results of echocardiography assessment will be only listed.

Absolute values of laboratory data (selected laboratory variables defined below), vital signs and QT/ QTcF (Fridericia's correction) will be summarized at individual time-points descriptively by cohort and all cohorts pooled. A more detailed overview will be provided with figures containing the profiles overtime, where the cohort (i.e., dose level) will be colored accordingly.

In all cases, tables and figures will present timepoints where at least 3 patients (or more) have data available at that timepoint.

8.7.4.1 ECG

In addition, analysis in line with ICH E14 guideline will be performed, i.e. number and percentage of patients who fit the criterial listed below will be presented in frequency table (All Cohort pooled and all time-point pooled).

- QTcF interval > 450
- QTcF interval > 480
- QTcF interval > 500
- QTcF interval increases from study baseline > 30
- QTcF interval increases from study baseline > 60
- Any criterion listed above met

QTcF levels which met the criteria above will be included in dedicated listing.

In case of any duplicated assessments, the assessment with the latest sequence (PAGESEQ in eCRF) will be selected.

8.7.4.2 Vital signs

In addition, the following will be provided:

- Mean profiles over time will be presented graphically by cohort and all cohorts pooled.

Vital signs will be analyzed irrespective of the position where the assessments were done.

8.7.4.3 Laboratory values

The selected laboratory variables: Total Bilirubin, Alanine Transaminase (ALT), Aspartate Transaminase (AST), Neutrophils, Platelets, Lymphocytes, Haemoglobin, C-reactive protein (CRP), Alkaline Phosphatase (ALP), Lactate Dehydrogenase (LDH).

Laboratory values will be converted to standard units: the conversion factors to SI units will be maintained in the lab repository database (IBMCD LAB). Changes will be audit trailed in the system. The conversion of laboratory results into SI units will be performed via SAS programming.

In addition, the following will be provided:

For selected laboratory variables not concerning liver enzymes (Neutrophils, Platelets, Lymphocytes, Haemoglobin, CRP, LDH):

- Mean profiles over time will be presented graphically by cohort and all cohorts pooled.

For selected laboratory variables concerning liver enzymes (Total Bilirubin, ALT, AST, ALP):

- Mean profiles over time will be presented graphically by cohort and all cohorts pooled.
- Patient profiles over time will be presented graphically for the RP2D and RP2D – 1 cohort, excluding the MTD.
- Maximal-levels per patient presented in figure with dose-level on X-axis.
- Maximal levels per patient will be also listed in dedicated listing.

For the profiles, if there are two or more values on the same day, the pre-dose value will be considered (as per protocol, safety laboratory measurements should be performed prior to dosing). If two or more pre-dose values are available, the one closest to the dosing will be selected for displaying purposes.

Hepatic function abnormality defined by an increase in AST and/or ALT to ≥ 3 × Upper limit of normal (ULN) concurrent with an increase in total bilirubin to ≥ 2 × ULN but without increase in alkaline phosphatase (i.e., alkaline phosphatase < 2 × ULN) meets the criteria for Hy's law and raises the concern for drug-induced liver injury when no other cause is identified. The summary of liver function tests will include the following categories, and the number and percentage of patients meeting Hy's Law at each scheduled visit during the on-treatment period will be summarized.

8.7.4.4 Prohibited medications

According to section 9.10.4.1 Prohibited medications in the Study Protocol medications which use is known to prolong QT/QTcF interval are prohibited. If such a prohibited medication is administered to the patients, then it will be taken into account in analysis of QT/ QTcF in the following way: patients with prohibited medications administered will be excluded from the analysis (tables) and further information will be provided: if the number of patients with prohibited medications administered is larger than 1, an extra table will be provided for the analysis of QT/QTcF including only these patients. Otherwise, a footnote specifying the case will be provided with the original table.

8.8 ANALYSES OF SOT101 CONCENTRATION DATA AND PK PARAMETERS

The PK analysis plan is provided b [redacted] nd attached to this SAP (section 12.1).

The following PK parameters will be calculated via non-compartmental model according to this plan:

- C_{max}
- T_{max}
- $t_{1/2,}$
- Termination elimination constant (λ_z)
- $t_{1/2\alpha}$ – distribution half-life (where possible)
- $AUC_{(0-6)}$, $AUC_{(0-t)}$, $AUC_{(0-24)}$, $AUC_{(0-inf)}$, same parameters per dose (AUC/D)
- CL - Clearance
- V_d - Volume of distribution
- R_{ac} - accumulation ratio over cohorts/dose levels

Concentration levels, C_{max}, T_{max}, AUC (all), and $t_{1/2}$ will be analyzed descriptively by cohorts (dose administered). In addition, dose-normalized C_{max} (C_{max}/D) and T_{max} will be presented for all cohorts

pooled. Mean concentration levels will be presented in figures with linear and semi-logarithmic scale (only for Cycle 1).

In line with Protocol Deviation Plan, PK samples taken out of schedule defined by the study protocol will be flagged in concentration listings and will not be a part of protocol deviation listing.

Dose proportionality analysis of AUC and C_{max} will be performed for exploratory purposes using standard "power-law model" according to approach describes by Brian Smith et al (2000) which is concisely described in paper by Zhou et al (2006).

The "power-law model" is defined as follows:

$PK = c \cdot Dose^{\beta 1} \cdot e^{\varepsilon}$

Dose-proportionality implies that $\beta 1 = 1$.

After the logarithmic transformation, the "power-law model" can be expressed as:

$\log(PK) = \beta 0 + \beta 1 \cdot \log(Dose) + \varepsilon$

Dose-proportionality corresponds to $r^{\beta 1 - 1} = 1$, where r=highest dose level/lowest dose level.

In order to conclude the dose-proportionality the following criterion has to be met:

$1 + (\log(\theta_L)/\log(r)) < 90\%$ CI of $\beta 1 < 1 + (\log(\theta_U)/\log(r))$.

The commonly used (θ_L, θ_U) will be (80%, 125%). If the SOT101 will be considered as highly variable drug (intra-patient variability >30%), then (77%, 130%) will be used as a margin.

PK samples are taken on cycle 1 day 1 for 20 hours after first administration of SOT101. Cycle 1 day 2 and cycle 3 day 1 are planned to be collected up to 24 hours from first administration of SOT101 at these days. PK sampling at 8 hours post dose will be followed by second administration of SOT101. All PK analyses will be conducted in PK/PD evaluable patients. Values below the BLQ will be treated as 0 when performing the analysis on a linear scale. On the logarithmic scale, these values will be disregarded.

Sensitivity analyses for hemolytic samples:

Any samples with presence of hemolysis will be flagged as follows: a keyword search (both in lower and upper case) of "Hemolytic", "Hemolysis" will be performed on concentration dataset, column PCREASND. Subsequently, a sensitivity on concentration levels and dose proportionality will be performed.

8.9 ANALYSES OF PHARMACODINAMIC MARKERS AND CYTOKINES

PD markers and cytokines levels will be provided by [redacted] nd will not be a part of eCRF database.

The PD marker of interest are as follows:

CD8 Panel
CD8+ Cells of CD3+ Cells (%)
CD8+ Cells of CD3+ Cells(%CD45+)
Ki-67+ Cells of CD8+ Cells (%)
Ki-67+ Cells of CD8+ Cells (%CD45+)
CD45RO+ CD45RA- (Memory) Cells of CD8+ Cells (%)
CD45RO+ CD45RA- (Memory) Cells of CD8+ Cells (%CD45+)
Ki-67+ Cells of CD8+CD45RO+ CD45RA- Cells (%)
Ki-67+ Cells of CD8+CD45RO+ CD45RA- Cells (%CD45+)
NKG2D+ Cells of CD8+ Cells (%)
NKG2D+ Cells of CD8+ Cells (MFI NKG2D)
NKG2D+ Cells of CD8+CD45RO+CD45RA- Cells (%)
NKG2D+ Cells of CD8+CD45RO+CD45RA- Cells (MFI NKG2D)
CD4+ Cells of CD3+ Cells (%)
CD4+ Cells of CD3+ Cells (%CD45+)
Ki-67+ Cells of CD4+ Cells (%)
Ki-67+ Cells of CD4+ Cells (%CD45+)

Natural killer cells (NK) Panel
CD25+Foxp3+ (Treg) Cells of CD4+ Cells (%)
CD25+Foxp3+ (Treg) Cells of CD4+ Cells (%CD45+)
Ki-67+ Cells of CD4+CD25+Foxp3+ (Treg) Cells (%)
Ki-67+ Cells of CD4+CD25+Foxp3+ (Treg) Cells (%CD45+)
CD3-CD56+ (NK) Cells of CD45+ Live Cells (%)
Ki-67+ Cells of CD3-CD56+ (NK) Cells (%)
Ki-67+ Cells of CD3-CD56+ (NK) Cells (%CD45+)
CD3+CD56+ (NKT) Cells of CD45+ Live Cells (%)
Ki-67+ Cells of CD3+CD56+ (NKT) Cells (%)
Ki-67+ Cells of CD3+CD56+ (NKT) Cells (%CD45+)
NKG2D+ Cells of CD3-CD56+ (NK) Cells (%)
NKG2D+ Cells of CD3-CD56+ (NK) Cells (MFI NKG2D)

Cytokines include the following variables:

Interleukin-2
Interleukin-4
Interleukin-6
Interleukin-8
Tumor Necrosis Factor Alpha
Interferon-gamma
Interleukin-1 beta
Interleukin-10
Interleukin-12p70

The eCRF Hematology data (specifically white blood cell count (WBC)) for each timepoint will be used to derive the Cell counts in 10^9/L. Once merged with the pharmacodynamic data by subject and timepoint, the following will be used as derivation:

- CD8+ Cells of CD3+ Cells (10^9/L) = CD8+ Cells of CD3+ Cells (%CD45+) x 0.01 x WBC
- Ki-67+ Cells of CD8+ Cells (10^9/L) = Ki-67+ Cells of CD8+ Cells (%CD45+) x 0.01 x WBC
- CD45RO+ CD45RA- (Memory) Cells of CD8+ Cells (10^9/L) = CD45RO+ CD45RA- (Memory) Cells of CD8+ Cells (%CD45+) x 0.01 x WBC
- CD4+ Cells of CD3+ Cells (10^9/L) = CD4+ Cells of CD3+ Cells (%CD45+) x 0.01 x WBC
- Ki-67+ Cells of CD4+ Cells (10^9/L) = Ki-67+ Cells of CD4+ Cells (%CD45+) x 0.01 x WBC

- CD25+Foxp3+ (Treg) Cells of CD4+ Cells (10^9/L) = CD25+Foxp3+ (Treg) Cells of CD4+ Cells (%CD45+) x 0.01 x WBC
- Ki-67+ Cells of CD4+CD25+Foxp3+ (Treg) Cells (10^9/L) = Ki-67+ Cells of CD4+CD25+Foxp3+ (Treg) Cells (%CD45+) x 0.01 x WBC
- CD3-CD56+ (NK) Cells of CD45+ Live Cells (10^9/L) = CD3-CD56+ (NK) Cells of CD45+ Live Cells (%) x 0.01 x WBC
- Ki-67+ Cells of CD3-CD56+ (NK) Cells (10^9/L) = Ki-67+ Cells of CD3-CD56+ (NK) Cells (%CD45+) x 0.01 x WBC
- CD3+CD56+ (NKT) Cells of CD45+ Live Cells (10^9/L) = CD3+CD56+ (NKT) Cells of CD45+ Live Cells (%) x 0.01 x WBC
- Ki-67+ Cells of CD3+CD56+ (NKT) Cells (10^9/L) = Ki-67+ Cells of CD3+CD56+ (NKT) Cells (%CD45+) x 0.01 x WBC

During the descriptive statistical analysis of PD markers and cytokines, it will be considered that the value can be below or above limits of quantification: the lower limit will be replaced by the actual value (e.g. “<0.5” should be considered as 0.5), similarly for the upper limit (e.g. “>20” should be considered as 20). In all cases, only Cycle 1 and Cycle 2 data will be used and analyzed to study the Pharmacodynamic activation. Only certain markers of interest will be included in the tables and figures, all markers will be listed.

The levels and fold increases will be analyzed descriptively at individual time-points by cohorts and all cohorts pooled. A more detailed overview will be provided with figures containing the profiles overtime, where the cohort (i.e., dose level) will be colored accordingly. A Boxplot for Cycle 1 Day 6 by dose level, and maximal levels of activation achieved by dose level (barplot), will be provided for selected PD markers:

- NK cells: Ki-67+ Cells of CD3-CD56+ (NK) Cells (%)
- NKT cells: Ki-67+ Cells of CD3+CD56+ (NKT) Cells (%)
- CD8+ T-cells: Ki-67+ Cells of CD8+ Cells (%)
- CD8+ Memory T cells: Ki-67+ Cells of CD8+CD45RO+ CD45RA- Cells (%)
- CD4+ T cells: Ki-67+ Cells of CD4+ Cells (%)
- T regs: Ki-67+ Cells of CD4+CD25+Foxp3+ (Treg) Cells (%)

The table summarizing the maximum levels of activation will contain the fold increase in cell counts (i.e., 10^9/L).

Additionally for cytokines, the mean fold increase overtime will also be plotted.

All PD analyses will be conducted on PK/PD evaluable patients.

Maximal levels of cytokines will also be listed.

8.10 ANALYSES OF EFFICACY

The efficacy population will be derived as follows: assuming at least one evaluable tumor assessment per iRECIST after the initiation of SOT101 treatment, a patient that receives 8 doses of SOT101 in cycle 1, will be included in the efficacy population; if a patient does not receive 8 doses of SOT101 in cycle 1 then the patient will be included in the efficacy population if monotherapy is not permanently discontinued in cycle 1 (i.e. patient starts cycle 2). The efficacy population will be used for the efficacy analyses.

Due to the lack of confirmation of progression (iCPD) and follow-up scans, any unconfirmed progression (iUPD) has been considered as progression if a discontinuation of any treatment is followed, and thus deviating from iRECIST guidelines.

Complete response (iCR), partial response (iPR), stable disease (iSD) and progression disease (iUPD and also after iCPD) will be identified according to iRECIST recorded to eCRF and cleaned via data management/medical review processes.

Tumor assessment data will be listed and disease response since the first SOT101 administration will be presented graphically per patient (swimmer plot). Additionally, tumor size evaluated via sum of diameters of target lesions will be presented graphically per patient (waterfall plot): the best change from baseline will be used. The change from baseline overtime will be graphically presented per patient as well (spaghetti plot).

If tumor assessment is performed after start of new anticancer therapy, it will be clearly indicated in the outputs. For tumor assessments with different dates (i.e. lesions are assessed at different dates), the earliest date will be used for efficacy derivations.

Overall response is defined as state when the patient achieves iPR or iCR. Clinical benefit is defined as state when patient achieves iSD, iPR, or iCR. iSD needs to last at least 6 weeks from the start of study treatment; if not, at least one follow-up scan assessed as iPR, iCR, or iSD is required to provide clinical benefit. Similarly, confirmation of iPR or iCR by a subsequent assessment of either iPR or iCR, at least 4 weeks apart, will be required to declare an overall response or clinical benefit.

Immune overall response rate (iORR) and Clinical benefit rate (iCBR):

- iORR will be defined as the proportion of patients with confirmed iPR or iCR, out of patients in efficacy population.
- iCBR will be defined as the proportion of patients with confirmed iPR, iCR, or iSD out of patients in efficacy population.

iORR and iCBR will be summarized for All cohorts pooled.

Progression free survival (iPFS):

iPFS is defined as the time from the first day of study treatment until the first date of iUPD (followed by iCPD, study treatment discontinuation or clinical progression) or death (whichever occurs earliest) and will be summarized using Kaplan-Meier estimates.

Patients with missing data or that start new anti-cancer therapy (other than palliative) will be censored at the date of the last evaluable tumor assessment.

iPFS will be summarized and presented for All cohorts pooled.

Duration of response (iDoR):

iDoR is defined as the time since the first iPR or iCR until the first date of iUPD (followed by iCPD, study treatment discontinuation or clinical progression) or death (whichever occurs earliest) for patients with confirmed iPR or iCR. DoR will be summarized using Kaplan-Meier estimates.

Patients with missing data or that start new anti-cancer therapy (other than palliative) will be censored at the date of the last evaluable tumor assessment.

iDoR will be summarized and presented for All cohorts pooled.

Overall survival (OS):

OS is defined as the time from the first day of study treatment until the date of death and will be summarized using Kaplan-Meier estimates.

Patients with missing data will be censored at the last time known to be alive: apart from trial visits/survival status, information from AE, new anti-cancer therapy, and prior and concomitant medications data from eCRF will also be used to derive the alive status – the latest complete date will be selected.

OS will be summarized and presented for All cohorts pooled.

Duration of follow-up:

A reverse Kaplan-Meier analysis will be performed on OS to estimate the median follow-up incorporating censoring rules and flipping event/censored events.

8.11 OTHER ASSESSMENTS

8.11.1 ECOG performance status

ECOG performance status will be summarized for All cohorts pooled and listed.

8.11.2 Immunogenicity

ADA levels, titration, and Neutralizing ADA levels will be provided by [redacted] nd will not be a part of eCRF database. Levels and titration will be analyzed descriptively for All cohorts pooled and by cohorts for SAF population. The summary table will be completed with listing of positive results.

8.12 INTERIM ANALYSES

No interim analysis is planned.

8.13 DETERMINATION OF SAMPLE SIZE

According to Study Protocol section 9.13.11 the traditional 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 in a cohort. The estimated number of patients is 6-15.

9 CONCLUSIONS BASED OF DATA REVIEW MEETING

From the statistical perspective the objectives of the meeting will be following:

- to agree on patients excluded from analysis sets and to agree on major protocol deviations/reportable protocol deviations
- to highlight any issue from statistical perspective and to decide the solution in joint decision.

The section below will state version of Protocol Deviation Plan valid at time of the data review meeting, refer to data review meeting minutes and summarize/ summarizes conclusion relevant to statistical analysis which were made during the data review meeting. All details are included in the corresponding section of the SAP. Slides of presentations used during the meeting are included and commented in the section below.

9.1 DATA REVIEW MEETING BEFORE ANALYSIS

The review has been performed under Protocol Deviation Plan version 2.0 dated 08 March 2023

No patients have been excluded from any of the populations. The following slides were presented during the data review meeting, conclusions are also summarized:

SC103_Database Lock Meeting_Part A

The review of PK data includes derivation of sampling out of window according to Protocol v10 following the derivation: PK blood sampling out of window will be flagged in listing of concentration levels. Note referring to that listing (attached below) will be added to output of CSR reportable PDs. Several values have been assessed as unreliable in Pharmacokinetic concentrations, such values are not to be used for the calculation of PK parameters and descriptive analysis of PK concentrations. Hemolytic samples have been considered as reliable; however, a sensitivity analysis is included in this SAP.

SC103 DRM Listing PK PartA1 20FEB202

Similarly, several values have been excluded from the review of Pharmacodynamic and Cytokine data, along with Immunogenicity, Tumor Biopsy, Genetic PBMC. Derivation of sampling out of window according to Protocol v10 following the derivation: sampling out of window will be flagged in listing of sampling dates and times. Note referring to that listing (attached below) will be added to output of CSR reportable PDs. Further derivation of rules for the exclusion of certain values in the analysis is described below.

SC103_ESP_DRM_PartA1_G28FEB23_ESP

Rules for exclusion of PBMC sample from the analysis (due to changes in dosing such as delays, dose modification, deviations, etc.) as follows.

Applicable to PBMC, all samples and all cycles:

- Any samples taken after a missed (including second doses) or delayed dose will be excluded within the cycle: for example, if C1D2 is not done then any day afterwards within the cycle should be excluded (C1D6, C1D8, ...). Similarly, if second dose on C1D2 is not administered, any day afterwards within the cycle should be excluded (C1D6, C1D8, ...).
  EXCEPT when that delay or deviation is shifting the CXD8 and CXD9 dosing to CXD9 and CXD10 dosing (consecutive) and both doses are administered.
- Any samples taken after a dose reduction or increase will be excluded
- Any dosing performed PRIOR to CXD8 (i.e., deviation) will lead to the exclusion of samples from CXD8 onwards within the cycle.
- Any sample taken with a deviation more than 1 day (>1 day) from the protocol schedule will be excluded

Furthermore, Cycle 3 will not be included in the PK/PD analysis. Only data listed will be provided.

The rules above will also be applied for Cytokines (CK). In addition, for CK, any sample taken outside of the protocol defined window will be excluded.

No data from other sampling (Immunogenicity, Tumor Biopsy, etc.) have been considered as unreliable and/or affected by deviations and no exclusion rules have been created.

10 LIST OF TABLES, FIGURES AND LISTINGS

The table hereunder presents preliminary list of content of tables, figures and listings which will be integrated in study report. The structure and numbering is proposed according the ICH guidelines - E3: Structure and Content of Clinical Study Reports.

10.1 SECTION 10 OF CSR (STUDY PATIENTS)

Selected tables from Section 14.1 of CSR (DEMOGRAPHIC DATA).

This section will cover the following:

- Summary of patient disposition
- Patient disposition by country
- Analysis populations
- Protocol deviations
- Summary of patient demographics and baseline characteristics
- Summary of disease history
- Summary of medical history
- Summary of prior, concomitant, and post-treatment therapies
- Exposure to study medication

10.2 SECTION 11 OF CSR (SAFETY AND PK/PD EVALUATIONS)

Selected tables from Section 14.3 (SAFETY DATA) and Section 14.2 (PK/PD DATA) of CSR.

This section will cover the following:

- DLTs
- Summary of TEAEs
- AE tables by PT within SOC
- Summary of causes of death

This section will cover also pharmacokinetic and pharmacodynamics evaluation.

10.3 SECTION 12 OF CSR (EFFICACY AND OTHER DATA)

Selected tables from Section 14.2 of CSR (EFFICACY AND OTHER DATA).

10.4 SECTION 13 OF CSR (DISCUSSION AND OVERALL CONCLUSIONS)

No tables are planned.

10.5 SECTION 14 OF CSR (TABLES, FIGURES AND GRAPHS REFERRED TO BUT NOT INCLUDED IN THE TEXT)

Output	Number	Title	Analysis Set
	Section 14.1	**Demographic data**	
		Patient disposition	
Table	14.1.1.1	Disposition of patients	All

Output	Number	Title	Analysis Set
Table	14.1.1.2	Disposition of patients by country	All
Table	14.1.1.3	Analysis populations and reasons for exclusion	All
Table	14.1.1.4	Reasons for discontinuation after treatment start	SAF
Table	14.1.1.5	Protocol deviations	SAF, Efficacy
		Baseline characteristics and disease history	
Table	14.1.2.1	Baseline characteristics	SAF, Efficacy, PK/PD
Table	14.1.2.2	Disease history	SAF, Efficacy, PK/PD
		Prior, concomitant, and post-treatment medication	
Table	14.1.3.1	Prior anticancer systemic therapy	SAF
Table	14.1.3.2	Prior anticancer non-systemic therapy	SAF
Table	14.1.3.3	Prior medication	SAF
Table	14.1.3.4	Prior non-pharmacological therapy	SAF
Table	14.1.3.5	Concomitant medication	SAF
Table	14.1.3.6	Concomitant non-pharmacological therapy	SAF
Table	14.1.3.7	Post-treatment medication	SAF
Table	14.1.3.8	Post-treatment non-pharmacological therapy	SAF
Table	14.1.3.9	New anticancer systemic therapy	SAF
Table	14.1.3.10	New anticancer non-systemic therapy	SAF
		Exposure	
Table	14.1.4.1	Exposure to study treatment	SAF
Table	14.1.4.2	SOT101 Dose intensity	SAF
Table	14.1.4.3	Dosing overview, summary of changes from dosing	SAF
	Section 14.2	**Efficacy and PK/PD evaluations**	
		Pharmacokinetics	
Table	14.2.1.1.1	SOT101 concentrations	PK/PD
Table	14.2.1.1.2	SOT101 concentrations	PK/PD (excluding hemolytic samples)
Table	14.2.1.2	SOT101 PK parameters	PK/PD

Output	Number	Title	Analysis Set
Figure	14.2.1.3	Patient profiles of SOT101 concentrations (linear and semi-logarithmic scale)	PK/PD
Figure	14.2.1.4.1	Mean SOT101 concentrations profiles (linear and semi-logarithmic scale)	PK/PD
Figure	14.2.1.4.2	Mean SOT101 concentrations profiles (linear and semi-logarithmic scale)	PK/PD (excluding hemolytic samples)
Table	14.2.1.5.1	Evaluation of dose proportionality	PK/PD
Table	14.2.1.5.2	Evaluation of dose proportionality	PK/PD (excluding hemolytic samples)
		Pharmacodynamics	
CD8+ T Cells			
Table	14.2.2.1	CD8+ Cells of CD3+ Cells (10^9/L): Values and fold increase	PK/PD
Table	14.2.2.2	CD8+ Cells of CD3+ Cells (%): Values and fold increase	PK/PD
Table	14.2.2.3	Ki-67+ Cells of CD8+ (%): Values and fold increase	PK/PD
Figure	14.2.2.4	Mean profiles of Ki-67+ Cells of CD8+ (%) by cohort and All cohorts pooled	PK/PD
CD8+ Memory T Cells			
Table	14.2.2.5	CD45RO+ CD45RA- (Memory) Cells of CD8+ Cells (10^9/L): Values and fold increase	PK/PD
Table	14.2.2.6	CD45RO+ CD45RA- (Memory) Cells of CD8+ Cells (%): Values and fold increase	PK/PD
Table	14.2.2.7	Ki-67+ Cells of CD8+CD45RO+ CD45RA- Cells (%): Values and fold increase	PK/PD
Figure	14.2.2.8	Mean profiles of Ki-67+ Cells of CD8+CD45RO+ CD45RA- Cells (%) by cohort and All cohorts pooled	PK/PD
NKG2D+ Cells (CD8)			
Table	14.2.2.9	NKG2D+ Cells of CD8+ Cells (%): Values and fold increase	PK/PD
Figure	14.2.2.10	Mean profiles of NKG2D+ Cells of CD8+ Cells (%) by cohort and All cohorts pooled	PK/PD
Table	14.2.2.11	NKG2D+ Cells of CD8+ Cells (MFI NKG2D): Values and fold increase	PK/PD

Output	Number	Title	Analysis Set
Figure	14.2.2.12	Mean profiles of NKG2D+ Cells of CD8+ Cells (MFI NKG2D) by cohort and All cohorts pooled	PK/PD
NKG2D+ Cells (CD8 Memory)			
Table	14.2.2.13	NKG2D+ Cells of CD8+ CD45RO+CD45RA- Cells (%): Values and fold increase	PK/PD
Figure	14.2.2.14	NKG2D+ Cells of CD8+ CD45RO+CD45RA- Cells (%) by cohort and All cohorts pooled	PK/PD
Table	14.2.2.15	NKG2D+ Cells of CD8+ CD45RO+CD45RA- Cells (MFI NKG2D): Values and fold increase	PK/PD
Figure	14.2.2.16	NKG2D+ Cells of CD8+ CD45RO+CD45RA- Cells (MFI NKG2D) by cohort and All cohorts pooled	PK/PD
CD4+ T Cells			
Table	14.2.2.17	CD4+ Cells of CD3+ Cells (10^9/L): Values and fold increase	PK/PD
Table	14.2.2.18	CD4+ Cells of CD3+ Cells (%): Values and fold increase	PK/PD
Table	14.2.2.19	Ki-67+ Cells of CD4+ Cells (%): Values and fold increase	PK/PD
Figure	14.2.2.20	Mean profiles of Ki-67+ Cells of CD4+ Cells (%) by cohort and All cohorts pooled	PK/PD
NK Cells			
Table	14.2.2.21	CD3-CD56+ (NK) Cells of CD45+ Live Cells (10^9/L): Values and fold increase	PK/PD
Table	14.2.2.22	CD3-CD56+ (NK) Cells of CD45+ Live Cells (%): Values and fold increase	PK/PD
Table	14.2.2.23	Ki-67+ Cells of CD3-CD56+ (%): Values and fold increase	PK/PD
Figure	14.2.2.24	Mean profiles of Ki-67+ Cells of CD3-CD56+ (%) by cohort and All cohorts pooled	PK/PD
Treg Cells			
Table	14.2.2.25	CD25+Foxp3+ (Treg) Cells of CD4+ Cells (10^9/L): Values and fold increase	PK/PD
Table	14.2.2.26	CD25+Foxp3+ (Treg) Cells of CD4+ Cells (%): Values and fold increase	PK/PD
Table	14.2.2.27	Ki-67+ Cells of CD4+CD25+Foxp3+ (Treg) Cells (%): Values and fold increase	PK/PD
Figure	14.2.2.28	Mean profiles of Ki-67+ Cells of CD4+CD25+Foxp3+ (Treg) Cells (%) by cohort and All cohorts pooled	PK/PD
NKT Cells			

Output	Number	Title	Analysis Set
Table	14.2.2.29	CD3+CD56+ (NKT) Cells of CD45+ Live Cells (10^9/L): Values and fold increase	PK/PD
Table	14.2.2.30	CD3+CD56+ (NKT) Cells of CD45+ Live Cells (%): Values and fold increase	PK/PD
Table	14.2.2.31	Ki-67+ Cells of CD3+CD56+ (NKT) Cells (%): Values and fold increase	PK/PD
Figure	14.2.2.32	Mean profiles of Ki-67+ Cells of CD3+CD56+ (NKT) Cells (%) by cohort and All cohorts pooled	PK/PD
NKG2D+ Cells (NK)			
Table	14.2.2.33	NKG2D+ Cells of CD3-CD56+ (NK) Cells (%): Values and fold increase	PK/PD
Figure	14.2.2.34	Mean profiles of NKG2D+ Cells of CD3-CD56+ (NK) Cells (%) by cohort and All cohorts pooled	PK/PD
Table	14.2.2.35	NKG2D+ Cells of CD3-CD56+ (NK) Cells (MFI NKG2D): Values and fold increase	PK/PD
Figure	14.2.2.36	Mean profiles of NKG2D+ Cells of CD3-CD56+ (NK) Cells (MFI NKG2D) by cohort and All cohorts pooled	PK/PD
Summary of pharmacodynamic activation			
Table	14.2.2.37	Overall activation levels (10^9/L) of selected PD markers in Cycle 1 Day 6	PK/PD
Table	14.2.2.38	Overall activation levels (%) of selected PD markers in Cycle 1 Day 6	PK/PD
Figure	14.2.2.39	Overall activation levels (%) of selected PD markers in Cycle 1 Day 6 (overview)	PK/PD
Figure	14.2.2.40	Overall activation levels (%) of selected PD markers in Cycle 1 Day 6 (specific)	PK/PD
Table	14.2.2.41	Maximum levels of fold increase in cell counts (10^9/L) for selected PD markers	PK/PD
Figure	14.2.2.42	Maximum levels of activation (%) for selected PD markers	PK/PD
		Immunocytokines	
Table	14.2.3.1	Interleukin-2: Values and fold increase	PK/PD
Figure	14.2.3.2	Mean profiles of Interleukin-2 by cohort and All cohorts pooled	PK/PD
Table	14.2.3.3	Interleukin-4: Values and fold increase	PK/PD
Figure	14.2.3.4	Mean profiles of Interleukin-4 by cohort and All cohorts pooled	PK/PD

Output	Number	Title	Analysis Set
Table	14.2.3.5	Interleukin-6: Values and fold increase	PK/PD
Figure	14.2.3.6	Mean profiles of Interleukin-6 by cohort and All cohorts pooled	PK/PD
Table	14.2.3.7	Interleukin-8: Values and fold increase	PK/PD
Figure	14.2.3.8	Mean profiles of Interleukin-8 by cohort and All cohorts pooled	PK/PD
Table	14.2.3.9	Tumor Necrosis Factor Alpha: Values and fold increase	PK/PD
Figure	14.2.3.10	Mean profiles of Tumor Necrosis Factor by cohort and All cohorts pooled	PK/PD
Table	14.2.3.11	Interferon-gamma: Values and fold increase	PK/PD
Figure	14.2.3.12	Mean profiles of Interferon-gamma by cohort and All cohorts pooled	PK/PD
Table	14.2.3.13	Interleukin-1 beta: Values and fold increase	PK/PD
Figure	14.2.3.14	Mean profiles of Interleukin-1 beta by cohort and All cohorts pooled	PK/PD
Table	14.2.3.15	Interleukin-10: Values and fold increase	PK/PD
Figure	14.2.3.16	Mean profiles of Interleukin-10 by cohort and All cohorts pooled	PK/PD
Table	14.2.3.17	Interleukin-12p70: Values and fold increase	PK/PD
Figure	14.2.3.18	Mean profiles of Interleukin-12p70 by cohort and All cohorts pooled	PK/PD
		Efficacy data	
Table	14.2.4.1	Duration of follow-up	SAF
Figure	14.2.4.2	Kaplan-Meier curve of duration of follow-up	SAF
Figure	14.2.4.3	Disease response since the first SOT101 administration per patient	SAF
Table	14.2.4.4	Tumor response (overall response rate and clinical benefit rate) as per iRECIST	Efficacy
Figure	14.2.4.5	Best change from baseline in tumor size per patient	Efficacy
Table	14.2.4.6	Duration of response as per iRECIST (iDoR)	Efficacy
Figure	14.2.4.7	Kaplan-Meier curve of iDoR as per iRECIST	Efficacy
Table	14.2.4.8	Progression free survival as per iRECIST (iPFS)	Efficacy
Figure	14.2.4.9	Kaplan-Meier curve of iPFS as per iRECIST	Efficacy
Table	14.2.4.10	Overall survival	Efficacy

Output	Number	Title	Analysis Set
Figure	14.2.4.11	Kaplan-Meier curve of overall survival	Efficacy
	Section 14.3	**Safety data**	
		DLT and TEAEs	
Table	14.3.1.1	Summary of dose limiting toxicity (DLT)	DLT evaluable
Table	14.3.2.1	Summary of Treatment-Emergent Adverse Events	SAF
Table	14.3.2.2	Summary of Treatment-Emergent Serious Adverse Events	SAF
Table	14.3.2.3	Summary of Treatment-Emergent Adverse Events by cycle	SAF
Table	14.3.2.4	Summary of Treatment-Emergent Serious Adverse Events by cycle	SAF
Table	14.3.3.1	Treatment-Emergent Adverse Events by MedDRA PT and primary SOC	SAF
Table	14.3.3.2	Treatment-Emergent Adverse Events by MedDRA PT and primary SOC reported in $\geq$10% of patients	SAF
Table	14.3.3.3	Non-serious Treatment-Emergent Adverse Events by MedDRA PT and primary SOC reported in $\geq$5% of patients	SAF
Table	14.3.3.4	Treatment-Emergent Adverse Events by MedDRA PT	SAF
Figure	14.3.3.5	Treatment-Emergent Adverse Events by MedDRA PT and Grade	SAF
Figure	14.3.3.6	Treatment-Emergent Adverse Events by MedDRA PT and Action Taken	SAF
Table	14.3.3.7	Treatment-Emergent Serious Adverse Events by MedDRA PT and primary SOC	SAF
Table	14.3.3.8	Fatal Treatment-Emergent Adverse Events by MedDRA PT and primary SOC	SAF
Table	14.3.3.9	Grade 3, 4, 5 Treatment-Emergent Adverse Events by MedDRA PT and primary SOC	SAF
Table	14.3.3.10	Immune-related Treatment-Emergent Adverse Events by MedDRA PT and primary SOC	SAF
Table	14.3.3.11	Treatment-Emergent Adverse Events leading to SOT101 dose modification by MedDRA PT and primary SOC	SAF
Table	14.3.3.12	Treatment-Emergent Adverse Events leading to SOT101 temporary discontinuation by MedDRA PT and primary SOC	SAF

Output	Number	Title	Analysis Set
Table	14.3.3.13	Treatment-Emergent Adverse Events leading to SOT101 permanent discontinuation by MedDRA PT and primary SOC	SAF
Table	14.3.3.14	Treatment Emergent Adverse Events symptoms of Cytokine release syndrome by MedDRA PT and primary SOC	SAF
Table	14.3.3.15	Treatment Emergent Adverse Events by MedDRA PT and Maximum CTCAE Grade	SAF
Table	14.3.4.1	Underlying causes of deaths by MedDRA PT and primary SOC	SAF
	Section 14.4	**Clinical Laboratory data**	
		Liver enzyme values	
Table	14.4.1.1	Total Bilirubin (µmol/L): Values, relative and absolute changes from baseline	SAF
Figure	14.4.1.2	Mean profile of Total Bilirubin (µmol/L) by cohort and All cohorts pooled	SAF
Figure	14.4.1.3	Patient profiles of Total Bilirubin (µmol/L) for RP2D and RP2D-1 cohorts (excluding the MTD)	SAF
Table	14.4.2.1	Alanine Transaminase (ALT) (µkat/L): Values, relative and absolute changes from baseline	SAF
Figure	14.4.2.2	Mean profile of Alanine Transaminase (ALT) (µkat/L) by cohort and All cohorts pooled	SAF
Figure	14.4.2.3	Patient profiles of Alanine Transaminase (ALT) (µkat/L) for RP2D and RP2D-1 cohorts (excluding the MTD)	SAF
Table	14.4.3.1	Aspartate Transaminase (AST) (µkat/L): Values, relative and absolute changes from baseline	SAF
Figure	14.4.3.2	Mean profile of Aspartate Transaminase (AST) (µkat/L) by cohort and All cohorts pooled	SAF
Figure	14.4.3.3	Patient profiles of Aspartate Transaminase (AST) (µkat/L) for RP2D and RP2D-1 cohorts (excluding the MTD)	SAF
Table	14.4.4.1	Alkaline Phosphatase (ALP) (µkat/L): Values, relative and absolute changes from baseline	SAF
Figure	14.4.4.2	Mean profiles of Alkaline Phosphatase (ALP) (µkat/L) by cohort and All cohorts pooled	SAF
Figure	14.4.4.3	Patient profiles of Alkaline Phosphatase (ALP) (µkat/L) for RP2D and RP2D-1 cohorts (excluding the MTD)	SAF
Table	14.4.4.4	Hepatic function (Hy's law)	SAF

Output	Number	Title	Analysis Set
Figure	14.4.4.5	Maximal levels per patient of Total Bilirubin (µmol/L), Alanine Transaminase (ALT) (µkat/L), Aspartate Transaminase (AST) (µkat/L), and Alkaline Phosphatase (ALP) (µkat/L) by cohort	SAF
		Other laboratory values	
Table	14.4.5.1	Haemoglobin (g/L): Values, relative and absolute changes from baseline	SAF
Figure	14.4.5.2	Mean profile of Haemoglobin (g/L) by cohort and All cohorts pooled	SAF
Table	14.4.6.1	Neutrophils (10^9/L): Values, relative and absolute changes from baseline	SAF
Figure	14.4.6.2	Mean profile of Neutrophils (10^9/L) by cohort and All cohorts pooled	SAF
Table	14.4.7.1	Neutrophils (%): Values and absolute changes from baseline	SAF
Figure	14.4.7.2	Mean profile of Neutrophils (%) by cohort and All cohorts pooled	SAF
Table	14.4.8.1	Lymphocytes (10^9/L): Values, relative and absolute changes from baseline	SAF
Figure	14.4.8.2	Mean profile of Lymphocytes (10^9/L) by cohort and All cohorts pooled	SAF
Table	14.4.9.1	Lymphocytes (%): Values and absolute changes from baseline	SAF
Figure	14.4.9.2	Mean profile of Lymphocytes (%) by cohort and All cohorts pooled	SAF
Table	14.4.10.1	Lactate Dehydrogenase (LDH) (ukat/L): Values, relative and absolute changes from baseline	SAF
Figure	14.4.10.2	Mean profile of Lactate Dehydrogenase (LDH) (ukat/L) by cohort and All cohorts pooled	SAF
Table	14.4.11.1	Platelet count (10^9/L): Values, relative and absolute changes from baseline	SAF
Figure	14.4.11.2	Mean profile of Platelet count (10^9/L) by cohort and All cohorts pooled	SAF
Table	14.4.12.1	C-reactive protein (CRP) (mg/L): Values, relative and absolute changes from baseline	SAF
Figure	14.4.12.2	Mean profile of C-reactive protein (CRP) (mg/L) by cohort and All cohorts pooled	SAF

Output	Number	Title	Analysis Set
	Section 14.5 Vital Signs		
Table	14.5.1.1	Systolic blood pressure (mmHg): Values and absolute changes from baseline	SAF
Figure	14.5.1.2	Mean profile of Systolic blood pressure (mmHg) by cohort and All cohorts pooled	SAF
Table	14.5.2.1	Diastolic blood pressure (mmHg): Values and absolute changes from baseline	SAF
Figure	14.5.2.2	Mean profile of Diastolic blood pressure (mmHg) by cohort and All cohorts pooled	SAF
Table	14.5.3.1	Heart rate (beats/min): Values and absolute changes from baseline	SAF
Figure	14.5.3.2	Mean profile of Heart rate (beats/min) by cohort and All cohorts pooled	SAF
Table	14.5.4.1	Respiratory rate (breaths/min): Values and absolute changes from baseline	SAF
Figure	14.5.4.2	Mean profile of Respiratory rate (breaths/min) by cohort and All cohorts pooled	SAF
Table	14.5.5.1	Body temperature (Celsius (°)): Values and absolute changes from baseline	SAF
Figure	14.5.5.2	Mean profile of Body temperature (Celsius (°)) by cohort and All cohorts pooled	SAF
	Section 14.6 ECG		
Table	14.6.1.1	QT [ms]: Values, relative and absolute changes from baseline	SAF
Table	14.6.2.1	QTcF [ms]: Values, relative and absolute changes from baseline	SAF
Figure	14.6.2.2	Mean profile of QTcF [ms] by cohort and All cohorts pooled	SAF
Table	14.6.3.1	QTcF [ms]: Frequency of Intervals	SAF
	Section 14.7 ECOG		
Table	14.7.1	ECOG performance status	SAF
	Section 14.8 Immunogenicity		
Table	14.8.1	Anti-drug Antibodies	SAF

Output	Number	Title	Analysis Set
Table	14.8.2	Titration of anti-drug Antibodies	SAF
Table	14.8.3	Neutralizing anti-drug Antibodies	SAF

10.6 APPENDIX 16.2 OF CSR (PATIENT DATA LISTINGS)

All patients included in clinical database will be listed (if not specified otherwise).

