# Clinical Study Protocol

NCT Number: NCT05976334

Title: A Phase 1 Study to Assess Mass Balance, Pharmacokinetics, and Metabolism of [14C]Subasumstat in Patients With Advanced or Metastatic Solid Tumors

Study Number: TAK-981-1004

Document Version and Date: Version 1, 25 Apr 2023

Certain information within this document has been redacted (ie, specific content is masked irreversibly from view) to protect either personally identifiable information or company confidential information.

**PROTOCOL**

# A Phase 1 Study to Assess Mass Balance, Pharmacokinetics, and Metabolism of [$^{14}$C]Subasumstat in Patients With Advanced or Metastatic Solid Tumors

| | |
|---|---|
| **Sponsor:** | Takeda Development Center Americas, Inc. (TDC Americas)<br>95 Hayden Avenue<br>Lexington, MA 02421<br>Please note: Takeda Development Center Americas, Inc. (TDC Americas) may be referred to in this protocol as "sponsor" or "Takeda". |
| **Study Number:** | TAK-981-1004 |
| **EU Trial Number:** | 2023-503449-79 |
| **Universal Trial Number:** | Not applicable |
| **Compound:** | Subasumstat or TAK-981 |
| **Date:** | 25 April 2023 |

# 1.0 ADMINISTRATIVE INFORMATION

## 1.1 Contacts

A separate contact information list will be provided to each site.

Serious adverse event (SAE), pregnancy, and other applicable safety reporting information is presented in the study manual, as is information on reporting product complaints.

TDC-Americas–sponsored investigators per individual country requirements will be provided with emergency medical contact information cards to be carried by each patient.

General advice on protocol procedures should be obtained through the monitor assigned to the study site. Information on service providers is given in Section 3.1 and relevant guidelines provided to the site.

The names and contact information for the medical monitor and responsible medical officer are in the study manual.

## 1.2 Approval

### REPRESENTATIVES OF TAKEDA

This study will be conducted with the highest respect for the individual participants in accordance with the requirements of this clinical study protocol and also in accordance with the following:

- The ethical principles that have their origin in the Declaration of Helsinki.
- International Council for Harmonisation (ICH) E6 (R2) Good Clinical Practice (GCP): Consolidated Guideline.
- All applicable laws and regulations, including, without limitation, data privacy laws, clinical trial disclosure laws, and regulations.

### SIGNATURES

The signature of the responsible Takeda medical officer (and other signatories, as applicable) can be found on the signature page.

Electronic signatures may be found on the last page of this document.



[redacted], MD Date
Oncology Clinical Research
(or designee)

[redacted], PhD Date
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SQS Oncology
(or designee)

[redacted], MD Date
Oncology Clinical Research
(or designee)

[redacted], PhD Date
[redacted],
Quantitative Clinical Pharmacology
(or designee)

## INVESTIGATOR AGREEMENT

I confirm that I have read and that I understand this protocol, the Investigator's Brochure (IB), prescribing information, and any other product information provided by the sponsor. I agree to conduct this study in accordance with the requirements of this protocol and also to protect the rights, safety, privacy, and well-being of study patients in accordance with the following:

- The ethical principles that have their origin in the Declaration of Helsinki.
- ICH, E6 GCP: Consolidated Guideline.
- All applicable laws and regulations, including, without limitation, data privacy laws and regulations.
- Regulatory requirements for reporting serious adverse events (SAEs) defined in Section 10.0 of this protocol.
- Terms outlined in the clinical study site agreement.
- Responsibilities of the investigator (Appendix B).

I further authorize that my personal information may be processed and transferred in accordance with the uses contemplated in Appendix C of this protocol.



Signature of Investigator Date

Investigator Name (print or type)

Investigator's Title

Location of Facility (City, State/Province)

Location of Facility (Country)

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## 2.0 STUDY SUMMARY

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| **Name of Sponsor(s):** TDC Americas | **Compound:** Subasumstat (TAK-981) |
| **Title of Protocol:** A Phase 1 Study to Assess Mass Balance, Pharmacokinetics, and Metabolism of [$^{14}$C]Subasumstat in Patients With Advanced or Metastatic Solid Tumors | **EU Trial No.:** 2023-503449-79 |
| **Study Number:** TAK-981-1004 | **Phase:** 1 |

**Study Design:**

This is a 2-part, open-label, mass balance and absorption, distribution, metabolism, excretion study in patients with advanced or metastatic solid tumors.

Part A is the period assessing the mass balance, pharmacokinetic (PK), metabolism, and excretion of subasumstat in this population.

The study will enroll patients diagnosed with locally advanced or metastatic solid tumors with measurable disease. If patients drop out, they may be replaced, to ensure approximately 6 PK evaluable patients complete all study assessments. Patients will be admitted to the study site for at least 5 days postdose and until all the discharge criteria are met for a maximum of 14 days postdose. Samples will be collected and patients confined until 90% or greater of the total dose of radioactivity administered is recovered in urine and fecal samples (combined) or until <1% of the dosed radioactivity is collected in 2 consecutive intervals when both urine and feces are collected. Patients who meet all inclusion criteria and none of the exclusion criteria will be assigned a patient identification number and will be admitted to the study site on Day -1 for predose assessments. On Day 1, patients will receive 90 mg [$^{14}$C]subasumstat intravenous (IV) solution containing 100 µCi (approximately 3.7 megabecquerels (MBq); equivalent to 2.74 mrem or 0.0274 mSv whole body effective dose for human male subjects and 1.41 mrem or 0.0141 mSv whole body effective dose for human female subjects) via a 1-hour IV infusion. All samples being assessed for total radioactivity (TRA) will be tested in batches. All samples from Day 1 to Day 5 will be assessed at the same time. For patients who do not meet the discharge criteria, the samples collected from Day 6 until the time when the TRA is available will be used for TRA determination. This process of batch measurement will continue until the discharge criteria are met. Since up to a 3-day time lag is anticipated for radioactivity counting of samples, actual patient discharge from the study site may occur 3 days after the discharge criteria are met.



Patients' safety will be closely monitored, and adverse events (AEs) will be collected throughout the study. Vital signs, physical examinations, electrocardiograms (ECGs), and clinical laboratory tests will be captured during the confinement (predose, during study, before discharge from study site).

In this clinical study, blood samples will be collected at prespecified time points to analyze subasumstat, TRA in blood and plasma, and metabolite profiling in plasma over the confinement. Complete urinary and fecal output will be collected throughout the confinement period until discharge; urine samples will be analyzed for PK, TRA, and metabolite profiling and fecal samples will be analyzed for TRA and metabolite profiling. For patients experiencing emesis after drug administration, the full vomitus will be collected as much as possible and assayed for TRA. If a subject vomits more than once during a period, vomitus corresponding to each vomiting event will be collected in a separate labeled container and separately counted. More detailed information will be provided in the study manual. Patients may be provided treatment for constipation if needed, as determined by the investigator.

After completion of Part A, patients will have the opportunity to participate in Part B. Participation in Part B is voluntary, and a consent is included in the main study consent form. The patient can withdraw from Part B at any time during the study, or the patient can be withdrawn from the study if there is toxicity or there is no evidence of clinical benefit to the patient at the discretion of the investigator.

During Part B, the patient will receive subasumstat 90 mg twice daily (on days 1, 4,8, and 11 of the 21-day cycle) for 3 cycles, followed by weekly maintenance dosing (on days 1 and 8 of the 21 day cycle). The treatment will be up to 1 year. For patients who have completed 1 year of treatment with subasumstat, the investigator(s) may discuss treatment options with the sponsor.

Safety and disease assessments will be collected in Part B. Investigators will use RECIST 1.1 criteria to assess the clinical response. Disease assessments will be conducted using radiological evaluations (computed tomography scan or magnetic resonance imaging).

Toxicity will be evaluated according to the National Cancer Institute Common Terminology Criteria for Adverse Events, Version 5.

**Primary Objectives:**

The primary objectives are:

- To assess the mass balance (ie, cumulative excretion of TRA in urine and feces) of subasumstat following a single 1-hour infusion of 90 mg [$^{14}$C]subasumstat IV solution containing 100 µCi (approximately 3.7 MBq) in patients with advanced or metastatic solid tumors in Part A.

**Secondary Objectives:**

The secondary objectives are:

- To characterize the PK of subasumstat in whole blood, plasma, and urine, and of TRA in plasma and whole blood following a single 1-hour infusion of 90 mg [$^{14}$C]subasumstat IV solution containing 100 µCi (approximately 3.7 MBq) in patients with advanced or metastatic solid tumors in Part A.
- To evaluate the safety and tolerability of subasumstat in patients with advanced or metastatic solid tumors during Part A and Part B.
- To collect samples for characterization of the metabolic profile of subasumstat in plasma, urine, and feces following a single 1-hour infusion of 90 mg [$^{14}$C]subasumstat IV solution containing 100 µCi (approximately 3.7 MBq) in patients with advanced or metastatic solid tumors in Part A.

**Patient Population:** Adult patients aged ≥18 years old with locally advanced or metastatic solid tumors with measurable disease

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|---|---|
| **Number of Patients:**<br>Approximately 10 patients enrolled for approximately 6 PK evaluable patients. | **Number of Sites:**<br>Two study sites in Hungary (1 for Part A and 1 for Part B). |
| **Dose Level(s):**<br>Part A: Single dose of 90 mg [$^{14}$C]subasumstat IV solution (containing approximately 3.7 MBq of total radioactivity).<br>Part B (optional): 90 mg subasumstat IV solution on Days 1, 4, 8, and 11 of a 21 day cycle for 3 cycles, followed by weekly maintenance dosing. | **Route of Administration:**<br>IV in 1-hour infusion. |
| **Duration of Treatment:**<br>Part A: Single IV infusion.<br>Part B: Up to 1 year. | **Period of Evaluation:**<br>Screening: Within 28 days before the first dose of study drug.<br>Part A: Patients will be required to stay at the study site for 5 to 8 days postdose and until the discharge criteria are met, with a maximum confinement period of 14 days postdose. Patients not participating in Part B will complete an end of study (EOS) visit 30 days (+10 days) after the last dose of study drug or before the start of the subsequent therapy for the patient's indication, if that occurs sooner.<br>Part B (optional): The maximum treatment duration is 1 year. An EOS visit will occur 30 days (+10 days) after the last dose of study drug in Part B or before the start of subsequent therapy for the patient's indication, if that occurs sooner. |

**Main Criteria for Inclusion:**

Male or female patients, aged 18 years or older, who (1) have histologically or cytologically confirmed advanced (locally regionally recurrent not amenable to curative therapy) or metastatic solid tumors with no standard therapeutic option with a proven clinical benefit, are intolerant or have refused them, (2) have a performance status of 0 or 1 on the Eastern Cooperative Oncology Group Performance Scale, (3) demonstrate adequate organ function, and (4) have recovered to Grade 1 or baseline from all toxicity associated with previous therapy or have the toxicity established as sequela.

**Main Criteria for Exclusion:**

Patients who (1) have uncontrolled brain metastasis, (2) had a second malignancy within the previous 3 years, except treated basal cell or localized squamous skin carcinomas, prostate cancer, cervical carcinoma in situ, resected colorectal adenomatous polyps, breast cancer in situ, or other malignancy for which the patient is not on active anticancer therapies, (3) have an active HIV, hepatitis B, or hepatitis C infection, (4) recent or continued use of specific medications or procedures, or (5) has certain types of uncontrolled heart diseases.

**Endpoints:**

The primary endpoints are:

- Cumulative percentage of urinary recovery, fecal recovery, and combined recovery, and percentage of recovered TRA in urine and feces for each interval over the entire period of collection.

The secondary endpoints are:

- PK parameters of subasumstat and TRA in plasma and whole blood: maximum observed concentration, time of first occurrence of $C_{max}$, and area under the concentration-time curve from time 0 to time of the last quantifiable concentration, and as permitted by data, terminal disposition phase half-life, clearance, volume of distribution at steady-state, and area under the concentration-time curve from time 0 to infinity, calculated using the observed value of the last quantifiable concentration.
- PK parameters of subasumstat in urine: cumulative amount of unchanged drug excreted into the urine ($Ae_{urine}$ and percentage of dose) and renal clearance.
- Safety parameters: AEs, serious adverse events, ECG, and abnormality of laboratory values.
- Metabolite profiling and identification in plasma, urine, and feces.



**Statistical Considerations:**

No formal statistical hypothesis testing will be performed.

**Sample Size Justification:**

Based on the ALARA principle (As Low [radioactive burden] As Reasonably Achievable) set forth in the 96/29/EURATOM directive, a sample size of approximately 6 PK-evaluable patients is considered sufficient to provide adequate characterization of the mass balance, PK, metabolism, and excretion of subasumstat in patients with cancer.

# 3.0 STUDY REFERENCE INFORMATION

## 3.1 Study-Related Responsibilities

The sponsor will perform all study-related activities with the exception of those identified in the clinical supplier list in the study manual. The identified vendors will perform specific study-related activities either in full with sponsor oversight or in partnership with the sponsor.

## 3.2 Coordinating Investigator

Takeda will select a signatory coordinating investigator from the investigators who participate in the study. Selection criteria for this investigator will include significant knowledge of the study protocol and the study medication, expertise in the therapeutic area and the conduct of clinical research, and study participation. The signatory coordinating investigator will be required to review and sign the clinical study report and by doing so agrees that it accurately describes the results of the study.

## 3.3 List of Abbreviations

| | |
|---|---|
| ADME | absorption, distribution, metabolism, excretion |
| AE | adverse event |
| $Ae_{urine}$ | cumulative amount of unchanged drug excreted into the urine |
| ALARA | as low (radioactive burden) as reasonable achievable |
| ASTCT | American Society for Transplantation and Cellular Therapy |
| $AUC_{\infty}$ | area under the concentration-time curve from time 0 to infinity |
| $AUC_{last}$ | area under the concentration-time curve from time 0 to time of the last quantifiable concentration |
| AxMP | auxiliary medicinal product |
| BIW | twice weekly |
| CL | clearance |
| $CL_R$ | renal clearance |
| $C_{max}$ | maximum observed concentration |
| CR | complete response |
| CRO | contract research organization |
| CRS | cytokine release syndrome |
| CT | computed tomography |
| CYP | cytochrome P450 |
| DC | dendritic cell |
| DOR | duration of response |
| ECG | electrocardiogram |
| ECOG | Eastern Cooperative Oncology Group |
| eCRF | electronic case report form |
| EDC | electronic data capture |
| EOS | end of study |
| FDA | [United States] Food and Drug Administration |
| GCP | Good Clinical Practice |
| GLP | Good Laboratory Practice |
| IB | Investigator's Brochure |
| ICF | informed consent form |
| ICH | International Council for Harmonisation |
| IEC | independent ethics committee |
| IFN | interferon |
| IMP | investigational medicinal product |
| IRB | institutional review board |
| IRR | infusion-related reaction |
| IV | intravenous |
| MBq | megabecquerels |
| MedDRA | Medical Dictionary for Regulatory Activities |
| MHRA | Medicines and Healthcare products Regulatory Agency |

| | |
|---|---|
| MOA | mechanism of action |
| MRI | magnetic resonance imaging |
| NCI CTCAE | National Cancer Institute Common Terminology Criteria for Adverse Events |
| NK | natural killer |
| ORR | overall response rate |
| PBMC | peripheral blood mononuclear cell |
| PD | pharmacodynamic |
| PFS | progression-free survival |
| Pgp | P-glycoprotein |
| PK | pharmacokinetic |
| PMDA | Pharmaceuticals and Medical Devices Agency of Japan |
| PR | partial response |
| QTcF | QT interval with Fridericia correction method |
| QW | once weekly |
| RBC | red blood cell |
| RECIST | Response Evaluation Criteria in Solid Tumors |
| RP2D | recommended phase 2 dose |
| SAE | serious adverse event |
| SOE | schedule of events |
| SSR | special situation report |
| SUMO | small ubiquitin-like modifier |
| $t_{1/2z}$ | terminal disposition phase half-life |
| TEAE | treatment-emergent adverse event |
| $t_{max}$ | time of first occurrence of maximum observed concentration |
| TRA | total radioactivity |
| UK | United Kingdom |
| ULN | upper limit of normal |
| US | United States |
| $V_{ss}$ | volume of distribution at steady-state |
| WHO | World Health Organization |



## 3.4 Corporate Identification

| | |
|---|---|
| TDC Japan | Takeda Development Center Japan |
| TDC Asia | Takeda Development Center Asia, Pte Ltd |
| TDC Europe | Takeda Development Centre Europe Ltd |
| TDC Americas | Takeda Development Center Americas, Inc |
| TDC | TDC Japan, TDC Asia, TDC Europe and/or TDC Americas, as applicable |
| Takeda | Millennium Pharmaceuticals, Inc, TDC Japan, TDC Asia, TDC Europe and/or TDC Americas, as applicable |

# 4.0 INTRODUCTION

## 4.1 Background

### 4.1.1 Protein SUMOylation Biology in Cancer

SUMOylation is a posttranslational modification that attaches a small ubiquitin-like modifier (SUMO) protein to protein substrates, regulating their activity, subcellular localization, and stability (Seeler and Dejean 2017). SUMO pathway components are ubiquitously expressed in eukaryotic cells (Geiss-Friedlander and Melchior 2007).

SUMOylation has been reported to regulate cellular processes important for tumor cell proliferation and survival (He et al. 2017; Seeler and Dejean 2017). In addition, SUMOylation has also been shown to play a key role in regulating innate immune responses. Inhibition of SUMOylation results in induction of type I interferon (IFN) expression, such that inhibiting SUMOylation by genetic means resulted in enhanced basal expression levels and sensitization of induction of type I IFNs (Decque et al. 2016). Type I IFNs, such as IFN-α and IFN-β, are potent immunomodulatory cytokines induced early in the innate immune response which act upon multiple cell types to mold both innate and adaptive immunity. They directly enhance natural killer (NK) cell cytotoxicity and stimulate interleukin-15 production by dendritic cells (DCs) to promote NK cell activation (Lee et al. 2000; Lucas et al. 2007). They also directly act upon T cells to stimulate survival, clonal expansion and the development of T cell effector function (Curtsinger et al. 2005; Marrack et al. 1999). Importantly, type I IFNs play a central role in propagating adaptive immune responses by promoting maturation of DCs and cross presentation of antigens to T cells (Diamond et al. 2011; Fuertes et al. 2011). Indeed, innate immune responses have been implicated in tumor surveillance, via sensing of tumor DNA through the pattern recognition receptor pathway (Woo et al. 2014), activation of which induces production of type I IFNs and propagation of an adaptive antitumor response as described above.



### 4.1.2 Subasumstat

#### *4.1.2.1 Mechanism of Action*

Subasumstat (TAK-981) is a small molecule inhibitor of the SUMOylation cascade by forming a covalent adduct with SUMO, preventing its transfer from SUMO-activating enzyme to the SUMO-conjugating enzyme ubiquitin carrier protein 9.

In vivo treatment with subasumstat resulted in a dose-dependent induction of a type I IFN gene signature in peripheral blood mononuclear cells (PBMCs) and upregulation of type I IFNs and type I IFN-stimulated genes in mouse splenocytes (Lightcap et al. 2021). In ex vivo assays, subasumstat was found to potently activate mouse and human DCs, promoting expression of T cell costimulatory markers and production of inflammatory cytokines. In vivo vaccination studies with ovalbumin protein demonstrated enhancement of antigen cross-presentation and T cell priming by subasumstat (Lightcap et al. 2021).

