



Domain Therapeutics SA

Protocol

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

NCT Number: 05582850

Protocol Date: 09 January 2024

PROTOCOL

PRODUCT NAME/NUMBER: DT-9081

PROTOCOL NUMBER: DT-9081-CLI-001

EUDRACT NUMBER: 2022-000092-40

DEVELOPMENT PHASE: 1

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

PROTOCOL DATE: Final, Version 4.0, 09-JAN-2024

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This study will be performed in compliance with ICH Good Clinical Practices and applicable regulatory requirements, including the archiving of essential documents. Information contained in this protocol is confidential in nature, and must not be used, divulged, published, or otherwise disclosed to others except to the extent necessary to obtain approval of the institutional review board or independent ethics committee, or as required by law. Persons to whom this information is disclosed should be informed that it is confidential and must not be further disclosed without the express permission of the Sponsor.

1. APPROVAL SIGNATURES

PROTOCOL NUMBER: DT-9081-CLI-001

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.

PROTOCOL DATE: Version 4.0, 09-JAN-24

I, the undersigned, have read this protocol and confirm that to the best of my knowledge it accurately describes the planned conduct of the study.

SIGNATURE:**DATE:**

2. PROTOCOL SUMMARY

2.1. Synopsis

PRODUCT NAME/NUMBER	DT-9081
PROTOCOL NUMBER	DT-9081-CLI-001
PROTOCOL VERSION and DATE	Version 4.0, 09-JAN-2024
DEVELOPMENT PHASE	1
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
INDICATION	Advanced (unresectable, recurrent, or metastatic) solid tumours
OBJECTIVES	<p>Primary objectives:</p> <ul style="list-style-type: none">• To determine the recommended Phase 2 dose (RP2D) of DT-9081• To assess the safety and tolerability profile of DT-9081 <p>Secondary objectives:</p> <ul style="list-style-type: none">• To determine the maximum tolerated dose (MTD) of DT-9081 (applicable only if MTD is reached within 8 escalation cohorts)• To determine the pharmacokinetics (PK) of DT-9081• To evaluate preliminary anti-tumour activity of DT-9081 <p>Exploratory objectives:</p> <p>To determine the PD activity of DT-9081</p>
STUDY DESIGN	<p>This is a Phase 1, multicentre, open-label study of DT-9081 to determine the MTD and/or the RP2D of DT-9081 in participants with advanced solid tumours.</p> <p>The study will be divided into 2 phases:</p> <ul style="list-style-type: none">• a dose escalation phase• a dose expansion phase <p>Dose Escalation Phase: will be based on a “3+3” modified design (as defined later in the document) with up to 8 dose levels. This phase will enrol a maximum of 48 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.</p> <ul style="list-style-type: none">• Participants will be recruited into cohorts in a 3+3 modified design to ensure an efficient dose escalation. The first participant in each cohort will be observed for 7 days for dose-limiting toxicities (DLTs) before the subsequent participants are dosed in that cohort.• The starting dose for Cohort 1 will be 25 mg once daily.

	<ul style="list-style-type: none"> • A maximum of 8 dose escalation cohorts at increasing levels are planned. <p>Each cohort will be dosed at a maximum increment of 100% of DT-9081 of the previous dose level depending on the safety, tolerability, PK and PD parameters.</p> <p>Enrolment of participants to a new cohort requires completion of DLT evaluation of at least 3 participants treated in the current cohort. Should a DLT be observed in the first 3 to 5 participants enrolled, additional participants will be enrolled so that 6 participants are available for DLT evaluation.</p> <p>The Safety Review Committee (SRC) will convene and review the safety data of the first 3 participants who complete the 28-day DLT observation periods and are evaluable for DLT evaluation. The SRC will also review any suitable available PK and PD data. The other participants enrolled at the same Dose Level who have not completed the DLT evaluation and have not experienced any DLT will be censored and not included in the dataset that will be reviewed by the SRC to authorize the escalation to the next dose level. Their safety data will be reviewed by the SRC at the next SRC meeting with all the safety data generated at lower doses.</p> <p>In the event that participants in the previous cohort experience DLTs after enrolment of participants to the next cohort has begun, dose level assignment of the next participants will be based on the review by the SRC of all the data generated from all assessed doses.</p> <p>Throughout the dose-escalation phase:</p> <ul style="list-style-type: none"> • 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 are 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 1/6 participants experienced a DLT. <p>If the Dose Escalation does not define a MTD during the evaluation of the 8 dose levels planned during the study or if the Sponsor decides to not evaluate higher dose levels because the PK and PD data establish that the doses explored include the RP2D, the RP2D will be chosen as the dose level reached during the dose escalation with no more than 1/6 participants who experienced a DLT and with relevant PK/PD data.</p> <p>A DLT is defined as one of the toxicities defined in section 7.1.1.2 that occur during the DLT assessment period (28 days) and is considered by the principal investigator (or designee) to be at least potentially related to DT-9081. Principal investigators (or designees) are encouraged to perform all</p>
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	<p>necessary investigations to determine the underlying aetiology and most appropriate attribution.</p> <p>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.</p> <p>A SRC charter will provide guidance for dose-escalation decisions.</p> <p>To improve tolerability of the investigational medicinal product (IMP), the total daily dose of DT-9081 may be administered as 2 divided doses per day, provided the total daily dose is not exceeded. Decision will be discussed with the SRC and taken by the Sponsor's medical monitor.</p> <p>Intra-participant dose escalation:</p> <p>Escalation will be permitted in the dose escalation phase:</p> <ul style="list-style-type: none"> - for participants with no history of grade 3/4 toxicity related to DT-9081 with a persisting good ECOG (0 – 1) - when 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 <p>Dose Expansion Phase:</p> <p>The Dose Expansion will explore up to 3 dose levels to better characterize the safety, PK and PD of DT-9081. The dose levels selected for expansion will be those suggested to provide a sufficient exposure to DT-9081, based on the emerging PK data and only at dose levels determined to be safe during the Dose Escalation phase.</p> <p>Each Dose Expansion Cohort will enrol a maximum of 12 participants. Based on the observed safety events in a given dose expansion cohort, the SRC will recommend the actions to be taken with the other ongoing cohort(s).</p> <p>The Inclusion/Exclusion criteria set forth for the Dose Escalation phase will be used to select participants in the Dose Expansion phase.</p> <p>Should more than one Dose Expansion cohort be opened at the same time, participants will be allocated to a particular Dose Expansion Cohort by the Sponsor.</p> <p>Definition of the RP2D</p> <p>The RP2D of DT-9081 will be selected based on the totality of data from the Dose Escalation and will be optimized at the end of the Dose Expansion based on the totality of data available considering:</p> <ul style="list-style-type: none"> • Overall safety/tolerability profile (DLT, Grade 3 treatment related adverse events (TRAEs) occurring after the DLT observation period and incidence of long-lasting Grade 2 TRAEs) • PK/PD data • Available observations on efficacy
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	<p>Throughout the study, the SRC comprised of at least two 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.</p> <p>Safety will be assessed by the occurrence and severity of treatment-emergent adverse events (TEAEs), treatment-related TEAEs and DLTs.</p> <p>biomarkers will be assessed during this study to determine the PD activity.</p>
RATIONALE	<p>DT-9081 is an orally administered, small molecule prostaglandin E receptor 4 (EP4R) antagonist developed to overcome the immune-suppressive effects of prostaglandin E2 (PGE2) and reverse resistance to immune checkpoint blockers. Overexpression of PGE2 in tumour tissues suppresses anti-tumour immunity in the tumour microenvironment and can lead to disease progression. The use of an EP4R antagonist-based therapy is proposed to inhibit the immune-suppressive and tumorigenic roles of PGE2 in tumours. In addition, it may sensitise the therapeutic effects of immune checkpoint inhibitors in patients with non-inflamed and cancer-immune-cycle-deficient tumours.</p>
PLANNED NUMBER OF PARTICIPANTS	<ol style="list-style-type: none"> 1. Dose-Escalation Phase: up to 48 participants will be enrolled and treated. Further participants may be recruited based on safety and PK data. This would be based on the recommendation of an SRC. 2. Dose Expansion phase: up to 36 participants will be enrolled and treated (maximum of 12 participants per cohort).
STUDY ENTRY CRITERIA	<p>Inclusion criteria:</p> <ol style="list-style-type: none"> 1. Participants must 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, and who have failed or are ineligible for standard of care therapies. Participants who are considered ineligible for standard of care therapies, may be eligible on discussion with the principal investigator (or designee). Such cases need to be agreed between principal investigator (or designee) and Sponsor. 2. Participants must be ≥ 18 years of age on the day of signing the informed consent form. 3. Participants must have measurable disease per Response Evaluation Criteria in Solid Tumours (RECIST) v1.1 as assessed by local site investigator/radiologist. Lesions situated in a previously irradiated area are considered measurable if progression has been demonstrated in such lesions. 4. Participants must have at least 1 tumour lesion with location accessible to safely biopsy per clinical judgement of the treating physician (not previously irradiated, or >2 months (at Screening) since last radiation and had tumour progression since radiation) and must consent to pre-treatment and on-treatment tumour biopsies for performance of correlative tissue studies. <p>Notes:</p>

	<ul style="list-style-type: none"> • If the fresh biopsy cannot be collected, formalin-fixed paraffin-embedded block containing tumour tissue is required. These biospecimens must be recently obtained, meaning at or after progression on the most recent line of anticancer treatment. Participants for whom tumour tissue is not available and a new biopsy is not feasible, may be deemed eligible for study after consultation with the Sponsor. • Once the Sponsor has considered that a sufficient number of biopsies have been collected, the paired-biopsy requirement will be waived for the next participants to be enrolled. <ol style="list-style-type: none"> 5. Participants must have an Eastern Cooperative Oncology Group (ECOG) performance status of 0 or 1. 6. Participants must have an international normalised ratio or activated partial thromboplastin time $\leq 1.5 \times$ upper limit of normal (ULN) unless participant is receiving anticoagulant therapies. 7. Participants must have a life expectancy of at least 12 weeks according to the principal investigator's (or designee's) judgement. 8. Participants must have adequate organ function defined as: <ul style="list-style-type: none"> Haematology: <ul style="list-style-type: none"> • Absolute neutrophil count $\geq 1000/\mu\text{L}$ or $\geq 1.0 \times 10^9/\text{L}$ • Platelets $\geq 75,000/\mu\text{L}$ or $\geq 75 \times 10^9/\text{L}$ • Haemoglobin $\geq 9.0 \text{ g/dL}$ or $\geq 5.59 \text{ mmol/L}$ Renal: <ul style="list-style-type: none"> • Serum creatinine $\leq 1.5 \times \text{ULN}$, or creatinine clearance (CrCl) $\geq 50 \text{ mL/min}$ using the Cockcroft Gault formula for participants in whom, in the principal investigator (or designee's) judgement, serum creatinine levels do not adequately reflect renal function. • Estimated glomerular filtration rate (eGFR) can be also used to assess renal function. Acceptable eGFR is $>40 \text{ mL/min/1.73m}^2$ per local laboratory. Hepatic: <ul style="list-style-type: none"> • Total bilirubin $\leq 1.5 \times \text{ULN}$ or direct bilirubin $\leq 1.5 \times \text{ULN}$ if total bilirubin is $>1.5 \times \text{ULN}$. Total bilirubin ≤ 3 times the ULN in participants with documented Gilbert's Syndrome (unconjugated hyperbilirubinemia) or in the presence of liver metastases. • Aspartate aminotransferase (AST) and alanine aminotransferase (ALT) $\leq 2.5 \times \text{ULN}$ ($\leq 5 \times \text{ULN}$ for participants with liver metastases). 9. Participants must have no uncontrolled endocrinopathies. Participants with diabetes must have HbA 1c $< 7\%$. 10. A female participant is eligible to participate if she is not pregnant and not breastfeeding, and at least one of the following conditions applies: <ol style="list-style-type: none"> a. Not a woman of childbearing potential (WOCBP)
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	<p>b. A WOCBP who commits to the consistent and correct use of a highly effective method of contraception throughout the study starting with the screening visit until 187 days after last dose of study drug.</p> <p>Note: If a WOCBP has a positive or suspected positive urine pregnancy test within 72 hours prior to treatment, a serum pregnancy test will be required.</p> <p>11. A male participant able to father a child must commit to the consistent and correct use of an effective method of contraception plus a highly effective method of contraception for the female partner starting with the screening visit and through 187 days after last dose of study drug.</p> <p>12. The participant (or legally authorised representative if applicable) must provide written informed consent for the study in accordance with ICH-GCP and local legislation prior to admission to the study.</p> <p>13. Participants must be able to swallow oral dose forms of medication.</p> <p>14. Participants must be willing and able to comply with all aspects of this protocol.</p> <p>Exclusion criteria:</p> <p>1. Participants using drugs interfering with the COX-2 pathways or prohibited drugs.</p> <p>Note: Participants stopping the prohibited treatment 14 days or a duration exceeding 5 half-lives (if earlier) of its elimination prior to DT-9081 administration may be considered.</p> <p>2. Participants with unresolved adverse events (AEs) from previous anti-cancer therapies of Grade ≥ 2 (National Cancer Institute Common Terminology Criteria for Adverse Events v5.0) with exception of alopecia. Participants with Grade ≤ 2 neuropathy may be eligible.</p> <p>3. Participants who underwent major surgery or significant traumatic injury within 4 weeks prior to Cycle 1 Day 1 who have not recovered adequately from any AEs and/or complications from the intervention prior to starting study drug.</p> <p>4. Participants who have received prior radiotherapy within the last 4 weeks before start of study drug treatment (limited field palliative radiotherapy within 2 weeks).</p> <p>5. Participants who have received a live vaccine within 30 days prior to the first dose of study drug. Coronavirus disease 2019 (COVID-19) vaccines and booster are allowed >14 days before study initiation (Cycle 1 Day 1).</p> <p>6. Participants who are currently participating in or have participated in a study of an investigational agent (e.g., small molecules, immunotherapy, chemotherapy monoclonal antibodies, or any other experimental drug in the neoadjuvant or adjuvant setting) or received prior systemic cancer-directed treatments within 30 days or at least 5 half-lives (whichever is shorter) prior to the first dose of study drug.</p> <p>7. Participants who have already received EP4R antagonist in an investigational trial.</p>
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	<ol style="list-style-type: none"> 8. Participants who have a diagnosis of immunodeficiency or are receiving chronic systemic steroid therapy (in doses exceeding 10 mg daily of prednisone equivalent), or an average cumulative dose of >140 mg prednisone (or dose equivalent) within the last 14 consecutive days prior to treatment start or any other form of immunosuppressive therapy within 7 days prior to the first dose of study drug. Inhaled non-absorbable and topical corticosteroid use is permitted as indicated. 9. Participants who have a known additional malignancy that is progressing or has required active treatment within the past 1 year. Note: Participants with basal cell carcinoma of the skin, squamous cell carcinoma of the skin, or carcinoma in situ (e.g., breast carcinoma, cervical cancer in situ) that have undergone potentially curative therapy are not excluded. 10. Participants who have known active central nervous system metastases and/or carcinomatous meningitis. Participants with previously treated brain metastases may participate provided they are radiologically stable, i.e., without evidence of progression for at least 4 weeks by repeat imaging (note that the repeat imaging should be performed during study screening), clinically stable, no oedema, and without requirement of steroid treatment for at least 14 days prior to first dose of study treatment. 11. Participants who have an active infection including COVID-19 requiring systemic therapy. 12. Participants who have a known history of human immunodeficiency virus (HIV) infection. 13. Participants who have a known history of hepatitis B (HBV) (defined as HVB surface antigen reactive) or known active hepatitis C virus (HCV) (defined as HCV ribonucleic acid [qualitative] is detected) infection unless treated with no detectable virus. 14. Participants who have a history or current evidence of any condition, therapy or laboratory abnormality that might confound the results of the study, interfere with the participant's participation for the full duration of the study, or that means participation in the study is not in the best interest of the participant, in the opinion of the treating investigator. 15. Participants who have known psychiatric or substance abuse disorders that would interfere with cooperating with the requirements of the study. 16. Participants who have had an allogenic tissue/solid organ transplant. 17. Participants who have significant cardiovascular/cerebrovascular disease including, but not limited to, any of the following: New York Heart Association Class III or IV cardiac disease, myocardial infarction or transient ischemic attack/stroke within the last 6 months, unstable arrhythmias or unstable angina. 18. Participants with corrected QT interval calculated by the Fridericia formula >470 milliseconds (females) or >450 milliseconds (males). 19. Participants with known hypersensitivity to one of the excipients present in the IMP.
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	20. Participants with recent digestive ulcer who has recovered less than 12 months ago.
INVESTIGATIONAL MEDICINAL PRODUCT (IMP)	<p>Name: DT-9081</p> <p>Dose, route, frequency: 25 mg capsule (starting dose), administered orally, once daily (up to twice daily depending on tolerability and PK data), until disease progression, unacceptable toxicity, participant consent withdrawal, or withdrawal from treatment for any reason</p>
TREATMENT REGIMENS	<p>During the dose escalation phase and the dose expansion phase: DT-9081 will be taken daily at the assigned dose without interruption until disease progression, unacceptable toxicity or participant consent withdrawal, or withdrawal from treatment for any reason. The participant must fast 2 hours before and 2 hours after ingestion of DT-9081 capsules.</p> <p>DT-9081 will be given orally once daily (this can be changed to twice daily depending on tolerability and PK data).</p>
COORDINATING/ PRINCIPAL INVESTIGATOR	<p>Professor Cliniques Universitaires Saint-Luc 10 Avenue Hippocrate 1200 Brussels Belgium</p>
PLANNED STUDY SITES	Approximately 10 study sites in approximately 2 countries (France and Belgium)
CRITERIA FOR EVALUATION	<p>Primary endpoints:</p> <ul style="list-style-type: none"> Endpoints contributing to the determination of the RP2D will include safety, efficacy, predicted target inhibition, PD results and PK/PD simulations. Safety and tolerability will be assessed by the incidence and severity of TEAEs, treatment-related TEAEs and DLTs. All AEs will be assessed according to Common Terminology Criteria for Adverse Events (CTCAE) v 5.0. <p>Secondary endpoints:</p> <ul style="list-style-type: none"> Maximum tolerated dose (MTD): Endpoints contributing to the determination of the MTD will be the DLTs. Pharmacokinetics (PK) parameters: C_{max}, T_{max}, $T_{1/2}$, area under the curve (AUC), apparent clearance and volume of distribution. Anti-tumour activity will be assessed with the following efficacy endpoints: <ul style="list-style-type: none"> Objective response rate (ORR) Best overall response (BOR) Clinical benefit rate (CBR) Progression free survival (PFS) Duration of response (DOR) <p>All clinical endpoints will be assessed according to RECIST v1.1 and immune RECIST (iRECIST).</p> <p>Exploratory endpoints will include the evaluation of PD biomarkers, inflammatory markers, and immune cell markers.</p>

STATISTICAL METHODS	<p><u>Analysis Populations:</u></p> <p>The following analysis populations will be used:</p> <ul style="list-style-type: none"> • Safety population: All participants who receive at least 1 dose of DT-9081. • Evaluable population: All participants who received 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 one post-baseline disease assessment (clinical and/or radiological). • Per Protocol population: All participants from the Evaluable population who don't have any major protocol deviation impacting the efficacy analysis and who also receive the planned daily dose of DT-9081 for at least 75% of the cycle duration in Cycle 2 (equivalent to 21 out of 28 days at the planned dose). • PK population: All participants who receive at least 1 dose of DT-9081 and have at least 1 post-dose PK measurement available • PD population: All participants who receive at least 1 dose of DT-9081 and have at least one post-dose PD measurement available <p>In general, data will be summarised by dose level.</p> <p><u>Descriptive Statistics:</u></p> <p>For the continuous variables, the number of non-missing values and the mean, standard deviation, minimum, median and maximum will be tabulated.</p> <p>For the qualitative variables, the number and percentage of participants with non-missing values will be tabulated. If applicable, exact 95% confidence intervals calculated using the Clopper-Pearson method will be provided.</p> <p><u>Participant Characteristics and Disposition:</u></p> <p>Number of participants in the study, in each population, completing or discontinuing the study with the reason will be tabulated.</p> <p>Baseline characteristics, demographic information and disease-related history will be summarised for the Safety population.</p> <p>Descriptive summaries of the medical/surgical history and prior medications will also be completed.</p> <p><u>Efficacy Analyses:</u></p>

	<p>Summaries of anti-tumour data will be based on the Evaluable population. For ORR, BOR and CBR, the percentages will be estimated and exact 95% confidence intervals calculated using the Clopper-Pearson method.</p> <p>For PFS and DOR, Kaplan-Meier plots and descriptive summaries will be used.</p> <p><u>Clinical Pharmacology Analyses:</u></p> <p>Standard PK parameters will be determined using non-compartmental methods, as data permit.</p> <p><u>Safety Analyses:</u></p> <p>Safety data will be presented based on the Safety population.</p> <p>All safety outcomes will be summarised using descriptive statistics. Adverse events starting at or after the first dose of DT-9081 (TEAEs) will be presented with the number and percentage of participants having a TEAE summarised by primary System Organ Class and Preferred Term according to the Medical Dictionary for Regulatory Activities (MedDRA). Separate tables showing all TEAEs, all serious TEAEs, and all TEAEs suspected to be related to DT-9081 will be generated. Number and percentage of participants with DLTs will be summarised; DLTs will be presented in by-participant listings.</p> <p>Vital signs, electrocardiograms (ECGs) and safety laboratory parameters will be analysed using descriptive statistics.</p> <p>Laboratory abnormalities will be summarised by parameter in frequency tables and in shift tables relative to the baseline value.</p>
SAMPLE SIZE DETERMINATION	<p>Dose Escalation Phase</p> <p>The sample size for the dose escalation phase is based on the standard expectation for a modified 3+3 design with up to 6 participants per cohort. At a particular dose level up to 5 participants will first be enrolled. The safety of that cohort will be first determined on the data generated on the first 3 participants to complete the DLT observation period. The participants enrolled at that dose level who have neither completed the DLT observation period nor 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.</p> <p>A maximum of 8 dose levels will be evaluated in the Phase 1. Therefore, up to 48 evaluable participants may be enrolled in the Dose Escalation phase.</p> <p>Dose Expansion Phase</p> <p>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.</p> <p>The sample size for each dose expansion cohort is not based on formal statistical estimation since the goal is to monitor safety, PK/PD data and assess anti-tumour activity only in an exploratory manner.</p>

STUDY AND TREATMENT DURATION	<p>The overall study duration is expected to be 36 months.</p> <p>The sequence and maximum duration of the study periods for the participant will be as follows:</p> <ol style="list-style-type: none">1. Screening: up to 28 days.2. Treatment: DT-9081 will be taken continuously in cycles of 28 days until disease progression, unacceptable toxicity, participant consent withdrawal, or withdrawal from treatment for any reason. Treatment cycles will occur consecutively without interruption.3. Follow-up: 1 month after last treatment dose and every 2 months after last treatment dose until resolution of treatment related toxicity. <p>After the end of study treatment, each participant will be followed for a minimum of 30 days for AE monitoring. Serious AEs (SAE) will be collected for up to 90 days following cessation of treatment or until the participant initiates new anti-cancer therapy, whichever is earlier.</p>
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2.2. Schedule of Events

Table 2-1: Schedule of Events (Dose Escalation)

Assessment/Evaluation	Study Period										
	Screening	Cycle 1					Cycle 2		Cycle 3 up to EOT	EOT ^a	Follow up ^b
	V1	V2	V3	V4	V5	V6	V7	V8	V9		
	Day -28 to Day -1	Day 1 ^{zzzz}	Day 2	Day 3	Day 8 ±1 day	Day 15 ±1 day	C2D1 ±2 days	C2D15 ±2 days	CnD1 ±3 days ^c		±7 days
Informed consent forms	X										
Inclusion/exclusion criteria	X										
Participant Identification card	X										
Participant demographics ^d	X										
Medical history	X										
Record concomitant medication use	X	X	X	X	X	X	X	X	X	X	X
Physical examination (full or directed) ^e	X	X		X	X	X	X	X	X	X	X
ECOG-PS	X	X		X	X	X	X	X	X	X	X
Vital signs ^f	X	X	X	X	X	X	X	X	X	X	X
Adverse events ^g	X	X	X	X	X	X	X	X	X	X	X
12-lead ECG	X ^h	X ⁱ					X ⁱ		X ⁱ	X ^j	X ^j
Cardiac echocardiography or MUGA	X									X	
Clinical chemistry ^k	X	X		X	X	X	X	X	X	X	X
Haematology ^l	X	X		X	X	X	X	X	X	X	X
Urinalysis ^m	X	X		X	X	X	X	X	X	X	X

Assessment/Evaluation	Study Period										
	Screening	Cycle 1					Cycle 2		Cycle 3 up to EOT	EOT ^a	Follow up ^b
	V1	V2	V3	V4	V5	V6	V7	V8	V9		
	Day -28 to Day -1	Day 1 ^{zzzz}	Day 2	Day 3	Day 8 ±1 day	Day 15 ±1 day	C2D1 ±2 days	C2D15 ±2 days	CnD1 ±3 days ^c		±7 days
HIV and HCV serology, detection of HBsAg	X										
Pregnancy test ⁿ	X	X					X		X	X	
Coagulation tests ^o	X	X		X	X	X	X	X	X	X	X
Dispense participant diary and give training		X					X		X		
Review returned participant diary							X		X	X	
DT-9081 administration ^p		X	X	X	X	X	X	X	X		
Disease stage	X										
Tumour imaging ^q	X ^r	X ^s									X ^t
Clinical disease assessment	X	X ^s									X ^t
Pharmacokinetic blood sampling		X ^u	X ^v	X ^v	X ^v	X ^u	X ^u				

Abbreviations: β -hCG = beta human chorionic gonadotropin; C = cycle; CT = computer tomography; D = day; ECG = electrocardiogram; ECOG-PS = Eastern Cooperative Oncology Group performance status; EOT = end of treatment; HBsAg = Hepatitis B surface antigen; HCV = hepatitis C; HIV = human immunodeficiency virus; iRECIST = immune Response Evaluation Criteria in Solid Tumours; MUGA = multiple gated acquisition; MRI = magnetic resonance imaging; PBMC = peripheral blood mononuclear cell; RECIST = Response Evaluation Criteria in Solid Tumours; ULN = upper limit of normal; V = visit.