Listing Number	Title
Section 16.2.1	**Discontinued patients**
16.2.1.1	Study dates and patients' discontinuation overview in treated patients
16.2.1.2	Screening failures and withdrawals prior study treatment start
Section 16.2.2	**Protocol Deviations**
16.2.2.1	CSR reportable protocol deviations
16.2.2.2	CSR not reportable protocol deviations
16.2.2.3	Eligibility criteria and eligibility verification
16.2.2.4	Protocol deviations related to COVID-19
Section 16.2.3	**Patients excluded from efficacy analysis**
16.2.3.1	Disposition of patients to analysis sets and reasons for exclusion
Section 16.2.4	**Demographic data**
16.2.4.1	Informed consent signatures
16.2.4.2	Demographic data, patients' characteristics and disease history details
16.2.4.3	Medical history
16.2.4.4	Medical history – MedDRA coding details
16.2.4.5	Previous medication
16.2.4.6	Prior medication (including WHODD coding)
16.2.4.7	Prior anticancer systemic therapy (including WHODD coding)
16.2.4.8	Prior anticancer non-systemic therapy (including MedDRA coding)
16.2.4.9	Concomitant medication
16.2.4.10	Concomitant medication (including WHODD coding)
16.2.4.11	Post-treatment medication
16.2.4.12	Post-treatment medication (including WHODD coding)
16.2.4.13	Prior non-pharmacological therapy (including MedDRA coding)
16.2.4.14	Concomitant non-pharmacological therapy (including MedDRA coding)
16.2.4.15	Post-treatment non-pharmacological therapy (including MedDRA coding)
16.2.4.16	New anticancer systemic therapy (including WHODD coding)

Listing Number	Title
16.2.4.17	New anticancer non-systemic therapy (including MedDRA coding)
Section 16.2.5	**Compliance and drug concentration data**
16.2.5.1	Exposure to SOT101
16.2.5.2	SOT101 Dose intensity
16.2.5.3	Body weight and compliance of study drug administration with Study Protocol
16.2.5.4	SOT101 concentration levels
16.2.5.5	SOT101 pharmacokinetic parameters
Section 16.2.6	**Individual efficacy response and pharmacodynamics data**
16.2.6.1	Tumor assessment
16.2.6.2	Disease response
16.2.6.3	Clinical progression
16.2.6.4	Pharmacodynamics markers and cytokine levels
16.2.6.5	Maximal levels of Cytokines
Section 16.2.7	**Adverse events listings**
16.2.7.1	Listing of DLT events
16.2.7.2	All treatment-emergent AEs
16.2.7.3	All treatment-emergent SAEs
16.2.7.4	Treatment-emergent AEs recorded in detailed description of dose limiting toxicities
16.2.7.5	All adverse events leading to death
16.2.7.6	Causes of death including MedDRA coding details
16.2.7.7	Treatment-emergent AEs leading to permanent discontinuation of SOT101
16.2.7.8	Treatment-emergent AEs leading to permanent discontinuation of pembrolizumab
16.2.7.9	Treatment-emergent AEs with suspected causal relationship with SOT101
16.2.7.10	Treatment-emergent AEs with suspected causal relationship with pembrolizumab
16.2.7.11	Treatment-emergent AE immune-related
16.2.7.12	Treatment-emergent clinical signs/symptoms of cytokine release syndrome
16.2.7.13	Adverse events started before the first study drug administration
16.2.7.14	Adverse events with missing or partial start date
16.2.7.15	Adverse events – MedDRA coding details
Section 16.2.8	**Listing of individual laboratory measurements**

Listing Number	Title
16.2.8.1	Hematology
16.2.8.2	Biochemistry
16.2.8.3	Coagulation
16.2.8.4	Urinalysis
16.2.8.5	Maximal levels of selected laboratory variables
16.2.8.6	Creatinine clearance levels
16.2.8.7	Thyroid function tests (TSH, free T3, free T4)
16.2.8.8	Cardiac troponin-T test
16.2.8.9	C-reactive protein (CRP) levels
16.2.8.10	Glycated hemoglobin (HbA1c)
16.2.8.11	24-hour urine protein test
16.2.8.12	Pregnancy test
16.2.8.13	Serology (HIV, hepatitis B and C tests)
16.2.8.14	Listing of abnormal laboratory results
Section 16.2.9	**Other safety data**
16.2.9.1	Vital signs
16.2.9.2	ECG results
16.2.9.3	Echocardiography results
16.2.9.4	Date of physical examination
Section 16.2.10	**Other data**
16.2.10.1	ECOG performance score
16.2.10.2	Immunogenicity

11 LAYOUT REQUIREMENTS OF TFLs

No layout requirements specified by the sponsor.

12 APPENDICES

12.1 PHARMACOKINETIC ANALYSIS PLAN

N-A-PH1-19-027_SC 103_Pharmacokineti

12.2 TIMEPOINT LABELS SPECIFICATIONS

For vital signs: Pre-dose, 15 min, 30 min, 1 h, 2 h, 3 h, 4 h, 5 h, 6 h, 7 h, 8 h will be used as per eCRF records. In the listings also real time since SOT101 administration will be presented. In the Follow-up period (Follow-up) the timepoints will be presented as EOT + X weeks as defined in the Study Protocol. Timepoints post 2nd dose of SOT101 will be labeled using "2nd dose".

For electrocardiogram (ECG): Pre-dose, 4h will be used as per eCRF records. In the listings also real time since SOT101 administration will be presented. At EOT visit, the timepoint will be presented as EOT as defined in the Study Protocol. Timepoints post 2nd dose of SOT101 will be labeled using "2nd dose".

For PK and/or Cytokine blood sampling: Pre-dose, 1 h, 2 h, 4h, 6h, 8 h, 9 h, 10 h, 12 h, 16 h, 20 h, 24 h will be used as per eCRF records. In the listings also real time since SOT101 administration will be presented. Timepoints post 2nd dose of SOT101 will be marked in the outputs.

For safety laboratory: as per standard medical practice the safety laboratory should be performed before the dosing then the label will be Cycle X Day Y – Pre-dose; otherwise, just Cycle X Day Y will be presented except in EOT visit which will be presented as EOT as defined in the Study Protocol.

Other assessments (Physical examination, body weight and Eastern Cooperative Oncology Group (ECOG) performance status) will be presented using the Cycle X Day Y label, except in the Follow-up period (Follow-up) where the label will be EOT + X weeks as defined in the Study Protocol.

In the listings, "UNS" will be added into assessments performed in addition to assessment planned in the Study Protocol, for example ScreeningUNS for some not required at screening by the Study Protocol or repeated assessment at screening, Follow-up UNS for hematologic assessment or Cycle 1 Day 9UNS for coagulation assessment or Cycle 1 Day 12UNS.

Time-points labels of tumor assessment: Tumor assessment will be recorded into eCRF as repeated pages and will be analyzed as iORR, iCBR, and time to event data. Therefore, time-point labels for tables will not be needed. In the listings the assessments will be identified by date, real treatment week (as defined in section 6.2, rounded to one decimal), and period label ("Cycle X" derived as defined below) or "Follow-up".

Cycle derivation:

- For each cycle will be identified Day 1 (as per eCRF records) and end of cycle as defined in section 5.1.

- Then, it will be identified which cycle the assessment date belongs to.

Time-points labels for survival follow-up information: The similar approach as for tumor assessment will be applied. Time-point labels for tables will not be needed. In the listings the information will be identified by date, real treatment week, and label "Follow-up".

Time-point labels used in tables of adverse events:

The tables of adverse events will present summary of treatment-emergent adverse events (TEAEs) recorded during the study and TEAEs depending on the time period:

- Cycle X: the time-point label will indicate treatment cycle when the adverse event (AE) started
- After last: the time-point label will indicate AEs started after end of last cycle

See treatment cycle definition in the section 5.1 above. Treatment cycle when TEAE started will only be derived for AEs with complete (and non-missing) start dates.

12.3 CANCER TYPE DERIVATION

Histological type	Primary tumor location	Cancer type (long name)	Cancer type (short name)
poorly differentiated	Cervix uteri	Cervix uteri	Cervix uteri
clear cell carcinoma	Kidney	Kidney	Kidney
Adenocarcinoma	Stomach	Gastric	Gastric
squamous cell carcinoma	Anus	Anal SCC	Anal SCC
high grade serous	Ovarian	Ovarian	Ovarian
Small Cell Lung Carcinoma	Lung	Small-cell Lung	SCLC
triple-negative breast	Breast	Triple-negative breast	TNBC
invasive cholangiocellular	Biliary tract	Biliary tract	Biliary tract

13 REFERENCES

[1] Seymour L, Bogaerts J, Perrone A, Ford R, Schwartz LH, Mandrekar S, Lin NU, Litière S, Dancey J, Chen A, Hodi FS, Therasse P, Hoekstra OS, Shankar LK, Wolchok JD, Ballinger M, Caramella C, de Vries EGE, group Rw. iRECIST: guidelines for response criteria for use in trials testing immunotherapeutics. The Lancet Oncology. 2017;18(3):e143-e152. ICH guidelines - E9: Statistical Principles for Clinical Trials, Adopted in EU by CPMP, March 1998, issued as CPMP/ICH/363/96

[2] ICH guidelines - E3: Structure and Content of Clinical Study Reports, Adopted in EU by CPMP, December 95, issued as CPMP/ICH/137/95

[3] U.S. Food and Drug Administration. E14 clinical evaluation of QT/QTc interval prolongation and proarrhythmic potential for non-antiarrhythmic drugs: Guidance for industry. 2018; https://www.fda.gov/downloads/Drugs/GuidanceComplianceRegulatoryInformation/Guidances/ucm073153.pdf. Accessed October 22, 2018.

[4] Smith BP, Vandenhende FR, deSante KA, et al (2000)., Confidence Interval Criteria for Assessment of Dose proportionality. Pharmaceutical Research, 17:1278-1283.

[5] Zhou, J., J. Li, and B. Coate. 2006. Empirical Power Estimation for Phase I Dose Proportionality Studies Based on Power-Law Model Using Confidence Interval Criteria. In SUGI 31, San Francisco, California.

[6] SAS 9.4; 2008 by SAS Institute Inc., Cary, NC, USA; OnLine Doc.

Statistical Analysis Plan
Study Part B

A multicenter open-label phase 1/1b study to evaluate the safety and preliminary efficacy of SO-C101 as monotherapy and in combination with pembrolizumab in patients with selected advanced/metastatic solid tumors.

Sponsor:	SOTIO Biotech AG
Study code:	SC103
EudraCT number:	2018-004334-15
VERSION:	Final 1.0
DATE:	08-APR-2024

STATISTICAL ANALYSIS PLAN APPROVAL

We, the undersigned, confirm that we have read and are in agreement with the contents of this document.

NAME	[redacted]	
JOB TITLE		
SIGNATURE		
DATE		
NAME		
JOB TITLE		
SIGNATURE		
DATE		
NAME		
JOB TITLE		
SIGNATURE		
DATE		
NAME		
JOB TITLE		
SIGNATURE		
DATE		

TABLE OF CONTENTS

ABBREVIATIONS

ADA	Anti-drug antibodies
AE	Adverse Event
ALP	Alkaline Phosphatase (ALP)
ALT	Alanine Transaminase
AST	Aspartate Transaminase
ATC	Anatomic, Therapeutic, Chemical (Classification System for Drugs)
AUC	Area under the plasma concentration-time curve
$AUC_{(0\text{-}inf)}$	Area under the plasma concentration-time curve from time zero to infinity
$AUC_{(0\text{-}t)}$	Area under the plasma concentration-time curve from time zero to time t
BLQ	Below Limit of Quantification
CBR	Clinical Benefit Rate
CD	Cluster of differentiation (cells)
CI	Confidence Interval
CK	Cytokines
CL	Apparent total body clearance of the drug from plasma
C_{max}	Maximum (or peak) serum concentration
CPI	Check Point Inhibitors
CRF	Case Report Form
CRP	C-Reactive Protein
CSR	Clinical Study Report
CV	Coefficient of Variation
DB	Database
DBL	Database lock
DEC	Dose Escalation Committee
DEM	Dose Escalation Meeting
DLT	Dose Limiting Toxicity
DOR	Duration of Response
ECG	Electro-cardiogram
ECOG	Eastern Cooperative Oncology Group
eCRF	Electronic Case Report Form
EOT	End of Treatment
FU	Follow-up
HLGT	High Group Level Term
HLT	High Level Term
IAP	Independent Advisory Panel
ICF	Informed Consent Form
ICH	International Conference of Harmonization
iCBR	(immune) Clinical Benefit Rate (based on response as per iRECIST)
iCPD	(immune) Confirmed Progression Disease (as per iRECIST)

iCR	(immune) Complete Response (as per iRECIST)
ID	(Patient) Identification Number
iDOR	(immune) Duration of Response (based on response as per iRECIST)
IMP	Investigational Medicinal Product
iORR	(immune) Overall Response Rate (based on response as per iRECIST)
iPFS	(immune) Progression Free Survival (as per iRECIST)
iPR	(immune) Partial Response (as per iRECIST)
iRECIST	(immune-based) Response Evaluation Criteria in Solid Tumors
iSD	(immune) Stable Disease (as per iRECIST)
iUPD	(immune) Unconfirmed Progression Disease (as per iRECIST)
IV	Intravenous
KM	Kaplan-Meier
LDH	Lactate Dehydrogenase
LLT	Lowest Level Term
Max	Maximum
MedDRA	Medical Dictionary for Regulatory Activities
Min	Minimum
MTD	Maximal Tolerated Dose
NCI CTCAE	National Cancer Institute Common Terminology Criteria for Adverse Events
NK	Natural Killer (cell)
NKT	Natural killer T (cell)
ORR	Objective Response Rate
OS	Overall Survival
PBMC	Peripheral Blood Mononuclear Cell
PD	Pharmacodynamic
PK	Pharmacokinetic
PT	Preferred Term
Q1	Lower Quartile
Q3	Upper Quartile
QT	QT interval
QTcF	Fridericia's correction of QT interval
R_{ac}	Accumulation ratio
RP2D	Recommended Phase 2 dose
SAE	Serious Adverse Event
SAF	Safety Set
SAP	Statistical Analysis Plan
SAS	Statistical Analysis Systems
SOC	System Organ Class
StD	Standard Deviation
$t_{1/2}$	Elimination half-life (to be used in one-or noncompartmental model)
$t_{1/2\alpha}$	Initial or disposition half-life
TEAE	Treatment-emergent Adverse Events
TFLs	Tables, Figures and Listings

T_{max}	Time to reach maximum (peak) plasma concentration following drug administration
Treg	Regulatory T (cells)
ULN	Upper limit of Normal
V_d	Apparent volume of distribution
WHODrugD	World Health Organizations Drug Dictionary
λ_z	Termination elimination constant (symbol k_e is also used)

INTRODUCTION

Statistical evaluation of each SC103 study (AURELIO-03) part will be performed separately after lock of the relevant study part data in clinical database. This Statistical Analysis Plan (SAP) describes the statistical analyses and planned outputs for Study Part B. It includes definition of objectives and endpoints as per Study Protocol, the definition of analysis sets, and details needed for statistical programming. The SAP outlines the tables, listings and figures (TFLs) to be compiled in the Clinical Study Report (CSR).

This SAP does not include pharmacokinetic analysis plan. SO (previously SO-C101, RLI-15) concentrations levels are measured by [redacted] who are also responsible for pharmacokinetic analysis and for writing pharmacokinetic analysis plan. This SAP does not include plan of statistical analysis to be performed on biomarkers collected from tumor tissue samples as collected data are limited and this analysis is intended to be fully exploratory.

This SAP is written according to the SC103 Study Protocol version 10.0 dated on 29-JUL-2021, current Mock Case Report Form (CRF), DEC charter version 4.0 dated on 26-MAR-2021, and IAP charter version 3.0 dated on 30-MAR-2021. The analyses and outputs closely follow the ICH guidelines for industry on topic E3 (Structure and Content of Clinical Study Reports) and E9 (Statistical Principles for Clinical Trials). Patients that crossover from Part A to Part B have been analyzed under Part A SAP and will not be considered in this SAP. Therefore, this SAP outlines the analysis of patients that were exclusively enrolled to Part B. Please refer to Part A SAP for details about the analysis on crossover patients.

DOCUMENT HISTORY

Version	Date	Description of change	Performed by
Draft 0.1	11-MAR-2024	First version of the document created based on SAPs for Part A and Part B1.	[redacted]
Draft 0.2	04-APR-2024	Reviewed by GCP Services and shared internally	
Final 1.0	08-APR-2024	Addressed and implemented feedback from GCP Services	

1 PLANNED CHANGES FROM STUDY PROTOCOL

In study protocol version 10.0, dated 29-JUL-2021, SO-C101 is specified in “Investigational medicinal products”. Throughout this SAP, SOT101 is used instead of SO-C101.

2 STUDY OBJECTIVES

2.1 PART B - SOT101 COMBINATION THERAPY

2.1.1 Primary objectives

- To assess the safety and tolerability of SOT101 when combined with pembrolizumab.
- To determine the maximal tolerated dose (MTD) and/or recommended Phase 2 dose (RP2D) of SOT101 when combined with pembrolizumab.

2.1.2 Secondary objectives

- To characterize the pharmacokinetics (PK) of SOT101 when combined with pembrolizumab.
- To characterize the pharmacodynamics (PD) of SOT101 in peripheral blood when combined with pembrolizumab.
- To determine the preliminary efficacy of the combination of SOT101 with pembrolizumab as measured by overall response rate (ORR), duration of response (DOR), clinical benefit rate (CBR), and progression-free survival (PFS) according to iRECIST
- To determine the immunogenicity of SOT101 when combined with pembrolizumab.

According to iRECIST terminology, responses assigned using iRECIST have a prefix of “i” (“i” stands for immune); therefore, abbreviations iORR, iDOR, iCBR, iPFS will be used afterwards.

2.1.3 Exploratory objectives

- To explore the mechanistic effects of SOT101 in combination with pembrolizumab on selected immune cell populations in tumor tissue samples. Analysis of this exploratory objective is not described in this SAP, instead, a separate Biomarker analysis plan will be prepared.
- To assess overall survival (OS)

3 STUDY DESIGN

Study design is briefly described below. Full description of study design is included in the Study Protocol. The schedule of procedures and assessments is presented in the Study Protocol Table 9.6 to 9.17.

3.1 DEFINITION OF MTD/RP2D AND IMPLEMENTATION OF 3+3 DOSE ESCALATION DESIGN

Part B will start once monotherapy SOT101 dose level 5 (6.0 µg/kg) in Part A is completed and deemed safe. The starting dose of Part B will be Part A dose level 3 (1.5 µg/kg) which will be combined with a fixed dose of pembrolizumab (200 mg intravenously [IV] every 3 weeks).

MTD is defined as the dose level associated with ≥33% of DLT evaluable patients experiencing a DLT. If the MTD is reached, the RP2D will be conventionally defined as the dose level just below this non-tolerated dose level. If the MTD is not reached, the RP2D will be selected based on integrated evaluation of safety, tolerability, clinical benefit, PK and PD data, for all dose levels tested.

The 3+3 dose escalation design to identify MTD/RP2D includes the following steps for each dose level until MTD/RP2D is identified:

1. One patient will be enrolled and will receive the first four doses of SOT101 (day 1, day 2, day 8, and day 9) together with a fixed dose of pembrolizumab (200 mg IV every 3 weeks) given with the first administration of SOT101 on day 1. This patient will be observed for safety for 7 days after the fourth dose of SOT101, starting from day 9.
    - If there are no safety concerns at the end of these 7 days, second and third patients will be allowed to be dosed. The second and third patients will not be dosed on the same day.
    - Otherwise, dose escalation meeting (DEM) will be organized and DEC/IAP will decide next steps.
2. Next steps will depend on the occurrence of DLT within the DLT evaluation period of 21 days:
    - If **no DLT occurs** in 3 DLT evaluable patients, then next patient cohort treated with **higher dose level will start**.
    - If **one DLT occurs** in 3 DLT evaluable patients, then the cohort will be **extended to 6 DLT evaluable patients in total**.
        - If **one DLT occurs** in the 6 DLT evaluable patients, then the next patient cohort treated with **higher dose level start**.
        - If **≥2 DLT occur** in the 6 DLT evaluable patients, then MTD is identified and **enrolment/escalation is stopped**.
    - If **≥2 DLT occur** in 3 DLT evaluable patients, then MTD is identified **and enrolment/escalation is stopped**.

3.2 RANDOMIZATION AND BLINDING

Not applicable.

4 STUDY ENDPOINTS

4.1 DEMOGRAPHY AND BASELINE CHARACTERISTICS TO BE SUMMARIZED

The following baseline characteristics will be summarized in the tables:

- Demographic characteristics:
  - Age at informed consent (ICF) signature [years]
  - Age at informed consent (ICF) signature [years] according to: <18 years, >18 and ≤64 years, >64 and ≤84, >84 or older
  - Gender
  - Ethnicity
  - Race
- Baseline characteristics
  - Weight [kg]
  - Body Mass Index (derived) [kg/m^2]
- Disease history
  - Primary tumor location
  - Histological type
  - Cancer type (derived)
  - Time since diagnosis at ICF signature (derived) [years]
  - Time since latest radiological or clinical disease progression at ICF signature (derived) [weeks]
  - Number of lines of previous systemic anticancer therapy
  - Number of lines of previous systemic anticancer therapy categories: ≤ 2, > 2.
  - Previous treatment with check point inhibitors (CPI) (Yes/ No/ Unknown)
  - CPI Response (if CPI received) (Refractory/ Relapsed/ Unknown)
  - Prior anticancer non-systemic therapy (Yes/ No)
  - ECOG
  - ECOG categories: 0, > 0

4.2 ENDPOINTS

4.2.1 Primary endpoints

- Safety and tolerability of SOT101 combined with pembrolizumab as evaluated by the incidence of DLTs, incidence of SOT101-related adverse events (AEs), SAEs, AEs leading to premature discontinuation of SOT101, deaths, and clinical laboratory test abnormalities.
- Further, endpoints of the study are to determine MTD and the RP2D of SOT101 combined with pembrolizumab (as defined in the section 3.1).

4.2.2 Secondary endpoints

- PK of SOT101 combined with pembrolizumab
- Immune response after administration of SOT101 in combination with pembrolizumab characterized by the changes in expression of immune markers in PBMCs
- iORR, iDOR, iCBR, and iPFS
- Detection of anti-drug antibodies (ADA)

4.2.3 Exploratory endpoints

- Changes in the expression of immune biomarkers after administration of SOT101 in combination with pembrolizumab as compared to baseline in tumor tissue (analysis of this endpoint is not described in this SAP).
- OS at 6 months after the EOT visit.

5 COMMON DEFINITIONS

General and common definition relevant for statistical analysis/ Statistical Analysis Systems (SAS) programming are listed below. Definitions used only in analysis of a particular endpoint are included directly in analysis section.

5.1 TREATMENT CYCLE

Each treatment cycle in Part B should include 4 SOT101 administrations and should take 21 days as per Study Protocol. However, treatment interruptions and delays can occur. Therefore, the cycle number will be taken from the electronic CRF (eCRF) database.

Throughout this SAP, start of study treatment is defined as the date of first SOT101 or pembrolizumab administration, whichever occurs first. The end of study treatment refers to the date of the last SOT101 or pembrolizumab administration, whichever occurs last.

The start of each cycle is defined by the date of the first SOT101 or pembrolizumab administration in the cycle, whichever occurs first.

The cycle lasts until Day 1 of the next cycle. The last cycle end is defined as Day 21 of the last cycle or end of the study participation (whatever occurs first).

5.2 LABELS USED IN SAP AND IN STATISTICAL OUTPUTS

EOT stands for end of treatment. FU stands for follow-up.

Cohort labels will include number of dose level (and dose administered µg/kg) as per Study Protocol. The label will be based on information recorded in eCRF in "Initial dose of SOT101 (ug/kg)".

- Example: 1 (1.5 µg/kg).

Individual time-points labels will be as follows:

- Screening
- Cycle X Day Y
    - Cycles will be identified by the number of the cycle as per eCRF data.
    - Days will be identified by the number of the day as per eCRF data.
- EOT
- EOT + X weeks, see below

The assignment to the time-point labels will be performed via SAS programming as follows:

- If Date of assessment – date of EOT ≤ 4+2 weeks then label = "EOT + 4 weeks"
- If 6 weeks < Date of assessment – date of EOT ≤ 8+2 then label = "EOT + 8 weeks"
- If 10 weeks < Date of assessment – date of EOT ≤ 12+2 then label = "EOT + 12 weeks", etc.

If two assessments are assigned to the same time-point label, the earliest assessment will be selected. In such case, the tables or summaries will contain a footnote specifying the case.

In the listings, the real post-treatment week (see section 6.2, rounded to one decimal) will be presented as well.

Timepoint labels used in the statistical outputs and derivations are described in the Appendix, Section 12.2.

5.3 BASELINE VALUES

5.3.1 Study baseline

Study baseline will be defined as the last non-missing measurement prior to start of study treatment, unless specified otherwise.

5.3.2 Handling of missing data needed for baseline identification

The definitions above consider date and time of the assessment and start of study treatment. If time is not known, then only dates will be used for identification of the baseline. Safety laboratory samples are supposed to be taken before study drug administration; therefore, if time of sample collection is not known and date is the same as date of administration then it will be considered as pre-dose sample.

Values which are identified as baseline via rule described in this paragraph will be flagged in the listings.

5.4 CODED TERMS AND DICTIONARIES USED

Data will be coded as described in the following table.

Table 3: Data to be coded

eCRF page name	Variable to be coded (Dictionary to be used for coding)
The previous therapies include the following pages:	
PRIOR ANTICANCER SYSTEMIC THERAPY	Medication (WHODD)
PRIOR ANTICANCER NON-SYSTEMIC THERAPY	Location and Surgery description (MedDRA)
Further, details about prior and concomitant medication/therapies will be collected on the following pages:	
MEDICATION DETAILS	Medication (WHODD)
NON-PHARMACOLOGICAL THERAPY DETAILS	Therapy (MedDRA)
NEW ANTICANCER SYSTEMIC THERAPY DETAILS	Medication (WHODD)
NEW ANTICANCER NON-SYSTEMIC THERAPY DETAILS	Location and Surgery description (MedDRA)
MEDICAL HISTORY DETAILS	Medical history term (MedDRA)
ADVERSE EVENT DETAILS	Adverse event term (MedDRA)
DEATH	Immediate cause of death and Underlying cause of death (MedDRA)

The coding will be performed directly in eCRF system. The terms will be coded with the most current version of Medical Dictionary for Regulatory Activities (MedDRA) and WHODD dictionaries at time of DB lock.

All MedDRA and WHODD levels listed below will be presented in the listings. Those used in the tables are underlined.

MedDRA coding levels will include:

- Preferred Term (PT)
- Lowest Level Term (LLT)
- High Level Term (HLT)
- High Group Level Term (HLGT)

- Primary System Organ Class (SOC)

WHODD coding will include the following Anatomic, Therapeutic, Chemical (ATC) levels:

- ATC Level 1: anatomical main group
- ATC Level 2: therapeutic subgroup
- ATC Level 3: pharmacological subgroup
- ATC Level 4: chemical subgroup
- WHODD preferred name

5.5 PREVIOUS/CONCOMITANT/POST-TREATMENT MEDICATIONS/ THERAPIES

The records of prior and concomitant medications will be classified as "Prior", "Concomitant" and "Post-treatment" according to the following definitions.

"Concomitant" medication/therapy is any medication/therapy which was administered in the period starting with the start of study treatment (including) and lasts until the end of study treatment. The only exception will be medication/therapy which started on day of the end of study treatment: this medication will be classified as "Post-treatment".

"Prior" medication/therapy is any medication/therapy ended before the start of study treatment.

"Post-treatment" medication/therapy is any medication/therapy which started after or at the end of study treatment.

For records of medication/therapy with unknown and incomplete dates which cannot be identified according to definitions described above, the following rules will be applied:

- If end date of medication/therapy is completely unknown and the medication/therapy started after or at the end of study treatment, the medication/therapy will be counted as "Post-treatment". Otherwise (i.e., the medication/therapy started before the end of study treatment), the medication/therapy will be counted as "Concomitant".
- If start date of medication/therapy is completely unknown and the medication/therapy ended after or at start of study treatment, the medication/therapy will be counted as "Concomitant". Otherwise (i.e., the medication/therapy ended before the start of study treatment), the medication/therapy will be counted as "Prior".
- If start or end date is incomplete: the first possible start date (e.g., for xxDEC2019 this is 01DEC2019, for xxxxx2019 this is 01JAN2019) or last possible end date (e.g., for xxDEC2019 this is 31DEC2019, for xxxxx2019 this is 31DEC2019) will be derived. Classification "Prior", "Concomitant" and "Post-treatment" medication/therapy will be performed using these derived dates.
- If both end date and start date of medication/therapy are completely unknown, then it will be counted as "Concomitant".

5.6 ADVERSE EVENT (AE)

Detailed definition of AE and its classification is presented in the Study Protocol (See section 9.11.5.1).

Each increase or decrease of severity of AE will be collected as separate AE record on "ADVERSE EVENT DETAILS" eCRF page.

Raw data will be used to identify AE episodes as follows:

- Linked AE records by the investigator (i.e. AE record with an outcome of "Change in severity" in the eCRF) with the same MedDRA preferred term, where the start date of the subsequent AE record is equal to (or +1 day) end date of the previous AE record, will be identified as one AE (continuous) and each AE record will be assigned the same AE ID (equal to the AE ID of the first AE record in the episode).

In order to assign the TEAE status to AEs with the same AE ID (linked AE records), unaggregated data will be used. After the TEAE assignment, AE episodes with the same AE ID will be aggregated as per section 5.8.

5.7 TREATMENT-EMERGENT ADVERSE EVENTS (TEAE)

According to the Study Protocol section 9.13.10.2 treatment-emergent AE is defined as an AE that

- emerges during treatment, having been absent at pretreatment (screening), or
- reemerges during treatment, having been present at pretreatment (screening), or
- worsens in severity during treatment relative to the pretreatment state.

Emerges or reemerges during treatment:

TEAEs are AEs with start date ≥ start of study treatment. Conditions when date/time is unknown or incomplete are defined below.

Worsening in severity:

When the AE belongs to an AE episode (as defined in section 5.6) where the first AE record is not TEAE, the subsequent AE record will be TEAE if:

- AE with start date ≥ start of study treatment, and
- Worsens in severity as compared to pretreatment state.

For adverse events with unknown or incomplete start date/time the following rules will be applied:

Incomplete date: when some information is available (e.g., month, year), but date is partially missing (e.g., missing day, month).

Unknown date/time: when no information is available and thus day, month and year are missing.

Unknown time for start or end of AE:

If time of AE start, or start of study treatment is unknown, the information will be derived only using dates – if AE start or end dates are unknown, conditions are defined below.

If start date is unknown and end date is known (and complete):

- If end date/time is < start of study treatment, the event will not be counted as TEAE.
- If end date/time is ≥ start of study treatment, the event will be counted as TEAE.

If start date is incomplete and end date is incomplete or unknown:

- last possible start date of AE (e.g., for xxDEC2019 this is 31DEC2019, for xxxxx2019 this is 31DEC2019) will be derived. If the last possible start date of AE ≥ start of study treatment the event will be counted as TEAE. Otherwise, if last possible start date of AE < start of study treatment, the event will not be counted as TEAE.

If start date is unknown and end date is incomplete:

- last possible end date of AE (e.g., for xxDEC2019 this is 31DEC2019, for xxxxx2019 this is 31DEC2019) will be derived. If the last possible end date of AE ≥ start of study treatment the

event will be counted as TEAE. Otherwise, if last possible end date of AE < start of study treatment, the event will not be counted as TEAE.

Unknown date for start and end of AE:

- If both start date and end date are unknown, the event will be counted as TEAE.

5.8 AGGREGATION OF CONTINUOUS AE AND TEAE

In order to aggregate AE and/or TEAE episodes (in text below referred just as 'AE') that are continuous, the following will be applied:

- AE will be TEAE if any of all AE records belonging to the AE is TEAE (as defined in section 5.7).
- Start date/time of AE will be start date of the first AE record belonging to the AE. This date will be used to derive the Cycle as defined in sections 5.1, as well as the last dose level of SOT101 before the start of the AE.
- End date /time of AE will be end date of the last AE record belonging to the AE.
- Outcome of AE will be outcome of the last AE record belonging to the AE.
- Severity will be the highest grade out of all AE records belonging to the AE.
- AE will be serious if any of all AE records belonging to the AE is evaluated as serious.
- AE will be immune-related if any of all AE records belonging to the AE is evaluated as AE immune-related. Secondly, AE will be not immune-related if any of all AE records belonging to the AE is evaluated as AE not immune-related.
- AE will have suspected relationship to SOT101 if any of all AE records belonging to the AE is evaluated as to have suspected relationship to SOT101.
- AE will have suspected relationship to pembrolizumab if any of all AE records belonging to the AE is evaluated as to have suspected relationship to pembrolizumab.
- Action taken to SOT101 will include all actions taken as per all AE records belonging to the AE.
- Action taken to pembrolizumab will include all actions taken as per all AE records belonging to the AE.

The definition above will be used for tables. Clinical signs/symptoms of cytokine release syndrome will not be aggregated.

Listings will present all AE and TEAE (not aggregated) as defined in Section 8.7.2 and Section 8.7.3.

6 GENERAL ALGORITHMS AND DERIVED VARIABLES

General and common algorithms to be used in SAS programming are listed below. Algorithms used only in analysis of particular endpoint are included directly in analysis section.

6.1 CONVERSION OF DAYS, MONTH, YEARS

Week will be counted as day/7. Planned to be used for presentation in listings where the value will be rounded for one decimal.

One year will be counted as 365.25 days.

One month will be counted as 365.25/12 days = 30.4375 days.

Number of calculated years and months will be used e.g. for calculation of age or survival time, rounding procedures are described in section 8.2.2.

6.2 TREATMENT/POST-TREATMENT DAY

Real treatment day will be calculated as date – date of the start of study treatment + 1. For dates before the start of study treatment, the treatment day will be negative and will be calculated as follows: date – start of study treatment.

Real post-treatment day will be calculated as date – date of the end of study treatment.

Real week, month and year will be converted from real day as defined in the section 6.1.

6.3 ALGORITHM FOR ALLOCATION OF DATA TO SCHEDULED VISITS/TIME-POINTS

The algorithms are described with definition of the time-point labels in Section 5.2.

6.4 APPLICATION OF CUT-OFF

No cut-off is planned to be applied for the final analysis.

7 ANALYSIS SETS

7.1 SAFETY SET (SAF)

The safety population will include all patients exposed to SOT101 or pembrolizumab in Part B.

The SAF will be used for analysis of safety endpoints.

7.2 DLT-EVALUABLE PATIENTS

A patient evaluable for DLT will be a patient who has completed cycle 1 and received all planned treatments without any treatment delay or interruptions for any other reason than DLT: for Part B, received all 4 doses of SOT101 and 1 dose of pembrolizumab as planned. Patients who do not fulfil these criteria for any other reason than DLT should be replaced.

The DLT evaluable patients will be used for ongoing safety evaluation needed for decisions as per 3+3 dose escalation design.

7.3 PK/PD EVALUABLE

PK analysis set will include patients with evaluable PK profile.

PD analysis set will include patients with evaluable PD profile.

Evaluation of PK and PD are secondary objectives of Study Part B which is a dose-escalation study; limited number of patients is included in the individual dose levels and in RP2D level. This needs to be considered when interpreting the data. The PK/PD profile is further explored in Part D.

Protocol deviations related to PK and PD assessment and compliance with dosing schedule will be reviewed. Only patients whose data would lead to biased conclusions or analysis interpretation will be excluded from the analysis sets.

The PK/PD analysis set will include patients in both PK analysis set, and PD analysis set. The PK/PD evaluable patients will be used for PK/PD analysis.

7.4 EFFICACY SET

All patients exposed to SOT101 (exposure for at least one treatment cycle) who had at least one evaluable tumor assessment per iRECIST after the initiation of SOT101 treatment.

Exposure for at least one treatment cycle is defined as 4 doses of SOT101 (regardless of dose level) in Cycle 1 and 1 dose of pembrolizumab, or if the patient is exposed to SOT101 or pembrolizumab (with any number of doses) in Cycle 1 and started Cycle 2.

The Efficacy set will be used for analysis of efficacy endpoints.

8 STATISTICAL METHODS AND DETERMINATION OF SAMPLE SIZE

This section describes the data analysis in detail (with exception of pharmacokinetic analysis which is described in separate document attached). The statistical methods are planned in accordance with the Study Protocol (section 9.9) and in accordance with ICH Topic E9 Statistical Principles for Clinical Trials.

SAS version 9.4 or newer will be used for statistical programming.

8.1 SOURCE DATA TO BE USED FOR ANALYSIS

Data collected in clinical study database including MedDRA and WHODD coding will be used for analysis. Laboratory conversion factors will be taken from the internal IBMCD laboratory DB (as per Laboratory Data Unit Conversions standards).

Plasma concentration data and pharmacokinetic parameters will be provided by [redacted] .sas7bdat format and will be directly used for analysis (will not be a part o c inica ata ase . Dates and times of blood sampling in the datasets provided by [redacted] and those recorded in the clinical database will be reconciled as a part of data management processes.

Description of the provided datasets:

- pc_cnp_DDMMMYYYY.sas7bdat: dataset providing the PK concentrations over time, per patient.
- pp_cnp_DDMMMYYYY.sas7bdat: dataset providing the calculated PK parameters, per patient.

Where n is the number of the cohort, p is the study part (e.g., 'b' for Part B), DDMMMYYYY is the date of transfer. Further details are specified in data transfer specification "SC103_Data Transfer Specification [redacted] 6.0_07Jul2023" dated 07-Jul-2023.

Anti-drug antibodies data will be provided by [redacted]

Description of the provided datasets:

- SC103ADASNAPSHO [redacted] DDMMMYYYY.csv: provides per patient and over time ADA positivity, titration, and NADA positivity. Where DDMMMYYYY is the date of transfer.

Further details are specified in data transfer specification "SC103_Data Transfer Specification [redacted] v6.0_07Jul2023" dated 07-Jul-2023.

Plasma concentration data and pharmacokinetic parameters will be rovided b [redacted] Materials for DEC/IAP will be directly prepared by [redacted] Sotio will provide outputs for CSR.

Pharmacodynamic variables and cytokines levels will be provided by Central LAB [redacted] as SAS® v.9 transport files and will be directly used for analysis (will not be a part of clinical database). Dates and times of blood sampling in the datasets provided by [redacted] nd those recorded in the clinical database will be reconciled as a part of data management processes.

Description of the provided datasets:

- SC103SNAPSHO [redacted] DMMMYYYY.xpt: includes per patient and over time the test results as per protocol. Where DDMMMYYYY is the date of file transfer.

Further details are specified in data transmission agreement "SC103_Data Transmission Agreement [redacted] 15Jun2021" dated 15-Jun-2021.

8.2 GENERAL PRINCIPLES

The study includes Study Part B.

