



Domain Therapeutics SA

Statistical Analysis Plan (SAP)

Protocol Title: A Phase 1, multicentre, open-label, dose-escalation and expansion study to determine a recommended phase 2 dose (RP2D) of DT-9081 in participants with advanced solid tumours

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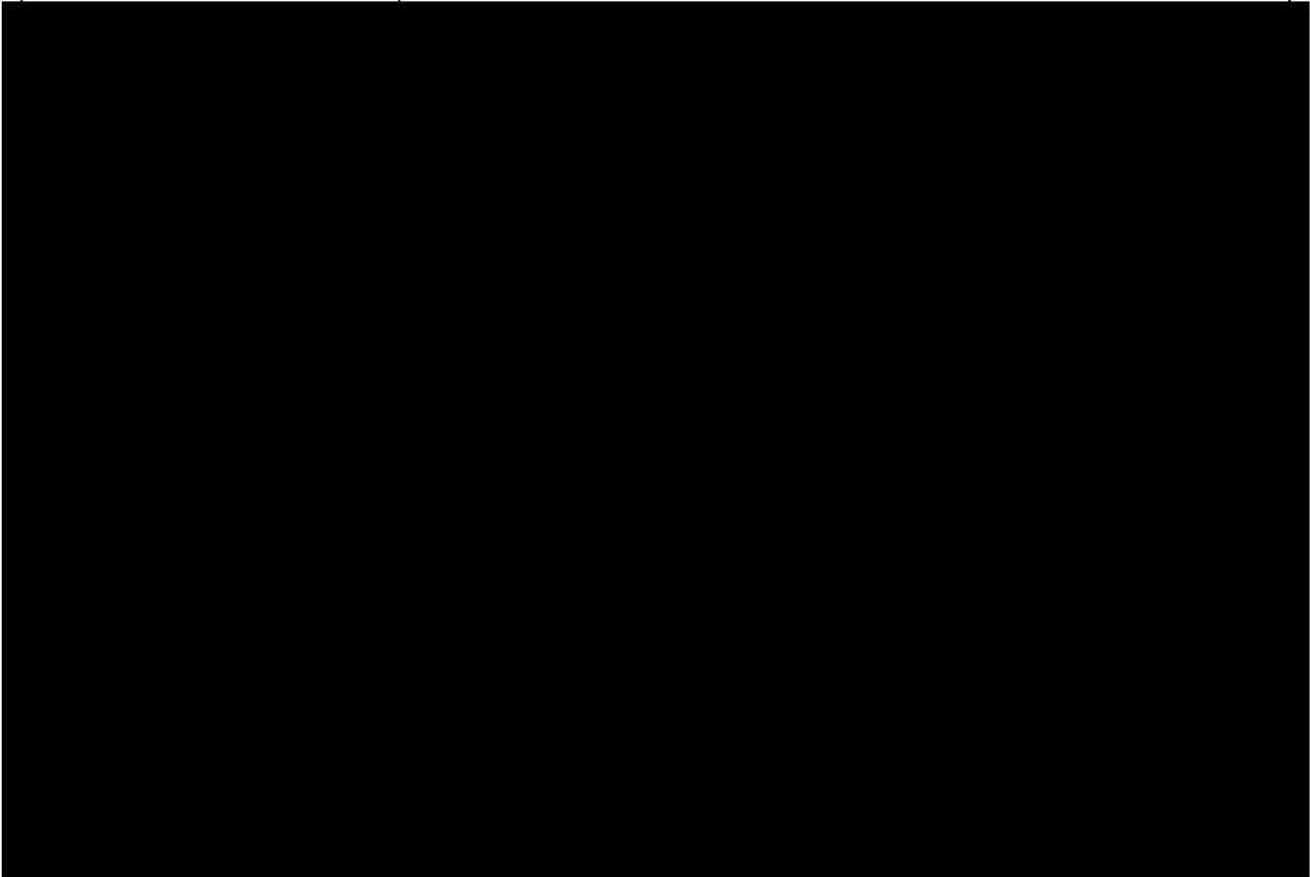
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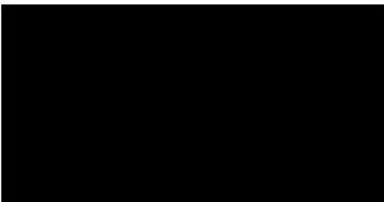
Statistical Analysis Plan

Sponsor	Domain Therapeutics SA
Protocol Title:	A Phase 1, multicentre, open-label, dose-escalation and expansion study to determine a recommended phase 2 dose (RP2D) of DT-9081 in participants with advanced solid tumours
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Approvals

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Date of Change	Version #	Author	Section #	Reason/Description of Change
12-Jul-2023	1.0	[Redacted]	All	First version.
20-Dec-2024	2.0	[Redacted]	All	The shells were revised to this current version primarily considering the protocol has been updated to version 4.0 (09-Jan-2024) from version 2.0 (01-Aug-2022).



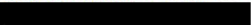


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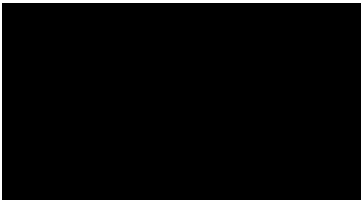
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List of Abbreviations

Abbreviation	Definition
AE	adverse event
ATC	Anatomical Therapeutic Chemical classification
AUC	area under the curve
BLQ	below the limit of quantification
BOR	best overall response
CBR	clinical benefit rate
CI	confidence interval
C _{max}	maximum concentration
COX-2	cyclooxygenase 2
CR	complete response
CSR	clinical study report
CTCAE	Common Terminology Criteria for Adverse Events
CV	coefficient of variation
DLT	dose-limiting toxicity
DOR	duration of response
ECG	electrocardiogram
ECOG	Eastern Cooperative Oncology Group
eCRF	electronic case report form

Abbreviation	Definition
EMA	European Medicines Agency
EP4R	prostaglandin E receptor 4
FDA	Food and Drug Administration
HBsAg	hepatitis B surface antigen
HCV	hepatitis C virus
HIV	human immunodeficiency virus
iBOR	immune best overall response
iCBR	immune clinical benefit rate
ICH	International Council for Harmonisation of Technical Requirements for Pharmaceuticals for Human Use
iCPD	confirmed immune progressive disease
iCR	immune complete response
iDOR	immune duration of response
IFN- γ	interferon γ
iORR	immune objective response rate
iPR	immune partial response
iRECIST	immune Response Evaluation Criteria in Solid Tumours
iSD	immune stable disease
iUPD	unconfirmed immune progressive disease
MedDRA	Medical Dictionary for Regulatory Activities

Abbreviation	Definition
MTD	maximum tolerated dose
MUGA	multiple gated acquisition
n	number of participants with non-missing values
NCA	noncompartmental analysis
NE	not evaluable
ORR	objective response rate
PD	progressive disease
PFS	progression-free survival
PGE2	prostaglandin E2
PGEM	prostaglandin E metabolite
PK	pharmacokinetics
PP	per protocol
PR	partial response
PT	preferred term
RP2D	recommended phase 2 dose
RECIST	Response Evaluation Criteria in Solid Tumours
SAE	serious adverse event
SAF	safety (population)
SAP	statistical analysis plan

Abbreviation	Definition
SD	stable disease
SOC	system organ class
SRC	safety review committee
Std	standard deviation
T _{1/2}	terminal elimination half-life
TEAE	treatment-emergent adverse event
T _{max}	time of maximum concentration (C _{max})
TNF- α	tumour necrosis factor α
WHO-DD	World Health Organization Drug Dictionary

1. Overview

This statistical analysis plan (SAP) describes the planned analysis and reporting for Domain Therapeutics SA protocol number DT-9081-CLI-001 (A Phase 1, multicentre, open-label, dose-escalation and expansion study to determine a recommended phase 2 dose (RP2D) of DT-9081, in participants with advanced solid tumours), dated 09-Jan-2024 version #4.0. Reference materials for this statistical plan are the protocol and the electronic case report form (eCRF). Operational aspects related to collection and timing of planned clinical assessments are not repeated in this SAP unless relevant to the planned analysis.

The structure and content of this SAP provide sufficient detail to meet the requirements identified by the Food and Drug Administration (FDA), European Medicines Agency (EMA), and International Conference on Harmonisation (ICH) of Technical Requirements for Registration of Pharmaceuticals for Human Use: Guidance on Statistical Principles in Clinical Trials.¹ All work planned and reported for this SAP will follow internationally accepted guidelines, published by the American Statistical Association² and the Royal Statistical Society,³ for statistical practice.

The planned analyses identified in this SAP may be included in clinical study reports (CSRs), regulatory submissions, or future manuscripts. Also, post-hoc exploratory analyses not necessarily identified in this SAP may be performed to further examine study data. Any post-hoc or unplanned, exploratory analysis performed will be clearly identified as such in the final CSR.