- a An EOT visit must be conducted for all participants within 7 days after permanent discontinuation of study drug.
- b Participants are to be followed up 1 month after study drug discontinuation and every 2 months after their last dose of DT-9081 until resolution of DT-9081 related toxicity.
- c Only for Cycle 3, Day1. For Cycle 4 and onward, the time window allowed is ± 7 days.
- d Demography includes sex and year of birth.
- e Full examination at screening and every Day 1 of each cycle. Check and describe any significant abnormal physical examinations or findings: heart, chest, abdomen, skin, oral cavity and lymph nodes. Directed examination can be performed at other time points or as clinically indicated to include symptom-driven examination.
- f Vital signs include blood pressure, heart rate, respiration rate, oxygen saturation, weight and temperature. Height will be measured at screening only.
- g Adverse events occurring after Informed Consent signature to be recorded.
- h Triplicate measurements separated by 5 minutes will be performed at screening.
- i Triplicate measurements separated by 5 minutes will be performed at Day 1 of cycle 1 to 5 and then at Day 1 of every 3 cycles before study drug administration. On Day 1 of Cycle 1, triplicate measurements separated by 5 minutes (± 3 min) will be performed at predose, postdose at 20 minutes (± 5 min), 1 hour (± 10 min), 2 hours (± 15 min), 4 hours (± 30 min), 6 hours (± 30 min), 10 hours (± 30 min) before blood sampling.
- J At end of treatment visit and at follow-up visit, single measurement is require.
- k Clinical chemistry includes albumin, alkaline phosphatase, alanine aminotransferase, aspartate aminotransferase, lactate dehydrogenase, CO₂ or bicarbonate, uric acid, calcium, chloride, glucose, phosphorus, potassium, sodium, magnesium, total bilirubin, direct bilirubin if total bilirubin is $>ULN$, total protein and blood urea nitrogen, or serum urea level, measured or calculated creatinine and creatinine clearance. Glomerular filtration rate can be used instead of creatinine or creatinine clearance, amylase, lipase serology, creatine kinase, thyroid stimulating hormone, thyroxine and triiodothyronine. CRP, Troponine and D-dimeres will be collected at screening and as clinically indicated. Participants must fast before the blood sampling. Lab samples can be collected up to 72 hours prior to the scheduled time point.
- l Haematology includes haematocrit, haemoglobin, platelet count, white blood cell (total and differential, bands, basophils, eosinophils, lymphocytes, monocytes, neutrophils), red blood cell count and absolute neutrophil count. Lab samples can be collected up to 72 hours prior to the scheduled time point.
- m Urinalysis includes: glucose, ketones, protein, and blood. Microscopic examination will be done if blood or protein is abnormal in dipstick analysis.
- n A pregnancy test is mandatory for women of childbearing potential within 72 hours prior to the start of treatment, repeat every month during the treatment period as required per local regulations and at EOT. If the urine test is positive or cannot be confirmed as negative, a serum pregnancy test (β -hCG) will be required.
- o Coagulation tests include prothrombin time, partial thromboplastin time (activated) and international normalised ratio. Lab samples can be collected up to 72 hours prior to the scheduled time point.
- p DT-9081 will be taken daily at the assigned dose for 28 days per cycle (“a cycle”) without interruption until disease progression, unacceptable toxicity or consent withdrawn. The participant must fast 2 hours before and 2 hours after ingestion of DT-9081 capsules. On visit days, participants should not take study drug before any visit procedure. Blood samples for the clinical laboratory tests must be taken prior to study drug administration and results reviewed prior to administration of study drug.
- q Tumour (radiological) imaging: CT scans of abdomen, chest and pelvis. An MRI scan can be used if CT contrast is contra-indicated. The same radiographic procedure must be used throughout the study.

- r At screening, include scan of brain to exclude active metastases or leptomeningeal metastases if known brain metastases or clinically indicated. Assess disease according to RECIST v1.1.
- s A new tumour imaging scan will be performed every 8 weeks (± 1 week) during the 4 first cycles after first administration of study drug and then every 12 weeks (± 1 week) until disease progression. Clinical disease assessment to be performed after each tumour imaging. Assess disease according to RECIST v1.1 and iRECIST.
- t For participants who stopped treatment for reasons other than disease progressions, tumour imaging should be performed within 8 weeks of the last tumour imaging. Clinical disease assessment to be performed after every tumour scan according to RECIST v1.1 and iRECIST.
- u PK blood samples to be taken at predose, and postdose at 30 min ± 5 min, 1 hour ± 10 min, 2 hours ± 15 min, 4 hours ± 30 min, 6 hours ± 30 min, 10 hours ± 30 min.
- v PK blood samples to be taken at predose.

Table 2-2: Schedule of Events (Expansion Phase)

Assessment/Evaluation	Study Period										
	Screening	Cycle 1					Cycle 2		Cycle 3 up to EOT	EOT ^a	Follow up ^b
	V1	V2	V3	V4	V5	V6	V7	V8	V9		
	Day -28 to Day -1	Day 1 ^{zzz}	Day 2	Day 3	Day 8 ±1 day	Day 15 ±1 day	C2D1 ±2 days	C2D15 ±2 days	CnD1 ±3 days ^c		±7 days
Informed consent forms	X										
Inclusion/exclusion criteria	X										
Participant identification card	X										
Participant demographics ^d	X										
Medical history	X										
Record concomitant medication use	X	X	X	X	X	X	X	X	X	X	X
Physical examination (full or directed) ^e	X	X		X	X	X	X	X	X	X	X
ECOG-PS	X	X		X	X	X	X	X	X	X	X
Vital signs ^f	X	X	X	X	X	X	X	X	X	X	X
Adverse events ^g	X	X	X	X	X	X	X	X	X	X	X
12-lead ECG	X ^h	X ⁱ					X ⁱ		X ^j	X ^j	X ^j
Cardiac echocardiography or MUGA	X									X	
Clinical chemistry ^k	X	X		X	X	X	X	X	X	X	X
Haematology ^l	X	X		X	X	X	X	X	X	X	X
HIV and HCV serology, detection of HbsAg	X										

Assessment/Evaluation	Study Period										
	Screening	Cycle 1					Cycle 2		Cycle 3 up to EOT	EOT ^a	Follow up ^b
	V1	V2	V3	V4	V5	V6	V7	V8	V9		
	Day -28 to Day -1	Day 1 ^{zzz}	Day 2	Day 3	Day 8 ±1 day	Day 15 ±1 day	C2D1 ±2 days	C2D15 ±2 days	CnD1 ±3 days ^c		±7 days
Urinalysis ^m	X	X		X	X	X	X	X	X	X	X
Pregnancy test ⁿ	X	X					X		X	X	
Coagulation tests ^o	X	X		X	X	X	X	X	X	X	X
Dispense participant diary and give training		X					X		X		
Review returned participant diary							X		X	X	
DT-9081 administration ^p		X	X	X	X	X	X	X	X		
Disease stage	X										
Tumour imaging ^q	X ^r	X ^s									X ^t
Clinical disease assessment	X	X ^s									X ^t
Pharmacokinetic blood sampling		X ^u	X ^v			X ^u					

Abbreviations: β-hCG = beta human chorionic gonadotropin; C = cycle; CT = computer tomography; D = day; ECG = electrocardiogram; ECOG-PS = Eastern Cooperative Oncology Group performance status; EOT = end of treatment; iRECIST= immune Response Evaluation Criteria in Solid Tumours; MRI =

magnetic resonance imaging; MUGA= multiple gated acquisition; PBMC = peripheral blood mononuclear cell; RECIST = Response Evaluation Criteria in Solid Tumours; ULN = upper limit of normal; V = visit.

- a An End of Treatment visit must be conducted for all participants at the time of permanent discontinuation of study drug.
- b Participants are to be followed-up 1 month after study drug discontinuation and every 2 months after study drug discontinuation until resolution of DT-9081 related toxicity.
- c Only for Cycle 3, Day 1. For Cycle 4 and onward, the time window allowed is ± 7 days.
- d Demography includes sex and year of birth.
- e Full examination at screening and Day 1 of each cycle. Check and describe any significant abnormal physical examinations or findings: heart, chest, abdomen, skin, oral cavity and lymph nodes. Directed examination can be performed at other time points or as clinically indicated to include symptom-driven examination.
- f Vital signs include sitting blood pressure (systolic and diastolic), heart rate, respiration rate, oxygen saturation, weight and temperature. Height will be measured at screening only.
- g Adverse events occurring after Informed Consent signature to be recorded.
- h A 12-lead ECG is performed where indicated as well as when clinically indicated. Triplicate measurements separated by 5 minutes will be performed at screening.
- i Triplicate measurements separated by 5 minutes will be performed at Day 1 of cycle 1 to 5 and then at Day 1 of every 3 cycles before study drug administration. On Day 1 of Cycle 1, triplicate measurements separated by 5 minutes (± 3 min) will be performed at predose, and postdose at 20 minutes (± 5 min), 1 hour (± 10 min), 2 hours (± 15 min), 4 hours (± 30 min), 6 hours (± 30 min), 10 hours (± 30 min) before blood sampling.
- j At end of treatment visit and at follow-up visit, single measurement is required.
- k Clinical chemistry includes albumin, alkaline phosphatase, alanine aminotransferase, aspartate aminotransferase, lactate dehydrogenase, CO₂ or bicarbonate, uric acid, calcium, chloride, glucose, phosphorus, potassium, sodium, magnesium, total bilirubin, direct bilirubin if total bilirubin is $>ULN$, total protein and blood urea nitrogen, or serum urea level, measured or calculated creatinine and creatinine clearance. Glomerular filtration rate can be used instead of creatinine or creatinine clearance, amylase, lipase serology, creatine kinase, TSH, T₃ and T₄. CRP, Troponine and D-dimeres will be collected at screening and as clinically indicated. Participants must fast before the blood sampling. Lab samples can be collected up to 72 hours prior to the scheduled time point.
- l Haematology includes haematocrit, haemoglobin, platelet count, white blood cell (total and differential, bands, basophils, eosinophils, lymphocytes, monocytes, neutrophils), red blood cell count and absolute neutrophil count. Lab samples can be collected up to 72 hours prior to the scheduled time point.
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- n A pregnancy test is mandatory for women of childbearing potential within 72 hours prior to the start of treatment, repeat every month during the treatment period as required per local regulations and at EOT. If the urine test is positive or cannot be confirmed as negative, a serum pregnancy test (β -hCG) will be required.
- o Coagulation tests include prothrombin time, partial thromboplastin time (activated) and INR. Lab samples can be collected up to 72 hours prior to the scheduled time point.
- p DT-9081 will be taken daily at the assigned dose for 28 days per cycle ("a cycle") without interruption until disease progression, unacceptable toxicity or consent withdrawn. The participant must fast 2 hours before and 2 hours after ingestion of DT-9081 capsules. On visit days, participants should not take study drug before any visit procedure. Blood samples for the clinical laboratory tests must be taken prior to study drug administration and results reviewed prior to administration of study drug.
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- r At screening, include scan of brain to exclude active metastases or leptomeningeal metastases [if known brain metastases or clinically indicated](#). Assess disease according to RECIST v1.1.

- s A new tumour imaging scan will be performed every 8 weeks (± 1 week) during the first 4 cycles after first administration of study drug and then every 12 weeks until disease progression. Clinical disease assessment to be performed after each tumour imaging according to RECIST v1.1 and iRECIST.
- t For participants who stopped treatment for reasons other than disease progressions, tumour imaging should be performed within 8 weeks of the last tumour imaging. Clinical disease assessment to be performed after every tumour scan according to RECIST v1.1 and iRECIST.
- u PK blood samples to be taken at predose, and postdose at 30 min ± 5 min, 1 hour ± 10 min, at 2 hours ± 15 min, 4 hours ± 30 min, 6 hours ± 30 min, 10 hours ± 30 min.
- v PK blood samples to be taken at predose.

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4. LIST OF ABBREVIATIONS AND DEFINITION OF TERMS

ABBREVIATION	EXPLANATION
ADR	Adverse drug reaction
AE	Adverse event
AESI	Adverse event of special interest
ALT	Alanine amino transferase (=SGOT)
APC	Antigen presenting cell
AST	Aspartate amino transferase (=SGPT)
AUC	Area-under-the-curve
BOR	Best overall response
cAMP	Cyclic adenosine monophosphate
CBR	Clinical benefit rate
C-IC	Cancer-immunity cycle
C _{max}	Rate of absorption using the maximum concentration
CNS	Central nervous system
COVID-19	Coronavirus disease 2019
COX-2	Cyclooxygenase 2
CRA	Clinical research associate
CR	Complete response
CrCl	Creatinine clearance
CSR	Clinical study report
CT	Computer tomography
CTCAE	Common terminology criteria for adverse event
CYP	Cytochrome P450
DDI	Drug-drug interaction
DLT	Dose-limiting toxicity
DOR	Duration of response
eCRF	Electronic case report form
CSR	clinical study report
EDC	Electronic data capture
eGFR	Estimated glomerular filtration rate
EP	Prostaglandin E
EP1R	Prostaglandin E receptor 1
EP2R	Prostaglandin E receptor 2
EP3R	Prostaglandin E receptor 3
EP4R	Prostaglandin E receptor 4
EOT	End of treatment
GCP	Good Clinical Practice

ABBREVIATION	EXPLANATION
HBsAg	Hepatitis B surface antigen
HBV	Hepatitis B virus
HCV	Hepatitis C virus
HED	Human equivalent dose
HIV	Human immunodeficiency virus
HR	Heart rate
IB	Investigator's brochure
ICF	Informed consent form
ICH	International Council for Harmonisation of Technical Requirements for Pharmaceuticals for Human Use
ICI	Immune checkpoint inhibitor
IEC	Independent ethics committee
IMP	Investigational medicinal product
irAE	Immune-related adverse event
irAR	Immune-related adverse reaction
iRECIST	Immune response evaluation criteria in solid tumours
IL-2	Interleukin 2
IL-12	Interleukin 12
IFN- γ	Interferon γ
IRB	Institutional review board
LFT	Liver function test
MDSC	Myeloid-derived suppressor cells
MedDRA	Medical Dictionary for Regulatory Activities
MRI	Magnetic resonance imaging
MTD	Maximum tolerated dose
MUGA	Multiple gated acquisition
NE	Non evaluable
NK	Natural killer
NOAEL	No observable adverse effect level
NSAID	Non-steroidal anti-inflammatory drugs
ORR	Objective response rate
pCREB	cAMP response element binding protein
PD	Pharmacodynamics
PFS	Progression free survival
PGE2	Prostaglandin E2
PGEM	Prostaglandin E metabolite
PK	Pharmacokinetics

ABBREVIATION	EXPLANATION
PR	Partial response
PS	Performance status
QT	Time taken for depolarisation of the ventricles
QTc	Time from the beginning of the QRS complex to the end of the T wave
RP2D	Recommended phase 2 dose
RECIST	Response Evaluation Criteria in Solid Tumours
RNA	Ribonucleic acid
SAE	Serious adverse event
SD	Standard deviation
SRC	Safety review committee
SAP	Statistical analysis plan
TAM	Tumour associated macrophages
TEAE	Treatment-emergent adverse event
Tmax	Time of rate-of-absorption using the maximum concentration
TME	Tumour microenvironment
TNF- α	Tumour necrosis factor α
T-reg	Regulatory CD4+ T lymphocytes
ULN	Upper limit of normal
WOCBP	Woman of childbearing potential

5. INTRODUCTION

5.1. Background and Rationale

Prostaglandin E2 (PGE2) is a bioactive lipid produced from arachidonic acid by cyclooxygenases (COX). PGE2 functions via activation of 7 transmembrane G-Protein-Coupled Receptors (GPCRs), EP1R, EP2R, EP3R, and EP4R. Prostaglandin E2 can elicit a wide range of biological effects associated with inflammation and cancer. In the tumour environment PGE2 has an immunosuppressive effect causing tumour immune evasion leading to disease progression. Cyclooxygenase-2, mainly via PGE2 production, promotes overall growth of tumours, and correlates with clinical outcome in a high percentage of common cancers, especially colorectal, gastric, oesophageal, pancreatic, breast and ovarian cancer ¹.

EP4R is aberrantly over-expressed in multiple types of cancers, especially in gastro-intestinal and pancreatic cancers. Furthermore, the overexpression of PGE2 and/or EP4R correlates with disease progression in some cancer types such as oesophageal squamous cell carcinoma ², squamous cell carcinoma of the lung ³, prostate cancer ^{4,5}, and head and neck squamous cell carcinoma ⁶.

Several pharmacological studies to inhibit tumour growth and progression using EP receptors antagonists or COX-2 inhibitors in different tumour models have been conducted in mice. Among others, EP receptors antagonists and/or COX-2 inhibitors reduced tumour growth and metastasis in experimental models of colorectal cancer ^{7,8}, lung carcinomas ⁹, gastro-intestinal cancer ^{10,11}, breast cancer ^{12,13}, prostate cancer ¹⁴ and pancreatic cancer ¹⁵.

PGE2 signalling via EP2R and EP4R can suppress the cytotoxicity and cytokine production of natural killer cells, skew the polarisation of tumour-associated macrophages towards tumour-promoting M2 macrophages, regulate the activation, expansion and effector function of both regulatory T cells and myeloid-derived suppressor cells, and down-regulate IFN- γ , TNF- α , IL-12 and IL-2 expression in immune cells.

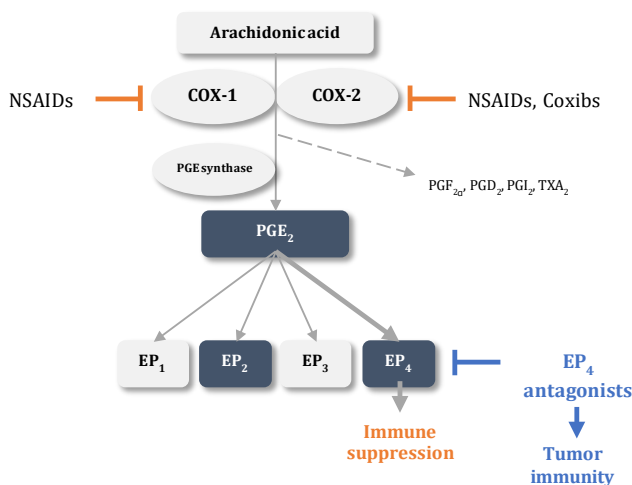
DT-9081 is an orally administered, small molecule EP4 receptor antagonist developed to overcome the immunosuppressive effects of PGE2 and reverse resistance to immune checkpoint blockers.

5.1.1. Mechanism of Action

DT-9081 is a small molecule compound that is a specific inhibitor of the prostaglandin receptor EP4R (Figure 5-1). Prostaglandins play a key role in mediating inflammatory responses, and their effects on differentiation of monocyte cells have been subverted by tumours to maintain an immunosuppressive tumour microenvironment (TME).

Through selective antagonism of EP4R, which is one the 4 receptors for prostaglandin E₂, DT-9081 inhibits the phosphorylation of cAMP response element binding protein (pCREB) of human CD4⁺ and CD8⁺ T lymphocytes. Through this mechanism, DT-9081 restores the production of TNF- α and IFN- γ , and inhibits IL-10, reversing the effect of T cell exhaustion. In parallel, DT-9081 induces the release of IL-2, essential for the proliferation and survival of T cells as well as the generation of effector and memory T cells. This mechanism of action is distinct from the T cell-targeting action of the immune checkpoint inhibitors (e.g., CTLA4 antibody, and PD1/PDL1 antibody).

Figure 5-1: Mechanism of Action of DT-9081



Abbreviations: COX1 = cyclooxygenase 1; COX2 = cyclooxygenase 2; coxib = cyclooxygenase inhibitor; EP1 = prostaglandin E receptor 1; EP2 = prostaglandin E receptor 2; EP3 = prostaglandin E receptor 3; EP4 = prostaglandin E receptor 4; NSAID = non-steroidal anti-inflammatory drugs; PGD₂ = prostaglandin D 2; PGE synthase = prostaglandin E synthase; PGE₂ = prostaglandin E 2; PGF_{2α} = prostaglandin F 2α; PGI₂ = prostaglandin I 2α; TXA₂ = thromboxane A2

5.1.2. Preclinical Summary

5.1.2.1. Pharmacology

DT-9081 selectively inhibits binding of PGE₂ to human EP₄ receptor and thus inhibits PGE₂-EP₄ mediated cellular signalling. Activity of DT-9081 is dependant of the presence of intact immune system. Daily administration of DT-9081 in immunocompetent mice showed significant *in vivo* antitumour activity in colorectal and sarcoma models of syngeneic murine tumours. Furthermore, the combination of DT-9081 with immune checkpoint blockade agents such as anti-CTLA4 antibodies or anti-PD1 antibodies showed significantly better activity compared with immunotherapies alone.

The number of complete responses (CR) was dramatically improved in combination therapies (DT-9081 with immunotherapies). In every model performed, all complete responder mice were rechallenged with similar tumours contralaterally; 100% of rechallenged mice fully rejected those tumours indicating an engagement of an efficient immune memory response. DT-9081 is thus considered as a novel cancer immune therapy that has potential therapeutic effects in multiple human tumour types.

5.1.2.2. Pharmacokinetics and Metabolism

Pharmacokinetic (PK) profiling of DT-9081 after oral administration in mouse, rat and dog were characterised by fast absorption (median t_{max} range: 0.4-4 h), extensive distribution (mean V_d range: 0.2-2 L/Kg), slow clearance (mean Cl range: 0.005-0.533 l/h/kg), and slow elimination (t_{1/2} range: 3.2- 29.2 h).

Bioavailability was high in all 3 species (%F range: 45 %-74 %) and was the highest in dog. Plasma protein unbound fraction of DT-9081 was 0.05 % to 0.3 %. The Ci/Cp ratio across species was

approximately between 0.53 and 0.70 suggesting an equal distribution between plasma and blood cells.

The major metabolites of DT-9081 were identified from cryopreserved hepatocytes of human, mouse, rat, beagle dog, mini-pig and monkey. No human-unique metabolite was found.

A potential of cytochrome P450 (CYP)-mediated drug-drug interaction (DDI) is predicted for CYP2C8 and CYP2C9 as DT-9081 is a reversible inhibitor of these two CYPs ($IC_{50} = 11.7$ and $3.2 \mu M$ respectively). DT-9081 did not induce any of the major CYP enzymes ($>20 \mu M$). DT-9081 did not show time-dependant inhibition of the 7 major human CYP tested. Regarding DDI with transporters, DT-9081 is likely to interact with concomitant medications which are substrates of OATP1B1 or OATP1B3 ($IC_{50} = 0.7$ and $7.4 \mu M$ respectively). DT-9081 is a weak inhibitor of BCRP ($IC_{50} = 114 \mu M$) and did not show any concentration dependent inhibition of permeability glycoprotein mediated transport. Human DT-9081 doses of 25 mg/day and 150 mg/day are predicted to sustain active drug concentration above human EP4R IC_{60} and IC_{90} respectively.

5.1.2.3. Toxicology and Safety Pharmacology

DT-9081 was assessed in repeated-dose oral toxicity studies of up to 1-month duration in male and female rats and dogs.

DT-9081 was generally well tolerated. In both species, there were dose-dependent clinical signs and minor reductions in reticulocytes, without histopathological correlate in the bone marrow. Gastrointestinal erosions or ulceration were observed in a small minority of rats at high doses after 28 days dosing. Following a 2-week recovery period, all DT-9081-related findings showed reversibility.

Safety pharmacology of DT-9081 was evaluated *in vitro* for hERG channel inhibition and *in vivo* on cardiovascular functions in dogs, respiratory and central nervous system (CNS) functions in rats. No significant adverse effect was observed in these studies. According to these findings, low risk of side effects in cardiovascular, respiratory and CNS system is anticipated for DT-9081 in humans.

Based on these observations with DT-9081 and on clinical safety of EP4R antagonists (ONO-4578, E7046) where adverse events (AEs) such as duodenal ulcers and duodenitis were reported, the gastrointestinal system may be the target organ in humans.

The proposed starting dose is a daily oral dose of 25 mg. It corresponds to 1/66 of the human equivalent dose (HED) of the NOAEL in dogs and to 1/58 of the HED of the NOAEL in rats.