This is a Phase I study with 3+3 dose escalation design with primary objective to determine MTD/RP2D. The analysis will be mainly descriptive. If appropriate regarding the number of patients (e.g., All cohorts pooled), the descriptive statistics will be presented with 95% confidence intervals. Descriptive statistics will include:

For categorical variables, standard set of summary statistics will be counts and percentages calculated from number of available observations. Number of available observations (and number of missing observations) will be presented as well. For baseline characteristics missing, not applicable/not available/not known will be counted as a category. The number of patients used for the percentages (denominator) is defined in each analysis section of this SAP.

For continuous variables, the following descriptive statistics will be presented: number of available observations (and number of missing observations), mean, standard deviation (StD), median, lower quartile (Q1), upper quartile (Q3), minimum (Min), and maximum (Max).

For time-to-event variables, Kaplan-Meier (KM) estimates of median, Q1 and Q3 will be presented. The number and percentage of patients with event and censored patients will be presented. KM curves will be provided as a part of descriptive analysis.

For pharmacokinetic parameters, the following descriptive statistics will be presented: number of available observations (and number of missing observations/ number of concentrations below limit of quantifications (BLQ)), arithmetic mean and geometric mean and their 95% confidence intervals, standard deviation (StD), StD of log-transformed data, median, inter-patients (between-patients, within-cycle) coefficient of variation, intra-patient (within-patient, between-cycles-days) coefficient of variation, minimum, and maximum. Coefficient of variation (CV) in % is computed as:

% CV = (StD x 100) / mean

8.2.1 Listings

Each listing will present the following variables/columns:

- Patient identification (ID), Cohort (dose level)
- If appropriate, analysis set relevant for particular listing

Listings will be sorted by ID and by chronological order of visits/assessments/events.

Dates will be presented in the listings in format YYMMDD10. (e.g., 2019-11-31). Partial dates as exported from the database will be listed (e.g., 2019-11-UNK, 2019-UNK-UNK, UNK-UNK-UNK).

8.2.2 Rounding procedures

Percentages will be presented with one decimal place with exception of efficacy data where two decimal places will be presented.

Mean, median, Q1 and Q3 will be presented with one more decimal place and StD will be presented with two more decimal places than the original data used for calculation of the statistics. The maximum number of decimal places will be up to three.

Other values such as temperature, number of weeks, coefficients of variation, etc. will be presented with one or two decimal places, according to the source data.

8.2.3 Unscheduled/ repeated assessments

Unscheduled/ repeated assessments which are performed in addition to those scheduled in the Study Protocol will not be used for analysis per time-point. Baseline values can include unscheduled/repeated assessment if they are the last before study drug administration (see section 5.3 for details).

8.2.4 Missing data

In general, missing data will not be imputed, i.e. complete case analyses will be performed. However, number of missing data is to be presented in descriptive statistics.

8.2.5 Methods for handling of incomplete/missing dates/ times

Methods for handling of incomplete and missing dates of medication/therapies and adverse events are presented in sections 5.5 and 5.7.

Similarly, methods for handling of incomplete and missing dates for Date of initial diagnosis are described in section 8.4.

8.2.6 Covariates and subgroups

The patients are planned to be analyzed by the cohorts (dose levels).

Subgroup analyses are not planned. No covariates to be used in analyses planned in this SAP.

8.2.7 Region/Country/Site analysis in multi-centric trial

Analysis by region, country or site is not planned.

8.2.8 Validation of statistical programming

Each SAS program will be validated by a second qualified SAS programmer to ensure a correct output and a correct presentation of the data. The validation process is documented in the validation sheet (GCPS_DMF_033 A-C), which also prespecifies criteria for risk categorization of programs and the corresponding validation actions.

Logs of all programs used for analysis and data preparation will be checked for errors and unexpected warnings. Any undocumented updating of raw study data in statistical programming instead of change in clinical DB (or source data) is not allowed.

8.3 DISPOSITION OF STUDY PATIENTS

Disposition of patients will be presented for Study Part B, for All cohorts pooled and by cohorts.

The following information will be presented in the table of patients' disposition:

No. of cohorts included (presented only for All cohorts pooled).

Count of the following groups of patients will be presented:

- Screened
  - Reason for screen failure with count and percentages* (from screened patients)
- Eligible (as per confirmation by the Sponsor)
- Treated

Count and percentages* of treated patients will be presented for the following groups of patients:

- DLT evaluable
- Ongoing patients (i.e., patients still in the study)
- Study discontinued patients
  - Reason for discontinuation with count and percentages* (from study discontinued patients)
- SOT101 discontinued patients
  - Reason for discontinuation with count and percentages* (from SOT101 discontinued patients)
- Pembrolizumab discontinued patients
  - Reason for discontinuation with count and percentages* (from pembrolizumab discontinued patients)

*The percentages will be presented by cohort and for all cohorts pooled.

Disposition of patients into analysis sets:

- Number of patients in analysis set (percentages calculated out of all treated patients), number of patients excluded from analysis set and reasons for exclusion from analysis sets (percentages calculated out of those patients excluded from analysis set).

Protocol deviations will be summarized for SAF and for All cohorts pooled, as well as listed.

8.4 DESCRIPTION OF BASELINE PATIENTS' CHARACTERISTICS

Baseline characteristics and disease history information defined in section 4.1 will be summarized with descriptive statistics.

Cancer type will be medically reviewed prior to DBL and derived based on the list specified in Appendix (Section 12.3).

Body Mass Index will be calculated as weight in kg divided by height in m^2. Values will be rounded to one decimal.

Date of birth is not collected in the eCRF. Age at ICF signature in years as recorded in eCRF will be used. Then, time since diagnosis at ICF signature in years and time since latest radiological or clinical disease progression at ICF signature in weeks will be calculated as follows: date of ICF signature (at time of entering the study) – date of diagnosis/progression + 1 and transformed to years/weeks respectively as per section 6.1.

If Date of initial diagnosis is incomplete or partially missing, the following rules will be applied for imputation of dates:

- If day and month is missing, day will be imputed as 01 and month as 06.
- If only day is missing, day will be imputed as 01.
- If only month is missing, month will be imputed as 06.

- If year is missing or the date is completely unknown, no imputation will be performed.

Date of latest radiological or clinical disease progression will not be imputed regardless of unknown or partially missing dates.

Explanatory footnote will be presented in corresponding table and listing.

The baseline patients' characteristics will be analyzed using SAF and presented for All cohorts pooled, as well as by cohort. Percentages will be computed from the number of treated patients in All cohorts pooled and, in each cohort, respectively.

Medical history recorded in eCRF will be only listed.

8.5 MEDICATION/THERAPIES

Medication and therapies as specified in Table 3 will be presented by count and percentages of patients. Separate tables for prior, concomitant, and post-treatment medication/therapies (see section 5.5) will be presented.

The tables will be generated using SAF and for All cohorts pooled. Percentages will be computed from the number of treated patients in All cohorts pooled for all cases: prior, concomitant, and post-treatment medication/therapies.

Prior, concomitant, and post-treatment procedures will also be listed.

8.6 EXPOSURE TO STUDY TREATMENTS

Duration of exposure to SOT101 will be calculated as: date of the last SOT101 administration - date of the first SOT101 administration + 1.

Duration of exposure to pembrolizumab will be calculated as: date of the last pembrolizumab administration - date of the first pembrolizumab administration + 1.

Descriptive statistics of duration of exposure to SOT101 and pembrolizumab will be presented in the table together with patient-years of exposure, analyzed as continuous variables.

Dose intensity will be calculated as follows, for each patient:

- Sum of (SOT101 administrations x dose level) / duration of exposure (in days)
- Sum of (pembrolizumab administrations x 200mg) / duration of exposure (in days)

Dose intensity will be summarized.

Additionally, to provide a dosing overview and a summary of changes from dosing (based on initial dose of SOT101 and actual dose of SOT101) the number of SOT101 and pembrolizumab administered doses will be analyzed descriptively as categorical variable.

Descriptive statistics for duration of exposure, dose intensity, and dosing overview will be provided for All cohorts pooled and by cohorts. Percentages will be computed from the number of treated patients in All cohorts pooled and, in each cohort, respectively. The tables will be generated using SAF.

Dose level, Dilution Fold, Total Volume Administered, Body Weight at Day 1 of each cycle, calculated Volume for Administration (as described in SC103_Instruction for handling of IMP and Trial Related Materials_v4.0_16Mar2021 (v4.0)) and compliance of dosing schedule for SOT101 with Study Protocol will be presented in Listings.

8.7 ANALYSES OF SAFETY

8.7.1 Summary of dose limiting toxicity events (DLTs) for determination of MTD/RP2D

AEs linked to DLTs will be summarized in frequency table as defined for summary table of TEAEs. Information in summary table will be completed by listing where information from dedicated DLT page in eCRF ("Dose Limiting Toxicity Details") will be merged in information recorded in "Adverse Event Details" eCRF page. Merging will be done on unaggregated data by Patient ID (AE.subnum, DLT.subnum) and AE number (AE.PAGESEQ, DLT.AENO).

8.7.2 Adverse events (AEs)

Details about AEs as collected on "Adverse Event Details" eCRF page will be used for analysis. Data collected on "Serious Adverse Event" eCRF page will be used for safety reporting in responsibility of pharmacovigilance department and will not be part of statistical outputs.

See section 5.8 for handling of AE records needed before programming of tables. All AE records will be presented in the listings without aggregation into AE episodes (derived number of episodes will indicate which AE records were aggregated for summaries).

8.7.3 Treatment-Emergent Adverse events (TEAEs)

TEAEs are defined in section 5.7 above. Note that as per Study Protocol AEs are collected in eCRF database until 90±2 days after last dose of SOT101.

Not TEAE will only be listed.

8.7.3.1 Grouping of TEAEs

For harmonization and safety data review purposes, the following grouping of Preferred Terms will be considered in the analysis and displayed as such in the tables. Listings of TEAEs will present the originally coded Preferred Term:

TEAE System Organ Class: Preferred Term	Preferred Term
Gastrointestinal disorders: Abdominal pain	Abdominal pain lower
	Abdominal pain upper
	Abdominal pain
Investigations: Blood bilirubin increased	Hyperbilirubinaemia
	Blood bilirubin increased
Investigations: Lymphocyte count decreased	Lymphopenia
	Lymphocyte count decreased
Investigations: Neutrophil count decreased	Neutropenia
	Neutrophil count decreased
Investigations: Platelet count decreased	Thrombocytopenia
	Platelet count decreased
General disorders and administration site conditions: Injection site reaction	Injection site reaction
	Injection site erythema
	Injection site rash
	Injection site pruritus
	Injection site induration

	Injection site inflammation Injection site oedema Injection site pain

8.7.3.2 General considerations for analysis of TEAEs

TEAEs will be displayed in frequency tables, presenting for all tables:

- Number of TEAEs and percentage of patients with at least one TEAE (TEAEs, n (%))
- Number of related TEAEs and percentage of patients with at least one related TEAE (related TEAEs, n (%))

Where percentages will be computed from the number of treated patients in All cohorts pooled and, in each cohort, respectively (unless stated otherwise, see below). Clinical sign/symptom of cytokine release syndrome (as per variable AE.AERELCRS) will be listed separately.

The following frequency tables will be generated for TEAEs, TESAEs:

- Summary table of TEAEs
- Frequencies of TEAEs by MedDRA preferred term (PT) and primary system organ class (SOC)

8.7.3.3 Summary tables of TEAEs

Summary table of TEAEs will present the frequencies of any TEAE and TEAEs by the following characteristics:

- Seriousness
- Outcome
- Severity (i.e., maximum severity reported for AE)
- Maximum severity per patient
- Severity of NCI CTCAE grade 3,4,5
- AE immune-related
- Action taken with SOT101
- Action taken with pembrolizumab

For frequencies by “Severity”, AEs and patients will be counted for each severity level which occurs (one patient can have several AEs with different severity). “Maximum severity per patient” will be calculated for each patient. Then, in frequency tables the patient will be counted only once (for the maximal severity) and only TEAEs with this maximal severity will be counted. Similarly, the worst action taken will be considered, from best to worst for SOT101: No action taken, Dose modified, Temporarily discontinued, Other (as temporarily discontinued + dose modified), Permanently discontinued. For pembrolizumab: No action taken, Delay of application, permanently discontinued, Other.

Summary table of TEAEs will be presented for All cohorts pooled and by cohort. In addition, the summary table of TEAEs by cycle will be presented for All cohorts pooled and for the RP2D cohort, up to Cycle 3 and only for TEAEs with an NCI CTCAE grade > 2; when presenting by Cycle, the number of patients treated within that Cycle will be used for the calculation of percentages. The TEAE will be assigned to a Cycle if the onset is within that Cycle, or if the TEAE worsens (relative to pretreatment state) within that Cycle.

Frequencies of TEAEs by MedDRA PT within SOC will present frequencies of any TEAE, by SOC and by PT within each SOC. The tables of the following groups of TEAEs will be provided:

- TEAEs

- TEAEs reported in ≥ 10% of patients
- Non-serious TEAEs reported in ≥5% of patients
- TESAEs
- Fatal TEAEs
- NCI CTCAE Grade 3, 4, 5 TEAEs
- Immune-related TEAEs
- TEAEs leading to SOT101 dose modification
- TEAEs leading to SOT101 temporary discontinuation
- TEAEs leading to pembrolizumab temporary discontinuation
- TEAEs leading to SOT101 permanent discontinuation
- TEAEs leading to pembrolizumab permanent discontinuation

Special cases regarding SOT101 or pembrolizumab Action Taken (e.g., Other, "free text" specified) will be reviewed before analysis and TEAEs will be counted as appropriate following the specification in other action taken: in general, certain keywords will be used to classify the TEAE into one of the above mentioned actions taken (e.g., a keyword of "dose" in the free text would lead to a classification of dose modified as action taken, a keyword of "discontinuation" or "discontinued" in the free text would lead to a classification of temporary discontinuation).

Frequencies of TEAEs by MedDRA PT within SOC will be presented for All cohorts pooled and by cohort.

Frequency table of TEAEs by MedDRA PT will be generated for All cohorts pooled. The table will be sorted by total number of patients with TEAE in descending order. Additionally, the proportion of patients with TEAE by MedDRA PT will also be presented graphically, by maximum grade and worse action taken.

Table of underlying causes of deaths by MedDRA PT and primary SOC will be generated for All cohorts pooled.

Renal TEAEs will be analyzed separately for all cohorts pooled. Renal TEAEs are defined as TEAEs with:

- SOC = "Renal and urinary disorders", or
- PT = "Blood creatinine increased"

8.7.3.4 Listing of AEs

Listings of AEs will present the following information in addition to data collected on eCRF page "ADVERSE EVENT DETAILS":

- Patient identification (ID), Study Part, Cohort (dose level), DLT evaluable (Yes/No)
- AE no. (derived as number of AE episode, see section 5.6, in chronological order of start date)
- TEAE (Yes/No) (derived)
- Cycle when AE started (derived)
- SOT101 Treatment Day when AE started (derived)
- Days* after the last SOT101 administration (derived)
- Last dose of SOT101 before AE start (derived)
- Total number of SOT101 doses administered before AE start**
- Duration of AE***
- MedDRA PT

* Days after last dose will be calculated as AE start date – administration date.

**If time of AE start is not recorded (or time of SOT101 administration is not recorded), the information will be derived only using dates (i.e., date of last SOT101 administered before date of AE start, SOT101 doses administered before date of AE start). The administration of SOT101 at the same date as date of AE start will be indicated as "(+1)", e.g. 5 (+1). If AE start date (or SOT101 administration date) is unknown or incomplete, the derivation will not be performed.

***Duration of AE will be calculated as AE end date - AE start date + 1. If end date or start date is missing or incomplete, the derivation will not be performed.

8.7.4 Other safety assessments

Other safety data include ECG, vital signs, clinical laboratory, physical examination, and echocardiography.

Date of physical examination, date and results of echocardiography assessment will be only listed.

Absolute values of laboratory data (selected laboratory variables defined below), vital signs and QT/ QTcF (Fridericia's correction) will be summarized at individual time-points descriptively by cohort and all cohorts pooled. A more detailed overview will be provided with figures containing the profiles over time, where the cohort (i.e., dose level) will be colored accordingly.

In all cases, tables and figures will present time-points where at least 3 patients (or more) have data available at that time-point.

8.7.4.1 ECG

In addition, analysis in line with ICH E14 guideline will be performed, i.e. number and percentage of patients who fit the criterial listed below will be presented in frequency table (All Cohort pooled and all time-points pooled).

- QTcF interval > 450
- QTcF interval > 480
- QTcF interval > 500
- QTcF interval increases from study baseline > 30
- QTcF interval increases from study baseline > 60
- Any criterion listed above met

QTcF levels which met the criteria above will be included in dedicated listing.

In case of any duplicated assessments, the assessment with the latest sequence (PAGESEQ in eCRF) will be selected.

8.7.4.2 Vital signs

In addition, the following will be provided:

- Mean profiles over time will be presented graphically by cohort and all cohorts pooled.

Vital signs will be analyzed irrespective of the position where the assessments were done.

8.7.4.3 Laboratory values

The selected laboratory variables: Total Bilirubin, Alanine Transaminase (ALT), Aspartate Transaminase (AST), Neutrophils, Platelets, Lymphocytes, Haemoglobin, C-reactive protein (CRP), Alkaline Phosphatase (ALP), Lactate Dehydrogenase (LDH).

Laboratory values will be converted to standard units: the conversion factors to SI units will be maintained in the lab repository database (IBMCD LAB). Changes will be audit trailed in the system. The conversion of laboratory results into SI units will be performed via SAS programming.

In addition, the following will be provided:

For selected laboratory variables not concerning liver enzymes (Neutrophils, Platelets, Lymphocytes, Haemoglobin, CRP, LDH):

- Mean profiles over time will be presented graphically by cohort and all cohorts pooled.

For selected laboratory variables concerning liver enzymes (Total Bilirubin, ALT, AST, ALP):

- Mean profiles over time will be presented graphically by cohort and all cohorts pooled.
- Patient profiles over time will be presented graphically for the RP2D and RP2D – 1 cohort, excluding the MTD.
- Maximal-levels per patient presented in figure with dose-level on X-axis.
- Maximal levels per patient will be also listed in dedicated listing.

For the profiles, if there are two or more values on the same day, the pre-dose value will be considered (as per protocol, safety laboratory measurements should be performed prior to dosing). In case of two or more pre-dose values, the one closest to the dosing will be selected for displaying purposes.

Hepatic function abnormality defined by an increase in AST and/or ALT to ≥ 3 × Upper limit of normal (ULN) concurrent with an increase in total bilirubin to ≥ 2 × ULN but without increase in alkaline phosphatase (i.e., alkaline phosphatase < 2 × ULN) meets the criteria for Hy's law and raises the concern for drug-induced liver injury when no other cause is identified. The summary of liver function tests will include the abovementioned categories, and the number and percentage of patients meeting Hy's Law at each scheduled visit during the on-treatment period will be summarized.

8.7.4.4 Prohibited medications

According to section 9.10.4.1 Prohibited medications in the Study Protocol medications which use is known to prolong QT/QTcF interval are prohibited. If such a prohibited medication is administered to the patients, then it will be taken into account in analysis of QT/ QTcF in the following way: patients with prohibited medications administered will be excluded from the analysis (tables) and further information will be provided: if the number of patients with prohibited medications administered is larger than 1, an extra table will be provided for the analysis of QT/QTcF including only these patients. Otherwise, a footnote specifying the case will be provided with the original table.

8.8 ANALYSES OF SOT101 CONCENTRATION DATA AND PK PARAMETERS

The PK analysis plan is provided b [redacted] nd attached to this SAP (section 12.1).

The following PK parameters will be calculated via non-compartmental model according to this plan:

- C_{max}
- T_{max}
- $t_{1/2,}$
- Termination elimination constant (λ_z)
- $t_{1/2\alpha}$ – distribution half-life (where possible)
- $AUC_{(0-6)}$, $AUC_{(0-t)}$, $AUC_{(0-24)}$, $AUC_{(0-inf)}$, same parameters per dose (AUC/D)
- CL - Clearance
- V_d - Volume of distribution
- R_{ac} - accumulation ratio over cohorts/dose levels

Concentration levels, C_{max}, T_{max} and $t_{1/2}$ will be analyzed descriptively by cohorts (dose administered). In addition, dose-normalized C_{max} (C_{max}/D) and T_{max} will be presented for all cohorts pooled. Mean concentration levels will be presented in figures with linear and semi-logarithmic scale (only for Cycle 1).

In line with Protocol Deviation Plan, PK samples taken out of schedule defined by the study protocol will be flagged in concentration listings and will not be a part of protocol deviation listing.

Dose proportionality analysis of AUC and C_{max} will be performed for exploratory purposes using standard "power-law model" according to approach describes by Brian Smith et al (2000) which is concisely described in paper by Zhou et al (2006).

The "power-law model" is defined as follows:

$PK = c \cdot Dose^{\beta 1} \cdot e^{\varepsilon}$

Dose-proportionality implies that $\beta 1 = 1$.

After the logarithmic transformation, the "power-law model" can be expressed as:

$\log(PK) = \beta 0 + \beta 1 \cdot \log(Dose) + \varepsilon$

Dose-proportionality corresponds to $r^{\beta 1-1}=1$, where r=highest dose level/lowest dose level.

In order to conclude the dose-proportionality the following criterion has to be met:

$1 + (\log(\theta_L)/\log(r)) < 90\%$ CI of $\beta 1 < 1 + (\log(\theta_U)/\log(r))$.

The commonly used (θ_L, θ_U) will be (80%, 125%). If the SOT101 will be considered as highly variable drug (intra-patient variability >30%), then (77%, 130%) will be used as a margin.

PK samples are taken on cycle 1 day 1 for 24 hours after administration. Cycle 1 day 9, cycle 2 day 1 and 9 and cycle 3 day 1 are planned to be collected up to 6 hours from administration. All PK analyses will be conducted in PK/PD evaluable patients. Values below the BLQ will be treated as 0 when performing the analysis on a linear scale. On the logarithmic scale, these values will be disregarded.

Sensitivity analyses for hemolytic samples:

Any samples with presence of hemolysis will be flagged in the analysis dataset and listings as follows: a keyword search (both in lower and upper case) of "Hemolytic", "Hemolysis" will be performed on concentration dataset, column LABCOM. Subsequently, a sensitivity analysis on concentration levels and dose proportionality will be performed.

Pembrolizumab PK evaluation will not be performed due to no samples being collected for such evaluation.

8.9 ANALYSES OF PHARMACODINAMIC MARKERS AND CYTOKINES

PD markers and cytokines levels will be provided b [redacted] nd will not be a part of eCRF database.

The PD marker of interest are as follows:

CD8 Panel
CD8+ Cells of CD3+ Cells (%)
CD8+ Cells of CD3+ Cells(%CD45+)
Ki-67+ Cells of CD8+ Cells (%)
Ki-67+ Cells of CD8+ Cells (%CD45+)
CD45RO+ CD45RA- (Memory) Cells of CD8+ Cells (%)
CD45RO+ CD45RA- (Memory) Cells of CD8+ Cells (%CD45+)
Ki-67+ Cells of CD8+CD45RO+ CD45RA- Cells (%)
Ki-67+ Cells of CD8+CD45RO+ CD45RA- Cells (%CD45+)
NKG2D+ Cells of CD8+ Cells (%)
NKG2D+ Cells of CD8+ Cells (MFI NKG2D)
NKG2D+ Cells of CD8+CD45RO+CD45RA- Cells (%)
NKG2D+ Cells of CD8+CD45RO+CD45RA- Cells (MFI NKG2D)
CD4+ Cells of CD3+ Cells (%)
CD4+ Cells of CD3+ Cells (%CD45+)
Ki-67+ Cells of CD4+ Cells (%)
Ki-67+ Cells of CD4+ Cells (%CD45+)

Natural killer cells (NK) Panel
CD25+Foxp3+ (Treg) Cells of CD4+ Cells (%)
CD25+Foxp3+ (Treg) Cells of CD4+ Cells (%CD45+)
Ki-67+ Cells of CD4+CD25+Foxp3+ (Treg) Cells (%)
Ki-67+ Cells of CD4+CD25+Foxp3+ (Treg) Cells (%CD45+)
CD3-CD56+ (NK) Cells of CD45+ Live Cells (%)
Ki-67+ Cells of CD3-CD56+ (NK) Cells (%)
Ki-67+ Cells of CD3-CD56+ (NK) Cells (%CD45+)
CD3+CD56+ (NKT) Cells of CD45+ Live Cells (%)
Ki-67+ Cells of CD3+CD56+ (NKT) Cells (%)
Ki-67+ Cells of CD3+CD56+ (NKT) Cells (%CD45+)
NKG2D+ Cells of CD3-CD56+ (NK) Cells (%)
NKG2D+ Cells of CD3-CD56+ (NK) Cells (MFI NKG2D)

Cytokines include the following variables:

Interleukin-2
Interleukin-4
Interleukin-6
Interleukin-8
Tumor Necrosis Factor Alpha
Interferon-gamma
Interleukin-1 beta
Interleukin-10
Interleukin-12p70

The eCRF Hematology data (specifically white blood cell count (WBC)) for each timepoint will be used to derive the Cell counts in 10^9/L. Once merged with the pharmacodynamic data by subject and timepoint, the following will be used as derivation:

- CD8+ Cells of CD3+ Cells (10^9/L) = CD8+ Cells of CD3+ Cells (%CD45+) x 0.01 x WBC
- Ki-67+ Cells of CD8+ Cells (10^9/L) = Ki-67+ Cells of CD8+ Cells (%CD45+) x 0.01 x WBC
- CD45RO+ CD45RA- (Memory) Cells of CD8+ Cells (10^9/L) = CD45RO+ CD45RA- (Memory) Cells of CD8+ Cells (%CD45+) x 0.01 x WBC
- CD4+ Cells of CD3+ Cells (10^9/L) = CD4+ Cells of CD3+ Cells (%CD45+) x 0.01 x WBC
- Ki-67+ Cells of CD4+ Cells (10^9/L) = Ki-67+ Cells of CD4+ Cells (%CD45+) x 0.01 x WBC

- CD25+Foxp3+ (Treg) Cells of CD4+ Cells (10^9/L) = CD25+Foxp3+ (Treg) Cells of CD4+ Cells (%CD45+) x 0.01 x WBC
- Ki-67+ Cells of CD4+CD25+Foxp3+ (Treg) Cells (10^9/L) = Ki-67+ Cells of CD4+CD25+Foxp3+ (Treg) Cells (%CD45+) x 0.01 x WBC
- CD3-CD56+ (NK) Cells of CD45+ Live Cells (10^9/L) = CD3-CD56+ (NK) Cells of CD45+ Live Cells (%) x 0.01 x WBC
- Ki-67+ Cells of CD3-CD56+ (NK) Cells (10^9/L) = Ki-67+ Cells of CD3-CD56+ (NK) Cells (%CD45+) x 0.01 x WBC
- CD3+CD56+ (NKT) Cells of CD45+ Live Cells (10^9/L) = CD3+CD56+ (NKT) Cells of CD45+ Live Cells (%) x 0.01 x WBC
- Ki-67+ Cells of CD3+CD56+ (NKT) Cells (10^9/L) = Ki-67+ Cells of CD3+CD56+ (NKT) Cells (%CD45+) x 0.01 x WBC

During the descriptive statistical analysis of PD markers and cytokines will be considered that the value can be below or above limits of quantification: the lower limit will be replaced by the actual value (e.g. “<0.5” should be considered as 0.5), similarly for the upper limit (e.g. “>20” should be considered as 20). In all cases, only Cycle 1 and Cycle 2 data will be used and analyzed to study the Pharmacodynamic activation. Only certain markers of interest will be included in the tables and figures, all markers will be listed.

The levels and fold increases will be analyzed descriptively at individual time-points by cohorts and all cohorts pooled. A more detailed overview will be provided with figures containing the profiles over time, where the cohort (i.e., dose level) will be colored accordingly. A Boxplot for Cycle 1 Day 6 by dose level, and maximal levels of activation achieved by dose level (barplot), will be provided for selected PD markers:

- NK cells: Ki-67+ Cells of CD3-CD56+ (NK) Cells (%)
- NKT cells: Ki-67+ Cells of CD3+CD56+ (NKT) Cells (%)
- CD8+ T-cells: Ki-67+ Cells of CD8+ Cells (%)
- CD8+ Memory T cells: Ki-67+ Cells of CD8+CD45RO+ CD45RA- Cells (%)
- CD4+ T cells: Ki-67+ Cells of CD4+ Cells (%)
- T regs: Ki-67+ Cells of CD4+CD25+Foxp3+ (Treg) Cells (%)

The table summarizing the maximum levels of activation will contain the fold increase in cell counts (i.e., 10^9/L).

Additionally for cytokines, the mean fold increase over time will also be plotted.

All PD analyses will be conducted on PK/PD evaluable patients.

Maximal levels of cytokines will also be listed.

8.10 ANALYSES OF EFFICACY

The efficacy population will be derived as follows: assuming at least one evaluable tumor assessment per iRECIST after the initiation of SOT101 treatment, a patient that receives 4 doses of SOT101 in cycle 1 and 1 dose of pembrolizumab, will be included in the efficacy population; if a patient does not receive 4 doses of SOT101 in cycle 1 then the patient will be included in the efficacy population if combination therapy is not permanently discontinued in cycle 1 (i.e. patient starts cycle 2). The efficacy population will be used for the efficacy analyses.

Due to the lack of confirmation of progression (iCPD) and follow-up scans, any unconfirmed progression (iUPD) has been considered as progression if a discontinuation of any treatment is followed, and thus deviating from iRECIST guidelines.

Complete response (iCR), partial response (iPR), stable disease (iSD) and progression disease (iUPD and also after iCPD) will be identified according to iRECIST, recorded to eCRF, and cleaned via data management/medical review processes.

Tumor assessment data will be listed and disease response since the first SOT101 administration will be presented graphically per patient (swimmer plot). Additionally, tumor size evaluated via sum of diameters of target lesions will be presented graphically per patient (waterfall plot): the best change from baseline will be used. The change from baseline over time will be graphically presented per patient as well (spaghetti plot).

If tumor assessment is performed after start of new anticancer therapy, it will be clearly indicated in the outputs. For tumor assessments with different dates (i.e. lesions are assessed at different dates), the earliest date will be used for efficacy derivations.

Overall response is defined as state when the patient achieves iPR or iCR. Clinical benefit is defined as state when patient achieves iSD, iPR, or iCR. iSD needs to last at least 6 weeks from the start of study treatment; if not, at least one follow-up scan assessed as iPR, iCR, or iSD is required to provide clinical benefit. Similarly, confirmation of iPR or iCR by a subsequent assessment of either iPR or iCR, at least 4 weeks apart, will be required to declare an overall response or clinical benefit.

Immune overall response rate (iORR) and Clinical benefit rate (iCBR):

- iORR will be defined as the proportion of patients with confirmed iPR or iCR, out of patients in efficacy population.
- iCBR will be defined as the proportion of patients with confirmed iPR, iCR, or iSD out of patients in efficacy population.

iORR and iCBR will be summarized for All cohorts pooled.

Progression free survival (iPFS):

iPFS is defined as the time from the first day of study treatment until the first date of iUPD (followed by iCPD, study treatment discontinuation or clinical progression) or death (whichever occurs earliest) and will be summarized using Kaplan-Meier estimates.

Patients with missing data or that start new anti-cancer therapy (other than palliative) will be censored at the date of the last evaluable tumor assessment.

iPFS will be summarized and presented for All cohorts pooled.

Duration of response (iDoR):

iDoR is defined as the time since the first iPR or iCR until the first date of iUPD (followed by iCPD, study treatment discontinuation or clinical progression) or death (whichever occurs earliest) for patients with confirmed iPR or iCR. DoR will be summarized using Kaplan-Meier estimates.

Patients with missing data or that start new anti-cancer therapy (other than palliative) will be censored at the date of the last evaluable tumor assessment.

iDoR will be summarized and presented for All cohorts pooled.

Overall survival (OS):

OS is defined as the time from the first day of study treatment until the date of death and will be summarized using Kaplan-Meier estimates.

Patients with missing data will be censored at the last time known to be alive: apart from trial visits/survival status, information from AE, new anti-cancer therapy, and prior and concomitant medications data from eCRF will also be used to derive the alive status – the latest complete date will be selected.

OS will be summarized and presented for All cohorts pooled.

Duration of follow-up:

A reverse Kaplan-Meier analysis will be performed on OS to estimate the median follow-up incorporating censoring rules and flipping event/censored events.

8.11 OTHER ASSESSMENTS

8.11.1 ECOG performance status

ECOG performance status will be summarized for All cohorts pooled and listed.

8.11.2 Immunogenicity

ADA levels, titration, and Neutralizing ADA levels will be provided b [redacted] nd will not be a part of eCRF database. Levels and titration will be analyzed descriptively for All cohorts pooled and by cohorts for SAF population. The summary table will be completed with listing of positive results.

8.12 INTERIM ANALYSES

No interim analysis is planned.

8.13 DETERMINATION OF SAMPLE SIZE

According to Study Protocol section 9.13.11 the traditional 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 in a cohort. The estimated number of patients is 21-42 for Study Part B.

9 CONCLUSIONS BASED OF DATA REVIEW MEETING

From the statistical perspective, the objectives of the meeting will be following:

- to agree on patients excluded from analysis sets and to agree on major protocol deviations/reportable protocol deviations
- to highlight any issue from statistical perspective and to decide the solution in joint decision.

The section below will state version of Protocol Deviation Plan valid at time of the data review meeting, refer to data review meeting minutes and summarize/ summarizes conclusion relevant to statistical analysis which were or will be made during the data review meeting.

9.1 DATA REVIEW MEETING BEFORE ANALYSIS

The review will be performed under Protocol Deviation Plan version 2.0 dated 08 March 2023

Prior to lock of database, a data review will be performed, and conclusions will be summarized separately in eTMF.

The review of PK data includes derivation of sampling out of window according to Protocol v10 following the derivation: PK blood sampling out of window will be flagged in listing of concentration levels. Note referring to that listing will be added to output of CSR reportable PDs. Unreliable PK concentrations will be flagged, such values are not to be used for the calculation of PK parameters and descriptive analysis of PK concentrations. Hemolytic samples have been considered reliable; however, a sensitivity analysis is included in this SAP.

The review of PK data will also be documented consistently in eTMF.

For PBCM data, applicable to all samples and all cycles:

- Any samples taken after a missed or delayed dose will be excluded within the cycle: for example, if C1D2 is not done then any day afterwards within the cycle should be excluded (C1D6, C1D8, ...). EXCEPT when that delay or deviation is shifting the CXD8 and CXD9 dosing to CXD9 and CXD10 dosing (consecutive)
- Any samples taken after a dose reduction or increase will be excluded.
- Any dosing performed PRIOR to CXD8 (i.e., deviation) will lead to the exclusion of samples from CXD8 onwards within the cycle.
- Any sample taken with a deviation more than 1 day (>1 day) from the protocol schedule will be excluded.

The rules above will also be applied for Cytokines (CK). In addition, for CK, any sample taken outside of the protocol defined window will be excluded.

No data from other sampling (Immunogenicity, Tumor Biopsy, etc.) will be considered as unreliable and/or affected by deviations and no exclusion rules will be created.

10 LIST OF TABLES, FIGURES AND LISTINGS

The table hereunder presents preliminary list of content of tables, figures and listings which will be integrated in study report. The structure and numbering is proposed according the ICH guidelines - E3: Structure and Content of Clinical Study Reports.

10.1 SECTION 10 OF CSR (STUDY PATIENTS)

Selected tables from Section 14.1 of CSR (DEMOGRAPHIC DATA).

This section will cover the following:

- Summary of patient disposition
- Patient disposition by country
- Analysis populations
- Protocol deviations
- Summary of patient demographics and baseline characteristics
- Summary of disease history
- Summary of medical history
- Summary of prior, concomitant, and post-treatment therapies
- Exposure to study medication

10.2 SECTION 11 OF CSR (SAFETY AND PK/PD EVALUATIONS)

Selected tables from Section 14.3 (SAFETY DATA) and Section 14.2 (PK/PD DATA) of CSR.

This section will cover the following:

- DLTs
- Summary of TEAEs
- AE tables by PT within SOC
- Summary of causes of death

This section will cover also pharmacokinetic and pharmacodynamics evaluation.

10.3 SECTION 12 OF CSR (EFFICACY AND OTHER DATA)

Selected tables from Section 14.2 of CSR (EFFICACY AND OTHER DATA).

10.4 SECTION 13 OF CSR (DISCUSSION AND OVERALL CONCLUSIONS)

No tables are planned.