In syngeneic mouse tumor models, subasumstat was shown to potently inhibit the growth of A20 B-cell lymphoma tumors, with some treated mice achieving complete response (CR). Flow cytometry demonstrated increased numbers of activated T and NK cells in A20 tumors responding to subasumstat (Lightcap et al. 2021). Blockade of type I IFN signaling by pretreatment with a blocking antibody against the type I IFN receptor resulted in complete loss of tumor growth inhibition, indicative of a key role for type I IFN signaling in the antitumor mechanism of action (MOA) of subasumstat. (Lightcap et al. 2021).

In ex vivo assays evaluating the activity of subasumstat on the function of human monocyte derived macrophages and human NK cells (both derived from PBMCs), subasumstat increased the phagocytic activity of monocyte derived macrophages and increased the cytotoxicity of NK cells in both the absence and presence of the anti-CD20 antibody rituximab (Nakamura et al. 2022). These activities were dependent on type I IFN signaling, demonstrating that subasumstat-mediated inhibition of SUMO-activating enzymes leads to the functional activation of human macrophages and human NK cells via type I IFN signaling ex vivo. Significant antitumor activity was demonstrated against OCI-Ly10 xenografts in severe combined immunodeficient mice (lacking B and T cells but retaining an intact innate immune system) following administration of single-agent subasumstat or the anti-CD20 antibody rituximab.



#### *4.1.2.2 Nonclinical Pharmacokinetics*

Subasumstat has an acceptable nonclinical pharmacokinetic (PK) profile for continuing evaluation and development in humans.

In plasma, after single intravenous (IV) administration, subasumstat showed moderate to high plasma clearance (CL) and volume of distribution at steady state after IV administration in mice, rats, dogs, and monkeys with half-lives varying from 2 to 6 hours among species.

#### *4.1.2.3 Nonclinical Toxicology*

Toxicology studies were conducted in rats and dogs because in vitro metabolism, homology, and tissue expression data indicated that these species are relevant for evaluation of subasumstat. Because intermittent dosing on a once weekly (QW) or twice weekly (BIW) schedule was demonstrated to be efficacious in mouse models, both QW and BIW schedules were examined in Good Laboratory Practice (GLP)-compliant toxicity studies. QW dosing (5 doses) was associated with multiorgan failure in rats at ≥20 mg/kg but was well-tolerated in dogs up to the highest dose of 6 mg/kg. BIW dosing (4 doses) was well-tolerated in both species up to the highest dose of 10 mg/kg in rats and 4 mg/kg in dogs.

The primary toxicity with BIW dosing was dose-dependent, mild to marked decreases in peripheral blood lymphocyte counts that affected T cells, T cell subsets (helper, cytotoxic, activated, memory, regulatory), B cells, and NK cells approximately equally. Decreases in lymphocyte counts were associated with decreases in lymphoid cellularity in the primary and secondary lymphoid organs, including the thymus, spleen, lymph nodes, and gut-associated lymphoid tissue. Decreases in other circulating cell types, including neutrophils, monocytes, basophils, and/or eosinophils, were also observed but were of decreased severity compared with

decreases in lymphocyte counts. Additional effects observed with BIW dosing were limited to myeloid hyperplasia in the bone marrow in rats at 10 mg/kg and dogs at 4 mg/kg, injection site reactions in rats at ≥0.5 mg/kg, single-cell necrosis in the stomach in dogs at ≥2 mg/kg, and renal pelvis inflammation and fibrinoid vascular necrosis (without involvement of the renal parenchyma or alterations in renal parameters) in dogs at 4 mg/kg. Additional subasumstat-related effects after repeat once daily or QW dosing, often at nontolerated doses only, were noted in the bone marrow, liver, kidney, urinary, and bladder (dog only); gastrointestinal tract, heart, musculoskeletal system, and lung (rat only); endocrine system (rat only); glandular organs (rat only); and reproductive tract (rat only). Injection site reactions have been observed only in rats at all doses tested. All target organ toxicities at tolerated doses were considered to be monitorable, except for inflammation and vascular necrosis in the renal pelvis in dogs. All target organ toxicities were completely or partially reversible.

Subasumstat had no effect on cytokines related to cytokine release syndrome (CRS) in an in vitro assay in human whole blood. Subasumstat was not mutagenic; however, it is considered genotoxic based on an in vivo micronucleus assay in rats and an in vitro mammalian chromosome aberration assay in human peripheral blood lymphocytes, which showed clastogenicity. Subasumstat did not demonstrate phototoxic potential in an in vitro assay.



#### *4.1.2.4 Clinical Experience*

Subasumstat is currently being evaluated in 4 clinical studies in adult patients with advanced solid tumors or hematologic malignancies. These studies include the following:

- Study TAK-981-1002 (ongoing): Phase 1/2 dose escalation study with subasumstat as a monotherapy in patients with advanced or metastatic tumors or relapsed or refractory hematoligic malignancies.
- Study TAK-981-1501 (closing): Phase 1/2 clinical efficacy and safety study with a combination therapy (subasumstat + rituximab) in patients with relapsed or refractory CD20+ non-Hodgkin's lymphoma.
- Study TAK-981-1502 (ongoing): Phase 1b/2 clinical efficacy and safety study with a combination therapy (subasumstat + pembrolizumab) in patients with select advanced or metastatic solid tumors.
- Study TAK-981-1503 (ongoing): Phase 1b/2 clinical efficacy and safety study with a combination therapy (subasumstat + anti-CD38 monoclonal antibodies) in patients with relapsed refractory multiple myeloma.

Overall, subasumstat has been well-tolerated, with the majority of treatment-emergent adverse events (TEAEs) being consistent with the induction of IFN signaling or the patients' underlying cancer. Overall, preliminary efficacy is being observed, and efficacy evaluations are ongoing.

Study TAK-981-1002 has completed dose escalation and dosing schedule evaluation. The 120 mg dose on Days 1, 4, 8, and 11 dosing regimen was determined as the subasumstat single-agent maximum tolerated dose. Subasumstat 90 mg (Days 1, 4, 8, and 11 dosing regimen) regimen was

determined to be the recommended phase 2 dose (RP2D) and schedule for the subsequent phase 2 portion of the single-agent study. Dose finding and schedule evaluation are continuing in the other 3 ongoing studies.

Refer to the current TAK-981 IB for additional details.

## 4.2 Rationale for the Proposed Study

Part A of this study is intended to provide a quantitative characterization of the mass balance, rates and routes of excretion, and metabolic profiles of subasumstat in humans. Such definitive characterization will help guide understanding of the potential for the intrinsic (eg, renal and hepatic impairment) or extrinsic (eg, concomitant medications with potential to affect drug metabolism and disposition) factors to affect subasumstat PK and, thereby, is important to inform the need for future clinical pharmacology studies (eg, special population studies in patients with organ impairment). Part B of this study is intended to provide opportunity for the patients with advanced or metastatic solid tumors to receive treatment with single agent subasumstat.

## 4.3 Rationale for Dose Selection of Subasumstat

Based on the totality of data (safety, tolerability, efficacy, PK, pharmacodynamic (PD) and PK/PD modeling) from Study TAK-981-1002 (single agent), 90 mg BIW has been selected as RP2D for subasumstat single agent study. Thus, patients will receive a single dose of 90 mg [$^{14}$C]subasumstat in Part A. In Part B, patients will receive 90 mg BIW dosing for 3 cycles (21-days), followed by 90 mg weekly maintenance dosing for the remainder of Part B.



## 4.4 Risks and Benefits

Subasumstat is currently being evaluated in 4 clinical studies (see Section 4.1.2.4) and, as such, the clinical benefits and risks are still emerging. The only serious adverse reaction considered expected for safety reporting purposes across the ongoing TAK-981 studies is pyrexia. Preliminary safety information is described in Sections 4.4.1 and 4.4.2.

Objective responses in clinical studies have been observed. Though additional data are needed to characterize the clinical benefit of subasumstat either alone or in a relevant combination, the emerging data support ongoing development of subasumstat.

The salient MOA of subasumstat in vivo is sensitization of the innate immune response, promoting production of type I IFNs. However, effects on SUMOylation-dependent cellular processes, other than a type I IFN signaling pathway, are possible in immune and nonimmune cells and may give rise to additional toxicities other than those related to increased type I IFN signaling.

During this study, risk mitigation strategies include but are not limited to the following: strict application of the study inclusion and exclusion criteria, frequent monitoring of clinical and laboratory results, guidelines for management and prophylaxis of potential toxicities, criteria for dose modification, and regular monitoring of TEAEs and serious adverse events (SAEs) by the sponsor.

Further details for subasumstat administration, safety events, and management can be found in Section 8.0 and the Guidance for Investigator section of the IB.

### 4.4.1 Potential Effects Based on Nonclinical Studies

The potential risks listed below are based on findings from GLP repeat-dose nonclinical toxicology studies with QW or BIW dosing in rats and dogs, and a single-dose safety pharmacology study in dogs. These events may or may not develop in human patients treated with subasumstat. The potential risks identified from nonclinical studies include infusion-related reactions (IRRs), potential for CRS, hematologic effects, kidney effects, injection site reactions, and reproductive and developmental toxicity.

Further details for subasumstat administration and safety event management can be found in the Guidance for Investigator section of the IB.

### 4.4.2 Effects Based on Clinical Studies

Clinical study protocols for subasumstat include monitoring for the potential adverse events (AEs) specified for this compound using routine laboratory evaluations, urinalysis, cardiac monitoring, physical examinations, and disease assessment. The timing of these tests and evaluations is detailed in the schedule of events (SOE) (Appendix A). Additional tests and evaluations will be considered based on symptoms and findings observed in the study. It is possible that administration of subasumstat will result in toxicities that were not observed or predicted from the completed nonclinical studies conducted in animals. Potential risks based on clinical studies include IRRs, potential for CRS, hematologic effects, and injection site reactions.



## 5.0 STUDY OBJECTIVES AND ENDPOINTS

### 5.1 Objectives

### 5.1.1 Primary Objectives

The primary objectives are:

- To assess the mass balance (ie, cumulative excretion of total radioactivity (TRA) in urine and feces) of subasumstat following a single 1-hour infusion of 90 mg [$^{14}$C]subasumstat IV solution containing 100 μCi (approximately 3.7 megabecquerels [MBq]) in patients with advanced or metastatic solid tumors in Part A.

### 5.1.2 Secondary Objectives

The secondary objectives are:

- To characterize the PK of subasumstat in whole blood, plasma, and urine, and of TRA in plasma and whole blood following a single 1-hour infusion of 90 mg [$^{14}$C]subasumstat IV solution containing 100 μCi (approximately 3.7 MBq) in patients with advanced or metastatic solid tumors in Part A.

- To evaluate the safety and tolerability of subasumstat in patients with advanced or metastatic solid tumors during Part A and Part B.
- To collect samples for characterization of the metabolic profile of subasumstat in plasma, urine, and feces following a single 1-hour infusion of 90 mg [$^{14}$C]subasumstat IV solution containing 100 μCi (approximately 3.7 MBq) in patients with advanced or metastatic solid tumors in Part A.

### 5.1.3 Exploratory Objectives

The exploratory objective is:

- To evaluate efficacy of subasumstat in patients with advanced or metastatic solid tumors during Part B.

## 5.2 Estimands

Not applicable.

## 5.3 Endpoints

### 5.3.1 Primary Endpoints

The primary endpoints are:

- Cumulative percentage of urinary recovery, fecal recovery, and combined recovery, and percentage of recovered TRA in urine and feces for each interval over the entire period of collection.



### 5.3.2 Secondary Endpoints

The secondary endpoints are:

- PK parameters of subasumstat and TRA in plasma and whole blood: maximum observed concentration ($C_{max}$), time of first occurrence of $C_{max}$ ($t_{max}$), and area under the concentration-time curve from time 0 to time of the last quantifiable concentration ($AUC_{last}$), and as permitted by data, terminal disposition phase half-life ($t_{1/2z}$), CL, volume of distribution at steady-state ($V_{ss}$), and area under the concentration-time curve from time 0 to infinity ($AUC_{\infty}$), calculated using the observed value of the last quantifiable concentration.
- PK parameters of subasumstat in urine: cumulative amount of unchanged drug excreted into the urine ($Ae_{urine}$ and percentage of dose) and renal clearance ($CL_R$).
- Safety parameters: AEs, SAEs, electrocardiogram (ECG) and abnormality of laboratory values.
- Metabolite profiling and identification in plasma, urine, and feces.

### 5.3.3 Exploratory Endpoints

- Efficacy parameters: overall response rate (ORR), progression-free survival (PFS), best response (CR, partial response [PR], etc.) and duration of response (DOR).

## 6.0 STUDY DESIGN

### 6.1 Overview of Study Design

This is a 2-part, open-label, mass balance and absorption, distribution, metabolism, excretion (ADME) study in patients with advanced or metastatic solid tumors.

#### 6.1.1 Part A: Mass Balance/ADME Assessment of Single Agent Subasumstat

Part A is the period assessing the mass balance, PK, metabolism, and excretion of subasumstat in this population.

The study will enroll patients diagnosed with locally advanced or metastatic solid tumors with measurable disease. If patients drop out, they may be replaced, to ensure approximately 6 PK evaluable patients complete all study assessments. Patients will be confined to the study site for 5 to 8 days postdose and until the discharge criteria are met (Section 6.1.1.1) for a maximum of 14 days postdose. Patients who sign an informed consent form (ICF) will be assigned a patient identification number, and those who meet all inclusion criteria and none of the exclusion criteria will be admitted to the study site on Day -1 for predose assessments. On Day 1, patients will receive 90 mg [$^{14}$C]subasumstat IV solution containing 100 µCi (approximately 3.7 MBq; equivalent to 2.74 mrem or 0.0274 mSv whole body effective dose for human male subjects and 1.41 mrem or 0.0141 mSv whole body effective dose for human female subjects) via a 1-hour IV infusion. All samples being assessed for TRA will be tested in batches. All samples from Day 1 to Day 5 will be assessed at the same time. For patients who do not meet the discharge criteria, the samples collected from Day 6 until the time when the TRA is available will be used for TRA determination. This process of batch measurement will continue until the discharge criteria are met. Since up to a 3-day time lag is anticipated for radioactivity counting of samples, actual patient discharge from the study site may occur 3 days after the discharge criteria are met.



Patients' safety will be closely monitored, and AEs will be collected throughout the study. Vital signs, physical examinations, ECGs, and clinical laboratory tests will be captured during the confinement (predose, during study, before discharge from study site).

In this clinical study, blood samples will be collected at prespecified time points to analyze subasumstat, TRA in blood and plasma, and metabolite profiling in plasma over the confinement. Complete urinary and fecal output will be collected throughout the confinement period until discharge; urine samples will be analyzed for PK, TRA, and metabolite profiling and fecal samples will be analyzed for TRA and metabolite profiling. For patients experiencing emesis after drug administration, the full vomitus will be collected as much as possible and assayed for TRA. If a subject vomits more than once during a period, vomitus corresponding to each vomiting event will be collected in a separate labeled container and separately counted. More detailed information will

be provided in the study manual. Patients may be provided treatment for constipation if needed, as determined by the investigator.

#### *6.1.1.1 Part A Discharge Criteria*

Samples will continue to be collected and patients confined until 90% or greater of the total dose of radioactivity administered is recovered in urine and fecal samples (combined) or until <1% of the dosed radioactivity is collected in 2 consecutive intervals when both urine and feces are collected. Patients will be confined for a minimum of 5 days postdose and up to a maximum of 14 days postdose.

### 6.1.2 Part B: Continued Treatment With Single Agent Subasumstat

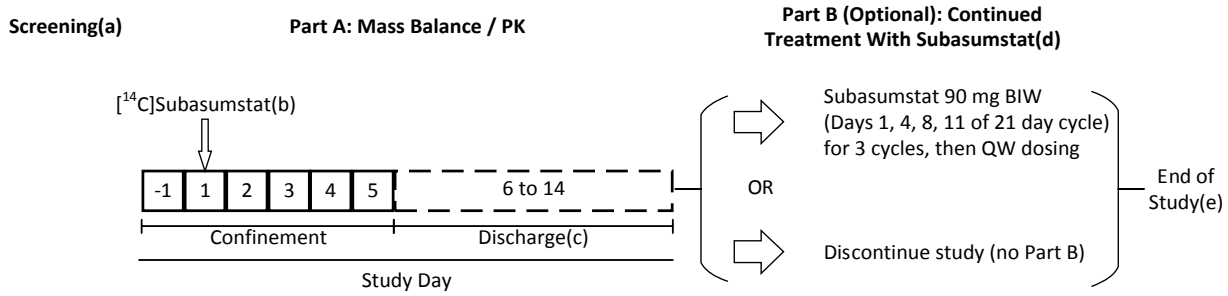
After completion of Part A, patients will have the opportunity to participate in Part B. Participation in Part B is voluntary, and a consent is included in the main study consent form. The patient can withdraw from Part B at any time during the study, or the patient can be withdrawn from the study if their medical condition changes and there is no clear evidence of clinical benefit to the patient at the discretion of the investigator.

During Part B, the patient will receive subasumstat 90 mg BIW (on days 1, 4, 8, and 11 of the 21 day cycle) for 3 cycles, followed by weekly maintenance dosing (on days 1 and 8 of the 21 day cycle). The treatment will be up to 1 year. For patients that complete 1 year of subasumstat treatment and experience clinical benefit in the opinion of the investigator, the investigator may discuss treatment options with the sponsor.

Safety and disease assessments will be collected in Part B. Disease assessments will be conducted using radiological evaluations (computed tomography [CT] scan or magnetic resonance imaging [MRI]) to evaluate the response. Investigators will use Response Evaluation Criteria in Solid Tumors (RECIST) 1.1 criteria to assess the clinical response.

Toxicity will be evaluated according to the National Cancer Institute Common Terminology Criteria for Adverse Events (NCI CTCAE), Version 5.

## Figure 6.a Schematic of Study Design




BIW: twice weekly; EOS: end of study; IV: intravenous; PK: pharmacokinetic; QW: once weekly.
[a] Screening assessments will be performed within 28 days before administration of [$^{14}$C]subasumstat.
[b] Patients will receive a single dose of [$^{14}$C]subasumstat 90 mg as a 1-hour IV infusion on Day 1. The clinic will be supplied with vials containing approximately 100 µCi (approximately 3.7 MBq) of [$^{14}$C] subasumstat as the radioactive tracer.
[c] Discharge criteria for Part A are in Section 6.1.1.1. Patients will be discharged between Days 6 and 14, given that the discharge criteria have been met. Discharge assessments are done only once on the day of discharge. Since up to a 3-day time lag is anticipated for radioactivity counting of samples, actual patient discharge from the study site may occur 3 days after the discharge criteria are met.
[d] The maximum treatment will be for 1 year. Patients will have at least 3 cycles (21 days each) on a BIW schedule on days 1, 4, 8, and 11) followed by maintenance with the QW schedule.
[e] Patients will attend an EOS visit 30 days (+10 days) after the last dose of study drug in Part B or before the start of subsequent therapy for the patient's indication, if that occurred sooner.