Considering the results of the preclinical studies, the safety profile of DT-9081 seems reasonable in the intended population at the proposed clinical doses.

5.1.3. Rationale For Conducting the Trial

The neoplastic immune microenvironment is extremely complex, as virtually all immune cell types, including macrophages, polymorphonuclear cells, mast cells, natural killer (NK) cells, dendritic cells, and T and B lymphocytes, can infiltrate cancer tissues. The role of these immune cell types in tumour evolution and growth is diverse and is tightly linked to their inherent functions and to the molecules they express (e.g., cytokines or inhibitory ligands).

The prototypical anti-tumour immune cell is the CD8+ T lymphocyte, which can recognise tumour cells in an antigen-specific manner and secrete cytotoxic molecules to kill them directly.

Other immune cells, such as tumour-promoting M2 macrophages and immature granulocytic and monocytic cells (myeloid-derived suppressor cells [MDSCs]) can favour tumour progression through the induction of stromal cell proliferation, vascularisation, extracellular matrix deposition, and cell migration. These and other immune cells can also promote tumour progression by inhibiting the in situ immune response. The prototypical immunosuppressor cells are regulatory CD4⁺ T lymphocytes (Treg), which directly secrete or facilitate the formation of immunosuppressive molecules (e.g., IL-10, adenosine), and modulate the antigen presenting cells (APC) function (e.g., via CTLA-4–CD80/86 interactions).

The expression of inhibitory receptors (e.g., CTLA-4, PD-1, Lag-3) by tumour-infiltrating lymphocytes cells has gained significant attention in recent years in the oncology field. Many of these molecules are expressed on T and B cells upon activation, and their physiologic role is to inhibit the immune function once they bind to their respective ligand. Within the TME however, activation of these pathways induces and maintains immune tolerance. Recent clinical successes have focused interest on the potential of immune checkpoint inhibitors (ICIs) such as monoclonal antibodies to block these receptor-ligand interactions. However, the proportion of patients who achieve a response with ICIs remains generally modest. Solid tumours often display the capacity to limit immune induction or to mediate early immune shutoff both locally and systemically. Identifying the key mediators of resistance to immunotherapy allows the development of more robust treatments with more predictable responses. The PGE2/EP4R pathway plays a pivotal inhibitory role in relation to the cancer-immunity cycle (C-IC). PGE2 slows down the C-IC by inhibiting NK cells functions, suppressing the recruitment of APCs leading to tumours poorly infiltrated with activated CD8⁺ T lymphocytes. Furthermore, PGE2 activates immunosuppressive cells (Treg, MDSC, M2 macrophages). The absence or functional failure of effector CD8⁺ cells is suggested to be one reason for not responding to ICI therapies. For these therapies to be effective, it is important to overcome the tumour's capacity to prematurely shutdown or curtail an immune response. We demonstrated that DT-9081, an EP4R antagonist, can significantly and dramatically reduce tumour growth in combination with immunotherapies such as anti-PD1 or anti-CTLA-4 antibodies in colorectal and sarcoma syngeneic mouse models. In addition, DT-9081 converts several resistant mice to complete responder ones.

This original approach to targeting tumour-induced local defects in the immune system, therefore, appears to be uniquely capable of targeting the highly suppressive MDSC population in the tumour itself. As a result, resistant tumours can be sensitised to other commonly used immunotherapies, such as immune checkpoint blockade. The broad applicability of this approach would be especially exciting in the development of combination of DT-9081 with immunotherapies to produce more reliable and robust responses in a variety of solid tumours.

Due to its receptor selectivity, oral bioavailability, strong preclinical safety profile and unique antitumour mechanism, DT-9081 is an excellent candidate to be developed as a novel anti-cancer immune therapy by targeting immunosuppressive TAM/MDSC and reaction of CD4⁺ and CD8⁺ T cells. DT-9081 is intended to modify the immunosuppressive TME by inhibiting the accumulation of MDSC and TAM, the activation of CD4⁺ and CD8⁺ T cells, and thus permitting enhanced host immune responses against the tumour.

Also, preclinical data of DT-9081 in syngeneic murine MCA205 sarcoma model in combination with an anti-PD-1 antibody show that anti-tumour efficacy is superior when mice were treated in combination with an anti-PD-1 antibody compared to DT-9081 in monotherapy. The effects also translated into a significant improvement of survival with respect to the observed one upon

treatment with anti-PD-1 antibody alone and a significantly higher number of complete responder mice were observed in the combo groups.

Based on the safety assessments analysis and after Safety Review Committee consultation, once the dose-escalation phase will be completed, other cohorts in disease specific settings may be added to assess the safety of the combination of DT-9081 with immune checkpoint inhibitors (such as anti-PD1 or anti-PDL1) or other anticancer agents. This will be introduced by a protocol amendment.

5.2. Clinical Experience

This is a first-in-human study thus DT-9081 has never been administered to humans.

5.3. Summary of Potential Risks and Benefits

The potential benefits of study participation are that participants with advanced/recurrent/metastatic solid tumours may experience a reduction in tumour burden (with decreased symptoms and increased quality of life) or an improvement in progression free survival (PFS) as a result of treatment with DT-9081. No other benefits of participation are anticipated.

The potential risks of study participation include those associated with the medical evaluation, including venepuncture, biopsy, and imaging procedures as well as exposure to DT-9081. Based on the observations with DT-9081 during the animal toxicology studies and on the clinical safety data with other EP4 antagonist (ONO-4578 and E7046) in patients with advanced malignancies, where AEs such as nausea, diarrhoea, duodenal ulcers, duodenitis were reported, the gastrointestinal system may be the targeted organ in humans.

A summary of the pharmaceutical properties and known potential risks of DT-9081 is provided in the current version of the investigator brochure (IB). The principal investigator (or designee) must become familiar with all sections of the DT-9081 IB before the start of the study.

6. OBJECTIVES

Objectives	Endpoints
Primary	
<ul style="list-style-type: none"> To determine the RP2D of DT-9081 	<ul style="list-style-type: none"> Endpoints contributing to the determination of the RP2D will include safety, efficacy, predicted target inhibition, PD results and PK/PD simulations.
<ul style="list-style-type: none"> To assess the safety and tolerability profile of DT-9081 	<ul style="list-style-type: none"> 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 AEs will be assessed according to Common Terminology Criteria for Adverse Events (CTCAE) v 5.0.
Secondary	
<ul style="list-style-type: none"> To determine the MTD of DT-9081 (only applicable if MTD is reached within 8 escalation cohorts) 	<ul style="list-style-type: none"> Endpoints contributing to the determination of the MTD will be the DLTs
<ul style="list-style-type: none"> To determine the PK of DT-9081 	<ul style="list-style-type: none"> Pharmacokinetics parameters: C_{max}, T_{max}, $T_{1/2}$, area under the curve (AUC), apparent clearance and volume of distribution
<ul style="list-style-type: none"> To evaluate preliminary anti-tumour activity of DT-9081 according to RECIST v1.1 and iRECIST 	<p>Anti-tumour activity will be assessed with the following efficacy endpoints:</p> <ul style="list-style-type: none"> Objective response rate (ORR): the sum of complete response [CR] rate and partial response [PR] rate Best overall response (BOR) Clinical benefit rate (CBR)* Progression free survival (PFS) Duration of response (DOR)
<p>*CBR is 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</p>	

Exploratory	
To determine the PD activity of DT-9081 on soluble, cellular and intra cellular markers.	

6.1. Primary Objectives

Primary objectives include the following:

- To determine the recommended phase 2 dose (RP2D) of DT-9081
- To assess the safety and tolerability profile of DT-9081

6.2. 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

6.3. Exploratory Objectives

To determine the PD activity of DT-9081

7. STUDY DESIGN

7.1. Overall Study Design and Plan

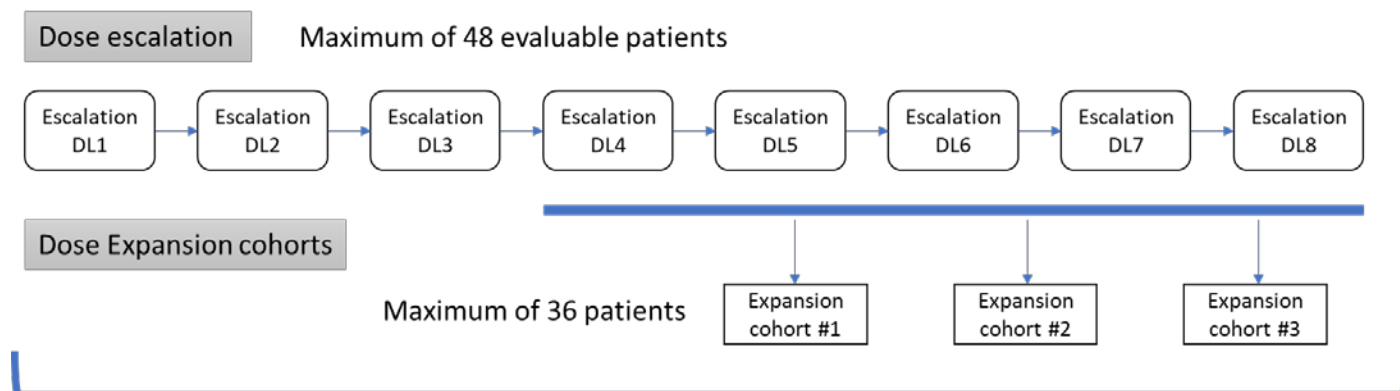
This phase 1, multicentre, open-label, dose-escalation clinical study is designed to determine the MTD and/or the Recommended Phase 2 Dose (RP2D) of DT-9081 in participants with advanced solid tumours. The study will be divided into 2 phases: a dose-escalation phase and a dose expansion phase. In both phases 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. [Figure 7-2](#) shows a schematic depiction of the study design for the dose escalation and expansion phases.

The Dose Escalation Phase will be based on a “3+3” modified design to ensure an efficient dose escalation. This phase will enrol a maximum of 48 evaluable participants in up to eight dose escalation cohorts at increasing levels (see [Figure 7-1](#)).

The Dose Expansion Phase will explore up to 3 dose levels and will enrol a maximum of 12 participants per Dose Expansion Cohort.

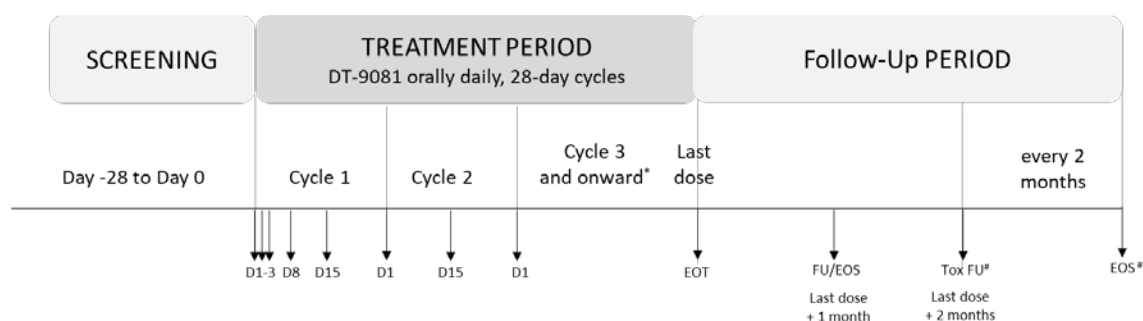
Participants must be at least 18 years of age and have histologically or cytologically confirmed advanced solid tumour that is locally advanced (i.e., not eligible for curative surgery or radiotherapy), recurrent, or metastatic, who have failed or are ineligible for standard of care therapies, measurable disease per Response Evaluation Criteria in Solid Tumors (RECIST) v1.1 and at least 1 accessible tumour lesion for biopsy. Participants will not be eligible if they have any unresolved AEs from previous immuno-therapy of \geq Grade 2 or anti-cancer therapies of $>$ Grade 2, if they use drugs interfering with the COX-2 pathways or if they are immunocompromised.

Figure 7-1: Overall Study Design



Abbreviations: D = day; DLT = dose-limiting toxicity; DL= dose level DL X= dose level X

Figure 7-2: Study Design for Dose Escalation and Expansion Phases



Abbreviations: D=day, EOS=End of study, EOT=End of treatment, FU=follow-up, Tox=toxicity

*Until disease progression, unacceptable toxicity, participant consent withdrawal

Only for participants who stopped treatment due to study drug toxicity until toxicity is resolved

Safety will be assessed by the occurrence and severity of treatment-emergent adverse events (TEAEs), treatment-related TEAEs and DLTs (severity will be assessed according to CTCAE v5.0). In addition, AEs, clinical laboratory test results, vital sign measurements, 12-lead electrocardiograms (ECGs) when applicable, and physical examination findings will be collected.

All AEs observed by the study personnel or reported by the participant during the study (from the time of the signing of the informed consent through the post-treatment visit) will be documented.

During the course of the study, several types of biomarkers will be assessed to further characterise the drug product (see section 10.3.2).

7.1.1 Dose-escalation Phase

7.1.1.1. Design

In the dose-escalation phase, participants will be recruited into cohorts in a 3+3 modified design and the DLT evaluation period will be 28 days per dose level. This phase will enrol 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. The dose escalation is capped at a maximum of 8 dose levels with a dose escalation limited to an increment of 100% from one dose level to the other.

Enrolment of participants to a new cohort requires completion of DLT evaluation of at least 3 participants treated in the current cohort. Should a DLT be observed in the first 3 to 5 participants enrolled, additional participants will be enrolled so that 6 participants are available for DLT evaluation.

The SRC will convene and review the safety data of the first 3 participants who complete the DLT observation periods and are evaluable for DLT evaluation. The SRC will also review any suitable available PK and PD data. The other participants enrolled at the same Dose Level who have not completed the DLT evaluation and have not experienced any DLT will be censored and not included in the dataset that will be reviewed by the SRC to authorize the escalation to the next dose level. Their safety data will be reviewed by the SRC at the next SRC meeting with all the safety data generated at lower doses. In the event that participants in the previous cohort experience DLTs after enrolment of participants to the next cohort has begun, dose level

assignment of the next participants will be based on the review of all the data generated from all assessed doses.

Throughout the study, a Safety Review Committee (SRC) comprised of at least two 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 (see Section 12).

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 administered.
- If only 3 participants were tested at the dose below 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 dose-limiting toxicity (DLT)

If the Dose Escalation does not define a MTD during the evaluation of the 8 dose levels planned during the study or if the Sponsor decides to not evaluate higher dose levels because the PK and PD data establish that the doses explored include the RP2D, the RP2D will be chosen as the dose level reached during the dose escalation with no more than 1/6 participants who experienced a DLT and with relevant PK/PD data.

7.1.1.1.1 Staggered dosing

This is a first-in-human clinical study therefore to ensure limited number of participants are exposed to the drug, a staggered dosing will be implemented for each cohort.

The first participant in each cohort will be observed for 7 days for DLTs. Then:

- If no DLT has been observed, the subsequent participants are dosed in that cohort.
 - If, after 28 days, the first 3 participants who have completed the DLT evaluation period have not experienced any DLTs, the next dose level will be opened.
 - If 1 participant experiences a DLT, the cohort will be expanded to 6 participants (i.e., 4th, 5th and 6th participants).
 - If 2 participants experience a DLT, dose escalation will be stopped.
- If a DLT is observed, the 2nd participant is dosed and observed for 7 days for DLT.
 - Then if no DLT has been observed, the 4 subsequent participants (i.e. 3rd, 4th, 5th and 6th participants) are dosed in that cohort.

- If, after 28 days, these 5 participants have not experienced any DLTs, the next dose level will recruit 3 new participants.
- If 2 participants experience a DLT, dose escalation will be stopped.
 - If a DLT is observed for the 2nd participant, dose level will be stopped.

7.1.1.2. Definition of Dose-Limiting Toxicity

7.1.1.3. Dose modifications due to Toxicities

For all the toxicities, DT-9081 doses will be modified in case of toxicity according to the SOC (system organ class). The toxicities will be graded according to the CTCAE V5.0.

A. Dose modifications Guidelines for immune-related adverse event (irAE) and other AE

An irAE, a subset of AEs, is defined as a clinically significant AE of any organ that is associated with study drug exposure, of unknown aetiology, and is consistent with an immune-mediated mechanism. Serologic, immunologic, and histologic (biopsy) data should be used to support an irAE diagnosis. Appropriate efforts should be made to rule out neoplastic, infectious, metabolic, toxin, or other etiologic causes of the irAE.

Additional information regarding management of immune-related adverse event (irAE) is available at : www.asco.org/supportive-care-guidelines

- DT-9081 must be discontinued in case of Electrocardiogram QT corrected interval prolongation (unless authorized by a specialist after cardiological consultation)

B. Dose modification Guidelines for Hepatic findings consistent with Hy's Law criteria

If Hy's law criteria are met in absence of cholestasis and other reasons for LFTs elevations, are excluded, the treatment will be permanently discontinued.

7.1.1.4. Intra-participant Dose Escalation

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

- For patients with no history of grade 3/4 toxicity related to DT-9081 with a persisting good ECOG (0 – 1)
- When 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

7.1.2. Dose Expansion Phase

The Dose Expansion will explore up to 3 dose levels to better characterize the safety, PK and PD of DT-9081. The dose levels selected for expansion will be those suggested to provide a sufficient exposure to DT-9081, based on the emerging PK data and only at dose levels determined to be safe during the Dose Escalation phase. Each Dose Expansion cohort will enrol a maximum of 12

participants. Based on the observed safety events in a given dose expansion cohort, the SRC will recommend the actions to be taken with the other ongoing cohort(s).

The Inclusion/Exclusion criteria set forth for the Dose Escalation phase will be used to select participants in the Dose Expansion phase.

Should more than one Dose Expansion cohort be opened at the same time, participants will be allocated to a particular Dose Expansion cohort by the Sponsor.

Like in the dose escalation 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 months 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. Enrollment will be discontinued in case of toxicity signal of high incidence is observed.

7.1.3. Recommended Phase 2 Dose

The RP2D of DT-9081 will be selected based on the totality of data from the Dose Escalation and will be optimized at the end of the Dose Expansion based on the totality of data available considering:

- Overall safety/tolerability profile (DLT, Grade 3 treatment related adverse events (TRAEs) occurring after the DLT observation period and incidence of long-lasting Grade 2 TRAEs)
- PK/PD data
- Available observations on efficacy

7.2. Rationale and Discussion of Study Design

The present study is an open-label, single-arm, phase 1 first-in-human clinical trial. This study will be conducted in 2 phases: a dose escalation phase and a dose expansion phase. The dose escalation phase is intended to evaluate the RP2D and the safety/tolerability profile of DT-9081. The Dose Expansion phase is intended to further characterize the safety, PK and PD of DT-9081. The study will enrol participants with advanced, recurrent or metastatic solid tumours who are ineligible for standard of care therapies. An open-label single-arm study is considered appropriate at this stage of the clinical development of DT-9081, with the present study being the first time DT-9081 has been administered in humans. Therefore, to ensure limited number of participants are exposed to the drug, a staggered dosing will be implemented for each cohort. (see Section 7.1.1.1.1)

Participants who are experiencing rapid disease progression as they may not benefit from DT-9081 will not be enrolled, as it will most likely not produce an immediate anti-cancer effect. Participants who are receiving COX-2 inhibitors are also excluded, since this may interfere with the mechanism of action of DT-9081. Additional exclusion criteria are intended to protect participant safety, and maintain the integrity of the data collected in the present study (see Section 8.2.2).

The dose escalation method proposed in this amendment will enable to enrol up to 5 participants before pausing and evaluating for DLTs, as long as the first two participants do not experience a DLT.

This approach is acceptable because:

- The GLP toxicology studies have not identified any DT 9081 toxicities at doses equivalent to 1650 mg/kg HED qd.
- Several anti EP4 have been administered at biologically active dose without major toxicities reported

7.3. Selection of Doses in the Study

The starting dose of the dose-escalation phase of DT-9081 will be 25 mg once daily and should be safe based on preclinical toxicology studies. It corresponds to 1/66 of the HED of the NOAEL in dogs and to 1/58 of the HED of the NOAEL in rats.

Using human dose prediction modelling based on the *in vitro* *in vivo* extrapolation correlation between *in vitro* hepatocyte clearance and *in vivo* clearance in rodent and non-rodent species, an oral dose of 25 mg is projected to sustain an unbound plasma concentration close to the IC₆₀ of DT-9081 for its target receptor *hEP4R*. In addition, this dose is projected to achieve a biologically effective blood concentration range based on pCREB inhibition and cytokine release modulation observed with DT-9081 in 2 distinct *ex vivo* assays in human whole blood.

From the nonclinical safety data, the human dose prediction correlated with the pharmacology and the biological activity, a starting dose of DT-9081 25 mg/daily is proposed as it is likely to be both safe and pharmacologically active.

Up to 8 dose-escalation cohorts at increasing levels are planned. Each cohort will be dosed at a maximum increment of 100% of the previous DT-9081 dose level depending on safety, tolerability, PK and PD parameters.

Enrolment of participants to a new cohort requires completion of DLT evaluation (the 28-day DLT evaluation period) of at least 3 participants treated in the current cohort. The decision will be made by the SRC and will be based primarily on safety assessments and on any suitable available PK and PD data.

A total daily dose of DT-9081 may be recommended by the SRC to be administered as 2 doses per day (morning and evening), provided the total daily dose is not exceeded. This may be required to improve tolerability of the investigational medicinal product (IMP). If necessary, this decision will be taken after discussion with the Sponsor medical monitor.

7.4. Study Sites

The study will take place at approximately 10 sites in France and Belgium. Each site is anticipated to screen a sufficient number of participants to enrol up to 48 evaluable participants in the dose escalation phase and up to 36 participants in the dose expansion phase. A study site with a high recruitment rate may be allowed to recruit more participants if other sites have slow enrolment.

7.5. End of Study Definition

A clinical study is considered completed when the last participant's last study visit has occurred.

8. PARTICIPANT POPULATION

8.1. Selection of Study Population and Diagnosis

This study is a first-in-human study. DT-9081 has never been administered to humans. According to the available non-clinical data of DT-9081 there are no sex-specific adverse effects known or to be expected. Thus, male and female participants could be included in the study. Up to 48 participants will be enrolled in the dose escalation phase and up to 36 participants in the expansion phase.

Due to the early development stage of DT-9081, enrolment will be limited to participants with advanced, recurrent or metastatic disease who are ineligible for standard of care treatment. Exclusion criteria, such as the exclusion of participants with pre-existing AEs from previous immunotherapies (\geq Grade 2) or from any unresolved toxicity from previous anti-cancer therapy ($>$ Grade 2 National Cancer Institute Common Terminology Criteria for Adverse Events v5.0) or participants who are taking drugs interfering with the COX-2 pathways, are intended to protect participants from potential risks associated with the use of DT-9081.

8.2. Study Entry Criteria

8.2.1. Inclusion Criteria

1. Participants must 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, and who have failed or are ineligible for standard of care therapies. Participants who are considered ineligible for standard of care therapies, may be eligible on discussion with the principal investigator (or designee). Such cases need to be agreed between investigator and Sponsor.
2. Participants must be ≥ 18 years of age on the day of signing the informed consent form.
3. Participants must have measurable disease per Response Evaluation Criteria in Solid Tumors (RECIST) v1.1 as assessed by local site investigator/radiologist. Lesions situated in a previously irradiated area are considered measurable if progression has been demonstrated in such lesions.
4. Participants must have at least 1 tumour lesion with location accessible to safely biopsy per clinical judgement of the treating physician (not previously irradiated, or >2 months (at screening) since last radiation and had tumour progression since radiation) and must consent to pre-treatment and on-treatment tumour biopsies for performance of correlative tissue studies.

Note:

- If the fresh biopsy cannot be collected, formalin-fixed paraffin-embedded block containing tumour tissue is required. These biospecimens must be recently obtained, meaning at or after progression on the most recent line of anticancer treatment. Participants for whom tumour tissue is not available and a new biopsy is not feasible, may be deemed eligible for study after consultation with the Sponsor.
- Once the Sponsor has considered that a sufficient number of biopsies have been collected, the paired-biopsy requirement will be waived for the next participants to be enrolled.

5. Participants must have an Eastern Cooperative Oncology Group (ECOG) performance status of 0 or 1.
6. Participants must have an international normalised ratio or activated partial thromboplastin time $\leq 1.5 \times$ upper limit of normal (ULN) unless participant is receiving anticoagulant therapies
7. Participants must have a life expectancy of at least 12 weeks according to the principal investigator (or designee's) judgement.
8. Participants must have adequate organ function defined as:

Haematology:

- Absolute neutrophil count $\geq 1000/\mu\text{L}$ or $\geq 1.0 \times 10^9/\text{L}$
- Platelets $\geq 75,000/\mu\text{L}$ or $\geq 75 \times 10^9/\text{L}$
- Haemoglobin $\geq 9.0 \text{ g/dL}$ or $\geq 5.59 \text{ mmol/L}$

Renal:

- Serum creatinine $\leq 1.5 \times$ ULN, or creatinine clearance (CrCl) $\geq 50 \text{ mL/min}$ using the Cockcroft Gault formula for participants in whom, in the principal investigator (or designee)'s judgement, serum creatinine levels do not adequately reflect renal function.
- Estimated glomerular filtration rate (eGFR) can be also used to assess renal function. Acceptable eGFR is $>40 \text{ mL/min/1.73m}^2$ per local laboratory.