10.5 SECTION 14 OF CSR (TABLES, FIGURES AND GRAPHS REFERRED TO BUT NOT INCLUDED IN THE TEXT)

Output	Number	Title	Analysis Set
	Section 14.1	**Demographic data**	
		Patient disposition	
Table	14.1.1.1	Disposition of patients	All

Output	Number	Title	Analysis Set
Table	14.1.1.2	Disposition of patients by country	All
Table	14.1.1.3	Analysis populations and reasons for exclusion	All
Table	14.1.1.4	Reasons for discontinuation after treatment start	SAF
Table	14.1.1.5	Protocol deviations	SAF, Efficacy
		Baseline characteristics and disease history	
Table	14.1.2.1	Baseline characteristics	SAF, Efficacy, PK/PD
Table	14.1.2.2	Disease history	SAF, Efficacy, PK/PD
		Prior, concomitant, and post-treatment medication	
Table	14.1.3.1	Prior anticancer systemic therapy	SAF
Table	14.1.3.2	Prior anticancer non-systemic therapy	SAF
Table	14.1.3.3	Prior medication	SAF
Table	14.1.3.4	Prior non-pharmacological therapy	SAF
Table	14.1.3.5	Concomitant medication	SAF
Table	14.1.3.6	Concomitant non-pharmacological therapy	SAF
Table	14.1.3.7	Post-treatment medication	SAF
Table	14.1.3.8	Post-treatment non-pharmacological therapy	SAF
Table	14.1.3.9	New anticancer systemic therapy	SAF
Table	14.1.3.10	New anticancer non-systemic therapy	SAF
		Exposure	
Table	14.1.4.1	Exposure to study treatment	SAF
Table	14.1.4.2	SOT101 and pembrolizumab Dose intensity	SAF
Table	14.1.4.3	Dosing overview, summary of changes from dosing	SAF
	Section 14.2	**Efficacy and PK/PD evaluations**	
		Pharmacokinetics	
Table	14.2.1.1.1	SOT101 concentrations	PK/PD
Table	14.2.1.1.2	SOT101 concentrations	PK/PD (excluding hemolytic samples)
Table	14.2.1.2	SOT101 PK parameters	PK/PD

Output	Number	Title	Analysis Set
Figure	14.2.1.3	Patient profiles of SOT101 concentrations (linear and semi-logarithmic scale)	PK/PD
Figure	14.2.1.4.1	Mean SOT101 concentrations profiles (linear and semi-logarithmic scale)	PK/PD
Figure	14.2.1.4.2	Mean SOT101 concentrations profiles (linear and semi-logarithmic scale)	PK/PD (excluding hemolytic samples)
Table	14.2.1.5.1	Evaluation of dose proportionality	PK/PD
Table	14.2.1.5.2	Evaluation of dose proportionality	PK/PD (excluding hemolytic samples)
		Pharmacodynamics	
CD8+ T Cells			
Table	14.2.2.1	CD8+ Cells of CD3+ Cells (10^9/L): Values and fold increase	PK/PD
Table	14.2.2.2	CD8+ Cells of CD3+ Cells (%): Values and fold increase	PK/PD
Table	14.2.2.3	Ki-67+ Cells of CD8+ (%): Values and fold increase	PK/PD
Figure	14.2.2.4	Mean profiles of Ki-67+ Cells of CD8+ (%) by cohort and All cohorts pooled	PK/PD
CD8+ Memory T Cells			
Table	14.2.2.5	CD45RO+ CD45RA- (Memory) Cells of CD8+ Cells (10^9/L): Values and fold increase	PK/PD
Table	14.2.2.6	CD45RO+ CD45RA- (Memory) Cells of CD8+ Cells (%): Values and fold increase	PK/PD
Table	14.2.2.7	Ki-67+ Cells of CD8+CD45RO+ CD45RA- Cells (%): Values and fold increase	PK/PD
Figure	14.2.2.8	Mean profiles of Ki-67+ Cells of CD8+CD45RO+ CD45RA- Cells (%) by cohort and All cohorts pooled	PK/PD
NKG2D+ Cells (CD8)			
Table	14.2.2.9	NKG2D+ Cells of CD8+ Cells (%): Values and fold increase	PK/PD
Figure	14.2.2.10	Mean profiles of NKG2D+ Cells of CD8+ Cells (%) by cohort and All cohorts pooled	PK/PD
Table	14.2.2.11	NKG2D+ Cells of CD8+ Cells (MFI NKG2D): Values and fold increase	PK/PD

Output	Number	Title	Analysis Set
Figure	14.2.2.12	Mean profiles of NKG2D+ Cells of CD8+ Cells (MFI NKG2D) by cohort and All cohorts pooled	PK/PD
NKG2D+ Cells (CD8 Memory)			
Table	14.2.2.13	NKG2D+ Cells of CD8+ CD45RO+CD45RA- Cells (%): Values and fold increase	PK/PD
Figure	14.2.2.14	NKG2D+ Cells of CD8+ CD45RO+CD45RA- Cells (%) by cohort and All cohorts pooled	PK/PD
Table	14.2.2.15	NKG2D+ Cells of CD8+ CD45RO+CD45RA- Cells (MFI NKG2D): Values and fold increase	PK/PD
Figure	14.2.2.16	NKG2D+ Cells of CD8+ CD45RO+CD45RA- Cells (MFI NKG2D) by cohort and All cohorts pooled	PK/PD
CD4+ T Cells			
Table	14.2.2.17	CD4+ Cells of CD3+ Cells (10^9/L): Values and fold increase	PK/PD
Table	14.2.2.18	CD4+ Cells of CD3+ Cells (%): Values and fold increase	PK/PD
Table	14.2.2.19	Ki-67+ Cells of CD4+ Cells (%): Values and fold increase	PK/PD
Figure	14.2.2.20	Mean profiles of Ki-67+ Cells of CD4+ Cells (%) by cohort and All cohorts pooled	PK/PD
NK Cells			
Table	14.2.2.21	CD3-CD56+ (NK) Cells of CD45+ Live Cells (10^9/L): Values and fold increase	PK/PD
Table	14.2.2.22	CD3-CD56+ (NK) Cells of CD45+ Live Cells (%): Values and fold increase	PK/PD
Table	14.2.2.23	Ki-67+ Cells of CD3-CD56+ (%): Values and fold increase	PK/PD
Figure	14.2.2.24	Mean profiles of Ki-67+ Cells of CD3-CD56+ (%) by cohort and All cohorts pooled	PK/PD
Treg Cells			
Table	14.2.2.25	CD25+Foxp3+ (Treg) Cells of CD4+ Cells (10^9/L): Values and fold increase	PK/PD
Table	14.2.2.26	CD25+Foxp3+ (Treg) Cells of CD4+ Cells (%): Values and fold increase	PK/PD
Table	14.2.2.27	Ki-67+ Cells of CD4+CD25+Foxp3+ (Treg) Cells (%): Values and fold increase	PK/PD
Figure	14.2.2.28	Mean profiles of Ki-67+ Cells of CD4+CD25+Foxp3+ (Treg) Cells (%) by cohort and All cohorts pooled	PK/PD
NKT Cells			

Output	Number	Title	Analysis Set
Table	14.2.2.29	CD3+CD56+ (NKT) Cells of CD45+ Live Cells (10^9/L): Values and fold increase	PK/PD
Table	14.2.2.30	CD3+CD56+ (NKT) Cells of CD45+ Live Cells (%): Values and fold increase	PK/PD
Table	14.2.2.31	Ki-67+ Cells of CD3+CD56+ (NKT) Cells (%): Values and fold increase	PK/PD
Figure	14.2.2.32	Mean profiles of Ki-67+ Cells of CD3+CD56+ (NKT) Cells (%) by cohort and All cohorts pooled	PK/PD
NKG2D+ Cells (NK)			
Table	14.2.2.33	NKG2D+ Cells of CD3-CD56+ (NK) Cells (%): Values and fold increase	PK/PD
Figure	14.2.2.34	Mean profiles of NKG2D+ Cells of CD3-CD56+ (NK) Cells (%) by cohort and All cohorts pooled	PK/PD
Table	14.2.2.35	NKG2D+ Cells of CD3-CD56+ (NK) Cells (MFI NKG2D): Values and fold increase	PK/PD
Figure	14.2.2.36	Mean profiles of NKG2D+ Cells of CD3-CD56+ (NK) Cells (MFI NKG2D) by cohort and All cohorts pooled	PK/PD
Summary of pharmacodynamic activation			
Table	14.2.2.37	Overall activation levels (10^9/L) of selected PD markers in Cycle 1 Day 6	PK/PD
Table	14.2.2.38	Overall activation levels (%) of selected PD markers in Cycle 1 Day 6	PK/PD
Figure	14.2.2.39	Overall activation levels (%) of selected PD markers in Cycle 1 Day 6 (overview)	PK/PD
Figure	14.2.2.40	Overall activation levels (%) of selected PD markers in Cycle 1 Day 6 (specific)	PK/PD
Table	14.2.2.41	Maximum levels of fold increase in cell counts (10^9/L) for selected PD markers	PK/PD
Figure	14.2.2.42	Maximum levels of activation (%) for selected PD markers	PK/PD
		Immunocytokines	
Table	14.2.3.1	Interleukin-2: Values and fold increase	PK/PD
Figure	14.2.3.2	Mean profiles of Interleukin-2 by cohort and All cohorts pooled	PK/PD
Table	14.2.3.3	Interleukin-4: Values and fold increase	PK/PD
Figure	14.2.3.4	Mean profiles of Interleukin-4 by cohort and All cohorts pooled	PK/PD

Output	Number	Title	Analysis Set
Table	14.2.3.5	Interleukin-6: Values and fold increase	PK/PD
Figure	14.2.3.6	Mean profiles of Interleukin-6 by cohort and All cohorts pooled	PK/PD
Table	14.2.3.7	Interleukin-8: Values and fold increase	PK/PD
Figure	14.2.3.8	Mean profiles of Interleukin-8 by cohort and All cohorts pooled	PK/PD
Table	14.2.3.9	Tumor Necrosis Factor Alpha: Values and fold increase	PK/PD
Figure	14.2.3.10	Mean profiles of Tumor Necrosis Factor by cohort and All cohorts pooled	PK/PD
Table	14.2.3.11	Interferon-gamma: Values and fold increase	PK/PD
Figure	14.2.3.12	Mean profiles of Interferon-gamma by cohort and All cohorts pooled	PK/PD
Table	14.2.3.13	Interleukin-1 beta: Values and fold increase	PK/PD
Figure	14.2.3.14	Mean profiles of Interleukin-1 beta by cohort and All cohorts pooled	PK/PD
Table	14.2.3.15	Interleukin-10: Values and fold increase	PK/PD
Figure	14.2.3.16	Mean profiles of Interleukin-10 by cohort and All cohorts pooled	PK/PD
Table	14.2.3.17	Interleukin-12p70: Values and fold increase	PK/PD
Figure	14.2.3.18	Mean profiles of Interleukin-12p70 by cohort and All cohorts pooled	PK/PD
		Efficacy data	
Table	14.2.4.1	Duration of follow-up	SAF
Figure	14.2.4.2	Kaplan-Meier curve of duration of follow-up	SAF
Figure	14.2.4.3	Disease response since the first SOT101 administration per patient	SAF
Table	14.2.4.4	Tumor response (overall response rate and clinical benefit rate) as per iRECIST	Efficacy
Figure	14.2.4.5.1	Best change from baseline in tumor size per patient	Efficacy
Figure	14.2.4.5.2	Change from baseline in tumor size per patient	Efficacy
Table	14.2.4.6	Duration of response as per iRECIST (iDoR)	Efficacy
Figure	14.2.4.7	Kaplan-Meier curve of iDoR as per iRECIST	Efficacy
Table	14.2.4.8	Progression free survival as per iRECIST (iPFS)	Efficacy
Figure	14.2.4.9	Kaplan-Meier curve of iPFS as per iRECIST	Efficacy

Output	Number	Title	Analysis Set
Table	14.2.4.10	Overall survival	Efficacy
Figure	14.2.4.11	Kaplan-Meier curve of overall survival	Efficacy
	Section 14.3	**Safety data**	
		DLT and TEAEs	
Table	14.3.1.1	Summary of dose limiting toxicity (DLT)	DLT evaluable
Table	14.3.2.1	Summary of Treatment-Emergent Adverse Events	SAF
Table	14.3.2.2	Summary of Treatment-Emergent Serious Adverse Events	SAF
Table	14.3.2.3	Summary of Treatment-Emergent Adverse Events by cycle	SAF
Table	14.3.2.4	Summary of Treatment-Emergent Serious Adverse Events by cycle	SAF
Table	14.3.3.1	Treatment-Emergent Adverse Events by MedDRA PT and primary SOC	SAF
Table	14.3.3.2	Treatment-Emergent Adverse Events by MedDRA PT and primary SOC reported in $\geq$10% of patients	SAF
Table	14.3.3.3	Non-serious Treatment-Emergent Adverse Events by MedDRA PT and primary SOC reported in $\geq$5% of patients	SAF
Table	14.3.3.4	Treatment-Emergent Adverse Events by MedDRA PT	SAF
Figure	14.3.3.5	Treatment-Emergent Adverse Events by MedDRA PT and Grade	SAF
Figure	14.3.3.6	Treatment-Emergent Adverse Events by MedDRA PT and Action Taken	SAF
Table	14.3.3.7	Treatment-Emergent Serious Adverse Events by MedDRA PT and primary SOC	SAF
Table	14.3.3.8	Fatal Treatment-Emergent Adverse Events by MedDRA PT and primary SOC	SAF
Table	14.3.3.9	Grade 3, 4, 5 Treatment-Emergent Adverse Events by MedDRA PT and primary SOC	SAF
Table	14.3.3.10	Immune-related Treatment-Emergent Adverse Events by MedDRA PT and primary SOC	SAF
Table	14.3.3.11	Treatment-Emergent Adverse Events leading to SOT101 dose modification by MedDRA PT and primary SOC	SAF
Table	14.3.3.12.1	Treatment-Emergent Adverse Events leading to SOT101 temporary discontinuation by MedDRA PT and primary SOC	SAF

Output	Number	Title	Analysis Set
Table	14.3.3.12.2	Treatment-Emergent Adverse Events leading to pembrolizumab temporary discontinuation by MedDRA PT and primary SOC	SAF
Table	14.3.3.13.1	Treatment-Emergent Adverse Events leading to SOT101 permanent discontinuation by MedDRA PT and primary SOC	SAF
Table	14.3.3.13.2	Treatment-Emergent Adverse Events leading to pembrolizumab permanent discontinuation by MedDRA PT and primary SOC	SAF
Table	14.3.3.14	Treatment Emergent Adverse Events symptoms of Cytokine release syndrome by MedDRA PT and primary SOC	SAF
Table	14.3.3.15	Treatment Emergent Adverse Events by MedDRA PT and Maximum CTCAE Grade	SAF
Table	14.3.3.16	Renal Treatment Emergent Adverse Events by MedDRA PT and Maximum CTCAE Grade	SAF
Table	14.3.4.1	Underlying causes of deaths by MedDRA PT and primary SOC	SAF
	Section 14.4	**Clinical Laboratory data**	
		Liver enzyme values	
Table	14.4.1.1	Total Bilirubin (µmol/L): Values, relative and absolute changes from baseline	SAF
Figure	14.4.1.2	Mean profile of Total Bilirubin (µmol/L) by cohort and All cohorts pooled	SAF
Figure	14.4.1.3	Patient profiles of Total Bilirubin (µmol/L) for RP2D and RP2D-1 cohorts (excluding the MTD)	SAF
Table	14.4.2.1	Alanine Transaminase (ALT) (µkat/L): Values, relative and absolute changes from baseline	SAF
Figure	14.4.2.2	Mean profile of Alanine Transaminase (ALT) (µkat/L) by cohort and All cohorts pooled	SAF
Figure	14.4.2.3	Patient profiles of Alanine Transaminase (ALT) (µkat/L) for RP2D and RP2D-1 cohorts (excluding the MTD)	SAF
Table	14.4.3.1	Aspartate Transaminase (AST) (µkat/L): Values, relative and absolute changes from baseline	SAF
Figure	14.4.3.2	Mean profile of Aspartate Transaminase (AST) (µkat/L) by cohort and All cohorts pooled	SAF
Figure	14.4.3.3	Patient profiles of Aspartate Transaminase (AST) (µkat/L) for RP2D and RP2D-1 cohorts (excluding the MTD)	SAF

Output	Number	Title	Analysis Set
Table	14.4.4.1	Alkaline Phosphatase (ALP) (µkat/L): Values, relative and absolute changes from baseline	SAF
Figure	14.4.4.2	Mean profiles of Alkaline Phosphatase (ALP) (µkat/L) by cohort and All cohorts pooled	SAF
Figure	14.4.4.3	Patient profiles of Alkaline Phosphatase (ALP) (µkat/L) for RP2D and RP2D-1 cohorts (excluding the MTD)	SAF
Table	14.4.4.4	Hepatic function (Hy's law)	SAF
Figure	14.4.4.5	Maximal levels per patient of Total Bilirubin (µmol/L), Alanine Transaminase (ALT) (µkat/L), Aspartate Transaminase (AST) (µkat/L), and Alkaline Phosphatase (ALP) (µkat/L) by cohort	SAF
		Other laboratory values	
Table	14.4.5.1	Haemoglobin (g/L): Values, relative and absolute changes from baseline	SAF
Figure	14.4.5.2	Mean profile of Haemoglobin (g/L) by cohort and All cohorts pooled	SAF
Table	14.4.6.1	Neutrophils (10^9/L): Values, relative and absolute changes from baseline	SAF
Figure	14.4.6.2	Mean profile of Neutrophils (10^9/L) by cohort and All cohorts pooled	SAF
Table	14.4.7.1	Neutrophils (%): Values and absolute changes from baseline	SAF
Figure	14.4.7.2	Mean profile of Neutrophils (%) by cohort and All cohorts pooled	SAF
Table	14.4.8.1	Lymphocytes (10^9/L): Values, relative and absolute changes from baseline	SAF
Figure	14.4.8.2	Mean profile of Lymphocytes (10^9/L) by cohort and All cohorts pooled	SAF
Table	14.4.9.1	Lymphocytes (%): Values and absolute changes from baseline	SAF
Figure	14.4.9.2	Mean profile of Lymphocytes (%) by cohort and All cohorts pooled	SAF
Table	14.4.10.1	Lactate Dehydrogenase (LDH) (µkat/L): Values, relative and absolute changes from baseline	SAF
Figure	14.4.10.2	Mean profile of Lactate Dehydrogenase (LDH) (µkat/L) by cohort and All cohorts pooled	SAF
Table	14.4.11.1	Platelet count (10^9/L): Values, relative and absolute changes from baseline	SAF

Output	Number	Title	Analysis Set
Figure	14.4.11.2	Mean profile of Platelet count (10^9/L) by cohort and All cohorts pooled	SAF
Table	14.4.12.1	C-reactive protein (CRP) (mg/L): Values, relative and absolute changes from baseline	SAF
Figure	14.4.12.2	Mean profile of C-reactive protein (CRP) (mg/L) by cohort and All cohorts pooled	SAF
	Section 14.5 Vital Signs		
Table	14.5.1.1	Systolic blood pressure (mmHg): Values and absolute changes from baseline	SAF
Figure	14.5.1.2	Mean profile of Systolic blood pressure (mmHg) by cohort and All cohorts pooled	SAF
Table	14.5.2.1	Diastolic blood pressure (mmHg): Values and absolute changes from baseline	SAF
Figure	14.5.2.2	Mean profile of Diastolic blood pressure (mmHg) by cohort and All cohorts pooled	SAF
Table	14.5.3.1	Heart rate (beats/min): Values and absolute changes from baseline	SAF
Figure	14.5.3.2	Mean profile of Heart rate (beats/min) by cohort and All cohorts pooled	SAF
Table	14.5.4.1	Respiratory rate (breaths/min): Values and absolute changes from baseline	SAF
Figure	14.5.4.2	Mean profile of Respiratory rate (breaths/min) by cohort and All cohorts pooled	SAF
Table	14.5.5.1	Body temperature (Celsius (°)): Values and absolute changes from baseline	SAF
Figure	14.5.5.2	Mean profile of Body temperature (Celsius (°)) by cohort and All cohorts pooled	SAF
	Section 14.6 ECG		
Table	14.6.1.1	QT (ms): Values, relative and absolute changes from baseline	SAF
Table	14.6.2.1	QTcF (ms): Values, relative and absolute changes from baseline	SAF
Figure	14.6.2.2	Mean profile of QTcF (ms) by cohort and All cohorts pooled	SAF
Table	14.6.3.1	QTcF (ms): Frequency of Intervals	SAF

Output	Number	Title	Analysis Set
	Section 14.7	**ECOG**	
Table	14.7.1	ECOG performance status	SAF
	Section 14.8	**Immunogenicity**	
Table	14.8.1	Anti-drug antibodies	SAF
Table	14.8.2	Titration of anti-drug antibodies	SAF
Table	14.8.3	Neutralizing anti-drug antibodies	SAF

10.6 APPENDIX 16.2 OF CSR (PATIENT DATA LISTINGS)

All patients included in clinical database will be listed (if not specified otherwise).

Listing Number	Title
Section 16.2.1	**Discontinued patients**
16.2.1.1	Study dates and patients' discontinuation overview in treated patients
16.2.1.2	Screening failures and withdrawals prior study treatment start
Section 16.2.2	**Protocol Deviations**
16.2.2.1	CSR reportable protocol deviations
16.2.2.2	CSR not reportable protocol deviations
16.2.2.3	Eligibility criteria and eligibility verification
16.2.2.4	Protocol deviations related to COVID-19
Section 16.2.3	**Patients excluded from efficacy analysis**
16.2.3.1	Disposition of patients to analysis sets and reasons for exclusion
Section 16.2.4	**Demographic data**
16.2.4.1	Informed consent signatures
16.2.4.2	Demographic data, patients' characteristics and disease history details
16.2.4.3	Medical history
16.2.4.4	Medical history – MedDRA coding details
16.2.4.5	Prior medication
16.2.4.6	Prior medication (including WHODD coding)
16.2.4.7	Prior anticancer systemic therapy (including WHODD coding)
16.2.4.8	Prior anticancer non-systemic therapy (including MedDRA coding)
16.2.4.9	Concomitant medication
16.2.4.10	Concomitant medication (including WHODD coding)
16.2.4.11	Post-treatment medication
16.2.4.12	Post-treatment medication (including WHODD coding)
16.2.4.13	Prior non-pharmacological therapy (including MedDRA coding)
16.2.4.14	Concomitant non-pharmacological therapy (including MedDRA coding)
16.2.4.15	Post-treatment non-pharmacological therapy (including MedDRA coding)
16.2.4.16	New anticancer systemic therapy (including WHODD coding)

Listing Number	Title
16.2.4.17	New anticancer non-systemic therapy (including MedDRA coding)
Section 16.2.5	**Compliance and drug concentration data**
16.2.5.1.1	Exposure to SOT101
16.2.5.1.2	Exposure to pembrolizumab
16.2.5.2.1	SOT101 Dose intensity
16.2.5.2.2	Pembrolizumab Dose intensity
16.2.5.3	Body weight and compliance of study drug administration with Study Protocol
16.2.5.4	SOT101 concentration levels
16.2.5.5	SOT101 pharmacokinetic parameters
Section 16.2.6	**Individual efficacy response and pharmacodynamics data**
16.2.6.1	Tumor assessment
16.2.6.2	Disease response
16.2.6.3	Clinical progression
16.2.6.4	Pharmacodynamics markers and cytokine levels
16.2.6.5	Maximal levels of Cytokines
Section 16.2.7	**Adverse events listings**
16.2.7.1	Listing of DLT events
16.2.7.2	All treatment-emergent AEs
16.2.7.3	All treatment-emergent SAEs
16.2.7.4	Treatment-emergent AEs recorded in detailed description of dose limiting toxicities
16.2.7.5	All adverse events leading to death
16.2.7.6	Causes of death including MedDRA coding details
16.2.7.7	Treatment-emergent AEs leading to permanent discontinuation of SOT101
16.2.7.8	Treatment-emergent AEs leading to permanent discontinuation of pembrolizumab
16.2.7.9	Treatment-emergent AEs with suspected causal relationship with SOT101
16.2.7.10	Treatment-emergent AEs with suspected causal relationship with pembrolizumab
16.2.7.11	Treatment-emergent AE immune-related
16.2.7.12	Treatment-emergent clinical signs/symptoms of cytokine release syndrome
16.2.7.13	Adverse events started before the first study drug administration
16.2.7.14	Adverse events with missing or partial start date

Listing Number	Title
16.2.7.15	Adverse events – MedDRA coding details
Section 16.2.8	**Listing of individual laboratory measurements**
16.2.8.1	Hematology
16.2.8.2	Biochemistry
16.2.8.3	Coagulation
16.2.8.4	Urinalysis
16.2.8.5	Maximal levels of selected laboratory variables
16.2.8.6	Creatinine clearance levels
16.2.8.7	Thyroid function tests (TSH, free T3, free T4)
16.2.8.8	Cardiac troponin-T test
16.2.8.9	C-reactive protein (CRP) levels
16.2.8.10	Glycated hemoglobin (HbA1c)
16.2.8.11	24-hour urine protein test
16.2.8.12	Pregnancy test
16.2.8.13	Serology (HIV, hepatitis B and C tests)
16.2.8.14	Listing of abnormal laboratory results
Section 16.2.9	**Other safety data**
16.2.9.1	Vital signs
16.2.9.2	ECG results
16.2.9.3	Echocardiography results
16.2.9.4	Date of physical examination
Section 16.2.10	**Other data**
16.2.10.1	ECOG performance score
16.2.10.2	Immunogenicity

11 LAYOUT REQUIREMENTS OF TFLs

No layout requirements specified by the sponsor.

12 APPENDICES

12.1 PHARMACOKINETIC ANALYSIS PLAN

N-A-PH1-19-027_SC 103_Pharmacokineti

12.2 TIMEPOINT LABELS SPECIFICATIONS

For vital signs: Pre-dose, 15 min, 30 min, 1 h, 2 h, 3 h, 4 h, 5 h, 6 h, 7 h, 8 h will be used as per eCRF records. In the listings also real time since SOT101 administration will be presented. In the Follow-up period (Follow-up) the timepoints will be presented as EOT + X weeks as defined in the Study Protocol.

For electrocardiogram (ECG): Pre-dose, 4 h will be used as per eCRF records. In the listings also real time since SOT101 administration will be presented. At EOT visit, the timepoint will be presented as EOT as defined in the Study Protocol.

For PK and Cytokine blood sampling: Pre-dose, 30 min, 1 h, 2 h, 4 h, 6 h, 8 h, 12 h, 24 h will be used as per eCRF records. In the listings, also real time since SOT101 administration will be presented.

For safety laboratory: as per standard medical practice the safety laboratory should be performed before the dosing then the label will be Cycle X Day Y – Pre-dose; otherwise, just Cycle X Day Y will be presented except in EOT visit which will be presented as EOT as defined in the Study Protocol.

Other assessments (Physical examination, body weight and Eastern Cooperative Oncology Group (ECOG) performance status) will be presented using the Cycle X Day Y label, except in the Follow-up period (Follow-up) where the label will be EOT + X weeks as defined in the Study Protocol.

In the listings, "^{UNS}" will be added to assessments performed in addition to assessments planned in the Study Protocol, for example Screening^{UNS} for some not required at screening by the Study Protocol or repeated assessment at screening, Follow-up ^{UNS} for hematologic assessment or Cycle 1 Day 9^{UNS} for coagulation assessment or Cycle 1 Day 12^{UNS}.

Time-points labels of tumor assessment: Tumor assessment will be recorded into eCRF as repeated pages and will be analyzed as iORR, iCBR, and time to event data. Therefore, time-point labels for tables will not be needed. In the listings the assessments will be identified by date, real treatment week (as defined in section 6.2, rounded to one decimal), and period label ("Cycle X" derived as defined below) or "Follow-up".

Cycle derivation:

- For each cycle will be identified Day 1 (as per eCRF records) and end of cycle as defined in section 5.1.
- Then, it will be identified which cycle the assessment date belongs to.

Time-points labels for survival follow-up information: The similar approach as for tumor assessment will be applied. Time-point labels for tables will not be needed. In the listings the information will be identified by date, real treatment week, and label "Follow-up".

Time-point labels used in tables of adverse events:

The tables of adverse events will present summary of treatment-emergent adverse events (TEAEs) recorded during the study and TEAEs depending on the time period:

- Cycle X: the time-point label will indicate treatment cycle when the adverse event (AE) started
- After last: the time-point label will indicate AEs started after end of last cycle

See treatment cycle definition in the section 5.1 above. Treatment cycle when TEAE started will only be derived for AEs with complete (and non-missing) start dates.

12.3 CANCER TYPE DERIVATION

Histological type	Primary tumor location	Cancer type (long name)	Cancer type (short name)
squamous	Anus	Anal SCC	Anal
adenocarcinoma	Other: Ampullary Carcinoma	Ampullary	Ampullary
carinosarcoma	Ovarian	Ovarian	Ovarian
squamous cell carcinoma of the anal canal	Anus	Anal SCC	Anal
gastric carcinoma with lymphoid stroma	Stomach	Gastric	Gastric
medullary thyroid carcinoma	Thyroid gland	Thyroid medullary	Thyroid
squamous cell carcinoma of the left leg	Skin	Skin SCC	Skin SCC
adenocarcinoma of the endocervical type	Cervix uteri	Cervix uteri	Cervix uteri
bladder urothelial carcinoma	Bladder	Bladder urothelial	Bladder
CHOLANGIOCARCINOMA	Liver	Liver	Liver
Adenocarcinoma	Stomach	Gastric	Gastric
adenocarcinoma	Colorectal	Colorectal	Colorectal
malignant melanoma	Skin	Melanoma	Melanoma
Lieberkuhnian adenocarcinoma	Colorectal	Colorectal	Colorectal
melanoma epithelioid type of the cervix	Other: Melanoma	Melanoma	Melanoma
Malignant mesothelioma of epithelioid type, peritoneum	Mesothelium	Mesothelioma	Mesothelioma
squamous cell carcinoma of the cervix FIGO IIIb	Cervix uteri	Cervix uteri	Cervix uteri
Achromic gingival mucosal melanoma	Other: Gum	Melanoma	Melanoma
epithelial and sarcomatoid right pleural	Mesothelium	Mesothelioma	Mesothelioma
adenocarcinoma	Colorectal	Colorectal	Colorectal
poorly differentiated adenocarcinoma of hepatocholedochus	Biliary tract	Biliary tract	Biliary tract

13 REFERENCES

[1] Seymour L, Bogaerts J, Perrone A, Ford R, Schwartz LH, Mandrekar S, Lin NU, Litière S, Dancey J, Chen A, Hodi FS, Therasse P, Hoekstra OS, Shankar LK, Wolchok JD, Ballinger M, Caramella C, de Vries EGE, group Rw. iRECIST: guidelines for response criteria for use in trials testing immunotherapeutics. The Lancet Oncology. 2017;18(3):e143-e152. ICH guidelines - E9: Statistical Principles for Clinical Trials, Adopted in EU by CPMP, March 1998, issued as CPMP/ICH/363/96

[2] ICH guidelines - E3: Structure and Content of Clinical Study Reports, Adopted in EU by CPMP, December 95, issued as CPMP/ICH/137/95

[3] U.S. Food and Drug Administration. E14 clinical evaluation of QT/QTc interval prolongation and proarrhythmic potential for non-antiarrhythmic drugs: Guidance for industry. 2018; https://www.fda.gov/downloads/Drugs/GuidanceComplianceRegulatoryInformation/Guidances/ucm073153.pdf. Accessed October 22, 2018.

[4] Smith BP, Vandenhende FR, deSante KA, et al (2000)., Confidence Interval Criteria for Assessment of Dose proportionality. Pharmaceutical Research, 17:1278-1283.

[5] Zhou, J., J. Li, and B. Coate. 2006. Empirical Power Estimation for Phase I Dose Proportionality Studies Based on Power-Law Model Using Confidence Interval Criteria. In SUGI 31, San Francisco, California.

[6] SAS 9.4; 2008 by SAS Institute Inc., Cary, NC, USA; OnLine Doc.

Statistical Analysis Plan
Study Part B1

A multicenter open-label phase 1/1b study to evaluate the safety and preliminary efficacy of SO-C101 as monotherapy and in combination with pembrolizumab in patients with selected advanced/metastatic solid tumors.

Sponsor:	SOTIO Biotech AG
Study code:	SC103
EudraCT number:	2018-004334-15
VERSION:	Final 1.0
DATE:	05-OCT-2023

STATISTICAL ANALYSIS PLAN APPROVAL

We, the undersigned, confirm that we have read and are in agreement with the contents of this document.

NAME	[redacted]	
JOB TITLE		
SIGNATURE		
DATE		
NAME		
JOB TITLE		
SIGNATURE		
DATE		
NAME		
JOB TITLE		
SIGNATURE		
DATE		
NAME		
JOB TITLE		
SIGNATURE		
DATE		

TABLE OF CONTENTS

ABBREVIATIONS

ADA	Anti-drug antibodies
AE	Adverse Event
ALT	Alanine Transaminase
AST	Aspartate Transaminase
ATC	Anatomic, Therapeutic, Chemical (Classification System for Drugs)
AUC	Area under the plasma concentration-time curve
$AUC_{(0\text{-}inf)}$	Area under the plasma concentration-time curve from time zero to infinity
$AUC_{(0\text{-}t)}$	Area under the plasma concentration-time curve from time zero to time t
BLQ	Below Limit of Quantification
CBR	Clinical Benefit Rate
CD	Cluster of differentiation (cells)
CK	Cytokines
CL	Apparent total body clearance of the drug from plasma
C_{max}	Maximum (or peak) serum concentration
CPI	Check Point Inhibitors
CRF	Case Report Form
CRP	C-Reactive Protein
CSR	Clinical Study Report
CV	Coefficient of Variation
DB	Database
DEC	Dose Escalation Committee
DEM	Dose Escalation Meeting
DLT	Dose Limiting Toxicity
DOR	Duration of Response
ECG	Electro-cardiogram
ECOG	Eastern Cooperative Oncology Group
eCRF	Electronic Case Report Form
EOT	End of Treatment
FU	Follow-up
HLGT	High Group Level Term
HLT	High Level Term
IAP	Independent Advisory Panel
ICF	Informed Consent Form
ICH	International Conference of Harmonization
iCBR	(immune) Clinical Benefit Rate (based on response as per iRECIST)
iCPD	(immune) Confirmed Progression Disease (as per iRECIST)
iCR	(immune) Complete Response (as per iRECIST)
ID	(Patient) Identification Number
iDOR	(immune) Duration of Response (based on response as per iRECIST)
IMP	Investigational Medicinal Product
iORR	(immune) Overall Response Rate (based on response as per iRECIST)

iPFS	(immune) Progression Free Survival (as per iRECIST)
iPR	(immune) Partial Response (as per iRECIST)
iRECIST	(immune-based) Response Evaluation Criteria in Solid Tumors
iSD	(immune) Stable Disease (as per iRECIST)
iUPD	(immune) Unconfirmed Progression Disease (as per iRECIST)
IV	Intravenous
KM	Kaplan-Meier
LDH	Lactate Dehydrogenase
LLT	Lowest Level Term
Max	Maximum
MedDRA	Medical Dictionary for Regulatory Activities
Min	Minimum
MTD	Maximal Tolerated Dose
NK	Natural Killer (cell)
NKT	Natural killer T (cell)
ORR	Objective Response Rate
OS	Overall Survival
PBMC	Peripheral Blood Mononuclear Cell
PD	Pharmacodynamic
PK	Pharmacokinetic
PT	Preferred Term
Q1	Lower Quartile
Q3	Upper Quartile
QT	QT interval
QTcF	Fridericia's correction of QT interval
R_{ac}	Accumulation ratio
RP2D	Recommended Phase 2 dose
SAE	Serious Adverse Event
SAF	Safety Set
SAP	Statistical Analysis Plan
SAS	Statistical Analysis Systems
SOC	System Organ Class
StD	Standard Deviation
$t_{1/2}$	Elimination half-life (to be used in one-or noncompartmental model)
$t_{1/2\alpha}$	Initial or disposition half-life
TEAE	Treatment-emergent Adverse Events
TFLs	Tables, Figures and Listings
T_{max}	Time to reach maximum (peak) plasma concentration following drug administration
Treg	Regulatory T (cells)
ULN	Upper limit of Normal
V_d	Apparent volume of distribution
WHODD	World Health Organizations Drug Dictionary
λ_z	Termination elimination constant (symbol k_e is also used)

INTRODUCTION

Statistical evaluation of each SC103 study (AURELIO-03) part will be performed separately after lock of the relevant study part data in clinical database. This Statistical Analysis Plan (SAP) describes the statistical analyses and planned outputs for Study Part B1. It includes definition of objectives and endpoints as per Study Protocol, the definition of analysis sets, and details needed for statistical programming. The SAP outlines the tables, listings and figures (TFLs) to be compiled in the Clinical Study Report (CSR).

This SAP does not include pharmacokinetic analysis plan. SO 101 (previously SO C101, RLI-15; INN nanrilkefusp alfa) concentrations levels are measured by [redacted] ho are also responsible for pharmacokinetic analysis and for writing pharmacokinetic analysis plan. This SAP does not include plan of statistical analysis to be performed on biomarkers collected from tumor tissue samples as collected data are limited and this analysis is intended to be fully exploratory.

This SAP is written according to the SC103 Study Protocol version 10.0 dated on 29-JUL-2021, current Mock Case Report Form (CRF), DEC charter version 4.0 dated on 26-MAR-2021, and IAP charter version 3.0 dated on 30-MAR-2021. The analyses and outputs closely follow the ICH guidelines for industry on topic E3 (Structure and Content of Clinical Study Reports) and E9 (Statistical Principles for Clinical Trials).

DOCUMENT HISTORY

Version	Date	Description of change	Performed b
Draft 0.1	18-SEP-2023	First version of the document created based on Part A1 SAP.	[redacted]
Final 1.0	05-OCT-2023	Final version after stakeholder feedback	

1 PLANNED CHANGES FROM STUDY PROTOCOL

In study protocol version 10.0, dated 29-JUL-2021, SO-C101 is specified in “Investigational medicinal products”. Throughout this SAP, SOT101 is used instead of SO-C101.

2 STUDY OBJECTIVES

2.1 PART B1 - SOT101 COMBINATION THERAPY, DOSING SCHEDULE 2

2.1.1 Primary objectives

- To assess the safety and tolerability of SOT101 when combined with pembrolizumab
- To determine the maximal tolerated dose (MTD) and/or recommended Phase 2 dose (RP2D) of SOT101 when combined with pembrolizumab

2.1.2 Secondary objectives

- To characterize the PK of SOT101 when combined with pembrolizumab
- To characterize the PD of SOT101 in peripheral blood when combined with pembrolizumab
- To determine the preliminary efficacy of the combination of SOT101 twice daily with pembrolizumab as measured by ORR, DOR, CBR, and PFS according to iRECIST
- To determine the immunogenicity of SOT101 in combination with pembrolizumab

According to iRECIST terminology, responses assigned using iRECIST have a prefix of “i” (“i” stands for immune); therefore, abbreviations iORR, iDOR, iCBR, iPFS will be used afterwards.

2.1.3 Exploratory objectives

- To explore the mechanistic effects of SOT101 in combination with pembrolizumab on selected immune cell populations in tumor tissue samples. Analysis of this exploratory objective is not described in this SAP, instead, a separate Biomarker analysis plan will be prepared.
- To assess overall survival (OS)

3 STUDY DESIGN

Study design is briefly described below. Full description of study design is included in the Study Protocol. The schedule of procedures and assessments is presented in the Study Protocol Table 9.6 to 9.17.

3.1 DEFINITION OF MTD/RP2D AND IMPLEMENTATION OF 3+3 DOSE ESCALATION DESIGN

Part B1 will start with the starting daily dose at 1 dose level below the RP2D identified in Part B (which will be split into two identical [50%:50%] daily doses) until the MTD and/or RP2D of SOT101 given as per dosing schedule 2 in combination with pembrolizumab is defined.

MTD is defined as the dose level associated with ≥33% of DLT evaluable patients experiencing a DLT. If the MTD is reached, the RP2D will be conventionally defined as the dose level just below this non-tolerated dose level. If the MTD is not reached, the RP2D will be selected based on integrated evaluation of safety, tolerability, clinical benefit, PK and PD data, for all dose levels tested.

The 3+3 dose escalation design to identify MTD/RP2D includes the following steps for each dose level until MTD/RP2D is identified:

1. One patient will be enrolled and will receive the first eight doses of SOT101 (2 on day 1, 2 on day 2, 2 on day 8, and 2 on day 9) together with a fixed dose of pembrolizumab (200 mg IV every 3 weeks) given with the first administration of SOT101 on day 1. This patient will be observed for safety for 7 days after the eighth dose of SOT101, starting from day 9.
    - If there are no safety concerns at the end of these 7 days, second and third patients will be allowed to be dosed. The second and third patients will not be dosed on the same day.
    - Otherwise, dose escalation meeting (DEM) will be organized and DEC/IAP will decide next steps.
2. Next steps will depend on the occurrence of DLT within the DLT evaluation period of 21 days:
    - If **no DLT occurs** in 3 DLT evaluable patients, then next patient cohort treated with **higher dose level will start**.
    - If **one DLT occurs** in 3 DLT evaluable patients, then the cohort will be **extended to 6 DLT evaluable patients in total**.
        - If **one DLT occurs** in the 6 DLT evaluable patients, then the next patient cohort treated with **higher dose level start**.
        - If **≥2 DLTs occur** in the 6 DLT evaluable patients, then MTD is identified and **enrolment/escalation is stopped**.
    - If **≥2 DLTs occur** in 3 DLT evaluable patients, then MTD is identified **and enrolment/escalation is stopped**.

3.2 RANDOMIZATION AND BLINDING

Not applicable.

4 STUDY ENDPOINTS

4.1 DEMOGRAPHY AND BASELINE CHARACTERISTICS

The following baseline characteristics are of interest:

- Demographic characteristics:
  - Age at informed consent (ICF) signature [years]
  - Age at informed consent (ICF) signature [years] according to: <18 years, >18 and ≤64 years, >64 and ≤84, >84 or older
  - Gender
  - Ethnicity
  - Race
- Baseline characteristics
  - Weight [kg]
  - Body Mass Index (derived)[kg/m^2]
- Disease history
  - Primary tumor location
  - Histological type
  - Cancer type (derived)
  - Time since diagnosis at ICF signature (derived) [years]
  - Time since latest radiological or clinical disease progression at ICF signature (derived) [weeks]
  - Number of lines of previous systemic anticancer therapy
  - Number of lines of previous systemic anticancer therapy categories: ≤ 2, > 2.
  - Previous treatment with check point inhibitors (CPI) (Yes/ No/ Unknown)
  - CPI Response (if CPI received) (Refractory/ Relapsed/ Unknown)
  - Prior anticancer non-systemic therapy (Yes/ No)
  - ECOG
  - ECOG categories: 0, > 0

4.2 ENDPOINTS

4.2.1 Primary endpoints

- Safety and tolerability of SOT101 combined with pembrolizumab as evaluated by the incidence of DLTs, incidence of SOT101-related adverse events (AEs), SAEs, AEs leading to premature discontinuation of SOT101, deaths, and clinical laboratory test abnormalities.
- Further, endpoints of the study are to determine MTD and the RP2D of SOT101 combined with pembrolizumab (as defined in the section 3.1).

4.2.2 Secondary endpoints

- PK of SOT101 combined with pembrolizumab
- Immune response after administration of SOT101 in combination with pembrolizumab characterized by the changes in expression of immune markers in PBMCs
- iORR, iDOR, iCBR, and iPFS
- Detection of Anti-drug antibodies (ADA)

4.2.3 Exploratory endpoints

- Changes in the expression of immune biomarkers after administration of SOT101 in combination with pembrolizumab as compared to baseline in tumor tissue (analysis of this endpoint is not described in this SAP).
- OS at 6 months after the EOT visit.

5 COMMON DEFINITIONS

General and common definition relevant for statistical analysis/ Statistical Analysis Systems (SAS) programming are listed below. Definitions used only in analysis of a particular endpoint are included directly in analysis section.

5.1 TREATMENT CYCLE

Each treatment cycle in Part B1 should include 8 SOT101 administrations and should take 21 days as per Study Protocol. However, treatment interruptions and delays can occur. Therefore, the cycle number will be taken from the electronic CRF (eCRF) database.

Throughout this SAP, start of study treatment is defined as the date of first SOT101 or pembrolizumab administration, whichever occurs first. The end of study treatment refers to the date of the last SOT101 or pembrolizumab administration, whichever occurs last.

The start of each cycle is defined by the date of the first SOT101 or pembrolizumab administration in the cycle, whichever occurs first.The cycle lasts until Day 1 of the next cycle. The last cycle end is defined as Day 21 of the last cycle or end of the study participation (whatever occurs first).

5.2 LABELS USED IN SAP AND IN STATISTICAL OUTPUTS

EOT stands for end of treatment. FU stands for follow-up.

Cohort labels will include number of dose level (and dose administered µg/kg) as per Study Protocol. The label will be based on information recorded in eCRF in "Initial dose of SOT101 (ug/kg)".