The statistical plan described hereafter is an *a priori* plan. It will be approved before any inferential or descriptive analysis of data pertaining to Domain Therapeutics SA's study DT-9081-CLI-001.

2. Study Objectives and Endpoints

2.1. Study Objectives

The investigation is designed with 2 separate stages to achieve a series of objectives outlined below.

2.1.1. Primary Objectives

Primary objectives include the following:

- To determine the RP2D of DT-9081
- To assess the safety and tolerability profile of DT-9081

2.1.2. Secondary Objectives

Secondary objectives include the following:

- To determine the maximum tolerated dose (MTD) of DT-9081 (applicable only if MTD is reached within the 8 escalation cohorts)
- To determine the pharmacokinetics (PK) of DT-9081
- To evaluate preliminary anti-tumour activity of DT-9081

2.1.3. Exploratory Objectives

To determine the pharmacodynamic activity of DT-9081 on [REDACTED]

2.2. Study Endpoints

2.2.1. Primary Endpoints

The primary endpoints of this study include the following safety endpoints:

- Endpoints contributing to the determination of the RP2D will include safety, efficacy, predicted target inhibition, pharmacodynamics results and pharmacokinetic/pharmacodynamic simulations.
- Safety and tolerability will be assessed by the incidence and severity of treatment-emergent adverse events (TEAEs), treatment-related TEAEs and dose-limiting toxicities (DLTs). All adverse events (AEs) will be assessed according to Common Terminology Criteria for Adverse Events (CTCAE) v 5.0.

2.2.2. Secondary Endpoints

The secondary endpoints of this study include the following:

- Maximum tolerated dose: Endpoints contributing to the determination of the MTD will be the DLTs.
- Anti-tumour activity will be assessed with the following efficacy endpoints:
 - Objective response rate (ORR)
 - Best overall response (BOR)
 - Clinical benefit rate (CBR) (defined as the percentage of advanced cancer participants who achieve complete response [CR], partial response [PR], or at least 6 months of stable disease as a result of therapy)
 - Progression-free survival (PFS)
 - Duration of response (DOR)

All clinical endpoints will be assessed according to Response Evaluation Criteria in Solid Tumours (RECIST) v1.1 and immune Response Evaluation Criteria in Solid Tumours (iRECIST).

2.2.3. Secondary Pharmacokinetic Endpoints

3. Overall Study Design and Plan

3.1. Overall Design

This phase 1, first-in-human study, multicentre, open-label, dose-escalation and expansion study is designed to determine a RP2D of DT-9081 in participants with advanced solid tumours.

The study will be divided into 2 phases:

- a dose-escalation phase,
- a dose-expansion phase.

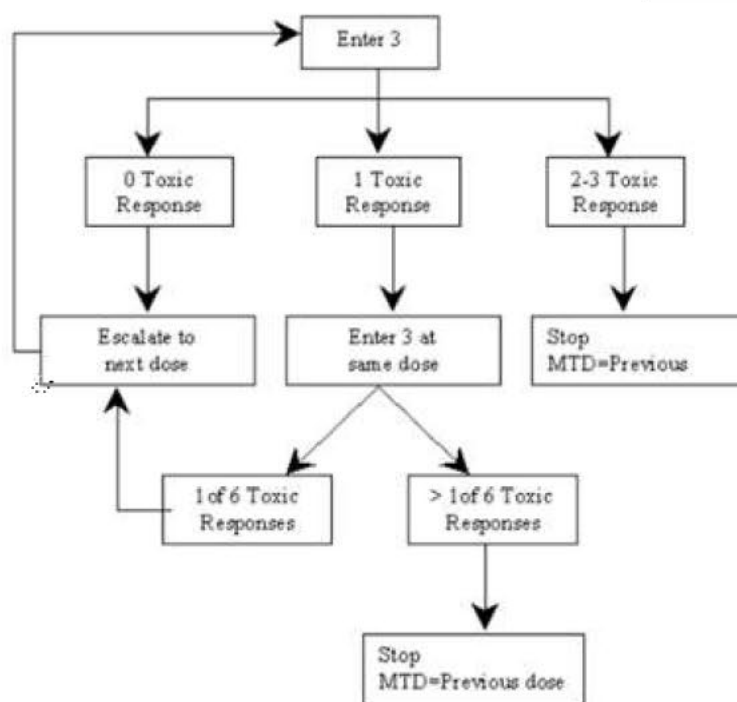
Dose-Escalation Phase

In the dose-escalation phase, participants will be recruited into cohorts in a modified 3+3 design with up to 8 dose levels (see [Figure 1](#)). This phase will enroll a maximum of 48 evaluable participants. Cohorts of at least 3, and no more than 5 participants will first be enrolled and assessed for DLT during the dose-escalation process.

Throughout the dose-escalation phase:

- If 1/3 participants experience a DLT, the cohort will be expanded to 6 participants.
- If 2/3 participants experience a DLT, dose escalation will be stopped. This dose will be the highest dose of DT-9081 administered.
- If 1/6 participants experience a DLT, dose escalation will continue.
- If $\geq 2/6$ participants experience a DLT, the dose escalation will stop. This dose will be the highest dose of DT-9081 administered.
- If only 3 participants were tested at the dose below the highest dose administered, 3 additional participants will receive the dose below to achieve a cohort of 6.
- The MTD is defined as the highest dose level of DT-9081 at which no more than 1 in 6 participants experienced a DLT

Figure 1: 3+3 Phase 1 Study Design Schematic



Abbreviation: MTD = maximum tolerated dose.

Note: Toxic Response is the same as DLT.

Each participant will have a 28-day screening period (Day -28 to Day -1), a treatment period, an end-of-treatment visit and a follow-up visit 1 month after the last treatment dose and every 2 months after last treatment dose until resolution of DT-9081-related toxicity. The treatment period will consist of consecutive 28-day cycles that repeat without interruption until disease progression, unacceptable toxicity, or consent withdrawal for any reason. Treatment could be continued after progression if participant experiences clinical benefit.

Throughout the study, a Safety Review Committee (SRC) comprised of at least 2 principal/site investigators, the PK subject matter expert, Premier Research's medical monitor and the sponsor's medical monitor (or designee) will be convened to evaluate safety and provide recommendations for cohort dosing. The decision to escalate to the next dose level in the dose-escalation phase will be made by the SRC.

Dose-expansion Phase

The dose-expansion phase will explore up to 3 dose levels to better characterize the safety, PK and pharmacodynamics of DT-9081. A SRC meeting will be organized in case of toxicities and safety issues.

Like in the dose-escalation phase, in the dose-expansion phase each participant will have a 28-day screening period (Day -28 to Day -1), a treatment period, an end-of-treatment visit and a follow-up visit 1 month after the end-of-treatment visit and every 2 months after the last treatment dose until resolution of DT-9081-related toxicity. The treatment period will consist of consecutive 28-day cycles that repeat without interruption until disease progression, unacceptable toxicity, or consent withdrawal for any reason. Enrolment will be discontinued if a toxicity signal of high incidence is observed.

3.2. Sample Size and Power

Dose-escalation Phase

The sample size for the dose-escalation phase is based on the standard expectation for a modified 3+3 design with up to 6 evaluable for DLTs participants per cohort. At a particular dose level, cohorts of at least 3, and up to 5 participants will first be enrolled. The safety of that cohort will be first determined on the data generated on at least the first 3 participants to complete the DLT observation period. The participants enrolled at that dose level who have not completed the DLT observation period and not experienced a DLT will be censored for the purpose of DLT evaluation, and their safety data will be reviewed at the next SRC meeting with all the safety data generated at lower doses. The dose escalation is capped at a maximum of 8 dose levels. Therefore, up to 48 evaluable participants may be enrolled in the dose-escalation phase.

Dose-expansion Phase

There will be a maximum of 3 dose cohorts with a maximum of 12 participants enrolled per cohort. The enrolment of participants in each dose-expansion cohort could be stopped based on ongoing safety assessment of available data by the SRC.

The sample size for each dose-expansion cohort is not based on formal statistical estimation since the goal is to monitor safety, PK/pharmacodynamics data and assess anti-tumour activity only in an exploratory manner.

Up to 36 participants will be enrolled and treated during the dose-expansion phase.

3.3. Study Population

Participants must be at least 18 years of age and have a histologically or cytologically confirmed advanced solid tumour that is locally advanced (i.e., not eligible for curative surgery or radiotherapy), recurrent, or metastatic, who have failed or are ineligible for standard of care therapies. Participants must have measurable disease per RECIST v1.1 and at least 1 accessible tumour lesion for biopsy.

A full list of inclusion/exclusion criteria is presented in the protocol (Section 8.2 Study Entry Criteria).