Hepatic:

- Total bilirubin $\leq 1.5 \times$ ULN or direct bilirubin $\leq 1.5 \times$ ULN if total bilirubin is $>1.5 \times$ ULN. Total bilirubin ≤ 3 times the ULN in participants with documented Gilbert's Syndrome (unconjugated hyperbilirubinemia) or in the presence of liver metastases.
 - AST and ALT $\leq 2.5 \times$ ULN ($\leq 5 \times$ ULN for participants with liver metastases).
9. Participants who have no uncontrolled endocrinopathies. Participants with diabetes must have HbA 1c $< 7\%$.
 10. A female participant is eligible to participate if she is not pregnant and not breastfeeding, and at least one of the following conditions applies:
 - a. Not a woman of childbearing potential (WOCBP)
 - b. A WOCBP who commits to the consistent and correct use of a highly effective method of contraception throughout the study starting with the screening visit until 187 days after last dose of study drug. Highly effective methods of contraception include: combined (oestrogen and progesterone containing) hormonal contraceptive agents associated with inhibition of ovulation (oral, transdermal, or intravaginal); progesterone-only hormone contraception associated with inhibition of ovulation (oral, injectable, implantable); implantable contraceptive devices (intrauterine device, intrauterine hormone-releasing system); bilateral tubal occlusion; vasectomised partner or sexual abstinence.

Note: Hormonal contraception may be susceptible to interaction with the IMP, which may reduce the efficacy of the contraceptive method. Vasectomised partner must be the

WOCBP study participant's sole sexual partner and have had medical assessment of the surgical success. Sexual abstinence must be practised for the duration of the study. If a WOCBP has a positive or suspected positive urine pregnancy test within 72 hours prior to treatment, a serum pregnancy test will be required.

11. A male participant able to father a child must commit to the consistent and correct use of an effective method of contraception plus a highly effective method of contraception for the female partner starting with the screening visit and through 187 days after last dose of study drug.
12. The participant (or legally authorised representative if applicable) must provide written informed consent for the study in accordance with ICH-GCP and local legislation prior to admission to the study.
13. Participants must be able to swallow oral dose forms of medication.
14. Participants must be willing and able to comply with all aspects of this protocol.

8.2.2. Exclusion Criteria

1. Participants using drugs interfering with the COX-2 pathways or prohibited drugs (refer to section 9.7.2).

Note: Participants stopping the prohibited treatment 14 days or a duration exceeding 5 half-lives (if earlier) of its elimination prior to DT-9081 administration may be considered.

2. Participants with unresolved AEs from previous anti-cancer therapies of Grade ≥ 2 (National Cancer Institute Common Terminology Criteria for Adverse Events v5.0) with exception of alopecia. Participants with Grade ≤ 2 neuropathy may be eligible.
3. Participants who underwent major surgery or significant traumatic injury within 4 weeks prior to Cycle 1 Day 1 who have not recovered adequately from any AEs and/or complications from the intervention prior to starting study drug.
4. Participants who have received prior radiotherapy within the last 4 weeks before start of study drug treatment (limited field palliative radiotherapy within 2 weeks).
5. Participants who have received a live vaccine within 30 days prior to the first dose of study drug. Coronavirus disease 2019 (COVID-19) vaccines and booster are allowed >14 days before study initiation (Cycle 1 Day 1).
6. Participants who are currently participating in or have participated in a study of an investigational agent (e.g., small molecules, immunotherapy, chemotherapy monoclonal antibodies, or any other experimental drug in the neoadjuvant or adjuvant setting) or received prior systemic cancer-directed treatment within 30 days or at least 5 half-lives (whichever is shorter) prior to the first dose of study drug.
7. Participants who have already received EP4R antagonist in an investigational trial.
8. Participants who have a diagnosis of immunodeficiency or are receiving chronic systemic steroid therapy (in doses exceeding 10 mg daily of prednisone equivalent), or an average cumulative dose of >140 mg prednisone (or dose equivalent) within the last 14 consecutive days prior to treatment start or any other form of immunosuppressive therapy within 7 days

prior to the first dose of study drug. Inhaled non-absorbable and topical corticosteroid use is permitted as indicated.

9. Participants who have a known additional malignancy that is progressing or has required active treatment within the past 1 year.

Note: Participants with basal cell carcinoma of the skin, squamous cell carcinoma of the skin, or carcinoma in situ (e.g., breast carcinoma, cervical cancer in situ) that have undergone potentially curative therapy are not excluded.

10. Participants who have known active central nervous system metastases and/or carcinomatous meningitis. Participants with previously treated brain metastases may participate provided they are radiologically stable, i.e., without evidence of progression for at least 4 weeks by repeat imaging (note that the repeat imaging should be performed during study screening), clinically stable, no oedema, and without requirement of steroid treatment for at least 14 days prior to first dose of study treatment.
11. Participants who have an active infection including COVID-19 requiring systemic therapy.
12. Participants who have a known history of human immunodeficiency virus (HIV) infection.
13. Participants who have a known history of hepatitis B (HBV) (defined as HBV surface antigen reactive) or known active hepatitis C virus (HCV) (defined as HCV ribonucleic acid [qualitative] is detected) infection unless treated with no detectable virus.
14. Participants who have a history or current evidence of any condition, therapy or laboratory abnormality that might confound the results of the study, interfere with the participant's participation for the full duration of the study, or that means participation in the study is not in the best interest of the participant, in the opinion of the treating investigator.
15. Participants who have known psychiatric or substance abuse disorders that would interfere with cooperating with the requirements of the study.
16. Participants who have had an allogenic tissue/solid organ transplant.
17. Participants who have significant cardiovascular/cerebrovascular disease including, but not limited to, any of the following: New York Heart Association Class III or IV cardiac disease, myocardial infarction or transient ischemic attack/stroke within the last 6 months, unstable arrhythmias or unstable angina.
18. Participants with corrected QT interval calculated by the Fridericia formula >470 milliseconds (females) or >450 milliseconds (males).
19. Participants with known hypersensitivity to one of the excipients present in the IMP.
20. Participants with recent digestive ulcer who has recovered less than 12 months ago.

8.3. Participant Withdrawal

All participants will be advised that they are free to withdraw from participation in this study at any time, for any reason, and without prejudice. The principal investigator (or designee) should make every reasonable attempt to keep participants in the study taking participants' rights and safety into consideration; however, participants must be withdrawn from the study if they withdraw consent to participate. Investigators must attempt to contact participants who fail to attend scheduled visits by telephone or other means to exclude the possibility of an AE being the

cause of withdrawal. Should this be the cause, the AE must be documented, reported, and followed as described in Section 11.2.

If a participant is withdrawn before completing the study, the reason for withdrawal and the date of discontinuation will be recorded in the participant source documents.

8.4. Participant Discontinuation from the Study

An investigator must discontinue or withdraw a participant from the study for the following reasons (unless otherwise indicated):

- If any clinical AE, laboratory abnormality, or other medical condition or situation occurs such that, based on medical judgement, continued participation in the study would not be in the best interest of the participant. For participants who discontinue treatment due to toxicity, AEs will be followed up as described in Section 11.2.
- Disease progression: while imaging performed for treatment response assessment may display radiographical disease progression according to iRECIST. If clinical evaluation performed by the principal investigator (or designee) may suggest that the participant is receiving clinical benefit from treatment (e.g., no decline in ECOG-PS, improvement in cancer related symptoms), the participant can continue to receive the study treatment. Participants with suspected progression who are not experiencing unacceptable toxicity can continue to receive study treatment until radiological confirmation of progression is obtained, at the principal investigator's (or designee)'s discretion. In these situations, principal investigator (or designee)s should also consider what alternative treatments the participant may have available, so as not to withhold potentially beneficial anti-cancer treatments from these participants. This should be discussed with the Sponsor medical monitor. Participants with clinical progression (e.g., decline in ECOG-PS, impairment in cancer related symptoms) must stop the treatment.
- If the participant meets an exclusion criterion (either newly developed or not previously recognised) that precludes further study participation
- Pregnancy
- Significant study intervention noncompliance (see Section 13.1.2.2)
- Physician decision, includes any reason in the opinion of the Investigator that would justify treatment discontinuation

The Sponsor reserves the right to request the discontinuation of a participant due to protocol deviations or other reasons.

For more information regarding stopping rules during the dose-escalation phase, see Section 9.4

Whenever possible and reasonable, evaluations that were to be conducted at the completion of the study should be performed at the time of discontinuation.

Participants who discontinue treatment will attend the end of treatment visit and the follow-up visit 1 month after their last dose of DT-9081 (see the Schedule of Events in Table 2-1 and Table 2-2).

For participants who discontinue treatment due to DT-9081 related toxicity, they will attend the follow-up visit 1 month after their last dose of IMP and follow-up visits will continue every 2 months after their last dose of IMP until resolution of toxicity.

The reason for participant discontinuation from the study must be clearly documented in the participant source documents and on the appropriate eCRF.

A participant will be considered lost to follow-up if he/she fails to return for 2 scheduled visits and is unable to be contacted by the study site staff.

The following actions must be taken if a participant fails to return to the clinic for a required study visit:

- The site will attempt to contact the participant and reschedule the missed visit within the appropriate time window (see Schedule of Events, [Table 2-1](#) and [Table 2-2](#)) and counsel the participant on the importance of maintaining the assigned visit schedule and ascertain if the participant wishes to and/or should continue in the study.
- Before a participant is deemed lost to follow-up, the principal investigator or designee will make every effort to regain contact with the participant (where possible, 3 telephone calls and, if necessary, a certified letter to the participant's last known mailing address or local equivalent methods). These contact attempts should be documented in the participant's medical record or study file.

8.5. Participant Replacement Criteria

Within the dose-escalation phase, if a participant drops out prior to completion of the DLT assessment period for reasons other than the occurrence of a DLT, that participant will be replaced. Dropouts at subsequent cycles do not need to be replaced.

Participants who for reasons other than drug-related toxicity or a DLT, fail to complete 75 % of the planned total dose (equivalent to 21 out of 28 days) in the DLT evaluation period, will be replaced.

Within the expansion phase, withdrawn participants will not be replaced. If a substantial number of participants are withdrawn from this phase, the Sponsor will evaluate the need for developing replacement criteria.

All treated participants will be considered in the assessment of safety and tolerability.

Enrolled participants withdrawn from the study may not re-enter. The participant number for a withdrawn participant will not be reassigned to another participant.

9. TREATMENTS

9.1. Identification of Investigational Product

For this first-in-human study, DT-9081 is formulated as a blend in capsules and will be provided at different strengths: 25 mg (size 3 capsule), 50 mg (size 1 capsule) and 100 mg (size 00 capsule).

The manufacturer is Upperton Pharma Solutions, Albert Einstein Centre, Nottingham Science Park, Nottingham, UK, NG7 2TN.

9.2. Selection of Timing of Dose for Each Participant

Participants will take DT-9081 orally once daily continuously for 28-day cycles.

Capsules of 25 mg, 50 mg and 100 mg will be available and depending on the dose required, participants will need to take several capsules.

The daily dose will be taken at home in the morning with a glass of water at approximately the same time each day. Participants will be required to fast for 2 hours before and 2 hours after dosing.

Based on safety and tolerability data from the participants, the SRC can propose to split the daily dose to a twice daily dose for the next cohort in order to decrease toxicity. The decision to give the daily dose into twice daily will be made after discussion with Sponsor's medical monitor. In such cases, participants will take DT-9081 capsules in the morning and in the evening with a glass of water at approximately the same time each day. Participants will be required to fast for 2 hours before and 2 hours after the morning and the evening doses.

9.3. Dose Adjustment Criteria

For all the toxicities, DT-9081 doses will be modified in case of toxicity according to the SOC (system organ class). The toxicities will be graded according to the CTCAE V5.0. Please refer to section [7.1.1.3](#).

9.4. Stopping Rules

Stopping rules criteria at population level will be based on safety parameters such as taking into account frequency and severity of the adverse events.

Participants will be permanently discontinued from further treatment with DT-9081 for the dose escalation phase and the expansion phase (unless indicated otherwise) in the event of the following reasons:

- Any (S)AE that meets the study discontinuation criteria for all toxicities including immune-mediated toxicities at any time during the study:
 - Hy's law definition,
 - Grade 4 adverse event,
 - Grade 3 Electrocardiogram QT corrected interval prolongation (Unless authorized by a specialist after cardiological consultation)
 - Grade ≥ 3 immune-related AE (except if not a recurrence and resolved to Grade 1 or less within 7 days)
 - Recurrent grade 2 pneumonitis

- Progressive disease confirmed radiographically.
- Clinical progression: participant with clinically progressive disease and health status degradation without CT scan available will be advised to stop treatment.
- Physician decision, includes any reason in the opinion of the principal investigator (or designee) that would justify treatment discontinuation.
- Withdrawal of consent by participant: Withdrawal of consent to continue treatment (participants may leave the study at any time for any reason if they wish to do so, without consequence)
- Death
- Pregnancy
- Lost to follow-up
- Protocol deviation: Significant deviation/violation from the protocol or eligibility criteria (after discussion with the Medical Monitor(s) and confirmation from the Sponsor as not all deviations will require discontinuation) including noncompliance with study procedures
- Concurrent illness that prevents further administration of treatment
- Administrative reasons, including but not limited to,
 - study terminated by the Sponsor
 - site terminated by the Sponsor

If a participant is discontinued from study treatment, every effort will be made by the principal investigator (or designee) to complete and report the reasons for treatment discontinuation as thoroughly as possible in the participant source documents and on the appropriate eCRF. This includes end of treatment observations, as required by the protocol at the time of treatment discontinuation, or before initiation of a new treatment, whichever comes first, as well as follow-up evaluations. Participants who discontinue study treatment for any reason other than disease progression will have post-treatment follow-up visits every 2 months after their last dose of DT-9081 until resolution of toxicity, disease progression, initiation of non-study anti-cancer treatment, withdrawal of consent, or lost to follow-up.

9.5. Treatment Compliance

Study personnel will assess treatment compliance with DT-9081 regimens via capsule counts of returned medication reported on the IMP accountability logs and on the appropriate form in the eCRF and with the participant diary, if necessary, at every visit. The participant will record the date, time and number of capsules of each strength taken. If the participant missed a dose, this should also be recorded with a reason why the dose was missed. If the participant experiences symptoms, this should be recorded with the date and time, severity, frequency (if applicable) and any medication taken.

A participant who is not compliant will be counselled at each visit on the importance of taking the IMP as instructed.

In case of noncompliance to the treatment for 7 days or more due to non-safety reason during the DLT evaluation period, the participant will be considered as non-evaluable and should be replaced.

The Sponsor will be informed as soon as possible and a decision will be taken whether the participant should be withdrawn from the study.

9.6. Method of Assigning Participants to Treatment Groups

All participants will receive the IMP. In the dose escalation phase, participants will be assigned to a dose level according to the order of study entry. In the dose expansion phase, all participants will be enrolled and allocated to one of the dose expansion cohorts based on Sponsor decision.

9.7. Permitted and Prohibited Therapies

All concomitant medications used (including over-the-counter medications and herbal supplements) will be recorded in the participant source documents and on the appropriate eCRF.

9.7.1. Permitted Therapies

The following therapies other than the study drug are allowed during the conduct of this study:

- Prophylaxis for other study drug-related toxicities. Participants experiencing other study drug-related reactions may be premedicated with standard therapies to reduce the potential for such reactions in the future.
 - Treatment of study drug-related AEs: clinical judgement should be used in the management of any drug-related AE that occurs during the study, including the follow-up period.
 - Treatment of concurrent diseases: pre-existing/concurrent diseases or conditions should be managed and treated as clinically appropriate.
 - Blood products and growth factors: prophylactic haematopoietic growth factors should not be administered within 1 week prior to the first study drug dose; thereafter prophylactic use of growth factors is allowed as clinically indicated. Interventional/therapeutic use of growth factors is allowed during study, including Cycle 1, if deemed necessary by the principal investigator (or designee). Growth factor use must be consistent with product package insert instructions.
 - Bisphosphonates and denosumab: Bisphosphonates and denosumab for bone metastases and other skeletal conditions are allowed, provided the participant is on a stable dose for at least 1 month prior to the first dose of study drugs and remains on the stable dose while receiving study treatment.
 - Immunosuppressive or systemic hormonal therapy not exceeding 10 mg daily prednisone equivalent, as well as:
 - Hormonal therapy for appetite stimulation (e.g., Megace)
 - Nasal, ophthalmic, inhaled, and topical glucocorticoid preparations
 - Hormone replacement therapy at standard doses for adrenal insufficiency, hypothyroidism, or other endocrine end-organ failure
 - Stable hormonal therapy for ovarian suppression, hormonal contraceptive therapy, or postmenopausal hormone replacement therapy
- Note:** Concomitant therapies are permitted; however, participants must have been on a stable dose for at least 3 months prior to study start, and if continuing must remain on the stable dose while receiving study treatment (i.e., such treatment will not be considered as systemic hormonal therapy for the purpose of study eligibility).
- Steroid therapy for contrast reaction prophylaxis
 - Intra-articular steroid injections
 - Low-dose (<10 mg daily prednisone equivalent) maintenance steroid therapy for other conditions (e.g., asthma exacerbation, stable steroid therapy [excluding tapering dose of steroids] for brain oedema/metastases/radiation)

Participants requiring a minor surgical procedure (e.g., port placement, stent placement, skin abscess drainage) may continue at the principal investigator's (or designee)'s discretion following discussion with the Sponsor's Medical Monitor(s) or designee. A brief interruption in therapy may be considered. Participants requiring a more extensive or major surgical procedure (e.g., resection of hepatic metastases) should have protocol therapy interrupted but may resume treatment once fully recovered and at a minimum 2 weeks after the procedure. Protocol retreatment criteria must be met.

Other concomitant medications (other than those excluded by the study protocol) are allowed if they will not interfere with the trial medication, but should be limited to those medications considered necessary.

9.7.2. Prohibited Therapies

The following therapies are prohibited at screening and during the course of the study (unless used to treat a drug-related AE):

- Any antineoplastic agent for the primary malignancy not specified in this protocol.
- Immunotherapy not specified in this protocol.
- Any other investigational treatments.
- Radiation therapy for target lesions.

Note: radiation therapy to a symptomatic solitary non-target lesion, including a brain lesion, may be allowed after discussion with the Sponsor, and provided that it would not interfere with the assessment of the target lesion(s), as this would render the participant not evaluable for response by tumour assessment according to RECIST v1.1.

- Drugs interfering with the COX-2 pathway (including steroids, non-steroidal anti-inflammatory drugs [NSAID], COX-2 inhibitors, acetaminophen, aspirin). In case NSAIDs must be provided to the participant, the investigator must discuss with the Sponsor medical monitor to have the instruction on the study treatment management. Acetaminophen (paracetamol) will be authorized after the end of the DLT evaluation period.
- Drugs interfering with the arachidonic acid pathway including Quinacrine and corticosteroids (Systemic glucocorticoids >10 mg daily prednisone or equivalent for any reason other than to manage a suspected immune-mediated AE. The use of a physiological dose of corticosteroids for management of immune-mediated AEs may be acceptable).
- Use of sensitive substrates of CYP2C8 (repaglinide) and CYP2C9 (celecoxib).
- Use of strong CYP2C8 inhibitors (gemfibrozil) and CYP2C19 inhibitors (fluconazole, fluoxetine, fluvoxamine, ticlopidine).
- Use of strong CYP3A4 inhibitors. Examples include, but are not limited to ketoconazole, clarithromycin, indinavir, itraconazole, lopinavir, nefazodone, nelfinavir, ritonavir, saquinavir, telaprevir, and voriconazole.
- Use of strong CYP3A4 inducers. Examples include, but are not limited to apalutamide, carbamazepine, enzalutamide, mitotane, phenytoin, rifampicin, and St. John's wort

- Use of strong substrates of OATP1B1 and OATP1B3. Examples include, but are not limited to statins.
- Use of strong inhibitors of P-gp transporter (amiodarone, carvedilol, clarithromycin, dronedarone, itraconazole, lapatinib, lopinavir, propafenone, quinidine, ranolazine, ritonavir, saquinavir, telaprevir, tipranavir, verapamil).
- Use of strong inducers of P-gp (Apalutamide, Carbamazepine, Fosphenytoin, Green tea (*Camellia sinensis*), Lorlatinib, Phenytoin, Rifampin (rifampicin) and St. John's wort)
- Use of strong inducers of CYP2C19, CYP2C8, and CYP2C9 (rifampicin)
- Use of CYP2C9 inhibitors

An exhaustive list is available on Appendix E of this protocol.

Also caution should be used when administering drugs substrates of CYP3A4, P-gp and BCRP transporters.

- Prophylactic use of haematopoietic growth factors within 1 week prior to the first study drug dose; thereafter prophylactic use of growth factors is allowed as clinically indicated.
- Major surgery (excluding prior diagnostic biopsy).
- Herbal remedies with immunostimulating properties (e.g., mistletoe extract) or known to potentially interfere with major organ function (e.g., hypericin).
- Use of warfarin if participant has a history of acute immune-related thrombocytopenia.
- Use of live/live-attenuated vaccines against infectious diseases.

Participants receiving excluded therapies will be ineligible for study enrolment. The exclusion criteria describe other medications that are prohibited in this trial. Other supportive therapies not prohibited in this protocol may be taken at the investigator's discretion or after discussion with medical monitor.

9.7.3. Restrictions

Participants will be required to fast for 2 hours before and 2 hours after dosing with DT-9081.

The use of curcumin is not permitted during the course of the study as it inhibits the activity of the phospholipase A2.

Grapefruit juice or grapefruit should be avoided during the course of the study.

9.8. Treatment After End of Study

After the end of the study, each participant will be treated according to standard clinical practice.

9.9. Dispensing and Storage

The IMP supplied by Domain Therapeutics SA is to be used exclusively in the clinical study according to the instructions of this protocol. The IMP will be supplied on behalf of Domain Therapeutics SA for this study at no cost to the study participant. The principal investigator (or designee) is responsible for dispensing the IMP according to the dosage scheme and for ensuring proper storage of the IMP.

The principal investigator (or designee) must confirm the receipt of the IMPs with their signature. A copy of this receipt must be kept by the principal investigator (or designee).

Until the IMP is dispensed to the participants, it must be stored in at room temperature between 15-25°C and in a dry place in a securely locked area that is not generally accessible. The IMP should not be refrigerated or frozen and must be kept away from cold or heat sources.

The key to the storage area is to be kept by the principal investigator (or designee) responsible for the IMP. The store will be accessible only to those persons authorised by the principal investigator to dispense the IMP.

9.10. Drug Accountability

The principal investigator must maintain adequate records showing the receipt of all study drug, dispensing of study drug to each participant, and return of study drug by the participant. Information of the IMP in the records must include the date, quantity, batch or code number, and identification of participants (participant number) who received the IMP. The principal investigator will not supply the IMP to any person except those named as sub-investigators, designated study personnel, and participants in this study. IMP cannot be reassigned for use by other participants. If any of the IMP is not dispensed, is lost, stolen, spilled, unusable, or is received in a damaged container, this information must be documented and reported to the Sponsor and appropriate regulatory agencies, as required. The IMP may be relabelled when more data on stability are available. The procedure for this will be provided to the sites.

There will be 18 capsules in each bottle. On Cycle 1 Day 1, the participant will receive the appropriate number of bottles of each strength for the first 14 days and on Cycle 1 Day 15 the participant will receive the appropriate number of bottles of each strength for the following 14 days. Sites are authorized to deliver 2 bottles of DT-9081 at C1D1 if this is easier for their process. Any unused capsules must be returned by participants to the sites. From Cycle 2 onwards, the participant will receive the appropriate number of bottles of each strength for the 28 days of the cycle. Unused capsules must be returned at Day 1 of subsequent cycles.

9.11. Labelling and Packaging

Labelling and packaging of IMP will be performed by Sharp Clinical Services, Rhymney, UK.

9.11.1. Labelling

The bottles will have a label affixed that meets the applicable regulatory requirements and may include the following: IMP name, dosage strength, lot number, protocol number, specified number of capsules, caution statement, storage, and Sponsor identification.

The label on the bottles will be in 3 different languages (French, German, Dutch) i.e. the languages of countries where the study is to be performed. Labels are compliant with applicable regulatory requirements.

9.11.2. Packaging

Investigational medicinal products will be packaged in high-density polyethylene bottles of 18 capsules each.

9.12. Disposal and Destruction or Return

During the course of the study, at the site close out visit or at termination of the study all unused DT-9081, bottles and packaging will be destroyed locally based on Sponsor's request. Approval for destruction to occur at the site must be provided by the Sponsor in advance.

Destruction will occur following the site's standard procedures and certificates of destruction will be completed and provided to the Sponsor (copy retained by the site).

If the site is not able to destroy all used/returned/unused/expired bottles and DT-9081 capsules locally, the products will be returned to Sharp Clinical Services, Rhymney, UK following all local regulatory requirements for destruction.

No product should remain on site upon termination of the study.

10. STUDY PROCEDURES

Participants must provide written informed consent before any study-related procedures are initiated, including the cessation of prohibited concomitant therapy.