- Example: 1 (4.5 µg/kg).

Individual time-points labels will be as follows:

- Screening
- Cycle X Day Y
    - Cycles will be identified by the number of the cycle as per eCRF data.
    - Days will be identified by the number of the day as per eCRF data.
- EOT
- EOT + X weeks, see below

The assignment to the time-point labels will be performed via SAS programming as follows:

- If Date of assessment – date of EOT ≤ 4+2 weeks then label = "EOT + 4 weeks"
- If 6 weeks < Date of assessment – date of EOT ≤ 8+2 then label = "EOT + 8 weeks"
- If 10 weeks < Date of assessment – date of EOT ≤ 12+2 then label = "EOT + 12 weeks", etc.

If two assessments are assigned to the same time-point label, the earliest assessment will be selected.

In the listings, the real post-treatment week (see section 6.2, rounded to one decimal) will be presented as well.

Timepoint labels used in the statistical outputs and derivations are described in the Appendix, Section 12.2.

5.3 BASELINE VALUES

5.3.1 Study baseline

Study baseline will be defined as the last non-missing measurement prior to start of study treatment, unless specified otherwise.

5.3.2 Handling of missing data needed for baseline identification

The definitions above consider date and time of the assessment and start of study treatment. If time is not known, then only dates will be used for identification of the baseline. Safety laboratory samples are supposed to be taken before study drug administration; therefore, if time of sample collection is not known and date is the same as date of administration then it will be considered as pre-dose sample.

Values which are identified as baseline via rule described in this paragraph will be flagged in the listings.

5.4 CODED TERMS AND DICTIONARIES USED

Data will be coded as described in the following table.

Table 3: Data to be coded

eCRF page name	Variable to be coded (Dictionary to be used for coding)
The previous therapies include the following pages:	
PRIOR ANTICANCER SYSTEMIC THERAPY	Medication (WHODD)
PRIOR ANTICANCER NON-SYSTEMIC THERAPY	Location and Surgery description (MedDRA)
Further, details about prior and concomitant medication/therapies will be collected on the following pages:	
MEDICATION DETAILS	Medication (WHODD)
NON-PHARMACOLOGICAL THERAPY DETAILS	Therapy (MedDRA)
NEW ANTICANCER SYSTEMIC THERAPY DETAILS	Medication (WHODD)
NEW ANTICANCER NON-SYSTEMIC THERAPY DETAILS	Location and Surgery description (MedDRA)
MEDICAL HISTORY DETAILS	Medical history term (MedDRA)
ADVERSE EVENT DETAILS	Adverse event term (MedDRA)
DEATH	Immediate cause of death and Underlying cause of death (MedDRA)

The coding will be performed directly in eCRF system. The terms will be coded with the most current version of Medical Dictionary for Regulatory Activities (MedDRA) and WHODD dictionaries at time of DB lock.

All MedDRA and WHODD levels listed below will be presented in the listings.

MedDRA coding levels will include:

- Preferred Term (PT)
- Lowest Level Term (LLT)
- High Level Term (HLT)
- High Group Level Term (HLGT)
- Primary System Organ Class (SOC)

WHODD coding will include the following Anatomic, Therapeutic, Chemical (ATC) levels:

- ATC Level 1: anatomical main group
- ATC Level 2: therapeutic subgroup
- ATC Level 3: pharmacological subgroup
- ATC Level 4: chemical subgroup
- WHODD preferred name

5.5 PREVIOUS/CONCOMITANT/POST-TREATMENT MEDICATIONS/ THERAPIES

The records of prior and concomitant medications/ therapies will be classified as "Prior", "Concomitant" and "Post-treatment" according to the following definitions.

"Concomitant" medication/therapy is any medication/therapy which was administered in the period starting with the start of study treatment (including) and lasts until the end of study treatment. The only exception will be medication/therapy which started on day of the end of study treatment: this medication will be classified as "Post-treatment".

"Prior" medication/therapy is any medication/therapy ended before the start of study treatment.

"Post-treatment" medication/therapy is any medication/therapy which started after or at the end of study treatment.

For records of medication/therapy with unknown and incomplete dates which cannot be identified according to definitions described above, the following rules will be applied:

- If end date of medication/therapy is completely unknown and the medication/therapy started after or at the end of study treatment, the medication/therapy will be counted as "Post-treatment". Otherwise (i.e., the medication/therapy started before the end of study treatment), the medication/therapy will be counted as "Concomitant".
- If start date of medication/therapy is completely unknown and the medication/therapy ended after or at start of study treatment, the medication/therapy will be counted as "Concomitant". Otherwise (i.e., the medication/therapy ended before the start of study treatment), the medication/therapy will be counted as "Prior".
- If start or end date is incomplete: the first possible start date (e.g., for xxDEC2019 this is 01DEC2019, for xxxxx2019 this is 01JAN2019) or last possible end date (e.g., for xxDEC2019 this is 31DEC2019, for xxxxx2019 this is 31DEC2019) will be derived. Classification "Prior", "Concomitant" and "Post-treatment" medication/therapy will be performed using these derived dates.
- If both end date and start date of medication/therapy are completely unknown, then it will be counted as "Concomitant".

5.6 ADVERSE EVENT (AE)

Detailed definition of AE and its classification is presented in the Study Protocol (See section 9.11.5.1).

Each increase or decrease of severity of AE will be collected as separate AE record on "ADVERSE EVENT DETAILS" eCRF page.

Raw data will be used to identify AE episodes as follows:

- Linked AE records by the investigator (i.e. AE record with an outcome of "Change in severity" in the eCRF) with the same MedDRA preferred term, where the start date of the subsequent AE record is equal to (or +1 day) end date of the previous AE record, will be identified as one

AE (continuous) and each AE record will be assigned the same AE ID (equal to the AE ID of the first AE record in the episode).

In order to assign the TEAE status to AEs with the same AE ID (linked AE records), unaggregated data will be used. After the TEAE assignment, AE episodes with the same AE ID will be aggregated as per section 5.8.

5.7 TREATMENT-EMERGENT ADVERSE EVENTS (TEAE)

According to the Study Protocol section 9.13.10.2 treatment-emergent AE is defined as an AE that

- emerges during treatment, having been absent at pretreatment (screening), or
- reemerges during treatment, having been present at pretreatment (screening), or
- worsens in severity during treatment relative to the pretreatment state.

Emerges or reemerges during treatment:

TEAEs are AEs with start date ≥ start of study treatment. Conditions when date/time is unknown or incomplete are defined below.

Worsening in severity:

When the AE belongs to an AE episode (as defined in section 5.6) where the first AE record is not TEAE, the subsequent AE record will be TEAE if:

- AE with start date ≥ start of study treatment, and
- Worsens in severity as compared to pretreatment state.

For adverse events with unknown or incomplete start date/time the following rules will be applied:

Incomplete date: when some information is available (e.g., month, year), but date is partially missing (e.g., missing day, month).

Unknown date/time: when no information is available and thus day, month and year are missing.

Unknown time for start or end of AE:

If time of AE start, or start of study treatment is unknown, the information will be derived only using dates – if AE start or end dates are unknown, conditions are defined below.

If start date is unknown and end date is known (and complete):

- If end date/time is < start of study treatment, the event will not be counted as TEAE.
- If end date/time is ≥ start of study treatment, the event will be counted as TEAE.

If start date is incomplete and end date is incomplete or unknown:

- last possible start date of AE (e.g., for xxDEC2019 this is 31DEC2019, for xxxxx2019 this is 31DEC2019) will be derived. If the last possible start date of AE ≥ start of study treatment the event will be counted as TEAE. Otherwise, if last possible start date of AE < start of study treatment, the event will not be counted as TEAE.

If start date is unknown and end date is incomplete:

- last possible end date of AE (e.g., for xxDEC2019 this is 31DEC2019, for xxxxx2019 this is 31DEC2019) will be derived. If the last possible end date of AE ≥ start of study treatment the event will be counted as TEAE. Otherwise, if last possible end date of AE < start of study treatment, the event will not be counted as TEAE.

Unknown date for start and end of AE:

- If both start date and end date are unknown, the event will be counted as TEAE.

5.8 AGGREGATION OF CONTINUOUS AE AND TEAE

In order to aggregate AE and/or TEAE episodes (in text below referred just as 'AE') that are continuous, the following will be applied:

- AE will be TEAE if any of all AE records belonging to the AE is TEAE (as defined in section 5.7).
- Start date/time of AE will be start date of the first AE record belonging to the AE. This date will be used to derive the Cycle as defined in sections 5.1 and 5.2, as well as the last dose level of SOT101 before the start of the AE.
- End date /time of AE will be end date of the last AE record belonging to the AE.
- Outcome of AE will be outcome of the last AE record belonging to the AE.
- Severity will be the highest grade out of all AE records belonging to the AE.
- AE will be serious if any of all AE records belonging to the AE is evaluated as serious.
- AE will be immune-related if any of all AE records belonging to the AE is evaluated as AE immune-related. Secondly, AE will be not immune-related if any of all AE records belonging to the AE is evaluated as AE not immune-related.
- AE will have suspected relationship to SOT101 if any of all AE records belonging to the AE is evaluated as to have suspected relationship to SOT101.
- AE will have suspected relationship to pembrolizumab if any of all AE records belonging to the AE is evaluated as to have suspected relationship to pembrolizumab.
- Action taken to SOT101 will include all actions taken as per all AE records belonging to the AE.
- Action taken to pembrolizumab will include all actions taken as per all AE records belonging to the AE.

The definition above will be used for analysis datasets. Clinical signs/symptoms of cytokine release syndrome will not be aggregated.

Listings will present all AE and TEAE (not aggregated) as defined in Section 8.7.2 and Section 8.7.3.

6 GENERAL ALGORITHMS AND DERIVED VARIABLES

General and common algorithms to be used in SAS programming are listed below. Algorithms used only in analysis of particular endpoint are included directly in analysis section.

6.1 CONVERSION OF DAYS, MONTH, YEARS

Week will be counted as day/7. Planned to be used for presentation in listings where the value will be rounded for one decimal.

One year will be counted as 365.25 days.

One month will be counted as 365.25/12 days = 30.4375 days.

Number of calculated years and months will be used e.g. for calculation of age or survival time, rounding procedures are described in section 8.2.2.

6.2 TREATMENT/POST-TREATMENT DAY

Real treatment day will be calculated as date – date of the start of study treatment + 1. For dates before the start of study treatment, the treatment day will be negative and will be calculated as follows: date – start of study treatment.

Real post-treatment day will be calculated as date – date of the end of study treatment.

Real week, month and year will be converted from real day as defined in the section 6.1.

6.3 ALGORITHM FOR ALLOCATION OF DATA TO SCHEDULED VISITS/TIME-POINTS

The algorithms are described with definition of the time-point labels in Section 5.2.

6.4 APPLICATION OF CUT-OFF

No cut-off is planned to be applied for the final analysis.

7 ANALYSIS SETS

7.1 SAFETY SET (SAF)

The safety population will include all patients exposed to SOT101 or pembrolizumab in Part B1.

The SAF will be used for analysis of safety endpoints.

7.2 DLT-EVALUABLE PATIENTS

A patient evaluable for DLT will be a patient who has completed cycle 1 and received all planned treatments without any treatment delay or interruptions for any other reason than DLT: for Part B1, received all 8 doses of SOT101 and 1 dose of pembrolizumab as planned. Patients who do not fulfil these criteria for any other reason than DLT should be replaced.

The DLT evaluable patients will be used for ongoing safety evaluation needed for decisions as per 3+3 dose escalation design.

7.3 PK/PD EVALUABLE

PK analysis set will include patients with evaluable PK profile.

PD analysis set will include patients with evaluable PD profile.

Evaluation of PK and PD are secondary objectives of Study Part B1 which is a dose-escalation study; limited number of patients is included in the individual dose levels and in RP2D level. This needs to be considered when interpreting the data. The PK/PD profile is further explored in Part D.

Protocol deviations related to PK and PD assessment and compliance with dosing schedule will be reviewed. Only patients which data would lead to biased conclusions or analysis interpretation will be excluded from the analysis sets.

The PK/PD analysis set will include patients in both PK analysis set, and PD analysis set. The PK/PD evaluable patients will be used for PK/PD analysis.

7.4 EFFICACY SET

All patients exposed to SOT101 (exposure for at least one treatment cycle) who had at least one evaluable tumor assessment per iRECIST after the initiation of SOT101 treatment.

Exposure for at least one treatment cycle is defined as 8 doses of SOT101 (regardless of dose level) in Cycle 1 and 1 dose of pembrolizumab, or if the patient is exposed to SOT101 or pembrolizumab (with any number of doses) in Cycle 1 and started Cycle 2.

The Efficacy set will be used for analysis of efficacy endpoints.

8 STATISTICAL METHODS AND DETERMINATION OF SAMPLE SIZE

This section describes the data analysis in detail (with exception of pharmacokinetic analysis which is described in separate document attached). The statistical methods are planned in accordance with the Study Protocol (section 9.9) and in accordance with ICH Topic E9 Statistical Principles for Clinical Trials.

SAS version 9.4 or newer will be used for statistical programming.

8.1 SOURCE DATA TO BE USED FOR ANALYSIS

Data collected in clinical study database including MedDRA and WHODD coding will be used for analysis. Laboratory conversion factors will be taken from the internal IBMCD laboratory DB (as per Laboratory Data Unit Conversions standards).

Plasma concentration data and pharmacokinetic parameters will be provided by [redacted] .sas7bdat format and will be directly used for analysis [redacted] will not be a [redacted] art of clinical database). Dates and times of blood sampling in the datasets provided by [redacted] nd those recorded in the clinical database will be reconciled as a part data management processes

Description of the provided datasets:

- pc_cnp_DDMMMYYYY.sas7bdat: dataset providing the PK concentrations overtime, per patient.
- pp_cnp_DDMMMYYYY.sas7bdat: dataset providing the calculated PK parameters, per patient.

Where n is the number of the cohort, p is the study part (e.g., 'b1' for Part B1), DDMMMYYYY is the date of transfer. Further details are specified in data transfer specification "SC103_Data Transfer Specification [redacted] 07Jul2023" dated 07-Jul-2023.

Anti-drug antibodies data will be provided by [redacted]

Description of the provided datasets:

- SC103ADASNAPSHO [redacted] DMMMYYYY.csv: provides per patient and overtime ADA positivity, titration, and NADA positivity. Where DDMMMYYYY is the date of transfer.

Further details are specified in data transfer specification "SC103_Data Transfer Specification [redacted] v6.0_07Jul2023" dated 07-Jul-2023.

Plasma concentration data and pharmacokinetic parameters will be provided b [redacted] Materials for DEC/IAP will be directly prepared by [redacted] Sotio will provide outputs for CSR.

Pharmacodynamic variables and cytokines levels will be provided by Central LA [redacted] SAS® v.9 transport files and will be directly used for analysis (will not be a art of clinical database). Dates and times of blood sampling in the datasets provided by [redacted] and those recorded in the clinical database will be reconciled as a part data management processes

Description of the provided datasets:

- SC103SNAPSHO [redacted] DMMMYYYY.xpt: includes per patient and overtime the test results as per protocol. Where DDMMMYYYY is the date of file transfer.

Further d[redacted] specified in data transmission agreement "SC103_Data Transmission Agreement[redacted]v5.0_15Jun2021" dated 15-Jun-2021.

8.2 GENERAL PRINCIPLES

The study includes Study Part B1.

This is a Phase I study with 3+3 dose escalation design with primary objective to determine MTD/RP2D.

Due to low number of patients enrolled and treated in Part B1 of this study, only data listings will be provided.

8.2.1 Listings

Each listing will present the following variables/columns:

- Patient identification (ID), Cohort (dose level)
- If appropriate, analysis set relevant for particular listing

Listings will be sorted by ID and by chronological order of visits/assessments/events.

Dates will be presented in the listings in format YYMMDD10. (e.g., 2019-11-31). Partial dates as exported from the database will be listed (e.g., 2019-11-UNK, 2019-UNK-UNK, UNK-UNK-UNK).

8.2.2 Rounding procedures

Percentages will be presented with one decimal place with exception of efficacy data where two decimal places will be presented.

Other values such as temperature, number of weeks, coefficients of variation, etc. will be presented with one or two decimal places, according to the source data.

8.2.3 Unscheduled/ repeated assessments

Unscheduled/ repeated assessments which are performed in addition to those scheduled in the Study Protocol will not be used for analysis per time-point. Baseline values can include unscheduled/repeated assessment if they are the last before study drug administration (see section 5.3 for details).

8.2.4 Missing data

In general, missing data will not be imputed, i.e. complete case analyses will be performed. However, number of missing data is to be presented in descriptive statistics.

8.2.5 Methods for handling of incomplete/missing dates/ times

Methods for handling of incomplete and missing dates of medication/therapies and adverse events are presented in sections 5.5 and 5.7.

Similarly, methods for handling of incomplete and missing dates for Date of initial diagnosis are described in section 8.4.

8.2.6 Covariates and subgroups

The patients are planned to be analyzed by the cohorts (dose levels).

Subgroup analyses are not planned. No covariates to be used in analyses planned in this SAP.

8.2.7 Region/Country/Site analysis in multi-centric trial

Analysis by region, country or site is not planned.

8.2.8 Validation of statistical programming

Each SAS program will be validated by a second qualified SAS programmer to ensure a correct output and a correct presentation of the data. The validation process is documented in the validation sheet (GCPS_DMF_033 A-C), which also prespecifies criteria for risk categorization of programs and the corresponding validation actions.

Logs of all programs used for analysis and data preparation will be checked for errors and unexpected warnings. Any undocumented updating of raw study data in statistical programming instead of change in clinical DB (or source data) is not allowed.

8.3 DISPOSITION OF STUDY PATIENTS

Disposition of patients will be presented for Study Part B1:

- Screened and reason for screen failure
- Eligible (as per confirmation by the Sponsor), treated, DLT evaluable
- Study discontinued patients with reason for discontinuation
- SOT101 discontinued patients with reason for discontinuation
- Pembrolizumab discontinued patients with reason for discontinuation
- Patients in analysis set, patients excluded from analysis set and reasons for exclusion from analysis sets.

Protocol deviations will be listed.

8.4 DESCRIPTION OF BASELINE PATIENTS' CHARACTERISTICS

Baseline characteristics and disease history information defined in section 4.1 will be listed.

Cancer type will be medically reviewed prior to DBL and derived based on the list specified in Appendix (Section 12.3).

Body Mass Index will be calculated as weight in kg divided by height in m^2. Values will be rounded to one decimal.

Date of birth is not collected in the eCRF. Age at ICF signature in years as recorded in eCRF will be used. Then, time since diagnosis at ICF signature and time since latest radiological or clinical disease progression at ICF signature in years will be calculated as follows: date of ICF signature (at time of entering the study) – date of diagnosis/progression + 1 and transformed to years/weeks respectively as per section 6.1.

If Date of initial diagnosis is incomplete or partially missing, the following rules will be applied for imputation of dates:

- If day and month is missing, day will be imputed as 01 and month as 06.
- If only day is missing, day will be imputed as 01.
- If only month is missing, month will be imputed as 06.
- If year is missing or the date is completely unknown, no imputation will be performed.

Date of latest radiological or clinical disease progression will not be imputed regardless of unknown or partially missing dates.

Explanatory footnote will be presented in corresponding listing.

Medical history recorded in eCRF will be only listed.

8.5 MEDICATION/THERAPIES

Medication and therapies as specified in Table 3 will be listed. Separate listings for prior, concomitant, and post-treatment medication/therapies (see section 5.5) will be presented.

Prior, concomitant, and post-treatment procedures will also be listed.

8.6 EXPOSURE TO STUDY TREATMENTS

Duration of exposure to SOT101 will be calculated as: date of the last SOT101 administration - date of the first SOT101 administration + 1.

Duration of exposure to pembrolizumab will be calculated as: date of the last pembrolizumab administration - date of the first pembrolizumab administration + 1.

Dose intensity will be calculated as follows, for each patient:

- Sum of (SOT101 administrations x dose level) / duration of exposure (in days)
- Sum of (pembrolizumab administrations x 200mg) / duration of exposure (in days)

Duration of exposure to SOT101/pembrolizumab and dose intensity will be listed together with patient-years of exposure.

Dose level, Dilution Fold, Total Volume Administered, Body Weight at Day 1 of each cycle, calculated Volume for Administration (as described in SC103_Instruction for handling of IMP and Trial Related Materials_v4.0_16Mar2021 (v4.0)) and compliance of dosing schedule for SOT101 with Study Protocol will be presented in listings.

8.7 ANALYSES OF SAFETY

8.7.1 Summary of dose limiting toxicity events (DLTs) for determination of MTD/RP2D

AEs linked to DLTs will be listed. Information from dedicated DLT page in eCRF ("Dose Limiting Toxicity Details") will be merged in information recorded in "Adverse Event Details" eCRF page. Merging will be done on unaggregated data by Patient ID (AE.subnum, DLT.subnum) and AE number (AE.PAGESEQ, DLT.AENO).

8.7.2 Adverse events (AEs)

Details about AEs as collected on "Adverse Event Details" eCRF page will be used for analysis. Data collected on "Serious Adverse Event" eCRF page will be used for safety reporting in responsibility of pharmacovigilance department and will not be part of statistical outputs.

See section 5.8 for handling of AE records needed before programming of analysis datasets. All AE records will be presented in the listings without aggregation into AE episodes (derived number of episodes will indicate which AE records were aggregated for summaries).

8.7.3 Treatment-Emergent Adverse events (TEAEs)

TEAEs are defined in section 5.7 above. Note that as per Study Protocol AEs are collected in eCRF database until 90±2 days after last dose of SOT101.

Not TEAE will be presented in a separate listing.

8.7.3.1 Grouping of TEAEs

For harmonization and safety data review purposes, the following grouping of Preferred Terms will be considered in the analysis datasets. Listings of TEAEs will present the originally coded Preferred Term:

TEAE System Organ Class: Preferred Term	Preferred Term
Gastrointestinal disorders: Abdominal pain	Abdominal pain lower
	Abdominal pain upper
	Abdominal pain
Investigations: Blood bilirubin increased	Hyperbilirubinaemia
	Blood bilirubin increased
Investigations: Lymphocyte count decreased	Lymphopenia
	Lymphocyte count decreased
Investigations: Neutrophil count decreased	Neutropenia
	Neutrophil count decreased
Investigations: Platelet count decreased	Thrombocytopenia
	Platelet count decreased
General disorders and administration site conditions: Injection site reaction	Injection site reaction
	Injection site erythema
	Injection site rash
	Injection site pruritus
	Injection site induration
	Injection site inflammation
	Injection site oedema
	Injection site pain

8.7.3.2 General considerations for analysis of TEAEs

TEAEs will be included in analysis datasets and listed.

Clinical signs/symptoms of cytokine release syndrome (as per variable AE.AERELCRS) will be listed separately.

TEAEs with maximum severity observed for the patient by different categories will be marked in the analysis dataset.

8.7.3.3 Listing of AEs

Listings of AEs will present the following information in addition to data collected on eCRF page "ADVERSE EVENT DETAILS":

- Patient identification (ID), Study Part, Cohort (dose level), DLT evaluable (Yes/No)
- AE no. (derived as number of AE episode, see section 5.6, in chronological order of start date)
- TEAE (Yes/No) (derived)
- Cycle when AE started (derived)
- SOT101 Treatment Day when AE start (derived)
- Days* after the last SOT101 administration (derived)
- Last dose of SOT101 before AE start (derived)
- Total number of SOT101 administered before AE start**
- Duration of AE***
- MedDRA PT

* Days after last dose will be calculated as AE start date – administration date.

**If time of AE start is not recorded (or time of SOT101 administration is not recorded), the information will be derived only using dates (i.e., date of last SOT101 administered before date of AE start, SOT101 doses administered before date of AE start). The administration of SOT101 at the same date as date of AE start will be indicated as "(+1)", e.g. 5 (+1). If AE start date (or SOT101 administration date) is unknown or incomplete, the derivation will not be performed.

***Duration of AE will be calculated as AE end date– AE start date + 1. If end date or start date is missing or incomplete, the derivation will not be performed.

8.7.4 Other safety assessments

Other safety data include ECG, vital signs, clinical laboratory, physical examination, and echocardiography.

Date of physical examination, date and results of echocardiography assessment will be only listed.

Absolute values of laboratory data, vital signs and ECG parameters will be listed.

8.7.4.1 ECG

The listing of QTcF intervals will include a column to indicate whether a QTcF level met the following criteria which are defined in line with ICH E14.

- QTcF interval > 450
- QTcF interval > 480
- QTcF interval > 500
- QTcF interval increases from study baseline > 30
- QTcF interval increases from study baseline > 60
- Any criterion listed above met

8.7.4.2 Laboratory values

Laboratory values will be converted to standard units: the conversion factors to SI units will be maintained in the lab repository database (IBMCD LAB). Changes will be audit trailed in the system. The conversion of laboratory results into SI units will be performed via SAS programming.

Laboratory values will be listed.

For selected laboratory variables concerning liver enzymes (Total Bilirubin, ALT, AST, ALP):

- Maximal levels per patient will be also listed in dedicated listing.

For the analysis datasets, if there are two or more values on the same day, the pre-dose value will be considered (as per protocol, safety laboratory measurements should be performed prior to dosing). If two or more pre-dose values are available, the one closest to the dosing will be selected for analysis purposes.

Hepatic function abnormality defined by an increase in AST and/or ALT to ≥ 3 × Upper limit of normal (ULN) concurrent with an increase in total bilirubin to ≥ 2 × ULN but without increase in alkaline phosphatase (i.e., alkaline phosphatase < 2 × ULN) meets the criteria for Hy's law and raises the concern for drug-induced liver injury when no other cause is identified. Each value for ALT, AST, total bilirubin or alkaline phosphatase which meets a single condition for Hy's law will be marked in the dedicated listing independent on whether the remaining conditions were met at that time-point.

8.8 ANALYSES OF SOT101 CONCENTRATION DATA AND PK PARAMETERS

The PK analysis plan is provided b [redacted] nd attached to this SAP (section 12.1).

The following PK parameters will be calculated via non-compartmental model according to this plan:

- C_{max}
- T_{max}
- $t_{1/2,}$
- Termination elimination constant (λ_z)
- $t_{1/2\alpha}$ – distribution half-life (where possible)
- $AUC_{(0-6)}$, $AUC_{(0-t)}$, $AUC_{(0-24)}$, $AUC_{(0-inf)}$, same parameters per dose (AUC/D)
- CL - Clearance
- V_d - Volume of distribution
- R_{ac} - accumulation ratio over cohorts/dose levels

Concentration levels, C_{max}, T_{max}, AUC (all), $t_{1/2}$, dose-normalized C_{max} (C_{max}/D), and T_{max} will be listed.

In line with Protocol Deviation Plan, PK samples taken out of schedule defined by the study protocol will be flagged in concentration listings and will not be a part of protocol deviation listing.

Values below the BLQ will be treated as 0 when performing the analysis on a linear scale. On the logarithmic scale, these values will be disregarded.

Hemolytic samples:
Any samples with presence of hemolysis will be flagged in the analysis dataset and listings as follows: a keyword search (both in lower and upper case) of "Hemolytic", "Hemolysis" will be performed on concentration dataset, column LABCOM.

8.9 ANALYSES OF PHARMACODINAMIC MARKERS AND CYTOKINES

PD markers and cytokines levels will be provided by [redacted] and will not be a part of eCRF database.

The PD marker of interest are as follows:

CD8 Panel
CD8+ Cells of CD3+ Cells (%)
CD8+ Cells of CD3+ Cells(%CD45+)
Ki-67+ Cells of CD8+ Cells (%)
Ki-67+ Cells of CD8+ Cells (%CD45+)
CD45RO+ CD45RA- (Memory) Cells of CD8+ Cells (%)
CD45RO+ CD45RA- (Memory) Cells of CD8+ Cells (%CD45+)
Ki-67+ Cells of CD8+CD45RO+ CD45RA- Cells (%)
Ki-67+ Cells of CD8+CD45RO+ CD45RA- Cells (%CD45+)
NKG2D+ Cells of CD8+ Cells (%)
NKG2D+ Cells of CD8+ Cells (MFI NKG2D)
NKG2D+ Cells of CD8+CD45RO+CD45RA- Cells (%)
NKG2D+ Cells of CD8+CD45RO+CD45RA- Cells (MFI NKG2D)
CD4+ Cells of CD3+ Cells (%)
CD4+ Cells of CD3+ Cells (%CD45+)
Ki-67+ Cells of CD4+ Cells (%)
Ki-67+ Cells of CD4+ Cells (%CD45+)

Natural killer cells (NK) Panel
CD25+Foxp3+ (Treg) Cells of CD4+ Cells (%)
CD25+Foxp3+ (Treg) Cells of CD4+ Cells (%CD45+)
Ki-67+ Cells of CD4+CD25+Foxp3+ (Treg) Cells (%)
Ki-67+ Cells of CD4+CD25+Foxp3+ (Treg) Cells (%CD45+)
CD3-CD56+ (NK) Cells of CD45+ Live Cells (%)
Ki-67+ Cells of CD3-CD56+ (NK) Cells (%)
Ki-67+ Cells of CD3-CD56+ (NK) Cells (%CD45+)
CD3+CD56+ (NKT) Cells of CD45+ Live Cells (%)
Ki-67+ Cells of CD3+CD56+ (NKT) Cells (%)
Ki-67+ Cells of CD3+CD56+ (NKT) Cells (%CD45+)
NKG2D+ Cells of CD3-CD56+ (NK) Cells (%)
NKG2D+ Cells of CD3-CD56+ (NK) Cells (MFI NKG2D)

Cytokines include the following variables:

Interleukin-2
Interleukin-4
Interleukin-6
Interleukin-8
Tumor Necrosis Factor Alpha
Interferon-gamma
Interleukin-1 beta
Interleukin-10
Interleukin-12p70

The eCRF Hematology data (specifically white blood cell count (WBC)) for each timepoint will be used to derive the Cell counts in 10^9/L. Once merged with the pharmacodynamic data by subject and timepoint, the following will be used as derivation:

- CD8+ Cells of CD3+ Cells (10^9/L) = CD8+ Cells of CD3+ Cells (%CD45+) x 0.01 x WBC
- Ki-67+ Cells of CD8+ Cells (10^9/L) = Ki-67+ Cells of CD8+ Cells (%CD45+) x 0.01 x WBC
- CD45RO+ CD45RA- (Memory) Cells of CD8+ Cells (10^9/L) = CD45RO+ CD45RA- (Memory) Cells of CD8+ Cells (%CD45+) x 0.01 x WBC
- CD4+ Cells of CD3+ Cells (10^9/L) = CD4+ Cells of CD3+ Cells (%CD45+) x 0.01 x WBC
- Ki-67+ Cells of CD4+ Cells (10^9/L) = Ki-67+ Cells of CD4+ Cells (%CD45+) x 0.01 x WBC

- CD25+Foxp3+ (Treg) Cells of CD4+ Cells (10^9/L) = CD25+Foxp3+ (Treg) Cells of CD4+ Cells (%CD45+) x 0.01 x WBC
- Ki-67+ Cells of CD4+CD25+Foxp3+ (Treg) Cells (10^9/L) = Ki-67+ Cells of CD4+CD25+Foxp3+ (Treg) Cells (%CD45+) x 0.01 x WBC
- CD3-CD56+ (NK) Cells of CD45+ Live Cells (10^9/L) = CD3-CD56+ (NK) Cells of CD45+ Live Cells (%) x 0.01 x WBC
- Ki-67+ Cells of CD3-CD56+ (NK) Cells (10^9/L) = Ki-67+ Cells of CD3-CD56+ (NK) Cells (%CD45+) x 0.01 x WBC
- CD3+CD56+ (NKT) Cells of CD45+ Live Cells (10^9/L) = CD3+CD56+ (NKT) Cells of CD45+ Live Cells (%) x 0.01 x WBC
- Ki-67+ Cells of CD3+CD56+ (NKT) Cells (10^9/L) = Ki-67+ Cells of CD3+CD56+ (NKT) Cells (%CD45+) x 0.01 x WBC

For calculations, it will be considered in the analysis dataset for PD markers and cytokines that the value can be below or above limits of quantification: the lower limit will be replaced by the actual value (e.g. “<0.5” should be considered as 0.5), similarly for the upper limit (e.g. “>20” should be considered as 20).

All markers will be listed. The fold increase in cell counts (i.e., 10^9/L) will also be calculated.

Selected PD markers:

- NK cells: Ki-67+ Cells of CD3-CD56+ (NK) Cells (%)
- NKT cells: Ki-67+ Cells of CD3+CD56+ (NKT) Cells (%)
- CD8+ T-cells: Ki-67+ Cells of CD8+ Cells (%)
- CD8+ Memory T cells: Ki-67+ Cells of CD8+CD45RO+ CD45RA- Cells (%)
- CD4+ T cells: Ki-67+ Cells of CD4+ Cells (%)
- T regs: Ki-67+ Cells of CD4+CD25+Foxp3+ (Treg) Cells (%)

Maximal levels of cytokines will also be listed.

8.10 ANALYSES OF EFFICACY

The efficacy population will be derived as follows: assuming at least one evaluable tumor assessment per iRECIST after the initiation of SOT101 treatment, a patient that receives 8 doses of SOT101 in cycle 1 and 1 dose of pembrolizumab, will be included in the efficacy population; if a patient does not receive 8 doses of SOT101 in cycle 1 then the patient will be included in the efficacy population if combination therapy is not permanently discontinued in cycle 1 (i.e. patient starts cycle 2). The efficacy population will be used for the efficacy analyses.

Due to the lack of confirmation of progression (iCPD) and follow-up scans, any unconfirmed progression (iUPD) has been considered as progression if a discontinuation of any treatment is followed, and thus deviating from iRECIST guidelines.

Complete response (iCR), partial response (iPR), stable disease (iSD) and progression disease (iUPD and also after iCPD) will be identified according to iRECIST recorded to eCRF and cleaned via data management/medical review processes.

Tumor assessment data and disease response (including change from baseline in sum of diameters) since the first SOT101 administration will be listed.

If tumor assessment is performed after start of new anticancer therapy, it will be clearly indicated in the listings. For tumor assessments with different dates (i.e. lesions are assessed at different dates), the earliest date will be used for efficacy derivations.

Overall response is defined as state when the patient achieves iPR or iCR. Clinical benefit is defined as state when patient achieves iSD, iPR, or iCR. iSD needs to last at least 6 weeks from the start of study treatment; if not, at least one follow-up scan assessed as iPR, iCR, or iSD is required to provide clinical benefit. Similarly, confirmation of iPR or iCR by a subsequent assessment of either iPR or iCR, at least 4 weeks apart, will be required to declare an overall response or clinical benefit.

Immune overall response rate (iORR) and Clinical benefit rate (iCBR):

- iORR will be defined as the proportion of patients with confirmed iPR or iCR, out of patients in efficacy population.
- iCBR will be defined as the proportion of patients with confirmed iPR, iCR, or iSD out of patients in efficacy population.

iORR and iCBR will be listed.

Progression free survival (iPFS):

iPFS is defined as the time from the first day of study treatment until the first date of iUPD (followed by iCPD, study treatment discontinuation or clinical progression) or death (whichever occurs earliest).

Patients with missing data or that start new anti-cancer therapy (other than palliative) will be censored at the date of the last evaluable tumor assessment.

iPFS will be listed.

Duration of response (iDoR):

iDoR is defined as the time since the first iPR or iCR until the first date of iUPD (followed by iCPD, study treatment discontinuation or clinical progression) or death (whichever occurs earliest) for patients with confirmed iPR or iCR..

Patients with missing data or that start new anti-cancer therapy (other than palliative) will be censored at the date of the last evaluable tumor assessment.

iDoR will be listed.

Overall survival (OS):

OS is defined as the time from the first day of study treatment until the date of death and will be listed.

Patients with missing data will be censored at the last time known to be alive: apart from trial visits/survival status, information from AE, new anti-cancer therapy, and prior and concomitant medications data from eCRF will also be used to derive the alive status – the latest complete date will be selected.

Duration of follow-up:

Duration of follow-up is defined as the time from the first day of study treatment until the date of study completion / discontinuation and will be listed.

Deceased patients will be censored at the day of death: apart from trial visits/survival status, information from AE, new anti-cancer therapy, and prior and concomitant medications data from eCRF will also be used to derive the alive status – the latest complete date will be selected.

8.11 OTHER ASSESSMENTS

8.11.1 ECOG performance status

ECOG performance status will be listed.

8.11.2 Immunogenicity

ADA levels, titration, and Neutralizing ADA levels will be provided b [redacted] nd will not be a part of eCRF database. Levels and titration will be listed.

8.12 INTERIM ANALYSES

No interim analysis is planned.

8.13 DETERMINATION OF SAMPLE SIZE

According to Study Protocol section 9.13.11 the traditional 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 in a cohort. The estimated number of patients is 6-15.

9 CONCLUSIONS BASED OF DATA REVIEW MEETING

From the statistical perspective the objectives of the meeting will be following:

- to agree on patients excluded from analysis sets and to agree on major protocol deviations/reportable protocol deviations
- to highlight any issue from statistical perspective and to decide the solution in joint decision.

The section below will state version of Protocol Deviation Plan valid at time of the data review meeting, refer to data review meeting minutes and summarize/ summarizes conclusion relevant to statistical analysis which were made during the data review meeting. All details are included in the corresponding section of the SAP. Slides of presentations used during the meeting are included and commented in the section below.

9.1 DATA REVIEW MEETING BEFORE ANALYSIS

The review has been performed under SC103_Protocol Deviation Plan_v2.0_08Mar2023

No patients have been excluded from any of the populations. The following slides were presented during the data review meeting, conclusions are also summarized in eTMF:

SC103/10 Data Management/10.05 General/10.05.03 Meeting Material/SC103_DRM_Database Lock Meeting_Part B1_02Oct2023

The review of PK data includes derivation of sampling out of window according to Protocol v10 following the derivation: PK blood sampling out of window will be flagged in listing of concentration levels. Note referring to that listing (attached below) will be added to output of CSR reportable PDs. Several values have been assessed as unreliable and/or excluded or not analyzed in Pharmacokinetic concentrations, such values are not to be used for the calculation of PK parameters and descriptive analysis of PK concentrations. Hemolytic samples have been considered as reliable.

SC103 DRM Listing PK PartB1 25SEP2023

Similarly, several values have been excluded from the review of Pharmacodynamic and Cytokine data, along with Immunogenicity, Tumor Biopsy, Genetic PBMC. Derivation of sampling out of window according to Protocol v10 following the derivation: sampling out of window will be flagged in listing of

sampling dates and times. Note referring to that listing (attached below) will be added to output of CSR reportable PDs. Further derivation of rules for the exclusion of certain values in the analysis is described below.

SC103_ESP_DRM_PartB1_G29SEP23_ESP2

Rules for exclusion of PBMC sample from the analysis (due to changes in dosing such as delays, dose modification, deviations, etc.) as follows.

Applicable to PBMC, all samples and all cycles:

- Any samples taken after a missed (including second doses) or delayed dose will be excluded within the cycle: for example, if C1D2 is not done then any day afterwards within the cycle should be excluded (C1D6, C1D8, ...). Similarly, if second dose on C1D2 is not administered, any day afterwards within the cycle should be excluded (C1D6, C1D8, ...).
  EXCEPT when that delay or deviation is shifting the CXD8 and CXD9 dosing to CXD9 and CXD10 dosing (consecutive) and both doses are administered.
- Any samples taken after a dose reduction or increase will be excluded
- Any dosing performed PRIOR to CXD8 (i.e., deviation) will lead to the exclusion of samples from CXD8 onwards within the cycle.
- Any sample taken with a deviation more than 1 day (>1 day) from the protocol schedule will be excluded

Furthermore, Cycle 3 will not be included in the PK/PD analysis. Only data listed will be provided.

The rules above will also be applied for Cytokines (CK). In addition, for CK, any sample taken outside of the protocol defined window will be excluded. For Part B1 Cytokines, any C1 or C2 8-hour sample taken 30 minutes after (>30) the second dose, will be excluded.

No data from other sampling (Immunogenicity, Tumor Biopsy, etc.) have been considered as unreliable and/or affected by deviations and no exclusion rules have been created.

10 LIST OF TABLES, FIGURES AND LISTINGS

The table hereunder presents preliminary list of listings which will be integrated in study report. The structure and numbering is proposed according the ICH guidelines - E3: Structure and Content of Clinical Study Reports.

10.1 SECTION 10 OF CSR (STUDY PATIENTS)

Selected listings from Section 16 of CSR:

- Disposition of patients and analysis populations
- Protocol deviations
- Patient demographics and baseline characteistics
- Disease and medical history
- Prior, concomitant and post treatment therapies
- Exposure to study medication

10.2 SECTION 11 OF CSR (SAFETY AND PK/PD EVALUATIONS)

Selected listings from Section 16 of CSR:

- DLTs
- TEAEs including PT and SOC
- Causes of death

10.3 SECTION 12 OF CSR (EFFICACY AND OTHER DATA)

Other selected listings from Section 16 of CSR.