3.4. Treatments Administered

DT-9081 will be taken orally daily at the assigned dose for 28 days per cycle (“a cycle”) without interruption until disease progression, unacceptable toxicity, participant consent withdrawal or

withdrawal from treatment for any reason. The participant must fast for 2 hours before and 2 hours after ingestion of DT-9081 capsules.

- Dose-escalation phase: single agent DT-9081 orally once daily (this can be changed to twice daily depending on tolerability and PK data).
- Dose-expansion phase: single agent DT-9081 at the MTD defined during dose-escalation phase or any other cleared dose level considered worth exploring (up to 3 different dose levels).

3.5. Method of Assigning Participants to Treatment Groups

Dose-escalation Phase

Participants will be recruited into cohorts in a modified 3+3 design. The first cohort is treated at a starting daily oral dose of 25 mg. Following the rules of dose-escalation described in the protocol, another cohort at the same dose can be enrolled, or the dose is increased in a new cohort (at a maximum increment of 100% of the previous dose level). In the dose escalation phase, participants will be assigned to a dose level according to the order of study entry.

Dose-expansion Phase

The dose-expansion phase will explore up to 3 dose levels of DT-9081, which may include the RP2D, as defined during the dose-escalation phase. Should more than 1 dose-expansion cohort be opened at the same time, participants will be allocated to a particular dose-expansion cohort by the sponsor.

3.6. Intra-participant Dose Escalation

Escalation within a participant will be permitted in the dose-escalation phase:

- for participants with no history of grade 3/4 toxicity related to DT-9081 with a persisting good Eastern Cooperative Oncology Group (ECOG) of 0 or 1
- when the next dose level has been shown to be safe in the dose-escalation phase as per SRC committee decision

The decision for which cycle this escalation will be authorized will be discussed in the SRC.

Participants who have an escalation in dose will still be displayed in the outputs in their initial cohort. A footnote may be added to outputs including this kind of participants to ease the data interpretation.

3.7. Blinding and Unblinding

The study will be open label so no blinding will occur.

3.8. Schedule of Events

A detailed schedule of assessments for the study is provided in Appendix 1: Schedule of Assessments.

4. Statistical Analysis and Reporting

4.1. Introduction

Data processing, tabulation of descriptive statistics, calculation of inferential statistics, and graphical representations except for PK parameter estimation will primarily use SAS (release 9.4 or higher). All PK parameter estimations will use WinNonlin® version 8.0 or later. If the use of other software is warranted, the final statistical methodology report will detail what software was used for what purposes.

Continuous (quantitative) variable summaries will include the number of participants (n) with non-missing values, mean, standard deviation (Std), median, first and third quartiles, minimum, and maximum.

Categorical (qualitative) variable summaries will include the frequency and percentage of participants who are in the particular category or each possible value. In general, the denominator for the percentage calculation will be based upon the total number of participants in the study population for the cohort or phase, unless otherwise specified. The denominator for by-visit displays will be the number of participants in the relevant study population with non-missing data at each visit.

The minimum and maximum will be reported with the same degree of precision (i.e., the same number of decimal places) as the observed data. Measures of location (mean and median) will be reported to 1 degree of precision more than the observed data, and measures of spread (Std, first and third quartiles) will be reported to 2 degrees of precision more than the observed data. Unless otherwise specified, a maximum of 3 decimal places will be taken into account for the observed data.

Percentages will be presented to 1 decimal place, unless otherwise specified, except for 100%. For zero count, percentages will not be displayed.

Unless otherwise indicated, all statistical tests will be conducted at the 0.05 significance level using 2-tailed tests, and *P* values will be reported. Corresponding 95% confidence intervals (CIs) will be presented for statistical tests.

This study is considered an exploratory study. Statistical tests will be interpreted in an exploratory sense only and will not be considered to be formal hypothesis tests.

4.2. Interim Analysis and Data Monitoring

No formal interim analyses are planned.

As described in Section 3.1, the decision to escalate to the next dose level in the dose-escalation phase will be made by the SRC. The role and responsibilities of the SRC, as well as the data review process, are outlined in detail in a separate charter.

4.3. Final Analysis

The final analysis of all data will be based on data from the complete study and will be performed after all participants have ended the study (follow-up phase or discontinuation) and all data from the study are in the database and the database is locked.

5. Analysis Populations

The following analysis populations are planned for this study:

- **Safety Population (SAF):** The SAF Population includes all participants who receive at least 1 dose of DT-9081
- **DLT Population:** The DLT Population includes all participants who complete the DLT evaluation period (Day 1 to Day 28 in Cycle 1) and receive the planned daily dose of DT-9081 for at least 75% of the cycle duration (equivalent to 21 out of 28 days at the planned dose) in Cycle 1, or who discontinue from the study due to an AE that fulfils the DLT criteria
- **Evaluable Population:** The Evaluable Population includes all participants who receive the planned daily dose of DT-9081 for at least 75% of the cycle duration (equivalent to 21 out of 28 days at the planned dose) in Cycle 1, have measurable disease at baseline, and at least 1 post-baseline disease assessment (clinical and/or radiological).
- **Per Protocol Population (PP):** The PP Population includes all participants from the Evaluable Population, who receive the planned daily dose of DT-9081 for at least 75% of the cycle duration during Cycle 2 (equivalent to 21 out of 28 days at the planned dose), and who do not have any major protocol deviation impacting the efficacy analysis as described in the protocol deviation plan.
- **Pharmacokinetic Population (PK):** The PK Population includes all participants who receive at least 1 dose of DT-9081 and have at least 1 post-dose PK measurement available

Inclusion in the analysis populations will be determined prior to database lock.

6. General Issues for Statistical Analysis

6.1. Statistical Definitions and Algorithms

6.1.1. Baseline

The last non-missing observation recorded before the first dose of DT-9081 will be used as the baseline observation for all calculations of change from baseline. An assessment performed the day of the first dose of DT-9081 with missing time will be considered performed as per protocol specification.

For the electrocardiogram (ECG) assessments which will be in triplicate, the baseline will be the

mean of the available values at the last measurement before the first dose of DT-9081.

6.1.2. Rescreening Data

Participants who do not meet all inclusion and exclusion criteria may be rescreened for the study after the sponsor's approval. A rescreened participant will have a new participant number with the original screening number entered on the eCRF. The unique participant number used in the datasets will be the first one that was introduced.

6.1.3. Handling of Dropouts or Missing Data

During the dose-escalation phase:

- Participants who withdraw before the end of the DLT period for reasons other than DLTs will be replaced to ensure that at least 3 participants in each cohort have been assessed for the full DLT period prior to moving to the next dose level
- Participants who, for reasons other than drug-related toxicity or a DLT, fail to complete 75% of the cycle duration in Cycle 1 (equivalent to 21 out of 28 days at the planned dose) will be replaced.

Participants who are replaced will be analysed as part of the Safety, Pharmacokinetic and Pharmacodynamic Populations if applicable but will not be part of the Evaluable nor DLT Populations.

Within the expansion phase, withdrawn participants will not be replaced.

No imputation of missing data will be performed, except AE and medication dates as described in Section 6.1.7.

6.1.4. Analysis Visit Windows

By-visit summaries will be based on eCRF-defined nominal visits. Data collected during unscheduled visits will be listed but not included in safety summary tables and efficacy tables. An exception will be the anti-tumour response and PFS analyses, where unscheduled disease assessments will be taken into account to determine the best response and the date of progression or death.

6.1.5. Pooling of Sites

All participants from a cohort or phase will be analysed together without distinction for sites.

6.1.6. Derived Variables

- **Change from baseline:** value at current time point – value at baseline.
- **Study Day:** Study Day 1 of Cycle 1 will be the day of first dose of DT-9081. This date is used as the reference start date for analysis.

- For days prior to Study Day 1: Study Day = assessment date – date of Study Day 1.
- For days on or following Study Day 1: Study Day = assessment date – date of Study Day 1 + 1.
- **Age at initial histological diagnosis** (years) will be calculated as year of initial histological diagnosis minus year of birth and rounded to 1 decimal place.
- **Time from initial histological diagnosis** (years) will be calculated as (informed consent date – date of initial histological diagnosis)/365.25 and rounded to 1 decimal place. In case day of diagnosis is missing, impute as 01. In case month of diagnosis is missing, impute as July.
- **Time from last progressive disease** (years) will be calculated as (informed consent date – date of last progressive disease)/365.25 and rounded to 1 decimal place. In case day of progressive disease is missing, impute as 01. In case month of progressive disease is missing, impute as July.
- **Time from end of last prior cancer therapy** (years) will be calculated as (informed consent date – end date of last prior cancer therapy)/365.25 and rounded to 1 decimal place. In case day of last prior cancer therapy is missing, impute as 01. In case month of last prior cancer therapy is missing, impute as July.
- **Time from end of last prior radiotherapy** (years) will be calculated as (informed consent date – end date of last prior radiotherapy)/365.25 and rounded to 1 decimal place. In case day of last prior radiotherapy is missing, impute as 01. In case month of last prior radiotherapy is missing, impute as July.
- **A treatment-emergent adverse event** is an AE on which the first onset or worsening is after the first administration of IMP and up to 30 days after the last administration of IMP. An AE occurring the day of study drug administration and with a missing time will be considered as a TEAE. The TEAE will be determined after the imputation of the start and/or end date according to the rules defined in Section 6.1.7.

