GI 289

Phase 1, Multicenter, Open-Label, First-in-Human Study of DS-6157a in Patients with Advanced Gastrointestinal Stromal Tumor

INNOVATIONS STUDY NUMBER:	GI 289
SPONSOR STUDY NUMBER:	DS6157-A-U101
IND NUMBER:	146740
STUDY DRUG:	DS-6157a
SPONSOR:	Daiichi Sankyo, Inc. 211 Mt. Airy Road Basking Ridge, NJ 07920-3211 908-992-6400
CONTRACT RESEARCH ORGANIZATION:	Sarah Cannon Development Innovations 1100 Dr. Martin L. King Jr. Blvd. Suite 800 Nashville, TN 37203 1-877-MY-1-SCRI asksarah@sarahcannon.com
STUDY CHAIR:	PPD Director of Clinical Research, Sarcoma Center Dana-Farber Cancer Institute 450 Brookline Ave., Boston, MA 02215 PPD (Office) / PPD (Fax)
MEDICAL MONITOR:	PPD Medical Director, Medical and Clinical Science Sarah Cannon Development Innovations 1100 Dr. Martin L. King Jr. Blvd. Suite 800 Nashville, TN 37203 PPD (Office) / PPD (Cell)
DATE FINAL:	17 November 2019

AMENDMENT NUMBER:	1	**AMENDMENT DATE:**	04 February 2020
EDITION NUMBER:	2		
AMENDMENT NUMBER:	2	**AMENDMENT DATE:**	05 March 2020
EDITION NUMBER:	3		

AMENDMENT NUMBER:	3	**AMENDMENT DATE:**	10 July 2020
EDITION NUMBER:	4		
AMENDMENT NUMBER:	4	**AMENDMENT DATE:**	08 March 2021
EDITION NUMBER:	5		
AMENDMENT NUMBER:	5	**AMENDMENT DATE:**	17 August 2021
EDITION NUMBER:	6		

Clinical Study Statement of Compliance

GI 289

Phase 1, Multicenter, Open-Label, First-in-Human Study of DS-6157a in Patients with Advanced Gastrointestinal Stromal Tumor

This clinical study shall be conducted in compliance with the protocol, as referenced herein, and all applicable local, national, and international regulatory requirements to include, but not be limited to:

- **International Council for Harmonisation (ICH) Guidelines on Good Clinical Practice (GCP)**
- **Ethical principles that have their origins in the Declaration of Helsinki**
- **Food and Drug Administration (FDA) Code of Federal Regulation (CFR):**
  - **Title 21CFR Part 50 & 45 CFR Part 46, Protection of Human Subjects**
  - **Title 21CFR Part 54, Financial Disclosure by Clinical Investigators**
  - **Title 21CFR Part 56, Institutional Review Boards (IRBs)**
  - **Title 21CFR Part 312, Investigational New Drug (IND) Application**
  - **Title 45 CFR Parts 160, 162, and 164, Health Insurance Portability and Accountability Act (HIPAA)**

As the Study Chair and/or Principal Investigator, I understand that my signature on the protocol constitutes my agreement and understanding of my responsibilities to conduct the clinical study in accordance to the protocol and applicable regulations. Furthermore, it constitutes my understanding and agreement that any changes initiated by myself, without prior agreement in writing from the Sponsor, shall be defined as a deviation from the protocol, and shall be formally documented as such.

As the Contract Research Organization (CRO) Representative, I understand that my signature constitutes agreement and understanding of acceptance of the defined and contracted sponsor responsibilities as defined by the protocol, applicable Clinical Trial Agreements (CTA), and/or business contracts. Additionally, my signature constitutes my understanding and agreement that any changes to the protocol, CTA, or contracts shall be implemented with the Sponsor's review and approval prior to implementation.

As the Sponsor Representative, I understand that my signature constitutes agreement and understanding of acceptance of the defined and contracted Sponsor responsibilities to the CRO and the Principal Investigator as defined by the protocol, applicable clinical trial agreements (CTA), and/or business contracts, but does not in any capacity relieve me of my responsibilities as the Sponsor. Additionally, my signature constitutes my understanding and agreement that any changes to the protocol, CTA, or contracts shall be implemented timely with my review and approval prior to implementation.

Clinical Study Approval Page

GI 289

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AMENDMENT NUMBER:	4	**AMENDMENT DATE:** 08 March 2021
AMENDMENT NUMBER:	**5**	**AMENDMENT DATE: 17 August 2021**

PPD	I am approving this document.	PPD	08/20/2021 06:02 PM EDT
Study Chair		**Study Chair Signature**	**Date**

PPD
Director of Clinical Research, Sarcoma Center
Dana-Farber Cancer Institute

PPD	I am approving this document.	PPD	08/20/2021 09:23 PM EDT
Medical Monitor		**Medical Monitor Signature**	**Date**

PPD
Medical Director, Medical and Clinical Science
Sarah Cannon Development Innovations

SARAH CANNON
Development Innovations

Daiichi-Sankyo

PPD I am approving this document.

PPD

08/20/2021
10:27 PM EDT

Sponsor Representative **Sponsor Representative Signature** **Date**

PPD
Executive Director
Daiichi Sankyo, Inc.

Clinical Study Principal Investigator Signature Form

GI 289

Phase 1, Multicenter, Open-Label, First-in-Human Study of DS-6157a in Patients with Advanced Gastrointestinal Stromal Tumor

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By signing this protocol acceptance page, I confirm I have read, understand, and agree to conduct the study in accordance with the current protocol.

Principal Investigator Name	**Principal Investigator Signature**	**Date**
<<Insert Site Name and ID info as applicable>> <<Insert Site Location>>		

Please retain a copy of this page for your study files and return the original signed and dated form to:

Sarah Cannon Development Innovations, LLC
1100 Dr. Martin L. King Jr. Blvd., Suite 800
Attention: GI 289 Study Team
Nashville, TN 37203

GI 289 CONTACT INFORMATION

Sponsor Contact Address and Phone#:	
Innovations Contact Address and Phone#:	Sarah Cannon Development Innovations, LLC 1100 Dr. Martin L. King Jr. Blvd. Suite 800 Nashville, TN 37203 USA 1-877-MY-1-SCRI asksarah@sarahcannon.com
Study Chair:	PPD Director of Clinical Research, Sarcoma Center Dana-Farber Cancer Institute 450 Brookline Ave., Boston, MA 02215 PPD (Office) / PPD (Fax)
Medical Monitor:	PPD Medical Director Medical and Clinical Science Sarah Cannon Development Innovations, LLC 1100 Dr. Martin L. King Jr. Blvd. Suite 800 Nashville, TN 37203 USA PPD (Office) / PPD (Cell)
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Innovations Enrollment Fax #:	1-877-MY-1-SCRI

CLINICAL PROTOCOL AMENDMENT SUMMARY OF CHANGES
DS6157-A-U101/GI 289

AMENDMENT NUMBER:	1	AMENDMENT DATE:	04 February 2020

Implementation of Amendment 1 occurred prior to the first patient enrollment. These changes were made to the protocol in response to comments from the FDA and IRB, and after pre-submission consultation with the PMDA.

Additions to the text are **bolded** and deletions from the text are ~~crossed-off~~. Only the parts of sections with changes are presented. Please note that formatting changes and minor changes to punctuation, spelling, and abbreviations that do not affect meaning are not noted in this summary.

Section 3.1 Inclusion Criteria and Synopsis

1. Is able to provide written informed consent, signed by the subject or by a legal guardian prior to the performance of any study-related procedures, and is willing and able to comply with the protocol. Subject **or his/her legal guardian** must be fully informed about their illness and the investigational nature of the study protocol (including foreseeable risks and possible toxicities) and must sign and date an Institutional Review Board (IRB)/Independent Ethics Committee (IEC) approved informed consent form (ICF)(including Health Insurance Portability and Accountability Act authorization [HIPAA], if applicable) before performance of any study-specific procedures or examinations.

4. Has a histopathologically documented unresectable and/or metastatic GIST meeting the criteria below:

~~**Subjects in US Sites Only**~~

- **Dose Escalation (Part 1)**: subjects should meet one of the following criteria:

a. **(For US sites only)** Subjects with GIST who have progressed on**,** or are intolerant to**,** imatinib (IM) and at least one post-IM treatment, or who are not candidates for post-IM standard of care treatment

b. **(For Japan sites only) Subjects with GIST who have received all the existing standard of care treatments or who are not candidates for one or more available post-IM standard of care treatments**

~~b.~~c. Subjects with GIST who are not candidates for IM or curative intent surgical treatment (~~e.g.,~~ **i.e.,** subjects without activating KIT or PDGFRa mutations, with PDGFRa D842V mutations, or are KIT negative by local results)

- **Dose Expansion (Part 2) Cohort 1:** subjects with GIST who have progressed on or are intolerant to IM and at least one post-IM treatment

- **Dose Expansion (Part 2) Cohort 2:** subjects with GIST who have progressed on IM and had not received a post-IM treatment (2nd line)

~~**Subjects in Japan Sites Only**~~

~~- **Dose Escalation (Part 1):** subjects should meet one of the following criteria:~~

~~a. Subjects with GIST who have received prior treatments with all the existing standard of care treatments or who are not candidates for one or more available post-IM standard of care treatments~~

~~b. Subjects with GIST who are not candidates for IM or curative intent surgical treatment (e.g., subjects without activating KIT or PDGFRa mutations, with PDGFRa D842V mutations, or are KIT negative by local results)~~

~~- **Dose Expansion (Part 2) Cohort 1:** subjects with GIST who have received prior treatment with IM and all the available post-IM standard of care treatments, or received IM and at least one post-IM treatment and are not candidates for subsequent standard of care treatments~~

~~- **Dose Expansion (Part 2) Cohort 2:** (not enrolling in Japan)~~

Section 5 Study Design, Figure 1 footnotes, and Synopsis

The phrase "Cohort 2 will be initiated in US only" was removed.

Section 5.1.2 Dose-Limiting Toxicity

For Hematologic Toxicities, a DLT is defined as follows:

- Grade 4 neutrophil count decreased lasting >7 days
- Grade ≥3 febrile neutropenia
- Grade ≥3 anemia requiring transfusion
- Grade 4 anemia
- Grade 4 platelet count decreased, or
- Grade ≥3 platelet count decreased lasting >7 days
- Grade ≥3 platelet count decreased associated with clinically significant hemorrhage and/or requiring transfusion
- Grade 4 lymphocyte count decreased lasting ≥14 days **(lymphocyte count decrease of Grade 3 will not be a DLT)**

For Non-Hematologic, Non-Hepatic Major Organ Toxicities, a DLT is defined as **all TEAEs of Grade ≥3 with the following ~~follows~~ exceptions**:

The following AEs will not be considered DLTs:

- Grade 3 fatigue lasting <7 days
- Grade 3 nausea, vomiting, diarrhea, or anorexia that has resolved to Grade ≤2 within 3 days with maximal medical management
- Grade 3 isolated laboratory findings not associated with signs or symptoms including alkaline phosphatase (ALP) increased, hyperuricemia, serum amylase increased, and lipase increased, and Grade 3 hyponatremia lasting <72 hours developed from Grade 1 at baseline. Symptomatic Grade 4 events will be considered DLTs unless there is documented evidence that the abnormality is associated with disease progression.
- ~~Grade 3 lymphocyte count decreased~~

For the following non-hematologic, non-hepatic major organ toxicities, a DLT is defined as:

- Symptomatic congestive heart failure
- Any LVEF decline from baseline leading to discontinuation of study treatment
- Grade ≥2 ILD or pneumonitis
- Grade 3 skin toxicity lasting >7 days or Grade 4 for any duration
- **All other Grade ≥3 non-hematologic, non-hepatic major organ toxicities will be a DLT**

Section 6 Dose Modifications

There will be no dose modifications for Grade 1 or Grade 2 AEs unless specified below in Table 2. **For a recurrent Grade ≥3 AE, the subject will be permanently discontinued from study treatment.**

Table 2. Dose Modifications for DS-6157a

LVEF <40% or >20% (absolute value) drop from baseline	**Permanently discontinue from study treatment** ~~Interrupt DS-6157a dosing~~ ~~Repeat LVEF assessment within 3 weeks~~ ~~If LVEF <40% or >20% drop from baseline is confirmed, discontinue subject from study treatment~~

Section 6.1 Other Risks Associated with Drugs of the Same Class

MAAA-1181a is a derivative of exatecan (DX-8951f), a topoisomerase I inhibitor. Other products of the same class include irinotecan (Irinotecan package inserts. 2016) and topotecan (Topotecan package inserts. 2015). Exatecan is a ~~camptotechin~~ **camptothecin** derivative, which has previously been developed by the former Daiichi Pharmaceuticals Co., Ltd. as an anti-cancer therapy.