## 6.2 Number of Patients

Approximately 10 patients will be enrolled in this study to get approximately 6 PK-evaluable patients. All enrolled patients will complete Part A at 1 study site in Hungary, with any participants in Part B completing Part B at a second study site. Enrollment is defined as the time of initiation of the first dose of study drug.

## 6.3 Duration of Study

### 6.3.1 Duration of an Individual Patient's Study Participation

Study screening will last up to 28 days before the first dose of the study drug, during which the patient's eligibility and baseline characteristics will be determined.

Patients will be required to stay at the study site in Part A for 5 to 8 days postdose and until the discharge criteria are met (Section 6.1.1.1), with a maximum estimated confinement of 14 days postdose. Since up to an approximate 3-day time lag is anticipated for radioactivity counting of samples, actual participant release from the CRU may occur 3 days after discharge criteria are met.

Patients will have the option to continue to receive treatment during Part B of the study. Patients who do not continue into Part B will have an end of study (EOS) visit when they are released from confinement in Part A.

Patients who choose to continue with Part B of the study will continue to receive subasumstat for up to 1 year or until the discontinuation criteria are met (see Section 9.8). Patients in Part B will complete an EOS visit 30 days (±10 days) after the last dose of study drug in Part B or at the start of subsequent therapy for the patient's indication, whichever occurs first.

### 6.3.2 EOS/Study Completion Definition and Planned Reporting

Primary Completion/Study Completion

Patients who have completed Part A, defined as completing the Part A EOS visit for patients not participating in Part B and the first dose of Part B for patients who do participate in Part B, will be considered to have completed the study.

The analyses for the clinical study report will be conducted after 6 PK-evaluable patients complete Part A. The estimated time frame for study completion, defined as the time from the first patient being enrolled until the last PK-evaluable patient completes Part A, is approximately 12 months.

Other Planned Analyses

A clinical study report addendum is planned when all enrolled patients who participate in Part B of the study complete 1 year of treatment or discontinue the study. The estimated time frame for the completion of Part B for all participating patients is approximately 24 months.



### 6.3.3 Timeframes for Primary and Secondary Endpoints to Support Disclosures

Refer to Table 6.a for disclosures information for all primary and secondary endpoints.

**Table 6.a Primary and Secondary Endpoints for Disclosures**

| Endpoint | Definition | Maximum Time Frame |
|---|---|---|
| Primary: Cumulative percentage of urinary recovery, fecal recovery, and combined recovery, and percentage of recovered TRA in urine and feces for each interval over the entire period of collection | Cumulative amount of [$^{14}$C]-radioactivity excreted in urine up to the last sampling interval<br>Cumulative amount of [$^{14}$C]-radioactivity excreted in feces up to the last sampling interval<br>Total cumulative excretion of [$^{14}$C]-radioactivity from the body | Up to 14 days postdose |
| Secondary: PK parameters of subasumstat and TRA in plasma and whole blood | $C_{max}$, $t_{max}$, $AUC_{last}$<br>as permitted by data: $t_{1/2z}$, CL, $V_{ss}$, $AUC_{\infty}$ | Up to 14 days postdose |
| Secondary: PK parameters in of subasumstat in urine | $Ae_{urine}$, $CL_R$ | Up to 14 days postdose |
| Secondary: Safety parameters: AEs, SAEs, ECG, and abnormal laboratory values | Abnormal laboratory values are those outside of normal range<br>See Section 10.1 for AE and SAE definitions | AEs will be recorded from the start of study drug administration through 30 days (+10 days) after the last dose of the study drug<br>SAEs, including serious pretreatment events will be reported from signing the ICF through 30 days (+10 days) after the last dose of the study drug<br>Laboratory tests up to EOS or early termination visit |
| Secondary: Metabolite profiling and identification in plasma, urine, and feces | Determination of relative percentage of circulatory and excretory metabolites | Up to 14 days postdose |

AE: adverse event; $Ae_{urine}$: cumulative amount of unchanged drug excreted into the urine; $AUC_{last}$: area under the concentration-time curve from time 0 to time of the last quantifiable concentration; $AUC_{\infty}$: area under the concentration-time curve from time 0 to infinity; CL: clearance; $CL_R$: renal clearance; $C_{max}$: maximum observed concentration; ECG: electrocardiogram; EOS: end of study; ICF: informed consent form; PK: pharmacokinetic; SAE: serious adverse event; $t_{1/2z}$: terminal disposition half-life; $t_{max}$: time of first occurrence of $C_{max}$; TRA: total radioactivity; $V_{ss}$: volume of distribution at steady-state.



### 6.3.4 Total Study Duration

It is anticipated that Part A of this study for all patients will last for approximately 12 months. Part B, which is optional, is anticipated to last for approximately 24 months for all patients.

### 6.4 Poststudy Access

Treatment with subasumstat will be administered as a part of this study for up to 1 year. For patients that complete 1 year of subasumstat treatment and experience clinical benefit in the opinion of the investigator, the investigator may discuss treatment options with the sponsor.

## 7.0 STUDY POPULATION

### 7.1 Inclusion Criteria

Each patient must meet all the following inclusion criteria to be enrolled in the study:

1. Adult male or female patients aged 18 years or older.
2. Be willing and able to provide written informed consent for the study.
3. Have histologically or cytologically confirmed advanced (local regionally recurrent not amenable to curative therapy) or metastatic solid tumors with no standard therapeutic option with a proven clinical benefit, are intolerant or have refused them.
4. Have a performance status of 0 or 1 on the Eastern Cooperative Oncology Group (ECOG) Performance Scale.
5. Demonstrate adequate organ function as described below:
   a) Platelet count $\geq 75.0 \times 10^9$/L.
   b) Absolute neutrophil count $\geq 1.0 \times 10^9$/L.
   c) Calculated creatinine CL ≥30 mL/min using the Cockcroft-Gault formula.
   d) Aspartate aminotransferase, glutamic-oxaloacetic transaminase, and alanine aminotransferase, glutamic-pyruvic transaminase ≤3.0 times the upper limit of normal (ULN), <5.0 times the ULN if liver enzyme elevations are due to liver metastases; bilirubin ≤1.5 times the ULN. Patients with Gilbert's syndrome may have a bilirubin level >3.0 times the ULN, per discussion between the investigator and the medical monitor.
6. Have recovered to Grade 1 or baseline from all toxicity associated with previous therapy or have the toxicity established as sequela.

   Note: Neuropathy Grade ≤2, any grade alopecia, or autoimmune endocrinopathies with stable replacement therapy are permitted.
7. Women of childbearing potential must have a negative serum or urine pregnancy test within 72 hours before receiving the first dose of study medication.
8. Female patients must meet 1 of the following:
   a) Postmenopausal for at least 1 year before the screening visit, or
   b) Surgically sterile, or

c) If they are of childbearing potential, agree to practice 1 highly effective method and 1 additional effective (barrier) method of contraception at the same time, from the time of signing of the ICF through 6 months after the last dose of study drug, or

d) Agree to practice true abstinence, when this is in line with the preferred and usual lifestyle of the patient. (Periodic abstinence [eg, calendar, ovulation, symptothermal, postovulation methods], withdrawal, spermicides only, and lactational amenorrhea are not acceptable methods of contraception. Female and male condoms should not be used together.)

9. Male patients, even if surgically sterilized (ie, status postvasectomy) must agree to 1 of the following:

   a) Agree to practice effective barrier contraception during the entire study treatment period and through 6 months after the last dose of study drug, or

   b) Agree to practice true abstinence, when this is in line with the preferred and usual lifestyle of the patient. (Periodic abstinence [eg, calendar, ovulation, symptothermal, postovulation methods], withdrawal, spermicides only, and lactational amenorrhea are not acceptable methods of contraception. Female and male condoms should not be used together.)

10. Must be willing and able to comply with clinic visits and procedures outlined in the study protocol.



### 7.2 Exclusion Criteria

Patients meeting any of the following exclusion criteria are not to be enrolled in the study:

1. Received treatment with systemic anticancer treatments or investigational products within 14 days before the first dose of study drug or 5 half-lives, whichever is shorter.

   Note: Low-dose steroids (oral prednisone or equivalent ≤10 mg per day), hormonal therapy for prostate cancer or breast cancer (as adjuvant treatment), and treatment with bisphosphonates and receptor activator of nuclear factor kappa-B ligand inhibitors are allowed.

2. Received treatment with radioisotopes within 5 half-lives before the first dose of the study drug

3. Received radiolabeled substances, were exposed to radiation sources within 12 months of the first dose in this study, or is likely to receive radiation exposure or radioisotopes within 12 months of the first dose in this study such that participation in this study would increase their total exposure beyond the recommended safe levels (ie, weighted annual limit recommended by the International Commission on Radiological Protection).

4. Received extended field radiotherapy ≤4 weeks before the start of treatment (≤7 days for limited field radiation for palliation outside the chest or brain).

5. Uncontrolled brain metastasis (evidence of progression by imaging over a period of 4 weeks and/or neurologic symptoms that have not returned to baseline). Patients with treated brain metastases are allowed provided they are radiologically stable, without evidence of progression for at least 4 weeks by repeat imaging, clinically stable, and without requirement

of steroid treatment for at least 14 days before first dose of study treatment. Note: For asymptomatic patients, screening brain imaging is not required.

6. Second malignancy within the previous 3 years, except treated basal cell or localized squamous skin carcinomas, prostate cancer, cervical carcinoma in situ, resected colorectal adenomatous polyps, breast cancer in situ, or other malignancy for which the patient is not on active anticancer therapy.
7. Major surgery ≤14 days from the first dose of study drug and not recovered fully from any complications from surgery.
8. Prior treatment with subasumstat.
9. Hypersensitivity to subasumstat or any component of the drug product.
10. Baseline prolongation of the QT interval when corrected using Fridericia's formula (QTcF) (eg, repeated demonstration of QTcF interval >480 ms, history of congenital long QT syndrome, or torsades de pointes).
11. Receiving or requires the continued use of medications that are known to be strong or moderate inhibitors and inducers of cytochrome P450 (CYP) 3A4/5 and strong P-glycoprotein (Pgp) inhibitors. To participate in this study, such patients should discontinue using CYP inducers for at least 2 weeks, and CYP/Pgp-inhibitors for 1 week before receiving a dose of subasumstat.
12. Has active noninfectious pneumonitis or interstitial lung disease that required steroids.
13. History of allogeneic tissue or solid organ transplant.
14. Has active bacterial infection requiring systemic therapy <14 days before the start of treatment.
15. Active HIV infection or any other relevant congenital or acquired immunodeficiency.
16. Active hepatitis B or hepatitis C infection. Note: Patients who have positive hepatitis B core antibody or hepatitis B surface antigen antibody can be enrolled but must have an undetectable hepatitis B viral load.
17. Any of the following uncontrolled heart diseases: congestive heart failure New York Heart Association Grade III or IV, unstable angina, myocardial infarction, unstable symptomatic ischemic heart disease, uncontrolled hypertension despite appropriate medical therapy, ongoing symptomatic cardiac arrhythmias >Grade 2, pulmonary embolism or symptomatic cerebrovascular events, or any other serious cardiac condition (eg, pericardial effusion or restrictive cardiomyopathy). Chronic atrial fibrillation on stable anticoagulant therapy is allowed.
18. Psychiatric illness/social circumstances that would limit compliance with study requirements and substantially increase the risk of AEs or has compromised ability to provide written informed consent.
19. Female patients who are pregnant or lactating and breastfeeding.

## 8.0 STUDY DRUG

Patients enrolled in the study will receive [$^{14}$C]subasumstat in Part A and subasumstat in Part B.

### 8.1 Study Drug Administration

All protocol-specific criteria for administration of study drug must be met and documented before drug administration. Study drug will be administered only to eligible patients under the supervision of the investigator or identified sub-investigator(s). All patients will receive subasumstat as specified in the SOE (Appendix A).

Subasumstat will be provided as a solution for infusion containing 0.9 mg/mL [$^{14}$C]subasumstat drug substance for Part A and 10 mg/mL subasumstat drug substance for Part B (refer to the pharmacy manual). Subasumstat will be administered as 60 (±10) minute IV infusion. In case infusion reactions are observed, the length of the infusion can be extended up to 2 hours for all patients without requiring a protocol amendment.

Subasumstat administration should occur in area with resuscitating equipment and medications such as antihistamines, acetaminophen, corticosteroids, epinephrine, and bronchodilators readily available. Patients' vital signs must be monitored before, during the, and at the end of administration of subasumstat. Treatment must be stopped if the patient experiences symptoms compatible with an infusion reaction of Grade 2 or greater. The management of infusion reactions and CRS is detailed in Sections 8.7.6 and 8.7.7, respectively.



As with other potentially toxic compounds, caution should be exercised in handling this drug. The use of gloves is recommended. Following topical exposure, events could include redness or blistering. Given the possibility of extravasation, it is advisable to closely monitor the infusion site for possible infiltration during drug administration. Administration through a central port if available is always preferred versus a peripheral line.

Patients will be asked to maintain adequate hydration (1.5-2 L/day) 48 hours before initiating therapy, and IV fluid administration is recommended for those who cannot maintain adequate oral hydration.

Patients in Part A will receive 90 mg [$^{14}$C]subasumstat IV solution containing 100 µCi (approximately 3.7 MBq; equivalent to 2.74 mrem or 0.0274 mSv whole body effective dose for human male subjects and 1.41 mrem or 0.0141 mSv whole body effective dose for human female subjects) on Day 1.

Patients continuing with Part B will receive subasumstat IV 90 mg BIW (on days 1, 4,8, and 11 of a 21-day cycle), starting on day 14 of the study. Patients will receive a total of 3 cycles(21-days) of subasumstat, followed by weekly maintenance dosing for up to 1 year.

### 8.2 List of European Union Auxiliary Medicinal Products

Auxiliary medicinal products (AxMPs) may be used in this study. Tocilizumab is an interleukin-6 (IL-6) receptor antagonist. Tocilizumab is an authorized AxMP in the European Union, and in this study, it is indicated for the management of CRS, which is a potential adverse event of the study

drug Subasumstat. Tocilizumab for intravenous infusion injection comes as: 80 mg/4 mL, 200 mg/10 mL, 400 mg/20 mL as a clear, colorless to pale yellow solution in 20 mg/mL single-dose vials for further dilution prior to intravenous infusion. The recommended dose of tocilizumab to treat CRS is 12 mg/kg for body weight <30 kg and 8 mg/kg for body weight ≥30 kg. The dose will be given as 60-minute intravenous infusion. For information on the preparation and administration of tocilizumab, refer to the individual product label.

## 8.3 Dose Modification Guidelines (Part B)

### 8.3.1 Criteria for Beginning or Delaying a Subsequent Treatment Cycle

Treatment with subasumstat in Part B will use a cycle length of 21 days. To initiate a new cycle of subasumstat treatment, the patient must meet the following dosing criteria:

- Absolute neutrophil count $\geq 1.0 \times 10^9$/L.
- Platelet count $\geq 75.0 \times 10^9$/L.

Additionally, subasumstat–related AEs or laboratory abnormalities must have returned to ≤Grade 1/baseline (other than those stated above). If the patient fails to meet the above-cited criteria for retreatment, initiation of the next cycle of treatment should be delayed for 1 week. At the end of that time, the patient should be re-evaluated to determine whether the criteria for retreatment have been met. Should the start of the next cycle need to be delayed for more than 2 weeks because of incomplete recovery from treatment-related toxicity, the patient may be withdrawn from treatment unless there is clinical benefit as assessed by the investigator, with agreement by the sponsor's medical monitor. If clinical benefit for the individual patient is confirmed, recovery period can be extended or retreatment at the same or reduced dose can be started without complete recovery.



### 8.3.2 Criteria for Dose Interruption or Reduction During a Cycle

All toxicities that occur during the study will be actively managed following the standard of care unless otherwise specified in the protocol. Patients with AEs attributed to subasumstat may continue study treatment, may have subasumstat treatment withheld, or may be permanently discontinued from the study. Patients who have study drug withheld because of treatment-related or possibly related AEs should resume study drug treatment after resolution of the AE to Grade ≤1 or baseline (or Grade 2 for some specified hematological AEs as shown in Table 8.b).

Dosing of subasumstat should be interrupted or reduced to 60 mg according to the dose modification recommendations listed in Table 8.a for nonhematologic toxicity, Table 8.b for hematologic toxicities, and Table 8.d for CRS events. When the dose of subasumstat is withheld based on the listed criteria, clinical and laboratory reevaluation should be repeated at least weekly or more frequently, depending on the nature of the toxicity observed, until the toxicity resolves to the Grade specified in Table 8.a, Table 8.b and Table 8.d. If indicated, TAK-981 dose should be reduced to 60 mg.

If subasumstat cannot be administered in a 48-hour window because of an AE, the dose will be missed, and the patient will be scheduled for the next administration per the SOE (Appendix A).

In general, after a dose is reduced, it should not be re-escalated even if there is minimal or no toxicity with the reduced dose. However, if further evaluation reveals that the AE that led to the dose reduction was not study drug-related, or there were other circumstances contributing to the AE that are unlikely to recur, the dose may be re-escalated to the original dose level. If the dose of subasumstat would need to be reduced below 60 mg to manage subasumstat-related AEs, treatment with subasumstat should be discontinued.

**Table 8.a General Dose Modification Recommendations for Subasumstat Nonhematologic Drug-Related AEs**

| Criteria | Action |
|---|---|
| Grade 1 AEs | No dose reductions or interruptions. |
| Grade 2 AEs | Treat according to local practice.<br>Patients experiencing Grade 2 AEs considered related to study treatment that are not easily managed or corrected and are not tolerable to the patient, or AEs that are not acceptable in the investigator's judgment, should have study treatment interrupted until the AE resolves to Grade ≤1 or baseline and then restarted at the same dose or, depending on the toxicity, at 60 mg. |
| Grade 3 and Grade 4 non–life-threatening AEs | Hold subasumstat until resolution to Grade ≤1 or baseline, and then resume treatment at 60 mg.<br>Note: Permanently discontinue treatment if Grade ≥3 QTcF prolongation occurs. |
| Grade 4 life-threatening AEs | Permanently withdraw the patient from the study. |
| AEs of all grades | If treatment has been held for >14 consecutive days without resolution of the toxicity (to baseline or Grade ≤1 or if considered a sequela), consider permanently discontinuing study treatment unless there is clinical benefit for the patient as assessed by the investigator and with sponsor's approval. Treatment should be resumed at 60 mg after resolution of AEs to Grade ≤1 or baseline. |

AE: adverse event; CRS: cytokine release syndrome; QTcF: QT interval with Fridericia correction method.
For specific instructions in case of CRS, refer to Table 8.d.