6.1.7. Data Adjustments/Handling/Conventions

All collected data will be presented in listings. Data not subject to analysis according to this plan will not appear in any tables or graphs but will be included only in the data listings.

Adverse events will be coded using the latest Medical Dictionary for Regulatory Activities (MedDRA) version available at time of primary analysis or database lock.

A treatment-related AE is any AE with a relationship to the study drug of “Potentially related”, “Probably related” or “Definitely related”. If a particular event is missing the relationship, then it will be considered as related for the analysis.

If partial dates occur, the convention for replacing missing dates for the purpose of statistical analysis is as follows: if just day is missing then the day assigned is the first day of the month or the date of first dose (if in the same month and year), whichever is later; if just month is missing then the month assigned is the month of the first dose if same year than the first dose, unless that results in a date before the first dose in which case the month after the first dose is used, and

assigned as January if the year is later; and if both month and day are missing then the month assigned is the month of the first dose and the day assigned is either the first day of the month or the first dose date, whichever is later if same year than the first dose, and assigned as 01 January if the year is later. In case year is missing, no imputation will be performed. Imputed start dates will be compared to the available information on the end date to ensure the start date is not after the end date. In this case, start dates will be imputed as the first day of the month of the end date.

These conventions will be applied only to AE onset dates and times with the following precaution. Replaced dates will not be presented in any listings.

If the start/stop dates of a medication are partially or completely missing, then the medication will be assumed to be concomitant if it cannot be definitely shown that it was not administered after the first dose. Missing dates will not be replaced.

6.1.8. General Presentation of Outputs

All tables will display a column for each dose-escalation cohort (up to Cohort 8 according to the protocol) with a column for Part 1 grouping all the participants from the dose-escalation phase and one column for each dose-expansion phase cohort. If more than 1 cohort is finally enrolled in this later phase (up to 3 different cohorts according to the protocol) an additional column for Part 2 grouping all the participants will be included. An 'Overall' column grouping all participants will also be reported. In the shells the minimum number of cohorts for Part 2 has been assumed so only the Part 2 column is shown. Additional columns as required will be included as described before following the same structure as for the escalation phase.

7. Study Participants and Demographics

7.1. Disposition of Participants and Withdrawals

Disposition will include tabulations of the number of participants screened, screen failures, rescreened, and the number of participants who received treatment. This analysis will be performed for all the participants screened (with informed consent form signed).

Additionally, the number of participants ending the treatment along with the reasons and completing the study along with reasons for ending the study will be reported based on the SAF Population. The number of participants in each analysis set will also be reported.

All disposition information will be listed.

7.2. Protocol Violations and Deviations

Protocol deviations will be identified and classified at a data review meeting happening prior to database lock before defining the analysis populations for the final analysis.

Protocol deviations will be listed.

7.3. Demographics and Other Baseline Characteristics

Summary statistics for age, sex, height, weight, and ECOG performance status at baseline will be presented. ECOG will be summarized as a categorical variable. Assessments of serology, including human immunodeficiency virus (HIV), hepatitis C virus (HCV), and hepatitis B surface antigen (HBsAg), will be presented at screening.

For the continuous variables, the number of non-missing values and the mean, Std, minimum, median, maximum, and first and third quartiles will be tabulated.

For the categorical variables, the counts and proportions of each value will be tabulated.

The number and percent of participants reporting various medical histories, grouped by MedDRA system organ class (SOC) percentage and preferred term (PT) (coded using the MedDRA version as described in the Data Management Plan), will be tabulated.

Cancer history will be reported with the following information: age at initial histological diagnosis (years), time from initial histological diagnosis (years), histological grade, site of primary tumour, initial status of disease, initial staging, time from last progressive disease (years), primary tumour grade, regional lymph nodes grade, distant metastasis grade, stage of disease at study entry, and staging.

Number and percentage of participants reporting a prior cancer therapy, the prior cancer therapy setting, the number of lines of treatment per participant, the participant's best response, the reason for therapy failure, the time from end of last prior cancer therapy (years), number and percentage of participants reporting prior radiotherapy, the radiotherapy setting, the intent of radiotherapy, and the time from end of last prior radiotherapy (years) will be summarised.

These analyses will be conducted for the SAF population.

Demographics data, serology parameters, cancer history data, prior cancer therapy, prior radiotherapy, and prior and concomitant cancer surgeries/procedures will be listed for all participants.

7.4. Prior and Concomitant Medication and Procedures

Prior medications will be presented separately from concomitant medications.

- Medications that started before the first study drug administration will be considered prior medications whether or not they were stopped before first study drug administration.
- Any medications continuing or starting after the first study drug administration will be considered to be concomitant medications.
- If a medication starts before the first study drug administration and continues after, it will be considered both prior and concomitant medication.

Prior medications (excluding those classified as concomitant too) and concomitant medications (including those that are also prior) will be summarized descriptively in two separate tables,

using counts and percentages, for the SAF population.

Medications will be coded using the version of the World Health Organization Drug Dictionary (WHO-DD) described in the Data Management Plan, and will be presented by Anatomical Therapeutic Chemical classification (ATC) level 1 and level 3.

Prior and concomitant surgeries and procedures and prior cancer therapies will not be coded and will only be listed.

7.5. Exposure and Compliance

DT-9081 will be taken orally daily at the assigned dose for 28 days per cycle. Number of cycles per participant, actual dose (in mg) per cycle and participant, and actual total dose per participant will be summarised including the mean, median, Std, minimum, maximum, and first and third quartiles. The total number of changes in dose (dose reduced, drug interrupted, drug withdrawn, frequency changed, dose increased, dose restored, dose partially restored) per cycle will be also reported.

Compliance by cycle and overall will be calculated based on the actual cumulative dose taken divided by the expected cumulative dose to be taken during the period based on an expected cycle duration of 28 days. Percent compliance will be reported. The actual cumulative dose taken will be determined based on counting the number of capsules returned at each visit and subtracting that number from the number of capsules dispensed multiplied by the capsules' dose. The expected cumulative dose to be taken will be determined based on the assigned dose and on an expected cycle duration of 28 days.

These analyses will be performed for the SAF Population.

All exposure data will be listed.

8. Efficacy Analysis

8.1. Secondary Efficacy Analysis

All the efficacy analyses will be performed by cohort, part and overall, for the Evaluable Population unless specifically stated.

Disease response assessments will use the overall assessment from eCRF and be performed according to RECIST v1.1 and iRECIST; missing data will not be imputed. The BOR determination will not require confirmation of CR or PR. It will then be defined as the best response across all time points until the end of study, including assessments performed after the end of treatment (a participant who has stable disease [SD] at first assessment, PR at second assessment, and progressive disease on last assessment would have a BOR of PR). Stable disease will be considered to be best overall response if it also meets a minimum time of 6 months from baseline. If this minimum time is not met when SD is otherwise the best time-point response, the participant's BOR will depend on the subsequent assessments. For example, a participant who

has SD at first assessment, progressive disease at second and does not meet minimum duration for SD, will have a best overall response of progressive disease (PD). The same participant lost to follow-up after the first SD assessment will be considered not evaluable (NE).

The order used to determine the BOR is CR>PR>SD>PD>NE ignoring visits with missing tumour assessments.

8.1.1. Assessment based on RECIST v1.1

Objective Response

Objective response at each tumour assessment will be displayed and the BOR of participants will be reported descriptively. Number and percentage of participants with anti-tumour response according to RECIST v1.1 will be summarised as per Section 15.3. The best response determination will not require confirmation of complete or partial response.

Objective Response Rate / Clinical Benefit Rate

The ORR, based on the percentage of participants with a CR or a PR at any time during the study, will be provided with the exact 95% CI using the Clopper-Pearson method.

In the same way, analyses will be performed for the CBR, based on the percentage of participants with a CR, PR at any time during the study or SD at least 6 months after the start of treatment.

The ORR analysis will be repeated on the PP Population.

Progression-free Survival

The PFS is defined as the time interval (in months) from the date of first study drug administration to the date of disease progression based upon RECIST v1.1 or the date of death due to any cause, whichever is earlier. In the absence of disease progression or death before participant study end, PFS will be censored at the date of the last valid tumour assessment showing CR, PR, or SD performed before participant study end. If a participant received prohibited therapy during the study before progression or death, the participant will be censored at the date of the last tumour assessment before the start of the first prohibited therapy. If a participant discontinues the study treatment because the investigator reported a clinical/symptomatic disease progression on the end of treatment form without tumour assessment available showing progression, the participant will be considered with an event at the end of treatment date. Summaries will include the number of participants experiencing the event and the number of participants censored; the median, first quartile and third quartile estimates of time-to-event alongside their corresponding 95% CI will be provided. This data will be summarized by cohort, by phase and overall. A Kaplan-Meier plot will also be provided including all participants.