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Section 7.2 Screening

The study will allow re-screening for any subject who failed to meet eligibility criteria upon initial screening. ~~The same subject number that was assigned during the first screening will be assigned at re-screening.~~ The failed screening test(s) and the other screening results that are out of window relative to the start of the study treatment, and any other protocol-specified screening tests per **the** Medical Monitor's guidance, will be re-tested during re-screening. The initial screening information and the reason why the subject was ineligible for the initial evaluation will be recorded in the Screening Log.

Section 7.2.1 Screen Failures and Rescreening

Screen failures are defined as subjects who signed the informed consent form to participate in the clinical study but are not subsequently entered in the study. Individuals who do not meet the criteria for participation in this study (screen failure) may be rescreened. Rescreened subjects should be assigned a new subject number that is different from the initial screening. Rescreening of a subject should be documented by recording the previous subject number on the eCRF so that its effect on study results, if any, can be assessed.

Section 7.8.6 Withdrawal of Consent for Use of Tissue Samples and Blood During the Study Period

Subjects have the right to withdraw permission for storage of biological samples for future research and the optional end-of-treatment biopsies, even if previously consented, and still continue on the study. Upon study withdrawal, if the patient exercises his/her right to withdraw permission for sample storage, any remaining specimens will be disposed of according to one of the procedures described below:

1. If specimens are temporarily stored at the study site, the Investigators will dispose of specimens from the withdrawing subject.

2. If specimens are stored at a specimen collection agency or analysis laboratories, the Investigators will report the site subject identifier or number to the Sponsor, and the Sponsor will direct the agency to dispose of the specimens.

If samples are already analysed, Daiichi Sankyo is not obliged to destroy the results of this research.

Additions to the text are **bolded** and deletions from the text are ~~crossed off~~. Only the parts of sections with changes are presented. Please note that formatting changes and minor changes to punctuation, spelling, and abbreviations that do not affect meaning are not noted in this summary.

Title page and Contact information page updated to reflect change in Medical Monitor. The Medical Monitor role has been transitioned to **Ololade Dosunmu, MD, MPH, MLA.**

Section 3.1 Inclusion Criteria and Synopsis

9. Has an adequate treatment washout period prior to start of study treatment, defined as:

- **Chloroquine/Hydroxychloroquine >14 days.**

Section 5.3.2 Prohibited Concomitant Medications and Appendix H

The following treatments are prohibited while in this study:

- **Concomitant treatment with chloroquine or hydroxychloroquine is not allowed during the study treatment. Refer to Appendix H for further details.**

Section 6 Dose Modification

All confirmed or suspected COVID-19 infection events must be recorded in the eCRF. Please refer to Appendix H for additional information on dose modification.

Table 2 Dose Modifications for DS-6157a

ILD/pneumonitis	If a subject develops **radiologic changes potentially consistent with ILD/pneumonitis or** an acute onset of new or worsening pulmonary function or other related signs/symptoms such as dyspnea, cough or fever, rule out ILD/pneumonitis. If the AE is confirmed to have an etiology other than ILD/pneumonitis, follow the management guidance outlined in the "Other Non-Laboratory Adverse Events" dose modification section below. If the AE is suspected to be ILD/pneumonitis, treatment with study drug should be interrupted pending further evaluations. Evaluations should include: • high resolution CT • pulmonologist consultation **(infectious Disease consultation as clinically indicated)** • **blood culture and CBC. Other blood tests could be considered as needed** • **Consider bronchoscopy and bronchoalveolar lavage**

	if clinically indicated and feasible. • pulmonary function tests and pulse oximetry (SpO_2) • arterial blood gases if clinically indicated • one blood sample collection for PK and exploratory biomarker analysis as soon as ILD/pneumonitis is suspected, if feasible. Other tests could be considered, as needed. ~~As soon as ILD/pneumonitis is suspected, corticosteroid treatment should be started promptly as per consensus statement (Kubo et al. 2013).~~ If the AE is confirmed to be ILD/pneumonitis, follow the management guidance as outlined below. All events of ILD/**pneumonitis** regardless of severity or seriousness will be followed until resolution including after drug discontinuation.
Grade 1	The administration of DS-6157a must be interrupted for any ILD/**pneumonitis** events regardless **of grade** ~~to Grade 0~~. • **Monitor and closely follow-up in 2 to 7 days for onset of clinical symptoms and pulse oximetry** • **Consider follow-up imaging in 1-2 weeks (or as clinically indicated).** • **Consider starting systemic steroids (e.g. at least 0.5 mg/kg/day prednisone or equivalent) until improvement, followed by gradual taper over at least 4 weeks.** • **If worsening of diagnostic observations despite initiation of corticosteroids, then follow Grade 2 guidelines.*** For Grade 1 events, DS-6157a can be restarted only if the event is fully resolved **to Grade 0**: - If resolved in ≤28 days from day of onset, maintain dose - If resolved in >28 days from day of onset, reduce dose 1 level **However, if the event Grade 1 ILD occurs beyond cycle Day 22 and has not resolved within 49 days from the last infusion, the drug should be discontinued.** *** If subject is asymptomatic, then subject should still be considered as Grade 1 even if steroid treatment is given.**
Grade 2	Permanently discontinue subject from study treatment.

	• **Promptly start and treat with systemic steroids (e.g., at least 1mg/kg/day prednisone or equivalent) for at least 14 days or until complete resolution of clinical and chest CT findings, then followed by a gradual taper over at least 4 weeks.**
	• **Monitor symptoms closely.**
	• **Re-image as clinically indicated.**
	• **If worsening or no improvement in clinical or diagnostic observations in 5 days,**
	  • **Consider increasing dose of steroids (e.g., 2 mg/kg/day prednisone or equivalent) and administration may be switched to intravenous (e.g. methylprednisolone).**
	  • **Re-consider additional work-up for alternative etiologies as described above.**
	  • **Escalate care as clinically indicated.**

Grade 3 or 4	**Permanently discontinue subject from study treatment.** • **Hospitalization required.** • **Promptly initiate empiric high-dose methylprednisolone IV treatment (e.g., 500-1000 mg/day for 3 days), followed by at least 1.0 mg/kg/day of prednisone (or equivalent) for at least 14 days or until complete resolution of clinical and chest CT findings, then followed by a gradual taper over at least 4 weeks.** • **Re-image as clinically indicated.** • **If still no improvement within 3 to 5 days,** • **Re-consider additional work-up for alternative etiologies as described above.** **Consider other immuno-suppressants and/or treat per local practice.**

Section 7.6 and Assessment Schedule amended to include PK Sampling for CQ/HCQ administration.

Section 7.8 COVID-19 Antibody Testing and Assessment Schedule

If subject provides consent, samples should be collected prior to study drug infusion at Cycle 1 Day 1, Cycle 5 Day 1, and every 4 cycles thereafter (Cycle 9, Cycle 13, etc.). For

subjects with suspected or confirmed COVID-19 infections, follow the dose modifications in Appendix H.

Section 11.2.1 Recording of Adverse Events and 11.11.1 Interstitial Lung Disease Adjudication Committee

Amended to clarify that **for broad surveillance of ILD, selected 42 Preferred Terms (all from the ILD Standard MedDRA Query [SMQ]) plus 2 PTs of acute respiratory failure and respiratory failure are included for enhanced data collections.**

Section 11.4 Expedited Reporting by Investigators

Amended to clarify that **all potential ILD cases should be reported within 24 hours: including both serious and non-serious potential ILD cases (potential ILD is defined by the Event Adjudication Site Manual List of PTs)**.

Added Appendix H COVID-19 Infection Management

Additions to the text are **bolded** and deletions from the text are ~~crossed off~~. Only the parts of sections with changes are presented. Please note that formatting changes and minor changes to punctuation, spelling, and abbreviations that do not affect meaning are not noted in this summary.

Global Change

References to "subject" were changed to "patient" per Sponsor request to more accurately reflect the population in the study.

Assessment Schedule Footnote b

At the discretion of the investigator, vital signs may be done more than 10 minutes after blood draws other than PK, but prior to administration of treatment.

Section 1.1 Background and Study Rationale

GPR20 expression is detected in more than 80% of all GIST tumor samples irrespective of the number of prior lines of TKI treatments received. GPR20 expression levels in KIT/PDGFRA wild type GIST and KIT mutant GIST are comparable. GPR20 is also highly expressed in GIST harboring TKI-resistant mutations in KIT (Iida et al. 2021).

Section 3.1 Inclusion Criteria and Synopsis

8. Has adequate organ function within 7 days before the start of study treatment, defined as:

- **International Normalization Ratio (INR)/prothrombin time (PT) and either partial thromboplastin time (PTT) or activated partial thromboplastin time (aPTT) ≤ 1.5 x ULN**

Section 3.2 Exclusion Criteria and Synopsis

10. Has a history of underlying pulmonary disorder, including but not limited to, pulmonary emboli within 3 months of the study randomization, severe asthma, severe COPD, restrictive lung disease, pleural effusion.

11 Has any autoimmune, connective tissue or inflammatory disorders (e.g., rheumatoid arthritis, Sjogren's, sarcoidosis) where there is documented, or a suspicion of pulmonary involvement at the time of screening.

12 Prior pneumonectomy

18. Has received a live vaccine within 30 days prior to the first dose of study drug. Examples of live vaccines include, but are not limited to, the following: measles, mumps, rubella, varicella/zoster (chicken pox), yellow fever, rabies, Bacillus Calmette-Guérin (BCG), and typhoid vaccine. Seasonal influenza vaccines for injection are generally killed virus vaccines and are allowed; however, intranasal influenza vaccines (eg, FluMist®) are live attenuated vaccines and are not allowed.

Section 5 Study Design, Section 5.1 Treatment Plan, Section 10.3 Sample Size Considerations, and Synopsis

Amended for Dose Expansion to enroll **up to** approximately 30 patients in each cohort.

Section 5 Study Design, Figure 1

Amended to add provisional doses of 9.6 mg/kg, 12.8 mg/kg, and 17.0 mg/kg.

Section 5.1 Treatment Plan, Synopsis, and Assessments Schedule

For Dose Escalation (Part 1), **on Cycle 1 Day 1 DS-6157a will be infused for 90 ±10 minutes** ~~an initial dose of DS-6157a 1.6 mg/kg IV will be administered over approximately 90 minutes on Cycle 1 Day 1~~. A 21-day observation period (Cycle 1) will then occur, at the end of which all relevant safety data will be reviewed. Patients will continue to receive DS-6157a (Q3W) until unacceptable toxicity, progressive disease (PD), death, or withdrawal of consent (Section 3.3). If there is no infusion-related reaction on Cycle 1 Day 1, **the subsequent dose of DS-6157a may be infused for 30 ± 5 minutes based on the clinical judgment of the Investigator and/or Medical Monitor, but this reduced infusion rate is not mandatory** ~~subsequent doses of DS-6157a may be infused IV over approximately 30 minutes~~.

For Dose Expansion (Part 2), **on Cycle 1 Day 1 the RDE of DS-6157a will be infused for 90 ± 10 minutes** ~~subjects will receive DS-6157a IV on Day 1 of Cycle 1 at the RDE determined in Part 1 over approximately 90 minutes~~. Patients will then continue to receive DS-6157a (Q3W) until unacceptable toxicity, PD, death, or withdrawal of consent (Section 3.3). If there is no infusion-related reaction after the initial dose, **the subsequent dose of DS-6157a may be infused for 30 ± 5 minutes based on the clinical judgment of the Investigator and/or Medical Monitor, but this reduced infusion rate is not mandatory** ~~subsequent doses of DS-6157a may be infused IV over approximately 30 minutes~~.