10.4 SECTION 13 OF CSR (DISCUSSION AND OVERALL CONCLUSIONS)

No tables are planned.

10.5 SECTION 14 OF CSR (TABLES, FIGURES AND GRAPHS REFERRED TO BUT NOT INCLUDED IN THE TEXT)

No tables, figures and graphs are planned.

10.6 APPENDIX 16.2 OF CSR (PATIENT DATA LISTINGS)

All patients included in clinical database will be listed (if not specified otherwise).

Listing Number	Title
Section 16.2.1	**Discontinued patients**
16.2.1.1	Study dates and patients' discontinuation overview in treated patients
16.2.1.2	Screening failures and withdrawals prior study treatment start
Section 16.2.2	**Protocol Deviations**
16.2.2.1	CSR reportable protocol deviations

Listing Number	Title
16.2.2.2	CSR not reportable protocol deviations
16.2.2.3	Eligibility criteria and eligibility verification
16.2.2.4	Protocol deviations related to COVID-19
Section 16.2.3	**Patients excluded from efficacy analysis**
16.2.3.1	Disposition of patients to analysis sets and reasons for exclusion
Section 16.2.4	**Demographic data**
16.2.4.1	Informed consent signatures
16.2.4.2	Demographic data, patients' characteristics and disease history details
16.2.4.3	Medical history
16.2.4.4	Medical history – MedDRA coding details
16.2.4.5	Previous medication
16.2.4.6	Prior medication (including WHODD coding)
16.2.4.7	Prior anticancer systemic therapy (including WHODD coding)
16.2.4.8	Prior anticancer non-systemic therapy (including MedDRA coding)
16.2.4.9	Concomitant medication
16.2.4.10	Concomitant medication (including WHODD coding)
16.2.4.11	Post-treatment medication
16.2.4.12	Post-treatment medication (including WHODD coding)
16.2.4.13	Prior non-pharmacological therapy (including MedDRA coding)
16.2.4.14	Concomitant non-pharmacological therapy (including MedDRA coding)
16.2.4.15	Post-treatment non-pharmacological therapy (including MedDRA coding)
16.2.4.16	New anticancer systemic therapy (including WHODD coding)
16.2.4.17	New anticancer non-systemic therapy (including MedDRA coding)
Section 16.2.5	**Compliance and drug concentration data**
16.2.5.1.1	Exposure to SOT101
16.2.5.1.2	Exposure to pembrolizumab
16.2.5.2.1	SOT101 Dose intensity
16.2.5.2.2	Pembrolizumab Dose intensity
16.2.5.3	Body weight and compliance of study drug administration with Study Protocol
16.2.5.4	SOT101 concentration levels

Listing Number	Title
16.2.5.5	SOT101 pharmacokinetic parameters
Section 16.2.6	**Individual efficacy response and pharmacodynamics data**
16.2.6.1	Tumor assessment
16.2.6.2	Disease response
16.2.6.3	Clinical progression
16.2.6.4	Pharmacodynamics markers and cytokine levels
16.2.6.5	Maximal levels of Cytokines
Section 16.2.7	**Adverse events listings**
16.2.7.1	Listing of DLT events
16.2.7.2	All treatment-emergent AEs
16.2.7.3	All treatment-emergent SAEs
16.2.7.4	Treatment-emergent AEs recorded in detailed description of dose limiting toxicities
16.2.7.5	All adverse events leading to death
16.2.7.6	Causes of death including MedDRA coding details
16.2.7.7	Treatment-emergent AEs leading to permanent discontinuation of SOT101
16.2.7.8	Treatment-emergent AEs leading to permanent discontinuation of pembrolizumab
16.2.7.9	Treatment-emergent AEs with suspected causal relationship with SOT101
16.2.7.10	Treatment-emergent AEs with suspected causal relationship with pembrolizumab
16.2.7.11	Treatment-emergent AE immune-related
16.2.7.12	Treatment-emergent clinical signs/symptoms of cytokine release syndrome
16.2.7.13	Adverse events started before the first study drug administration
16.2.7.14	Adverse events with missing or partial start date
16.2.7.15	Adverse events – MedDRA coding details
Section 16.2.8	**Listing of individual laboratory measurements**
16.2.8.1	Hematology
16.2.8.2	Biochemistry
16.2.8.3	Coagulation
16.2.8.4	Urinalysis
16.2.8.5	Maximal levels of selected laboratory variables
16.2.8.6	Creatinine clearance levels

Listing Number	Title
16.2.8.7	Thyroid function tests (TSH, free T3, free T4)
16.2.8.8	Cardiac troponin-T test
16.2.8.9	C-reactive protein (CRP) levels
16.2.8.10	Glycated hemoglobin (HbA1c)
16.2.8.11	24-hour urine protein test
16.2.8.12	Pregnancy test
16.2.8.13	Serology (HIV, hepatitis B and C tests)
16.2.8.14	Listing of abnormal laboratory results
Section 16.2.9	**Other safety data**
16.2.9.1	Vital signs
16.2.9.2	ECG results
16.2.9.3	Echocardiography results
16.2.9.4	Date of physical examination
Section 16.2.10	**Other data**
16.2.10.1	ECOG performance score
16.2.10.2	Immunogenicity

11 LAYOUT REQUIREMENTS OF TFLs

No layout requirements specified by the sponsor.

12 APPENDICES

12.1 PHARMACOKINETIC ANALYSIS PLAN

N-A-PH1-19-027_SC 103_Pharmacokineti

12.2 TIMEPOINT LABELS SPECIFICATIONS

For vital signs: Pre-dose, 15 min, 30 min, 1 h, 2 h, 3 h, 4 h, 5 h, 6 h, 7 h, 8 h will be used as per eCRF records. In the listings also real time since SOT101 administration will be presented. In the Follow-up period (Follow-up) the timepoints will be presented as EOT + X weeks as defined in the Study Protocol. Timepoints post 2nd dose of SOT101 will be labeled using "2nd dose".

For electrocardiogram (ECG): Pre-dose, 4h will be used as per eCRF records. In the listings also real time since SOT101 administration will be presented. At EOT visit, the timepoint will be presented as EOT as defined in the Study Protocol. Timepoints post 2nd dose of SOT101 will be labeled using "2nd dose".

For PK and/or Cytokine blood sampling: Pre-dose, 1 h, 2 h, 4h, 6h, 8 h, 9 h, 10 h, 12 h, 16 h, 20 h, 24 h will be used as per eCRF records. In the listings also real time since SOT101 administration will be presented. Timepoints post 2nd dose of SOT101 will be marked in the outputs.

For safety laboratory: as per standard medical practice the safety laboratory should be performed before the dosing then the label will be Cycle X Day Y – Pre-dose; otherwise, just Cycle X Day Y will be presented except in EOT visit which will be presented as EOT as defined in the Study Protocol.

Other assessments (Physical examination, body weight and Eastern Cooperative Oncology Group (ECOG) performance status) will be presented using the Cycle X Day Y label, except in the Follow-up period (Follow-up) where the label will be EOT + X weeks as defined in the Study Protocol.

In the listings, "UNS" will be added into assessments performed in addition to assessment planned in the Study Protocol, for example ScreeningUNS for some not required at screening by the Study Protocol or repeated assessment at screening, Follow-up UNS for hematologic assessment or Cycle 1 Day 9UNS for coagulation assessment or Cycle 1 Day 12UNS.

Time-points labels of tumor assessment: Tumor assessment will be recorded into eCRF as repeated pages and will be analyzed as iORR, iCBR, and time to event data. In the listings the assessments will be identified by date, real treatment week (as defined in section 6.2, rounded to one decimal), and period label ("Cycle X" derived as defined below) or "Follow-up".

Cycle derivation:

- For each cycle will be identified Day 1 (as per eCRF records) and end of cycle as defined in section 5.1.
- Then, it will be identified which cycle the assessment date belongs to.

Time-points labels for survival follow-up information: The similar approach as for tumor assessment will be applied. In the listings the information will be identified by date, real treatment week, and label "Follow-up".

Time-point labels for treatment-emergent adverse events:

The listings of treatment-emergent adverse events (TEAEs) will include the time period during which the TEAE occurred:

- Cycle X: the time-point label will indicate treatment cycle when the adverse event (AE) started
- After last: the time-point label will indicate AEs started after end of last cycle

See treatment cycle definition in the section 5.1 above. Treatment cycle when TEAE started will only be derived for AEs with complete (and non-missing) start dates.

12.3 CANCER TYPE DERIVATION

Histological type	Primary tumor location	Cancer type (long name)	Cancer type (short name)
Stomach adenocarcinoma	Stomach	Gastric	Gastric
cholangio-carcinoma	Biliary tract	Billiary tract	Billiary tract
BRCA1 mutated high grade serous ovarian adenocarcinoma	Ovarian	Ovarian	Ovarian
cholangiocarcinoma	Biliary tract	Billiary tract	Billiary tract

13 REFERENCES

[1] Seymour L, Bogaerts J, Perrone A, Ford R, Schwartz LH, Mandrekar S, Lin NU, Litière S, Dancey J, Chen A, Hodi FS, Therasse P, Hoekstra OS, Shankar LK, Wolchok JD, Ballinger M, Caramella C, de Vries EGE, group Rw. iRECIST: guidelines for response criteria for use in trials testing immunotherapeutics. The Lancet Oncology. 2017;18(3):e143-e152. ICH guidelines - E9: Statistical Principles for Clinical Trials, Adopted in EU by CPMP, March 1998, issued as CPMP/ICH/363/96

[2] ICH guidelines - E3: Structure and Content of Clinical Study Reports, Adopted in EU by CPMP, December 95, issued as CPMP/ICH/137/95

[3] U.S. Food and Drug Administration. E14 clinical evaluation of QT/QTc interval prolongation and proarrhythmic potential for non-antiarrhythmic drugs: Guidance for industry. 2018; https://www.fda.gov/downloads/Drugs/GuidanceComplianceRegulatoryInformation/Guidances/ucm073153.pdf. Accessed October 22, 2018.

[4] Smith BP, Vandenhende FR, deSante KA, et al (2000)., Confidence Interval Criteria for Assessment of Dose proportionality. Pharmaceutical Research, 17:1278-1283.

[5] Zhou, J., J. Li, and B. Coate. 2006. Empirical Power Estimation for Phase I Dose Proportionality Studies Based on Power-Law Model Using Confidence Interval Criteria. In SUGI 31, San Francisco, California.

[6] SAS 9.4; 2008 by SAS Institute Inc., Cary, NC, USA; OnLine Doc.

Statistical Analysis Plan
Study Part D

A multicenter open-label phase 1/1b study to evaluate the safety and preliminary efficacy of SO-C101 as monotherapy and in combination with pembrolizumab in patients with selected advanced/metastatic solid tumors.

Sponsor:	SOTIO Biotech AG
Study code:	SC103
EudraCT number:	2018-004334-15
VERSION:	Final 1.0
DATE:	08-APR-2024

STATISTICAL ANALYSIS PLAN APPROVAL

We, the undersigned, confirm that we have read and are in agreement with the contents of this document.

NAME	[redacted]	
JOB TITLE		
SIGNATURE		
DATE		
NAME		
JOB TITLE		
SIGNATURE		
DATE		
NAME		
JOB TITLE		
SIGNATURE		
DATE		
NAME		
JOB TITLE		
SIGNATURE		
DATE		

TABLE OF CONTENTS

ABBREVIATIONS

ADA	Anti-drug antibodies
AE	Adverse Event
ALP	Alkaline Phosphatase (ALP)
ALT	Alanine Transaminase
AST	Aspartate Transaminase
ATC	Anatomic, Therapeutic, Chemical (Classification System for Drugs)
AUC	Area under the plasma concentration-time curve
$AUC_{(0\text{-}inf)}$	Area under the plasma concentration-time curve from time zero to infinity
$AUC_{(0\text{-}t)}$	Area under the plasma concentration-time curve from time zero to time t
BLQ	Below Limit of Quantification
CBR	Clinical Benefit Rate
CD	Cluster of differentiation (cells)
CI	Confidence Interval
CK	Cytokines
CL	Apparent total body clearance of the drug from plasma
C_{max}	Maximum (or peak) serum concentration
CPI	Check Point Inhibitors
CRF	Case Report Form
CRP	C-Reactive Protein
CSR	Clinical Study Report
CV	Coefficient of Variation
DB	Database
DBL	Database lock
DEC	Dose Escalation Committee
DEM	Dose Escalation Meeting
DOR	Duration of Response
ECG	Electro-cardiogram
ECOG	Eastern Cooperative Oncology Group
eCRF	Electronic Case Report Form
EOT	End of Treatment
FU	Follow-up
HLGT	High Group Level Term
HLT	High Level Term
IAP	Independent Advisory Panel
ICF	Informed Consent Form
ICH	International Conference of Harmonization
iCBR	(immune) Clinical Benefit Rate (based on response as per iRECIST)
iCPD	(immune) Confirmed Progression Disease (as per iRECIST)
iCR	(immune) Complete Response (as per iRECIST)
ID	(Patient) Identification Number
iDOR	(immune) Duration of Response (based on response as per iRECIST)

IMP	Investigational Medicinal Product
iORR	(immune) Overall Response Rate (based on response as per iRECIST)
iPFS	(immune) Progression Free Survival (as per iRECIST)
iPR	(immune) Partial Response (as per iRECIST)
iRECIST	(immune-based) Response Evaluation Criteria in Solid Tumors
iSD	(immune) Stable Disease (as per iRECIST)
iUPD	(immune) Unconfirmed Progression Disease (as per iRECIST)
IV	Intravenous
KM	Kaplan-Meier
LDH	Lactate Dehydrogenase
LLT	Lowest Level Term
Max	Maximum
MedDRA	Medical Dictionary for Regulatory Activities
Min	Minimum
NCI CTCAE	National Cancer Institute Common Terminology Criteria for Adverse Events
NK	Natural Killer (cell)
NKT	Natural killer T (cell)
ORR	Objective Response Rate
OS	Overall Survival
PBMC	Peripheral Blood Mononuclear Cell
PD	Pharmacodynamic
PK	Pharmacokinetic
PT	Preferred Term
Q1	Lower Quartile
Q3	Upper Quartile
QT	QT interval
QTcF	Fridericia's correction of QT interval
R_{ac}	Accumulation ratio
RP2D	Recommended Phase 2 dose
SAE	Serious Adverse Event
SAF	Safety Set
SAP	Statistical Analysis Plan
SAS	Statistical Analysis Systems
SOC	System Organ Class
StD	Standard Deviation
$t_{1/2}$	Elimination half-life (to be used in one-or noncompartmental model)
$t_{1/2\alpha}$	Initial or disposition half-life
TEAE	Treatment-emergent Adverse Events
TFLs	Tables, Figures and Listings
T_{max}	Time to reach maximum (peak) plasma concentration following drug administration
Treg	Regulatory T (cells)
ULN	Upper limit of Normal
V_d	Apparent volume of distribution

WHODrugD	World Health Organizations Drug Dictionary
λ_z	Termination elimination constant (symbol k_e is also used)

INTRODUCTION

Statistical evaluation of each SC103 study (AURELIO-03) part will be performed separately after lock of the relevant study part data in clinical database. This Statistical Analysis Plan (SAP) describes the statistical analyses and planned outputs for Study Part D. It includes definition of objectives and endpoints as per Study Protocol, the definition of analysis sets, and details needed for statistical programming. The SAP outlines the tables, listings and figures (TFLs) to be compiled in the Clinical Study Report (CSR).

This SAP does not include pharmacokinetic anal sis lan. SO (previously SO-C101, RLI-15) concentrations levels are measured by [redacted] who are also responsible for pharmacokinetic analysis and for writing pharmacokinetic analysis plan. This SAP does not include plan of statistical analysis to be performed on biomarkers collected from tumor tissue samples as collected data are limited and this analysis is intended to be fully exploratory.

This SAP is written according to the SC103 Study Protocol version 10.0 dated on 29-JUL-2021, current Mock Case Report Form (CRF), DEC charter version 4.0 dated on 26-MAR-2021, and IAP charter version 3.0 dated on 30-MAR-2021. The analyses and outputs closely follow the ICH guidelines for industry on topic E3 (Structure and Content of Clinical Study Reports) and E9 (Statistical Principles for Clinical Trials).

DOCUMENT HISTORY

Version	Date	Description of change	Performed b
Draft 0.1	12-MAR-2024	First version of the document created based on SAPs for Part A and Part B1.	[redacted]
Draft 0.2	04-APR-2024	Reviewed by GCP Services and shared internally	
Final 1.0	08-APR-2024	Addressed and implemented feedback from GCP Services	

1 PLANNED CHANGES FROM STUDY PROTOCOL

In study protocol version 10.0, dated 29-JUL-2021, SO-C101 is specified in “Investigational medicinal products”. Throughout this SAP, SOT101 is used instead of SO-C101.

2 STUDY OBJECTIVES

2.1 PART D - SOT101 MONOTHERAPY

2.1.1 Primary objectives

- To assess the safety and tolerability of SOT101 given as monotherapy

2.1.2 Secondary objectives

- To characterize the pharmacokinetics (PK) of SOT101
- To characterize the pharmacodynamics (PD) of SOT101 in peripheral blood
- To determine the preliminary efficacy of SOT101 monotherapy as measured by overall response rate (ORR), duration of response (DOR), clinical benefit rate (CBR), and progression-free survival (PFS) according to iRECIST
- To determine the immunogenicity of SOT101 given as monotherapy

According to iRECIST terminology responses assigned using iRECIST have a prefix of “i” (“i” stands for immune); therefore, abbreviations iORR, iDOR, iCBR, iPFS will be used afterwards.

2.1.3 Exploratory objectives

- To explore the mechanistic effects of SOT101 on selected immune cell populations in tumor tissue samples. Analysis of this exploratory objective is not described in this SAP, instead, a separate Biomarker analysis plan will be prepared.
- To assess overall survival (OS)

3 STUDY DESIGN

Study design is briefly described below. Full description of study design is included in the Study Protocol. The schedule of procedures and assessments is presented in the Study Protocol Table 9.6 to 9.17.

3.1 IMPLEMENTATION OF DOSE EXPANSION

Part D will start after the RP2D of SOT101 monotherapy given as per dosing schedule 1 is identified in Part A. SOT101 will be given as per dosing schedule 1 at this RP2D.

Part D will enroll patients with relapsed/refractory advanced/metastatic renal cell carcinoma, patients with relapsed/refractory advanced/metastatic skin squamous-cell carcinoma, and patients with relapsed/refractory advanced/metastatic melanoma.

3.2 RANDOMIZATION AND BLINDING

Not applicable.

4 STUDY ENDPOINTS

4.1 DEMOGRAPHY AND BASELINE CHARACTERISTICS TO BE SUMMARIZED

The following baseline characteristics will be summarized in the tables:

- Demographic characteristics:
  - Age at informed consent (ICF) signature [years]
  - Age at informed consent (ICF) signature [years] according to: <18 years, >18 and ≤64 years, >64 and ≤84, >84 or older
  - Gender
  - Ethnicity
  - Race
- Baseline characteristics
  - Weight [kg]
  - Body Mass Index (derived) [kg/m^2]
- Disease history
  - Primary tumor location
  - Histological type
  - Cancer type (derived)
  - Time since diagnosis at ICF signature (derived) [years]
  - Time since latest radiological or clinical disease progression at ICF signature (derived) [weeks]
  - Number of lines of previous systemic anticancer therapy
  - Number of lines of previous systemic anticancer therapy categories: ≤ 2, > 2.
  - Previous treatment with check point inhibitors (CPI) (Yes/ No/ Unknown)
  - CPI Response (if CPI received) (Refractory/ Relapsed/ Unknown)
  - Prior anticancer non-systemic therapy (Yes/ No)
  - ECOG
  - ECOG categories: 0, > 0

4.2 ENDPOINTS

4.2.1 Primary endpoints

- Safety and tolerability of SOT101 as evaluated by the incidence of SOT101-related adverse events (AEs), SAEs, AEs leading to premature discontinuation of SOT101, deaths, and clinical laboratory test abnormalities.

4.2.2 Secondary endpoints

- PK of SOT101
- Immune response characterized by the changes in expression of immune markers in PBMCs
- iORR, iDOR, iCBR, and iPFS
- Detection of anti-drug antibodies (ADA)

4.2.3 Exploratory endpoints

- Changes in the expression of immune biomarkers as compared to baseline in tumor tissue (analysis of this endpoint is not described in this SAP).
- OS at 6 months after the EOT visit.

5 COMMON DEFINITIONS

General and common definition relevant for statistical analysis/ Statistical Analysis Systems (SAS) programming are listed below. Definitions used only in analysis of a particular endpoint are included directly in analysis section.

5.1 TREATMENT CYCLE

Each treatment cycle in Part D should include 4 SOT101 administrations and should take 21 days as per Study Protocol. However, treatment interruptions and delays can occur. Therefore, the cycle number will be taken from the electronic CRF (eCRF) database.

The start of each cycle is defined by the date of the first SOT101 administration in the cycle.

The cycle lasts until Day 1 of the next cycle. The last cycle end is defined as Day 21 of the last cycle or end of the study participation (whatever occurs first).

5.2 LABELS USED IN SAP AND IN STATISTICAL OUTPUTS

EOT stands for end of treatment. FU stands for follow-up.

Indication labels will include information on the indication as per Study Protocol and derivation will be based on primary tumor location and histological type from the eCRF (Appendix 12.3).

- Examples: RCC (Renal cell carcinoma), cSCC (skin squamous cell carcinoma), Melanoma.

Individual time-points labels will be as follows:

- Screening
- Cycle X Day Y
  - Cycles will be identified by the number of the cycle as per eCRF data.
  - Days will be identified by the number of the day as per eCRF data.

- EOT
- EOT + X weeks, see below

The assignment to the time-point labels will be performed via SAS programming as follows:

  - If Date of assessment – date of EOT ≤ 4+2 weeks then label = "EOT + 4 weeks"
  - If 6 weeks < Date of assessment – date of EOT ≤ 8+2 then label = "EOT + 8 weeks"
  - If 10 weeks < Date of assessment – date of EOT ≤ 12+2 then label = "EOT + 12 weeks", etc.

If two assessments are assigned to the same time-point label, the earliest assessment will be selected. In such case, the tables or summaries will contain a footnote specifying the case.

In the listings, the real post-treatment week (see section 6.2, rounded to one decimal) will be presented as well.

Timepoint labels used in the statistical outputs and derivations are described in the Appendix, Section 12.2.

5.3 BASELINE VALUES

5.3.1 Study baseline

Study baseline will be defined as the last non-missing measurement prior to the first SOT101 administration, unless specified otherwise.

5.3.2 Handling of missing data needed for baseline identification

The definitions above consider date and time of the assessment and SOT101 administration. If time is not known, then only dates will be used for identification of the baseline. Safety laboratory samples are supposed to be taken before study drug administration; therefore, if time of sample collection is not known and date is the same as date of administration then it will be considered as pre-dose sample.

Values which are identified as baseline via rule described in this paragraph will be flagged in the listings.

5.4 CODED TERMS AND DICTIONARIES USED

Data will be coded as described in the following table.

Table 3: Data to be coded

eCRF page name	Variable to be coded (Dictionary to be used for coding)
The previous therapies include the following pages:	
PRIOR ANTICANCER SYSTEMIC THERAPY	Medication (WHODD)
PRIOR ANTICANCER NON-SYSTEMIC THERAPY	Location and Surgery description (MedDRA)
Further, details about prior and concomitant medication/therapies will be collected on the following pages:	
MEDICATION DETAILS	Medication (WHODD)
NON-PHARMACOLOGICAL THERAPY DETAILS	Therapy (MedDRA)
NEW ANTICANCER SYSTEMIC THERAPY DETAILS	Medication (WHODD)
NEW ANTICANCER NON-SYSTEMIC THERAPY DETAILS	Location and Surgery description (MedDRA)
MEDICAL HISTORY DETAILS	Medical history term (MedDRA)

ADVERSE EVENT DETAILS	Adverse event term (MedDRA)
DEATH	Immediate cause of death and Underlying cause of death (MedDRA)

The coding will be performed directly in eCRF system. The terms will be coded with the most current version of Medical Dictionary for Regulatory Activities (MedDRA) and WHODD dictionaries at time of DB lock.

All MedDRA and WHODD levels listed below will be presented in the listings. Those used in the tables are underlined.

MedDRA coding levels will include:

- Preferred Term (PT)
- Lowest Level Term (LLT)
- High Level Term (HLT)
- High Group Level Term (HLGT)
- Primary System Organ Class (SOC)

WHODD coding will include the following Anatomic, Therapeutic, Chemical (ATC) levels:

- ATC Level 1: anatomical main group
- ATC Level 2: therapeutic subgroup
- ATC Level 3: pharmacological subgroup
- ATC Level 4: chemical subgroup
- WHODD preferred name

5.5 PREVIOUS/CONCOMITANT/POST-TREATMENT MEDICATIONS/ THERAPIES

The records of prior and concomitant medications will be classified as “Prior”, “Concomitant” and “Post-treatment” according to the following definitions.

The start of study treatment refers to the date of the first SOT101 administration.

The end of study treatment refers to the date of the last SOT101 administration.

“Concomitant” medication/therapy is any medication/therapy which was administered in the period starting with the start of study treatment (including) and lasts until the end of study treatment. The only exception will be medication/therapy which started on day of the end of study treatment: this medication will be classified as “Post-treatment”.

“Prior” medication/therapy is any medication/therapy ended before the start of study treatment.

“Post-treatment” medication/therapy is any medication/therapy which started after or at the end of study treatment.

For records of medication/therapy with unknown and incomplete dates which cannot be identified according to definitions described above, the following rules will be applied:

- If end date of medication/therapy is completely unknown and the medication/therapy started after or at the end of study treatment, the medication/therapy will be counted as “Post-treatment”. Otherwise (i.e., the medication/therapy started before the end of study treatment), the medication/therapy will be counted as “Concomitant”.
- If start date of medication/therapy is completely unknown and the medication/therapy ended after or at start of study treatment, the medication/therapy will be counted as “Concomitant”.

Otherwise (i.e., the medication/therapy ended before the start of study treatment), the medication/therapy will be counted as "Prior".

- If start or end date is incomplete: the first possible start date (e.g., for xxDEC2019 this is 01DEC2019, for xxxxx2019 this is 01JAN2019) or last possible end date (e.g., for xxDEC2019 this is 31DEC2019, for xxxxx2019 this is 31DEC2019) will be derived. Classification "Prior", "Concomitant" and "Post-treatment" medication/therapy will be performed using these derived dates.
- If both end date and start date of medication/therapy are completely unknown, then it will be counted as "Concomitant".

5.6 ADVERSE EVENT (AE)

Detailed definition of AE and its classification is presented in the Study Protocol (See section 9.11.5.1).

Each increase or decrease of severity of AE will be collected as separate AE record on "ADVERSE EVENT DETAILS" eCRF page.

Raw data will be used to identify AE episodes as follows:

- Linked AE records by the investigator (i.e. AE record with an outcome of "Change in severity" in the eCRF) with the same MedDRA preferred term, where the start date of the subsequent AE record is equal to (or +1 day) end date of the previous AE record, will be identified as one AE (continuous) and each AE record will be assigned the same AE ID (equal to the AE ID of the first AE record in the episode).

In order to assign the TEAE status to AEs with the same AE ID (linked AE records), unaggregated data will be used. After the TEAE assignment, AE episodes with the same AE ID will be aggregated as per section 5.8.

5.7 TREATMENT-EMERGENT ADVERSE EVENTS (TEAE)

According to the Study Protocol section 9.13.10.2 treatment-emergent AE is defined as an AE that

- emerges during treatment, having been absent at pretreatment (screening), or
- reemerges during treatment, having been present at pretreatment (screening), or
- worsens in severity during treatment relative to the pretreatment state.

The start of study treatment refers to the date of the first SOT101 administration.

Emerges or reemerges during treatment:

TEAEs are AEs with start date ≥ start of study treatment. Conditions when date/time is unknown or incomplete are defined below.

Worsening in severity:

When the AE belongs to an AE episode (as defined in section 5.6) where the first AE record is not TEAE, the subsequent AE record will be TEAE if:

- AE with start date ≥ start of study treatment, and
- Worsens in severity as compared to pretreatment state.

For adverse events with unknown or incomplete start date/time the following rules will be applied:

Incomplete date: when some information is available (e.g., month, year), but date is partially missing (e.g., missing day, month).

Unknown date/time: when no information is available and thus day, month and year are missing.

Unknown time for start or end of AE:

If time of AE start, or start of study treatment is unknown, the information will be derived only using dates – if AE start or end dates are unknown, conditions are defined below.

If start date is unknown and end date is known (and complete):

- If end date/time is < start of study treatment, the event will not be counted as TEAE.
- If end date/time is ≥ start of study treatment, the event will be counted as TEAE.

If start date is incomplete and end date is incomplete or unknown:

- last possible start date of AE (e.g., for xxDEC2019 this is 31DEC2019, for xxxxx2019 this is 31DEC2019) will be derived. If the last possible start date of AE ≥ start of study treatment the event will be counted as TEAE. Otherwise, if last possible start date of AE < start of study treatment, the event will not be counted as TEAE.

If start date is unknown and end date is incomplete:

- last possible end date of AE (e.g., for xxDEC2019 this is 31DEC2019, for xxxxx2019 this is 31DEC2019) will be derived. If the last possible end date of AE ≥ start of study treatment the event will be counted as TEAE. Otherwise, if last possible end date of AE < start of study treatment, the event will not be counted as TEAE.

Unknown date for start and end of AE:

- If both start date and end date are unknown, the event will be counted as TEAE.

5.8 AGGREGATION OF CONTINUOUS AE AND TEAE

In order to aggregate AE and/or TEAE episodes (in text below referred just as 'AE') that are continuous, the following will be applied:

- AE will be TEAE if any of all AE records belonging to the AE is TEAE (as defined in section 5.7).
- Start date/time of AE will be start date of the first AE record belonging to the AE. This date will be used to derive the Cycle as defined in sections 5.1, as well as the last dose level of SOT101 before the start of the AE.
- End date /time of AE will be end date of the last AE record belonging to the AE.
- Outcome of AE will be outcome of the last AE record belonging to the AE.
- Severity will be the highest grade out of all AE records belonging to the AE.
- AE will be serious if any of all AE records belonging to the AE is evaluated as serious.
- AE will be immune-related if any of all AE records belonging to the AE is evaluated as AE immune-related. Secondly, AE will be not immune-related if any of all AE records belonging to the AE is evaluated as AE not immune-related.
- AE will have suspected relationship to SOT101 if any of all AE records belonging to the AE is evaluated as to have suspected relationship to SOT101.
- Action taken to SOT101 will include all actions taken as per all AE records belonging to the AE.

The definition above will be used for tables. Clinical signs/symptoms of cytokine release syndrome will not be aggregated.

Listings will present all AE and TEAE (not aggregated) as defined in Section 8.7.1 and Section 8.7.2.

6 GENERAL ALGORITHMS AND DERIVED VARIABLES

General and common algorithms to be used in SAS programming are listed below. Algorithms used only in analysis of particular endpoint are included directly in analysis section.

6.1 CONVERSION OF DAYS, MONTH, YEARS

Week will be counted as day/7. Planned to be used for presentation in listings where the value will be rounded for one decimal.

One year will be counted as 365.25 days.

One month will be counted as 365.25/12 days = 30.4375 days.

Number of calculated years and months will be used e.g. for calculation of age or survival time, rounding procedures are described in section 8.2.2.

6.2 TREATMENT/POST-TREATMENT DAY

Real treatment day will be calculated as date – date of the start of study treatment + 1. For dates before the start of study treatment, the treatment day will be negative and will be calculated as follows: date – start of study treatment..

Real post-treatment day will be calculated as date – date of the end of study treatment.

Real week, month and year will be converted from real day as defined in the section 6.1.

6.3 ALGORITHM FOR ALLOCATION OF DATA TO SCHEDULED VISITS/TIME-POINTS

The algorithms are described with definition of the time-point labels in Section 5.2.

6.4 APPLICATION OF CUT-OFF

No cut-off is planned to be applied for the final analysis.

7 ANALYSIS SETS

7.1 SAFETY SET (SAF)

The safety population will include all patients exposed to SOT101 in Part D.

The SAF will be used for analysis of safety endpoints.

7.2 PK/PD EVALUABLE

PK analysis set will include patients with evaluable PK profile.

PD analysis set will include patients with evaluable PD profile.

Protocol deviation related to PK and PD assessment and compliance with dosing schedule will be reviewed. Only patients whose data would lead to biased conclusions or analysis interpretation will be excluded from the analysis sets.

The PK/PD analysis set will include patients in both PK analysis set, and PD analysis set. The PK/PD evaluable patients will be used for PK/PD analysis.

7.3 EFFICACY SET

All patients exposed to SOT101 (exposure for at least one treatment cycle) who had at least one evaluable tumor assessment per iRECIST after the initiation of SOT101 treatment.

Exposure for at least one treatment cycle is defined as 4 doses of SOT101 (regardless of dose level) in Cycle 1, or if the patient is exposed to SOT101 (with any number of doses) in Cycle 1 and started Cycle 2.

The Efficacy set will be used for analysis of efficacy endpoints.

8 STATISTICAL METHODS AND DETERMINATION OF SAMPLE SIZE

This section describes the data analysis in detail (with exception of pharmacokinetic analysis which is described in separate document attached). The statistical methods are planned in accordance with the Study Protocol (section 9.9) and in accordance with ICH Topic E9 Statistical Principles for Clinical Trials.

SAS version 9.4 or newer will be used for statistical programming.

8.1 SOURCE DATA TO BE USED FOR ANALYSIS

Data collected in clinical study database including MedDRA and WHODD coding will be used for analysis. Laboratory conversion factors will be taken from the internal IBMCD laboratory DB (as per Laboratory Data Unit Conversions standards).

Plasma concentration data and pharmacokinetic parameters will be provided b [redacted] n .sas7bdat format and will be directly used for analysis (will not be a part of clinical database). Dates and times of blood sampling in the datasets provided by [redacted] and those recorded in the clinical database will be reconciled as a part of data management processes.

Description of the provided datasets:

- pc_1p_DDMMMYYYY.sas7bdat: dataset providing the PK concentrations over time, per patient.
- pp_1p_DDMMMYYYY.sas7bdat: dataset providing the calculated PK parameters, per patient.

Where p is the study part (e.g., 'd' for Part D), DDMMMYYYY is the date of t [redacted] rther details are specified in data transfer specification "SC103_Data Transfer Specification [redacted] 6.0_07Jul2023" dated 07-Jul-2023.

Anti-drug antibodies data will be provided by [redacted]

Description of the provided datasets:

- SC103ADASNAPSHO [redacted] DMMMYYYY.csv: provides per patient and over time ADA positivity, titration, and NADA positivity. Where DDMMMYYYY is the date of transfer.

Further details are specified in data transfer specification "SC103_Data Transfer Specification [redacted] v6.0_07Jul2023" dated 07 2023. Plasma concentration data and pharmacokinetic parameters will be provided by [redacted] Materials for DEC/IAP will be directly prepared by [redacted] Sotio will provide outputs for CSR.

Pharmacodynamic variables and cytokines levels will be provided by Central LAB [redacted] SAS® v.9 transport files and will be directly used for analysis (will not be a art of clinical database). Dates and times of blood sampling in the datasets provided b [redacted] nd those recorded in the clinical database will be reconciled as a part of data management processes.

Description of the provided datasets:

- SC103SNAPSHO [redacted] DMMMYYYY.xpt: includes per patient and over time the test results as per protocol. Where DDMMMYYYY is the date of file transfer.

Further details are s ecified in data transmission agreement "SC103_Data Transmission Agreement [redacted] 15Jun2021" dated 15-Jun-2021.

8.2 GENERAL PRINCIPLES

The study includes Study Part D.

This is a Phase I dose expansion study with primary objective to further explore safety and tolerability of SOT101 at the RP2D dose level identified in Study Part A. The analysis will be mainly descriptive. If appropriate regarding the number of patients (e.g., All indications pooled), the descriptive statistics will be presented with 95% confidence intervals. Descriptive statistics will include:

For categorical variables, standard set of summary statistics will be counts and percentages calculated from number of available observations. Number of available observations (and number of missing observations) will be presented as well. For baseline characteristics missing, not applicable/not available/not known will be counted as a category. The number of patients used for the percentages (denominator) is defined in each analysis section of this SAP.

For continuous variables, the following descriptive statistics will be presented: number of available observations (and number of missing observations), mean, standard deviation (StD), median, lower quartile (Q1), upper quartile (Q3), minimum (Min), and maximum (Max).

For time-to-event variables, Kaplan-Meier (KM) estimates of median, Q1 and Q3 will be presented. The number and percentage of patients with event and censored patients will be presented. KM curves will be provided as a part of descriptive analysis.

For pharmacokinetic parameters, the following descriptive statistics will be presented: number of available observations (and number of missing observations/ number of concentrations below limit of quantifications (BLQ)), arithmetic mean and geometric mean and their 95% confidence intervals, standard deviation (StD), StD of log-transformed data, median, inter-patients (between-patients, within-cycle) coefficient of variation, intra-patient (within-patient, between-cycles-days) coefficient of variation, minimum, and maximum. Coefficient of variation (CV) in % is computed as:

% CV = (StD x 100) / mean

8.2.1 Listings

Each listing will present the following variables/columns:

- Patient identification (ID), indication
- If appropriate, analysis set relevant for particular listing

Listings will be sorted by ID and by chronological order of visits/assessments/events.

Dates will be presented in the listings in format YYMMDD10. (e.g., 2019-11-31). Partial dates as exported from the database will be listed (e.g., 2019-11-UNK, 2019-UNK-UNK, UNK-UNK-UNK).

8.2.2 Rounding procedures

Percentages will be presented with one decimal place with exception of efficacy data where two decimal places will be presented.

Mean, median, Q1 and Q3 will be presented with one more decimal place and StD will be presented with two more decimal places than the original data used for calculation of the statistics. The maximum number of decimal places will be up to three.

Other values such as temperature, number of weeks, coefficients of variation, etc. will be presented with one or two decimal places, according to the source data.

8.2.3 Unscheduled/ repeated assessments

Unscheduled/ repeated assessments which are performed in addition to those scheduled in the Study Protocol will not be used for analysis per time-point. Baseline values can include unscheduled/repeated assessment if they are the last before study drug administration (see section 5.3 for details).

8.2.4 Missing data

In general, missing data will not be imputed, i.e. complete case analyses will be performed. However, number of missing data is to be presented in descriptive statistics.

8.2.5 Methods for handling of incomplete/missing dates/ times

Methods for handling of incomplete and missing dates of medication/therapies and adverse events are presented in sections 5.5 and 5.7.

Similarly, methods for handling of incomplete and missing dates for Date of initial diagnosis are described in section 8.4.

8.2.6 Covariates and subgroups

The patients are planned to be analyzed by the indications.

Subgroup analyses are not planned. No covariates to be used in analyses planned in this SAP.

8.2.7 Region/Country/Site analysis in multi-centric trial

Analysis by region, country or site is not planned.

8.2.8 Validation of statistical programming

Each SAS program will be validated by a second qualified SAS programmer to ensure a correct output and a correct presentation of the data. The validation process is documented in the validation sheet (GCPS_DMF_033 A-C), which also prespecifies criteria for risk categorization of programs and the corresponding validation actions.

Logs of all programs used for analysis and data preparation will be checked for errors and unexpected warnings. Any undocumented updating of raw study data in statistical programming instead of change in clinical DB (or source data) is not allowed.

8.3 DISPOSITION OF STUDY PATIENTS

Disposition of patients will be presented for Study Part D, for All indications pooled and by indications.

The following information will be presented in the table of patients' disposition:

Count of the following groups of patients will be presented:

- Screened
  - Reason for screen failure with count and percentages* (from screened patients)
- Eligible (as per confirmation by the Sponsor)
- Treated

Count and percentages* of treated patients will be presented for the following groups of patients:

- Ongoing patients (i.e., patients still in the study)
- Study discontinued patients
  - Reason for discontinuation with count and percentages* (from study discontinued patients)
- SOT101 discontinued patients
  - Reason for discontinuation with count and percentages* (from SOT101 discontinued patients)

*The percentages will be presented by indication and for all indications pooled.

Disposition of patients into analysis sets:

- Number of patients in analysis set (percentages calculated out of all treated patients), number of patients excluded from analysis set and reasons for exclusion from analysis sets (percentages calculated out of those patients excluded from analysis set).

Protocol deviations will be summarized for SAF and for All indications pooled, as well as listed.

8.4 DESCRIPTION OF BASELINE PATIENTS' CHARACTERISTICS

Baseline characteristics and disease history information defined in section 4.1 will be summarized with descriptive statistics.