Duration of Response

The DOR is defined as the time (in months) from the date of the first documented RECIST v1.1

defined response (CR or PR) to the date of subsequent progressive disease or death, whichever is earlier. In the absence of disease progression or death before participant study end, DOR will be censored at the date of the last valid tumour assessment. If a participant received new anti-cancer therapy during the study before progression, the participant will be censored at the date of the last tumour assessment before the start of the first prohibited therapy. The starting date of this new treatment is collected within the corresponding protocol deviation details.

If a participant is discontinued from the study because the investigator reported a clinical/symptomatic disease progression on the end of treatment form without tumour assessment available showing progression, the participant will be considered with an event at the date of discontinuation. Duration of response will be determined only for participants with a CR or PR. Summaries will be as for PFS and a Kaplan-Meier plot will be provided.

8.1.2. Assessment based on iRECIST

After a participant has had an initial overall response of progressive disease using RECIST v1.1 criteria the participant will be followed up using iRECIST. The data initially assessed with RECIST v1.1 will be converted to iRECIST for a full iRECIST analysis as follows:

- RECIST v1.1 CR will correspond to iRECIST iCR
- RECIST v1.1 PR will correspond to iRECIST iPR
- RECIST v1.1 SD will correspond to iRECIST iSD
- RECIST v1.1 PD will correspond to iRECIST iUPD

After RECIST v1.1 PD is recorded, all further assessments will be conducted exclusively using the iRECIST criteria and will be combined with the translated RECIST v1.1 data for the appropriate analysis.

Objective Response

Number and percentage of participants with anti-tumour response according to iRECIST will be summarised and immune best overall response (iBOR) will be reported based on Appendix 3: iRECIST Best Overall Response (iBOR).

Objective Response Rate / Clinical Benefit Rate

The immune objective response rate (iORR), based on the percentage of participants with an immune complete response (iCR) or an immune partial response (iPR) at any time during the study after unconfirmed immune progressive disease (iUPD), will be provided with the exact 95% CI using the Clopper-Pearson method.

In the same way, analyses will be performed for the immune clinical benefit rate (iCBR), based on the percentage of participants with an iCR, iPR at any time during the study after iUPD or immune stable disease (iSD) at least 6 months after the start of iUPD.

The iORR analysis will be repeated on the PP Population.

Progression-free Survival

The PFS will also be calculated based on iRECIST (iPFS) as the time interval (in months) from the date of first study drug administration to the first date at which progression criteria are met (i.e., the date of iUPD) provided that confirmed immune progressive disease (iCPD) is confirmed at the next assessment. If iUPD occurs, but is disregarded because of later iSD, iPR, or iCR, then that iUPD date should not be used as the progression event date.

If progression is not confirmed and there is no subsequent iSD, iPR, or iCR, then the iUPD date should still be used in the following scenarios: if the participant stops protocol treatment because they were not judged to be clinically stable, or no further response assessments are done (because of participant refusal, protocol noncompliance, or participant death); the next time-point responses are all iUPD, and iCPD never occurs; or the participant dies from their cancer.

The scenarios listed above are translated into the following checks against the eCRF data:

- Not judged to be clinically stable:
 - EOT reason = “Physician decision, includes any reason in the opinion of the investigator that would justify treatment discontinuation” or
 - EOT reason = “Disease progression” and Type of Progression = “Clinical/symptomatic PD”
- Participant refusal:
 - EOS reason = “Withdrawal by subject”
- Protocol noncompliance:
 - EOT reason = “Significant study intervention noncompliance” and/or
 - EOS reason = “Protocol deviation”
- Participant death:
 - EOS reason = “Death”

Similarly to what is planned for RECIST v1.1-based analyses, summaries will be as for iPFS and a Kaplan-Meier plot will be provided.

Duration of Response

The immune duration of response (iDOR) is defined as the time (in months) from the date of the first documented iRECIST defined response (iCR or iPR) to the date of subsequent progressive disease (i.e., the date of iUPD) provided that iCPD is confirmed at the next assessment or death, whichever is earlier. In the absence of disease progression or death before participant study end, iDOR will be censored at the date of the last valid tumour assessment. If a participant received a new anti-cancer therapy during the study before progression, the participant will be censored at the date of the last tumour assessment before the start of the first prohibited therapy. iDOR will be determined only for participants with an iCR or iPR. Summaries will be as for PFS, and a Kaplan-Meier plot will be provided.

Additionally, to the previous endpoints, all individual efficacy assessments (ECOG, details of tumour assessments, ...) will be listed.

9. Safety and Tolerability Analysis

Safety will be evaluated from reported AEs, changes in clinical laboratory values, changes in vital signs, electrocardiogram (ECG results), echography/multiple gated acquisition (MUGA) scan and physical exams.

All safety analyses will be performed on the SAF Population.

9.1. Adverse Events

All AEs, TEAEs, and serious adverse events (SAEs) will be coded using the latest MedDRA version available at time of primary analysis or database lock. Severity is reported according to CTCAE v5 grading when applicable for the AEs. No inferential statistical tests will be performed.

An overall summary table for TEAEs will be prepared containing number and percentage of participants reporting TEAEs (overall and by severity), treatment-related TEAEs (overall and by severity), treatment-emergent SAEs, treatment-related treatment-emergent SAEs, DLTs, fatal TEAEs, treatment-related fatal TEAEs, TEAEs and treatment-related TEAEs leading to study drug interruption, TEAEs and treatment-related TEAEs leading to study drug dose reduction, TEAEs and treatment-related TEAEs leading to withdrawal of study drug, and TEAEs and treatment-related TEAEs leading to study discontinuation.

The number and percent of participants reporting TEAEs, grouped by MedDRA SOC and PT, will be tabulated, with the number of events. In the case of multiple occurrences of the same TEAE within the same participant, each participant will only be counted once for each PT.

Summaries of TEAEs by SOC and PT will also be produced by CTCAE grade when applicable, by severity and for study-drug-related event (by SOC and PT and by severity).

For treatment-related TEAE summaries, relationships coded as potentially, probably, or definitely related or missing will be analysed as “Related”. All others are considered as “Not Related”. If a particular event is missing the relationship, then the strongest possible relationship will be assumed for analysis (relationship = related).

In the summaries showing CTCAE grading and relationship to study medication, the event with the highest CTCAE grade or the strongest relationship (Related > Not Related) will be reported. If a particular event is not applicable for CTCAE grading, its severity (Mild, Moderate, Severe) will be collected instead. For the final analysis this scale will be translated into CTCAE scale following these rules:

- A “Mild” severity will be considered as a Grade 1 event
- A “Moderate” severity will be considered as a Grade 2 event
- Any events reporting a “Severe” severity will be queried to provide the corresponding value for CTCAE grading (Grades 3-5) for reporting. If the query is finally not resolved, the event will be imputed to:
 - Grade 5 if Death = Yes for that event,

- Grade 4 if Death = No but Life Threatening = Yes,
- Grade 3 if Death = No and Life Threatening = No.

All the summary tables will be presented by cohort and part.

In the AE data listings, all AEs will be displayed. Adverse events that are not treatment emergent will be flagged.

9.1.1. Adverse Events Leading to Withdrawal

A summary of incidence rates (frequencies and percentages) of TEAEs leading to withdrawal of study drug, by SOC, and PT will be prepared for the SAF Population. Treatment emergent adverse events leading to study discontinuation will be reported in the same way.

A data listing of AEs leading to withdrawal of study drug or to study discontinuation will also be provided, displaying details of the events captured on the eCRF.

9.1.2. Deaths and Serious Adverse Events

Any deaths that occur during the study will be listed.

Number and percentage of participants with treatment-emergent SAEs and treatment-related SAEs will be tabulated by SOC and PT.

All SAEs will also be listed.

9.1.3. Other Significant Adverse Events

Number and percentage of participants with DLTs will be summarised with associated Clopper-Pearson 95% CI and tabulated by SOC and PT.

Dose-limiting toxicities will be also listed.

9.2. Clinical Laboratory Evaluations

Laboratory evaluations are performed at local laboratories. All measurements will be summarised and analysed together. Measurements not performed in International System of Units at a local study site laboratory will be converted into standard units in the database.

Descriptive summaries of observed values and changes from baseline values for haematology, chemistry, and coagulation parameters will be presented by scheduled visit. A summary of frequency of observed data for urinalysis parameters will be reported in the same way.