Section 5.1 Treatment Plan

For both Dose Escalation and Dose Expansion, the patient's weight at screening (baseline) will be used to calculate the initial dose. The dose will be recalculated if the patient's weight changes by more than 10% from baseline, or per institutional standard even if the weight change is less than ±10%. **This new body weight will be used to calculate the dose for subsequent cycles of DS-6157 infusion.**

Section 5.1.1 Dose Escalation Procedure and Synopsis

~~The actual number of dose cohorts to be explored in this study will depend on determination of the MTD based on DLTs reported during the DLT evaluation period (Day 1 to Day 21 of Cycle 1 in Dose Escalation). Information about the MTD will be used along with other safety data as well as the PK profile observed during the conduct of the study to determine the RDE for further evaluation in Dose Expansion.~~

~~During Dose Escalation, the first two subjects at each dose level in the Dose Escalation part will start the study treatment (first dose) at least 24 hours apart.~~ Dose escalation of DS-6157a will be guided by a Bayesian logistic regression model (BLRM) (Neuenschwander et al. 2008)

following the escalation with overdose control (EWOC) principle (Babb et al. 1998, Rogatko et al. 2005). The details of the methodology are described in Section 10.7.

Cohorts of 3 to 6 patients will be enrolled and assessed for DLT during Dose Escalation. The first two patients at each dose level in Dose Escalation will start the study treatment (first dose) at least 24 hours apart. Dose escalation decision and enrollment of patients to a new cohort requires completion of the DLT evaluation of at least 3 patients treated in the current cohort. Patients who have neither completed DLT evaluation period with full dose nor experienced a DLT will not be included in the BLRM update. In the event that additional patients in the previous cohort experience a DLT after the enrollment of patients to a new cohort has begun, dose level assignment of the next patient in the study will be based on an updated BLRM using DLT outcome data from all assessed doses thus far and clinical assessment of the overall safety data by the Sponsor and Investigator(s). The model will also be re-evaluated before enrolment of any additional patients to a cohort if 2 evaluable patients in the cohort experience DLT before the enrollment of the next patient.

The next dose level will be chosen by the Sponsor and Investigator(s) based on the dose recommendation by the BLRM as outlined in Section 10.7.3, and clinical assessment of the overall safety data. In addition, any available PK, pharmacodynamics, and efficacy data may be considered for dose escalation decisions. The dose level increase will not be greater than 100% even if the BLRM suggests a dose higher than 100% for next cohort.

The actual number of dose cohorts to be explored in this study will depend on determination of the MTD based on DLTs reported during the DLT evaluation period (Day 1 to Day 21 of Cycle 1 in Dose Escalation). Additional patients may be enrolled at any lower doses below the MTD in order to collect sufficient safety and PK data or to characterize safety and PK in specific ethnicities.

Section 5.1.4 Recommended Dose for Expansion

If multiple doses or regimens are selected for Dose Expansion, **up to** approximately 30 eligible patients may be randomized into each dose or regimen in one or more cohort(s) in Dose Expansion. **Alternatively, if a selected RDE is found to be not suitable due to safety or efficacy related reasons during evaluation in Dose Expansion, further enrollment may be continued at a different dose level not exceeding MTD as the new RDE.**

Section 5.3.1 Permitted Concomitant Treatments ~~Medications~~

Medical marijuana or other types of legally available cannabis products (e.g., CBD) are permitted as concomitant herbal medicines throughout screening, the treatment phase, and during the post-study follow up. If its use for palliative care began within a 7-day timeframe of study initiation, please discuss with the Medical Monitor.

Supportive care and other medications considered necessary for the patient's safety and well-being may be given at the discretion of the Investigator with the exception of those listed in Section 5.3.2.

Section 5.3.2 Prohibited Concomitant Treatments ~~Medications~~

The following treatments are prohibited while in this study:

- **The live flu vaccine (including the nasal mist version)**

Section 5.3.3 Restricted Concomitant Treatments

Use of e-cigarettes and vaping is strongly discouraged but not prohibited.

Section 6 Dose Modifications

For a recurrent Grade ≥3 AE, the patient will be permanently discontinued from study treatment **based on Investigator discretion**.

During the dose escalation part of the trial, intra-patient dose escalation (IPDE) of DS-6157a may be allowed on a case by case basis in patients who may benefit from IPDE based on the clinical judgement of the investigator and in agreement with the Medical Monitor and Sponsor. The eligibility criteria for consideration of patients for IPDE are the following:

- **Patient must provide consent for IPDE.**
- **A minimum of 4 cycles of treatment and evaluations must be completed before IPDE**
- **Patient must meet inclusion criteria of #1-3, 6 and 8 based on the most recent data, and 9 (except for DS-6157 treatment) again. Any criteria that did not meet the eligibility can be re-tested.**
- **Patient who meets any of exclusion criteria based on the most recent data, or who experienced ILD of any grade or any other dose modification toxicity event during DS-6157a treatment will not be eligible for IPDE.**

IPDE may be conducted up to a dose that is 1 dose level below the dose already established to be safe and tolerable. Dose escalation should not be more than 3 dose levels at a time. The actual dose level will be decided based on the overall individual clinical status and PK profile. A patient may be allowed further IPDE after completing a minimum of another 4 cycles after the first IPDE, as long as the conditions for IPDE are met. AEs arising after IPDE should follow dose modifications/reductions per Table 2, but further re-escalations will be prohibited after such events.

~~Intrasubject dose escalations of DS-6157a are not allowed in any cohort in Dose Escalation or Dose Expansion~~.

Section 6 Dose Modifications, Table 2

Table 2 Dose Modifications for DS-6157a

Infusion-Related Reaction	
Grade 1	**No interruption or change in the infusion rate is indicated.**

(Mild transient reaction; infusion interruption not indicated; intervention not indicated)	~~If infusion-related reaction (such as fever and chills, with or without nausea/vomiting, pain, headache, dizziness, dyspnea, hypotension) is observed during administration, the infusion rate must be reduced by 50% and subjects must be closely monitored.~~ ~~If no other reactions appear, the subsequent infusion rate could be resumed at the initial planned rate.~~
Grade 2 (Therapy or infusion interruption indicated but responds promptly to symptomatic treatment (e.g., antihistamines, nonsteroidal anti-inflammatory drugs (NSAIDs), narcotics, IV fluids); prophylactic medications indicated for ≤24 hrs)	**Grade 2 IRR occurring during infusion of DS-6157a:** • **Administration of DS-6157a must be interrupted and symptomatic treatment started (e.g. antihistamines, NSAIDs, narcotics, IV fluids).** • **If the event resolves or improves to Grade 1, infusion can be re started at a 50% reduced infusion rate.** **Grade 2 IRR occurring post infusion of DS-6157a:** • **Symptomatic treatment must be started (e.g., antihistamines, antiemetics, NSAIDs, IV fluids) until the event resolves or improves to Grade 1.** **Subsequent administrations of DS-6157a after any Grade 2 IRR occurring during or post infusion of DS 6157a:** • **Premedication (e.g., acetaminophen, diphenhydramine, and/or corticosteroids or equivalents) should be considered at the Investigator's discretion. If the Grade 2 event recurs despite pre-medication, then all subsequent administrations of DS-6157a must be conducted at the 50% reduced infusion rate and/or with pre-medication.** • **If the infusion rate is reduced by 50% (regardless of pre-medication) and the Grade 2 event does not recur at a given cycle, then administrations of DS-6157a at subsequent cycles can be conducted at the initial infusion rate at the investigator's discretion. If the Grade 2 event recurs at the initial infusion rate, then all subsequent administrations of DS-6157a must be conducted at the 50% reduced infusion rate and with pre-medication**.

Cardiac Toxicity	
LVEF 40% to 45% and decrease is 10% - **20%** (absolute value) from baseline	Interrupt DS-6157a dosing Repeat LVEF assessment within 3 weeks If LVEF has not recovered to within 10% **(absolute value)** from baseline, discontinue patient from study treatment **If LVEF recovers to within 10% from baseline, resume treatment with study drug**

Electrocardiogram QT prolonged ~~QTc Prolongation~~	
Grade 3 (Average QTcF >500 ms or >60 ms change from baseline)	Repeat the ECG in triplicate within 1 hour and then monitor at the frequency determined by the Investigator's discretion. Delay dose until resolved to ≤ Grade 1 (QTcF ≤480 ms or change from baseline ≤30 msec), determine if another medication the patient was taking may be responsible and can be adjusted **or if there are any changes in serum electrolytes that can be corrected**, **then~~. If~~ if** attributed to DS-6157a and confirmed on repeat ECG triplicate, ~~then~~ reduce dose 1 level.

Aspartate aminotransferase ~~transaminase~~ (AST) or alanine aminotransferase ~~transaminase~~ (ALT)	
Grade 3 (>5.0 - 20.0 × ULN if baseline was normal; >5.0 - 20.0 × baseline if baseline was abnormal) In patients without liver metastases and patients with liver metastases and baseline level ≤3 × ULN	Repeat testing within 3 days. Delay dose until resolved to ≤ Grade 1, **if baseline ≤ 3 x ULN, otherwise delay dose until resolved to ≤ baseline,** then: If resolved in ≤7 days from day of onset, maintain dose If resolved in >7 days from day of onset, reduce dose 1 level

Section 7.2 Screening and Schedule of Assessments Footnotes

- Vital signs **(blood pressure, SpO2, body temperature, and pulse rate)**
- Biochemistry (sodium, potassium, phosphate, chloride, creatinine, calcium, venous bicarbonate [HCO_3] **or carbon dioxide [CO_2]**, albumin, total protein, AST, ALT, alkaline phosphatase [ALP], bilirubin (total [required]/fractionated [direct/indirect] bilirubin, if available), lactate dehydrogenase, glucose, creatine kinase [CK: if CK is elevated, then CK-MB, CK-MM, troponin I, and myoglobin should be reactively tested,

with further follow-up as clinically warranted], blood urea nitrogen (BUN), or urea, and serum uric acid)

- Coagulation (PT, aPTT **or PTT**, and INR)
- ~~Pulse oximetry (SpO_2)~~

Section 7.5 ECG Measurements, 7.6 Pharmacokinetic Assessments, and Schedule of Assessments

When ECG and PK assessments coincide, ECGs must be done within 10 minutes before the scheduled PK sample. When ECG and blood draws other than PK coincide, ECGs should be done before these blood draws, however these blood draws (other than PK) may be taken more than 10 minutes after ECGs, or ECGs may be done more than 10 minutes after these blood draws (other than PK).

~~When multiple assessments coincide, ECGs will be done within 10 minutes before the scheduled PK sample and/or any other blood draw.~~

Section 7.6 Pharmacokinetic Assessments and Schedule of Assessments

Additional blood samples will be taken from patients who undergo IPDE.

- **Day 1 of the first 4 cycles of IPDE: Pre-dose (within 8 hours before treatment) and within 15 minutes after EOI**

Section 7.7 Anti-drug Antibody Assessments and Schedule of Assessments

Blood samples (5 mL) for determination of potential anti-drug antibody against DS-6157a will be collected pre-dose from all patients treated with DS-6157a on Day 1 and Day 8 of Cycle 1, pre-dose on Day 1 of Cycle 2 to Cycle 4, and thereafter every 2 cycles from Cycle 4 through the EOT visit, and 30-day safety follow-up visit. **Additional blood samples will be collected at pre-dose of the first 4 dosing cycles from patients who undergo IPDE.**

Section 7.8 COVID-19 Antibody Testing

If patient provides consent, samples should be collected prior to study drug infusion at Cycle 1 Day 1, Cycle 5 Day 1, every 4 cycles thereafter (Cycle 9, Cycle 13, etc.), **and at the EOT visit**.