## Table 8.b Dose Adjustments for Hematologic Toxicities

| Criteria | Action |
|---|---|
| Neutropenia (ANC) | |
| Grade 1 (ANC < LLN- 1.5 × $10^9$ cells/L) | Continue subasumstat at the same dose. |
| Grade 2 (ANC 1.0- <1.5 × $10^9$ cells/L) | Continue subasumstat at the same dose. |
| Grade 3 (ANC 0.5- <1 × $10^9$ cells/L) without fever | Withhold dose until resolved to ≤Grade 2 or baseline, then:<br>If resolved in ≤7 days, resume treatment at the same dose.<br>If resolved in >7 days, resume treatment at 60 mg. |
| Grade 4 (ANC <0.5 × $10^9$ cells/L) without fever | Withhold dose until resolved to ≤Grade 2 or baseline, then if resolved in ≤7 days, resume treatment at the same dose. If recovered in >7 days, second Grade 4 neutropenia event, ANC >0.1 × $10^9$/L, or concomitant occurrence of mucositis or thrombocytopenia, resume treatment at 60 mg. |
| Febrile neutropenia (ANC <1.0 × $10^9$ cells/L, with a single temperature of >38.3°C or sustained temperature of ≥38°C for more than 1 hour) | Withhold dose until fever/infection have recovered and ANC ≤Grade 2 or baseline, then resume treatment at 60 mg. |
| Thrombocytopenia (PLT) | Continue subasumstat at the same dose. |
| Grade 1 (PLT < LLN- 75.0 $10^9$ cells/L) | Continue subasumstat at the same dose. |
| Grade 2 (PLT <75.0 - 50.0 × $10^9$ cells/L) | Withhold dose until resolved to ≤Grade 1 or baseline, then: |
| Grade 3 (PLT <50.0 - 25.0 × $10^9$ cells/L) without bleeding | If resolved in ≤7 days, resume treatment at the same dose.<br>If resolved in >7 days, resume treatment at 60 mg. |
| Grade 4 (PLT <25.0 × $10^9$ cells/L) without bleeding | Withhold dose until resolved to ≤Grade 1 or baseline, then if resolved in ≤7 days, resume treatment at the same dose, if resolved in >7 days, then resume treatment at 60 mg. |
| PLT <10.0 × $10^9$ cells/L, thrombocytopenia ≥Grade 3 associated clinically significant bleeding, second event of Grade 4 thrombocytopenia >7 days | Consider permanently withdrawing the patient from the study, except when the investigator determines that the patient is obtaining clinical benefit and has discussed this with the sponsor, then resume treatment at 60 mg. |

ANC: absolute neutrophil count; LLN: lower limit of normal; PLT: platelet.

## Table 8.c TAK-981 Dose Modification Guidelines for CRS

| ASTCT Grade | TAK-981 Dose Modification |
|---|---|
| Grade 1:<br>Fever [a] (≥38°C) | Continue subasumstat at the same dose. |
| Grade 2:<br>Fever [a] (≥38°C)<br>with hypotension not requiring vasopressors;<br>and/or [b] hypoxia requiring low-flow [c] nasal cannula | Withhold dose until resolved to Grade ≤1, then:<br>• If resolved in ≤14 days, maintain dose.<br>• If resolved in >14 days or repeat event, reduce dose to 60 mg.<br>• If >2 consecutive doses of subasumstat are skipped due to CRS, permanently discontinue treatment with subasumstat. |
| Grade 3:<br>Fever [a] (≥38°C)<br>with hypotension requiring a vasopressor with or without vasopressin;<br>and/or [b] hypoxia requiring high-flow [c] nasal cannula, facemask, nonrebreather mask, or Venturi mask | Withhold dose until resolved to Grade ≤1, then:<br>• If resolved in ≤14 days, reduce dose and if toxicity does not recur, consider re-escalating to original dose.<br>• If resolved in >14 days or repeat event, reduce dose to 60 mg.<br>• If >2 consecutive doses of subasumstat are skipped due to CRS, permanently discontinue treatment with subasumstat. |
| Grade 4:<br>Fever [a] (≥38°C)<br>with hypotension requiring multiple vasopressors (excluding vasopressin);<br>and/or [b] hypoxia requiring positive pressure (eg, CPAP, BiPAP, intubation, and mechanical ventilation) | Permanently discontinue subasumstat. |

ASTCT: American Society for Transplantation and Cellular Therapy; BiPAP: bilevel positive airway pressure; CPAP: continuous positive airway pressure; CRS: cytokine release syndrome; DL: dose level.

ASTCT consensus grade adapted from Lee et. Al. 2019 (Lee et al. 2019); CRS management recommendations are adapted from Neelapu et al, 2018 (Neelapu et al. 2018) and should be implemented at the investigator's discretion.

[a] Fever is defined as temperature ≥38°C not attributable to any other cause. In patients who have CRS then receive antipyretic or anticytokine therapy such as tocilizumab or steroids, fever is no longer required to grade subsequent CRS severity. In this case, CRS grading is driven by hypotension and/or hypoxia.

[b] CRS grade is determined by the more severe event: hypotension or hypoxia not attributable to any other cause. For example, a patient with temperature of 39.5°C, hypotension requiring 1 vasopressor, and hypoxia requiring low-flow nasal cannula is classified as Grade 3 CRS.

[c] Low-flow nasal cannula is defined as oxygen delivered at ≤6 L/minute. High-flow nasal cannula is defined as oxygen delivered at >6 L/minute.

### 8.3.3 Criteria for Discontinuation of Subasumstat

In the event of discontinuation of study therapy, patients will undergo the early termination visit. Patients should discontinue treatment with subasumstat if they meet the criteria listed below.

Treatment with subasumstat must be discontinued for any of the following reasons:

- Occurrence of drug-related AEs that require study drug discontinuation per dose modification guidelines in Section 8.3.2.
- If subsequent cycle is delayed by >21 days for treatment-related AEs despite supportive treatment per standard clinical practice. (Exceptions to this criterion may be made after discussion and agreement between the investigator and the sponsor based on the benefit-risk assessment.)
- If more than 1 dose-level reductions of TAK-981 are required for a patient. (Exceptions to this criterion may be made after discussion and agreement between the investigator and the sponsor based on the benefit-risk assessment.)
- Occurrence of AEs resulting in discontinuation of study drug that is desired or considered necessary by the investigator and/or the patient (if applicable).



## 8.4 Prohibited Concomitant Medications and Procedures

The following medications and procedures are prohibited during the study:

- Strong and moderate CYP3A4/5 inhibitors and inducers (see list in Appendix E). During the study, should patients require the use of medications that are known to be strong and moderate inhibitors/inducers of CYP3A4/5, they should temporarily discontinue the use of subasumstat. Patients can resume treatment with subasumstat approximately 2 weeks or 5 times the half-life (whichever is shorter) after discontinuing the use of these strong and moderate inhibitors and inducers of CYP3A4/5.
- Concomitant corticosteroid administration of >20 mg of prednisone or equivalent unless given as treatment or prophylaxis for IRRs, as premedication for administration of certain blood products (80 mg methylprednisolone is accepted) or short courses (<96 hours) for exacerbations of respiratory tract disorders or for acute control of emerging tumor pain.
- Strong inhibitors of Pgp (see list in Appendix F).
- Initiation of prophylactic use of myeloid growth factors (eg, granulocyte-colony stimulating factor) are not allowed in the first cycle, but may be administered to manage patients who experience Grade 4 and/or febrile neutropenia if clinically indicated in accordance with American Society of Clinical Oncology guidelines and/or institutional practices. For the first episode of neutropenia, dose reduction is preferred.
- Patients currently on chronic erythropoietin support for anemia may continue to receive erythropoietin, but initiation of new erythropoietin therapy is not allowed during the first cycle.
- Any investigational agent other than subasumstat.

- Any concurrent antineoplastic therapy (eg, chemotherapy, hormonal therapy, immunotherapy, radiation therapy except for palliative radiation therapy and once progressive disease is ruled out) or standard or investigational agents for treatment of cancer.
- Drugs known to prolong QTc interval (see list in Appendix G).
- Because the safety of immunization with live viral vaccines following subasumstat therapy has not been studied, vaccination with live virus vaccines is prohibited while the patient is being treated on study.

## 8.5 Permitted Concomitant Medications and Procedures

All prescription and over-the-counter medications, including influenza vaccines, taken by a patient as of the first study drug administration through the EOS visit or before initiation of new anticancer therapy (whichever comes first) will be recorded in the designated electronic case report form (eCRF). Patients must be instructed not to take any medications, including over-the-counter medications and herbal supplements, without first consulting with the investigator.

The following medications and procedures are permitted while the patient is receiving the study drug:

- Topical or inhaled steroids (eg, for the treatment of asthma) are permitted.
- Patients should be transfused with red blood cells (RBCs) and platelets as clinically indicated.
- Concomitant treatment with bisphosphonates or receptor activator of nuclear factor kappa-B ligand inhibitors will be allowed for patients with evidence of lytic destruction of bone or with osteopenia, according to the American Society of Clinical Oncology Clinical Practice guidelines or institutional practice in accordance with the product label, unless specifically contraindicated.
- Narrow therapeutic range Pgp substrates such as digoxin or dabigatran may be used with caution, and patients requiring use of these drugs will be closely monitored.
- Coronavirus disease 2019 (COVID-19) vaccination is generally allowed for patients enrolled in the study with the exception of live attenuated vaccines, which must be completed at least 4 weeks before treatment initiation. COVID-19 vaccination should follow local guidances and regulations. Ideally, patients will have completed vaccination before treatment initiation. Vaccination should be avoided within ±3 days of subasumstat administration and should be administered after the last dose of subasumstat of a given cycle; study treatment may be delayed for up to 7 days to accommodate a vaccine dose administration after discussion with the sponsor. COVID-19 vaccine should be captured as a concomitant medication.

Additional concomitant medications and procedures are permitted during the study to prevent and actively manage AEs. Treatment of AEs with prohibited concomitant medications (except anticancer treatments) is allowed per the investigator's judgment. In this situation, treatment with subasumstat must be interrupted. Treatment with subasumstat may be resumed, if the patients

meets criteria for resuming treatment with subasumstat, once treatment with the prohibited medication is stopped and a washout period (7 days or 5 half-lives whichever is shorter) is completed. This situation requires discussion between the investigator and the medical monitor. Supportive measures consistent with optimal patient care may be given throughout the study.

## 8.6 Precautions and Restrictions

Precautions and requirements for a safe subasumstat administration are detailed in Section 8.1.

It is not known what effects subasumstat has on human pregnancy or development of the embryo or fetus; therefore, patients participating in this study should avoid becoming pregnant or avoid impregnating a partner. Nonsterilized female patients of reproductive age with a uterus and/or ovaries and patients with testes/testis should use effective methods of contraception through defined periods during and after study treatment as specified below.

Reproductively female patients must meet 1 of the following:

- Postmenopausal for at least 1 year before the screening visit, OR
- Surgically sterile, OR
- If they are of childbearing potential, agree to practice 1 highly effective method and 1 additional effective (barrier) method of contraception at the same time, from the time of signing of the ICF through 6 months after the last dose of study drug, OR
- Agree to practice true abstinence, when this is in line with the preferred and usual lifestyle of the patient. (Periodic abstinence [eg, calendar, ovulation, symptothermal, postovulation methods], withdrawal, spermicides only, and lactational amenorrhea are not acceptable methods of contraception. Female and male condoms should not be used together.)

Reproductively male patients, even if surgically sterilized (ie, status postvasectomy), must agree to 1 of the following:

- Agree to practice effective barrier contraception during the entire study treatment period and through 6 months after the last dose of study drug, OR
- Agree to practice true abstinence, when this is in line with the preferred and usual lifestyle of the patient. (Periodic abstinence [eg, calendar, ovulation, symptothermal, postovulation methods], withdrawal, spermicides only, and lactational amenorrhea are not acceptable methods of contraception. Female and male condoms should not be used together.)

Before starting treatment, patients should be advised to seek counseling on sperm or egg storage.

## 8.7 Management of Clinical Events

Therapies that are required to manage AEs and control cancer symptoms are allowed based on standard clinical practice, unless specifically excluded. Supportive care agents, such as erythropoietin, granulocyte-colony stimulating factor, blood products (RBC and platelet transfusions), and pain medications are permitted as needed per American Society of Hematology/American Society of Clinical Oncology guidelines or local institutional practice.

However, these agents should not be used in this study in a manner that would either help establish eligibility for the study. If dose alterations are necessary as a result of the events detailed below, refer to Section 8.3.

AxMP identified in the protocol as those that may be administered to patients when the effect of the investigational medicinal product (IMP) is likely to cause a hazard to the patient, or to manage an emergency situation.

In the sections below is guidance for the management of some expected AEs based on observations in nonclinical toxicology or other AEs that have not been substantiated in these experiments but that could be expected because of the MOA of TAK-981. This guidance is not expected to replace investigator judgment in the management of AEs.

### 8.7.1 Nausea or Vomiting

This study will not initially employ prophylactic antiemetics before the first dose of the study drug. However, a patient who develops nausea or vomiting will be actively managed by employing optimal antiemetic treatment based on local standard practice. Additionally, antiemetics may be used prophylactically as clinically indicated following the occurrence of a first event of study drug-related or possibly related nausea and/or vomiting. An optimal antiemetic regimen is defined as one that employs both a 5-hydroxytryptamine 3 serotonin receptor antagonist and a short course of corticosteroid given in standard doses and according to standard schedules. If these are inadequate, an NK-1 antagonist may be added.



### 8.7.2 Diarrhea

This study will not initially employ prophylactic antidiarrheals; however, there is no prohibition against their use in the management of a patient who develops diarrhea. Patients will be instructed to take antidiarrheal medication(s) at the physician's discretion until they are diarrhea-free for at least 12 hours. Fluid intake should be maintained to avoid dehydration.

### 8.7.3 Anemia, Thrombocytopenia, or Neutropenia

Please refer to Table 8.b for dose delay and reduction recommendations for hematologic toxicities. Subasumstat should be held if a significant treatment-emergent cytopenia or bleeding is suspected to be related to, or can be worsened by, study treatment. Precautionary measures should be taken to prevent bleeding and overwhelming infections. Blood transfusions (RBCs or platelet) and hematopoietic or thrombopoietic stimulating factors may be used to treat cytopenia/thrombocytopenia at the discretion of the investigator per standard clinical practice. In case of a first event, a dose reduction is preferred over the usage of myeloid growth factors.

### 8.7.4 Infusion Site Care

Skin lesions, which may include inflammation or necrosis, represent a potential risk and were observed at the injection site in rats. Local institutional guidelines must be applied to stress proper administration and prevention of accidental extravasation of subasumstat. Usage of IV ports is highly recommended. The IV line should be flushed at the end of the infusion accordingly to local

procedures. Monitoring at the beginning and during infusion must be ensured. If extravasation occurs, the infusion must be discontinued immediately, and institutional guidelines applied. Treatment and monitoring of patients until symptoms resolve should be consistent with institutional standards and guidelines as appropriate. Patients should be instructed to report any discomfort, pain or swelling at the infusion site.

### 8.7.5 Lymphopenia and Opportunistic Infection Prophylaxis

Because lymphopenia is an expected AE, patients may be at an increased risk of opportunistic pathogens. Subasumstat lymphopenia is expected to be fully reversible and limited in time, therefore no antibiotic or antiviral primary prophylaxis is indicated. It is also not known if all lymphocyte populations or just a subset are affected. Follow-up with standard hemograms and serial CD4/8 counts will help to make clinical decisions about the risk of immunosuppression. However, in the event of long-lasting lymphopenia, pneumocystis, or herpes zoster infection, prophylaxis can be started at investigator's discretion.



### 8.7.6 IRRs

Although subasumstat is not a biological, its immune activating properties may produce AEs in the category of IRRs. If they were to occur, it might manifest with fever, chills, rigors, headache, rash, pruritus, arthralgias, hypotension or hypertension, bronchospasm, or other symptoms. Treatment and monitoring of patients until symptoms resolve should be consistent with institutional standards and guidelines as appropriate. The patient should be closely monitored until recovery of symptoms. The patient will be permanently discontinued from the trial in case of a Grade 4 life-threatening reaction. All Grade 3 or 4 infusion reactions should be reported within 24 hours to the medical monitor and communicated as an SAE if criteria are met. Concomitant medications administered for infusion reaction treatment should be collected in the eCRF. If a patient presents signs and symptoms compatible with infusion reaction, and at investigator discretion, premedication can be instituted for the rest of the treatment.

### 8.7.7 CRS

CRS is a disorder characterized by fever, tachypnea, headache, tachycardia, hypotension, rash, and/or hypoxia caused by the release of cytokines. CRS should be diagnosed and managed following institutional guidelines. CRS should be graded following the American Society for Transplantation and Cellular Therapy (ASTCT) Consensus Grading for CRS (Lee et al. 2019). Investigators should try to differentiate CRS syndrome from other IRRs. Recommendations for management of CRS are shown in Table 8.d and can be implemented at the investigator's discretion.

## Table 8.d CRS Management Recommendations and Subasumstat Dose Modification

| ASTCT Consensus Grade | CRS Management Recommendations and TAK-981 Dose Modification |
|---|---|
| Grade 1:<br>Fever [a] (≥38°C) | • Monitor fluid status.<br>• Supportive care: antipyretics, analgesics.<br>*Subasumstat dosing*<br>• Continue subasumstat at the same dose level. |
| Grade 2:<br>Fever [a] (≥38°C)<br>with hypotension not requiring vasopressors;<br>and/or [b] requiring low-flow [c] nasal cannula | As per Grade 1 and:<br>• Closely monitor all organ functions, including cardiac function.<br>• IV fluid bolus.<br>• Supportive care.<br>*Subasumstat dosing*<br>• Withhold subasumstat until recovers to ≤Grade 1.<br>• Once recovered, restart subasumstat at the same dose level.<br>A maximum of 2 consecutive subasumstat doses can be skipped; otherwise TAK-981 must be permanently discontinued. |
| Grade 3:<br>Fever [a] (≥38°C)<br>with hypotension requiring a vasopressor with or without vasopressin;<br>and/or [b] requiring high-flow [c] nasal cannula, facemask, nonrebreather mask, or Venturi mask | As Grade 2 and:<br>• Closely monitor all organ functions, including cardiac function.<br>• Tocilizumab (8 mg/kg IV; maximum dose 800 mg) can be repeated after 6 hours.<br>• If refractory to tocilizumab, dexamethasone 10 mg IV every 6 hours; if refractory, increase to 20 mg every 6 hours or equivalent methylprednisone.<br>• Vasopressors as needed.<br>• Supplemental oxygen as needed for hypoxia (including high-flow $O_2$ and CPAP).<br>• Transfer to ICU.<br>*Subasumstat dosing*<br>• Withhold subasumstat until recovers to ≤Grade 1.<br>• If recovered within 2 weeks, reduce subasumstat by 1 dose level.<br>A maximum of 2 consecutive subasumstat doses can be skipped; otherwise subasumstat must be permanently discontinued. |
| Grade 4:<br>Fever [a] (≥38°C)<br>with hypotension requiring multiple vasopressors (excluding vasopressin);<br>and/or [b] requiring positive pressure (eg, CPAP, BiPAP, intubation and mechanical ventilation) | As per Grade 3 and:<br>• Substitute dexamethasone with methylprednisone 1 g IV per day.<br>• Mechanical ventilation.<br>*Subasumstat dosing*<br>• Permanently discontinue subasumstat. |

ASTCT: American Society for Transplantation and Cellular Therapy; BiPAP: bilevel positive airway pressure; CPAP: continuous positive airway pressure; CRS: cytokine release syndrome; ICU: intensive care unit; IV: intravenous; $O_2$: supplemental oxygen.
ASTCT consensus grade adapted from (Lee et al. 2019); CRS management recommendations are adapted from (Neelapu et al. 2018) and should be implemented at the investigator's discretion.
[a] Fever is defined as temperature ≥ 38°C not attributable to any other cause. In patients who have CRS then receive antipyretic or anticytokine therapy such as tocilizumab or steroids, fever is no longer required to grade subsequent CRS severity. In this case, CRS grading is driven by hypotension and/or hypoxia.
[b] CRS grade is determined by the more severe event: hypotension or hypoxia not attributable to any other cause. For example, a patient with temperature of 39.5°C, hypotension requiring 1 vasopressor, and hypoxia requiring low-flow nasal cannula is classified as grade 3 CRS.
[c] Low-flow nasal cannula is defined as oxygen delivered at ≤6 L/minute. High-flow nasal cannula is defined as oxygen delivered at >6 L/minute.