The number of participants with clinical laboratory values below, within, or above the normal ranges by scheduled visit and in relation to baseline will be tabulated for each parameter as applicable using shift tables for chemistry and haematology parameters. For some of these parameters (total bilirubin, alanine aminotransferase, aspartate aminotransferase and alkaline phosphatase for Chemistry; haemoglobin, absolute neutrophil count, absolute lymphocyte count

and platelets for Hematology) a figure to describe their evolution over time will be generated for each of the parameters. For urinalysis, parameters will be analysed based on the interpretation of the result (normal, abnormal not clinically significant, and abnormal clinically significant).

Descriptions will be given for:

- Clinical chemistry: sodium, potassium, chloride, bicarbonate or CO₂, glucose, blood urea nitrogen or serum urea level, creatinine, creatinine clearance or glomerular filtration rate, albumin, creatine kinase, total bilirubin, direct bilirubin if total bilirubin is greater than upper limit of normal, alanine aminotransferase, aspartate aminotransferase, alkaline phosphatase, lactate dehydrogenase, uric acid, calcium, phosphorus, magnesium, total protein, amylase, lipase, thyroid stimulating hormone, triiodothyronine, thyroxine, CRP, troponin, D-dimers.
- Haematology: haemoglobin, haematocrit, white blood cell count, absolute basophil count, basophils/leukocytes, absolute neutrophil count, neutrophils/leukocytes, absolute eosinophil count, eosinophils/leukocytes, absolute lymphocyte count, lymphocytes/leukocytes, absolute monocyte count, monocytes/leukocytes, band neutrophils/leukocytes, red blood cell count and platelet count
- Coagulation: prothrombin time, international normalised ratio, and activated partial thromboplastin time
- Urinalysis: glucose, ketones, protein, blood, microscopic analysis evaluation (if available, this will only be done if blood or protein is abnormal in dipstick analysis)

Chemistry, haematology, coagulation, and urinalysis parameters will be listed. Laboratory values that are outside the normal range will also be flagged in the data listings, along with corresponding normal ranges.

Pregnancy test will be only listed.

9.3. Vital Signs

Descriptive summaries of actual values and changes from baseline will be calculated by scheduled visit for weight (kg), temperature (°C), heart rate (beats/min), respiratory rate (breaths/min), systolic blood pressure (mmHg), diastolic blood pressure (mmHg), and oxygen saturation (%).

Frequencies and percentages of vital sign interpretation results (normal, abnormal clinically significant, and abnormal not clinically significant) will be summarised for each parameter by scheduled visit.

If a participant has done multiple assessments at the same visit time point, only the last result will be considered in the analysis.

All vital signs data will be also listed.

9.4. Electrocardiograms

As the same measurement is taken 3 times at the same scheduled visit, the mean value for the measurements and the worst investigator interpretation will be considered for the summaries.

Descriptive summaries of ECG will be presented by scheduled visit for measures of heart rate (beats/min), PR interval (ms), QRS duration (ms), QT interval (ms), QT_cB interval (with Bazett's Correction) (ms), and QT_cF interval (with Fridericia's Correction) (ms). In addition, the number and percent of participants who experienced an absolute value in QT interval, QT_cB interval, or QT_cF interval >450ms or >480ms or >500 ms or an increase from baseline in QT interval, QT_cB interval, or QT_cF interval >30 ms or a change >60 ms will be presented by scheduled visit.

The number and percentage of participants with normal and abnormal ECG findings will be summarised at each scheduled visit. Abnormal results will be grouped as clinically significant and not clinically significant.

All ECG data will be also listed.

9.5. Further Safety Evaluations

9.5.1. Cardiac Echocardiography

Cardiac echocardiography data will only be listed.

9.5.2. Physical Examination

Physical examination data will only be listed.

10. Changes from Planned Analysis

- The Appendix Table 3 “Best Overall Response When Confirmation of CR and PR Required” from the protocol of this study is not applicable because this trial does not require confirmation of CR or PR as per RECIST v1.1 paper (Eisenhauer et al 2009): “confirmation of response is required for trials with response primary endpoint”. In summary, as efficacy is not the primary endpoint for this study, these responses do not need to be confirmed.
- According to the protocol “only participants with an initial response of progressive disease will be reported” within the iRECIST analysis. This is not following the iRECIST guidelines which instruct to start the iRECIST evaluation since the first tumor assessment and not only for those patients progressing. The RECIST v1.1 assessments will be used to described iRECIST until the first progression reported (RECIST v1.1 PD).
- The vital signs values will not be categorized as below, within, or above normal ranges as described in the protocol but will be displayed using the interpretation results (normal, abnormal clinically significant, and abnormal not clinically significant) as collected in the

eCRF.

11. Other Planned Analysis

11.1. Pharmacokinetic Analysis

Pharmacokinetic analyses will be performed on the PK population. Any exclusion will be flagged and presented in the individual data listings. The PK characterization of drug concentrations for each dose to be profiled will be performed using noncompartmental analysis (NCA).

The PK parameter estimates will be performed using Phoenix WinNonlin v8.3.5 or higher (Pharsight Corporation) software using the actual elapsed times from dose administration to sample collection. For plasma concentration data, all values below the limit of quantification (BLQ) will be set to 0 for summary statistics and graphs. They will be set to half of the BLQ's value for log scale figures. For the PK parameter calculation, BLQ plasma concentrations occurring before T_{max} will be set to 0, with the exception of a BLQ value occurring between 2 measurable concentrations, in which case it will be set to missing. Any BLQ plasma concentrations occurring after T_{max} will be set to missing.

Standard PK parameters assessed will include measures of the extent of absorption using estimates of the area under the plasma concentration-time curve from time 0 to the time of the last quantifiable plasma concentration (AUC_{0-t}), area under the plasma concentration-time curve from time 0 to infinity (if data permit) (AUC_{0-inf}), rate of absorption using the maximum plasma concentration (C_{max}), the time of C_{max} (T_{max}), apparent first order terminal elimination half-life ($T_{1/2}$) and apparent terminal phase rate constant (λ_z) (if data permit). Any participant for whom the portion of the AUC extrapolated to infinity exceeds 20% of the total AUC_{0-inf} will be excluded from the calculation of the descriptive statistics for AUC_{0-inf} .

Other PK parameters may be derived, where appropriate, and as data permit.

For NCA, plasma concentrations will be listed and summarized at each time point by treatment cohort using descriptive statistics. Descriptive statistics reported will include the arithmetic mean, Std, coefficient of variation (CV)%, minimum, maximum, and median. Only the range and the median will be reported for T_{max} , if calculated, as these are categorical parameters. The PK parameters will also be summarized by treatment cohort using descriptive statistics for which geometric mean will also be included.

Individual plasma concentration plots and mean data graphs will be produced using both linear and semi-logarithmic scales. Mean data graphs will show plasma concentration profiles by treatment group. Pharmacokinetic parameter estimates and summaries will be completed for all participants in the PK population.

11.2. Pharmacodynamic Analysis

12. References

1. US Federal Register. (1998) International Conference on Harmonisation; Guidance on Statistical Principles for Clinical Trials. Department of Health and Human Services: Food and Drug Administration [Docket No. 97D-0174]. Federal Register Volume 63, Number 179, pages 49583-49598. September 16, 1998.
2. ASA. (2018) Ethical Guidelines for Statistical Practice. Prepared by the Committee on Professional Ethics, April 2018. <http://www.amstat.org/about/ethicalguidelines.cfm>
3. RSS. (2014) The Royal Statistical Society: Code of Conduct, 2014. <https://rss.org.uk/about/policy-and-guidelines/code-of-conduct/>.

13. Tables, Listings, and Figures

All listings, tables, and graphs will have a header showing the sponsor company name and protocol and a footer showing the version of SAS, the file name and path, and the source of the data (listing number).

The following are planned summary tables for protocol number DT-9081-CLI-001. The table numbers and page numbers are place holders only and will be determined when the tables are produced.