Section 7.9.1 Archival Tumor Samples, Synopsis, and Schedule of Assessments

Archival sample collection is recommended, but not mandated, and every effort should be made to obtain a sample. If the patient only has bone lesions that can be biopsied at the screening time, archival tumor sample taken from a non-bone lesion must be submitted.

Section 7.9.2 Fresh Biopsies and Schedule of Assessments

All patients will be required to undergo mandatory pre-treatment and on-treatment biopsies if the patient is clinically stable as judged by the Investigator. In addition, consenting patients may

undergo an optional EOT tumor biopsy. If the patient agrees to the optional EOT biopsy, that biopsy must be obtained prior to the start of a new anticancer treatment. **If IPDE is conducted, it is highly recommended to collect additional fresh biopsies after IPDE, if clinically feasible.**

If the patient has multiple lesions suitable for biopsy, bone biopsy is to be avoided. However, if the patient only has bone lesions that can be biopsied, bone biopsy is still required for exploratory biomarkers assays.

If a pre-existing biopsy collected within 6 months of starting DS- 6157a is provided at screening (i.e., if the fresh pre-treatment tumor biopsy is not feasible or unsafe), the cfRNA and cfDNA samples will be collected at screening (within -28 to 0 days) and prior to DS-6157a infusion on Cycle 1 Day 1.

If IPDE is conducted, it is highly recommended to collect additional four core needle biopsies in the second cycle after IPDE, if clinically feasible. It should be collected between Day 8 and Day 15 of the cycle.

Section 7.9.3 Blood Samples for cfDNA and cfRNA and Schedule of Assessments

cfDNA and cfRNA

- Screening: **within 7 days after the screening tumor biopsy but prior to the first infusion of DS-6157a on Cycle 1 Day 1**
- Cycle 2 between Day 8 and 15, **irrespective of biopsy date. However, collection on the same day as the tumor biopsy is recommended.**

- ~~Screening: on the same day as the tumor biopsy~~
- ~~Cycle 2 between Day 8 and 15: on the same day as the tumor biopsy~~

Section 7.9.4 Exploratory Blood Biomarker Samples

Biomarker blood samples will be taken at the following time points:

- **Any time that ILD is suspected**

If IPDE is conducted, it's recommended to collect additional blood biomarker samples at the following time points:

- **Pre-dose on Day 1 of first cycle of IPDE**
- **Day 8 of first cycle of IPDE**
- **Pre-dose on Day 1 of second cycle of IPDE**
- **Pre-dose on Day 1 of third cycle of IPDE**

Section 8.1.2 Preparation and Administration of DS-6157a, Synopsis, and Schedule of Assessments

An initial dose of DS-6157a will be infused for 90 ± 10 minutes. If there is no infusion-related reaction after the initial dose, the subsequent dose of DS-6157a may be infused for

30 ± 5 minutes based on the clinical judgment of the Investigator and/or Medical Monitor, but this reduced infusion rate is not mandatory.

~~DS-6157a is administered as an IV infusion over approximately 90 minutes. If there is no infusion related reaction after the initial dose, the subsequent DS-6157a dose may be infused over approximately 30 minutes.~~

Section 10.4 Analysis Populations

- **Full Analysis Set (FAS) will include all patients who received any DS-6157a.**
- ~~For non-randomized subjects: FAS will include all subjects who received any DS-6157a.~~

~~For randomized subjects (if randomization is used in one or more cohorts in Dose Expansion [Part 2]): The FAS will include all subjects for whom study treatment has been assigned by randomization. Following the Intent to Treat (ITT) principle, subjects will be analyzed according to the treatment they have been assigned to during the randomization process.~~

Efficacy and safety endpoints observed after IPDE will be summarized separately from the rest of the results; these summaries may include tables, listings, or figures as appropriated depending on the number of patients and amount of data observed post-IPDE. Further details on this will be given in the SAP.

Section 10.5.3.1 Adverse Events and DLTs

SAEs starting or worsening after the on-treatment period, if reported as related to study treatment, will be summarized.

Section 10.5.5 Anti-drug Antibody

ADA status will be determined (e.g., negative or positive) at the scheduled protocol time points for all patients. Titer and neutralizing antibodies will be determined for ADA positive time points only.

The treatment-emergent ADA incidence will be calculated by dose cohort, which is the proportion of patients having ADA positive during study period. Treatment-emergent ADA-positive patients will include the following:

- **patients who are ADA negative at baseline and become ADA positive post-treatment (treatment-induced ADA); and**
- **patients who are ADA positive at baseline and post-treatment but also have a two-fold increase in ADA titer from baseline to post-treatment (treatment-boosted ADA); and**
- **patients who have missing ADA data at baseline but are ADA positive post-treatment.**

Individual ADA status and titer data will be reported in data listings. Neutralizing antibodies will be tabulated by dose cohort.

~~Anti-drug antibody incidence will be determined and the ADA titer data from ADA-positive subjects will be summarized by visit using descriptive summary statistics.~~

Section 10.7.4 Dose Increment During Dose Escalation and Appendix G Section 2.4

- ~~The dose level increment should be no less than 30% in order to have distinction among dose levels considering the inter-subject variability in exposure.~~

Section 11.2.1 Reporting of Adverse Events

For broad surveillance of ILD/pneumonitis, a set of pre-defined list of preferred terms eligible for adjudication as described in the Event Adjudication Site Manual, is utilized for enhanced data collection.

Disease progression/worsening of the cancer will not be recorded as an AE on the Adverse Event eCRF. However, events associated with disease progression, such as clinical symptoms, may be recorded as AEs. Death due to disease progression should be recorded on the Death eCRF.

~~For broad surveillance of ILD, selected 42 Preferred Terms (all from the ILD Standard MedDRA Query [SMQ)]) plus 2 PTs of acute respiratory failure and respiratory failure are included for enhanced data collections.~~

~~Disease progression is a study endpoint and consequently will not be reported as an AE/SAE. However, when a subject dies from disease progression with no other immediate cause, disease progression must be reported as an SAE.~~

Section 11.2.2.1 Safety Reporting for Covid-19

The following guidance is for reporting COVID-19 cases that have occurred in the context of a clinical trial with a Daiichi Sankyo product or compound:

- **All confirmed or suspected COVID-19 events must be recorded in the eCRF.**
  - **Patients who test positive for COVID-19 should be reported as "Confirmed COVID-19," either as an adverse event (AE) or serious adverse event (SAE).**
  - **Patients whose medical history and clinical manifestations, signs, and possible exposure are consistent with COVID-19 but for whom no PCR or antibody test for COVID-19 is available, should be reported as "Suspected COVID-19", either as an AE or SAE.**
- **The usual protocol mandated SAE reporting requirements should be followed for confirmed or suspected COVID-19 (or SARS-CoV-2) as done for any other AE, i.e. the investigator should assess whether any seriousness criteria are met per protocol, and appropriate protocol reporting requirements should be followed.**
  - **In the event that the Investigator assesses that a COVID-19 case does not meet any seriousness criteria as outlined in the protocol, it should be reported as a non-serious adverse event in the case report form (CRF).**
- **When assessing the severity of the COVID-19 adverse event, please use the severity grading criteria in the appropriate protocol.**

- **All study drug interruption or dose reduction or discontinuation due to the COVID-19 event must be recorded on the AE and drug administration eCRFs.**
- **For both serious or non-serious COVID-related AEs, the following information should be provided as a minimum:**
  - **Date and laboratory results confirming the COVID-19 diagnosis (including viral antigen test and/or antiviral antibody serological test) in the lab eCRF, if available.**
  - **Clinical course of the case including presenting signs, symptoms, exposure, actions taken with the investigational products, medications used for treatment or prophylaxis of COVID- 19, and outcome in relevant eCRF (e.g., concomitant medication, AE).**

Findings from diagnostic imaging (including CT scan or other chest imaging).

Section 11.4 Expedited Reporting by Investigators

The following types of events must be reported by the Investigator in the eCRF within 24 hours of awareness:

- All potential ILD/**pneumonitis** cases should be reported within 24 hours: including both serious and non-serious potential ILD cases (potential ILD is **described** ~~defined~~ by the Event Adjudication Site Manual ~~List of PTs~~).
- Hepatic events (both serious and non-serious, and clinical laboratory result) which meet the potential Hy's Law criteria defined as an elevated [ALT or AST] ≥3 × ULN and an elevated total bilirubin >2 × ULN that may occur simultaneously or at different time points during the study, regardless of whether these hepatic events are symptomatic, lead to study drug discontinuation, dose reduction or dose interruption, require corrective treatment, constitute an AE in the Investigator's clinical judgment. A targeted questionnaire is built within the eCRF to collect relevant additional information for these potential cases. **For broad surveillance of hepatotoxicity, hepatic events that meet the biochemical criteria (AST or ALT ≥ 3 x ULN, TBL > 2 x ULN) are included for enhanced data collection.**
- **Overdose is always serious. By definition an overdose is medically important, which meets the seriousness criterion of important medical event. An overdose can occur with or without an AE. AEs can either be serious or non-serious. Details of the overdose including DS-6157a dosage, clinical course, associated AEs, and outcome must be captured in the narrative form of the eCRF**. ~~Overdose, for DS-6157a, defined as the accidental or intentional administration of any dose of a product that is considered both excessive and medically important. An excessive and medically important overdose includes any overdose in which either an SAE, a non-serious AE, or no AE occurs and is considered by the Investigator as clinically relevant, i.e., poses an actual or potential risk to the subject.~~

Section 11.9 Pregnancy, Abortion, Birth Defects/Congenital Anomalies

If a patient becomes pregnant while enrolled in the study, EIU Reporting Form (a paper report form, not available within the eCRF) must be completed and **Faxed (866.807.4325)/Emailed (CANN.SAE@scri-innovations.com)** to the Innovations Safety Department.

Section 11.11.1 Interstitial Lung Disease Adjudication Committee

This data collection will be triggered based on a set of pre-defined list of preferred terms eligible for adjudication as described in the Event Adjudication Site Manual. ~~This data collection will be triggered for AEs reported using selected 42 preferred terms (PTs) (all from the ILD Standard MedDRA Query ([SMQ)]) plus 2 PTs of acute respiratory failure and respiratory failure are included for enhanced data collection.~~

Section 15 References

Iida et al. 2021

Iida K, Ahmed AHA, Nagatsuma AK, Shibutani T, Yasuda S, Kitamura M, et al. Identification and therapeutic targeting of GPR20, selectively expressed in gastrointestinal stromal tumors, with DS-6157a, a first-in-class antibody-drug conjugate. Cancer Discov. February 12 2021 DOI: 10.1158/2159-8290.CD-20-1434.

Appendix H Instruction Related to Covid-19

Amended Appendix H to include the most recent instructions related to Covid-19.

Additions to the text are **bolded** and deletions from the text are ~~crossed off~~. Only the parts of sections with changes are presented. Please note that formatting changes and minor changes to punctuation, spelling, and abbreviations that do not affect meaning are not noted in this summary.

Section 1.1.3 Clinical Experience

~~No clinical studies with DS-6157a have been conducted.~~ **Details of the information regarding the clinical experience of DS-6157a are provided in the IB.**

Section 1.2 Potential Risks and Benefits of the Treatment Regimen

DS-6157a is being developed for the treatment of GIST, which is characterized by high expression of GPR20. ~~The product is in the early stages of development, and no efficacy or safety in humans has been demonstrated.~~

Nonclinical studies have demonstrated the potent antitumor activity of DS-6157a in GPR20 positive tumor-bearing mouse models. Thus, DS-6157a is expected to demonstrate efficacy in GIST patients.

Nonclinical toxicology studies for DS-6157a and MAAA-1181a indicated potential risks of gastrointestinal toxicity, skin toxicity, lymphatic/hematopoietic organ toxicity, nephrotoxicity, hepatotoxicity, pulmonary toxicity, corneal toxicity, and reproductive organ toxicity in humans. As with any therapeutic antibody, there is a possibility of IRR and immune responses causing allergic or anaphylactic reactions **to** DS-6157a.