## 8.8 Blinding and Unblinding

This is an open-label study.

## 8.9 Description of Investigational Agents

Subasumstat drug product is an injection for IV use (solution for infusion). The solution provided to the clinical sites will contain 0.9 mg/mL [$^{14}$C]subasumstat in Part A and 10 mg/mL subasumstat in Part B. [redacted]

For specific information about the storage and handling of subasumstat drug product, refer to the study manual or pharmacy manual associated with a given study protocol or the instructions for use contained in the shipping package.

Full details are available in the IB.

## 8.10 Preparation, Reconstitution, and Dispensation

The reconstituted product will be administered by IV infusion over 1 hour (±10 minutes). After the end of the infusion the IV line should be flushed accordingly to local standards. Detailed reconstitution and dosage preparation instructions are provided in the directions for use located in the pharmacy manual.

In the absence of compatibility studies, this medicinal product must not be mixed with other medicinal products.

Subasumstat is an anticancer drug and, as with other potentially toxic compounds, caution should be exercised when handling subasumstat.

Reconstituted study products should be inspected visually for particulate matter and discoloration before administration, whenever solution and container permit.



## 8.11 Packaging and Labeling

All label information will fulfill requirements specified by local governing regulations. Additional details are provided in the pharmacy manual.

## 8.12 Storage, Handling, and Accountability

Complete receipt, inventory, accountability, reconciliation, and destruction records will be maintained for all used and unused study drug vials. A drug dispensing log, including records of drug received from the sponsor and drug dispensed to patients, will be provided and kept at the study site. Disposal instructions are provided in the pharmacy manual.

The required storage condition for subasumstat study drug is -20°C ± 5°C. Study drug must be stored under the conditions specified on the label and remain in the original container until dispensed. The investigator or designee must confirm that appropriate temperature conditions have been maintained for all subasumstat received and that any discrepancies are reported and resolved before use of subasumstat.

### 8.13 Other Protocol-Specified Materials

Information on supplies required by the site for drug administration is provided in the pharmacy manual. Clinical supplies other than study drug to be provided by the sponsor or designee are specified in the study manual.

## 9.0 STUDY CONDUCT

This trial will be conducted in compliance with the protocol, GCP, applicable regulatory requirements, and ICH guidelines.

### 9.1 Study Personnel and Organizations

The contact information for the project clinician for this study, the central laboratory and any additional clinical laboratories, the coordinating investigator for each member state/country, and other vendors, such as the interactive response technology provider and the contract research organization (CRO) team may be found in the study manual. A full list of investigators is available in the sponsor's investigator database.

For 24-hour contact information, please refer to the study manual or equivalent.



### 9.2 Arrangements for Recruitment of Patients

Recruitment and enrollment strategies for this study may include recruitment from the investigator's local practice or referrals from other physicians. If advertisements become part of the recruitment strategy, they will be reviewed by the institutional review board (IRB)/ independent ethics committee (IEC). Prisoners (or other populations that might be subject to coercion or exploitation) will not be enrolled into this study.

### 9.3 Informed Consent

Each patient must provide written or electronic informed consent before any protocol-directed procedures are conducted unless those procedures are performed as part of the patient's standard care.

The requirements of informed consent are described in Section 15.2.

### 9.4 Treatment Group Assignments

This is not a randomized study. All patients will receive the same study treatment.

### 9.5 Study Procedures

Refer to the SOE (Appendix A) for timing of assessments. Additional details are provided as necessary in the sections that follow. Unless otherwise noted, evaluations during the treatment period must occur before drug administration on scheduled visits. Tests and procedures should be performed on schedule for all visits.

### 9.5.1 Patient Demographics

The age, race, ethnicity, and sex of the patient are to be recorded during screening.

### 9.5.2 Medical History

During the screening period, a complete medical history will be compiled for each patient. The history will emphasize the background and progress of the patient's malignancy and include a description of prior therapies for it. In addition, concomitant medications will be recorded as specified in Section 8.5.

### 9.5.3 Confinement

In Part A, patients will check into the clinic on Day -1 and be confined from Day -1 to Day 5 as specified in the SOE (Table A-1, Appendix A). Patients will be required to stay at the study site through Day 5 or until the discharge criteria are met (Section 6.1.1.1), with a maximum estimated confinement period of 14 days.



### 9.5.4 Physical Examination

A full or symptom-directed physical examination will be completed per standard of care at the times specified in the SOE (Appendix A).

### 9.5.5 Patient Weight

Weight will be measured at screening, before and after dosing at the Day 1 visit and at the start of each cycle. If the weight measurement that occurs during screening occurs within 3 days of Day 1, this measurement can also be used as predose evaluations, and it does not need to be repeated.

### 9.5.6 Patient Height

Height will be measured only during screening (within 28 days before the first dose of subasumstat).

### 9.5.7 Vital Signs

Vital signs include measurements of systolic and diastolic blood pressure, heart rate, and body temperature. All vital signs are measured with the patient in a sitting or supine position. On days when subasumstat is administered, vital signs will be measured 20 minutes (±10 minutes) before the infusion, 30 minutes (±10 minutes) after the start of the infusion, 1 hour (±10 minutes) and 3 hours (±30 minutes) after end of the infusion. When the timing of the vital signs assessment coincides with the timing of a blood draw, vital signs will be measured before blood sample collection.

### 9.5.8 Pregnancy Test

A serum or urine pregnancy test will be obtained for women of childbearing potential as indicated in the SOEs (Table A-1 and A-2, Appendix A).

The result of the pregnancy test performed at screening must be negative before dosing. If the screening pregnancy test is performed within 3 days of Day 1, this test result can be used as the predose evaluation and does not need to be repeated.

Pregnancy tests are required for women of childbearing potential at the start of every cycle. Urine pregnancy tests are typically performed on Day 1 of the cycle. However, if a serum pregnancy test is used, this can be performed up to 3 days before Day 1. The negative results of the pregnancy test must be available before the first dose of the cycle is administered. A pregnancy test will also be performed for women of childbearing potential at the EOS/early termination visit. For women of childbearing potential, if menstrual period is delayed during the study, absence of pregnancy must be confirmed by serum pregnancy test. Pregnancy tests will be repeated during the study if requested by an IEC/IRB or if required by local regulations.

### 9.5.9 Concomitant Medications and Procedures

Concomitant medications and therapeutic procedures received by the patient will be recorded in the eCRF from the start of study drug administration through 30 days (+10 days) after the last dose of the study drug. See Section 8.4 and Section 8.5 for a list of medications and therapies that are prohibited or allowed during the study.



### 9.5.10 AEs

Monitoring of AEs, serious and nonserious, will be conducted throughout the study as specified in the SOE. Refer to Section 10.0 for details regarding definitions, documentation, and reporting of AEs and SAEs.

### 9.5.11 Enrollment

A patient is considered to be enrolled in the study when they receive the first dose of the study drug.

Procedures for completing enrollment information are described in the study manual.

### 9.5.12 ECG

A 12-lead ECG will be performed at the time points specified in the SOEs in Table A-1 and Table A-2 for Part A and B, respectively (Appendix A). ECGs are to be performed with the patient rested for 5 minutes.

ECGs will be performed before administration within 3 hours before and within 10 minutes (±30 minutes) after the subasumstat infusion on Day 1 in Part A and on Day 1 of Cycles 1 and 2 in Part B. From Cycle 3 onward, pre-subasumstat infusion and post-subasumstat infusion ECGs will be performed on Day 1 of every other cycle. Starting in Cycle 3, the post-subastumstat infusion ECG can be performed within 1 hour of the end of infusion.

When the timing of the ECG measurements coincides with the timing of a blood draw, the ECG should be completed before the blood sample collection, with the exception of the end of infusion PK sample, which will be collected before the ECG is completed.

### 9.5.13 Clinical Laboratory Evaluations

Clinical laboratory evaluations will be performed locally. Handling and shipment of clinical laboratory samples will be outlined in the study manual. Clinical laboratory evaluations will be performed as outlined below.

#### *9.5.13.1 Clinical Chemistry, Hematology, and Urinalysis*

Blood samples for analysis of the clinical chemistry and hematologic parameters are shown in Table 9.a and urine samples for analysis of the parameters shown in Table 9.b will be obtained as specified in the SOE (Appendix A).

**Table 9.a Clinical Chemistry and Hematology Tests**

| Hematology | Serum Chemistry | Coagulation |
|---|---|---|
| Hematocrit | Albumin | Activated partial thromboplastin time (aPTT) |
| Hemoglobin | Alkaline phosphatase | Prothrombin time (PT) |
| Leukocytes with differential | Alanine aminotransferase | Fibrinogen |
| ANC | Aspartate aminotransferase | |
| Platelets (count) | Bilirubin (total) | |
| | (Blood) Urea nitrogen (BUN) | |
| | Corrected calcium | |
| | Bicarbonate ($HCO3^-$) or Carbon dioxide ($CO_2$) | |
| | Creatinine | |
| | Chloride | |
| | Glucose | |
| | Lactate dehydrogenase (LDH) | |
| | Magnesium | |
| | Phosphate | |
| | Potassium | |
| | Sodium | |
| | Protein (total) | |
| | Urate | |

ANC: absolute neutrophil count.

**Table 9.b Clinical Urinalysis Tests**

| **Urinalysis** | |
|---|---|
| Bilirubin | pH |
| Glucose | Protein |
| Ketones | Specific gravity |
| Leukocytes | Turbidity and color |
| Nitrite | Urobilinogen |
| Occult blood | |

If creatinine CL is to be estimated, the Cockroft-Gault formula will be employed as follows:

$$Estimated\ creatinine\ clearance = [(140 - Age) * Mass(kg)\ ] / [72 * serum\ creatinine(mg/dL)]$$

For female patients, the result of the formula above should be multiplied by 0.85.

For transgender patients, use the sex at birth for patients not using hormone therapy or for patients who have used hormone therapy for <6 months; use the current gender for patients who have used hormone therapy for ≥6 months.



### 9.5.14 ECOG Performance Status

Performance status is to be assessed using the ECOG scale (see Appendix D for a description of the scale) at the times specified in the SOEs (Appendix A).

### 9.5.15 Disease Assessment by Imaging

Patients will undergo CT and/or MRI scans imaging to assess disease response and progression, using RECIST v1.1 criteria for solid tumors (Eisenhauer et al. 2009). The disease response will be assessed by the same radiological measurement throughout the study. For this study CT and/or MRI scans should be acquired with at least IV contrast. CT scans of the chest, abdominal cavity, and pelvis will be obtained at screening. The imaging modalities used for a patient should remain consistent throughout the study. If contrast-enhanced CT scans are contraindicated for a particular patient, a noncontrast CT of the chest, in addition to contrast-enhanced abdomen and pelvis MRIs should be acquired, if possible. Anatomical measurements (summed across target lesions) will be collected at baseline and each subsequent evaluation. In addition, nonmeasurable disease and new lesions will be documented and their status evaluated. Objective assessments of the disease burden (target, nontarget, and potential new lesions) will be performed at each time point as described in the SOE (Appendix A). Radiographic images will be maintained at the site and can be requested by the sponsor at a later date for centralized review of the images.

Bone scans should be collected as clinically indicated.

Imaging tests performed before the screening consent date, if of diagnostic quality, may be used as screening tests if Day 1 of the study is planned within the 28 days after the date of the test.

### 9.5.16 PK Measurements

Details regarding the preparation, handling, and shipping of samples are provided in the study and laboratory manuals. Any necessary actions will be taken to comply with the applicable rules and regulations regarding the collection, storage, and future use of biological samples from clinical trial subjects, where applicable.

#### *9.5.16.1 Blood Sampling*

During Part A, blood samples for TRA and PK assessments in whole blood (approximately 6 mL) and plasma (approximately 7 mL) will be drawn at the time points specified in Table A-1-a (Appendix A). Additional blood samples will be collected at each time point for metabolite profiling in plasma (approximately 10 mL).

The exact date and time of each sample collection and the actual start and stop times of the infusion should be recorded accurately, with particular care given to the recording of blood sampling times that occur close to the infusion. If the IV infusion is interrupted for more than 10 minutes, 2 additional PK samples (1 sample drawn when the infusion is stopped and 1 sample drawn when the infusion is restarted) should be collected so that the patient may be considered evaluable. The exact date and time of each additional sample collection and the actual start and stop times of the infusion should be recorded accurately.

Blood/plasma samples should be collected from the contralateral arm (not the arm which was used for drug infusion) if a peripheral line is used. If only a single arm is available, blood should be drawn as distal to the infusion site as feasible, and the site of the blood draw should be documented.



#### *9.5.16.2 Urine and Fecal Sampling*

In Part A, urine and fecal output will be collected over the minimum 5-day confinement period or until the discharge criteria are met (Section 6.1.1.1). Urine samples will be analyzed for PK, TRA, and metabolite profiling. Fecal samples will be analyzed for TRA, and metabolite profiling as specified in Table A-1-b (Appendix A).

#### *9.5.16.3 Vomitus Sampling*

For patients experiencing emesis after drug administration, the full vomitus will be collected as much as possible and assayed for TRA. If a subject vomits more than once during the period, vomitus corresponding to each vomiting event will be collected in a separated labeled container and separately counted.

## 9.6 Completion of Study Treatment (for Individual Patients)

Patients will be considered to have completed study treatment if they discontinue study drug for any of the reasons outlined in Section 9.8.

## 9.7 Completion of Study (for Individual Patients)

Based on the study purpose and endpoints, patients have completed Part A will be considered to have completed the study.

Patients who are not participating in Part B will be considered to have completed Part A if they received the single dose of [$^{14}$C]subasumstat, have completed the protocol-specified assessments, and finished the EOS visit. Patients who are participating in Part B will be considered to have completed Part A when they receive the first dose of Part B.

## 9.8 Discontinuation of Treatment With Study Drug, Patient Withdrawal, and Patient Replacement

Study drug can be permanently discontinued for patients meeting any of the following criteria:

- AE.
- Major protocol deviation.
- Progressive disease.
- Symptomatic deterioration.
- Unsatisfactory therapeutic response.
- Pregnancy (patient must be discontinued).
- Study terminated by sponsor.
- Withdrawal by patient.
- Lost to follow-up.
- Death.
- Other.



If a patient is withdrawn from the study during Part A, all study procedures outlined in the EOS visit will be completed as specified in the SOE. The primary reason for study drug discontinuation will be recorded on the eCRF. These patients will be replaced.

If a patient discontinues study drug treatment during Part B, all study procedures outlined in the early termination visit will be completed as specified in the SOE. The primary reason for study drug discontinuation will be recorded on the eCRF. A phone call, 14 days postdischarge phone call, will be arranged 14 days postdischarge for AE collection purposes. These patients will not be replaced.

## 9.9 Study Compliance

Study drug will be administered or dispensed only to eligible patients under the supervision of the investigator or identified sub-investigator(s). The appropriate study personnel will maintain records of study drug receipt and dispensing.

# 10.0 ADVERSE EVENTS

## 10.1 Definitions

### 10.1.1 Pretreatment Event Definition

A pretreatment event is any untoward medical occurrence in a patient who has provided informed consent to participate in a study but before administration of any study medication; it does not necessarily have to have a causal relationship with study participation.

### 10.1.2 AE Definition

AE means any untoward medical occurrence in a patient or subject administered a pharmaceutical product; the untoward medical occurrence does not necessarily have a causal relationship with this treatment. An AE can therefore be any unfavorable and unintended sign (including an abnormal laboratory finding), symptom, or disease temporally associated with the use of a medicinal (investigational) product whether or not it is related to the medicinal product. This includes any newly occurring event or a previous condition that has increased in severity or frequency since the administration of study drug.

An abnormal laboratory value will not be assessed as an AE unless that value leads to discontinuation or delay in treatment, dose modification, therapeutic intervention, or is considered by the investigator to be a clinically significant change from baseline.



### 10.1.3 SAE Definition

SAE means any untoward medical occurrence that at any dose:

- Results in **death.**
- Is **life-threatening** (refers to an AE in which the patient was at risk of death at the time of the event. It does not refer to an event which hypothetically might have caused death if it were more severe).
- Requires inpatient **hospitalization or prolongation of an existing hospitalization** (see clarification in the paragraph in Section 10.2 on planned hospitalizations).
- Results in **persistent or significant disability or incapacity**. (Disability is defined as a substantial disruption of a person's ability to conduct normal life functions).
- Is a **congenital anomaly/birth defect**.
- Is a **medically important event**. This refers to an AE that may not result in death, be immediately life-threatening, or require hospitalization, but may be considered serious when, on the basis of appropriate medical judgment, it may jeopardize the patient, require medical or surgical intervention to prevent one of the outcomes listed above, or involves suspected transmission via a medicinal product of an infectious agent. Examples of such medical events include allergic bronchospasm requiring intensive treatment in an emergency room or at home, blood dyscrasias or convulsions that do not result in inpatient hospitalization, or the

development of drug dependency or drug abuse; any organism, virus, or infectious particle (eg, prion protein transmitting transmissible spongiform encephalopathy), pathogenic or nonpathogenic, is considered an infectious agent.

In this study, intensity for each AE, including any laboratory abnormality, will be determined using the NCI CTCAE, version 5.0, effective 27 November 2017 (ctep.cancer.gov/protocoldevelopment/electronic_applications/docs/CTCAE_v5_Quick_Reference_8.5x11.pdf, CTCAE, Accessed 27 February 2023), except for CRS events, which will be graded according to the ASTCT Consensus Grading for CRS (Lee et al. 2019).

Clarification should be made between an SAE and an AE that is considered severe in intensity (Grade 3 or 4) because the terms *serious* and *severe* are NOT synonymous. The general term *severe* is often used to describe the intensity (severity) of a specific event; the event itself, however, may be of relatively minor medical significance (such as a Grade 3 headache). This is NOT the same as *serious*, which is based on patient/event outcome or action criteria described above and is usually associated with events that pose a threat to a patient's life or ability to function. A severe AE (Grade 3 or 4) does not necessarily need to be considered serious. For example, a white blood cell count of 1000/mm$^3$ to less than 2000/mm$^3$ is considered Grade 3 (severe) but may not be considered serious. Seriousness (not intensity) serves as a guide for defining regulatory reporting obligations.



### 10.1.4 Special Situation Report Definition

A special situation report (SSR) is defined as any of the following events:

- Abuse: persistent or sporadic, intentional excessive use of medicinal products which is accompanies by harmful physical or psychological effects.
- Misuse: situations where the medicinal product is intentionally and inappropriately used not in accordance with the prescribed or authorized dose, route of administration, and/or the indication(s) or within the legal status of its supply.
- Medication Error: an unintentional error in the drug treatment process (prescribing, dispensing or administration, including incorrect dose or poor quality administration) of a medicinal product while in the control of a health care provider, patient, or consumer, which leads to harm or has the potential to lead to harm.
- Overdose: the administration of a quantity of medicinal product given per administration or per day, which is above the maximal dose according to protocol.