For the timing of assessments and procedures throughout the study, refer to the Schedule of Events (Section 2). Throughout the study, every reasonable effort should be made by study personnel to follow the timing of assessments and procedures in the Schedule of Events for each participant. If a participant misses a study visit for any reason, the visit should be rescheduled as soon as possible.

10.1. Study Duration

10.1.1. Overall Study Schedule

The overall study duration is expected to be 36 months (24 months of dose escalation, and 12 months of expansion phase).

The planned sequence and maximum duration of the study periods will be as follows:

1. Screening: 28 days.
2. Treatment: Participants will start the treatment at Cycle 1 Day 1 after the screening period. DT-9081 will be taken continuously in 28-day cycles until disease progression (clinical and/or radiological), unacceptable toxicity, or consent withdrawal from treatment for any reason. Treatment cycles will occur continuously without interruption.
3. Follow-up: 1 month after end of treatment visit and every 2 months after the last treatment dose until resolution of DT-9081 related toxicity.

10.2. Study Periods and Visits

10.2.1. Screening Visit

The participant must be screened within 28 days before the start of treatment. The following procedures will be carried out at screening:

1. Obtain written informed consent.
2. Assess inclusion/exclusion criteria.
3. Collect demographic information (including sex, year of birth, childbearing potential status, smoking and alcohol habits).
4. Record medical history, disease stage and date of diagnosis, prior cancer therapy and current therapies (e.g., prescription and non-prescription medications).
5. Perform a full physical examination and ECOG-PS.
6. Measure vital signs.
7. Collect AEs and SAEs from the date of signature of the ICF.
8. Perform 12-lead ECG. Triplicate measurements separated by 5 minutes will be performed.
9. Perform a cardiac echocardiography or multiple gated acquisition (MUGA) scan.
10. Perform blood chemistry analysis. Participants must fast before blood sampling.

11. Perform blood haematology analysis.
12. Perform blood coagulation tests.
13. Perform serology for Human Immunodeficiency Virus (HIV) or Hepatitis C Virus (HCV); and presence in the serum of the Hepatitis B surface antigen (HBsAg).
14. Perform urinalysis.
15. Perform a pregnancy test. A pregnancy test is mandatory for women of childbearing potential within 72 hours prior to the start of treatment. If the urine test is positive or cannot be confirmed as negative, a serum pregnancy test (β -hCG) will be required.
16. Perform tumour imaging, including a scan of the brain to exclude active metastases or leptomeningeal metastases if known brain metastases or clinically indicated, and computer tomography (CT) scans of abdomen, chest and pelvis. A magnetic resonance imaging (MRI) scan can be used if CT contrast is contra-indicated.
17. Perform clinical disease assessment.
- 18.
- 19.
- 20.
- 21.
- 22.

Note: tests performed prior to ICF signature per standard of care within 28 days prior to start of study treatment may not need to be repeated.

Procedures for rescreening participants who initially fail to meet study entry criteria are described in Section 14.3.

Assessments will be carried out in accordance with the Schedule of Events in Table 2-1 (dose escalation) or Table 2-2 (dose expansion).

10.2.2. During the Study Treatment Period

The treatment period is defined as the period from the day of the first treatment with DT-9081 until the day of the last treatment with DT-9081.

The time window allowed for the visits are:

- For Cycle 1 Days 8 and 15, ± 1 day
- Cycle 2, Days 1 and 15, ± 2 days
- Cycle 3, Day 1, ± 3 days
- Cycle 4 and onward, Day 1, ± 7 days

The following procedures will be carried out for both the dose-escalation and expansion phases of the study:

1. Perform a physical examination and ECOG-PS evaluation.
2. Measure vital signs.

10.2.3. End of Treatment Visit

The following procedures will be carried out:

1. Perform a full physical examination and ECOG-PS evaluation.
2. Measure vital signs.
3. Record concomitant medication use.
4. Collect AEs and SAEs.

5. Perform 12-lead ECG. Single measurement is required.
6. Perform a cardiac echocardiography or MUGA scan.
7. Perform blood chemistry analysis. Participants must fast before blood sampling.
8. Perform blood haematology analysis.
9. Perform blood coagulation tests.
10. Perform urinalysis.
11. Perform a pregnancy test
- 12.
13. Review participant diary.

Tumour imaging will be performed until disease progression every 8 weeks (± 1 week) during the first 4 cycles and then every 12 weeks (± 7 days). Tumour imaging will include CT scans of abdomen, chest and pelvis. An MRI scan can be used if CT contrast is contra-indicated. The same radiographic procedure must be used throughout the study. Assess disease response according to RECIST v1.1 and iRECIST. Perform clinical disease assessment. For participants who stopped treatment for reasons other than disease progression, tumour imaging should be performed within 8 weeks after the last tumour imaging.

Assessments will be carried out in accordance with the Schedule of Events in [Table 2-1](#) (dose escalation) or [Table 2-2](#) (expansion).

10.2.4. Follow-up Evaluation

Follow-up Evaluation will be performed 1 month after the last administration of DT-9081. If participant discontinues treatment due to toxicity, follow-up visits will occur every 2 months until resolution of DT-9081 related toxicity. The time window allowed for the visits is ± 7 days. The following procedures will be carried out:

1. Perform a full physical examination and ECOG-PS evaluation.
2. Measure vital signs.
3. Record concomitant medication use.
4. Collect AEs and SAEs.
5. Perform 12-lead ECG. Single measurement is required.
6. Perform blood chemistry analysis. Participants must fast before blood sampling.
7. Perform blood haematology analysis.
8. Perform blood coagulation tests.
9. Perform urinalysis.

Tumour imaging will be performed until disease progression every 8 weeks (± 1 week) during the first 4 cycles and then every 12 weeks (± 7 days). Tumour imaging will include CT scans of abdomen, chest and pelvis. A MRI scan can be used if CT contrast is contra-indicated. The same radiographic procedure must be used throughout the study. Assess disease response according to RECIST v1.1 and iRECIST and perform clinical disease assessment. For participants who stopped

treatment for reasons other than disease progression, tumour imaging should be performed within 8 weeks after the last tumour imaging.

Assessments will be carried out in accordance with the Schedule of Events in [Table 2-1](#) (dose escalation) or [Table 2-2](#) (dose expansion).

10.3. Assessments

10.3.1. Efficacy Variables

10.3.1.1. Response Evaluation Criteria in Solid Tumours v1.1 and iRECIST

Standard response criteria will be applied for disease assessments and response evaluations (RECIST v1.1 [[Appendix A](#)] and iRECIST [[Appendix B](#)]). Assessments should be performed at the intervals specified in the Schedule of Events (Section 2) and in the event of suspected progressive disease. The same method(s) of disease evaluation and the same technique should be used throughout the study.

Tumour imaging by CT or MRI (chest, abdomen, and pelvis) will be performed every 8 weeks (± 7 days) during the first 4 cycles and every 12 weeks (± 7 days) for the following cycles to assess the status of the underlying malignancy (refer to [Table 2-1](#) and [Table 2-2](#)). CT or MRI of the chest with each evaluation for disease assessment must be performed to assess for evidence of pulmonary fibrosis. The imaging schedule should follow calendar days and not be delayed for any dose interruptions that may occur.

For participants who stopped treatment for reasons other than disease progression, tumour imaging should be performed within 8 weeks after the last tumour imaging.

Use of contrast is preferred but is at the discretion of the principal investigator (or designee), as medically indicated. Participants with known or suspected CNS metastases will require baseline imaging to establish stability of known lesion(s), or to assess for appearance of new brain lesion(s), or progression of existing lesion(s). MRI imaging is preferred for assessment of CNS lesions.

For all imaging timepoints, lesions will be recorded as per RECIST v1.1 [[Appendix A](#)] and iRECIST [[Appendix B](#)].

Imaging data (imaging studies and derived assessments) will be stored according to usual practice by the sites and will be available upon request for potential review by the Sponsor or an independent radiology reviewer.

Response Assessment

Response will be assessed by the principal investigator or qualified designee and will be noted at each evaluation point as CR, PR, stable disease, progressive disease, or not evaluable (NE). Response should be confirmed per iRECIST by repeat imaging assessment not less than 4 weeks from the date the response was first documented or at the next scheduled scan (8-week interval from last scan), whichever is clinically indicated.

iRECIST will be used by the principal investigator (or designee) to assess tumour response and progression after initial radiographic progression per iRECIST v1.1; treatment decisions may be made accordingly. Assessments will be noted as iCR, iPR, iSD (stable disease), iUPD (unconfirmed progression), iCPD (confirmed progression) or NE. If initial disease progression is

verified by radiological assessment, the principal investigator (or designee) is advised to continue treatment if participant is stable until progression is confirmed by repeat imaging ≥ 4 weeks later. The principal investigator (or designee)'s decision to continue treatment while waiting for repeat imaging should be based on following criteria for assessing clinical stability of the participant:

- Absence of signs and symptoms of disease progression
- No decline in ECOG-PS
- Absence of rapid disease progression
- Absence of progressive tumour at critical anatomical sites (e.g., cord compression, etc.)
- Requiring urgent medical intervention for the disease

If repeat imaging shows $< 20\%$ increase in the tumour burden as compared to nadir and stable or improved set of lesions (target lesions and/or non-target lesions and/or new lesions that were identified as cause of initial progression), then the treatment may be continued/resumed and subsequent tumour imaging follow protocol schedule. If repeat imaging confirms disease progression due to any of the scenarios listed below, the participant should be discontinued from the study treatment:

- Tumour burden stays $\geq 20\%$ as per RECIST v1.1 with absolute increase of at least 5 mm as compared to nadir
- Non-target disease resulting in initial disease progression worsens (qualitatively)
- New lesion resulting in initial disease progression is worse (qualitatively)
- Additional new lesion(s) discovered since last evaluation

The principal investigator (or designee) should consider all lesions (target and non-target) in assessing the tumour burden at repeat imaging prior to making a decision whether to continue of treatment. When feasible, study treatment should be continued until disease progression is radiologically confirmed. Participants who are clinically unstable are not required to undergo repeat imaging for the confirmation of progressive disease.

Table 10-1: Imaging Treatment After First Radiological Evidence of Disease Progression

Scenario	Clinically Stable		Clinically Unstable	
	Imaging	Treatment	Imaging	Treatment
First radiological evidence of disease progression	Repeat imaging at ≥ 4 weeks to confirm disease status	Advised to continue study treatment while waiting confirmation scan	Repeat imaging at ≥ 4 weeks to confirm disease progression per principal investigator (or designee) discretion only	Discontinue treatment
Repeat scan confirms disease progression	No additional imaging required	Discontinue treatment (exception upon consultation with Sponsor)	No additional imaging required	N/A
Repeat scan shows stable disease, PR, or CR	Continue tumour Imaging assessment at scheduled intervals	Continue study treatment per principal investigator	Continue regularly scheduled imaging assessment	May restart study treatment if condition has improved and/or is clinically stable as

Scenario	Clinically Stable		Clinically Unstable	
	Imaging	Treatment (or designee) discretion	Imaging	Treatment per principal investigator (or designee) discretion

Abbreviations: CR = Complete Response; N/A= not applicable; PR = Partial Response .

Note: if a participant has confirmed radiological disease progression (2 scans at least 4 weeks apart demonstrating disease progression), but the participant is achieving a clinically meaningful benefit, an exception to continue treatment may be considered after consultation with the Sponsor.

10.3.2. Clinical Pharmacology

10.3.2.1. Pharmacokinetic Analysis Methods

The pharmacokinetic characterization of drug concentrations for each dose to be profiled will be performed through a noncompartmental analysis (NCA). Standard PK parameters assessed will include measures of the extent of absorption using estimates of the area-under-the-curve (AUC) and rate-of-absorption using the maximum concentration (C_{max}) and the time of C_{max} (T_{max}). Additional details of the parameters and their calculation and evaluation will be included in the SAP.

10.3.2.1.1 Pharmacokinetic Parameters

The PK parameter estimates will be completed using Phoenix WinNonlin (Pharsight Corporation). Actual sampling time will be used for all parameter estimation.

Table 10-2 shows the PK parameters that will be computed for each participant for samples obtained over the planned sampling intervals as data permit. Other PK parameters may be calculated if deemed necessary.

Table 10-2: Pharmacokinetic Parameters

Parameter	Description of Parameter
AUC	Area under concentration-time curve
C _{max}	Peak plasma concentration
T _{max}	Time of peak plasma concentration
T _{1/2}	Elimination half-life
CL	Apparent clearance
V _z	Volume of distribution

10.3.2.1.2 Sample Collection

Blood samples for PK analyses will be collected at the timepoints specified below:

Table 10-3: Pharmacokinetic Timepoints

Cycle / Day	Time point (h)	Pharmacokinetics sample
Cycle 1 / Day 1	Predose	X
	0.5 (\pm 5 min)	X
	1 (\pm 10 min)	X
	2 (\pm 15 min)	X
	4 (\pm 30 min)	X
	6 (\pm 30 min)	X
	10 (\pm 30 min)	X
Cycle 1 / Day 2	Predose	X
Cycle 1 / Day 3*	Predose	X
Cycle 1 / Day 8*	Predose	X
Cycle 1 / Day 15	Predose	X
	0.5 (\pm 5 min)	X
	1 (\pm 10 min)	X
	2 (\pm 15 min)	X
	4 (\pm 30 min)	X
	6 (\pm 30 min)	X
	10 (\pm 30 min)	X
Cycle 2 / Day 1*	Predose	X
	0.5 (\pm 5 min)	X
	1 (\pm 10 min)	X
	2 (\pm 15 min)	X
	4 (\pm 30 min)	X
	6 (\pm 30 min)	X
	10 (\pm 30 min)	X

*only in dose escalation phase

Each blood sample will be 5 mL in volume. The total amount of blood to be collected during screening period, Cycle 1 and first day of Cycle 2 Day 1 will be a maximum of 115 mL per participant for samples for PK parameters.

10.3.2.2. Pharmacodynamic, Pharmacogenomic and Other Biomarker Assessment Variables

10.3.2.2.1 Overview of Biomarker Approach

Table 10-4: Objectives of the Biomarkers Analyses

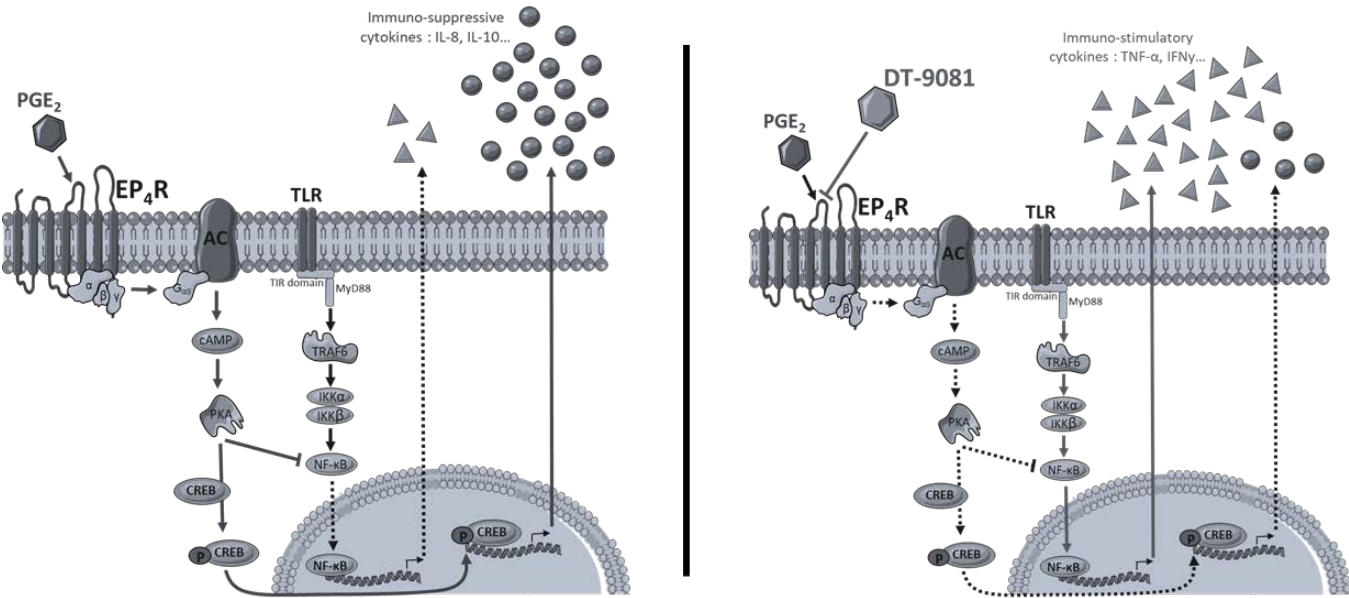
Type of samples	Analyses	Objective

10.3.2.2.2 Blood Samples

10.3.2.2.2.1 Biomarker Blood Sampling

[Figure 10-1](#) gives an overview of the changes induced by DT-9081, EP4R antagonist, on the PGE2-EP4R pathway.

Figure 10-1: Activity of PGE2 and EP4R Antagonist on the PGE2-EP4R Pathway.



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10.3.2.2.5 Transport and Storage of Biomarker Samples

All tumour tissue samples, urine samples, and other blood samples (other than those used for real-time analysis) will be stored at the end of this study and may be used for the purpose of further research. Samples for banking will be transported to the central lab ACM (23 Hospital Fields Road York, YO10 4DZ, UK) for banking on regular basis.

10.3.3. Safety Variables

Safety assessments will include the evaluation of AEs/SAEs, clinical laboratory assessments, ECOG assessment, vital signs, 12-lead ECGs, cardiac echocardiography, and physical examinations findings.

10.3.3.1. Clinical Laboratory Safety Assessments

10.3.3.1.1 Clinical Laboratory Tests to be Performed

Laboratory specimens will be analysed at local laboratories, as specified in the study laboratory manual. Samples for the following laboratory tests will be collected at the time points specified in the Schedule of Events (Section 2).

Table 10-7: Clinical Laboratory Parameters

Category	Parameters
Haematology	haematocrit, haemoglobin, platelet count, white blood cell total and differential (bands, basophils, eosinophils, lymphocytes, monocytes, neutrophils), red blood cell count and absolute neutrophil count
Clinical Chemistry	albumin, alkaline phosphatase, alanine aminotransferase, aspartate aminotransferase, lactate dehydrogenase, CO ₂ or bicarbonate, uric acid, calcium, chloride, glucose, phosphorus, potassium, sodium, magnesium, total bilirubin, direct bilirubin if total bilirubin is >ULN, total protein and blood urea nitrogen or serum urea level, measured or calculated creatinine and creatinine clearance. Glomerular filtration rate can be used instead of creatinine or creatinine clearance, amylase, lipase serology, creatine kinase, thyroid stimulating hormone, thyroxine and triiodothyronine, CRP, Troponine, D-Dimer.
Coagulation Panel	prothrombin time, partial thromboplastin time (activated) and international normalised ratio
Serology	HIV, HCV and detection of HBsAg
Urinalysis (dipstick)	Glucose, ketones, protein, and blood. Microscopic examination (if blood or protein is abnormal in dipstick analysis)
Pregnancy Test	for women of childbearing potential only

Abbreviations: HBsAg = Hepatitis B surface antigen; HCV = hepatitis C; HIV = human immunodeficiency virus; ULN = upper limit of normal

All blood samples for the clinical laboratory tests must be taken prior to study drug administration (can be collected up to 72 hours prior to the scheduled time point) and results reviewed prior to administration of study drug. Participants must fast before blood sampling and should be in a seated position during blood collection.

A significant laboratory abnormality will be qualified as an AE the participants source documents and will be recorded on the AE eCRF.

10.3.3.1.2 Specimen Handling Requirements

The transmission of infectious agents may occur through contact with contaminated needles and blood or blood products. Consequently, appropriate blood and body fluid precautions should be employed by all study personnel involved in the collection of blood and handling of specimens in both the clinic and laboratory settings. Refer to current recommendations of the appropriate authorities.

In addition to appropriate handling of participant samples, specific regulations exist regarding the shipment of biologic/etiologic samples. Procedures and regulations for the packaging and shipping of infectious samples are outlined in the study laboratory manual. The principal investigator (or designee) is responsible for ensuring that all study samples that are to be transported to another location are packed and shipped appropriately according to the applicable regulations.

10.3.3.1.3 Evaluation of Clinical Laboratory Values

The normal ranges of values for the clinical laboratory assessments in this study will be provided by the responsible laboratory and submitted to Domain Therapeutics SA or designee prior to the beginning of the study. They will be regarded as the reference ranges on which decisions will be made.

If a laboratory value is out of the reference range, it is not necessarily clinically relevant. The principal investigator (or designee) must evaluate the out-of-range values and record his or her assessment of the clinical relevance in the appropriate eCRF.

All clinical laboratory values that in the principal investigator (or designee)'s opinion show clinically relevant or pathological changes during or after termination of treatment must be reported as AEs/SAEs and followed, as described in Section [11.2.5](#).

All measurements described in this section are recognised standard methods.

10.3.3.2. Clinical Examinations

10.3.3.2.1 Vital Signs

Vital signs, including height (cm) (only assessed at screening), weight (kg), heart rate (beats per minute), respiratory rate (per minute), oxygen saturation (%), and sitting blood pressure (systolic and diastolic, mmHg) will be measured after the participant has been in a sitting position for at least 5 minutes. Temperature will also be measured (°C).

When vital signs need to be performed the same day as blood samples (PK, biomarkers etc.), the vital signs will be assessed prior to the blood sampling.

Any significant abnormality will be recorded in participants source documents and on the appropriate AE eCRF.

10.3.3.2.2 Twelve-lead Electrocardiogram

Standard 12-lead ECG will be performed with measurement of PR interval, QRS duration, QT interval, QTc interval (msec), and heart rate (beats per minute; bpm).

ECG will be performed:

- at screening
- prior to the study drug administration on Day 1 of Cycle 1 to Cycle 5 and then every 3 cycles. On Day 1 of Cycle 1, Triplicate measurements separated by 5 minutes will be performed at predose, postdose at 20 minutes (+/- 5min), 1 hour (+/- 10min), 2 hours (+/- 15min), 4 hours (+/- 30min), 6 hours (+/- 30min), 10 hours (+/- 30min) before blood sampling.
- at the end of treatment visit
- at the follow-up visit

Triplicate measurements separated by 5 minutes will be performed during the treatment period. For EOT and FU visit single measurement ECG is requested. ECG assessments will be made by the treating physician, in consultation with a cardiologist if appropriate.

ECGs at additional timepoints should be collected if clinically necessary. ECGs will be performed using the same calibrated instrument at each site and should be conducted after the participant has been supine (or semi-recumbent) for ≥ 10 minutes. ECGs will be evaluated locally. Participants with a QTc interval ≥ 500 msec should not be treated; dosing should be delayed.

In the event of ECG abnormalities suggestive of new evidence of myocardial ischemia while on study, isoenzyme analysis should be performed (to include at minimum CK-MB, serial troponins, and measurement of brain natriuretic peptide [BNP]).

A significant ECG abnormality will be recorded in participants source documents and on the appropriate AE eCRF.

10.3.3.2.3 Physical Examination

A full physical examination and ECOG-PS will be performed as indicated in the Schedule of Events. Documentation of the physical examination will be included in the participant source documents. Full physical examination to include heart, chest, abdomen, skin, oral cavity and lymph nodes.

A directed physical examination (e.g., specified examinations) will be performed as clinically indicated to include symptom-driven examination.

Significant findings will be recorded in participants source documents and on the appropriate AE eCRF.

10.3.3.2.4 Cardiac Echocardiography

Echocardiogram or MUGA will be performed for measurement of left ventricular ejection fraction in participants with a history of congestive heart failure. Individual participants should be followed with the same testing procedure throughout the study. Echocardiogram or MUGA assessments will be made by the treating physician, in consultation with a cardiologist if appropriate.

Significant findings will be recorded in participants source documents and on the appropriate AE eCRF.

10.3.3.3. Adverse Events

The definitions and management of AEs, and any special considerations for AEs, are provided in Section [11](#).

11. ADVERSE EVENTS

11.1. Definitions

11.1.1. Adverse Events

An AE is defined as any untoward medical occurrence in a participant or clinical investigation participant administered a pharmaceutical product that does not necessarily have a causal relationship with this treatment. An AE can therefore be any unfavourable and unintended sign (including an abnormal laboratory finding, for example), symptom, or disease temporally associated with the use of a medicinal product, whether or not related to the medicinal product.

Pre-existing diseases or conditions will not be considered AEs unless there is an increase in the frequency or severity, or a change in the quality, of the disease or condition. (Worsening of a pre-existing condition is considered an AE.)

11.1.2. Adverse Drug Reaction

All noxious and unintended responses to an IMP related to any dose should be considered adverse drug reactions (ADRs).

The phrase “responses to an IMP” means that a causal relationship between an IMP and an AE is at least a reasonable possibility, i.e., the relationship cannot be ruled out. All AEs judged by either the principal investigator (or designee) or the Sponsor as having a reasonable causal relationship to an IMP qualify as ADRs.

All AEs for which the judgement of relationship to IMP is “potentially related” or higher will be considered ADRs. If a relationship to IMP is not provided, then the AE must be treated as if it were “potentially related.”

11.1.3. Unexpected Adverse Event/Adverse Drug Reaction

An expected AE or ADR is one for which the nature or severity is consistent with the known AE profile of the product. For a pre-approval test product, the known information is contained in the IB. For a marketed product, the known information is contained in the current package insert for the product.