As of 04 August 2021, 34 subjects have received at least one dose of DS-6157a in the DS6157-A-U101 clinical study. Of these 34 subjects, 4 had dose-limiting toxicities (DLTs) (1 subject with intolerable intermittent diarrhea, nausea and vomiting [Grade 2 for each event] at 12.8 mg/kg; 1 subject with Grade 3 febrile neutropenia at 12.8 mg/kg; 1 subject with Grade 4 hepatic function abnormal, Grade 4 platelet count decreased, and Grade 3 renal disorder at 9.6 mg/kg; and 1 subject with Grade 5 hepatic function abnormal at 6.4 mg/kg).

Among the 4 subjects with DLTs, 2 experienced serious hepatic events that were considered by the Investigator as related to DS-6157a. One subject developed an SAE of Grade 5 hepatic function abnormal (Cycle 1 Day 8) after 1 dose of DS-6157a 6.4 mg/kg IV. Another subject had SAEs of Grade 4 hepatic function abnormal (Cycle 1 Day 8), Grade 4 platelet count decreased (Cycle 1 Day 8), and Grade 3 renal disorder (Cycle 1 Day 10) and a decrease in hemoglobin (Grade 4, not reported as AE/SAE) (Cycle 1 Day 9) after 1 dose of DS-6157a 9.6 mg/kg IV. There have been no other severe hepatotoxicity events observed in subjects treated with DS-6157a. These hepatic SAEs are being further evaluated. No interstitial lung disease (ILD)/pneumonitis events have been reported.

Based on the safety data from the nonclinical studies and the ongoing study, ILD/pneumonitis and hepatotoxicity are important potential risks. Nausea and vomiting

are classified as identified risks or adverse drug reactions. Other potential risks include IRR, other gastrointestinal events (i.e., diarrhea and colitis), hematological events (i.e., anemia, neutropenia, and thrombocytopenia), dermatological events, left ventricular ejection fraction (LVEF) decreased, renal events, and corneal events. These risks will be monitored closely in the DS-6157a clinical development program.

Although DS-6157a exhibits an acceptable safety profile, with close monitoring strategies in place, Daiichi Sankyo is further conducting a full analysis of all available dose escalation trial data to determine a dose level with a positive benefit-risk ratio.

Further details are provided in the IB. ~~Based on the efficacy and safety data generated in the nonclinical studies and the information from other products of the same class, the benefit-risk balance supports clinical development of DS-6157a.~~

Section 3.2 Exclusion Criteria and Synopsis

1. Treatment with any of the following:
    - History of an allogeneic bone marrow or solid organ transplant within 3 months before the start of study treatment
    - Concomitant treatment with any medication that is classified as having a known **or possible** risk of Torsades de pointes should be avoided from the start of study treatment through the end of Cycle 3 (see www.crediblemeds.org and Appendix E). Consult with Medical Monitor if such medication is needed during the study.

DS6157-A-U101/GI 289 PROTOCOL SYNOPSIS

Title of Study:	Phase 1, Multicenter, Open-Label, First-in-Human Study of DS-6157a in Patients with Advanced Gastrointestinal Stromal Tumor	
Sponsor/Innovations Study Numbers:	DS6157-A-U101/GI 289	
Sponsor:	Daiichi Sankyo, Inc.	
Study Duration:	The total duration of the study is planned to be approximately 5 years.	**Phase of Study:** 1
Study Centers:	This study will be conducted in the United States (US), Japan, and other country(ies) at approximately 10 sites.	
Number of Patients:	Approximately 100 patients are planned to be enrolled in this study.	
Objectives:	**Primary Objectives** The primary objectives of this study are: • Dose Escalation (Part 1): Investigate the safety and tolerability of DS-6157a, determine the maximum tolerated dose (MTD), and/or the recommended dose for expansion (RDE) • Dose Expansion (Part 2): Investigate the safety, tolerability, and efficacy of DS-6157a at RDE **Secondary Objectives** The secondary objectives for both Part 1 and Part 2 of this study are to: • Characterize the pharmacokinetic (PK) properties of DS-6157a, total anti-G-protein receptor 20 (GPR20) antibody and drug component (MAAA-1181a) • Evaluate the efficacy of DS-6157a (Part 1 only) • Assess the incidence of anti-drug antibodies (ADAs) against DS-6157a **Exploratory Objective** The exploratory objective of this study is to: • To identify biomarkers that correlate with efficacy, toxicity, and mechanism of action of DS-6157a	
Study Design:	This study is a two-part, multicenter, open-label, multiple-dose, first-in-human study of the antibody-drug conjugate (ADC) DS-6157a given as a single agent to patients with gastrointestinal stromal tumor (GIST). This study will include 2 parts: 1. Dose Escalation (Part 1) 2. Dose Expansion (Part 2) **Dose Escalation:** Approximately 40 patients with histopathologically documented advanced GIST not amenable to curative therapy may be included in which the MTD and/or RDE of DS-6157a monotherapy will be determined. Intra-patient dose escalation (IPDE) may be allowed for selected patients (Section 6). **Dose Expansion:** Once the RDE(s) is established for DS-6157a (Part 1), enrollment in Dose Expansion (Part 2) will commence in 2 cohorts. Up to approximately 30 patients with GIST who have progressed on or are intolerant to imatinib (IM) and at least one post-IM treatment will be enrolled in Cohort 1, and up to approximately 30 patients with GIST who progressed on IM or who are intolerant to IM (2nd line) will be enrolled in Cohort 2. Enrollment into Part 1 will not be restricted to patients with evidence of	

	GPR20 expression. Patient selection may be considered for Part 2 based on the biomarker assessments and its correlation with safety/efficacy signals in Part 1. Based on all available data collected in Dose Escalation (e.g., PK, safety, efficacy, and biomarker data), multiple doses or regimens less than or at the MTD (if attained, or the highest dose evaluated) may be selected as RDE(s) for further evaluation in Dose Expansion. In this case, up to approximately 30 patients may be randomized into each dose or regimen in one or more cohorts during Dose Expansion.
Study Drugs, Doses, and Modes of Administration:	During Dose Escalation (Part 1), the patient's weight at screening (baseline) will be used to calculate the initial dose of DS-6157a. On Cycle 1 Day 1, DS-6157a will be infused for 90 ± 10 minutes. A 21-day observation period (Cycle 1) will then occur, at the end of which all relevant safety data will be reviewed. Patients will continue to receive DS-6157a (once every 3 weeks [Q3W]) until progression of disease (PD) according to Response Evaluation Criteria in Solid Tumors (RECIST) v1.1 as assessed by the Investigator, unacceptable toxicity, death, or withdrawal of consent. If there is no infusion-related reaction after the initial 90-minute infusion on Cycle 1 Day 1, the subsequent dose of DS-6157a may be infused for 30 ± 5 minutes based on the clinical judgment of the Investigator and/or Medical Monitor, but this reduced infusion rate is not mandatory. During Dose Expansion (Part 2), on Cycle 1 Day 1 the RDE of DS-6157a will be infused for 90 ± 10 minutes. If there is no infusion-related reaction after the initial 90-minute infusion on Cycle 1 Day 1, the subsequent dose of DS-6157a may be infused for 30 ± 5 minutes based on the clinical judgment of the Investigator and/or Medical Monitor, but this reduced infusion rate is not mandatory. Patients will then continue to receive DS-6157a Q3W, until PD according to RECIST v1.1 as assessed by the Investigator, unacceptable toxicity, death, or withdrawal of consent. As exceptions, patients in both Part 1 and Part 2 may be treated beyond initial radiological progression (according to RECIST v1.1) on a case-by-case basis (with agreement from the Medical Monitor), if the Investigator feels that it is in the patient's best interest, the patient re-consents to continue receiving study treatment in a separate consent form, and as long as the patient is deriving benefit from the treatment and all the following criteria are met: • Absence of clinical symptoms or signs indicating clinically significant disease progression • No decline in performance status • Absence of rapid disease progression or threat to vital organs or critical anatomical sites (e.g., CNS metastasis, respiratory failure due to tumor compression, spinal cord compression) requiring urgent alternative medical intervention • No significant, unacceptable or irreversible toxicities related to study treatment • Patient agrees to continue protocol-specified assessments and monitoring However, the first evidence of radiographic progression will be captured as the progression event for efficacy assessments in these patients who are allowed continued treatment beyond progression.
Inclusion Criteria:	1. Is able to provide written informed consent, signed by the patient or by a legal guardian prior to the performance of any study-related procedures, and is willing and able to comply with the protocol. Patient or his/her legal guardian must be fully informed about their illness and the investigational nature of the study protocol (including foreseeable risks and possible toxicities) and must sign and date an Institutional Review Board (IRB)/Independent Ethics Committee (IEC) approved informed consent form (ICF) (including Health Insurance Portability and

	Accountability Act authorization [HIPAA], if applicable) before performance of any study-specific procedures or examinations. 2. At least 20 years old in Japan or 18 years old in other countries at the time of signature of the informed consent form (ICF), following local regulatory requirements. 3. Eastern Cooperative Oncology Group (ECOG) Performance Status score of 0 or 1. 4. Has histopathologically documented unresectable and/or metastatic GIST meeting the criteria below: - **Dose Escalation (Part 1):** patients should meet one of the following criteria: a. **(For US sites only)** Patients with GIST who have progressed on, or are intolerant to, imatinib (IM) and at least one post-IM treatment, or who are not candidates for post-IM standard of care treatment b. **(For Japan sites only)** Patients with GIST who have received all the existing standard of care treatments or who are not candidates for one or more available post-IM standard of care treatments c. Patients with GIST who are not candidates for IM or curative intent surgical treatment (i.e., patients without activating KIT or PDGFRa mutations, with PDGFRa D842V mutations, or are KIT negative by local results) - **Dose Expansion (Part 2) Cohort 1:** patients with GIST who have progressed on or are intolerant to IM and at least one post-IM treatment - **Dose Expansion (Part 2) Cohort 2:** patients with GIST who have progressed on IM and had not received a post-IM treatment (2nd line) 5. Consents to provide fresh tumor biopsy tissue samples both before and on DS-6157a treatment for the measurement of GPR20 levels by immunohistochemistry and other biomarkers. Evidence of GPR20 expression is not required for participation in the study unless the biomarker assessments in Part 1 suggest that patient selection in Part 2 should be enriched by biomarker confirmation. 6. Has a left ventricular ejection fraction (LVEF) ≥50% by either echocardiogram (ECHO) or multi-gated acquisition scan (MUGA) within 28 days before study treatment. 7. Has at least 1 measurable lesion based on RECIST Version 1.1 as assessed by the Investigator. 8. Has adequate organ function within 7 days before the start of study treatment, defined as: - Platelet count ≥100,000/mm^3 - Hemoglobin ≥8.5 g/dL - Absolute neutrophil count ≥1,500/mm^3 - Creatinine clearance ≥50 mL/min as calculated using the Cockcroft-Gault equation - Aspartate aminotransferase ≤3 × ULN (if liver metastases are present, ≤5 × ULN) - Alanine aminotransferase ≤3 × ULN (if liver metastases are present, ≤5 × ULN) - Total bilirubin ≤1.5 × ULN or ≤3.0 × ULN for patients with documented history of Gilbert's Syndrome - International Normalization Ratio (INR)/prothrombin time (PT) and either partial thromboplastin time (PTT) or activated partial thromboplastin time (aPTT) ≤ 1.5 x ULN