## 10.2 Procedures for Recording and Reporting AEs and SAEs

All AEs spontaneously reported by the patient or in response to an open question from study personnel or revealed by observation, physical examination, or other diagnostic procedures will be recorded on the appropriate page of the eCRF (see Section 10.3 for the period of observation). Any clinically relevant deterioration in laboratory assessments or other clinical finding is considered an AE. When possible, signs and symptoms indicating a common underlying pathology should be noted as a single comprehensive event.

Regardless of causality, SAEs must be reported (see Section 10.3 for the period of observation) by the investigator to the Takeda Global Pharmacovigilance department or designee within 24 hours of becoming aware of the event. This will be done by transmitting an electronic data capture (EDC) SAE report. If transmission of an EDC SAE report is not feasible, then a facsimile of the completed Takeda paper-based SAE form will be sent. A sample of the paper-based SAE form and processing directions are in the Study Manual. Information in the SAE report or form must be consistent with the data provided on the eCRF.

If information not available at the time of the first report becomes available at a later date, then the investigator will transmit a follow-up EDC SAE report (or a paper-based SAE form if an EDC SAE report is not feasible) or provide other documentation immediately within 24 hours of receipt. Copies of any relevant data from the hospital notes (eg, ECGs, laboratory tests, discharge summary, postmortem results) should be sent to the addressee, if requested.

All SAEs should be followed up until resolution or permanent outcome of the event. The timelines and procedure for follow-up reports are the same as those for the initial report.

Planned hospital admissions or surgical procedures for an illness or disease that existed before the patient was enrolled in the study are not to be considered AEs unless the condition deteriorated in an unexpected manner during the study, eg, surgery was performed earlier or later than planned.

For both serious and nonserious AEs, the investigator must determine both the severity (toxicity grade) of the event and the relationship of the event to study drug and AxMP administration.

Severity (toxicity grade) for each AE, including any laboratory abnormality and excluding CRS events, will be determined using the NCI CTCAE, version 5.0. The criteria are provided in the study manual. The severity of CRS events will be graded according to the ASTCT Consensus Grading for CRS (Lee et al. 2019).



**Relationship** of the event to study drug administration or AxMP (ie, its causality) will be determined by the investigator responding yes (related) or no (unrelated) to this question: Is there a reasonable possibility that the AE is associated with the study drug?

### 10.2.1 Recording and Reporting AEs and SAEs Related to AxMPs

The use of AxMPs is required in this study for the management of CRS (Section 8.2). The investigator must report nonserious AEs related to an AxMP (ie, adverse drug reactions) within 7 calendar days of awareness by transmitting an EDC report and provide a causality assessment for each SAE as it relates to an AxMP, and report the SAE to Takeda Global Pharmacovigilance within 24 hours of awareness. If transmission of the EDC report is not feasible, a paper SAE report form must be sent.

## 10.3 Monitoring of AEs and Period of Observation

AEs, both nonserious and serious, will be monitored throughout the study as follows:

- AEs will be reported from the signing of informed (e)consent through 30 days (+/-5 days [where +/-5 days is the possible collection window]) after administration of the last dose of study drug and recorded in the eCRFs.
- SAEs will be reported to the Takeda Global Pharmacovigilance department or designee from the signing of informed (e)consent through 30 days (+/-5 days [where +/-5 days is the possible collection window]) after administration of the last dose of study drug and recorded in the eCRF. After this period, only related SAEs must be reported to the Takeda Global Pharmacovigilance department or designee. SAEs should be monitored until they are resolved or are clearly determined to be due to a patient's stable or chronic condition or intercurrent illness(es).
- AEs of special interest will be reported and monitored as stated in the SAE section.



## 10.4 Procedures for Reporting Drug Exposure During Pregnancy and Birth Events

If a patient becomes pregnant or suspects pregnancy while participating in this study, the patient must inform the investigator immediately and permanently discontinue study drug. The sponsor must also be contacted immediately by sending a completed pregnancy form to the Takeda Global Pharmacovigilance department or designee. The pregnancy must be followed for the final pregnancy outcome.

If a patient impregnates a partner during participation in this study, the sponsor must also be contacted immediately by sending a completed pregnancy form to the Takeda Global Pharmacovigilance department or designee. Every effort should be made to follow the pregnancy for the final pregnancy outcome.

## 10.5 Procedures for Reporting Product Complaints or SSRs (Including Overdose)

A product complaint is a verbal, written, or electronic expression that implies dissatisfaction regarding the identity, strength, purity, quality, or stability of a drug product, device, or combination product. Individuals who identify a potential product complaint situation should immediately report this via the contact information provided in the study manual.

SSRs are defined as medication errors and uses outside of what is foreseen in the protocol, including overdose, misuse, and abuse of the product. SSRs may or may not be associated with an AE/SAE. SSRs must be reported to Takeda Global Patient Safety Evaluation (Takeda Global Pharmacovigilance department or designee) using a paper SSR form within 7 calendar days of awareness via the contact information provided in the study manual. If an SSR is associated with an SAE, the SAE must be reported to Takeda Global Patient Safety Evaluation within 24 hours of awareness.

Product complaints and SSRs in and of themselves are not AEs. If a product complaint or SSR results in an SAE, the SAE should be reported.

### 10.6 Safety Reporting to Investigators, IRBs or IECs, and Regulatory Authorities

The sponsor will be responsible for reporting all suspected unexpected serious adverse reactions and any other applicable SAEs to regulatory authorities, including the European Medicines Agency, investigators, and IRBs and IECs, as applicable, in accordance with national regulations in the countries where the study is conducted. Relative to the first awareness of the event by/or further provision to the sponsor or sponsor's designee, suspected unexpected serious adverse reactions will be submitted to the regulatory authorities as expedited reports within 7 days for fatal and life-threatening events and within 15 days for other serious events, unless otherwise required by national regulations. The sponsor will also prepare an expedited report for other safety issues where these might materially alter the current benefit-risk assessment of an IMP or that would be sufficient to consider changes in the IMP's administration or in the overall conduct of the study. The investigational site also will forward a copy of all expedited reports to his or her IRB or IEC in accordance with national regulations.

## 11.0 STUDY-SPECIFIC COMMITTEES

No steering committee, data safety monitoring committee, adjudication committee, or clinical endpoint committee will be used in this study

## 12.0 DATA HANDLING AND RECORDKEEPING

The full details of procedures for data handling will be documented in the data management plan. If selected for coding, AEs, medical history, and concurrent conditions will be coded using the Medical Dictionary for Regulatory Activities (MedDRA). Drugs will be coded using the World Health Organization (WHO) Drug Dictionary.



### 12.1 eCRFs

Completed eCRFs are required for each patient who signs an informed consent.

The sponsor or its designee will supply investigative sites with access to eCRFs and will make arrangements to train appropriate site staff in the use of the eCRF. These forms are used to transmit the information collected in the performance of this study to the sponsor, CRO partners, and regulatory authorities. Investigative sites must complete eCRFs in English.

After completion of the entry process, computer logic checks will be run to identify items such as inconsistent dates, missing data, and questionable values. Queries may be issued by Takeda personnel (or designee) and will be answered by the site.

Any change of, modification of, or addition to the data on the eCRFs should be made by the investigator or appropriate site personnel. Corrections to eCRFs are recorded in an audit trail that captures the old information, the new information, identification of the person making the correction, the date the correction was made, and the reason for the change.

The principal investigator must review the eCRFs for completeness and accuracy and must sign and date the appropriate eCRFs as indicated. Furthermore, the principal investigator must retain full responsibility for the accuracy and authenticity of all data entered on the eCRFs.

eCRFs will be reviewed for completeness and acceptability at the study site during periodic visits by study monitors. The sponsor (or designee) will be permitted to review the patient's medical and hospital records pertinent to the study to ensure accuracy of the eCRFs. The completed eCRFs are the sole property of the sponsor and should not be made available in any form to third parties, except for authorized representatives of appropriate governmental health or regulatory authorities, without written permission of the sponsor.

## 12.2 Record Retention

The investigator agrees to keep the records stipulated in Section 12.1 and those documents that include (but are not limited to) the study-specific documents, the identification log of all participating patients, medical records, temporary media such as thermal-sensitive paper, source worksheets, all original signed and dated informed (e)consent forms, patient authorization forms regarding the use of personal health information (if separate from the ICFs), electronic copies of eCRFs including the audit trail, and detailed records of drug disposition to enable evaluations or audits from regulatory authorities and the sponsor (or designees). Any source documentation printed on degradable thermal-sensitive paper should be photocopied by the site and filed with the original in the patient's chart to ensure long-term legibility. Furthermore, ICH E6 Section 4.9.5 requires the investigator to retain essential documents specified in ICH E6 (Section 8) until at least 2 years after the last approval of a marketing application for a specified drug indication being investigated or, if an application is not approved, until at least 2 years after the investigation is discontinued and regulatory authorities are notified. In addition, ICH E6 Section 4.9.5 states that the study records should be retained until an amount of time specified by applicable regulatory requirements or for a time specified in the clinical study site agreement between the investigator and sponsor.



Refer to the clinical study site agreement for the sponsor's requirements for record retention. The investigator should contact and receive written approval from the sponsor before disposing of any such documents.

Should the sponsor request a longer retention period, the head of the institution should discuss how long and how to retain those documents with the sponsor. In addition, the investigator and the head of the institution should retain the essential relevant documents until the receipt of a sponsor-issued notification to state the retention is no longer required.

When proceeding to a local post-marketing study, the investigator and the head of the institution are required to retain essential relevant documents until the later of the end of the re-examination or re-evaluation. However, if the sponsor requests a longer time period for retention, the head of the institution should discuss how long and how to retain those documents with the sponsor.

## 12.3 Data Protection

The confidentiality of records that may be able to identify patients will be protected in accordance with applicable laws, regulations, and guidelines.

After patients have consented to take part in the study, the sponsor and/or its representatives reviews their source documents and data collected during the study. These records and data may,

in addition, be reviewed by others including the following: independent auditors who validate the data on behalf of the sponsor; national or local regulatory authorities; and the IRB(s)/IEC(s) that gave approval for the study to proceed. The sponsor and/or its representatives accessing the records and data will take all reasonable precautions in accordance with applicable laws, regulations, and guidelines to maintain the confidentiality of patients' identities. Patients are assigned a unique identifying number; however, their initials and date of birth may also be collected, if permitted under local laws governing privacy.

The results of studies containing participants' unique identifying number, relevant source documents, and possibly initials and dates of birth, where allowed per local law, may be transferred to, and used in, other countries that may not afford the same level of protection applied within the countries where this study is conducted. The purpose of any such transfer would include: to support regulatory submissions, to conduct new data analyses to publish or present the study results, or to answer questions asked by regulatory or health authorities.

- Patients will be assigned a unique identifier by the sponsor. Any patient records or datasets that are transferred to the sponsor will contain the identifier only; patient names or any information that would make the patient identifiable will not be transferred.
- The patient must be informed that their personal study-related data will be used by the sponsor in accordance with local data protection law. The level of disclosure must also be explained to the patient, who will be required to give consent for their data to be used as described in the ICF.
- The patient must be informed that their source documents may be examined by Clinical Quality Assurance auditors or study monitors, by appropriate IRB/IEC members, and by inspectors from regulatory authorities.



In the event that a serious data breach affecting personal data is detected, the sponsor or its designee and the investigator (as applicable) will take appropriate corrective and preventive actions in response. These actions will be documented, and the relevant regulatory agency(ies) will be notified as appropriate. Where appropriate, the relevant individuals materially affected by the breach would also be notified; in the case of study patients, this would be done through the investigator.

Takeda applies certain measures to protect participants' personal data and prevent data breaches, detailed in a separate document (Compliance with National Requirements on Data Protection).

## 13.0 STATISTICAL METHODS

### 13.1 Statistical and Analytical Plans

A statistical analysis plan will be prepared and finalized before database lock. This document will provide further details regarding the definition of analysis variables and analysis methodology to address all study objectives.

### 13.1.1 Analysis Sets

The analysis sets are:

- Safety analysis set: Patients who have received at least 1 dose of study drug, even if incomplete. This set will be used for all safety analyses and some efficacy analyses.
- PK analysis set: Patients with sufficient dosing and PK data to reliably estimate at least 1 PK parameter. This set will be used for PK analyses.
- Tumor response-evaluable analysis set: Patients who have received at least 1 dose of study drug, with measurable disease at baseline, and have at least 1 postbaseline disease assessment, or was discontinued due to symptomatic deterioration or death before a postbaseline evaluation occurs. This set will be used for analyses of response.

### 13.1.2 Analysis of Demographics and Other Baseline Characteristics

Demographic and baseline characteristics will be summarized descriptively. Variables to be analyzed include sex, age, race, medical history, baseline disease characteristics, prior medications/therapies, ECG findings, and other parameters as appropriate. For continuous variables, descriptive statistics (number, mean, standard deviation, median, minimum, and maximum) will be provided. For categorical variables, patient counts and percentages will be provided. Categories for missing data will be presented as needed.



### 13.1.3 Efficacy Analysis

All efficacy analyses may be performed depending upon data availability.

#### *13.1.3.1 Primary Efficacy Analysis*

Efficacy is not a primary objective for this study.

#### *13.1.3.2 Secondary Efficacy Analysis*

Efficacy is not a secondary objective for this study.

#### *13.1.3.3 Exploratory Efficacy Analysis*

ORR is defined as the proportion of patients who achieve CR and PR (determined by the investigator) during the study and estimates of the ORR (CR + PR) will be presented with 2-sided 90% exact binomial CIs.

Response assessments are based on RECIST v1.1 for solid tumors.

Other exploratory efficacy endpoints for Part B include PFS, best response (CR, PR, etc.) and DOR.

PFS is defined as the time from the date of the first dose administration to the date of first documentation of progressive disease or death due to any cause, whichever occurs first. Patients

without documentation of progressive disease will be censored at the date of the last response assessment that is SD or better.

DOR is the time from the date of the first documentation of PR or better to the date of first documentation of progressive disease for responders (PR or better). Responders without documentation of progressive disease will be censored at the date of the last response assessment that is SD or better.

Best response is defined as the best response recorded after the first dose of the study drug until subsequent anti-cancer therapy or end of treatment, whichever is earlier. Responses assessed after disease progression will not be considered in determination of the best response.

PFS and DOR will be summarized descriptively using the Kaplan-Meier method. ORR and best response will be analyzed using the tumor response-evaluable analysis set.

### 13.1.4 PK Analysis

All data will be summarized using descriptive statistics and will be listed and summarized in tabular and/or graphical form. The following PK parameters will be calculated by noncompartmental analysis and tabulated for each individual:

- TRA in plasma and whole blood: $C_{max}$, $t_{max}$, $AUC_{last}$, and as permitted by data, $t_{1/2z}$ and $AUC_{\infty}$.
- TRA in urine: amount of [$^{14}$C]-radioactivity excreted into urine per sampling interval ($Ae_{urine}$, $^{14}C_{,t1-t2}$ in ng-eq and percentage of dose) and cumulative amount of [$^{14}$C]-radioactivity excreted in urine up to the last sampling interval ($Ae_{urine}$, $^{14}C$ in ng-eq and percentage of dose).
- TRA in feces: amount of [$^{14}$C]-radioactivity excreted into feces per sampling interval ($Ae_{feces}$, $^{14}C_{,t1-t2}$ in ng-eq and percentage of dose) and cumulative amount of [$^{14}$C]-radioactivity excreted in feces up to the last sampling interval ($Ae_{feces}$, $^{14}C$ in ng-eq and percentage of dose).
- The total cumulative excretion of [$^{14}$C]-radioactivity per interval and over the total collection period will be calculated as the sum of the cumulative excretion in urine and feces: total cumulative excretion of [$^{14}$C]-radioactivity from the body ($Ae_{total}$, $^{14}C = Ae_{urine}$, $^{14}C + Ae_{feces}$, $^{14}C$) (in ng-eq and percentage of dose).
- Subasumstat in plasma and whole blood: $C_{max}$, $t_{max}$, $AUC_{last}$, and as permitted by data, $t_{1/2z}$, $AUC_{\infty}$, CL, and $V_{ss}$.
- Subasumstat in urine (per sampling interval and total): cumulative amount excreted in urine ($Ae_{urine}$ and percentage of dose) and $CL_R$.

Additionally, one of the secondary objectives of this study is to collect plasma, urine, and feces for metabolite profiling and identification. While the results of the PK of subasumstat and TRA, time course of excretion of TRA in urine and feces, and overall mass balance will be included in the clinical study report, the metabolite profiling and identification results will be reported separately.

### 13.1.5 Safety Analysis

Safety will be evaluated by the frequency of AEs, severity and types of AEs, and by changes from baseline in patients' vital signs, weight, and clinical laboratory results using the safety analysis set. All safety analyses will be performed based on data availability.

Exposure to study drug and reasons for discontinuation will be tabulated.

TEAEs that occur after administration of the first dose of the study drug and through 30 days after the last dose of the study will be tabulated.

AEs will be tabulated according to the MedDRA coding system and will include the following categories:

- TEAEs.
- Study drug-related TEAEs.
- Grade 3 or higher TEAEs.
- Grade 3 or higher study drug-related TEAEs.
- The most commonly reported TEAEs (ie, those reported by ≥10% of all patients).
- SAEs.
- Study drug-related SAEs.
- On-study deaths (ie, death that occurs between the first dose of any study drug and within 30 days of the last dose of any study drug).
- TEAE leading to study dose modification and discontinuation.



Descriptive statistics for the actual values of clinical laboratory parameters and/or change from baseline in clinical laboratory parameter will be presented for all scheduled measurements over time. Mean laboratory values over time will be plotted for key laboratory parameters.

Descriptive statistics for the actual values and/or the changes from baseline of vital signs and weight will be tabulated by scheduled time point. ECOG performance statuses will be summarized using a shift table.

Shift tables for laboratory parameters will be generated for changes in NCI CTCAE grade from baseline to the worst postbaseline value. Graphical displays of key safety parameters, such as scatter plots of baseline versus worst baseline values may be used to understand the subasumstat safety profile. The number and percentage of patients with clinically significant abnormal laboratory values will also be tabulated as appropriate.

All concomitant medications collected from the first dose of study drug throughout the study period will be classified to preferred terms according to the WHO Drug Dictionary.

Additional safety analyses may be performed to clearly enumerate rates of toxicities and to further define the safety profile of subasumstat.

### 13.2 Interim Analysis and Criteria for Early Termination

No interim analysis is planned.

### 13.3 Determination of Sample Size

The sample size for this study is not based on statistical considerations. On the basis of the As Low (radioactive burden) As Reasonable Achievable (ALARA) principle set forth in the 96/29/EURATOM directive, a sample size of approximately 6 PK-evaluable patients is considered sufficient to provide adequate characterization of the mass balance, PK, metabolism and excretion of subasumstat in patients with cancer. Patients will be replaced if they are not evaluable for PK.

## 14.0 QUALITY CONTROL AND QUALITY ASSURANCE

### 14.1 Study-Site Monitoring Visits

Monitoring visits to the study site will be made periodically during the study to ensure that all aspects of the protocol are followed. Where permitted by local and country regulations, alternative approaches such as remote source data review via phone or video may be used to ensure data quality and integrity and patient safety. Additional details are in the monitoring plan. Source documents will be reviewed for verification of data recorded on the eCRFs. Source documents are defined as original documents, data, and records. The investigator and institution guarantee access to source documents by the sponsor or its designee (CRO) and by the IRB or IEC.