13.1. Demographic Data Summary Tables and Figures

Table 1: Demographic Data Summary Tables and Figures

Table Number	Population	Table Title/Summary
Table 14.1.1.1	All Participants	Participant Disposition
Table 14.1.2.1	Safety	Summary of Demographics and Baseline Characteristics
Table 14.1.2.2	Safety	Summary of Medical History by System Organ Class and Preferred Term
Table 14.1.2.3	Safety	Summary of Cancer History
Table 14.1.2.4	Safety	Summary of Prior Cancer Therapies
Table 14.1.3.1	Safety	Summary of Prior Medications by Anatomical Therapeutic Chemical Classification and Preferred Name
Table 14.1.3.2	Safety	Summary of Concomitant Medications by Anatomical Therapeutic Chemical Classification and Preferred Name
Table 14.1.4	Safety	Overall Study Drug Exposure

13.2. Efficacy Data

Table 2: Efficacy Data

Table Number	Population	Table Title / Summary
Table 14.2.1	Evaluable	Descriptive Summary of Overall Tumor Assessment (RECIST)
Table 14.2.2	Evaluable	Descriptive Summary of Best Overall Response (RECIST)
Table 14.2.3.1	Evaluable	Descriptive Summary of Objective Response Rate (RECIST)
Table 14.2.3.2	PP	Descriptive Summary of Objective Response Rate (RECIST)
Table 14.2.4	Evaluable	Descriptive Summary of Clinical Benefit Rate (RECIST)
Table 14.2.5	Evaluable	Progression-free Survival – Kaplan-Meier Estimates
Table 14.2.6	Evaluable	Duration of Response – Kaplan-Meier Estimates
Table 14.2.7	Evaluable	Descriptive Summary of Immune Overall Tumor Assessment (iRECIST)
Table 14.2.8	Evaluable	Descriptive Summary of Immune Best Overall Response (iRECIST)
Table 14.2.9.1	Evaluable	Descriptive Summary of Immune Objective Response Rate (iRECIST)
Table 14.2.9.2	PP	Descriptive Summary of Immune Objective Response Rate (iRECIST)
Table 14.2.10	Evaluable	Descriptive Summary of Immune Clinical Benefit Rate (iRECIST)
Table 14.2.11	Evaluable	Immune Progression-free Survival – Kaplan-Meier Estimates
Table 14.2.12	Evaluable	Duration of Immune Response – Kaplan-Meier Estimates

13.3. Safety Data

Table 3: Safety Data

Table Number	Population	Table Title / Summary
14.3.1 Displays of Adverse Events		
Table 14.3.1.1	Safety	Overall Summary of Treatment-emergent Adverse Events
Table 14.3.1.2	Safety	Summary of Treatment-emergent Adverse Events by System Organ Class and Preferred Term
Table 14.3.1.3	Safety	Summary of Treatment-emergent Adverse Events by System Organ Class, Preferred Term, and Highest Grade of Severity
Table 14.3.1.4	Safety	Summary of Treatment-related Treatment-emergent Adverse Events by System Organ Class, Preferred Term
Table 14.3.1.5	Safety	Summary of Treatment-related Treatment-emergent Adverse Events by System Organ Class, Preferred Term, and Highest Grade of Severity
14.3.2 Serious Adverse Events and Adverse Events Leading to Study Withdrawal		

Table Number	Population	Table Title / Summary
Table 14.3.2.1	Safety	Summary of Treatment-emergent Adverse Events Leading to Study Drug Withdrawal by System Organ Class and Preferred Term
Table 14.3.2.2	Safety	Summary of Treatment-emergent Adverse Events Leading to Study Discontinuation by System Organ Class and Preferred Term
Table 14.3.2.3	Safety	Summary of Treatment-emergent Serious Adverse Events by System Organ Class and Preferred Term
Table 14.3.2.4	Safety	Summary of Treatment-related Serious Adverse Events by System Organ Class and Preferred Term
Table 14.3.2.5	Safety	Summary of Dose-limiting Toxicity Events by System Organ Class and Preferred Term
14.3.5 Laboratory Data Summary Tables		
Table 14.3.5.1.1	Safety	Descriptive Summary of Clinical Chemistry by Study Visit
Table 14.3.5.1.2	Safety	Shift Table of Clinical Chemistry by Study Visit
Table 14.3.5.2.1	Safety	Descriptive Summary of Haematology by Study Visit
Table 14.3.5.2.2	Safety	Shift Table of Haematology by Study Visit
Table 14.3.5.3	Safety	Descriptive Summary of Coagulation by Study Visit
Table 14.3.5.4.1	Safety	Descriptive Summary of Categorical Urinalysis Parameters by Study Visit
Table 14.3.5.4.2	Safety	Shift Table of Urinalysis by Study Visit
14.3.6 Other Safety Data Summary Tables		
Table 14.3.6.1	Safety	Descriptive Summary of Vital Signs by Study Visit
Table 14.3.6.2	Safety	Descriptive Summary of Categorical Vital Signs Parameters Interpretation by Study Visit
Table 14.3.6.3	Safety	Descriptive Summary of Electrocardiograms by Study Visit
Table 14.3.6.4	Safety	Descriptive Summary of Categorical Electrocardiograms by Study Visit

13.4. Pharmacokinetic Data

Table 4: Pharmacokinetic Data

Table Number	Population	Table Title / Summary
14.4 Pharmacokinetic and Pharmacodynamic Data Summary Tables		
Table 14.4.1.1	PK	Descriptive Summary of Pharmacokinetic Concentrations by Timepoint and Study Visit
Table 14.4.1.2	PK	Descriptive Summary of Pharmacokinetic Parameters

13.5. Planned Listing Descriptions

The following are planned data and participant data listings for protocol number DT-9081-CLI-001.

In general, 1 listing will be produced per eCRF domain. All listings will be sorted by part/cohort, site, and participant number. All calculated variables will be included in the listings.

In all listings a blank line will be placed between each participant. Within a data listing, if an item appears line after line (e.g., repetition of participant number), then only the first occurrence will be displayed.

In data listings, the information for 1 participant will be kept on 1 page if at all possible, rather than splitting a participant's information across pages.

Table 5: Planned Listings

Data Listing Number	Population	Data Listing Title / Summary
16.2 Participant Data Listings		
16.2.1 Participant Disposition		
Listing 16.2.1.1	All Participants	Participant Disposition
Listing 16.2.1.2	Safety	Study Completion Status
Listing 16.2.1.3	All Participants	Study Populations
Listing 16.2.1.4	All Participants	Inclusion/Exclusion Criteria
Listing 16.2.1.5	All Participants	Study Visits
16.2.2 Protocol Deviations		
Listing 16.2.2.1	Safety	Protocol Deviations
16.2.3 Participants Excluded from the Efficacy Analyses		
Listing 16.2.3.1	Safety	Participants Excluded from Efficacy Analysis

Data Listing Number	Population	Data Listing Title / Summary
16.2 Participant Data Listings		
16.2.4 Demographic Data and Other Baseline Characteristics		
Listing 16.2.4.1	Safety	Demographics and Baseline Characteristics
Listing 16.2.4.2	Safety	Medical History
Listing 16.2.4.3	Safety	Cancer History
Listing 16.2.4.4	Safety	Prior Cancer Therapy
Listing 16.2.4.5	Safety	Prior Radiotherapy
Listing 16.2.4.6	Safety	Prior and Concomitant Cancer Surgeries and Procedures
Listing 16.2.4.7	Safety	Prior and Concomitant Medications
Listing 16.2.4.8	Safety	Prior and Concomitant Surgeries and Procedures
16.2.5 Compliance and/or Drug Concentration Data		
Listing 16.2.5.1	Safety	Study Drug Compliance
Listing 16.2.5.2	Safety	Participant Dosing
Listing 16.2.5.3	Safety	Intra-participant Escalation
Listing 16.2.5.4	Safety	Drug Accountability
16.2.6 Individual Efficacy Response Data		
Listing 16.2.6.1	Evaluable	Response Assessment – RECIST v1.1
Listing 16.2.6.2	Evaluable	Response Assessment – iRECIST
Listing 16.2.6.3	Evaluable	Tumour Assessment per RECIST v1.1 – Target Lesions
Listing 16.2.6.4	Evaluable	Tumour Assessment per RECIST v1.1 – Non-Target Lesions
Listing 16.2.6.5	Evaluable	Tumour Assessment per RECIST v1.1 – New Lesions
Listing 16.2.6.6	Evaluable	Tumour Assessment – RECIST v1.1 Response
Listing 16.2.6.7	Evaluable	Tumour Assessment – iRECIST Response
Listing 16.2.6.8	Evaluable	Tumour Biopsy
Listing 16.2.6.9	Evaluable	Eastern Cooperative Oncology Group Performance Status
16.2.7 Adverse Events Listings		
Listing 16.2.7.1	Safety	Adverse Events
Listing 16.2.7.2	Safety	Adverse Events Leading to Withdrawal of Study Drug or Study Discontinuation

Data Listing Number	Population	Data Listing Title / Summary
16.2 Participant Data Listings		
Listing 16.2.7.3	Safety	Serious Adverse Events
Listing 16.2.7.4	Safety	Adverse Events Leading to Death
Listing 16.2.7.5	Safety	Dose-limiting Toxicity Events
16.2.8 Listing of Individual Laboratory Measurements by Participant		
Listing 16.2.8.1	Safety	Clinical Chemistry Laboratory Evaluations
Listing 16.2.8.2	Safety	Haematology Laboratory Evaluations
Listing 16.2.8.3	Safety	Coagulation Laboratory Evaluations
Listing 16.2.8.4	Safety	Serology Results
Listing 16.2.8.5	Safety	Urinalysis Laboratory Evaluations
Listing 16.2.8.6	Safety	Pregnancy Test Results
Listing 16.2.8.7	Safety	Pharmacodynamic Blood Sampling (Cytokines release)
Listing 16.2.8.8	Safety	Urine Sampling for PGE2/PGEM Analysis
Listing 16.2.8.9	Safety	Peripheral Blood Mononuclear Cell Sampling
16.2.9 Other Safety and Tolerability Listings		
Listing 16.2.9.1	Safety	Vital Signs Measurements
Listing 16.2.9.2	Safety	Electrocardiograms Measurements
Listing 16.2.9.3	Safety	Echocardiography and Multiple Gated Acquisition Measurements
Listing 16.2.9.4	Safety	Physical Examination
Listing 16.2.9.5	PK	Pharmacokinetic Concentration Results
Listing 16.2.9.6	PK	Individual Pharmacokinetic Parameters

13.6. Planned Figure Descriptions

The following are planned summary figures for protocol number DT-9081-CLI-001. The figure numbers and page numbers are place holders only and will be determined when the figures are produced.