	9. Has an adequate treatment washout period prior to start of study treatment, defined as: - Major surgery: ≥4 weeks (or 2 weeks for minor surgeries). - Radiation therapy: ≥3 weeks (or 2 weeks for palliative radiation excluding pelvic radiation). - Systemic anti-cancer therapy (except for anti-androgen for prostate cancer and bisphosphonate, denosumab, or medroxyprogesterone acetate for bone metastases): • Cytotoxic chemotherapy: ≥3 weeks or 5 times the terminal elimination half-life ($t_{½}$) of the chemotherapeutic agent, whichever is shorter. • Antibody and antibody-conjugates therapy: ≥3 weeks or 5 times the $t_{½}$, whichever is longer. • Prior tyrosine kinase inhibitors (TKIs): washout period as listed in Appendix F. • Immunotherapy: ≥4 weeks • Chloroquine/Hydroxychloroquine >14 days. 10. Male patients with female partners of childbearing potential and female patients of child-bearing potential must agree to use a highly effective form of contraception, or avoid intercourse during and upon completion of the study and for at least 4 months (for males) and for at least 7 months (for females) after the last dose of study drug. Male patients must agree not to freeze or donate sperm starting at screening and throughout the study period, and at least 4 months after the final study drug administration. Female patients must agree not to donate, or retrieve for their own use, ova from the time of screening and throughout the study treatment period, and for at least 7 months after the final study drug administration.
Exclusion Criteria:	1. Treatment with any of the following: - History of an allogeneic bone marrow or solid organ transplant within 3 months before the start of study treatment - Concomitant treatment with any medication that is classified as having a known or possible risk of Torsades de pointes should be avoided from the start of study treatment through the end of Cycle 3 (see www.crediblemeds.org). Consult with Medical Monitor if such medication is needed during the study. - Prophylactic administration of G-CSF, filgrastim, pegfilgrastim, erythropoietin, or the transfusion of blood, red blood cells, or platelets within 14 days before the start of treatment and during Cycle 1. Chronic therapy with erythropoietin at stable dose that started at least 14 days before the first dose of DS-6157a may continue. 2. Has unresolved toxicities from previous anticancer therapy, defined as toxicities (other than alopecia) not yet resolved to NCI CTCAE version 5.0, Grade ≤1. Patients with chronic Grade 2 toxicities may be eligible following discussion with the Medical Monitor. 3. Has spinal cord compression or clinically active CNS metastases (including brain metastases), defined as untreated and symptomatic, or requiring therapy with steroids or anticonvulsants to control associated symptoms. Patients with treated brain metastases that are no longer symptomatic and who require no treatment with

	steroids may be included in the study if they have recovered from the acute toxic effect of radiotherapy. 4. Has known hypersensitivity to either the drug substances or inactive ingredients in the drug product. 5. Has a prior or concurrent malignancy whose natural history or treatment has the potential to interfere with the safety, efficacy, or any other assessments of the investigational regimen based on consultation with the Medical Monitor 6. Has a documented history of myocardial infarction or unstable angina within 6 months before study treatment. 7. Has a medical history of symptomatic congestive heart failure (New York Heart Association classes II–IV) or a serious cardiac arrhythmia requiring treatment. 8. Has a corrected QT by Fridericia's formula (QTcF), of >470 ms based on the average of triplicate 12-lead electrocardiogram (ECG) per local read. 9. Has a documented history of (non-infectious) interstitial lung disease (ILD)/pneumonitis that required corticosteroids, has current ILD/pneumonitis, or where suspected ILD/pneumonitis cannot be ruled out by imaging at screening. 10. Has a history of underlying pulmonary disorder, including but not limited to, pulmonary emboli within 3 months of the study randomization, severe asthma, severe COPD, restrictive lung disease, pleural effusion. 11. Has any autoimmune, connective tissue or inflammatory disorders (e.g., rheumatoid arthritis, Sjogren's, sarcoidosis) where there is documented, or a suspicion of pulmonary involvement at the time of screening. 12. Prior pneumonectomy. 13. Has clinically significant pulmonary compromise or requirement for supplemental oxygen. 14. Has clinically significant corneal disease. 15. Has an uncontrolled infection requiring IV antibiotics, antivirals, or antifungals. 16. Has active human immunodeficiency virus (HIV) infection as determined by plasma HIV RNA viral load. 17. Has evidence of active hepatitis B virus (HBV) or hepatitis C virus (HCV) infection, as manifest by the detectable viral load (HBV-DNA or HCV-RNA, respectively) 18. Has received a live vaccine within 30 days prior to the first dose of study drug. Examples of live vaccines include, but are not limited to, the following: measles, mumps, rubella, varicella/zoster (chicken pox), yellow fever, rabies, Bacillus Calmette-Guérin (BCG), and typhoid vaccine. Seasonal influenza vaccines for injection are generally killed virus vaccines and are allowed; however, intranasal influenza vaccines (eg, FluMist®) are live attenuated vaccines and are not allowed. 19. Is a lactating mother (women who are willing to temporarily interrupt breastfeeding will also be excluded), or pregnant as confirmed by pregnancy tests performed within 7 days before study treatment. 20. Women who plan to become pregnant while in the study and for at least 7 months after the last administration of study treatment. 21. Men who plan to father a child while in the study and for at least 4 months after the last administration of study treatment. 22. As judged by the Investigator, any evidence of severe or uncontrolled systemic diseases, including uncontrolled hypertension, uncontrolled diabetes mellitus, active bleeding diatheses, substance abuse, or other medical condition that would increase the risk of toxicity or interfere with participation of the patient or evaluation of the clinical study.

Correlative Testing:	Archival tumor samples, if available, will be collected at screening with the purpose of retrospectively identifying GPR20 expression status. Archival sample collection is recommended, but not mandated, and every effort should be made to obtain a sample. Fresh tumor samples will be collected from all patients at study entry and during treatment for biomarker testing. If a pre-treatment biopsy during screening is not feasible or is unsafe, a pre-existing biopsy collected after the termination of the most recent prior therapy and within 6 months of starting the first dose of DS-6157a will be acceptable. **Dose Escalation** • Evaluate pharmacodynamic effects by obtaining pre- and on-treatment fresh biopsies in Dose Escalation. **Dose Expansion** • Evaluate correlation of GPR20 expression with response • Evaluate GPR20 expression levels for potential use as a diagnostic assay • Characterize the pharmacodynamic effects of DS-6157a on tumor cells and gene expression profiling using biopsies • Identify additional selection marker(s) correlating with DS-6157a drug response and/or resistance by protein and RNA expression profiling, and with cell-free (cf)RNA and cfDNA from blood samples • Explore the DS-6157a response and resistance mechanisms with gene mutations and gene expression analysis
Statistical Methodology:	**Dose Escalation** The dose-escalation part of this study will utilize the Bayesian logistic regression model and following the escalation with overdose control principle to guide dose-finding, with at least 3 DLT-evaluable patients per dose level. The average sample size is 18 based on the simulation assuming 8.0% and 24.5% at 1.6 mg/kg and at 9.6 mg/kg, respectively, with 9.6 mg/kg as the highest dose tested. The number of patients required will depend on actual data. In addition, to refine the RDE, additional patients may be enrolled into selected dose levels. Intra-patient dose escalation (IPDE) may be allowed for selected patients (Section 6). **Dose Expansion** For the dose-expansion part, up to approximately 30 patients will be enrolled in each cohort. The sample size is determined such that sufficient precision is achieved to exclude a clinically non-interesting objective response rate (ORR) associated with the current standards of care. Assuming the ORR is approximately 20.0% in current standards of care, with 30 patients, if the observed ORR in the cohort is greater than or equal to 36.7%, the lower bound of the 90% confidence interval will be 22.1%. If multiple doses or regimens are selected as RDEs for one or more cohorts in Dose Expansion, up to approximately 30 patients may be randomized at each dose or regimen in one or more expansion cohorts.

DS6157-A-U101/GI 289 ASSESSMENT SCHEDULE

Study period	Screening	Dose Escalation and Dose Expansion DS-6157a Monotherapy Treatment Period																	EOT[p]	30-day Safety FU[q]	Long-term FU[r]
Cycle		C1						C2				C3						C4+		After EOT	After 30-day Safety FU
Treatment day (d)	Within -28 to 0 days	1	2	4 ±1 d	8 ±1 d	15 ±1 d	22 ±2d[h]	1 +2d	8 ±2d	15 ±2d	22 ±2d[h]	1 ±2d	2	4 ±2d	8 ±2d	15 ±2d	22 ±2d[h]	1±2d			
Informed consent	X																				
Inclusion / exclusion criteria	X																				
Medical history (including cancer history, prior cancer therapies, and smoking history) and demographics[a]	X[a]																				
Physical examination, including skin assessments, height (screening only), and weight[a,b]	X[a]	X			X	X		X	X	X		X						X	X	X	

Study period	Screening	Dose Escalation and Dose Expansion DS-6157a Monotherapy Treatment Period																	EOT[p]	30-day Safety FU[q]	Long-term FU[r]
Cycle		C1						C2				C3						C4+		After EOT	After 30-day Safety FU
Treatment day (d)	Within -28 to 0 days	1	2	4 ±1 d	8 ±1 d	15 ±1 d	22 ±2d[h]	1 +2d	8 ±2d	15 ±2d	22 ±2d[h]	1 ±2d	2	4 ±2d	8 ±2d	15 ±2d	22 ±2d[h]	1±2d			
ECOG performance status[a,b]	X[a]	X						X				X						X	X	X	
12-Lead electrocardiograms (triplicate)[a,c]	X[a]	X	X	X	X	X	(X)[h]	X	X	X	(X)[h]	X	X	X	X	X	(X)[h]	X	X[c]		
Vital signs[a,b]	X[a]	X	X	X	X	X		X	X	X		X	X	X	X	X		X	X	X	
ECHO or MUGA[d]	X[d]							X[d]										X[d]	X[d]		
Pregnancy test[a,e]	X[a]							X				X						X	X		
Safety laboratory (hematology, biochemistry)[a]	X[a]	X	X		X	X		X	X	X		X			X	X		X	X	X	
Safety laboratory (coagulation)[a]	X[a]	X				X		X		X		X				X		X	X	X	
Safety laboratory (urine)[a]	X[a]	X				X		X		X		X				X		X	X	X	

Study period	Screening	Dose Escalation and Dose Expansion DS-6157a Monotherapy Treatment Period																EOT[p]	30-day Safety FU[q]	Long-term FU[r]
Cycle		**C1**						**C2**				**C3**						**C4+**		**After EOT**	**After 30-day Safety FU**
Treatment day (d)	**Within -28 to 0 days**	**1**	**2**	**4 ±1 d**	**8 ±1 d**	**15 ±1 d**	**22 ±2d[h]**	**1 +2d**	**8 ±2d**	**15 ±2d**	**22 ±2d [h]**	**1 ±2d**	**2**	**4 ±2d**	**8 ±2d**	**15 ±2d**	**22 ±2d[h]**	**1±2d**			
HIV, HBV, HCV testing[a]	X[a]																				
Eye exam[f]	X																		X		
Tumor assessment[g]	X[a]	Every 6 weeks (±7 days) in the first 36 weeks from Day 1 of Cycle 1, and every 9 weeks (±7 days) thereafter.																	X[g]		X[r]
Blood sampling for pharmacokinetics[h]		X	X	X	X	X	(X)[h]	X	X	X	(X) [h]	X	X	X	X	X	(X)[h]	X[h]				
Blood sampling for anti-drug antibodies (ADAs)[i]		X			X			X				X						X[i]	X[i]	X[i]	(X)[i]
COVID-19 sample		X																X[s]	X		
Blood sampling for cfDNA analysis[j]	X[j]								DAY 8 TO 15[j]									X[j]	X[j]		
Blood sampling for cfRNA analysis[k]	X[k]								DAY 8 TO 15[k]									X[k]	X[k]		

Study period	Screening	Dose Escalation and Dose Expansion DS-6157a Monotherapy Treatment Period																EOT[p]	30-day Safety FU[q]	Long-term FU[r]
Cycle		C1						C2				C3						C4+		After EOT	After 30-day Safety FU
Treatment day (d)	Within -28 to 0 days	1	2	4 ±1 d	8 ±1 d	15 ±1 d	22 ±2d[h]	1 +2d	8 ±2d	15 ±2d	22 ±2d[h]	1 ±2d	2	4 ±2d	8 ±2d	15 ±2d	22 ±2d[h]	1±2d			
Archival tumor sample (optional)[l]	X																				
Fresh tumor sample[m]	X								DAY 8 TO 15											(X)[m] optional	
PBMC and serum biomarker collection[n]		X			X			X				X									
DS-6157a infusion[o]		X						X				X						X			
Concomitant medication/procedures	X	X	X	X	X	X		X	X	X		X	X	X	X	X		X	X	X	
Adverse events[p]	X	X	X	X	X	X		X	X	X		X	X	X	X	X		X	X	X	
Patient status																				X	X
PK Sampling for CQ/HCQ administration		If chloroquine (CQ) or hydroxychloroquine (HCQ) is administered for COVID-19, additional PK blood samples should be collected at the following visits, if feasible: • Prior to the first CQ or HCQ dose (Day 1)																			

Study period	Screening	Dose Escalation and Dose Expansion DS-6157a Monotherapy Treatment Period																	EOT[p]	30-day Safety FU[q]	Long-term FU[r]
Cycle		C1						C2				C3						C4+		After EOT	After 30-day Safety FU
Treatment day (d)	Within -28 to 0 days	1	2	4 ±1 d	8 ±1 d	15 ±1 d	22 ±2d[h]	1 +2d	8 ±2d	15 ±2d	22 ±2d[h]	1 ±2d	2	4 ±2d	8 ±2d	15 ±2d	22 ±2d[h]	1±2d			
		• Day 3 or Day 4 of CQ or HCQ treatment, prior to CQ or HCQ dose (within 4 hours) • Last day of the CQ/HCQ treatment, prior to CQ/HCQ dose (within 4 hours) • The day of DS-6157 resumption, after the CQ/HCQ washout period[t] (within 8 hours before initiating DS-6157) If possible, these PK samples should always be collected.																			