All aspects of the study and its documentation will be subject to review by the sponsor or designee including, but not limited to, the investigator's binder, study medication, patient medical records, informed consent documentation, documentation of patient authorization to use personal health information (if separate from the ICFs), and review of eCRFs and associated source documents. It is important that the investigator and other study personnel are available during the monitoring visits and that sufficient time is devoted to the process.

### 14.2 Protocol Deviations

The investigator should not deviate from the protocol, except where necessary to eliminate an immediate hazard to study patients. Should other unexpected circumstances arise that will require deviation from protocol-specified procedures, the investigator should consult with the sponsor or designee (and IRB or IEC, as required) to determine the appropriate course of action. There will be no exemptions (a prospectively approved deviation) from the inclusion or exclusion criteria.

The site should document all protocol deviations in the patient's source documents. In the event of a significant deviation, the site should notify the sponsor or its designee (and IRB or EC, as required). Significant deviations include, but are not limited to, those that involve fraud or misconduct, increase the health risk to the patient, or confound interpretation of the primary study assessment.

The sponsor will assess any protocol deviation; if it is likely to affect to a significant degree the safety and rights of a patient or the reliability and robustness of the data generated, it may be reported to regulatory authorities as a serious breach of GCP or the protocol. In the event that a

protocol deviation has been identified as being a serious breach of GCP or the protocol, the serious breach shall be documented and reported to the appropriate regulatory authorities. Appropriate corrective and preventive actions shall be taken in response to any serious breach of GCP or the protocol.

### 14.3 Quality Assurance Audits and Regulatory Agency Inspections

The study site also may be subject to quality assurance audits by the sponsor or designees. In this circumstance, the sponsor-designated auditor will contact the site in advance to arrange an auditing visit. The auditor may ask to visit the facilities where laboratory samples are collected, where the medication is stored and prepared, and any other facility used during the study. In addition, there is the possibility that this study may be inspected by regulatory agencies, including those of foreign governments (eg, the United States [US] Food and Drug Administration [FDA], the United Kingdom [UK] Medicines and Healthcare products Regulatory Agency [MHRA], the Pharmaceuticals and Medical Devices Agency of Japan [PMDA]). If the study site is contacted for an inspection by a regulatory body, the sponsor should be notified immediately. The investigator and institution guarantee access for quality assurance auditors to all study documents as described in Section 14.1.



## 15.0 ETHICAL ASPECTS OF THE STUDY

This study will be conducted with the highest respect for the individual participants (herein "patients") according to the protocol, the ethical principles that have their origin in the Declaration of Helsinki, and the ICH Harmonised Tripartite Guideline for GCP. Each investigator will conduct the study according to applicable local or regional regulatory requirements and align his or her conduct in accordance with the responsibilities of the investigator that are listed in Appendix B. The principles of Helsinki are addressed through the protocol and through appendices containing requirements for informed consent and investigator responsibilities.

### 15.1 IRB and/or IEC Approval

IRBs and IECs must be constituted according to the applicable state and federal/local requirements of each participating region. The sponsor or designee will require documentation noting all names and titles of members who make up the respective IRB or IEC. If any member of the IRB or IEC has direct participation in this study, written notification regarding his or her abstinence from voting must also be obtained.

The sponsor or designee will supply relevant documents for submission to the respective IRB or IEC for the protocol's review and approval. This protocol, the IB, a copy of the ICF, and, if applicable, patient recruitment materials and advertisements and other documents required by all applicable laws and regulations must be submitted to a central or local IRB or IEC for approval. The IRB's or IEC's written approval of the protocol and patient informed consent must be obtained and submitted to the sponsor or designee before commencement of the study, ie, before shipment of the sponsor-supplied drug or study-specific screening activity. The IRB or IEC approval must refer to the study by its exact protocol title, number, and version date; identify versions of other documents (eg, ICF) reviewed; and state the approval date. If required by country

or regional regulations or procedures, approval from the competent regulatory authority will be obtained before commencement of the study or implementation of a substantial amendment. The sponsor will ship drug/notify site once the sponsor has confirmed the adequacy of site regulatory documentation and, when applicable, the sponsor has received permission from the competent authority to begin the trial. Until the site receives drug/notification, no protocol activities, including screening, may occur.

Sites must adhere to all requirements stipulated by their respective IRB or IEC. This may include notification to the IRB or IEC regarding protocol amendments, updates to the ICF, recruitment materials intended for viewing by patients, local safety reporting requirements, reports and updates regarding the ongoing review of the study at intervals specified by the respective IRB or IEC, and submission of the investigator's final status report to IRB or IEC. All IRB and IEC approvals and relevant documentation for these items must be provided to the sponsor (or designee).

Patient incentives should not exert undue influence for participation. Payments to patients must be approved by the IRB or IEC and sponsor.



## 15.2 Patient Information, Informed Consent, and Patient Authorization

Written and electronic consent documents will embody the elements of informed consent as described in the Declaration of Helsinki and the ICH Guidelines for GCP and will be in accordance with all applicable laws and regulations. The ICF, patient authorization form (if applicable), and patient information sheet (if applicable) describe the planned and permitted uses, transfers, and disclosures of the patient's personal and personal health information for purposes of conducting the study, including the use of electronic devices and associated technologies (if applicable). The ICF and the patient information sheet (if applicable) further explain the nature of the study, its objectives, and potential risks and benefits, and the date informed consent is given. The ICF will detail the requirements of the participant and the fact that he or she is free to withdraw at any time without giving a reason and without prejudice to his or her further medical care.

The investigator is responsible for the preparation, content, and IRB or IEC approval of the ICF and, if applicable, the patient authorization form. The ICF, patient authorization form (if applicable), and patient information sheet (if applicable) must be approved by both the IRB or IEC and the sponsor before use.

The ICF, patient authorization form (if applicable), and patient information sheet (if applicable) must be written in a language fully comprehensible to the prospective patient. It is the responsibility of the investigator to explain the detailed elements of the ICF, patient authorization form (if applicable), and patient information sheet (if applicable) to the patient. Information should be given in both oral and written form whenever possible and in the manner deemed appropriate by the IRB or IEC. If the patient is not capable of rendering adequate written or electronic informed consent, then the patient's legally acceptable representative may provide such consent for the patient in accordance with applicable laws and regulations.

The patient, or the patient's legally acceptable representative, must be given ample opportunity to (1) inquire about details of the study and (2) decide whether to participate in the study. If the

patient, or the patient's legally acceptable representative, determines that he or she will participate in the study, then the ICF and patient authorization form (if applicable) must be signed and dated by the patient, or the patient's legally acceptable representative, at the time of consent and before the patient enters into the study. The patient or the patient's legally acceptable representative should be instructed to sign using their legal names, not nicknames, using a ballpoint pen with either blue or black ink in the case of written informed consent. The investigator must also sign and date the ICF and patient authorization (if applicable) at the time of consent and before the patient enters into the study; however, the sponsor may allow a designee of the investigator to sign to the extent permitted by applicable law.

Once signed, the original ICF, patient authorization form (if applicable), and patient information sheet (if applicable) will be stored in the investigator's site file. The investigator must document the date the patient signs the informed consent in the patient's medical record. Copies of the signed ICF, the signed patient authorization form (if applicable), and patient information sheet (if applicable) shall be provided to the patient.

All revised ICFs must be reviewed and signed by relevant patients or the relevant patient's legally acceptable representative in the same manner as the original informed consent. The date the revised (e)consent was obtained should be recorded in the patient's medical record, and the patient should receive a copy of the revised ICF.



### 15.3 Patient Confidentiality

The sponsor and designees affirm and uphold the principle of the patient's right to protection against invasion of privacy. Throughout this study, a patient's source data will be linked to the sponsor's clinical study database or documentation only via a unique identification number. As permitted by all applicable laws and regulations, limited patient attributes, such as sex, age, or date of birth, and patient initials may be used to verify the patient and accuracy of the patient's unique identification number. In the event that a serious data breach is detected, the sponsor or its designee and the investigator (as applicable) will take appropriate corrective and preventive actions in response. These actions will be documented, and the relevant regulatory agency(ies) will be notified as appropriate. Where appropriate, the relevant individuals materially affected by the breach would also be notified; in the case of study patients, this would be done through the investigator.

To comply with ICH Guidelines for GCP and to verify compliance with this protocol, the sponsor requires the investigator to permit its monitor or designee's monitor, representatives from any regulatory authority (eg, US FDA, UK MHRA, Japan PMDA), the sponsor's designated auditors, and the appropriate IRBs and IECs to review the patient's original medical records (source data or documents) including, but not limited to, laboratory test result reports, ECG reports, admission and discharge summaries for hospital admissions occurring during a patient's study participation, and autopsy reports. Access to a patient's original medical records requires the specific authorization of the patient as part of the informed (e)consent process (see Section 15.2).

Copies of any patient source documents that are provided to the sponsor must have certain identifying personal information removed, eg, patient name, address, and other identifier fields not collected on the patient's eCRF.

## 15.4 Publication, Disclosure, and Clinical Trial Registration Policy

### 15.4.1 Publication

The investigator is obliged to provide the sponsor with complete test results and all data derived by the investigator from the study. During and after the study, only the sponsor may make study information available to other study investigators or to regulatory agencies, except as required by law or regulation. Except as otherwise allowable in the clinical study site agreement, any public disclosure (including publicly accessible websites) related to the protocol or study results, other than study recruitment materials and advertisements, is the sole responsibility of the sponsor.

The sponsor may publish any data and information from the study (including data and information generated by the investigator) without the consent of the investigator. Manuscript authorship for any peer-reviewed publication will appropriately reflect contributions to the production and review of the document. All publications and presentations must be prepared in accordance with this section and the clinical study site agreement. In the event of any discrepancy between the protocol and the clinical study site agreement, the clinical study site agreement will prevail.



### 15.4.2 Clinical Trial Registration

To ensure that information on clinical trials reaches the public in a timely manner and to comply with applicable laws, regulations, and guidance, Takeda will, at a minimum, register interventional clinical trials it sponsors anywhere in the world on ClinicalTrials.gov or other publicly accessible websites on or before start of study, as defined by Takeda policy/standards. Takeda contact information, along with investigator's city, state (for Americas investigators), country, and recruiting status will be registered and available for public viewing.

As needed, Takeda and investigator/site contact information may be made public to support participant access to trials via registries. In certain situations/registries, Takeda may assist participants or potential participants in finding a clinical trial by helping them locate trial sites closest to their homes by providing the investigator name, address, and phone number via email/phone or other methods preferred by callers requesting trial information. Once patients receive investigator contact information, they may call the site requesting enrollment into the trial. The investigative sites are encouraged to handle the trial inquiries according to their established patient screening process. If the caller asks additional questions beyond the topic of trial enrollment, they should be referred to the sponsor.

Any investigator who objects to Takeda providing this information to callers must provide Takeda with a written notice requesting that their information not be listed on the registry site.

### 15.4.3 Clinical Trial Results Disclosure

Takeda will post the results of clinical trials on ClinicalTrials.gov, clinicaltrialsregister.eu, and other publicly accessible websites (including the Takeda corporate site) and registries, as required by Takeda policy/standards, applicable laws, and/or regulations.

Data Sharing

The sponsor is committed to responsible sharing of clinical data with the goal of advancing medical science and improving patient care. Qualified independent researchers will be permitted to use data collected from patients during the study to conduct additional scientific research, which may be unrelated to the study drug or the patient's disease. The data provided to external researchers will not include information that identifies patients personally.

## 15.5 Insurance and Compensation for Injury

Each patient in the study must be insured in accordance with the regulations applicable to the site where the patient is participating. If a local underwriter is required, then the sponsor or sponsor's designee will obtain clinical study insurance against the risk of injury to clinical study patients. Refer to the clinical study site agreement regarding the sponsor's policy on patient compensation and treatment for injury. If the investigator has questions regarding this policy, he or she should contact the sponsor or sponsor's designee.



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# Appendix A Schedule of Events

## Table A-1 Schedule of Study Procedures: Part A

| | ADME Assessment Period | | | | | | | | | |
|---|---|---|---|---|---|---|---|---|---|---|
| | | Week 1 Confinement | | | | | | | Week 2 Discharge [b] | EOS [c] |
| | Screening [a] | Day -1 Predose | Day 1 Predose | Day 1 | Day 2 | Day 3 | Day 4 | Day 5 | Between Days 6 and 14 | |
| Confinement [d] | | X | X | X | X | X | X | X | | |
| **Study Drug Administration** | | | | | | | | | | |
| Single [$^{14}$C]subasumstat IV solution administration [e] | | | | X | | | | | | |
| **Study Procedures** | | | | | | | | | | |
| Informed consent | X | | | | | | | | | |
| Inclusion/exclusion criteria | X | | | | | | | | | |
| Demographics | X | | | | | | | | | |
| Medical history/prior therapy | X | | | | | | | | | |
| Full physical examination | X | | | | | | | | X | X |
| Symptom-directed physical examination | | X | X | | | | | | | |
| Height | X | | | | | | | | | |
| Weight | X | X [f] | | | | | | | | X |
| Vital signs [g] | X | X | | X | | | | | X | X |
| ECOG performance status | X | | | | | | | | X | X |
| 12-lead ECG [h] | X | | X [f] | X | | | | | | X |
| Disease assessment by imaging | X | | | | | | | | | |
| Monitoring of concomitant medications, therapies, and procedures | Recorded from start of study drug administration through 30 days (+/-5 days [where +/-5 days is the possible collection window]) after the last dose of study drug | | | | | | | | | |
| AE reporting [i] | Recorded from start of study drug administration through 30 days (+/-5 days [where +/-5 days is the possible collection window]) after the last dose of study drug | | | | | | | | | |

## Table A-1 Schedule of Study Procedures: Part A

| | ADME Assessment Period | | | | | | | | | EOS [c] |
|---|---|---|---|---|---|---|---|---|---|---|
| | | Week 1 Confinement | | | | | | | Week 2 Discharge [b] | |
| | Screening [a] | Day -1 Predose | Day 1 Predose | Day 1 | Day 2 | Day 3 | Day 4 | Day 5 | Between Days 6 and 14 | |
| | SAEs will be reported from signing of the ICF through 30 days (+/-5 days [where +/-5 days is the possible collection window]) after the last dose of study drug. | | | | | | | | | |
| **Samples/Laboratory Assessments** | | | | | | | | | | |
| Pregnancy test | X | X [f] | | | | | | | | X |
| Hematology/ chemistry [j, k] | X | X [f] | X [f] | | | | X | | X | X |
| Urinalysis | X | X [f] | X [f] | | | | | | X | X |
| Blood sample collection | See Table A-1-a for Blood Sampling Schedule | | | | | | | | | |
| Urine sample collection | See Table A-1-b for Urine Collection Sample Schedule | | | | | | | | | |
| Fecal sample collection [l] | See Table A-1-b for Fecal Collection Sample Schedule | | | | | | | | | |
| Vomitus | Vomitus to be collected if event occurred during first 24 hours after dosing and at any other vomiting events afterward | | | | | | | | | |

ADME: absorption, distribution, metabolism, excretion; AE: adverse event; ECG: electrocardiogram; ECOG: Eastern Cooperative Oncology Group; EOS: end of study; IV: intravenous; PK: pharmacokinetic; SAE: serious adverse event.

[a] Unless otherwise noted, the screening visit must occur within 28 days before the day of the first dose of study drug in Part A.

[b] Discharge criteria for Part A can be found in Section 6.1.1.1. Patients will be discharged between Days 6 and 14 given the discharge criteria has been met. Discharge assessments are done only once on the day of discharge.

[c] An EOS visit is needed in Part A only if the patient did not continue into Part B, and will occur 30 days (+/-5 days [where +/-5 days is the possible collection window]) after the last dose of study drug or before the start of subsequent therapy for the patient's indication, if that occurred sooner.

[d] During Part A, patients are required to stay at the Part A study site for at least 5 days postdose and until the discharge criteria are met, with a maximum estimated confinement period of 14 days postdose.

[e] Patients will receive a single dose of [$^{14}$C]subasumstat 90 mg given as a 1-hour IV infusion on Day 1. The clinic will be supplied with vials containing approximately 100 µCi (approximately 3.7 MBq) of [$^{14}$C]subasumstat as the radioactive tracer.

[f] Procedures conducted during screening that are performed within 3 days of Day 1 could also be used as the Day 1 predose evaluation and would not need to be repeated, with the exception of an ECG that was required to be repeated predose on Day 1.

[g] On days when subasumstat is administered, vital signs will be measured predose (20 minutes [±10 min]) before the infusion of subasumstat; 30 minutes (±10 min) after the start of

subasumstat dosing; and 1 hour (±10 min) and 3 hours (±30 min) after the completion of subasumstat dosing. All vital signs are measured with the patient in the sitting or supine position. When the timing of vital signs assessment coincides with the timing of a blood draw, vital signs will be measured before blood sample collection.

[h] A 12-lead ECG will be performed during screening and before administration (within 3 hours) of subasumstat on Day 1 and immediately after the subasumstat infusion is completed (±20 min) on Day 1. When the timing of ECG measurements coincide with the timing of a blood draw, the ECG should be completed before the blood sample collection, with the exception of the end of infusion PK sample, which will be collected before the ECG is completed.

[i] Including pretreatment serious adverse events; see Section 10.1.1.

[j] Hematology samples will be collected during screening and before dosing with study drug on Day 1. It is permitted that these samples may be drawn up to 1 day before dosing. If dosing falls on a Monday, the collection window could be extended to collect samples on the previous Friday. In addition, samples will be collected on Day 1 predose and postdose, at the time of discharge, and at the EOS visit.

[k] Clinical chemistry samples will be collected during screening, before dosing with study drug, and 3 hours (±30 min) after completion of the subasumstat infusion. Predose samples can be drawn within 24 hours predose. If dosing falls on a Monday, the collection window can be extended to collect samples on the previous Friday. In addition, samples will be collected on Day 1 predose and postdose, at the time of discharge, and at the EOS visit.

[l] Patients may be provided treatment for constipation if needed, as determined by the investigator.

## Table A-1-a Blood Sampling Schedule: Part A

| | | Whole Blood Sample Collection | Plasma Sample Collection | Plasma Sample Collection |
|---|---|---|---|---|
| **Study Day** | **Time Point (hour)** | **Blood 1 [a] Blood 2 [a]** | **Plasma 1 [b] Plasma 2 [b]** | **Plasma 3 [b]** |
| Day 1 | Predose [c] | X2 | X2 | X |
| Day 1 | EOI [d] (-5 to +1 min) | X2 | X2 | X |
| Day 1 | 0.5 hour post-infusion [e] (±5 min) | X2 | X2 | X |
| Day 1 | 1 hour post-infusion [e] (±15 min) | X2 | X2 | X |
| Day 1 | 2 hours post-infusion [e] (±15 min) | X2 | X2 | X |
| Day 1 | 4 hours post-infusion [e] (±45 min) | X2 | X2 | X |
| Day 1 | 8 hours post-infusion [e] (±1 hour) | X2 | X2 | X |
| Day 2 | 24 hours post-dose [f] (±1 hour) | X2 | X2 | X |
| Day 3 | 48 hours post-dose [f] (±2 hours) | X2 | X2 | X |
| Day 4 | 72 hours post-dose [f] (±3 hours) | X2 | X2 | X |
| Day 5 | 96 hours post-dose [f] (±4 hours) | X2 | X2 | X |
| Day 6 | 120 hours post-dose [f] (±4 hours) | X2 | X2 | X |
| Day 7 | 144 hours post-dose [f] (±4 hours) | X2 | X2 | |
| Day 8 | 168 hours post-dose [f] (±4 hours) | X2 | X2 | X |
| Day 9-14 | [g] | X2 | X2 | |

ADME: absorption, distribution, metabolism, excretion; EOI: end of infusion; IV: intravenous; X2: 2 samples will be collected; X: 1 sample will be collected.