Cancer type will be medically reviewed prior to DBL and derived based on the list specified in Appendix (Section 12.3).

Body Mass Index will be calculated as weight in kg divided by height in m^2. Values will be rounded to one decimal.

Date of birth is not collected in the eCRF. Age at ICF signature in years as recorded in eCRF will be used. Then, time since diagnosis at ICF signature in years and time since latest radiological or clinical disease progression at ICF signature in weeks will be calculated as follows: date of ICF signature (at time of entering the study) – date of diagnosis/progression + 1 and transformed to years/weeks respectively as per section 6.1.

If Date of initial diagnosis is incomplete or partially missing, the following rules will be applied for imputation of dates:

- If day and month is missing, day will be imputed as 01 and month as 06.
- If only day is missing, day will be imputed as 01.
- If only month is missing, month will be imputed as 06.
- If year is missing or the date is completely unknown, no imputation will be performed.

Date of latest radiological or clinical disease progression will not be imputed regardless of unknown or partially missing dates.

Explanatory footnote will be presented in corresponding table and listing.

The baseline patients' characteristics will be analyzed using SAF and presented for All indications pooled, as well as by indication. Percentages will be computed from the number of treated patients in All indications pooled and, in each indication, respectively.

Medical history recorded in eCRF will be only listed.

8.5 MEDICATION/THERAPIES

Medication and therapies as specified in Table 3 will be presented by count and percentages of patients. Separate tables for prior, concomitant, and post-treatment medication/therapies (see section 5.5) will be presented.

The tables will be generated using SAF and by indication, together with all indications pooled. Percentages will be computed from the number of treated patients in each indication and for All indications pooled for all cases: prior, concomitant, and post-treatment medication/therapies.

Prior, concomitant, and post-treatment procedures will also be listed.

8.6 EXPOSURE TO STUDY TREATMENTS

Duration of exposure to SOT101 will be calculated as: date of the last SOT101 administration - date of the first SOT101 administration + 1.

Descriptive statistics of duration of exposure to SOT101 will be presented in the table together with patient-years of exposure, analyzed as continuous variables.

Dose intensity will be calculated as follows, for each patient:

- Sum of (SOT101 administrations x dose level) / duration of exposure (in days)

Dose intensity will be summarized.

Additionally, to provide a dosing overview and a summary of changes from dosing (based on initial dose of SOT101 and actual dose of SOT101) the number of SOT101 administered doses will be analyzed descriptively as categorical variable.

Descriptive statistics for duration of exposure, dose intensity, and dosing overview will be provided for All indications pooled and by indications. Percentages will be computed from the number of treated patients in All indications pooled and, in each indication, respectively. The tables will be generated using SAF.

Dose level, Dilution Fold, Total Volume Administered, Body Weight at Day 1 of each cycle, calculated Volume for Administration (as described in SC103_Instruction for handling of IMP and Trial Related Materials_v4.0_16Mar2021 (v4.0)) and compliance of dosing schedule for SOT101 with Study Protocol will be presented in Listings.

8.7 ANALYSES OF SAFETY

8.7.1 Adverse events (AEs)

Details about AEs as collected on "Adverse Event Details" eCRF page will be used for analysis. Data collected on "Serious Adverse Event" eCRF page will be used for safety reporting in responsibility of pharmacovigilance department and will not be part of statistical outputs.

See section 5.8 for handling of AE records needed before programming of tables. All AE records will be presented in the listings without aggregation into AE episodes (derived number of episodes will indicate which AE records were aggregated for summaries).

8.7.2 Treatment-Emergent Adverse events (TEAEs)

TEAEs are defined in section 5.7 above. Note that as per Study Protocol AEs are collected in eCRF database until 90±2 days after last dose of SOT101.

Not TEAE will only be listed.

8.7.2.1 Grouping of TEAEs

For harmonization and safety data review purposes, the following grouping of Preferred Terms will be considered in the analysis and displayed as such in the tables. Listings of TEAEs will present the originally coded Preferred Term:

TEAE System Organ Class: Preferred Term	Preferred Term
Gastrointestinal disorders: Abdominal pain	Abdominal pain lower
	Abdominal pain upper Abdominal pain
Investigations: Blood bilirubin increased	Hyperbilirubinaemia
	Blood bilirubin increased
Investigations: Lymphocyte count decreased	Lymphopenia
	Lymphocyte count decreased
Investigations: Neutrophil count decreased	Neutropenia
	Neutrophil count decreased
Investigations: Platelet count decreased	Thrombocytopenia
	Platelet count decreased
General disorders and administration site conditions: Injection site reaction	Injection site reaction
	Injection site erythema Injection site rash Injection site pruritus Injection site induration Injection site inflammation Injection site oedema Injection site pain

8.7.2.2 General considerations for analysis of TEAEs

TEAEs will be displayed in frequency tables, presenting for all tables:

- Number of TEAEs and percentage of patients with at least one TEAE (TEAEs, n (%))
- Number of related TEAEs and percentage of patients with at least one related TEAE (related TEAEs, n (%))

Where percentages will be computed from the number of treated patients in All indications pooled and, in each indication, respectively (unless stated otherwise, see below). Clinical sign/symptom of cytokine release syndrome (as per variable AE.AERELCRS) will be listed separately.

The following frequency tables will be generated for TEAEs, TESAEs:

- Summary table of TEAEs

- Frequencies of TEAEs by MedDRA preferred term (PT) and primary system organ class (SOC)

8.7.2.3 Summary tables of TEAEs

Summary table of TEAEs will present the frequencies of any TEAE and TEAEs by the following characteristics:

- Seriousness
- Outcome
- Severity (i.e., maximum severity reported for AE)
- Maximum severity per patient
- Severity of NCI CTCAE grade 3,4,5
- AE immune-related
- Action taken with SOT101

For frequencies by "Severity", AEs and patients will be counted for each severity level which occurs (one patient can have several AEs with different severity). "Maximum severity per patient" will be calculated for each patient. Then, in frequency tables the patient will be counted only once (for the maximal severity) and only TEAEs with this maximal severity will be counted. Similarly, the worst action taken will be considered, from best to worst: No action taken, Dose modified, Temporarily discontinued, Other (as temporarily discontinued + dose modified), Permanently discontinued.

Summary table of TEAEs will be presented for All indications pooled and by indication. In addition, the summary table of TEAEs by cycle will be presented for All indications pooled, up to Cycle 3 and only for TEAEs with an NCI CTCAE grade > 2; when presenting by Cycle, the number of patients treated within that Cycle will be used for the calculation of percentages. The TEAE will be assigned to a Cycle if the onset is within that Cycle, or if the TEAE worsens (relative to pretreatment state) within that Cycle.

Frequencies of TEAEs by MedDRA PT within SOC will present frequencies of any TEAE, by SOC and by PT within each SOC. The tables of the following groups of TEAEs will be provided:

- TEAEs
- TEAEs reported in $\geq$ 10% of patients
- Non-serious TEAEs reported in ≥5% of patients
- TESAEs
- Fatal TEAEs
- NCI CTCAE Grade 3, 4, 5 TEAEs
- Immune-related TEAEs
- TEAEs leading to SOT101 dose modification
- TEAEs leading to SOT101 temporary discontinuation
- TEAEs leading to SOT101 permanent discontinuation

Special cases regarding SOT101 Action Taken (e.g., Other, "free text" specified) will be reviewed before analysis and TEAEs will be counted as appropriate following the specification in other action taken: in general, certain keywords will be used to classify the TEAE into one of the abovementioned actions taken(e.g., a keyword of "dose" in the free text would lead to a classification of dose modified as action taken, a keyword of "discontinuation" or "discontinued" in the free text would lead to a classification of temporary discontinuation).

Frequencies of TEAEs by MedDRA PT within SOC will be presented for All indications pooled and by indication.

Frequency table of TEAEs by MedDRA PT will be generated for All indications pooled. The table will be sorted by total number of patients with TEAE in descending order. Additionally, the proportion of patients with TEAE by MedDRA PT will also be presented graphically, by maximum grade and worse action taken.

Table of underlying causes of deaths by MedDRA PT and primary SOC will be generated for All indications pooled.

Renal TEAEs will be analyzed separately for all indications pooled. Renal TEAEs are defined as TEAEs with:

- SOC = "Renal and urinary disorders", or
- PT = "Blood creatinine increased"

8.7.2.4 Listing of AEs

Listings of AEs will present the following information in addition to data collected on eCRF page "ADVERSE EVENT DETAILS":

- Patient identification (ID), Study Part, Indication
- AE no. (derived as number of AE episode, see section 5.6, in chronological order of start date)
- TEAE (Yes/No) (derived)
- Cycle when AE started (derived)
- SOT101 Treatment Day when AE started (derived)
- Days* after the last SOT101 administration (derived)
- Last dose of SOT101 before AE start (derived)
- Total number of SOT101 doses administered before AE start**
- Duration of AE***
- MedDRA PT

* Days after last dose will be calculated as AE start date – administration date.

**If time of AE start is not recorded (or time of SOT101 administration is not recorded), the information will be derived only using dates (i.e., date of last SOT101 administered before date of AE start, SOT101 doses administered before date of AE start). The administration of SOT101 at the same date as date of AE start will be indicated as "(+1)", e.g. 5 (+1). If AE start date (or SOT101 administration date) is unknown or incomplete, the derivation will not be performed.

***Duration of AE will be calculated as AE end date – AE start date + 1. If end date or start date is missing or incomplete, the derivation will not be performed.

8.7.3 Other safety assessments

Other safety data include ECG, vital signs, clinical laboratory, physical examination, and echocardiography.

Date of physical examination, date and results of echocardiography assessment will be only listed.

Absolute values of laboratory data (selected laboratory variables defined below), vital signs and QT/QTcF (Fridericia's correction) will be summarized at individual time-points descriptively by indication and all indications pooled. A more detailed overview will be provided with figures containing the profiles over time, where the indication will be colored accordingly.

In all cases, tables and figures will present time-points where at least 3 patients (or more) have data available at that time-point.

8.7.3.1 ECG

In addition, analysis in line with ICH E14 guideline will be performed, i.e. number and percentage of patients who fit the criterial listed below will be presented in frequency table (All Indication pooled and all time-points pooled).

- QTcF interval > 450
- QTcF interval > 480
- QTcF interval > 500
- QTcF interval increases from study baseline > 30
- QTcF interval increases from study baseline > 60
- Any criterion listed above met

QTcF levels which met the criteria above will be included in dedicated listing.

In case of any duplicated assessments, the assessment with the latest sequence (PAGESEQ in eCRF) will be selected.

8.7.3.2 Vital signs

In addition, the following will be provided:

- Mean profiles over time will be presented graphically by indication and all indications pooled.

Vital signs will be analyzed irrespective of the position where the assessments were done.

8.7.3.3 Laboratory values

The selected laboratory variables: Total Bilirubin, Alanine Transaminase (ALT), Aspartate Transaminase (AST), Neutrophils, Platelets, Lymphocytes, Haemoglobin, C-reactive protein (CRP), Alkaline Phosphatase (ALP), Lactate Dehydrogenase (LDH).

Laboratory values will be converted to standard units: the conversion factors to SI units will be maintained in the lab repository database (IBMCD LAB). Changes will be audit trailed in the system. The conversion of laboratory results into SI units will be performed via SAS programming.

In addition, the following will be provided:

For selected laboratory variables not concerning liver enzymes (Neutrophils, Platelets, Lymphocytes, Haemoglobin, CRP, LDH):

- Mean profiles over time will be presented graphically by indication and all indications pooled.

For selected laboratory variables concerning liver enzymes (Total Bilirubin, ALT, AST, ALP):

- Mean profiles over time will be presented graphically by indication and all indications pooled.
- Maximal-levels per patient presented in figure with dose-level on X-axis.
- Maximal levels per patient will be also listed in dedicated listing.

For the profiles, if there are two or more values on the same day, the pre-dose value will be considered (as per protocol, safety laboratory measurements should be performed prior to dosing). In case of two or more pre-dose values, the one closest to the dosing will be selected for displaying purposes.

Hepatic function abnormality defined by an increase in AST and/or ALT to ≥ 3 × Upper limit of normal (ULN) concurrent with an increase in total bilirubin to ≥ 2 × ULN but without increase in alkaline

phosphatase (i.e., alkaline phosphatase < 2 × ULN) meets the criteria for Hy's law and raises the concern for drug-induced liver injury when no other cause is identified. The summary of liver function tests will include the abovementioned categories, and the number and percentage of patients meeting Hy's Law at each scheduled visit during the on-treatment period will be summarized.

8.7.3.4 Prohibited medications

According to section 9.10.4.1 Prohibited medications in the Study Protocol medications which use is known to prolong QT/QTcF interval are prohibited. If such a prohibited medication is administered to the patients, then it will be taken into account in analysis of QT/ QTcF in the following way: patients with prohibited medications administered will be excluded from the analysis (tables) and further information will be provided: if the number of patients with prohibited medications administered is larger than 1, an extra table will be provided for the analysis of QT/QTcF including only these patients. Otherwise, a footnote specifying the case will be provided with the original table.

8.8 ANALYSES OF SOT101 CONCENTRATION DATA AND PK PARAMETERS

The PK analysis plan is provided b [redacted] nd attached to this SAP (section 12.1).

The following PK parameters will be calculated via non-compartmental model according to this plan:

- C_{max}
- T_{max}
- $t_{1/2,}$
- Termination elimination constant (λ_z)
- $t_{1/2\alpha}$ – distribution half-life (where possible)
- $AUC_{(0-6)}$, $AUC_{(0-t)}$, $AUC_{(0-24)}$, $AUC_{(0-inf)}$, same parameters per dose (AUC/D)
- CL - Clearance
- V_d - Volume of distribution
- R_{ac} - accumulation ratio

Concentration levels, C_{max}, T_{max} and $t_{1/2}$ will be analyzed descriptively. In addition, dose-normalized C_{max} (C_{max}/D) and T_{max} will be presented. Mean concentration levels will be presented in figures with linear and semi-logarithmic scale (only for Cycle 1).

In line with Protocol Deviation Plan, PK samples taken out of schedule defined by the study protocol will be flagged in concentration listings and will not be a part of protocol deviation listing.

PK samples are taken on cycle 1 day 1 for 24 hours after administration. Cycle 1 day 9, cycle 2 day 1 and 9 and cycle 3 day 1 are planned to be collected up to 6 hours from administration. All PK analyses will be conducted in PK/PD evaluable patients. Values below the BLQ will be treated as 0 when performing the analysis on a linear scale. On the logarithmic scale, these values will be disregarded.

Sensitivity analyses for hemolytic samples:

Any samples with presence of hemolysis will be flagged in the analysis datasets and listings as follows: a keyword search (both in lower and upper case) of "Hemolytic", "Hemolysis" will be performed on concentration dataset, column LABCOM. Subsequently, a sensitivity analysis on concentration levels and dose proportionality will be performed.

8.9 ANALYSES OF PHARMACODINAMIC MARKERS AND CYTOKINES

PD markers and cytokines levels will be provided by [redacted] and will not be a part of eCRF database.

The PD marker of interest are as follows:

CD8 Panel
CD8+ Cells of CD3+ Cells (%)
CD8+ Cells of CD3+ Cells(%CD45+)
Ki-67+ Cells of CD8+ Cells (%)
Ki-67+ Cells of CD8+ Cells (%CD45+)
CD45RO+ CD45RA- (Memory) Cells of CD8+ Cells (%)
CD45RO+ CD45RA- (Memory) Cells of CD8+ Cells (%CD45+)
Ki-67+ Cells of CD8+CD45RO+ CD45RA- Cells (%)
Ki-67+ Cells of CD8+CD45RO+ CD45RA- Cells (%CD45+)
NKG2D+ Cells of CD8+ Cells (%)
NKG2D+ Cells of CD8+ Cells (MFI NKG2D)
NKG2D+ Cells of CD8+CD45RO+CD45RA- Cells (%)
NKG2D+ Cells of CD8+CD45RO+CD45RA- Cells (MFI NKG2D)
CD4+ Cells of CD3+ Cells (%)
CD4+ Cells of CD3+ Cells (%CD45+)
Ki-67+ Cells of CD4+ Cells (%)
Ki-67+ Cells of CD4+ Cells (%CD45+)

Natural killer cells (NK) Panel
CD25+Foxp3+ (Treg) Cells of CD4+ Cells (%)
CD25+Foxp3+ (Treg) Cells of CD4+ Cells (%CD45+)
Ki-67+ Cells of CD4+CD25+Foxp3+ (Treg) Cells (%)
Ki-67+ Cells of CD4+CD25+Foxp3+ (Treg) Cells (%CD45+)
CD3-CD56+ (NK) Cells of CD45+ Live Cells (%)
Ki-67+ Cells of CD3-CD56+ (NK) Cells (%)
Ki-67+ Cells of CD3-CD56+ (NK) Cells (%CD45+)
CD3+CD56+ (NKT) Cells of CD45+ Live Cells (%)
Ki-67+ Cells of CD3+CD56+ (NKT) Cells (%)
Ki-67+ Cells of CD3+CD56+ (NKT) Cells (%CD45+)
NKG2D+ Cells of CD3-CD56+ (NK) Cells (%)
NKG2D+ Cells of CD3-CD56+ (NK) Cells (MFI NKG2D)

Cytokines include the following variables:

Interleukin-2
Interleukin-4
Interleukin-6
Interleukin-8
Tumor Necrosis Factor Alpha
Interferon-gamma
Interleukin-1 beta
Interleukin-10
Interleukin-12p70

The eCRF Hematology data (specifically white blood cell count (WBC)) for each timepoint will be used to derive the Cell counts in 10^9/L. Once merged with the pharmacodynamic data by subject and timepoint, the following will be used as derivation:

- CD8+ Cells of CD3+ Cells (10^9/L) = CD8+ Cells of CD3+ Cells (%CD45+) x 0.01 x WBC
- Ki-67+ Cells of CD8+ Cells (10^9/L) = Ki-67+ Cells of CD8+ Cells (%CD45+) x 0.01 x WBC
- CD45RO+ CD45RA- (Memory) Cells of CD8+ Cells (10^9/L) = CD45RO+ CD45RA- (Memory) Cells of CD8+ Cells (%CD45+) x 0.01 x WBC
- CD4+ Cells of CD3+ Cells (10^9/L) = CD4+ Cells of CD3+ Cells (%CD45+) x 0.01 x WBC

- Ki-67+ Cells of CD4+ Cells (10^9/L) = Ki-67+ Cells of CD4+ Cells (%CD45+) x 0.01 x WBC
- CD25+Foxp3+ (Treg) Cells of CD4+ Cells (10^9/L) = CD25+Foxp3+ (Treg) Cells of CD4+ Cells (%CD45+) x 0.01 x WBC
- Ki-67+ Cells of CD4+CD25+Foxp3+ (Treg) Cells (10^9/L) = Ki-67+ Cells of CD4+CD25+Foxp3+ (Treg) Cells (%CD45+) x 0.01 x WBC
- CD3-CD56+ (NK) Cells of CD45+ Live Cells (10^9/L) = CD3-CD56+ (NK) Cells of CD45+ Live Cells (%) x 0.01 x WBC
- Ki-67+ Cells of CD3-CD56+ (NK) Cells (10^9/L) = Ki-67+ Cells of CD3-CD56+ (NK) Cells (%CD45+) x 0.01 x WBC
- CD3+CD56+ (NKT) Cells of CD45+ Live Cells (10^9/L) = CD3+CD56+ (NKT) Cells of CD45+ Live Cells (%) x 0.01 x WBC
- Ki-67+ Cells of CD3+CD56+ (NKT) Cells (10^9/L) = Ki-67+ Cells of CD3+CD56+ (NKT) Cells (%CD45+) x 0.01 x WBC

During the descriptive statistical analysis of PD markers and cytokines will be considered that the value can be below or above limits of quantification: the lower limit will be replaced by the actual value (e.g. “<0.5” should be considered as 0.5), similarly for the upper limit (e.g. “>20” should be considered as 20). In all cases, only Cycle 1 and Cycle 2 data will be used and analyzed to study the Pharmacodynamic activation. Only certain markers of interest will be included in the tables and figures, all markers will be listed.

The levels and fold increases will be analyzed descriptively at individual time-points by indication and all indications pooled. A more detailed overview will be provided with figures containing the profiles over time, where the indication will be colored accordingly. A Boxplot for Cycle 1 Day 6 by indication, and maximal levels of activation achieved by indication (barplot), will be provided for selected PD markers:

- NK cells: Ki-67+ Cells of CD3-CD56+ (NK) Cells (%)
- NKT cells: Ki-67+ Cells of CD3+CD56+ (NKT) Cells (%)
- CD8+ T-cells: Ki-67+ Cells of CD8+ Cells (%)
- CD8+ Memory T cells: Ki-67+ Cells of CD8+CD45RO+ CD45RA- Cells (%)
- CD4+ T cells: Ki-67+ Cells of CD4+ Cells (%)
- T regs: Ki-67+ Cells of CD4+CD25+Foxp3+ (Treg) Cells (%)

The table summarizing the maximum levels of activation will contain the fold increase in cell counts (i.e., 10^9/L).

Additionally for cytokines, the mean fold increase over time will also be plotted.

All PD analyses will be conducted on PK/PD evaluable patients.

Maximal levels of cytokines will also be listed.

8.10 ANALYSES OF EFFICACY

The efficacy population will be derived as follows: assuming at least one evaluable tumor assessment per iRECIST after the initiation of SOT101 treatment, a patient that receives 4 doses of SOT101 in cycle 1, will be included in the efficacy population; if a patient does not receive 4 doses of SOT101 in cycle 1 then the patient will be included in the efficacy population if monotherapy is not permanently discontinued in cycle 1 (i.e. patient starts cycle 2). The efficacy population will be used for the efficacy analyses.

Due to the lack of confirmation of progression (iCPD) and follow-up scans, any unconfirmed progression (iUPD) has been considered as progression if a discontinuation of any treatment is followed, and thus deviating from iRECIST guidelines.

Complete response (iCR), partial response (iPR), stable disease (iSD) and progression disease (iUPD and also after iCPD) will be identified according to iRECIST, recorded to eCRF, and cleaned via data management/medical review processes.

Tumor assessment data will be listed and disease response since the first SOT101 administration will be presented graphically per patient (swimmer plot). Additionally, tumor size evaluated via sum of diameters of target lesions will be presented graphically per patient (waterfall plot): the best change from baseline will be used. The change from baseline over time will be graphically presented per patient as well (spaghetti plot).

If tumor assessment is performed after start of new anticancer therapy, it will be clearly indicated in the outputs. For tumor assessments with different dates (i.e. lesions are assessed at different dates), the earliest date will be used for efficacy derivations.

Overall response is defined as state when the patient achieves iPR or iCR. Clinical benefit is defined as state when patient achieves iSD, iPR, or iCR. iSD needs to last at least 6 weeks from the start of study treatment; if not, at least one follow-up scan assessed as iPR, iCR, or iSD is required to provide clinical benefit. Similarly, confirmation of iPR or iCR by a subsequent assessment of either iPR or iCR, at least 4 weeks apart, will be required to declare an overall response or clinical benefit.

Immune overall response rate (iORR) and Clinical benefit rate (iCBR):

- iORR will be defined as the proportion of patients with confirmed iPR or iCR, out of patients in efficacy population.
- iCBR will be defined as the proportion of patients with confirmed iPR, iCR, or iSD out of patients in efficacy population.

iORR and iCBR will be summarized by indication and for All indications pooled.

Progression free survival (iPFS):

iPFS is defined as the time from the first day of study treatment until the first date of iUPD (followed by iCPD, study treatment discontinuation or clinical progression) or death (whichever occurs earliest) and will be summarized using Kaplan-Meier estimates.

Patients with missing data or that start new anti-cancer therapy (other than palliative) will be censored at the date of the last evaluable tumor assessment.

iPFS will be summarized and presented by indication and for All indications pooled.

Duration of response (iDoR):

iDoR is defined as the time since the first iPR or iCR until the first date of iUPD (followed by iCPD, study treatment discontinuation or clinical progression) or death (whichever occurs earliest) for patients with confirmed iPR or iCR. DoR will be summarized using Kaplan-Meier estimates.

Patients with missing data or that start new anti-cancer therapy (other than palliative) will be censored at the date of the last evaluable tumor assessment.

iDoR will be summarized and presented by indication and for All indications pooled.

Overall survival (OS):

OS is defined as the time from the first day of study treatment until the date of death and will be summarized using Kaplan-Meier estimates.

Patients with missing data will be censored at the last time known to be alive: apart from trial visits/survival status, information from AE, new anti-cancer therapy, and prior and concomitant medications data from eCRF will also be used to derive the alive status – the latest complete date will be selected.

OS will be summarized and presented by indication and for All indications pooled.

Duration of follow-up:

A reverse Kaplan-Meier analysis will be performed on OS to estimate the median follow-up incorporating censoring rules and flipping event/censored events.

8.11 OTHER ASSESSMENTS

8.11.1 ECOG performance status

ECOG performance status will be summarized for All indications pooled, by indication, and listed.

8.11.2 Immunogenicity

ADA levels, titration, and Neutralizing ADA levels will be provided by [redacted] nd will not be a part of eCRF database. Levels and titration will be analyzed descriptively for All indications pooled and by indication for SAF population. The summary table will be completed with listing of positive results.

8.12 INTERIM ANALYSES

No interim analysis is planned.

8.13 DETERMINATION OF SAMPLE SIZE

The number of patients in Part D together with or without Part D1 to be treated for at least one cycle is set to a maximum of 20 per indication (60 in total). This number of patients is deemed to be appropriate to provide further safety, PK, PD, and efficacy data per indication at the RP2D dose level identified in Part A (SOT101, dosing schedule 1, monotherapy) and the RP2D dose level identified in Part A1 (SOT101, dosing schedule 2, monotherapy). In case biomarker data in Part A1 suggest a more competitive efficacy as compared to once daily dosing, a switch to twice daily dosing (Part D1) will be made during the course of the study without affecting the overall number of patients enrolled.

Since no patients have been enrolled into Part D1, this sample size has been used for Part D exclusively.

9 CONCLUSIONS BASED OF DATA REVIEW MEETING

From the statistical perspective the objectives of the meeting will be following:

- to agree on patients excluded from analysis sets and to agree on major protocol deviations/reportable protocol deviations
- to highlight any issue from statistical perspective and to decide the solution in joint decision.

The section below will state version of Protocol Deviation Plan valid at time of the data review meeting, refer to data review meeting minutes and summarize/ summarizes conclusion relevant to statistical analysis which were made during the data review meeting.

9.1 DATA REVIEW MEETING BEFORE ANALYSIS

The review will be performed under Protocol Deviation Plan version 2.0 dated 08 March 2023

Prior to lock of database, a data review will be performed, and conclusions will be summarized separately in eTMF.

The review of PK data includes derivation of sampling out of window according to Protocol v10 following the derivation: PK blood sampling out of window will be flagged in listing of concentration levels. Note referring to that listing will be added to output of CSR reportable PDs. Unreliable PK concentrations will be flagged, such values are not to be used for the calculation of PK parameters and descriptive analysis of PK concentrations. Hemolytic samples have been considered reliable; however, a sensitivity analysis is included in this SAP.

The review of PK data will also be documented consistently in eTMF.

For PBCM data, applicable to all samples and all cycles:

- Any samples taken after a missed or delayed dose will be excluded within the cycle: for example, if C1D2 is not done then any day afterwards within the cycle should be excluded (C1D6, C1D8, ...). EXCEPT when that delay or deviation is shifting the CXD8 and CXD9 dosing to CXD9 and CXD10 dosing (consecutive)
- Any samples taken after a dose reduction or increase will be excluded.
- Any dosing performed PRIOR to CXD8 (i.e., deviation) will lead to the exclusion of samples from CXD8 onwards within the cycle.
- Any sample taken with a deviation more than 1 day (>1 day) from the protocol schedule will be excluded.

The rules above will also be applied for Cytokines (CK). In addition, for CK, any sample taken outside of the protocol defined window will be excluded.

No data from other sampling (Immunogenicity, Tumor Biopsy, etc.) will be considered as unreliable and/or affected by deviations and no exclusion rules will be created.

10 LIST OF TABLES, FIGURES AND LISTINGS

The table hereunder presents preliminary list of content of tables, figures and listings which will be integrated in study report. The structure and numbering is proposed according the ICH guidelines - E3: Structure and Content of Clinical Study Reports.

10.1 SECTION 10 OF CSR (STUDY PATIENTS)

Selected tables from Section 14.1 of CSR (DEMOGRAPHIC DATA).

This section will cover the following:

- Summary of patient disposition
- Patient disposition by country
- Analysis populations
- Protocol deviations
- Summary of patient demographics and baseline characteristics
- Summary of disease history
- Summary of medical history
- Summary of prior, concomitant, and post-treatment therapies
- Exposure to study medication

10.2 SECTION 11 OF CSR (SAFETY AND PK/PD EVALUATIONS)

Selected tables from Section 14.3 (SAFETY DATA) and Section 14.2 (PK/PD DATA) of CSR.

This section will cover the following:

- Summary of TEAEs
- AE tables by PT within SOC
- Summary of causes of death

This section will cover also pharmacokinetic and pharmacodynamics evaluation.

10.3 SECTION 12 OF CSR (EFFICACY AND OTHER DATA)

Selected tables from Section 14.2 of CSR (EFFICACY AND OTHER DATA).

10.4 SECTION 13 OF CSR (DISCUSSION AND OVERALL CONCLUSIONS)

No tables are planned.

10.5 SECTION 14 OF CSR (TABLES, FIGURES AND GRAPHS REFERRED TO BUT NOT INCLUDED IN THE TEXT)

Output	Number	Title	Analysis Set
	Section 14.1	**Demographic data**	
		Patient disposition	
Table	14.1.1.1	Disposition of patients	All
Table	14.1.1.2	Disposition of patients by country	All

Output	Number	Title	Analysis Set
Table	14.1.1.3	Analysis populations and reasons for exclusion	All
Table	14.1.1.4	Reasons for discontinuation after treatment start	SAF
Table	14.1.1.5	Protocol deviations	SAF, Efficacy
		Baseline characteristics and disease history	
Table	14.1.2.1	Baseline characteristics	SAF, Efficacy, PK/PD
Table	14.1.2.2	Disease history	SAF, Efficacy, PK/PD
		Prior, concomitant, and post-treatment medication	
Table	14.1.3.1	Prior anticancer systemic therapy	SAF
Table	14.1.3.2	Prior anticancer non-systemic therapy	SAF
Table	14.1.3.3	Prior medication	SAF
Table	14.1.3.4	Prior non-pharmacological therapy	SAF
Table	14.1.3.5	Concomitant medication	SAF
Table	14.1.3.6	Concomitant non-pharmacological therapy	SAF
Table	14.1.3.7	Post-treatment medication	SAF
Table	14.1.3.8	Post-treatment non-pharmacological therapy	SAF
Table	14.1.3.9	New anticancer systemic therapy	SAF
Table	14.1.3.10	New anticancer non-systemic therapy	SAF
		Exposure	
Table	14.1.4.1	Exposure to study treatment	SAF
Table	14.1.4.2	SOT101 Dose intensity	SAF
Table	14.1.4.3	Dosing overview, summary of changes from dosing	SAF
	Section 14.2	**Efficacy and PK/PD evaluations**	
		Pharmacokinetics	
Table	14.2.1.1.1	SOT101 concentrations	PK/PD
Table	14.2.1.1.2	SOT101 concentrations	PK/PD (excluding hemolytic samples)
Table	14.2.1.2	SOT101 PK parameters	PK/PD

Output	Number	Title	Analysis Set
Figure	14.2.1.3	Patient profiles of SOT101 concentrations (linear and semi-logarithmic scale)	PK/PD
Figure	14.2.1.4.1	Mean SOT101 concentrations profiles (linear and semi-logarithmic scale)	PK/PD
Figure	14.2.1.4.2	Mean SOT101 concentrations profiles (linear and semi-logarithmic scale)	PK/PD (excluding hemolytic samples)
		Pharmacodynamics	
CD8+ T Cells			
Table	14.2.2.1	CD8+ Cells of CD3+ Cells (10^9/L): Values and fold increase	PK/PD
Table	14.2.2.2	CD8+ Cells of CD3+ Cells (%): Values and fold increase	PK/PD
Table	14.2.2.3	Ki-67+ Cells of CD8+ (%): Values and fold increase	PK/PD
Figure	14.2.2.4	Mean profiles of Ki-67+ Cells of CD8+ (%) by indication and All indications pooled	PK/PD
CD8+ Memory T Cells			
Table	14.2.2.5	CD45RO+ CD45RA- (Memory) Cells of CD8+ Cells (10^9/L): Values and fold increase	PK/PD
Table	14.2.2.6	CD45RO+ CD45RA- (Memory) Cells of CD8+ Cells (%): Values and fold increase	PK/PD
Table	14.2.2.7	Ki-67+ Cells of CD8+CD45RO+ CD45RA- Cells (%): Values and fold increase	PK/PD
Figure	14.2.2.8	Mean profiles of Ki-67+ Cells of CD8+CD45RO+ CD45RA- Cells (%) by indication and All indications pooled	PK/PD
NKG2D+ Cells (CD8)			
Table	14.2.2.9	NKG2D+ Cells of CD8+ Cells (%): Values and fold increase	PK/PD
Figure	14.2.2.10	Mean profiles of NKG2D+ Cells of CD8+ Cells (%) by indication and All indications pooled	PK/PD
Table	14.2.2.11	NKG2D+ Cells of CD8+ Cells (MFI NKG2D): Values and fold increase	PK/PD
Figure	14.2.2.12	Mean profiles of NKG2D+ Cells of CD8+ Cells (MFI NKG2D) by indication and All indications pooled	PK/PD
NKG2D+ Cells (CD8 Memory)			
Table	14.2.2.13	NKG2D+ Cells of CD8+ CD45RO+CD45RA- Cells (%): Values and fold increase	PK/PD

Output	Number	Title	Analysis Set
Figure	14.2.2.14	NKG2D+ Cells of CD8+ CD45RO+CD45RA- Cells (%) by indication and All indications pooled	PK/PD
Table	14.2.2.15	NKG2D+ Cells of CD8+ CD45RO+CD45RA- Cells (MFI NKG2D): Values and fold increase	PK/PD
Figure	14.2.2.16	NKG2D+ Cells of CD8+ CD45RO+CD45RA- Cells (MFI NKG2D) by indication and All indications pooled	PK/PD
CD4+ T Cells			
Table	14.2.2.17	CD4+ Cells of CD3+ Cells (10^9/L): Values and fold increase	PK/PD
Table	14.2.2.18	CD4+ Cells of CD3+ Cells (%): Values and fold increase	PK/PD
Table	14.2.2.19	Ki-67+ Cells of CD4+ Cells (%): Values and fold increase	PK/PD
Figure	14.2.2.20	Mean profiles of Ki-67+ Cells of CD4+ Cells (%) by indication and All indications pooled	PK/PD
NK Cells			
Table	14.2.2.21	CD3-CD56+ (NK) Cells of CD45+ Live Cells (10^9/L): Values and fold increase	PK/PD
Table	14.2.2.22	CD3-CD56+ (NK) Cells of CD45+ Live Cells (%): Values and fold increase	PK/PD
Table	14.2.2.23	Ki-67+ Cells of CD3-CD56+ (%): Values and fold increase	PK/PD
Figure	14.2.2.24	Mean profiles of Ki-67+ Cells of CD3-CD56+ (%) by indication and All indications pooled	PK/PD
Treg Cells			
Table	14.2.2.25	CD25+Foxp3+ (Treg) Cells of CD4+ Cells (10^9/L): Values and fold increase	PK/PD
Table	14.2.2.26	CD25+Foxp3+ (Treg) Cells of CD4+ Cells (%): Values and fold increase	PK/PD
Table	14.2.2.27	Ki-67+ Cells of CD4+CD25+Foxp3+ (Treg) Cells (%): Values and fold increase	PK/PD
Figure	14.2.2.28	Mean profiles of Ki-67+ Cells of CD4+CD25+Foxp3+ (Treg) Cells (%) by indication and All indications pooled	PK/PD
NKT Cells			
Table	14.2.2.29	CD3+CD56+ (NKT) Cells of CD45+ Live Cells (10^9/L): Values and fold increase	PK/PD
Table	14.2.2.30	CD3+CD56+ (NKT) Cells of CD45+ Live Cells (%): Values and fold increase	PK/PD

Output	Number	Title	Analysis Set
Table	14.2.2.31	Ki-67+ Cells of CD3+CD56+ (NKT) Cells (%): Values and fold increase	PK/PD
Figure	14.2.2.32	Mean profiles of Ki-67+ Cells of CD3+CD56+ (NKT) Cells (%) by indication and All indications pooled	PK/PD
NKG2D+ Cells (NK)			
Table	14.2.2.33	NKG2D+ Cells of CD3-CD56+ (NK) Cells (%): Values and fold increase	PK/PD
Figure	14.2.2.34	Mean profiles of NKG2D+ Cells of CD3-CD56+ (NK) Cells (%) by indication and All indications pooled	PK/PD
Table	14.2.2.35	NKG2D+ Cells of CD3-CD56+ (NK) Cells (MFI NKG2D): Values and fold increase	PK/PD
Figure	14.2.2.36	Mean profiles of NKG2D+ Cells of CD3-CD56+ (NK) Cells (MFI NKG2D) by indication and All indications pooled	PK/PD
Summary of pharmacodynamic activation			
Table	14.2.2.37	Overall activation levels (10^9/L) of selected PD markers in Cycle 1 Day 6	PK/PD
Table	14.2.2.38	Overall activation levels (%) of selected PD markers in Cycle 1 Day 6	PK/PD
Figure	14.2.2.39	Overall activation levels (%) of selected PD markers in Cycle 1 Day 6 (overview)	PK/PD
Figure	14.2.2.40	Overall activation levels (%) of selected PD markers in Cycle 1 Day 6 (specific)	PK/PD
Table	14.2.2.41	Maximum levels of fold increase in cell counts (10^9/L) for selected PD markers	PK/PD
Figure	14.2.2.42	Maximum levels of activation (%) for selected PD markers	PK/PD
		Immunocytokines	
Table	14.2.3.1	Interleukin-2: Values and fold increase	PK/PD
Figure	14.2.3.2	Mean profiles of Interleukin-2 by indication and All indications pooled	PK/PD
Table	14.2.3.3	Interleukin-4: Values and fold increase	PK/PD
Figure	14.2.3.4	Mean profiles of Interleukin-4 by indication and All indications pooled	PK/PD
Table	14.2.3.5	Interleukin-6: Values and fold increase	PK/PD
Figure	14.2.3.6	Mean profiles of Interleukin-6 by indication and All indications pooled	PK/PD
Table	14.2.3.7	Interleukin-8: Values and fold increase	PK/PD

Output	Number	Title	Analysis Set
Figure	14.2.3.8	Mean profiles of Interleukin-8 by indication and All indications pooled	PK/PD
Table	14.2.3.9	Tumor Necrosis Factor Alpha: Values and fold increase	PK/PD
Figure	14.2.3.10	Mean profiles of Tumor Necrosis Factor by indication and All indications pooled	PK/PD
Table	14.2.3.11	Interferon-gamma: Values and fold increase	PK/PD
Figure	14.2.3.12	Mean profiles of Interferon-gamma by indication and All indications pooled	PK/PD
Table	14.2.3.13	Interleukin-1 beta: Values and fold increase	PK/PD
Figure	14.2.3.14	Mean profiles of Interleukin-1 beta by indication and All indications pooled	PK/PD
Table	14.2.3.15	Interleukin-10: Values and fold increase	PK/PD
Figure	14.2.3.16	Mean profiles of Interleukin-10 by indication and All indications pooled	PK/PD
Table	14.2.3.17	Interleukin-12p70: Values and fold increase	PK/PD
Figure	14.2.3.18	Mean profiles of Interleukin-12p70 by indication and All indications pooled	PK/PD
		Efficacy data	
Table	14.2.4.1	Duration of follow-up	SAF
Figure	14.2.4.2	Kaplan-Meier curve of duration of follow-up	SAF
Figure	14.2.4.3	Disease response since the first SOT101 administration per patient	SAF
Table	14.2.4.4	Tumor response (overall response rate and clinical benefit rate) as per iRECIST	Efficacy
Figure	14.2.4.5.1	Best change from baseline in tumor size per patient	Efficacy
Figure	14.2.4.5.2	Change from baseline in tumor size per patient	Efficacy
Table	14.2.4.6	Duration of response as per iRECIST (iDoR)	Efficacy
Figure	14.2.4.7	Kaplan-Meier curve of iDoR as per iRECIST	Efficacy
Table	14.2.4.8	Progression free survival as per iRECIST (iPFS)	Efficacy
Figure	14.2.4.9	Kaplan-Meier curve of iPFS as per iRECIST	Efficacy
Table	14.2.4.10	Overall survival	Efficacy
Figure	14.2.4.11	Kaplan-Meier curve of overall survival	Efficacy