Dose Escalation and Dose Expansion Monotherapy Assessment Schedule Footnotes

a Safety laboratory assessments including hematology, biochemistry, coagulation, serum pregnancy test, and urinalysis will be performed locally. The following screening parameters must be done ≤7 days prior to initiation of treatment:

- medical history (including cancer history and prior cancer therapies, smoking history) and demographics, physical examination (including height, weight, and skin assessments), Eastern Cooperative Oncology Group (ECOG) performance status, vital signs (blood pressure, SpO2, body temperature, and pulse rate), and triplicate electrocardiogram (ECGs)
- **hematology:** red blood cell (RBC) count, hemoglobin (Hb), hematocrit, reticulocytes, total white blood cell (WBC) count, absolute neutrophil count (ANC), absolute lymphocyte count, 5-part % differential (neutrophils, lymphocytes, monocytes, basophils, eosinophils), and platelet count
- **biochemistry:** sodium, potassium, phosphate, chloride, creatinine, calcium, venous bicarbonate (HCO_3) or carbon dioxide (CO_2), albumin, total protein, aspartate aminotransferase (AST), alanine aminotransferase (ALT), alkaline phosphatase (ALP), bilirubin (total [required]/fractionated [direct/indirect] bilirubin, if available), lactate dehydrogenase (LDH), serum glucose, creatinine kinase (CK: if CK is elevated, then CK-MB, CK-MM, troponin I, and myoglobin should be reactively tested, with further follow-up as clinically warranted), blood urea nitrogen (BUN) or urea, and serum uric acid

- **coagulation:** prothrombin time (PT), international normalized ratio (INR) (extrinsic pathways) and either activated partial thromboplastin time (aPTT) or partial thromboplastin time (PTT) (intrinsic pathways)
- **urinalysis** (dipstick): if abnormal and clinically significant, the Investigator must order a microscopic analysis of the urine sediment
- screening pregnancy test (serum)

If these assessments are performed within 72 hours of initiation of treatment, they do not need to be repeated on Cycle 1 Day 1 with the exception of the ECOG performance status, an abbreviated physical examination, vital signs, and triplicate ECG that need to be performed prior to the administration of study treatment on Cycle 1 Day 1, as is the case for safety labs, if not done within 72 hours of treatment. Tumor assessments (scans) must be performed ≤28 days prior to initiation of treatment. Tests for HIV infection, hepatitis B, and hepatitis C must be performed at screening.

b Physical examinations including the measurements of height (screening only), weight, and skin assessments will be done at screening, on Days 1, 8, and 15 of Cycles 1 and 2, on Day 1 of each subsequent cycle prior to treatment, at the end-of-treatment (EOT) visit, and at the 30-day safety FU visit. ECOG performance status will be assessed at screening, on Day 1 of each cycle prior to treatment, at the EOT visit, and at the 30-day safety FU visit. Skin assessments will include physical examination, dermatological consult (if necessary), and/or skin biopsy as per dermatologist / Investigator's clinical judgment. Vital signs (systolic and diastolic blood pressure, SpO_2, body temperature, and pulse rate) are checked at every visit prior to blood work and/or administration of treatment and at the discretion of the Investigator. For subsequent cycles, all Day 1 assessments will have a 48-hour window prior to treatment administration. At the discretion of the investigator, vital signs may be done more than 10 minutes after blood draws other than PK, but prior to administration of treatment.

c Triplicate 12-lead ECGs will be done at the time points as outlined in Section 7.5 and whenever the Investigator deems it necessary. A single ECG will be performed on EOT. For each set of triplicate ECGs, three standard resting 12-lead ECGs will be obtained not more than three minutes apart each from the previous ECG. ECGs will be obtained after the patient has been resting quietly in semi-supine or supine position for at least 5 minutes before the first ECG and during the triplicate. When ECG and PK assessments coincide, ECGs must be done **within** 10 minutes **before** the scheduled PK sample. When ECG and blood draws other than PK coincide, ECGs should be done before these blood draws, however these blood draws (other than PK) may be taken more than 10 minutes after ECGs, or ECGs may be done more than 10 minutes after these blood draws (other than PK). Parameters to be included are: Heart Rate; RR, PR, and QT intervals; QRS duration; ECG body position; interpretation of ECG. Depending on the emerging ECG data during dose escalation, ECGs may be transmitted to a central reading vendor, as an option.

d Echocardiogram (ECHO) or multi-gated acquisition scan (MUGA) to be performed at screening (within 28 days before the start of treatment), within ±3 days of Day 1 of Cycle 2, then within 7 days before treatment on Day 1 of Cycles 5, 8, and every 3rd Cycle thereafter, and within 7 days before the EOT visit (unless ECHO or MUGA has been done within 3 weeks before the EOT). The Investigator may order unscheduled ECHO or MUGA at more frequent intervals if indicated. The LVEF assessment method used at screening should also be used throughout the study.

e Pregnancy tests are mandatory for women of child-bearing potential within 7 days of starting study treatment (serum), on Day 1 of each cycle (except Cycle 1) (urine dipstick) prior to treatment, and at the EOT treatment (urine dipstick or serum). A positive dipstick pregnancy test must be confirmed by a serum beta human chorionic gonadotropin (β-HCG) pregnancy test.

f An eye examination performed by an ophthalmologist includes a visual acuity test, slit lamp examination, tonometry, and fundoscopy at screening, EOT, and as clinically indicated.

g Tumor assessments must be done according to Response Evaluation Criteria in Solid Tumors (RECIST) Version 1.1 (see Appendix B) and should include computed tomography (CT) scans or magnetic resonance imaging (MRI) of **the chest** and **abdominopelvic cavity** at screening and, if clinically indicated, imaging of any other known or suspected sites of disease (e.g., brain) using an appropriate method (CT scan or MRI). If there is a history or suspicion of CNS metastasis a CT scan of the head or MRI of the brain must be performed. The same radiographic procedure must be used throughout the study. In case of suspected (but not otherwise confirmed) bone metastasis at screening or in subsequent cycles, tumor assessment should include a bone scan. CT scans or MRI of **the abdominopelvic cavity** (and chest ONLY if the screening imaging documented sites of disease in the chest) and correlative imaging should then be repeated at each tumor assessment. Assessments will be performed by the Investigator at screening and every 6 weeks (±7 days) during the first 36 weeks, and then every 9 weeks (±7 days), taking as reference the first dose date for non-randomized patients and randomization date for randomized patients. Thereafter, patients will be evaluated at the EOT visit by CT scans or MRI of **the chest** and **abdominopelvic cavity**, and as clinically indicated, until PD as per RECIST Version 1.1 as assessed by the Investigator, initiation of new anti-cancer treatment, unacceptable toxicity, death, lost to follow up, or withdraw of consent from any further participation and at the discretion of the Investigator. Baseline tumor assessments must be performed within 28 days before first administration of study drug for non-randomized patients and must be before randomization date for randomized patients. Tumor assessments should occur regardless of dose interruptions/delays. Additionally, all images including CT and MRI may be submitted to a central imaging vendor for independent retrospective review (Section 7.3).

h Pharmacokinetic (PK) sampling (blood) will be collected pre- and post-DS-6157a dosing. When ECG measurement and blood collection for PK are scheduled at the same time point, blood collection will be performed after the end of ECG measurement. The visit days and sampling time points as outlined below and in Section 7.6 are to be followed. One blood sample collection for PK and exploratory biomarker analysis as soon as ILD/pneumonitis is suspected, if feasible.

- Cycle 1 Day 1: Pre-dose (within 8 hours before treatment), after end of infusion (EOI) collected within 15 minutes after EOI, and 2, 4 and 7 hours (±15 minutes) after EOI
- Cycle 1 Day 2: 24 hours (±2 hours) after the start of Day 1 infusion
- Cycle 1 Days 4, 8, and 15 (±1 day)
- Cycle 1 Day 22: Only applicable to patients whose scheduled Day 1 dose of the next cycle is delayed for ≥3 days or who cannot continue the next cycle of study treatment.
- Cycle 2 Day 1: Pre-dose (within 8 hours before treatment) and within 15 minutes after EOI
- Cycle 2 Days 8 and 15 (±2 days)
- Cycle 2 Day 22: Only applicable to patients whose scheduled Day 1 dose of the next cycle is delayed for ≥3 days or who cannot continue the next cycle of study treatment.
- Cycle 3 Day 1: Pre-dose (within 8 hours before treatment), after EOI collected within 15 minutes after EOI, and 2, 4, and 7 hours (±15 minutes) after EOI
- Cycle 3 Day 2: 24 hours (±2 hours) after the start of Day 1 infusion
- Cycle 3 Day 4 (±1 day), Days 8 and 15 (±2 days)

- Cycle 3 Day 22: Only applicable to patients whose scheduled Day 1 dose of the next cycle is delayed for ≥3 days or who cannot continue the next cycle of study treatment.
- Cycle 4 Day 1, Cycle 6 Day 1, Cycle 8 Day 1: Pre-dose (within 8 hours before treatment)

Additional blood samples will be taken from patients who undergo IPDE.