An unexpected adverse event (UAE) or unexpected adverse drug reaction is one for which the nature or severity of which is not consistent with the applicable product information (e.g., IB for an unapproved IMP or package insert/summary of product characteristics for an approved product). For example, hepatic necrosis would be unexpected (greater severity) if the IB only listed elevated hepatic enzymes or hepatitis. Likewise, cerebral thromboembolism and cerebral vasculitis would be unexpected (greater specificity) if the IB only listed cerebral vascular accidents.

Furthermore, reports that add significant information on specificity or severity of a known, already documented adverse reaction constitute unexpected events. Examples would be (a) acute renal failure as an expected adverse reaction with a subsequent new occurrence of interstitial nephritis (interstitial nephritis would be unexpected) and (b) hepatitis with a first occurrence of fulminant hepatitis (fulminant hepatitis would be unexpected.)

11.1.4. Serious Adverse Events/Drug Reaction

A serious adverse event (SAE) is any untoward medical occurrence that at any dose:

- Results in death
- Is life-threatening
Note: The term “life-threatening” in the definition of “serious” refers to an event in which the participant was at risk of death at the time of the event; it does not refer to an event that hypothetically might have caused death if it were more severe.
- Requires inpatient hospitalisation or prolongation of existing hospitalisation
Note: Inpatient hospitalisation is defined as 24 hours in a hospital or an overnight stay. An elective hospital admission to treat a condition present before exposure to the IMP, or a hospital admission for a diagnostic evaluation of an AE, does not qualify the condition or event as an SAE. Further, an overnight stay in the hospital that is only due to transportation, organisation, or accommodation problems and without medical background does not need to be considered an SAE. Hospitalisation planned for protocol requirements, hospitalisation for anticipated day-to-day fluctuations of pre-existing disease(s) or condition(s) present or detected at the start of the study that do not worsen and hospitalisation for device maintenance that was in place before study entry will not be considered as SAEs.
- Results in persistent or significant disability/incapacity
- Is a congenital anomaly/birth defect
Note: A congenital anomaly in an infant born to a mother who was exposed to the IMP during pregnancy is an SAE.
- Is an important medical event
Note: Medical and scientific judgement should be exercised in deciding whether it is appropriate to consider other situations serious, such as important medical events that may not be immediately life-threatening or result in death or hospitalisation but may jeopardise the participant or may require intervention to prevent one of the other outcomes listed in the definition above. Examples of such events are intensive treatment in an emergency room or at home for allergic bronchospasm, blood dyscrasias, or convulsions that do not result in hospitalisation, development of drug dependency or drug abuse.

Note:

Disease progression must not be considered as a SAE.

During screening period, only SAE related to study procedures must be reported.

11.1.5. Significant Adverse Events

Other significant AEs are defined as marked haematological and other laboratory abnormalities (other than those meeting the definition of serious) and any events that led to an intervention, including withdrawal of test drug, dose reduction, or significant additional concomitant therapy.

11.1.6. Treatment-emergent Adverse Events

An AE is defined as treatment emergent if the first onset or worsening is after the first administration of IMP and 30 days after the last administration of IMP.

11.1.7. Dose-limiting Toxicity

For a definition of DLT see Section [7.1.1.2](#).

11.2. Event Assessment and Follow-up of Adverse Events

The occurrence of an AE or SAE may come to the attention of study personnel during study visits and interviews of a study participant presenting for medical care or upon review by a study monitor.

All AEs including local and systemic reactions not meeting the criteria for SAEs will be captured on the appropriate eCRF. Information to be collected includes event description, time of onset, clinician's assessment of severity, relationship to study product (assessed only by those with the training and authority to make a diagnosis), and time of resolution/stabilisation of the event. All AEs occurring while on study must be documented appropriately regardless of relationship. All AEs will be followed to adequate resolution.

Any medical condition that is present at the time that the participant is screened will be considered as baseline and not reported as an AE. However, if the study participant's condition deteriorates at any time during the study, it will be recorded as an AE.

Changes in the severity of an AE will be documented to allow an assessment of the duration of the event at each level of severity to be performed. AEs characterized as intermittent require documentation of onset and duration of each episode.

The principal investigator (or designee) will record all SAEs and events of clinical interest for up to 90 days following cessation of treatment or until the participant initiates new anti-cancer therapy, whichever is earlier.

At each study visit, the principal investigator (or designee) will inquire about the occurrence of AE/SAEs since the last visit. Events will be followed for outcome information until resolution or stabilisation.

11.2.1. Assessment

The principal investigator (or designee) is responsible for the detection and documentation of events meeting the criteria and definition of an AE or SAE described previously. At each visit, the participant will be allowed time to spontaneously report any issues since the last visit or evaluation. The principal investigator (or designee) will then monitor and/or ask about or evaluate AEs using nonleading questions, such as

- “How are you feeling?”
- “Have you experienced any issues since your last visit?”
- “Have you taken any new medications since your last visit?”

Any clinically relevant observations made during the visit will also be considered AEs.

11.2.2. Evaluation

11.2.2.1. Severity of Adverse Events

The clinical severity of an AE will be classified as:

Mild	Usually transient and may require only minimal treatment or therapeutic intervention. The event does not generally interfere with usual activities of daily living.
Moderate	Usually alleviated with additional specific therapeutic intervention. The event interferes with usual activities of daily living, causing discomfort but poses no significant or permanent risk of harm to the participant.
Severe	Interrupts usual activities of daily living, or significantly affects clinical status, or may require intensive therapeutic intervention.

It is important to distinguish between severe AEs and SAEs. Severity is a classification of intensity whereas an SAE is an AE that meets serious criteria, as described in Section 11.1.4.

The clinical severity of an AE will be graded using CTCAE v5.0.

11.2.2.2. Seriousness

The principal investigator (or designee) is to evaluate whether the AE meets serious criteria, as described in Section 11.1.4.

11.2.2.3. Actions Taken

Actions taken may consist of:

Dose not changed	An indication that a medication schedule was maintained.
Dose reduced	An indication that a medication schedule was modified by subtraction, either by changing the frequency, strength, or amount.
Drug interrupted	An indication that a medication schedule was modified by temporarily terminating a prescribed regimen of medication.
Drug withdrawn	An indication that a medication schedule was modified through termination of a prescribed regimen of medication.
Not applicable	Determination of a value is not relevant in the current context.
Unknown	Not known, not observed, not recorded, or refused.

11.2.2.4. Outcome at the Time of Last Observation

The outcome at the time of last observation will be classified as:

- Recovered/resolved
- Recovered/resolved with sequelae
- Recovering/resolving
- Not recovered/not resolved
- Fatal*
- Unknown

*Only select fatal as an outcome when the AE results in death. If more than one AE is judged to be possibly related to the participant's death, the outcome of death should be indicated for each

such AE. Although “fatal” is usually an event outcome, events such as sudden death or unexplained death should be reported as SAEs.

11.2.2.5. Adverse Event Relationship to Investigational Product

The principal investigator (or designee) must assess each AE’s relationship to the IMP. The categories for classifying the principal investigator (or designee)’s opinion of the relationship are as follows:

Not related	An AE with sufficient evidence to accept that there is no causal relationship to IMP administration (e.g., no temporal relationship to drug administration, because the drug was administered after onset of event; investigation shows that the drug was not administered; another cause was proven.)
Unlikely related	An AE, including laboratory test abnormality, with a temporal relationship to IMP administration that makes a causal relationship improbable, and in which other drugs, events, or underlying disease provide plausible explanations.
Potentially related	An AE with a reasonable time sequence to administration of the IMP, but that could also be explained by concurrent disease or other drugs or events. Information on drug withdrawal may be lacking or unclear.
Probably related	An AE with evidence to suggest a causal relationship, and the influence of other factors is unlikely. The clinical event, including an abnormal laboratory test result, occurs within a reasonable time after administration of the study intervention, is unlikely to be attributed to concurrent disease or other drugs or chemicals, and follows a clinically reasonable response on withdrawal (dechallenge). Rechallenge information is not required to fulfil this definition.
Definitely related	An AE occurring in a plausible time relationship to IMP administration and that cannot be explained by a concurrent disease or other drugs or events. The response to withdrawal of the drug (dechallenge) is clinically reasonable.

The AE relationship to the IMP must be assessed separately by the principal investigator (or designee) and Domain Therapeutics SA.

11.2.3. Documentation

All AEs that occur within the period of observation for the study must be documented in participant source documents and in the appropriate eCRF with the following information, where appropriate. (The period of observation for the study is described in Section 11.2.)

- AE name or term
- When the AE first occurred (start date and time)
- When the AE stopped (stop date and time or an indication of “ongoing”)
- Severity of the AE
- Seriousness (hospitalisation, death, etc.)
- Actions taken
- Outcome

- Principal investigator (or designee) opinion regarding the AE relationship to the IMP

Any significant worsening or abnormality noted during interim or final physical examinations including vital signs, ECG, cardiac echocardiography or MUGA scans, laboratory results, any other potential safety assessment required or not required by protocol should also be recorded as a nonserious or serious AE, as appropriate, and reported accordingly.

11.2.4. Treatment of Adverse Events

Adverse events that occur during the study will be treated, if necessary, by established standards of care. If such treatment constitutes a deviation from the protocol, the participant should be withdrawn from the study and the reason must be documented in the participant source documents and in the appropriate eCRF. The decision about whether the participant may continue or not in the study will be made by the Sponsor after consultation with the principal investigator (or designee) and/or medical monitor.

If AEs occur in a participant that are not tolerable, the principal investigator (or designee) must decide whether to stop the participant's involvement in the study and/or treat the participant. Special procedures may be recommended for the specific IMP, such as the collection of a serum sample for determining blood concentrations of IMP, specific tapering procedures, or treatment regimens, as appropriate.

11.2.5. Follow-up

Any SAEs and events of clinical interest will be followed for up to 90 days following cessation of treatment or until the participant initiates new anti-cancer therapy, whichever is earlier. Any AE will be followed (up to 30 days after the last dose of IMP) to a satisfactory resolution, until it becomes stable, or until it can be explained by another known cause(s) (i.e., concurrent condition or medication) and clinical judgement indicates that further evaluation is not warranted. All findings relevant to the final outcome of an AE must be reported in the participant's medical record and recorded on the appropriate eCRF page.

11.2.6. Reporting

11.2.6.1. Adverse Events of Special Interest

Adverse events of special interest (AESIs) are events of scientific and medical interest specific to the further understanding of DT-9081 safety profile and require close monitoring and rapid communication by the investigator to the sponsor.

DT-9081 AESIs may be serious or non-serious.

The rapid reporting of these AESIs allows ongoing analysis of these events in order to characterize and understand them in association with the use of this investigational product.

DT-9081 selectively inhibits binding of PGE₂ to human EP₄ receptor and thus inhibits PGE₂-EP₄R mediated cellular signalling., thus promoting anti-tumour immunity and tumour cell killing.

Potential risks based on this mechanism of action of DT-9081 may be anticipate from the safety profile of other immune-stimulating agents that increase the anti-tumour immune response and, occasionally, induce detrimental immune-mediated reactions such as enterocolitis, dermatitis, hepatotoxicity or hepatitis, endocrinopathy, neuropathy and pneumonitis.

The class including anti-PD-L1 drugs and other immune checkpoint antibodies such as anti-PD-1 or anti-CTLA-4, have a wide spectrum of immune-mediated reactions that have been considered inflammatory in nature and can affect any organs of the body. These events are called immune-related adverse events because of their immune mediated mechanism. In the context of a limited clinical experience with DF-9081, the irAEs that have been observed with checkpoint inhibitors may provide a frame to define AESI and to enable the optimal detection, evaluation and mitigation.

The reporting of the AESI will be made to the CRO supporting the study pharmacovigilance department using an SAE form even if the event is not serious.

Pneumonitis

Pneumonitis has been reported in association with use of anti-PD-L1/anti-PD-1 antibodies. Initial work-up should include a high-resolution CT scan, ruling out infection, and pulse oximetry. Pulmonary consultation is recommended.

Hepatic Function Abnormalities (Hepatotoxicity)

Increased transaminases have been reported during treatment with anti-PD(L)-1, anti PD-1 and anti CTLA-4. Inflammatory hepatitis has been reported in 3% to 9% of subjects treated with anti-CTLA-4 MABs (eg, ipilimumab). The clinical manifestations of ipilimumab-treated patients included general weakness, fatigue, nausea and/or mild fever and increased liver function tests such as AST, ALT, alkaline phosphatase, and/or total bilirubin.

Hepatic function abnormality is defined as any increase in ALT or AST to greater than $3 \times \text{ULN}$ with or without a concurrent increase in bilirubin to greater than $2 \times \text{ULN}$ (which would define a Hy's law)).

Concurrent findings are those that derive from a single blood draw or from separate blood draws taken within 8 days of each other. Follow-up investigations and inquiries will be initiated promptly by the investigational site to determine whether the findings are reproducible and/or whether there is objective evidence that clearly supports causation by a disease (eg, cholelithiasis and bile duct obstruction with distended gallbladder) or an agent other than the investigational product.

If the underlying diagnosis for the hepatic function abnormality is known (including progression of pre-existing disease such as primary or metastatic malignancy), the diagnosis should be recorded as an AE/SAE.

If the underlying diagnosis for the hepatic function abnormality remains unknown, the term "hepatic function abnormal" should be used to report the AE/SAE.

Hepatic function abnormality of unknown aetiology, or which is considered attributable to investigational product, is required to be reported as "hepatic function abnormal" within 24 hours of knowledge of the event to the CRO supporting the execution of the clinical study using the SAE Report Form, even if the event is considered to be non-serious.

The investigator will review the data with the medical monitor. The investigator should then use clinical judgment to establish the cause based on local standard of care and follow the participant by conducting testing as clinically indicated.

During the GLP toxicology evaluation, the stomach and duodenum were identified as target organ because of the presence of gastritis and duodenitis at the highest dose, which may be a class effect because such events were also reported with other EP4 antagonists. Therefore, gastritis Grade 2

(defined as Symptomatic; altered GI function; medical intervention indicated) will be considered an AESI and be reported to the CRO PV department using an SAE report form, even if the event is not an SAE.

11.2.6.2. Serious Adverse Events

The principal investigator (or designee) must report all SAEs promptly to *Premier Research* (*scanned paper copy of SAE initial report*) within 24 hours of first becoming aware of the event by completing the Serious Adverse Event Report Form, verifying the accuracy of the information recorded in the form with the source documents and in parallel and within 24 hours after awareness entering all SAE report related data in the appropriate eCRF, and sending the SAE form to *Premier Research* by one of the following methods:

Email: PVDS-ROW@premier-research.com

Fax number:

This written report should be submitted on the SAE form provided for this purpose. At the time of first notification, the investigator or designee should provide the following information, if available:

- Protocol number
- Reporter (study site and investigator)
- Suspect IMP
- Participant's study number
- Participant's year of birth
- Participant's sex
- Date of first dose of IMP(s)
- Date of last dose of IMP(s), if applicable
- Adverse event term
- Date of occurrence of the event
- A brief description of the event, outcome to date, and any actions taken
- The seriousness criteria(on) that were met
- Concomitant medication at onset of the event
- Relevant medical history information
- Relevant laboratory test findings
- Principal investigator's (or designee's) opinion of the relationship to IMP(s) ("Is there a reasonable possibility that the IMP caused the SAE? Yes or No?")

During screening period, only SAE related to study procedures must be reported. Any missing or additional relevant follow-up information concerning the SAE should be sent to the Sponsor/Sponsor representative via the same contact details above as soon as possible on a follow-up SAE Report Form, together with the following minimal information (initial report, adverse

event, date of occurrence, participant identification [ID], study ID, IMP, and site number); this will allow the follow-up information to be linked to the initial SAE report.

Specific information may be requested by the Premier Research Pharmacovigilance Department using a follow-up request form via email communication.

The principal investigator (or designee) is required to comply with applicable regulations (including local laws and guidance) regarding the notification of his or her health authorities, IEC, principal and coordinating investigators, study investigators, and institutions. Each investigator is obligated to learn about the reporting requirements for investigators in his/her country. The study monitor may be able to assist with this.

11.2.6.3. Protocol Excluded Events

A pre-existing condition (i.e., a disorder that is present before the AE recording period starts and is noted on the medical history/physical examination form) should not be recorded as an AE unless the condition worsens, or episodes increase in frequency during the AE recording period.

AEs/SAEs occurring during the screening period (i.e. before the first DT-9081 intake) should not be recorded as AEs except if related to screening study procedures.

Progressive disease will not be captured as an AE as this will be recorded as part of the participant's efficacy evaluation. Progressive disease should be reported as an AE if the nature of the progressive disease is different to what is expected (i.e., signs/symptoms are not typical of progressive disease).

An abnormal laboratory value or an abnormal physiological test finding (e.g., ECG) need not be reported as an AE unless one of the following applies:

- The investigator considers the abnormality clinically significant.
- The event meets the definition of an SAE.
- The event requires an intervention.
- The event results in an action taken with the study drug(s) (e.g., dose delay and/or discontinuation).

Diagnostic and therapeutic non-invasive and invasive procedures, such as surgery, should not be recorded as AEs. A medical condition for which an unscheduled procedure was performed, should however be recorded if it meets the definition of an AE. For example, acute appendicitis should be recorded as the AE and not the appendectomy.

Procedures to support the treatment regimens, such as insertion of central venous catheters, etc., should not be recorded as AEs, unless the procedures result in complications.

Progressive disease will not be captured as an SAE unless the nature of the progressive is different than expected (i.e., signs/symptoms that are not typical of progressive disease). Elective surgery or other scheduled hospitalisation periods that were planned before the participant was included in this study are not to be recorded as SAEs, unless an outcome of the surgery/hospitalisation is considered serious.

Hospitalisation for observation or convenience prior to or following study drug(s) administration without an SAE occurring should not be recorded as an SAE, e.g., if a participant is hospitalised merely for observation, or if a participant begins or finalises the infusion at a time of day requiring a convenience overnight stay in the hospital.

Procedures to support the treatment regimen that require hospitalisation should not be recorded as SAEs; however, in cases where a procedure results in complications requiring/prolonging hospitalisation, this must be recorded and reported as an SAE.

11.2.6.4. Adverse Drug Reactions

All ADRs should be documented in the participants source documents and reported in the appropriate eCRF.

Suspected serious ADRs must be reported to the Sponsor immediately, regardless of the time elapsed since the end of the observation period.

11.2.6.5. Nonserious Adverse Events

Nonserious AEs will be documented in the participants source documents and recorded in the appropriate eCRF.

11.3. Special Considerations

11.3.1. Pregnancy

All WOCBP who participate in the study should be counselled on the need to practice adequate birth control and on the importance of avoiding pregnancy during study participation. A woman is considered of childbearing potential (WOCBP), i.e. fertile, following menarche and until becoming post-menopausal unless permanently sterile. Permanent sterilisation methods include hysterectomy, bilateral salpingectomy and bilateral oophorectomy. A postmenopausal state is defined as no menses for 12 months without an alternative medical cause. A high follicle stimulating hormone (FSH) level in the postmenopausal range may be used to confirm a post-menopausal state in women not using hormonal contraception or hormonal replacement therapy. A man is considered fertile after puberty unless permanently sterile by bilateral orchidectomy. The investigator or a designated associate is requested to advise the participant (WOCBP or men who have not undergone bilateral orchidectomy) how to achieve highly effective birth control method (failure rate of less than 1%). Such methods include: combined (estrogen and progestogen containing) hormonal contraception associated with inhibition of ovulation: oral, intravaginal, transdermal. Progestogen-only hormonal contraception associated with inhibition of ovulation: oral, injectable and implantable. Intrauterine device (IUD), intrauterine hormone-releasing system (IUS), bilateral tubal occlusion, vasectomised partner, sexual abstinence. In addition, the use of condoms by participants or their partners is required unless participant or partner is permanently sterile.

Women should be instructed to contact the principal investigator (or designee) or study staff immediately if pregnancy occurs or is suspected.

Pregnancy testing will be conducted prior to administration of the IMP on every WOCBP. A woman who is found to be pregnant at the Screening Visit will be excluded from the study and considered to be a screening failure.

If a pregnancy is reported, the principal investigator (or designee) will record pregnancy information on the appropriate form and submit it to the sponsor within 24 hours of learning of the pregnancy. While pregnancy itself is not considered to be an AE or SAE, any pregnancy complication affecting a female study participant that meets the SAE criteria must be reported as

an SAE. Abnormal pregnancy outcomes (e.g., spontaneous abortion, foetal death, stillbirth, congenital anomalies, ectopic pregnancy) are considered SAEs and will be reported as such. The participant will be followed to determine the outcome of the pregnancy. The principal investigator (or designee) will collect follow-up information on the participant and the neonate, and the information will be forwarded to the sponsor (see Section 11.2.6.2). Any post study pregnancy-related SAE considered reasonably related to the IMP by the principal investigator (or designee) will be reported to the sponsor (see Section 11.2.6.2). Any female participant who becomes pregnant while participating in the study will be discontinued from IMP.

End of treatment assessments are required as soon as possible after learning of the pregnancy. The principal investigator (or designee) is also responsible for following the pregnancy until delivery or termination. These findings must be reported on the SAE form and forwarded to the designated individual(s).

11.3.2. Overdose

An overdose is defined as the accidental or intentional administration of any dose of a product that is considered both excessive and medically important. For this study, any dose of IMP greater than the assigned dose, and considered excessive and medically important by the principal investigator (or designee), will be considered an overdose. The maximal dose of DT-9081 assigned to each participant should not be exceeded during the study.

Overdose that occurs during the study will be treated and documented as an AE or SAE if a serious criterion is fulfilled (see Section 11.2.6.2) and the quantity of the excess dose and the date and time must be documented in the participant source document and in the appropriate eCRF. In the event of an overdose, closely monitor the participant and laboratory abnormalities. Any AE associated with any overdose must be reported as an AE, or SAE if a serious criterion is fulfilled. If severe reactions occur in participants, study drug should be discontinued, and all appropriate supportive medical care should be instituted to ameliorate these potential AEs.

- Suspected abuse/misuse of an IMP
- Accidental or occupational exposure to an IMP
- Medication error, intercepted medication error, or potential medication error

Special reporting situations should be recorded on the AE page in the eCRF. Any special reporting situation that meets the criteria of an SAE should be recorded on the SAE page of the eCRF.

Decisions regarding dose interruptions or modifications secondary to an overdose will be made by the principal investigator (or designee) in consultation with the Sponsor Medical Monitor based on the clinical evaluation of the participant.

12. SAFETY REVIEW COMMITTEE

The SRC will evaluate all available safety and efficacy data. The SRC will review the data with the focus on safety and tolerability and to assess the risk/benefit profiles, or as required to consider other emerging safety issues.

Furthermore, the SRC (including at least two principal/site investigators, the PK subject matter expert, Premier Research's medical monitor and the Sponsor's medical monitor (or designee)) will meet prior to each dose-escalation to discuss the available PK and PD data, safety data and clinical findings of each participant. Confirmation by the SRC will not be required prior to a re-escalation to a previously administered higher dose. The SRC will also participate in the review and management of emerging safety issues, and will provide written documentation directly to the principal investigator (or designee) for inclusion in the trial master file. Details of the composition and standard operating procedures of the SRC will be given in a separate charter that will be finalised prior to the start of the study.

13. STATISTICS

13.1. Statistical Analysis

This section presents a summary of the planned statistical analyses. A statistical analysis plan (SAP) that describes the details of the analyses to be conducted will be written prior to database lock. Possible deviations from the planned analyses as described here will be mentioned in the SAP.

Unless otherwise indicated, all testing of statistical significance will be two-sided, and a difference resulting in a P value of ≤ 0.05 will be considered statistically significant.

In general, data will be summarised by cohort, phase and for the entire population.

Summary statistics will be provided for the variables described below. For continuous variables, these statistics will typically include the number of participants, mean, standard deviation (SD), median, minimum, and maximum. For categorical variables, these statistics will typically include the number and percentage of participants in each category.

13.1.1. Analysis Populations

The following 4 analysis populations are planned for this study:

- Safety population: All participants who receive at least 1 dose of DT-9081
- Evaluable population: 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 one post-baseline clinical disease assessment (clinical and/or radiological)
- Per Protocol population: All participants from the Evaluable population who don't have any major protocol deviation impacting the efficacy analysis and who also receive the planned daily dose of DT-9081 for at least 75% of the cycle duration in Cycle 2 (equivalent to 21 out of 28 days at the planned dose).
- PK population: All participants who receive at least one dose of DT-9081 and have at least one post-dose PK measurement available
- PD population: All participants who receive at least one dose of DT-9081 and have at least one post-dose PD measurement available

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

Baseline and safety data will be presented based on the Safety population using the actual treatment. Summaries of anti-tumour data will be based on the Evaluable population. Pharmacokinetic and pharmacodynamic analyses will be based on the specific analysis sets.

13.1.2. Study Participants and Demographics

13.1.2.1. Disposition and Withdrawals

The numbers of participants enrolled, screened, screen failed, treated, completing, and withdrawing, along with reasons for withdrawal, will be tabulated overall and by cohort, phase and for the entire population. The number of participants in each analysis population will be reported.