Table 6: Planned Figures

Figure Number	Population	Figure Title/Summary
Figure 14.5.1	Evaluable	Swimmer Plot of Tumour Response over Time (RECIST v1.1)
Figure 14.5.2	Evaluable	Waterfall Plot for Best Percent Change from Baseline in Sums of Diameters by Best Overall Response (RECIST v1.1)
Figure 14.5.3	Evaluable	Kaplan-Meier Survival Plot of Progression-free Survival
Figure 14.5.4	Evaluable	Kaplan-Meier Survival Plot of Duration of Response
Figure 14.5.5	Evaluable	Kaplan-Meier Survival Plot of Immune Progression-free Survival
Figure 14.5.6	Evaluable	Kaplan-Meier Survival Plot of Duration of Immune Response
Figure 14.5.7	Safety	Safety Laboratories - Chemistry Parameters Over Time
Figure 14.5.8	Safety	Safety Laboratories - Hematology Parameters Over Time
Figure 14.5.9	PK	Mean (\pm SD) Plasma Concentration over Time - Linear Scale
Figure 14.5.10	PK	Mean (\pm SD) Plasma Concentration over Time - Semi-log Scale
Figure 14.5.11	PK	Individual Plasma Concentration over Time - Linear Scale
Figure 14.5.12	PK	Individual Plasma Concentration over Time - Semi-log Scale

14. Tables, Listings, and Listing Shells

14.1. Standard Layout for all Tables, Listings, and Figures

The following standard layout will be applied to all Tables, Listings, and Figures in support of this study. Note that programming notes may be added if appropriate after each TLF shell.

14.2. Planned Table Shells

Provided in separate document.

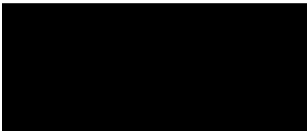
14.3. Planned Listing Shells

Provided in separate document.

14.4. Planned Figure Shells

Provided in separate document.

15. Appendices




15.2. Appendix 3: iRECIST Best Overall Response (iBOR)

TPR1	TPR2	TPR3	TPR4	TPR5	iBOR
iCR	iCR, iPR, iUPD, NE	iCR, iPR, iUPD, NE	iUPD	iCPD	iCR
iUPD	iPR, iSD, NE	iCR	iCR, iPR, iSD, iUPD, NE	iCR, iPR, iSD, iUPD, iCPD, NE	iCR
iUPD	iPR	iPR, iSD, iUPD, NE	iPR, iSD, iUPD, NE, iCPD	iPR, iSD, iUPD, NE, iCPD	iPR
iUPD	iSD, NE	PR	iPR, iSD, iUPD, NE	iPR, iSD, iUPD, iCPD, NE	iPR
iUPD	iSD	iSD, iUPD, NE	iSD, iUPD, iCPD, NE	iSD, iUPD, iCPD, NE	iSD
iUPD	iCPD	Anything	Anything	Anything	iCPD
iUPD	iUPD	iCPD	Anything	Anything	iCPD
iUPD	NE	NE	NE	NE	iUPD


NE = not evaluable that cycle.
iBOR can be considered as iSD if the condition of iSD meets a minimum time of 6 months from iUPD.
Designation 'T' for BOR can be used to indicate prior iUPD to aid in data interpretation.

Abbreviations: TP = time point; R = RECIST 1.1; iR = iRECIST; TPR = response at that time point; iBOR = iRECIST best overall response; iUPD = unconfirmed immune progressive disease; iCPD = confirmed immune progressive disease; iCR = immune complete response; iPR = immune partial response; iSD = immune stable disease; NE = not evaluable/evaluated.

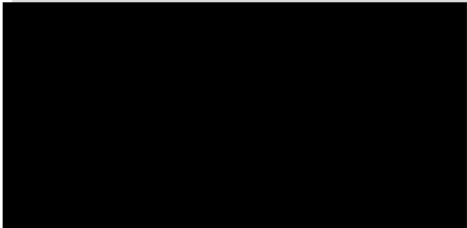

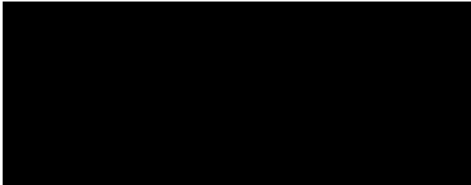

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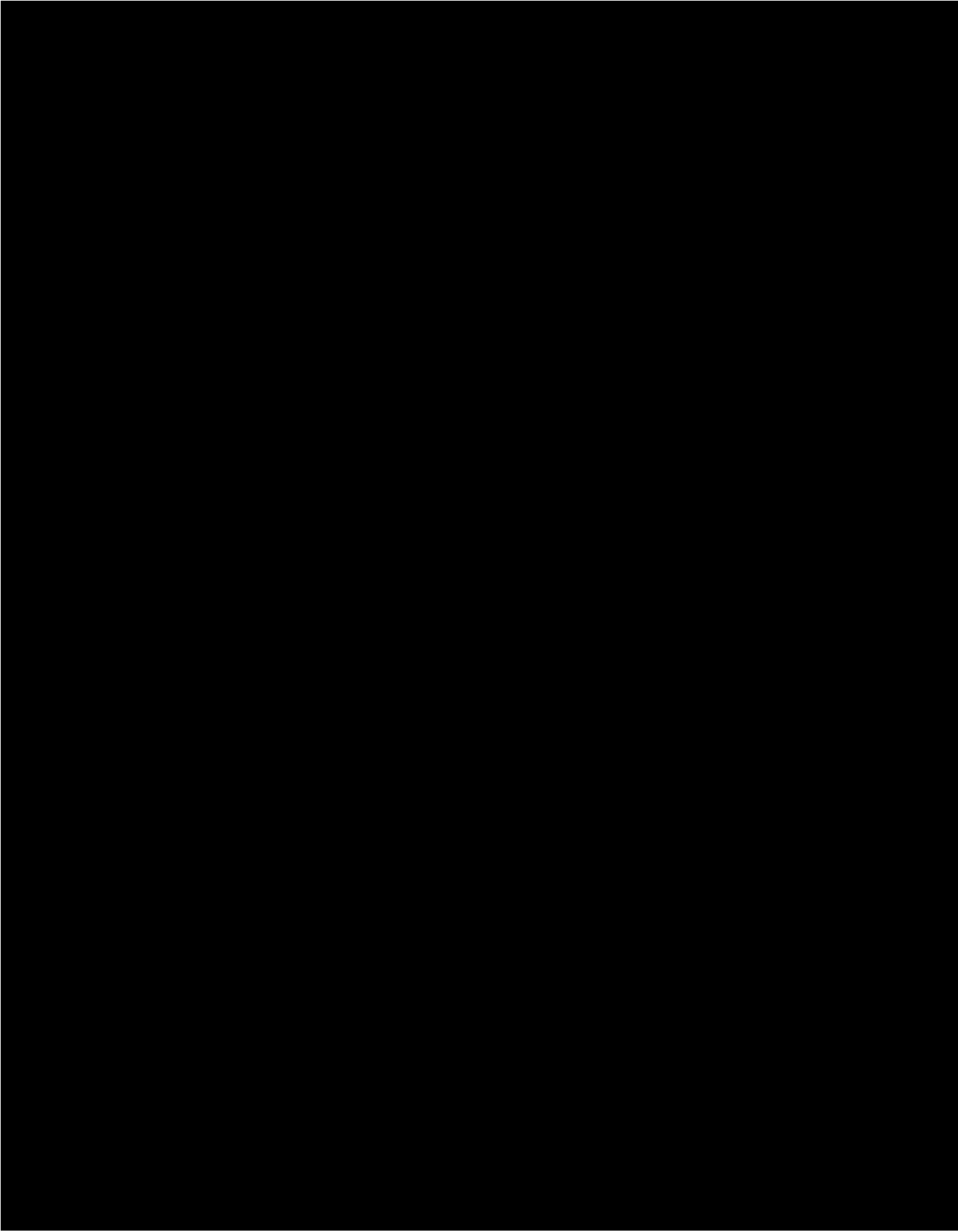
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