[a] For determination of TRA (Blood 1) and subasumstat (Blood 2).

[b] For determination of TRA (Plasma 1), subasumstat (Plasma 2), and metabolite profiling (Plasma 3).

[c] The sample will be collected within 1 hour before the start of subasumstat infusion on Day 1.

[d] The window for collection of the EOI time point is between 5 minutes before completion of infusion and 1 minute after completion of infusion. If, during Part A, IV infusion of study drug is interrupted or slowed, the project clinician or designee will be contacted as soon as possible for consideration of patient replacement, as appropriate. If the IV infusion is interrupted, 2 additional PK samples (1 sample will be drawn when the infusion is stopped and 1 sample will be drawn when the infusion is restarted) will be collected so that the patient will be considered evaluable. The exact date and time of each additional sample collection and the actual start and stop times of the infusion will be recorded accurately.

[e] Samples will be collected after completion of subasumstat IV infusion on Day 1.

[f] Samples will be collected after initiation of the subasumstat IV infusion on Day 1.

[g] Samples will be continued to be collected at 24-hour intervals until discharge criteria has been met (ie, 90% or greater of the total dose of radioactivity administered is recovered from urine and fecal samples or until <1% of the dosed radioactivity is collected in 2 consecutive intervals when both urine and feces are collected).

## Table A-1-b Urine and Fecal Sample Collection Schedule: Part A

| | Time Interval (hour) [a] | Urine Sample Collection | Feces Sample Collection |
|---|---|---|---|
| **Study Day** | **Matrix** | **Urine [b]** | **Fecal [c]** |
| Day -1 | 0 (pre-dose) | X | X |
| Day 1 | 0-6 hours | X | X (0-24 hours) |
| Day 1 | 6-12 hours | X | |
| Day 2 | 12-24 hours | X | |
| Day 3 | 24-48 hours | X | X |
| Day 4 | 48-72 hours | X | X |
| Day 5 | 72-96 hours | X | X |
| Day 6-14 | d | X | X |

ADME: absorption, distribution, metabolism, excretion; IV: intravenous; TRA: total radioactivity; X: 1 sample will be collected.

[a] Sampling times are relative to the initiation of the IV infusion on Day 1.

[b] For determination of TRA, metabolite profiling, and subasumstat (urine).

[c] For determination of TRA and metabolite profiling (feces).

[d] Samples will be continued to be collected at 24-hour intervals until discharge criteria has been met (ie, 90% or greater of the total dose of radioactivity administered is recovered from urine and fecal samples or until <1% of the dosed radioactivity is collected in 2 consecutive intervals when both urine and feces are collected).

## Table A-2 Schedule of Study Procedures: Part B

| | Single Agent Subasumstat Treatment 21-Day Cycle, Cycles 1-3 [a] | | | | | Single Agent Subasumstat Treatment 21-Day Cycle, Cycles 4+ [a] | | | |
|---|---|---|---|---|---|---|---|---|---|
| | Day 1 Predose [b] | Day 1 | Day 4 | Day 8 | Day 11 | Day 1 Predose [b] | Day 1 | Day 8 | EOS/ Early Termination [c] |
| **Study Drug Administration** | | | | | | | | | |
| Subasumstat administration [d] | | X | X [e] | X | X [e] | | X | X | |
| **Study Procedures** | | | | | | | | | |
| Full physical examination | X | | | | | | | | X |
| Symptom-directed physical examination | | X | X [e] | X | X [e] | | X | X | |
| ECOG performance status | X [f] | X [f] | | | X | X [f] | X [f] | | X |
| Weight | X | | | | | | | | X |
| Vital signs [g] | X | X | X [e] | X | X [e] | X | X | X | X |
| 12-Lead ECG [h] | X | X | | | | X | X | | |
| Tumor assessments [i] | To be completed before dosing in Part B, end of Cycle 2, and every 3 cycles thereafter | | | | | | | | X |
| Monitoring of concomitant medications, therapies, and procedures | | Recorded from start of study drug administration in Part A through 30 days (+/-5 days [where +/-5 days is the possible collection window]) after the last dose of study drug in Part B | | | | | | | |
| AE reporting | | Recorded from start of study drug administration in Part A through 30 days (+/-5 days [where +/-5 days is the possible collection window]) after the last dose of study drug in Part B | | | | | | | |
| | | SAEs reported from signing of the ICF in Part A through 30 days (+/-5 days [where +/-5 days is the possible collection window]) after the last dose of study drug in Part B | | | | | | | |
| **Samples/Laboratory Assessments** | | | | | | | | | |
| Pregnancy test [j] | X | | | | | X | | | X |
| Hematology/chemistry [k] | X | X | X [e] | X | X [e] | X | X | X | X |
| Urinalysis | X | | | | | X | | | X |

AE: adverse event; BIW: twice weekly; CT: computed tomography; ECG: electrocardiogram; ECOG: Eastern Cooperative Oncology Group; EOS: end of study; ICF: informed consent form; IV: intravenous; MRI: magnetic resonance imaging; PK: pharmacokinetic; QW: once weekly; SAE: serious adverse event.

Tests and procedures are to be performed on schedule, but occasional changes are allowable (±2 days) for holidays, vacations, and other administrative reasons.

[a] Patients will receive subasumstat 90 mg in an induction treatment period of at least 3 cycles with BIW schedule (on days 1, 4, 8, and 11 of the 21-day cycle) schedule followed by maintenance with the QW schedule. From Cycle 4 onwards, patients can continue to receive treatment for up to 1 year.

[b] For patients to be eligible for dosing with subasumstat (Part B), they should meet certain entry criteria (see Section 7.0).

[c] If the patient continues into Part B, the EOS visit will occur 30 days (+/-5 days [where +/-5 days is the possible collection window]) after the last dose of study drug in Part B or before the start of subsequent therapy for the patient's indication, if that occurred sooner. A 14 days postdischarge phone call will be arranged for AE collection purpose.

[d] The infusion of subasumstat can be slowed or stopped and restarted for any associated infusion-related reactions. The dose of subasumstat can be reduced because of toxicities, in accordance with Section 8.3.2.

[e] Subasumstat administration, symptom-directed physical examination, vital signs, and hematology and chemistry samples only need to be collected if the patient is on the BIW dosing schedule(the first 3 cycles).

[f] If ECOG performance status is measured at screening, it does not need to be repeated on Day 1 predose and Day 1. Only one ECOG measurement is needed on Day 1 predose and Day 1.

[g] On days when study drug is administered, vital signs will be measured predose (20 minutes [±10 min]) before the infusion of subasumstat; 30 minutes (±10 min) after the start of subasumstat dosing; and 1 hour (±10 min) after the completion of subasumstat dosing. All vital signs will be measured with the patient in the sitting or supine position. When the timing of vital signs assessment coincides with the timing of a blood draw, vital signs will be measured before blood sample collection.

[h] A 12-lead ECG will be performed on Day 1 within 3 hours of administration and within 10 minutes (±30 minutes) after the subasumstat infusion. When the timing of ECG measurements coincides with the timing of a blood draw, the ECG will be completed before the collection of the blood sample, with the exception of the end of infusion PK sample, which will be taken before the ECG is completed. From Cycle 3 onwards, ECGs will be collected on Day 1 of every other cycle before the subasumstat dosing and within 1 hour of finishing the infusion. Additional ECGs may be obtained as clinically indicated at the discretion of the investigator. ECG assessments are to be performed with the patient rested for 5 minutes.

[i] Contrast enhanced Radiological evaluations (CT scan or MRI) (unless contrast is contraindicated) of the chest, abdomen, and pelvis (and any other known suspected disease area) are required as entry criteria for Part B to assess the status of the patient's underlying disease. If the patient has had appropriate imaging scans performed within 28 days of Cycle 1 Day 1 of Part B, then the results of those scans could be used. During the study, CT scans or MRIs encompassing the known sites of disease will be performed at the end of Cycle 2 and every 3 cycles thereafter. An EOS/early termination CT scan is not needed to be completed/repeated if a scan was performed within the previous 28 days. Same technique with appropriate contrast usage (CT or MRI) used at screening should be utilized throughout the study.

[j] A pregnancy test is required to be performed for women of childbearing potential at every cycle (typically performed on Day 1 of the cycle; however, if a serum pregnancy test is used, this could be performed up to 3 days before Day 1) with negative results available before the first dose is administered in that cycle. A pregnancy test will also be performed for women of childbearing potential at the EOS/early termination visit. Pregnancy tests will be repeated during the study if requested by an independent ethics committee/institutional review board or if required by local regulations.

[k] Hematology and chemistry samples will be collected as part of the entry criteria for Part B. Hematology, chemistry, and urinalysis may be taken up to 3 days before the Day 1 visit. Hematology and chemistry assessments on Days 4, 8, and 11 (Cycle 1) and Days 1 and 8 (Cycle 2 and onwards) are to be performed on dosing days depending on treatment schedule. If dosing falls on a Monday, the collection window can be extended to collect samples on the previous Friday.

## Appendix B Responsibilities of the Investigator

Clinical research studies sponsored by the sponsor are subject to ICH GCP and all the applicable local laws and regulations.

The investigator agrees to assume the following responsibilities:

1. Conduct the study in accordance with the protocol.
2. Personally conduct or supervise the staff who will assist in the protocol.
3. If the investigator/institution retains the services of any individual or party to perform trial-related duties and functions, the investigator/institution should ensure that this individual or party is qualified to perform those study-related duties and functions and should implement procedures to ensure the integrity of the study-related duties and functions performed and any data generated.
4. Ensure that study-related procedures, including study-specific (nonroutine/nonstandard panel) screening assessments, are NOT performed on potential patients before the receipt of written approval from relevant governing bodies/authorities.
5. Ensure that all colleagues and employees assisting in the conduct of the study are informed of these obligations.
6. Secure prior approval of the study and any changes by an appropriate IRB/IEC that conform to ICH and local regulatory requirements.
7. Ensure that the IRB/IEC will be responsible for initial review, continuing review, and approval of the protocol. Promptly report to the IRB/IEC all changes in research activity and all anticipated risks to patients. Make at least yearly reports on the progress of the study to the IRB/IEC, and issue a final report within 3 months of study completion.
8. Ensure that requirements for informed (e)consent, as outlined in ICH and local regulations, are met.
9. Obtain valid informed (e)consent from each patient who participates in the study, and document the date of (e)consent in the patient's medical chart. Valid informed (e)consent is the most current version approved by the IRB/IEC. Each ICF should contain a patient authorization section that describes the uses and disclosures of a patient's personal information (including personal health information) that will take place in connection with the study. If an ICF does not include such a patient authorization, then the investigator must obtain a separate patient authorization form from each patient or the patient's legally acceptable representative.
10. Prepare and maintain adequate case histories of all persons entered into the study, including eCRFs, hospital records, laboratory results, etc, and maintain these data for a minimum of 2 years following notification by the sponsor that all investigations have been discontinued or that the regulatory authority has approved the marketing application. The investigator should contact and receive written approval from the sponsor before disposing of any such documents.

11. Allow possible inspection and copying by the regulatory authority of GCP-specified essential documents.
12. Maintain current records of the receipt, administration, and disposition of sponsor-supplied drugs, and return all unused sponsor-supplied drugs to the sponsor.
13. Report adverse reactions to the sponsor promptly. In the event of an SAE, notify the sponsor within 24 hours.

## Appendix C Investigator Consent to Use of Personal Information

Takeda will collect and retain personal information of the investigator, including his or her name, address, and other identifying personal information. In addition, the investigator's personal information may be transferred to other parties located in countries throughout the world (eg, the UK, US, and Japan), including the following:

- Takeda, its affiliates, and licensing partners.
- Business partners assisting Takeda, its affiliates, and licensing partners.
- Regulatory agencies and other health authorities.
- IRBs and IECs.

The investigator's personal information may be retained, processed, and transferred by Takeda and these other parties for research purposes including the following:

- Assessment of the suitability of the investigator for the study and/or other clinical studies.
- Management, monitoring, inspection, and audit of the study.
- Analysis, review, and verification of the study results.
- Safety reporting and pharmacovigilance relating to the study.
- Preparation and submission of regulatory filings, correspondence, and communications to regulatory agencies relating to the study.
- Preparation and submission of regulatory filings, correspondence, and communications to regulatory agencies relating to other medications used in other clinical studies that may contain the same chemical compound present in the study medication.
- Inspections and investigations by regulatory authorities relating to the study.
- Self-inspection and internal audit within Takeda, its affiliates, and licensing partners.
- Archiving and audit of study records.
- Posting investigator site contact information, study details, and results on publicly accessible clinical trial registries, databases, and websites.

The investigator's personal information may be transferred to other countries that do not have data protection laws that offer the same level of protection as data protection laws in the investigator's own country.

The investigator acknowledges and consents to the use of his or her personal information by Takeda and other parties for the purposes described above.

## Appendix D ECOG Scale for Performance Status

| Grade | Description |
|---|---|
| 0 | Normal activity. Fully active, able to carry on all predisease 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 (eg, 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. |

Source: Oken MM, 1982 (Oken et al. 1982).
ECOG: Eastern Cooperative Oncology Group.

## Appendix E Drugs that Interact With the CYP3A Family of CYPs

Drugs listed in the table that are strong or moderate inducers or inhibitors of the CYP3A family of CYPs are prohibited as concomitant medications with subasumstat. This list is not intended to be exhaustive, and a similar restriction will apply to other agents that are known to strongly modulate CYP3A activity. Appropriate medical judgment is required. Please contact the sponsor's medical monitor with any queries.

| **Drugs Inducing or Inhibiting CYP3A Metabolism That Are Prohibited Concomitant Medications With Subasumstat** | |
|---|---|
| **Strong CYP3A Inducers** [a] | **Strong CYP3A Inhibitors** [b] |
| apalutamide<br>carbamazepine<br>enzalutamide<br>mitotane<br>phenytoin<br>rifampin<br>St John's wort | boceprevir<br>cobicistat<br>danoprevir and ritonavir<br>elvitegravir and ritonavir<br>grapefruit juice<br>indinavir and ritonavir<br>itraconazole<br>ketoconazole<br>lopinavir and ritonavir<br>paritaprevir and ritonavir and (ombitasvir and/or dasabuvir)<br>posaconazole<br>ritonavir<br>saquinavir and ritonavir<br>telaprevir<br>tipranavir and ritonavir<br>telithromycin<br>troleandomycin<br>voriconazole<br>clarithromycin<br>idelalisib<br>nefazodone<br>nelfinavir |

| Drugs Inducing or Inhibiting CYP3A Metabolism That Are Prohibited Concomitant Medications With Subasumstat | |
|---|---|
| **Moderate CYP3A Inducers [a]** | **Moderate CYP3A Inhibitors [b]** |
| bosentan<br>efavirenz<br>etravirine<br>phenobarbital<br>primidone | aprepitant<br>ciprofloxacin<br>conivaptan<br>crizotinib<br>cyclosporine<br>diltiazem<br>dronedarone<br>erythromycin<br>fluconazole<br>fluvoxamine<br>imatinib<br>tofisopam<br>verapamil |

CYP: cytochrome P450.

[a] Reference:
fda.gov/drugs/drug-interactions-labeling/drug-development-and-drug-interactions-table-substrates-inhibitors-and-inducers#table3-3 (accessed 13 October 2021).

[b] Reference:
fda.gov/drugs/drug-interactions-labeling/drug-development-and-drug-interactions-table-substrates-inhibitors-and-inducers#table3-2 (accessed 13 October 2021).

## Appendix F Examples of Clinical Inhibitors of Pgp

Drugs listed below that are inhibitors of Pgp are prohibited as concomitant medications with subasumstat.

| Transporter | Gene | Inhibitor |
|---|---|---|
| Pgp | ABCB1 | amiodarone<br>carvedilol<br>clarithromycin<br>dronedarone<br>itraconazole<br>lapatinib<br>lopinavir and ritonavir<br>propafenone<br>quinidine<br>ranolazine<br>ritonavir<br>saquinavir and ritonavir<br>telaprevir<br>tipranavir and ritonavir<br>verapamil |

Source:
fda.gov/drugs/drug-interactions-labeling/drug-development-and-drug-interactions-table-substrates-inhibitors-and-inducers#table5-2 (accessed 13 October 2021).
Pgp: P-glycoprotein.

## Appendix G Examples of QTc Interval Prolonging Agents

The use of the following drugs known to prolong QTc interval are prohibited.

| Drug Class | Examples of Drugs that Increase the Risk of TdP, Name (Brand name) |
|---|---|
| Antiarrhythmic | amiodarone (Cordarone, Pacerone)<br>bepridil (Vascor)<br>disopyramide (Norpace)<br>dofetilide (Tikosyn)<br>flecainide (Tambocor)<br>ibutilide (Corvert)<br>procainamide (Pronestyl, Procan)<br>quinidine (Cardioquin, Quinaglute)<br>sotalol (Betapace) |
| Antibiotic | azithromycin (Zithromax)<br>clarithromycin (Biaxin)<br>erythromycin (Erythrocin, EES)<br>moxifloxacin (Avelox)<br>pentamidine (NebuPent, Pentam)<br>sparfloxacin (Zagam) |
| Anticancer | arsenic trioxide (Trisenox)<br>vandetanib (Caprelsaa) |
| Antidepressant | citalopram (Celexa) |
| Antiemetic | domperidone (Motilium)<br>droperidol (Inapsine) |
| Antihistamine | astemizole (Hismanal)<br>terfenadine (Seldane) |
| Antilipemic/hypercholesterolemia | probucol (Lorelco) |
| Antimalarial | chloroquine (Aralen)<br>halofantrine (Halfan) |
| Antipsychotic | chlorpromazine (Thorazine)<br>haloperidol (Haldol)<br>mesoridazine (Serentil)<br>pimozide (Orap)<br>thioridazine (Mellaril) |
| Gastrointestinal stimulant/heartburn | cisapride (Propulsid) |
| Opiate agonist | levomethadyl (Orlaam)<br>methadone (Dolophine, Methadose) |

TdP: torsade de pointe.

## ELECTRONIC SIGNATURES

| Signed by | Meaning of Signature | Server Date (dd-MMM-yyyy HH:mm 'UTC') |
|---|---|---|
| [redacted] | Clinical Science Approval | 27-Apr-2023 20:56 UTC |
| [redacted] | Clinical Pharmacology Approval | 27-Apr-2023 20:59 UTC |
| [redacted] | Biostatistics Approval | 28-Apr-2023 01:19 UTC |
| [redacted] | Clinical Approval | 28-Apr-2023 19:33 UTC |