13.1.2.2. Protocol Deviations

A protocol deviation is any noncompliance with the clinical study protocol or ICH GCP and study plan requirements. The noncompliance may be either on the part of the participant, the investigator or the study staff. As a result of deviations, corrective actions are to be developed by the site and implemented promptly.

It is the responsibility of the site investigator to use continuous vigilance to identify and report any protocol deviations promptly. All deviations must be addressed in study source documents and reported to Premier Research or Domain Therapeutics SA. Protocol deviations must be sent to the reviewing IECs as per local regulations. The site investigator is responsible for knowing and adhering to the reviewing IEC requirements. Further details about the handling of protocol deviations will be included in the protocol deviation guidance plan.

Protocol deviations will be identified prior to database lock as major and minor deviations and will be listed.

13.1.2.3. Demographics and Other Baseline Characteristics

These analyses will be conducted for the Safety population. Demographics will be repeated for the Evaluable population.

Demographic variables will include age, sex, height, and weight. ECOG-PS at baseline will also be reported. Baseline participant characteristics will include medical history findings and disease history information such as tumour type and location of metastases.

Prior and concomitant medications will be summarized by treatment group, by the number and percentage of participants taking each medication, classified using the World Health Organization Drug Dictionary (WHO-DD) Anatomical Therapeutic Chemical (ATC) classification system.

13.1.3. Exposure and Compliance

Investigational medicinal product administration will be summarised in terms of number of cycles per participant, actual dose per cycle, and actual total dose. Descriptive statistics for these quantities, including the mean, median, SD, minimum, maximum, and 1st and 3rd quartiles, will be provided by cohort, phase, and for the entire population. 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. 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.

13.1.4. Safety and Tolerability Analyses

The primary analysis will be based on the Safety population.

The primary analysis for the dose-escalation phase will assess number and percentage of DLTs as described in Section [13.1.4.1](#).

The primary analysis for the expansion phase will assess safety and tolerability of DT-9081 as described in Section [13.1.4.1](#).

Safety analyses will be conducted using data from the safety population (as defined in Section [13.1.1](#)). Safety variables include treatment-emergent AEs, clinical laboratory values, vital

signs, ECG readings, cardiac echocardiography, and physical examination results. No formal inferential analyses will be conducted for safety variables, unless otherwise noted.

13.1.4.1. Adverse Events

All AEs will be coded using the Medical Dictionary for Regulatory Activities (MedDRA), Version 24.1 or higher.

Number and percentage of participants with DLTs will be summarised with associated 95% CI. DLTs will be presented in participant listings and by dose level in the escalation phase.

The number and percentage of participants with TEAEs as defined in Section 11.1.6 will be displayed for each cohort, phase, and for the entire population by system organ class and preferred term. Summaries of TEAEs by severity according to CTCAE grade v 5.0 and relationship to DT-9081 will also be provided. Serious TEAEs, TEAEs resulting in study discontinuation and fatal TEAEs will be summarized separately in a similar manner.

Participant listings of all AEs, SAEs and AEs causing study discontinuation will be produced.

13.1.4.2. Clinical Laboratory Evaluations

For haematology, serum chemistry, HBsAg, HCV and HIV serology and urinalysis parameters, descriptive summaries (mean, SD, median, minimum, and maximum) of actual (absolute) values and changes from baseline values will be presented for clinical laboratory values for each cohort, phase, and for the entire population at each scheduled time point.

The number of participants with clinical laboratory values categorized as below, within or above normal ranges, or other specific ranges of interest will be tabulated showing change from baseline (shift tables) for each clinical laboratory analyte by cohort, phase, and for the entire population and by study visit.

Laboratory values that are outside the normal range will also be flagged in the data listings and presented with the corresponding normal ranges. Any out-of-range values that are identified by the principal investigator (or designee) as being clinically significant will also be shown in a data listing.

Any other laboratory assessments will be provided in data listings.

13.1.4.3. Vital Signs

Descriptive summaries (mean, SD, median, minimum and maximum) of actual values and changes from baseline will be calculated for systolic blood pressure, diastolic blood pressure, heart rate (HR), respiratory rate, oxygen saturation, temperature, and weight.

The number of participants with vital signs values categorized as below, within, or above normal ranges or other specific ranges of interest will be tabulated showing change from baseline (shift tables) for each parameter by treatment group and by study visit.

13.1.4.4. Twelve-lead Electrocardiograms

The number and percentage of participants with normal and abnormal ECG findings will be summarized for each treatment group at each time point. Abnormal results will be grouped as clinically significant and not clinically significant.

A comparison of QT results will be presented. Summary statistics for baseline values at Screening, scheduled visits, and Follow-up will be displayed by cohort, phase, and for the entire population for QT and the QT interval corrected for heart rate (QTc) calculated using Bazett's and Fridericia's QT correction methods. In addition, the number and percent of participants by cohort, phase, and for the entire population who experienced a change >30 ms or a change >60 ms will be presented.

Descriptive summaries (mean, SD, median, minimum and maximum) will be presented for ECG measures of PR interval, QRS interval, QT interval, QTc interval (both correction methods), and HR by cohort, phase, and for the entire population at each scheduled time point.

13.1.4.5. Other Safety Findings

Physical examination findings will not be displayed but should be used to determine medical history or AEs.

Cardiac echocardiography assessments will be listed.

13.1.5. Efficacy Analysis

Efficacy variables will be summarized and analysed using the Evaluable or Per Protocol populations, unless otherwise specified.

13.1.5.1. Efficacy Endpoints

There are no primary efficacy endpoints in this study.

- The secondary efficacy endpoints are the following:
- Objective response rate
- Best overall response
- Clinical benefit rate
- Progression free survival
- Duration of response

13.1.5.2. Primary Analysis

There is no primary efficacy analysis in this study.

13.1.5.3. Secondary Analyses

Analyses of secondary endpoints will be performed for the Evaluable population by part and on the entire population. The ORR analysis will be repeated on the Per Protocol population.

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

minimum duration for stable disease, will have a best response of progressive disease. The same participant lost to follow-up after the first stable disease assessment will be considered NE.

Assessment based on RECIST v1.1:

Objective response at each tumour assessment will be calculated based on [Appendix Table 2](#). The best overall response of participants will be reported descriptively.

Number and percentage of participants with anti-tumour response according to RECIST v1.1 when confirmation of CR and PR required will be summarized based on [Appendix Table 3](#).

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 at least 6 months of stable disease after the start of treatment.

The PFS is defined as the time interval from the date of first 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 stable disease performed before participant study end. If a participant received prohibited 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. 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. A Kaplan-Meier plot will also be provided.

The DOR is defined as the time 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. DOR 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.

Assessment based on iRECIST:

After a participant has had an initial overall response of progressive disease using iRECIST v1.1 criteria the participant will be followed up using iRECIST based on [Appendix B](#).

Number and percentage of participants with anti-tumour response according to iRECIST will be summarized. iBOR will be calculated based on [Appendix B](#).

The iORR, based on the percentage of participants with a iCR or a iPR at any time during the study after iUPD, will be provided with the exact 95% CI using the Clopper-Pearson method. In the same way, analyses will be performed for the iCBR, based on the percentage of participants with a iCR, iPR at any time during the study after iUPD or at least 6 months of iSD after the start of iUPD.

The iPFS will also be calculated based on iRECIST using the first date at which progression criteria are met (ie, the date of iUPD) provided that iCPD is confirmed at the next assessment. If iUPD occurs, but is disregarded because of later iSD, iPR, or iCR, then 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 timepoint responses are all iUPD, and iCPD never occurs; or the participant dies from their cancer.

The iDOR is defined as the time from the date of the first documented iRECIST defined response (iCR or iPR) to the date of subsequent progressive disease (ie, 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. iDOR will be determined only for participants with a iCR or iPR. Summaries will be as for PFS and a Kaplan-Meier plot will be provided.

13.1.5.4. Exploratory, Corroborative, Sensitivity, and Other Analyses

Exploratory analyses related to PD activities are defined in Section [13.1.5.6](#).

13.1.5.5. Pharmacokinetics

For noncompartmental analysis, plasma concentrations will be listed and summarised at each time point using descriptive statistics; graphical representations will also be provided. The PK parameters will be summarised by dose using descriptive statistics. Testing of PK parameters will be outlined in the SAP.

13.1.5.6. Pharmacodynamics

The pharmacodynamic variables will be summarised using descriptive statistics based on the Pharmacodynamic population.

The following pharmacodynamic markers will be analysed descriptively to assess the PD activity:

13.1.6. Interim Analysis

No interim analyses are planned. Review of the data at end of each cohort will be conducted by the SRC.

13.2. Sample Size Determination

The sample size for the dose-escalation phase is based on a 3+3 modified design with up to 6 participants per cohort and with up to 8 dose levels.

Further cohorts may be initiated based on safety and PK data obtained in planned cohorts, which will include at least 3 evaluable participants each. Higher or lower doses, increase in cohort size, additional regimens (e.g., changing from once daily to twice daily) may be considered based on the decision of the SRC.

The sample size for the expansion phase is not based on formal statistical estimation since the goal is to monitor safety and assess efficacy only in an exploratory manner. The justifications for this

sample size are based on rationale about feasibility, precision about the mean and variance, and regulatory considerations¹⁶.

Dose Expansion Cohorts will be opened at Dose Levels suggested to provide a sufficient exposure to DT-9081, based on the emerging PK data generated during the Dose Escalation phase. There will be a maximum of 3 dose expansion cohorts explored in order to better characterize the safety, PK and PD of DT-9081. Each Dose Expansion Cohort will enrol a maximum of 12 participants.

14. STUDY CONDUCT

Steps to ensure the accuracy and reliability of data include the selection of qualified investigators and appropriate study sites, review of protocol procedures with the investigator and associated personnel before the study, periodic monitoring visits, and meticulous data management.

14.1. Sponsor and Investigator Responsibilities

14.1.1. Sponsor Responsibilities

The Sponsor is obligated to conduct the study in accordance with strict ethical principles (Section 16). The Sponsor reserves the right to withdraw a participant from the study (Section 8.3), to terminate participation of a study site at any time (Section 14.6.3), and/or to discontinue the study (Section 14.6.1).

Domain Therapeutics SA agrees to provide the principal investigator (or designee) with sufficient material and support to permit the principal investigator (or designee) to conduct the study according to the study protocol.

14.1.2. Principal Investigator (or Designee) Responsibilities

By signing the Investigator's Agreement (Section 18.1), the principal investigator (or designee) indicates that he or she has read the protocol carefully, fully understands the requirements, and agrees to conduct the study in accordance with the procedures and requirements described in this protocol.

Investigators should ensure that all persons who are delegated study-related responsibilities are adequately qualified and informed about the protocol, the IMP, and their specific duties within the context of the study. Investigators are responsible for providing Domain Therapeutics SA with documentation of the qualifications, GCP training and research experience for themselves and their staff as required by the Sponsor and the relevant governing authorities.

To ensure compliance with the guidelines, the study may be audited by an independent person. The investigator agrees, by written consent to this protocol, to cooperate fully with compliance checks by allowing access to all study documentation by authorized individuals.

14.1.3. Confidentiality and Privacy

Domain Therapeutics SA, as Data Controller, ensures that all processing activities involving personal data performed in the scope of this Study are compliant with, but not limited to, the requirements set by EU General Data Protection Regulation (GDPR 679/2016), its subsequent amendments and any additional national laws on Data Protection, recommendations and guidelines as applicable.

Participant confidentiality and privacy is strictly held in trust by the participating investigators, their staff, and the Sponsor and their interventions. This confidentiality is extended to cover testing of biological samples and genetic tests in addition to the clinical information relating to participants. Therefore, the study protocol, documentation, data and all other information generated will be held in strict confidence. No information concerning the study or the data will be released to any unauthorized third party without prior written approval of the Sponsor.

All research activities will be conducted in as private a setting as possible.

The study monitor, other authorised representatives of the Sponsor, representatives of the IEC, regulatory agencies, may inspect all documents and records required to be maintained by the investigator, including, but not limited to, medical records (office, clinic or hospital) and pharmacy records for the participants in this study. The clinical study site will permit access to such records.

The study participant's contact information will be securely stored at each clinical site for internal use during the study. At the end of the study, all records will continue to be kept in a secure location for as long a period as dictated by the reviewing IRB, institutional policies, or Sponsor requirements.

With the exception of the activities in the scope of the on-site monitoring, inspections, or audits, the name of the participant will neither be asked for, nor recorded by Domain Therapeutics SA. Study participant research data, which is for purposes of statistical analysis and scientific reporting, will not include the participant's contact or identifying information. Rather, individual participants and their research data will be identified by a unique study identification number. The study data entry and study management systems will be secured and password protected. At the end of the study, all study databases will be de-identified and archived.

The technical and organisational measures aiming to avoid unauthorised access, disclosure, dissemination, alteration or loss of information and processed personal data are described in Appendix F.

14.2. Site Initiation

Study personnel may not screen or enrol participants into the study until after receiving notification from the Sponsor or its designee that the study can be initiated at the study site. The study site will not be authorised for study initiation until:

1. The study site has received the appropriate EC approval for the protocol and the appropriate ICF.
2. All GCP documents have been submitted to and approved by the Sponsor or its designee.
3. The study site has a Clinical Trial Agreement in place.
4. Study site personnel, including the investigator, have participated in a study initiation meeting.

14.3. Screen Failures

Screen failures are defined as participants who consent to participate in the clinical study but are not subsequently assigned to the study intervention or entered in the study.

Participants who fail inclusion and/or exclusion criteria may be rescreened for the study after Sponsor's approval. If a participant is eligible to enter the study after having previously failed screening, the participant will be assigned a new participant identification number.

A minimal set of screen failure information is required to ensure transparent reporting of screen failure participants to meet the Consolidated Standards of Reporting Trials (CONSORT) publishing requirements and to respond to queries from regulatory authorities. Minimal information includes demography, screen failure details, eligibility criteria and any SAE.

14.4. Study Documents

All documentation and material provided by Domain Therapeutics SA for this study are to be retained in a secure location and treated as confidential material.

14.4.1. Informed Consent

Consent forms describing in detail the study intervention, study procedures and risks are given to the participant and written documentation of informed consent is required prior to starting intervention/administering study intervention.

Informed consent is a process that is initiated prior to the individual's agreeing to participate in the study and continues throughout the individual's study participation. Consent forms will be IEC-approved and the participant will be asked to read and review the document. The principal investigator (or designee) will explain the research study to the participant and answer any questions that may arise. A verbal explanation will be provided in terms suited to the participant's comprehension of the purposes, procedures and potential risks of the study and of their rights as research participants. Participants will have the opportunity to carefully review the written consent form and ask questions prior to signing. The participants should have the opportunity to discuss the study with their family or surrogates or think about it prior to agreeing to participate. The participant (or legal representative) will sign the informed consent document prior to any procedures being done specifically for the study. Participants must be informed that participation is voluntary and that they may withdraw from the study at any time, without prejudice. A copy of the informed consent document will be given to the participants for their records and a copy will be filed in the participant's source documents. The informed consent process will be conducted and documented in the source document (including the date). The rights and welfare of the participants will be protected by emphasising to them that the quality of their medical care will not be adversely affected if they decline to participate in this study.

14.4.2. Good Clinical Practice Documents

The GCP documents are listed below:

- Signed original protocol (i.e., Investigator's Agreement)
- Curricula vitarum of all investigators and sub-investigators
- Name and address of the laboratories
- List of laboratory reference ranges, and if available, a quality certificate
- Form Signature Log/Delegation of Study-related Duties
- Any other relevant GCP documents

The GCP documents must be received from the investigator and reviewed and approved by Domain Therapeutics SA or its designee before the study site can initiate the study and before Domain Therapeutics SA will authorise shipment of IMP to the study site. Copies of the investigator's GCP documents must be retained at the study site in a secure location. Additional documents, including a copy of the protocol and applicable amendment(s), the DT-9081 IB, eCRF completion guidelines, copies of regulatory references, copies of IEC correspondence, and IMP accountability records should also be retained as part of the investigator's GCP documents. It is

the investigator's responsibility to ensure that copies of all required GCP documents are organized, current and available for inspection.

14.4.3. Case Report Forms

By signing the Investigator's Agreement (Section 18.1), the investigator agrees to maintain source documentation as part of the case histories for all participants who sign an ICF and accurate eCRFs.

Case report forms are considered confidential documents and shall be secured against unauthorised access. The Sponsor or its designee will provide the necessary training on the use of the specific eCRF system used during the study to ensure that the study information is captured accurately and appropriately.

To ensure data accuracy, eCRF data for individual participant visits should be completed as soon as possible after the visit. All requested information must be entered in the electronic data capture (EDC) system according to the completion guidelines provided by the Sponsor or its designee.

The eCRFs must be reviewed and signed by the investigator or a sub-investigator. These signatures serve to attest that the information contained in the eCRF is accurate and true.

14.4.4. Source Documents

Information recorded in the EDC system should be supported by corresponding source documentation. Source data are all the information in original records and certified copies of original records of clinical findings, observations, or other activities in a clinical study necessary for the reconstruction and evaluation of the trial. Examples of acceptable source documentation include, but are not limited to, hospital records, clinic and office charts, laboratory notes, and recorded data from automated instruments, memoranda and pharmacy dispensing records.

14.5. Data Quality Control

Domain Therapeutics SA and its designees will perform quality control checks on this clinical study.

14.5.1. Monitoring Procedures

Domain Therapeutics SA and/or its designee will conduct site visits to monitor the study and ensure compliance with the protocol, GCP, and applicable regulations and guidelines. The assigned clinical research associate(s) (CRA[s]) will visit the principal investigator (or designee) and study site at periodic intervals and maintain periodic communication. The principal investigator (or designee) agrees to allow the CRA(s) and other authorized Domain Therapeutics SA personnel or designee access. The CRA(s) will maintain current personal knowledge of the study through observation, review of study records and source documentation, and discussion of the conduct of the study with the investigator and staff. While on site, the CRA(s) will review

- Regulatory documents, directly comparing entries in the EDC system with the source documents
- Consenting procedures
- AE/SAE procedures
- Storage and accountability of IP and study materials

The CRA will ask for clarification and/or correction of any noted inconsistencies. Procedures for correcting eCRF are described in the study plan. As representatives of the Sponsor, CRAs are responsible for notifying project management of any noted protocol deviations.

By signing the Investigator's Agreement (Section 18.1), the principal investigator (or designee) agrees to meet with the CRA(s) during study site visits; to ensure that study staff is available to the CRA(s) as needed; to provide the CRA(s) access to all study documentation, to the clinical supplies dispensing and storage area; and to assist the monitors in their activities, if requested. Further, the principal investigator (or designee) agrees to allow Domain Therapeutics SA or designee auditors or inspectors from regulatory agencies to review records and to assist the inspectors in their duties, if requested.

For additional information, please refer to the clinical monitoring plan.

14.5.2. Data Management

Domain Therapeutics SA or designee will be responsible for activities associated with the data management of this study. The standard procedures for handling and processing records will be followed per GCP and Premier Research's standard operating procedures. A comprehensive data management plan will be developed, including a data management overview, description of database contents, annotated eCRF, pre-entry review list, self-evident correction conventions, query contacts and consistency checks.

Study site personnel will be responsible for providing resolutions to all data queries in 10 days. The principal investigator (or designee) will be required to document electronic data review to ensure the accuracy of the corrected and/or clarified data. Procedures for soliciting and documenting resolution to data queries are described in the study plan.

14.5.3. Quality Assurance/Audit

This study will be subject to audit by Domain Therapeutics SA or its designee. Audits may be performed to check compliance with GCP guidelines and can include:

- Site audits
- Trial Master File audits
- Database audits
- Document audits (e.g., protocol and/or clinical study report [CSR])

Domain Therapeutics SA or its designee may conduct additional audits on a selection of study sites, requiring access to participant source documents, study documentation, and facilities or laboratories used for the study.

The study site, facilities, all data (including source data), and documentation will be made available for audit by quality assurance auditors and for IEC or regulatory authorities according to GCP guidelines. The principal investigator (or designee) agrees to cooperate with the auditor during the visit and will be available to supply the auditor with eCRFs or other files necessary to conduct that audit. Any findings will be strictly confidential.

If a regulatory authority informs the principal investigator (or designee) that it intends to conduct an inspection, the principal investigator (or designee) shall notify Domain Therapeutics SA immediately.

14.6. Study Termination

14.6.1. Regular Study Termination

The end of this study is defined as the date of the last visit of the last participant (last participant out or last participant last visit) participating in the study. Within 90 days of the end of the clinical study, Domain Therapeutics SA or designee will notify the IECs and regulatory authorities about the regular termination of the study as required according to national laws and regulations.

14.6.2. Premature Study Termination

The study may be temporarily suspended or terminated prematurely if there is sufficient reasonable cause at any time by Domain Therapeutics SA, IECs, regulatory authorities, respective steering committees, or the coordinating investigator. A decision to prematurely terminate the study is binding to all investigators of all study sites.

Within 15 days of premature termination of a clinical study, Domain Therapeutics SA or its designee will notify the IECs and regulatory authorities about the premature termination as required according to national laws and regulations. Domain Therapeutics SA or its designee must clearly explain the reasons for premature termination.

Circumstances that may warrant termination or suspension include, but are not limited to:

- Determination of unexpected, significant, or unacceptable risk to participants
- Demonstration of efficacy that would warrant stopping
- Insufficient compliance to protocol requirements
- Data that are not sufficiently complete and/or evaluable
- Determination that the primary endpoint has been met
- Determination of futility

If the study is terminated prematurely, all investigators have to inform their participants and take care of appropriate follow-up and further treatment of the participants to ensure protection of the participants' interests. Study sites may be asked to have all participants currently participating in the study complete all of the assessments for the End of Treatment Visit (see Section 2).

14.6.3. Study Site Closure

At the end of the study, all study sites will be closed. Domain Therapeutics SA may terminate participation of a study site at any time. Examples of conditions that may require premature termination of a study site include, but are not limited to, the following:

- Noncompliance with the protocol and/or applicable regulations and guidelines
- Inadequate participant enrolment

14.6.4. Record Retention

After completing the study, Domain Therapeutics SA will receive the original eCRFs or a legible copy and retain the documents for at least 25 years after the completion of the study. Source data is retained at the clinical sites until completion of the trial and then will be stored for a period of at least 25 years after the closure of the site.

14.6.5. Sample Retention

Samples may be used for purposes related to this research. The samples will be stored until the Sponsor has determined that specimens are no longer needed, and the decision has been made that none of the samples needs to be reanalysed. In addition, identifiable samples can be destroyed at any time at the request of the participant.

Data collected for this study will be analysed and stored by Domain Therapeutics SA.

After the study is completed, the de-identified, archived data will be transmitted to and stored by Domain Therapeutics SA for use by other researchers, including those outside of the study. Permission to transmit data to Domain Therapeutics SA will be included in the informed consent.

With the participant's approval and as approved by local IECs, de-identified biological samples (i.e., residual from biological samples collected for the purposes of this study) will be stored at a central laboratory (repository) chosen by the Sponsor, with the same goal as the sharing of data with future researchers. These samples could be used to research the causes of solid tumour progression, its complications, and other conditions for which individuals with advanced, recurrent, or metastatic solid tumours are at increased risk and to improve treatment. The central laboratory (repository) chosen by the Sponsor will also be provided with a code-link that will allow linking the biological specimens with the phenotypic data from each participant, maintaining the blinding of the identity of the participant.

During the conduct of the study, an individual participant can choose to withdraw consent to have biological specimens stored for future research.

Participants may withdraw consent at any time by contacting the study Investigator.

- If the medical records for the study are available, the Investigator will contact the Sponsor. The participant's specimens will be flagged in the biorepository and restricted to study use only. If specimens were collected from study participants specifically for future biomedical research, these specimens will be removed from the biorepository and destroyed. Documentation will be sent to the Investigator confirming withdrawal and/or destruction, if applicable. It is the responsibility of the Investigator to inform participants of the completion of the withdrawal and/or destruction, if applicable. Any analyses in progress at the time of request for withdrawal/destruction or already performed before the request is received by the Sponsor will continue as outlined in the original consent; no new analyses would be generated after the request is received.
- If the medical records of the participant are no longer available (e.g., if the Investigator is no longer required by regulatory authorities to retain the study records) or specimens have been completely anonymised, there will no longer be a link between the participant's personal information and their specimens. In this situation, the request for withdrawal of consent and/or destruction cannot be processed.

When the study is completed, access to study data and/or samples will be provided through requests to the Sponsor.

No information obtained from future biomedical research will be reported to the participant, family, or physicians. If important research findings are discovered, the results may be published, presented at scientific meetings, and/or provided on a public website in order to rapidly report this

information to doctors and the public. Participants will not be identified by name in any published reports about the future biomedical research or in any other scientific publication or presentation.

14.7. Changes to the Protocol

This protocol cannot be altered or changed except through a formal protocol amendment, which requires the written approval of Domain Therapeutics SA. The protocol amendment must be signed by the principal investigator and approved by the IEC/appropriate regulatory agency(s) before it may be implemented. Protocol amendments will be filed with the appropriate regulatory agency(s) having jurisdiction over the conduct of the study.

14.8. Use of Information and Publication

All information concerning DT-9081, Domain Therapeutics SA's operations, patent applications, formula, manufacturing processes, basic scientific data, and formulation information supplied by Domain Therapeutics SA or its designee to the principal investigator, and not previously published, is considered confidential and remains the sole property of Domain Therapeutics SA. Case report forms also remain the property of Domain Therapeutics SA. The principal investigator agrees to use this information for purposes of study execution through finalisation and will not use it for other purposes without the written consent of the Sponsor.