Output	Number	Title	Analysis Set
	Section 14.3	**Safety data**	
		TEAEs	
Table	14.3.2.1	Summary of Treatment-Emergent Adverse Events	SAF
Table	14.3.2.2	Summary of Treatment-Emergent Serious Adverse Events	SAF
Table	14.3.2.3	Summary of Treatment-Emergent Adverse Events by cycle	SAF
Table	14.3.2.4	Summary of Treatment-Emergent Serious Adverse Events by cycle	SAF
Table	14.3.3.1	Treatment-Emergent Adverse Events by MedDRA PT and primary SOC	SAF
Table	14.3.3.2	Treatment-Emergent Adverse Events by MedDRA PT and primary SOC reported in $\geq$10% of patients	SAF
Table	14.3.3.3	Non-serious Treatment-Emergent Adverse Events by MedDRA PT and primary SOC reported in $\geq$5% of patients	SAF
Table	14.3.3.4	Treatment-Emergent Adverse Events by MedDRA PT	SAF
Figure	14.3.3.5	Treatment-Emergent Adverse Events by MedDRA PT and Grade	SAF
Figure	14.3.3.6	Treatment-Emergent Adverse Events by MedDRA PT and Action Taken	SAF
Table	14.3.3.7	Treatment-Emergent Serious Adverse Events by MedDRA PT and primary SOC	SAF
Table	14.3.3.8	Fatal Treatment-Emergent Adverse Events by MedDRA PT and primary SOC	SAF
Table	14.3.3.9	Grade 3, 4, 5 Treatment-Emergent Adverse Events by MedDRA PT and primary SOC	SAF
Table	14.3.3.10	Immune-related Treatment-Emergent Adverse Events by MedDRA PT and primary SOC	SAF
Table	14.3.3.11	Treatment-Emergent Adverse Events leading to SOT101 dose modification by MedDRA PT and primary SOC	SAF
Table	14.3.3.12	Treatment-Emergent Adverse Events leading to SOT101 temporary discontinuation by MedDRA PT and primary SOC	SAF
Table	14.3.3.13	Treatment-Emergent Adverse Events leading to SOT101 permanent discontinuation by MedDRA PT and primary SOC	SAF
Table	14.3.3.14	Treatment Emergent Adverse Events symptoms of Cytokine release syndrome by MedDRA PT and primary SOC	SAF

Output	Number	Title	Analysis Set
Table	14.3.3.15	Treatment Emergent Adverse Events by MedDRA PT and Maximum CTCAE Grade	SAF
Table	14.3.3.16	Renal Treatment Emergent Adverse Events by MedDRA PT and Maximum CTCAE Grade	SAF
Table	14.3.4.1	Underlying causes of deaths by MedDRA PT and primary SOC	SAF
	Section 14.4	**Clinical Laboratory data**	
		Liver enzyme values	
Table	14.4.1.1	Total Bilirubin (µmol/L): Values, relative and absolute changes from baseline	SAF
Figure	14.4.1.2	Mean profile of Total Bilirubin (µmol/L) by indication and All indications pooled	SAF
Table	14.4.2.1	Alanine Transaminase (ALT) (µkat/L): Values, relative and absolute changes from baseline	SAF
Figure	14.4.2.2	Mean profile of Alanine Transaminase (ALT) (µkat/L) by indication and All indications pooled	SAF
Table	14.4.3.1	Aspartate Transaminase (AST) (µkat/L): Values, relative and absolute changes from baseline	SAF
Figure	14.4.3.2	Mean profile of Aspartate Transaminase (AST) (µkat/L) by indication and All indications pooled	SAF
Table	14.4.4.1	Alkaline Phosphatase (ALP) (µkat/L): Values, relative and absolute changes from baseline	SAF
Figure	14.4.4.2	Mean profiles of Alkaline Phosphatase (ALP) (µkat/L) by indication and All indications pooled	SAF
Table	14.4.4.4	Hepatic function (Hy's law)	SAF
Figure	14.4.4.5	Maximal levels per patient of Total Bilirubin (µmol/L), Alanine Transaminase (ALT) (µkat/L), Aspartate Transaminase (AST) (µkat/L), and Alkaline Phosphatase (ALP) (µkat/L) by indication	SAF
		Other laboratory values	
Table	14.4.5.1	Haemoglobin (g/L): Values, relative and absolute changes from baseline	SAF
Figure	14.4.5.2	Mean profile of Haemoglobin (g/L) by indication and All indications pooled	SAF

Output	Number	Title	Analysis Set
Table	14.4.6.1	Neutrophils (10^9/L): Values, relative and absolute changes from baseline	SAF
Figure	14.4.6.2	Mean profile of Neutrophils (10^9/L) by indication and All indications pooled	SAF
Table	14.4.7.1	Neutrophils (%): Values and absolute changes from baseline	SAF
Figure	14.4.7.2	Mean profile of Neutrophils (%) by indication and All indications pooled	SAF
Table	14.4.8.1	Lymphocytes (10^9/L): Values, relative and absolute changes from baseline	SAF
Figure	14.4.8.2	Mean profile of Lymphocytes (10^9/L) by indication and All indications pooled	SAF
Table	14.4.9.1	Lymphocytes (%): Values and absolute changes from baseline	SAF
Figure	14.4.9.2	Mean profile of Lymphocytes (%) by indication and All indications pooled	SAF
Table	14.4.10.1	Lactate Dehydrogenase (LDH) (µkat/L): Values, relative and absolute changes from baseline	SAF
Figure	14.4.10.2	Mean profile of Lactate Dehydrogenase (LDH) (µkat/L) by indication and All indications pooled	SAF
Table	14.4.11.1	Platelet count (10^9/L): Values, relative and absolute changes from baseline	SAF
Figure	14.4.11.2	Mean profile of Platelet count (10^9/L) by indication and All indications pooled	SAF
Table	14.4.12.1	C-reactive protein (CRP) (mg/L): Values, relative and absolute changes from baseline	SAF
Figure	14.4.12.2	Mean profile of C-reactive protein (CRP) (mg/L) by indication and All indications pooled	SAF
	Section 14.5 Vital Signs		
Table	14.5.1.1	Systolic blood pressure (mmHg): Values and absolute changes from baseline	SAF
Figure	14.5.1.2	Mean profile of Systolic blood pressure (mmHg) by indication and All indications pooled	SAF
Table	14.5.2.1	Diastolic blood pressure (mmHg): Values and absolute changes from baseline	SAF
Figure	14.5.2.2	Mean profile of Diastolic blood pressure (mmHg) by indication and All indications pooled	SAF

Output	Number	Title	Analysis Set
Table	14.5.3.1	Heart rate (beats/min): Values and absolute changes from baseline	SAF
Figure	14.5.3.2	Mean profile of Heart rate (beats/min) by indication and All indications pooled	SAF
Table	14.5.4.1	Respiratory rate (breaths/min): Values and absolute changes from baseline	SAF
Figure	14.5.4.2	Mean profile of Respiratory rate (breaths/min) by indication and All indications pooled	SAF
Table	14.5.5.1	Body temperature (Celsius (°)): Values and absolute changes from baseline	SAF
Figure	14.5.5.2	Mean profile of Body temperature (Celsius (°)) by indication and All indications pooled	SAF
	Section 14.6 ECG		
Table	14.6.1.1	QT (ms): Values, relative and absolute changes from baseline	SAF
Table	14.6.2.1	QTcF (ms): Values, relative and absolute changes from baseline	SAF
Figure	14.6.2.2	Mean profile of QTcF (ms)by indication and All indications pooled	SAF
Table	14.6.3.1	QTcF (ms): Frequency of Intervals	SAF
	Section 14.7 ECOG		
Table	14.7.1	ECOG performance status	SAF
	Section 14.8 Immunogenicity		
Table	14.8.1	Anti-drug antibodies	SAF
Table	14.8.2	Titration of anti-drug antibodies	SAF
Table	14.8.3	Neutralizing anti-drug antibodies	SAF

10.6 APPENDIX 16.2 OF CSR (PATIENT DATA LISTINGS)

All patients included in clinical database will be listed (if not specified otherwise).

Listing Number	Title
Section 16.2.1	**Discontinued patients**
16.2.1.1	Study dates and patients' discontinuation overview in treated patients
16.2.1.2	Screening failures and withdrawals prior study treatment start
Section 16.2.2	**Protocol Deviations**
16.2.2.1	CSR reportable protocol deviations
16.2.2.2	CSR not reportable protocol deviations
16.2.2.3	Eligibility criteria and eligibility verification
16.2.2.4	Protocol deviations related to COVID-19
Section 16.2.3	**Patients excluded from efficacy analysis**
16.2.3.1	Disposition of patients to analysis sets and reasons for exclusion
Section 16.2.4	**Demographic data**
16.2.4.1	Informed consent signatures
16.2.4.2	Demographic data, patients' characteristics and disease history details
16.2.4.3	Medical history
16.2.4.4	Medical history – MedDRA coding details
16.2.4.5	Prior medication
16.2.4.6	Prior medication (including WHODD coding)
16.2.4.7	Prior anticancer systemic therapy (including WHODD coding)
16.2.4.8	Prior anticancer non-systemic therapy (including MedDRA coding)
16.2.4.9	Concomitant medication
16.2.4.10	Concomitant medication (including WHODD coding)
16.2.4.11	Post-treatment medication
16.2.4.12	Post-treatment medication (including WHODD coding)
16.2.4.13	Prior non-pharmacological therapy (including MedDRA coding)
16.2.4.14	Concomitant non-pharmacological therapy (including MedDRA coding)
16.2.4.15	Post-treatment non-pharmacological therapy (including MedDRA coding)
16.2.4.16	New anticancer systemic therapy (including WHODD coding)

Listing Number	Title
16.2.4.17	New anticancer non-systemic therapy (including MedDRA coding)
Section 16.2.5	**Compliance and drug concentration data**
16.2.5.1	Exposure to SOT101
16.2.5.2	SOT101 Dose intensity
16.2.5.3	Body weight and compliance of study drug administration with Study Protocol
16.2.5.4	SOT101 concentration levels
16.2.5.5	SOT101 pharmacokinetic parameters
Section 16.2.6	**Individual efficacy response and pharmacodynamics data**
16.2.6.1	Tumor assessment
16.2.6.2	Disease response
16.2.6.3	Clinical progression
16.2.6.4	Pharmacodynamics markers and cytokine levels
16.2.6.5	Maximal levels of Cytokines
Section 16.2.7	**Adverse events listings**
16.2.7.2	All treatment-emergent AEs
16.2.7.3	All treatment-emergent SAEs
16.2.7.4	Treatment-emergent AEs recorded in detailed description of dose limiting toxicities
16.2.7.5	All adverse events leading to death
16.2.7.6	Causes of death including MedDRA coding details
16.2.7.7	Treatment-emergent AEs leading to permanent discontinuation of SOT101
16.2.7.9	Treatment-emergent AEs with suspected causal relationship with SOT101
16.2.7.11	Treatment-emergent AE immune-related
16.2.7.12	Treatment-emergent clinical signs/symptoms of cytokine release syndrome
16.2.7.13	Adverse events started before the first study drug administration
16.2.7.14	Adverse events with missing or partial start date
16.2.7.15	Adverse events – MedDRA coding details
Section 16.2.8	**Listing of individual laboratory measurements**
16.2.8.1	Hematology
16.2.8.2	Biochemistry
16.2.8.3	Coagulation

Listing Number	Title
16.2.8.4	Urinalysis
16.2.8.5	Maximal levels of selected laboratory variables
16.2.8.6	Creatinine clearance levels
16.2.8.7	Thyroid function tests (TSH, free T3, free T4)
16.2.8.8	Cardiac troponin-T test
16.2.8.9	C-reactive protein (CRP) levels
16.2.8.10	Glycated hemoglobin (HbA1c)
16.2.8.11	24-hour urine protein test
16.2.8.12	Pregnancy test
16.2.8.13	Serology (HIV, hepatitis B and C tests)
16.2.8.14	Listing of abnormal laboratory results
Section 16.2.9	**Other safety data**
16.2.9.1	Vital signs
16.2.9.2	ECG results
16.2.9.3	Echocardiography results
16.2.9.4	Date of physical examination
Section 16.2.10	**Other data**
16.2.10.1	ECOG performance score
16.2.10.2	Immunogenicity

11 LAYOUT REQUIREMENTS OF TFLs

No layout requirements specified by the sponsor.

12 APPENDICES

12.1 PHARMACOKINETIC ANALYSIS PLAN

N-A-PH1-19-027_SC 103_Pharmacokineti

12.2 TIMEPOINT LABELS SPECIFICATIONS

For vital signs: Pre-dose, 15 min, 30 min, 1 h, 2 h, 3 h, 4 h, 5 h, 6 h, 7 h, 8 h will be used as per eCRF records. In the listings also real time since SOT101 administration will be presented. In the Follow-up period (Follow-up) the timepoints will be presented as EOT + X weeks as defined in the Study Protocol.

For electrocardiogram (ECG): Pre-dose, 4 h will be used as per eCRF records. In the listings also real time since SOT101 administration will be presented. At EOT visit, the timepoint will be presented as EOT as defined in the Study Protocol.

For PK and Cytokine blood sampling: Pre-dose, 1 h, 2 h, 4 h, 6 h, 8 h, 12 h, 16 h, 24 h will be used as per eCRF records. In the listings also real time since SOT101 administration will be presented.

For safety laboratory: as per standard medical practice the safety laboratory should be performed before the dosing then the label will be Cycle X Day Y – Pre-dose; otherwise, just Cycle X Day Y will be presented except in EOT visit which will be presented as EOT as defined in the Study Protocol.

Other assessments (Physical examination, body weight and Eastern Cooperative Oncology Group (ECOG) performance status) will be presented using the Cycle X Day Y label, except in the Follow-up period (Follow-up) where the label will be EOT + X weeks as defined in the Study Protocol.

In the listings, "^{UNS}" will be added to assessments performed in addition to assessments planned in the Study Protocol, for example Screening^{UNS} for some not required at screening by the Study Protocol or repeated assessment at screening, Follow-up ^{UNS} for hematologic assessment or Cycle 1 Day 9^{UNS} for coagulation assessment or Cycle 1 Day 12^{UNS}.

Time-points labels of tumor assessment: Tumor assessment will be recorded into eCRF as repeated pages and will be analyzed as iORR, iCBR, and time to event data. Therefore, time-point labels for tables will not be needed. In the listings the assessments will be identified by date, real treatment week (as defined in section 6.2, rounded to one decimal), and period label ("Cycle X" derived as defined below) or "Follow-up".

Cycle derivation:

- For each cycle will be identified Day 1 (as per eCRF records) and end of cycle as defined in section 5.1.
- Then, it will be identified which cycle the assessment date belongs to.

Time-points labels for survival follow-up information: The similar approach as for tumor assessment will be applied. Time-point labels for tables will not be needed. In the listings the information will be identified by date, real treatment week, and label "Follow-up".

Time-point labels used in tables of adverse events:

The tables of adverse events will present summary of treatment-emergent adverse events (TEAEs) recorded during the study and TEAEs depending on the time period:

- Cycle X: the time-point label will indicate treatment cycle when the adverse event (AE) started
- After last: the time-point label will indicate AEs started after end of last cycle

See treatment cycle definition in the section 5.1 above. Treatment cycle when TEAE started will only be derived for AEs with complete (and non-missing) start dates.

12.3 CANCER TYPE & INDICATION DERIVATION

Renal cell carcinoma:

Histological type	Primary tumor location	Cancer type (long name)	Cancer type (short name)
clear cell adenocarcinoma	Kidney	Kidney	Kidney
papillary renal cell carcinoma	Kidney	Kidney	Kidney
metastatic clear cell renal cell carcinoma	Kidney	Kidney	Kidney
Clear cell renal cell carcinoma	Kidney	Kidney	Kidney
clear cell carcinoma	Kidney	Kidney	Kidney
Clear cell renal cell carcinoma grade ISUP 3	Kidney	Kidney	Kidney
clear cell carcinoma	Kidney	Kidney	Kidney
clear cell carcinoma	Kidney	Kidney	Kidney
papillary renal cell carcinoma (right kidney)	Kidney	Kidney	Kidney
Papillary Renal Cell Carcinoma type 2	Kidney	Kidney	Kidney
clear cell carcinoma	Kidney	Kidney	Kidney
clear cell renal cancer	Kidney	Kidney	Kidney
clear cell renal carcinoma	Kidney	Kidney	Kidney
chromophobe carcinoma	Kidney	Kidney	Kidney
clear cell carcinoma	Kidney	Kidney	Kidney
renal cell adenocarcinoma	Kidney	Kidney	Kidney
Papillary renal cell carcinoma type 2	Kidney	Kidney	Kidney
clear cell renal carcinoma	Kidney	Kidney	Kidney
papillary renal cell carcinoma type 1	Kidney	Kidney	Kidney
left clear cell renal cell carcinoma	Kidney	Kidney	Kidney
clear and eosinophilic cell variant chromophobe renal cell carcinoma, solid pattern, nuclear G 3,	Kidney	Kidney	Kidney

Skin squamous cell carcinoma:

Histological type	Primary tumor location	Cancer type (long name)	Cancer type (short name)
Moderately differentiated invasive squamous cell carcinoma	Skin	Skin SCC	Skin SCC
differentiated invasive cutaneous squamous cell carcinoma	Skin	Skin SCC	Skin SCC
Cutaneous squamous cell carcinoma of the right thumb	Skin	Skin SCC	Skin SCC
squamous-cell carcinoma	Skin	Skin SCC	Skin SCC
squamous cell carcinoma	Skin	Skin SCC	Skin SCC
unresectable advanced localized cutaneous squamous cell carcinoma	Skin	Skin SCC	Skin SCC
squamous cell carcinoma	Skin	Skin SCC	Skin SCC
skin squamous cell carcinoma	Skin	Skin SCC	Skin SCC
moderately-to-poorly differentiated cSCC	Skin	Skin SCC	Skin SCC

Melanoma:

Histological type	Primary tumor location	Cancer type (long name)	Cancer type (short name)
metastatic melanoma	Skin	Melanoma	Melanoma
invasive melanoma of the right leg with lymph node and subcutaneous location	Skin	Melanoma	Melanoma
Superficial spreading Melanoma of the right jaw (negative sentinel node)	Skin	Melanoma	Melanoma
melanoma of the left buttock	Skin	Melanoma	Melanoma
Right plantar achromic melanoma	Skin	Melanoma	Melanoma
uveal melanoma	Other: uveal melanoma of the right eye	Melanoma	Melanoma
Superficial spreading melanoma of the right thigh	Skin	Melanoma	Melanoma
scapular melanoma	Skin	Melanoma	Melanoma
endonasal mucous melanoma	Skin	Melanoma	Melanoma
Superficial spreading melanoma	Skin	Melanoma	Melanoma
melanoma of the lower rectum	Skin	Melanoma	Melanoma
Melanoma	Skin	Melanoma	Melanoma
uveal melanoma	Skin	Melanoma	Melanoma
vaginal melanoma	Skin	Melanoma	Melanoma
Nodular Melanoma	Skin	Melanoma	Melanoma
melanoma of the left lower limb	Skin	Melanoma	Melanoma
epitheloid melanoma	Skin	Melanoma	Melanoma
choroidal melanoma	Skin	Melanoma	Melanoma
malignant melanoma - epithelioid type	Skin	Melanoma	Melanoma
mixed type	Other: Uveal melanoma of the left eye	Melanoma	Melanoma
nodular malignant melanoma	Skin	Melanoma	Melanoma
malignant melanoma	Skin	Melanoma	Melanoma

13 REFERENCES

[1] Seymour L, Bogaerts J, Perrone A, Ford R, Schwartz LH, Mandrekar S, Lin NU, Litière S, Dancey J, Chen A, Hodi FS, Therasse P, Hoekstra OS, Shankar LK, Wolchok JD, Ballinger M, Caramella C, de Vries EGE, group Rw. iRECIST: guidelines for response criteria for use in trials testing immunotherapeutics. The Lancet Oncology. 2017;18(3):e143-e152. ICH guidelines - E9: Statistical Principles for Clinical Trials, Adopted in EU by CPMP, March 1998, issued as CPMP/ICH/363/96

[2] ICH guidelines - E3: Structure and Content of Clinical Study Reports, Adopted in EU by CPMP, December 95, issued as CPMP/ICH/137/95

[3] U.S. Food and Drug Administration. E14 clinical evaluation of QT/QTc interval prolongation and proarrhythmic potential for non-antiarrhythmic drugs: Guidance for industry. 2018; https://www.fda.gov/downloads/Drugs/GuidanceComplianceRegulatoryInformation/Guidances/ucm073153.pdf. Accessed October 22, 2018.

[4] Smith BP, Vandenhende FR, deSante KA, et al (2000)., Confidence Interval Criteria for Assessment of Dose proportionality. Pharmaceutical Research, 17:1278-1283.

[5] Zhou, J., J. Li, and B. Coate. 2006. Empirical Power Estimation for Phase I Dose Proportionality Studies Based on Power-Law Model Using Confidence Interval Criteria. In SUGI 31, San Francisco, California.

[6] SAS 9.4; 2008 by SAS Institute Inc., Cary, NC, USA; OnLine Doc.

Pharmacokinetic analysis plan
Study title: A multicenter open-label phase 1/1b study to evaluate the safety and preliminary efficacy of SO-C101 as monotherapy and in combination with pembrolizumab in patients with selected advanced/metastatic solid tumors
Protocol Number: SC103

[redacted] H1-19-027

Version: Final 4.0
Date: 21-MAR-2022

PREPARED BY: [redacted] _____ Date

REVIEWED BY: _____ Date

REVIEWED BY: _____ Date

APPROVED: _____ Date

[redacted]

INDEX

[redacted]

1. INTRODUCTION

The objective of this pharmacokinetic analysis plan is to specify calculation of pharmacokinetic parameters (PK) and generation of listings and graphs presenting individual patients' data. Outputs generated according to this SAP will be used for sponsor-specific internal reviews and for final presentation of data/analysis. Outputs will be generated by batches (for each dose level cohort it will be generated at least one batch of outputs using concentration data up to cycle 3 day 1), final outputs based on this SAP will be generated for Part A and Part B as well as Parts A1, B1, D, and D1. This analysis plan does not change the analysis described in the protocol, but it should be precise enough to serve as a guideline for calculation of PK parameters and generation of outputs.

This analysis plan was developed with reference to the approved protocol, version 10.0, 29-Jul-2021. Supplementary text gives a full specification of analyses and presentation.

Final datasets generated according to this pharmacokinetic analysis plan will be used for the final statistical analysis of concentration data and PK parameters which will be performed by SOTIO according to main SAP.

Final version 1.0 is dated on 25-JUL-2019 and was approved and signed. After finalization of version 1.0 and before any outputs provided scope of the activities changed upon request of the sponsor (in line with updated DEM charter v3.0 dated on 13-AUG2019); therefore, this plan was updated. Version Final 2.0 03-SEP-2019 was not approved by the sponsor; therefore, not considered as effective one. The update was finalized in version Final 3.0, dated on 12-SEP-2019, as well as approved and signed.

This PK analysis plan is an update of version Final 3.0 which additionally includes a description of the calculation of PK parameters and generation of listings and graphs presenting individual patients' data for the additional study parts A1, B1, D, and D1.

All approved and signed versions will become an attachment of the main SAP.

The following source of data will be used for calculation of PK parameters:

- PK sampling times (shipped [redacted]
- Drug Concentration Data [redacted]
- Dosing Data (provided by ponsor ase on e a a ase

2. RESPONSIBILITIES

The following persons will perform the pharmacokinetic analysis (including SAS®-programming of listings and graphs), the reporting of pharmacokinetic parameters and the internal quality control:

Responsible bi m tri i n r ject biometrician:
Name: [redacted]
Title: Biostatistician

PK expert:
Name: [redacted]
Title: expert

Project SAS®- ro rammer / data anal st
Name: [redacted]
Title: Stats Programmer / PK Analyst

3. STUDY OBJECTIVES AND ENDPOINTS

The primary objective of the study is to assess the safety and tolerability and to determine the maximal tolerated dose (MTD) and/or recommended phase 2 dose (RP2D) of SO-C101 given as monotherapy (Part A, Part A1, Part D, and Part D1) and SO-C101 when combined with pembrolizumab (Part B and Part B1).

[redacted]

This pharmacokinetic analysis plan is associated with the secondary objective to characterize the pharmacokinetics (PK) of SO-C101 when given as monotherapy (Part A, Part A1, Part D, and Part D1) and to characterize the pharmacokinetics (PK) of SO-C101 when combined with pembrolizumab (Part B, Part B1).

4. DESIGN OF THE STUDY

Study SC103 will assess the safety and tolerability of SO-C101 administered as monotherapy (Part A, Part A1, Part D, and Part D1) and in combination with an anti-PD-1 antibody (pembrolizumab) (Part B, and Part B1) in patients with selected relapsed/refractory advanced/metastatic solid tumors (renal cell carcinoma, non-small cell lung cancer, small-cell lung cancer, bladder cancer, melanoma, Merkel-cell carcinoma, skin squamous-cell carcinoma, microsatellite instability high solid tumors, triple-negative breast cancer, mesothelioma, thyroid cancer, thymic cancer, cervical cancer, biliary track cancer, hepatocellular carcinoma, ovarian cancer, gastric cancer, head and neck squamous-cell carcinoma, and anal cancer) who are refractory to or intolerant of existing therapies known to provide clinical benefit for their condition.

The study will have the following parts:

- Part A will be a First-In-Human (FIH) SO-C101 monotherapy dose escalation part for dosing schedule 1.

- Part A1 will be a SO-C101 monotherapy dose escalation part for dosing schedule 2 which will start once the RP2D of SO-C101, dosing schedule 1, is identified in Part A; the starting daily dose of Part A1 will be 1 dose level below the RP2D identified in Part A. The dose will be split into two identical (50%:50%) daily doses with the second dose on each treatment day being administered 8 hours (±15 min) after the first dose.

- Part B will study SO-C101 dosing schedule 1 in combination with pembrolizumab and will start after dose level 5 in Part A is completed and deemed safe and will use SO-C101 monotherapy level 3 dose, dosing schedule 1, as the starting dose in combination with pembrolizumab.

- Part B1 will study SO-C101 dosing schedule 2 in combination with pembrolizumab and will start once the RP2D of SO-C101, dosing schedule 1, in combination with pembrolizumab is identified in Part B; the starting daily dose of Part B1 will be 1 dose level below the RP2D identified in Part B. The dose will be split into two identical (50%:50%) daily doses with the second dose on each treatment day being administered 8 hours (±15 min) after the first dose.

- Part D will be a dose expansion part which will start once the RP2D of SO-C101, dosing schedule 1, is identified in Part A; SO-C101 will be given at the Part A RP2D.

- Part D1 will be a dose expansion part which will start once the RP2D of SO-C101, dosing schedule 2, is identified in Part A1; SO-C101 will be given at the Part A1 RP2D.

Patients of Part A (monotherapy) and B (in combination with pembrolizumab) will be treated with escalating doses of SO-C101 given as per dosing schedule 1 via subcutaneous (SC) route following the dose escalation scheme described in the protocol section 9.1 and 9.3, respectively. This schedule should be strictly adhered to with no dose schedule and/or dose delays to be allowed for especially cycle 1 for maximum exposure for safety evaluation.

Patients of Part A1 (monotherapy) and B1 (in combination with pembrolizumab) will be treated with escalating doses of SO-C101 given as per dosing schedule 2 via SC route following the dose escalation scheme described in the protocol section 9.2 and 9.4, respectively. The dose will be split into two identical (50%:50%) daily doses with the second dose on each treatment day being administered 8 hours (±15 min) after the first dose. This schedule should be strictly adhered to with no dose schedule and/or dose delays to be allowed for especially cycle 1 for maximum exposure for safety evaluation.

Patients of Part D will be treated with SO-C101 dosing schedule 1, given as monotherapy at the RP2D identified in Part A. This schedule should be strictly adhered to with no dose delays/reductions to be allowed for especially in cycle 1 for maximum exposure for safety evaluation.

[redacted]

Patients of Part D1 will be treated with SO-C101 given as per dosing schedule 2 as monotherapy at the RP2D identified in Part A1.

5. SAMPLE SIZE AND POWER ESTIMATION

Parts A, A1, B, B1 are 3+3 dose escalation design. 3 to 6 DLT-evaluable patients per dose level will be included in a cohort. The number of patients depends on number of cohorts needed for determination of MTD/RP2D (as described in previous section).

The number of patients in Part D together with or without Part D1 to be treated for at least one cycle is set to a maximum of 20 per indication (60 in total). This number of patients is deemed to be appropriate to provide further safety, PK, PD, and efficacy data per indication at the RP2D dose level identified in Part A (SO-C101, dosing schedule 1, monotherapy) and the RP2D dose level identified in Part A1 (SO-C101, dosing schedule 2, monotherapy). In case biomarker data in Part A1 suggest a more competitive efficacy as compared to once daily dosing, a switch to twice daily dosing (Part D1) will be made during the course of the study without affecting the overall number of patients enrolled.

6. ANALYSIS SETS

The PK evaluable analysis set is defined as all patients exposed to SO-C101, who have a valid PK profile on at least one cycle and no important protocol deviation affecting PK. A valid PK profile is defined as having one pre-dose (pre first dose for Part A1, B1 and D1) and at least one post-dose measurement. An invalid PK profile in any Cycle and Day will not be used for statistical evaluation.

Before DB lock PK profile of each patient will be reviewed and PK evaluable patients will be identified. Decisions will be documented in meeting minutes which will be incorporated/attached to the main SAP and the clinical study report (CSR). Statistical analysis of PK parameters and concentrating data described in the main SAP is planned only on PK evaluable patients.

7. PRESENTATION OF DATA

Listings and graphs presenting individual patients' data and corresponding SAS datasets will be provided for each cohort, will include all patients in the cohort and will be produced in accordance with the principles outlined by the International Council of Harmonisation (ICH) E3 guideline. All data will be presented in the data listings. Concentrations measured in blood samples not scheduled as defined in the study protocol will be annotated accordingly in the listings.

Patient ID presented in the outputs will be in form as defined in the clinical database (i.e., SC103CXXXBYYY).

8. SOFTWARE

Software to produce individual listings and individual figures will be SAS® version 9.4 or higher, if not stated otherwise. The non-compartmental pharmacokinetic analysis of the data will be accomplished by using Phoenix WinNonlin® version 7.0 or higher. If a pharmacokinetic parameter is not automatically calculated within WinNonlin® (e.g. accumulation ratio AR for cycles), then WinNonlin® derived parameters will be used to determine these subsequent PK parameters and will be calculated within SAS® version 9.4 or higher.

9. PHARMACOKINETIC PARAMETERS

Concentrations in ng/mL for PK analyses will be used as supplied by the analytical laboratory. The units of concentration and resulting PK parameters, with amount or concentration in the unit, will be presented as they are received from the analytical laboratory. The analytical laboratory will also provide the PK sampling times. Information on dosing will be provided by the sponsor.

A PK profile of SO-C101 is collected on Day 1 and Day 9 of cycle 1, Day 1 and Day 9 of cycle 2, Day 1 of cycle 3 for Part A and Part B. A PK profile of SO-C101 is collected on Day 1 and Day 2 of Cycle 1 and Day 1 of Cycle 3 for Part A1, Part B1, Part D **(patients 1-5 in each indication)**, and Part D1 **(patients 1-5 in each indication)**. The following pharmacokinetic parameters will be calculated from these daily profiles for each

[redacted]

patient by non-compartmental analysis (according to [redacted] OP BST_HPU_05, if not stated otherwise) for serum levels of SO-C101 if possible:

$AUC_{0\text{-}inf}$	AUC from time zero to infinity estimated by adding to $AUC_{0\text{-}tlast}$ a value equal to C_{last}/λ_z, where C_{last} is the measured last quantifiable concentration (occurring at time t_{last}) and λ_z is the apparent elimination rate constant (only on Cycle 1 Day 1 of Part A and Part B, as well as on Cycle 1 Day 1 and Cycle 3 Day 1 of Part A1, B1, and Part D, and D1), in h*ng/mL
$AUC_{0\text{-}tlast}$	Area under the serum concentration-time curve calculated from time zero (time of drug administration) to the latest time point with a quantifiable serum concentration, using linear trapezoidal summation, in h*ng/mL
$AUC_{0\text{-}6}$	AUC from time zero to 6 hours post-dose. Interpolation will be done for the 6 hour value at day 1, where blood sampling is scheduled at 8 hours (only for Part A and B), in h*ng/mL;
$AUC_{0\text{-}24}$	AUC from time zero to 24 hours post-dose (only Cycle 1 Day 1 of Part A and B, and Cycle 1 Day 1, Cycle 1 Day 2 and Cycle 3 Day 1 of Part A1, B1, D, and D1), in h*ng/mL
$AUC_{0\text{-}inf}/D$	$AUC_{0\text{-}inf}$ divided by actual dose (only on Cycle 1 Day 1 of Part A and Part B, as well as on Cycle 1 Day 1 and Cycle 3 Day 1 of Part A1, B1, and Part D, and D1), in (h*ng/mL)/(µg/kg); in case of dosing scheme 2, use the complete dose for calculation.
$AUC_{0\text{-}tlast}/D$	$AUC_{0\text{-}tlast}$ divided by actual dose, in (h*ng/mL)/(µg/kg); in case of dosing scheme 2, use the complete dose for calculation.
$AUC_{0\text{-}6}/D$	$AUC_{0\text{-}6}$ divided by actual dose (only for Part A and B), in (h*ng/mL)/(µg/kg);
$AUC_{0\text{-}24}/D$	$AUC_{0\text{-}24}$ divided by actual dose (only on Cycle 1 Day 1 of Part A and B, and Cycle 1 Day 1, Cycle 1 Day 2 and Cycle 3 Day 1 of Part A1, B1, D and D1), in (h*ng/mL)/(µg/kg); in case of dosing scheme 2, use the complete dose for calculation.
C_{max}	Measured maximal concentration, in ng/mL
t_{max}	Time corresponding to occurrence of C_{max} (after the zero hour time point), in h.
$t_{1/2}$	Apparent terminal elimination half-life; calculated as ln(2)/λz, in h; in case of dosing scheme 2 after second dose
CL/f	Apparent total serum clearance of drug after oral administration; calculated as $D/AUC_{0\text{-}inf}$, in mL/(h*kg); in case of dosing scheme 2, use the complete dose for calculation.
V_d/f	Apparent volume of distribution during terminal phase; calculated as $D/(AUC_{0\text{-}inf}*\lambda_z)$, in mL/kg); in case of dosing scheme 2, use the complete dose for calculation.
AR	Accumulation ratio per cycle (where possible) calculated for $AUC_{0\text{-}6}$ and C_{max} of Part A and B as well as $AUC_{0\text{-}tlast}$ and C_{max} of Part A1, B1, D, and D1. PK parameters calculated on Day 9 will be divided by the parameters calculated on Day 1 for Part A and B. PK parameters calculated on Day 2 will be divided by the parameters calculated on Day 1 for Part A1, B1, D, and D1. This is not a real accumulation index but should show the change of SO-C101 levels from Day 1 to

[redacted]

Day 9 for Part A and Part B and Day 1 to Day 2 for Part A1, Part B1, Part D, Part D1.

Note: For the patients with a “simplified” PK drawing schedule in Part D and D1 (starting with patient 6) as according to Table 9.15 and 9.16 in the clinical study protocol, no PK parameters will be calculated.

The pre-dose sample (the sample before first dose of each day per cycle) always will be considered as if it had been taken simultaneously with the drug administration (at zero hour time point). If there should have been any deviations in post-dose sampling, the actual sampling times relative to morning drug administration of each day will be used unless stated otherwise.

Missing blood sampling times will be replaced by the scheduled blood sampling time based on concentration value. Other missing data will not be replaced or imputed in any way if not stated otherwise.

Concentrations below the LLOQ within the PK profile (with quantifiable previous and following concentrations) will be disregarded.

Concentrations below the lower limit of quantification (LLOQ) preceding the first quantifiable concentration level and after last quantifiable concentration level will be treated as zero. Unquantifiable low results are disregarded for calculations based on logarithms of values.

AUC will be regarded as unreliable if >= two consecutive results are missing or if the concentrations were quantifiable for fewer than 4 time points.

For the calculation of partial AUC, i.e. $AUC_{0\text{-}t2}$, log-linear interpolation will be conducted if the sample scheduled for t2 was performed with a delay or if the sample was collected too early and there is a sample available after t2. Extrapolation will be conducted via λ_z if the sample at t2 was collected too early and if there are no other sample available after t2.

C_{max} and t_{max} will be regarded as unreliable if the maximum was observed preceding or following a sample with missing data.

In case of multiple peaks, C_{max} and t_{max} refer to the highest measured concentration even if there should be earlier peaks. In case of two or more samples with the same concentration (as supplied by the analyst), t_{max} refers to the earlier of these.

The data points (at least 3) to be used for calculation of λ_z will be determined by visual inspection of concentration-time curves in log-linear scaling. The calculation will be considered sufficiently reliable in case of a coefficient of determination $r^2>0.85$ and unreliable in case of $r^2<0.8$. Cases in-between will be considered case-by-case. The starting time (T_k) for calculation of λ_z and the number of data points in the regression (N_z) as well as the coefficient of determination r^2 will also be tabulated.

λ_z, $t_{1/2}$, $AUC_{0\text{-}inf}$, V_d/f and CL/f will be considered as reliable if the log-linear terminal phase can clearly be defined and the serum concentration time curve is long enough to provide a reliable estimate of the extent of absorption. This is generally achieved if the AUC derived from measurements is at least 80% of the AUC extrapolated to infinity. Otherwise, they will be regarded as unreliable.

Further investigations about the reliability of PK parameters and profiles will be done by visual inspection of the concentration-time curves.

Unreliable parameters will be listed and flagged accordingly and set to missing for further statistical analyses described in the main SAP.

9.1. Tabulation of Individual Data

The results of subject samples measured will be listed for each cohort by Patient ID, cycle and real time. Individual concentration data will be listed with actual and scheduled sampling times (time deviation from

[redacted]

scheduled sampling times [absolute and in %]). Samples below LLOQ will be identified in listings (i.e., <LLOQ). Also, concentrations measured from blood samples not scheduled as per protocol will be flagged. Similar listings will be prepared for pharmacokinetic parameters. Unreliable PK parameters will be flagged in the listings.

For each subject, concentration-time curves will be plotted by cycle on a linear as well as on a log-linear scale, showing each day within a cycle simultaneously in each plot using actual sampling times. Values below LLOQ will be set to zero for curves on a linear scale but disregarded for curves on a log-linear scale.

Datasets of concentrations and dataset of PK parameters will be delivered together with the listings and figures.

List of listings and figures is included in the section 10 below.

9.2. Drug Administration and Blood Sampling

Information on drug administration and blood samplings will be listed together with concentration data. This listing will also include blood sampling times and time deviations (absolute and in %) as stated in the subsection above.

10. Appendix

Individual figures and listings specified below will be provided after each cohort. Final deliveries are described in the section 10.4.

10.1. List of Tables

Not applicable.

10.2. List of Figures

Not applicable for mean/sd plots. Not applicable for mean/sd plots. Only individual concentration profiles for each patient and cycle will be provided. Title of the figure will be as follows:

- Patient <patient ID> Cycle <number of cycle>: Serum concentration levels of SO-C101

10.3. List of Listings

The following listings will be provided for each cohort:

- Drug Administration, Pharmacokinetic Blood Sampling Times and Time Deviations, and SO-C101 Concentration Levels
- SO-101 Pharmacokinetic Parameters

10.4. Final Deliveries

The following final deliveries will be provided for Part A, B, A1, B1, D, and D1:

- Datasets with final PK parameters and drug concentration data, respectively, including all parts.
- Outputs from SAS separately for Parts A, B, A1, B1, D, and D1, respectively: One document with all concentration profiles by patient and cycle (the same figures as provided by cohort) will be provided if concentration levels or blood sampling time is changed since generation of outputs for the cohorts.
- Outputs from WinNonlin separately for Parts A, B, A1, B1, D, and D1, respectively: One document with all profiles for final analysis will be provided.

11. References

PK parameters will be calculated according to

- [redacted] OP BST_HPU_05

[redacted]

- Cawello, W ed.: Parameters for Compartment-free Pharmocokinetics. Standardisation of Study Design, Data Analysis and Reporting. Aachen, Shaker Verlag 1999
- Gibaldi M, Perrier D. Pharmacokinetics. 2nd ed. New York: Marcel Dekker, 1982
- European Medicies Agency: Guideline on the Investigation of Bioequivalence. Doc. Ref.: CPMP/EWP/QWP/1401/98 Rev. 1/ Corr. 2010

[redacted]