The information developed in this study will be used by Domain Therapeutics SA in connection with the continued development of DT-9081 and thus may be disclosed as required to principal investigators or government regulatory agencies.

The information generated by this study is the property of Domain Therapeutics SA. Publication or other public presentation of DT-9081 data resulting from this study requires prior review and written approval of Domain Therapeutics SA. Abstracts, manuscripts, and presentation materials should be provided to Domain Therapeutics SA for review and approval at least 30 days prior to the relevant submission deadline. Data from individual study sites must not be published separately.

It is agreed that the results of the study will not be submitted for presentation, abstract, poster exhibition, or publication by the principal investigator until Domain Therapeutics SA has reviewed and commented on such a presentation or manuscript for publication. If applicable, this study will be registered at ClinicalTrials.gov, and results information from this study will be submitted to ClinicalTrials.gov.

15. FINAL CLINICAL STUDY REPORT

It is an EU requirement that the final CSR be written within 1 year of study completion.

Domain Therapeutics SA will retain ownership of the data.

The final CSR will be written within 1 year of completion of the clinical part of the study. This report will include a summary of the study results based on a statistical evaluation and clinical assessment of the protocol-defined endpoints.

The final CSR may be submitted to the regulatory authorities.

16. ETHICAL AND LEGAL CONSIDERATIONS

16.1. Declaration of Helsinki

This study will be conducted in compliance with the April 1996 ICH Guidance for Industry GCP E6 (including archiving of essential study documents), the Integrated Addendum to ICH E6 (R2) of November 2016, the Declaration of Helsinki, the applicable regulations of the country(ies) in which the study is conducted, and with European Regulation No. 536/2014.

See Appendix G for regulation and guidelines.

16.2. Participant Information and Informed Consent

According to the Declaration of Helsinki and ICH GCP, participants must provide their written informed consent prior to enrolment in a clinical study and before any protocol-specified procedures are performed. Participants must declare their consent by personally signing and dating the ICF. The written ICF will embody the elements of informed consent as described in the Declaration of Helsinki and will also comply with local regulations.

Each participant should be made aware by the principal investigator (or designee) of the nature of the study (objectives, methods and potential hazards and benefits) and the procedures involved, using the information on the ICF. Information should be given in both oral and written form whenever possible and deemed appropriate by the IEC. Participants, their relatives, or, if necessary, legal representatives must be given ample opportunity to inquire about details of the study.

Participant information and the ICF must be in a language fully comprehensible to the prospective participant. The written information must be provided to the participant to give him or her sufficient time to understand the information and to prepare questions before being asked for his or her consent. The principal investigator (or designee) must confirm that the text was understood by the participant. The participant will then sign and date the IEC-approved consent form indicating that he or she has given his or her consent to participate in the study. The signature confirms that the consent is based on information that has been understood. The form will also be signed by the principal investigator (or designee) obtaining the consent and annotated with the study participant number. Each participant's signed ICF must be kept on file by the principal investigator (or designee) for possible inspection by regulatory authorities, Domain Therapeutics SA, and/or the Sponsor's designee. Collection of informed consent and/or assent has to be documented on the eCRF.

Furthermore, the participant will be informed that if he or she wishes to drop out or withdraw (see Section 8.3) at any time during the study, this will not have any negative consequences. Participants may be withdrawn by the principal investigator (or designee) if any change related to safety or ethics precludes further participation in the study. Participants will be asked to agree to a final assessment in the event of an early termination of the study.

Participants will be informed that data from their case may be stored without inclusion of their name and that such data will not be revealed to any unauthorized third party. Data will be reviewed by the monitor, the sponsor or designee, and possibly by representatives of regulatory authorities and/or IECs. The terms of the local data protection legislation will be applied as appropriate.

16.3. Approval by Independent Ethics Committee

A valid IEC must review and approve this protocol before study initiation. Written notification of approval from the IEC needs to be available before shipment of investigational drug supplies, and will include the date of the committee's approval and the chairperson's signature.

Until written approval by the IEC has been received by the Sponsor, no participant may undergo any procedure not part of routine care for the participant's condition.

Protocol amendments must also be reviewed and approved by the IEC. Written approval from the IEC, or a designee, must be received by Domain Therapeutics SA before implementation. This written approval will consist of a completed IEC Approval written documentation.

16.4. Finance and Insurance

Details on finance and insurance will be provided in a separate agreement between the principal investigator (or designee) and the Sponsor.

17. REFERENCES

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16. Julious SA. Sample size of 12 per group rule of thumb for a pilot study. *Pharmaceutical Statistics*. 2005;4(4):287-291.

18. ATTACHMENTS

18.1. Investigator's Agreement

PROTOCOL NUMBER: DT-9081-CLI-001

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

FINAL PROTOCOL: 09-JAN-2024

The undersigned acknowledges possession of and has read the product information (e.g., Investigator's Brochure) on the IMP and has discussed these data with the study monitor. Having considered fully all the available information, the undersigned considers that it is ethically justifiable to give the IMP to selected participants in his/her care, according to the study protocol.

He or she agrees to use the study material, including IMP, only as specified in the protocol. He or she understands that changes cannot be made to the protocol without prior written approval of Domain Therapeutics SA.

He or she understands that any deviation from the protocol may lead to early termination of the study.

He or she agrees to report to Domain Therapeutics SA within time any clinical AE or abnormal laboratory value that is serious, whether or not considered related to the administration of IMP.

He or she agrees to comply with Domain Therapeutics SA and regulatory requirements for the monitoring and auditing of this study.

In addition, he or she agrees that the study will be carried out in accordance ICH, the Declaration of Helsinki, and the local laws and regulations relevant to the use of new therapeutic agents.

I, the undersigned, have carefully read this protocol and agree that it contains all the necessary information required to conduct the study.

Principal Investigator:

Printed Name:

Signature:

Date:

Investigator's name and address (stamp)

APPENDICES

- A. Response Evaluation Criteria in Solid Tumors (RECIST) v1.1
- B. iRECIST Criteria
- C. Performance Status (PS) According to Eastern Cooperative Oncology Group Scale
- D. Common Terminology Criteria for Adverse events (V5.0)
- E. Substrates, inducers and inhibitors list
- F. Technical and Organisational Measures Regarding Data Protection
- G. Regulations and Good Clinical Practice Guidelines

A. Response Evaluation Criteria in Solid Tumors (RECIST) v1.1

Eisenhauer et al. *Eur J Cancer*. 2009;45(2):228-47.

Tables summarising RECIST v1.1 are provided.

Appendix Table 1: RECIST v1.1 Objective Tumour Response Evaluation Criteria

Evaluation of Target Lesions	
Complete Response (CR):	Disappearance of all target lesions. Any pathological lymph nodes (whether target or non-target) must have reduction in short axis to <10 mm.
Partial Response (PR):	At least a 30% decrease in the sum of diameters of target lesions, taking as reference the baseline sum diameters.
Progressive Disease :	At least a 20% increase in the sum of diameters of target lesions, taking as reference the smallest sum on study (this includes the baseline sum if that is the smallest on study). In addition to the relative increase of 20%, the sum must also demonstrate an absolute increase of at least 5 mm. (Note: the appearance of one or more new lesions is also considered progression).
Stable Disease :	Neither sufficient shrinkage to qualify for PR nor sufficient increase to qualify for progressive disease, taking as reference the smallest sum diameters while on study.
Evaluation of Non-target Lesions	
Complete Response (CR):	Disappearance of all non-target lesions and normalisation of tumour marker level. All lymph nodes must be non-pathological in size (<10 mm short axis).
Non-CR/Non-progressive disease:	Persistence of one or more non-target lesion(s) and/or maintenance of tumour marker level above the normal limits.
Progressive Disease:	Unequivocal progression (see comments below) of existing non-target lesions. (Note: the appearance of one or more new lesions is also considered progression).

Source: Eisenhauer et al, 2009¹

Abbreviations: CR = complete response; PR = partial response; RECIST = response evaluation criteria in solid tumors;

¹Eisenhauer EA, Therasse P, Bogaerts J, et al. New response evaluation criteria in solid tumours: revised RECIST guideline (version 1.1). *Eur J Cancer*. 2009;45(2):228-247.

Appendix Table 2: Best Overall Response Per RECIST v1.1

Target lesions	Non-target lesions	New lesions	Overall response
CR	CR	No	CR
CR	Non-CR/non-progressive disease	No	PR
CR	Not evaluated	No	PR
PR	Non-progressive disease or not all evaluated	No	PR
Stable disease	Non-progressive disease or not all evaluated	No	Stable disease
Not all evaluated	Non-progressive disease	No	NE
Progressive disease	Any	Yes or No	Progressive disease
Any	Progressive disease	Yes or No	Progressive disease
Any	Any	Yes	Progressive disease

Source: Eisenhauer et al, 2009¹

Abbreviations: CR = complete response; NE = not evaluable; PR = partial response; RECIST = response evaluation criteria in solid tumors;

¹Eisenhauer EA, Therasse P, Bogaerts J, et al. New response evaluation criteria in solid tumours: revised RECIST guideline (version 1.1). *Eur J Cancer*. 2009;45(2):228-247.

Appendix Table 3: Best Overall Response When Confirmation of CR and PR Required

Overall response First timepoint	Overall response Subsequent timepoint ^a	BEST overall response
CR	CR	CR
CR	PR	Stable disease, progressive disease or PR ^b
CR	Stable disease	Stable disease provided minimum criteria for stable disease duration met, otherwise, progressive disease
CR	Progressive disease	Stable disease provided minimum criteria for stable disease duration met, otherwise, progressive disease
CR	NE	Stable disease provided minimum criteria for stable disease duration met, otherwise NE
PR	CR	PR
PR	PR	PR
PR	Stable disease	Stable disease
PR	Progressive disease	Stable disease provided minimum criteria for stable disease duration met, otherwise, progressive disease
PR	NE	Stable disease provided minimum criteria for stable disease duration met, otherwise NE
NE	NE	NE

Source: Eisenhauer et al, 2009¹

Abbreviations: CR = complete response; NE = not evaluable; PR = partial response;;

a Responses should be confirmed 4-8 weeks after the initial assessment

- b. If a CR is truly met at first timepoint, then any disease seen at a subsequent timepoint, even disease meeting PR criteria relative to baseline, makes the disease progressive disease at that point (since disease must have reappeared after CR). Best response would depend on whether minimum duration for stable disease was met. However, sometimes 'CR' may be claimed when subsequent scans suggest small lesions were likely still present and in fact the participant had PR, not CR at the first timepoint. Under these circumstances, the original CR should be changed to PR and the best response is PR.

¹Eisenhauer EA, Therasse P, Bogaerts J, et al. New response evaluation criteria in solid tumours: revised RECIST guideline (version 1.1). *Eur J Cancer*. 2009;45(2):228-247.

B. iRECIST Criteria

The iRECIST guidelines are described in Seymour et al. 2017¹.

iRECIST criteria are an expansion for disease evaluation in immunotherapy and are based on RECIST 1.1².

Measurable Disease:

Tumour lesions: measurable lesions are defined as those that can be accurately measured in at least one dimension (longest diameter to be recorded) with the following:

- A minimum size of 10 mm by CT scan (CT scan slice thickness no greater than 5 mm).
- A minimum size of 10 mm calliper measurement by clinical exam (lesions that cannot be accurately measured with callipers should be recorded as nonmeasurable).
- A minimum size of 20 mm by chest X-ray.

All tumour measurements must be recorded in millimetres (or decimal fractions of centimetres).

Malignant lymph nodes: To be considered pathologically enlarged and measurable, a lymph node must be ≥ 15 mm in short axis when assessed by CT scan (CT scan slice thickness recommended to be not greater than 5 mm). At baseline and in follow-up, only the short axis will be measured and followed.

Nonmeasurable Disease:

All other lesions (or sites of disease), including small lesions (longest diameter < 10 mm or pathological lymph nodes with ≥ 10 to < 15 mm short axis), as well as truly nonmeasurable lesions, are considered nonmeasurable disease. Lesions considered truly nonmeasurable include leptomeningeal disease, ascites, pleural/pericardial effusions, inflammatory breast disease, lymphangitic involvement of skin and lung, and abdominal masses/abdominal organomegaly identified by physical exam that is not measurable by reproducible imaging techniques.

Guidelines for the evaluation of measurable disease using iRECIST

Overall response will be assessed using iRECIST. Immunotherapeutics may result in infiltration of immune cells leading to transient increase in the size in malignant lesions, or undetectable lesions becoming detectable. The criteria are identical to those of RECIST 1.1 in many respects but have been adapted to account for instances where an increase in tumour burden, or the appearance of new lesions, does not reflect true tumour progression.

Key differences are described below. All responses defined using iRECIST criteria are designated with a prefix. iRECIST time-point and best overall responses will be recorded separately.

Confirming Progression:

Unlike RECIST 1.1, iRECIST requires the confirmation of progression and uses the terms iUPD (unconfirmed progression) and iCPD (confirmed progression). Confirmatory scans should be performed at least 4 weeks, but no longer than 8 weeks after iUPD.

iCPD is confirmed if further increase in tumour burden, compared to the last assessment, is seen as evidenced by one or more of the following:

- Continued increase in tumour burden (from iUPD) where RECIST 1.1 definitions of progression had been met (from nadir) in target, non-target disease or new lesions

- Progression in target disease worsens with an increase of at least 5 mm in the absolute value of the sum
- Continued unequivocal progression in non-target disease with an increase in tumour burden
- Increase in size of previously identified new lesion (s) (an increase of at least 5 mm in the absolute value of the sum of those considered to be target new lesions) or additional new lesions.
- RECIST 1.1 criteria are met in lesion types (target or non-target or new lesions) where progression was not previously identified, including the appearance of additional new lesions.

If iUPD is not confirmed at the next assessment, then the appropriate response will be assigned (iUPD if the criteria are still met, but no worsening, or iSD, iPR or iCR if those criteria are met compared to baseline). As can be seen in table 2, the prior documentation of iUPD does not preclude assigning iCR, iPR, or iSD in subsequent time-point assessments or as best overall response (BOR) providing that iCPD is not documented at the next assessment after iUPD.

Continued treatment after iUPD:

Treatment beyond iUPD is permitted for participants who are clinically stable to continue on treatment until the next assessment (≥ 4 weeks later). This next imaging assessment should be no longer than 8 weeks later, to ensure that participants remain fit for salvage therapies.

An assignment of clinical stability requires that no worsening of performance status has occurred, that no clinically relevant increases in disease-related symptoms such as pain or dyspnoea occur that are thought to be associated with disease progression (these symptoms are generally understood to mean a requirement for increased palliative intervention), and that no requirement for intensified management of disease-related symptoms exists, including increased analgesia, radiotherapy, or other palliative care. The imaging findings and the recommendation to continue with treatment despite iUPD should be discussed with the participant before a decision is made about whether or not to continue therapy.

New lesions:

New lesions should be assessed and measured as they appear using RECIST 1.1 criteria (maximum of 5 lesions, no more than 2 per site, at least 10 mm in long axis (or 15 mm in short axis for nodal lesions), and recorded as New Lesions-Target (NLT) and New Lesion-Non-Target (NLNT) to allow clear differentiation from baseline target and non-target lesions.

New lesions may either meet the criteria of NLT or NLNT to drive iUPD (or iCPD). However, the measurements of target lesions should NOT be included in the sum of measures of original target lesions identified at baseline. Rather, these measurements will be collected on a separate table in the case record form.

Progressive disease is confirmed in the New Lesion category if the next imaging assessment, conducted at least 4 weeks (but not more than 8 weeks) after iUPD confirms further progression from iUPD with either an increase of at least 5 mm in the absolute value of the sum of NLT OR an increase (but not necessarily unequivocal increase) in the size of NLNT lesions OR the appearance of additional new lesions.

Appendix Table 4: Time point (TP) iResponse

Target lesions*	Non-Target Lesions*	New Lesions*	Time Point Response	
			No prior iUPD**	Prior iUPD**, ***
iCR	iCR	iCR	iCR	iCR
iCR	iCR	iCR	iCR	iCR
No	No	No	No	No
iCR	iCR	iCR	iCR	iCR
iUPD with no change OR decrease from last TP	iUPD with no change OR decrease from last TP	Yes	NA	NLs confirms iCPD if NLs were previously identified and increase in size (≥ 5 mm in SOM for NLT or any increase for NLNT) or number. If no change in NLs (size or number) from last TP, remains iUPD
iSD	iUPD	No	iUPD	Remains iUPD unless iCPD confirmed based in further increase in size of NT disease (need not meet RECIST 1.1 criteria for unequivocal PD)
iUPD	Non-iCR/Non-iUPD	No	iUPD	Remains iUPD unless iCPD confirmed based on: further increase in SOM of at least 5 mm, otherwise remains iUPD
iUPD	iUPD	No	iUPD	Remains iUPD unless iCPD confirmed based on further increase in: previously identified T lesion iUPD SOM ≥ 5 mm and / or NT lesion iUPD (prior assessment - need not be unequivocal progressive disease)

iUPD	iUPD	Yes	iUPD	Remains iUPD unless iCPD confirmed based on further increase in: previously identified T lesion iUPD ≥ 5 mm and / or previously identified NT lesion iUPD (need not be unequivocal) and /or size or number of new lesions previously identified
Non-iUPD/PD	Non-iUPD/PD	Yes	iUPD	Remains iUPD unless iCPD confirmed based on increase in size or number of new lesions previously identified
* Using RECIST 1.1 principles. If no PSPD occurs, RECIST 1.1 and iRECIST categories for CR, PR and stable disease would be the same. ** in any lesion category. *** previously identified in assessment immediately prior to this TP.				
Abbreviations : TP = time-point; R = RECIST 1.1; iR = iRECIST; TPR = response at that time-point; BOR = best overall response; UNE = unequivocal increase in NT; NT = non-target, T = target; UC = unchanged; INC = increase but not meeting definition of unequivocal increase in NT; NL = new lesions; iUPD = unconfirmed immune progressive disease; iCPD = confirmed immune progressive disease; + = 1 or more NL; ++ = additional NL or increase in NL size; progressive disease date = date used for RECIST 1.1 survival analyses; iPD date = date of progressive disease to be used for exploratory iRECIST analyses; NE = not evaluable/evaluated; ABS = absent; SOM = sum of measures. iCR – immune complete response; iPR – immune partial response; iSD – immune stable disease				

Appendix Table 5: 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.					
Designation “T” for BOR can be used to indicate prior iUPD to aid in data interpretation.					
For participants with non-target disease only at baseline, only CR or non-CR/non- progressive disease can be assigned at each TPR but is not shown in the table for ease of presentation.					
Abbreviations: TP = time-point; R = RECIST 1.1; iR = iRECIST; TPR = response at that time-point; BOR = best overall response; iUPD = unconfirmed immune PD; iCPD = confirmed immune PD; iCR – immune complete response; iPR – immune partial response; iSD – immune stable disease; NE = not evaluable/evaluated.					

References:

1. Seymour L, Bogaerts J, Perrone A, et al. RECIST working group. iRECIST: guidelines for response criteria for use in trials testing immunotherapeutics. *Lancet Oncol.* 2017 Mar;18(3):e143-e152.
2. Eisenhauer EA, Therasse P, Bogaerts J, et al. New response evaluation criteria in solid tumours: revised RECIST guideline (version 1.1). *Eur J Cancer.* 2009;45(2):228-247.

C. Performance Status (PS) According to Eastern Cooperative Oncology Group Scale

ECOG Performance Status Scale	
Grade	Description
0	Normal activity. Fully active, able to carry on all pre-disease performance without restriction.
1	Symptoms but ambulatory. Restricted in physically strenuous activity, but ambulatory and able to carry out work of a light or sedentary nature (<i>e.g.</i> , light housework, office work).
2	In bed <50% of the time. Ambulatory and capable of all self-care, but unable to carry out any work activities. Up and about more than 50% of waking hours.
3	In bed >50% of the time. Capable of only limited self-care, confined to bed or chair more than 50% of waking hours.
4	100% bedridden. Completely disabled. Cannot carry on any self-care. Totally confined to bed or chair.
5	Dead.

(*) *ECOG* = Eastern Cooperative Oncology Group

D. Common Terminology Criteria for Adverse events (V5.0)

The National Cancer Institute's Common Terminology Criteria for Adverse Events (CTCAE v5.0 published 27 November 2017) is a descriptive terminology to be utilized for Adverse Event (AE) reporting in clinical trials. A grading (severity) scale is provided for each AE term.

CTCAE v5.0 incorporates certain elements of the MedDRA terminology. For further details on MedDRA refer to the MedDRA MSSO Web site (<https://www.meddra.org/>).

Grade refers to the severity of the AE. The CTCAE displays Grades 1 through 5 with unique clinical descriptions of severity for each AE based on this general guideline:

Grade 1	Mild; asymptomatic or mild symptoms; clinical or diagnostic observations only; intervention not indicated.
Grade 2	Moderate; minimal, local or noninvasive intervention indicated; limiting age-appropriate instrumental ADL*.
Grade 3	Severe or medically significant but not immediately life-threatening; hospitalization or prolongation of hospitalization indicated; disabling; limiting self care ADL**.
Grade 4	Life-threatening consequences; urgent intervention indicated.
Grade 5	Death related to AE.

*Instrumental ADL refer to preparing meals, shopping for groceries or clothes, using the telephone, managing money, etc.

**Self care ADL refer to bathing, dressing and undressing, feeding self, using the toilet, taking medications, and not bedridden

CTCAE v5.0 is available on line:

https://ctep.cancer.gov/protocoldevelopment/electronic_applications/docs/ctcae_v5_quick_reference_5x7.pdf

E. Substrates, inducers, inhibitors list

An exhaustive list of substrates/inducers/inhibitors not permitted or to be used with caution are available here: <http://medicine.iupui.edu/clinpharm/ddis/main-table>.

F. Technical and Organisational Measures Regarding Data Protection

To comply with the applicable rules on the protection of personal data, specifically regarding the implementation of the organisational and technical arrangements aiming to avoid unauthorised access, disclosure, dissemination, alteration, or loss of information and processed personal data, Domain Therapeutics SA will implement and maintain the following measures:

- restriction and monitoring of physical access to the offices and information processing facilities to employees, personnel, and approved visitors.
- appropriate and restricted user access relevant to the function and type of activity performed in relation to the clinical trial.
- effective pseudonymisation of personal data in compliance with the European Data Protection Board's Recommendations 01/2020 (V2.0 adopted 18 June 2021).
- encryption of personal data, where appropriate.
- ability to ensure the ongoing confidentiality, integrity, availability and resilience of processing systems and services.
- network, application, and database security by means of firewalls and antivirus/anti-malware; ensuring detection of malware purposed for unauthorised deletion, blocking, copying of information, disabling security measures and response to such attacks.
- means to restore the availability and access to personal information in a timely manner in the event of a physical or technical incident.
- logging of security events/incidents in information systems.
- procedures that cover reporting, analysis, monitoring and resolution of security incidents.
- ensuring that information systems, computers and software involved in the performance of the services provided in the study are backed up.
- a process for regularly testing, assessing, and evaluating the effectiveness of technical and organisational measures for ensuring the security of the processing.
- procedures to detect and handle within reasonable timely manner a personal data breach.
- procedures for destruction of paper documents containing personal data.
- business continuity procedures ensuring that the Sponsor can continue to provide services through operational interruption

All locations, personnel and information systems that are used to perform services for the study will be covered.

Domain Therapeutics SA will ensure the technical and organisational security measures described above, are regularly reviewed, and updated to consider the technological developments.

Domain Therapeutics SA may apply additional specific statutory requirements, where required by national laws, and will implement the necessary security measures even if they are not expressly listed above.

Besides the already above-mentioned technical and organisational measures, Domain Therapeutics SA, by means of internal measures and imposed contractual clauses to the selected vendors and partners (in their role of processors), will ensure the confidentiality of records and personal data of the participants.

Domain Therapeutics SA will ensure a functional process for reporting of any data breach occurring at Domain Therapeutics SA or its vendor's and partner's (in their role of processor) facilities and premises. In case of the occurrence of any data breach, Domain Therapeutics SA will immediately apply relevant measures to mitigate the risks to data participants as appropriate in relation to the specific context of the data breach, considering its source, underlying intentions, possibilities of recovery, etc. Any data breach presenting risks to the rights and freedoms of data participants will be reported to the relevant supervisory data protection authority within 72 hours of Domain Therapeutics SA becoming aware of the data breach. In addition, in case of occurrence of a high-risk breach, data participants will be informed by Domain Therapeutics SA (via investigation site).

G. Regulations and Good Clinical Practice Guidelines**1. Regulations**

Refer to the following European Directives (and applicable regulations/guidances):

1. European Directive 2001/20/EC and related guidance documents
2. European Directive 2005/28/EC and related guidance documents

2. Good Clinical Practice Guidelines

ICH GCP guidelines can be found at the following URLs:

http://www.ich.org/fileadmin/Public_Web_Site/ICH_Products/Guidelines/Efficacy/E6/E6_R1_Guideline.pdf

http://www.ich.org/fileadmin/Public_Web_Site/ICH_Products/Guidelines/Efficacy/E6/E6_R2__Step_4.pdf