- Day 1 of the first 4 cycles of IPDE: Pre-dose (within 8 hours before treatment) and within 15 minutes after EOI.

i Blood samples for DS-6157a ADAs will be collected pre-dose on Cycle 1 Day 1, on Cycle 1 Day 8, and pre-dose on Day 1 of Cycle 2 through Cycle 4. Thereafter, collect the ADA blood samples every 2 cycles (i.e., Cycles 6, 8, 10…), at EOT and 30-day safety FU visit. Additional blood samples will be collected at pre-dose of the first 4 dosing cycles from patients who undergo IPDE. For patients with a positive ADA at 30-day safety FU visit, additional blood samples for ADA should be collected every 3 months (± 1 month) up to 1 year from the last dose of DS-6157a, or if the ADA becomes negative, or if ADA titer is equal to or less than baseline (applicable when pre-existing ADA is observed), or if the patient starts another therapy for cancer, or withdraws consent from the study, whichever occurs first (Section 7.7).

j Blood samples for cfDNA analysis will be collected at screening (within 7 days after the screening tumor biopsy but prior to the first infusion of DS-6157a on Cycle 1 Day 1), Cycle 2 between Day 8 and 15, irrespective of biopsy date (However, collection on the same day as the tumor biopsy is recommended.), then every 3 cycles during treatment (i.e., Cycle 5 Day 1, Cycle 8 Day 1, Cycle 11 Day 1…), and at the EOT visit (Section 7.9.3).

k Blood samples for cfRNA analysis will be collected at screening (within 7 days after the screening tumor biopsy but prior to the first infusion of DS-6157a on Cycle 1 Day 1), Cycle 2 between Day 8 and 15, irrespective of biopsy date (However, collection on the same day as the tumor biopsy is recommended.), Cycle 5 (at the 12-week [±7 days] tumor assessment), and at the EOT visit. (Section 7.9.3).

l Archival samples include resected and/or biopsy samples obtained before anticancer systemic treatment will be collected from patients if available. Archival sample collection is recommended, but not mandated, and every effort should be made to obtain a sample. If the patient only has bone lesions that can be biopsied at the screening time, archival tumor sample taken other than from a non-bone lesion must be submitted. Archival samples will be tested for GPR20/KIT expression and mutation analysis.

m Fresh tumor biopsies will be collected from all patients, when possible as described in Section 7.9.2. All fresh biopsies will be preserved according to the lab manual. Core needle biopsies must be freshly taken after determination that the patient is eligible and before the first dose of DS-6157a. If a pre-treatment biopsy during screening is not feasible or is unsafe, a pre-existing biopsy with equivalent quality collected after the termination of the most recent prior therapy and within 6 months of starting the first dose of DS-6157a will be acceptable. If a pre-existing biopsy collected within 6 months of starting DS-6157a is provided at screening (i.e., if the fresh pre-treatment tumor biopsy is not feasible or unsafe), the cfRNA and cfDNA samples will be collected at screening (within -28 to 0 days) and prior to DS-6157a infusion on Cycle 1 Day 1. Another equivalent of four core needle biopsies must be collected at Cycle 2 between Day 8 and Day 15, if the patient is clinically stable as judged by Investigator. The third core needle biopsies **(optional)** can be collected between the EOT and follow-up visits prior to starting new treatments (see Section 7.9.2).

n For exploratory biomarker research, blood for peripheral blood mononuclear cell (PBMC) and serum will be collected pre-dose on Cycle 1 Day 1, Cycle 1 Day 8, and pre-dose on Cycle 2 Day 1 and Cycle 3 Day 1. The visit days and sampling time points as outlined in Section 7.9.4 are to be followed. If IPDE is conducted, it's recommended to collect additional blood biomarker samples at the following time points:

- Pre-dose on Day 1 of first cycle of IPDE

- Day 8 of first cycle of IPDE
- Pre-dose on Day 1 of second cycle of IPDE
- Pre-dose on Day 1 of third cycle of IPDE

o DS-6157a will administered IV every 3 weeks on Day 1 of each cycle as follows:

During **Dose Escalation**, the patient's weight at screening (baseline) will be used to calculate the initial dose of DS-6157a. The dose will be recalculated if the patient's weight changes by more than 10% from baseline, or per institutional standard even if the weight change is less than ±10%. On Day 1 of Cycle 1, DS-6157a will be infused for 90 ± 10 minutes. A 21-day observation period (Cycle 1) will then occur, at the end of which all relevant safety data will be reviewed. Patients will then continue to receive DS-6157a (once every 3 weeks [Q3W]) until unacceptable toxicity, progressive disease (PD) according to RECIST Version 1.1 as assessed by the Investigator, death or withdrawal of consent. If there is no infusion-related reaction after the initial dose, the subsequent dose of DS-6157a may be infused for 30 ± 5 minutes based on the clinical judgment of the Investigator and/or Medical Monitor, but this reduced infusion rate is not mandatory. .

During **Dose Expansion**, the patient's weight at screening (baseline) will be used to calculate the initial dose of DS-6157a. The dose will be recalculated if the patient's weight changes by more than 10% from baseline, or per institutional standard even if the weight change is less than ±10%. The RDE of DS-6157a IV will be for 90 ± 10 minutes on Day 1 of Cycle 1. If there is no infusion-related reaction after the initial dose for each patient, the subsequent dose of DS-6157a may be infused for 30 ± 5 minutes based on the clinical judgment of the Investigator and/or Medical Monitor, but this reduced infusion rate is not mandatory. Patients will then continue to receive DS-6157a Q3W until unacceptable toxicity, PD according to RECIST Version 1.1 as assessed by the Investigator, death or withdrawal of consent. Dosing of DS-6157a will be determined by the Sponsor and communicated separately as each new cohort opens for recruitment.

p The EOT visit will be performed after the Investigator decides with the patient to permanently discontinue the study treatment for any reason, as soon as possible but within 30 days of the last dose of treatment or before the patients starts another anti-cancer therapy, whichever occurs sooner. If the decision to permanently discontinue treatment is made at a scheduled visit, the EOT visit should be performed instead of the scheduled visit.

q 30-day safety follow-up will be performed for at least 30 days after the last study drug administration or before starting new anti-cancer treatment, whichever comes first, as described in Section 7.4.2. If the day of treatment discontinuation is over 30 days from last study drug administration, this follow up visit is not needed.

r Patients who did not experience progressive disease or death during the 30-day safety follow-up will be followed until the start of a new anti-cancer treatment, progressive disease, death, lost to follow up, withdrawal of consent from any further participation, or at the discretion of the Investigator. Tumor assessment per RECIST v1.1 will be performed at the same frequency as for patients receiving treatment depending on when the discontinuation occurs (i.e., every 6 weeks [±7 days] for the first 36 weeks and, every 9 weeks [±7 days] thereafter). If a new anticancer therapy is planned to start before the next planned tumor assessment, the tumor assessment may be performed just before starting the new therapy.

s If patient provides consent, samples should be collected prior to study drug infusion. Starting at Cycle 5, Day 1, every 4 cycles thereafter (Cycle 9, Cycle 13, etc.), and at the EOT visit. For patients with suspected or confirmed COVID-19 infections, follow the dose modifications in Appendix H.

t A washout period of no less than 14 days is required before restarting DS-6157.

LIST OF ABBREVIATIONS

ADA	Anti-drug antibody
ADC	Antibody-drug conjugate
AE	Adverse event
AESI	Adverse event of special interest
ALP	Alkaline phosphatase
ALT	Alanine aminotransferase
ANC	Absolute neutrophil count
AR	Adverse reaction
AST	Aspartate aminotransferase
AUC_{inf}	Area under the plasma concentration-time curve up to time infinity
AUC_{last}	Area under the plasma concentration-time curve up to the last quantifiable time
AUC_{tau}	Area under the plasma concentration-time curve in the dosing interval
BOR	Best overall response
CBR	Clinical benefit rate
cfDNA/RNA	Cell-free DNA/RNA
CFR	Code of Federal Regulations
CI	Confidence interval
CL	Elimination clearance
C_{max}	Maximum plasma concentration
COVID-19	Coronavirus disease 2019
CR	Complete response
CSPV	Clinical Safety and Pharmacovigilance
CT	Computed tomography
C_{trough}	Lowest concentration reach after a single dose
DCR	Disease control rate
DLT	Dose-limiting toxicity
DoR	Duration of response
EC	Ethics Committee
ECG	Electrocardiogram
ECOG	Eastern Cooperative Oncology Group
eCRF	Electronic Case Report Form
EIU	Exposure in utero
EOI	End of infusion
EOT	End of treatment
EWOC	Escalation with overdose control
FDA	Food and Drug Administration
GCP	Good Clinical Practice
GIST	Gastrointestinal stromal tumors
HED	Human equivalent dose

HIPAA	Health Insurance Portability and Accountability Act
HNSTD	Highest non-severely toxic dose
HSD	Human starting dose
IB	Investigator's Brochure
ICF	Informed consent form
ICH	International Council for Harmonisation
ILD	Interstitial lung disease
IM	Imatinib
IND	Investigational New Drug
Innovations	Sarah Cannon Development Innovations
IPDE	Intra-patient dose escalation
IRB	Institutional Review Board
IRR	Infusion-related reaction
ISF	Investigator Study File
IV	Intravenous
JSMT	Joint Safety Management Team
Kel	Terminal elimination rate constant
LVEF	Left ventricular ejection fraction
MRI	Magnetic resonance imaging
MTD	Maximum-tolerated dose
NCI CTCAE	National Cancer Institute Common Terminology Criteria for Adverse Events
NE	Not evaluable
OR	Objective response
ORR	Objective response rate
PBMC	Peripheral blood mononuclear cell
PD	Progressive disease
PET	Positron emission tomography
PFS	Progression-free survival
PHI	Protected health information
PK	Pharmacokinetic
PR	Partial response
PT	Prothrombin time
QT	ECG interval measured from the onset of the QRS complex to the end of the T wave
QTc	QT interval corrected for heart rate
RDE	Recommended dose for expansion
RECIST	Response Evaluation Criteria in Solid Tumors
SAE	Serious adverse event
SAP	Statistical Analysis Plan
SAR	Suspected adverse reaction
SCRI	Sarah Cannon Research Institute
SD	Stable disease

SOC	System organ class
SUSAR	Suspected unexpected serious adverse reaction
$t_{1/2}$	Terminal half-life
TKI	Tyrosine kinase inhibitor
T_{max}	Time to maximum plasma concentration
TTR	Time to response
ULN	Upper limit of normal
V_{ss}	Apparent volume of distribution at steady-state
V_z	Apparent volume of distribution at steady-state during terminal phase

TABLE OF CONTENTS

LIST OF TABLES

LIST OF FIGURES

LIST OF APPENDICES

1. INTRODUCTION

1.1 Background and Study Rationale

A key function of DNA topoisomerase I is the relaxation of DNA supercoiling by inducing transient single-strand DNA breaks for DNA replication and transcription (Pommier Y. 2006). DNA topoisomerase I inhibitors bind to topoisomerase I-DNA cleavage complexes and stabilize them, resulting in the induction of double-strand DNA breaks and cell apoptosis (Pommier Y. 2006).

G protein-coupled receptor 20, also known as GPR20, is a 358 amino acid seven-pass transmembrane protein, belonging to the class A G protein-coupled receptor (GPCR) superfamily (Hase et al. 2008). GPR20 is an orphan GPCR whose ligand has not been identified. GPR20 constitutively activates Gi proteins without ligand stimulation when exogenously expressed in HEK293 cells (Hase et al. 2008). GPR20 deficient mice exhibit hyperactivity disorder characterized by increased total distance travelled in an open field test (Brennan et al. 2002). GPR20 is abundantly expressed in gastrointestinal stromal tumors (GIST), which are well known as the most common mesenchymal tumors of digestive tracts (Allander et al. 2001). GPR20 expression is detected in more than 80% of all GIST tumor samples irrespective of the number of prior lines of TKI treatments received. GPR20 expression levels in KIT/PDGFRA wild type GIST and KIT mutant GIST are comparable. GPR20 is also highly expressed in GIST harboring TKI-resistant mutations in KIT (Iida et al. 2021). The expression of GPR20 is regulated by FOXF1 and ETV1 transcription factors that play critical roles in GIST initiation, proliferation, and survival (Chi et al. 2010, Ran et al. 2018). In mice, GPR20 is expressed in subsets of the interstitial cells of Cajal (ICC), the pacemaker cells for peristaltic contractions of gut (Ran et al. 2018). The ICC is thought to be the cell-of-origin of GIST (Corless et al. 2011). The function of GPR20 in GIST or ICC has not yet been reported.

1.1.1 DS-6157a

DS-6157a is an antibody-drug conjugate (ADC) comprised of a humanized anti-GPR20 IgG1 monoclonal antibody, MABS-9025a, which is covalently conjugated to a drug-linker, MAAA-1162a. MAAA-1162a is conjugated via thioether bonds to reduced cysteine residues at the inter-chain disulfide bonds between light chain and heavy chain or between heavy chain and heavy chain of MABS-9025a. The released drug, MAAA-1181a, inhibits topoisomerase I and leads to apoptosis of the target cells. On average, the target drug-to-antibody ratio is 8. Further details on the structural formula of DS-6157a are provided in the DS-6157a Investigator's Brochure (IB).

MABS-9025a is a heterotetrameric glycoprotein with a molecular weight of approximately 150 kDa. The molecule consists of two heavy chains of the gamma 1 class and two light chains of the kappa class covalently linked through disulfide bonds. The heavy and light chains are each composed of 453 and 214 amino acids, respectively.

1.1.2 Nonclinical Experience

DS-6157a specifically binds to GPR20 on the cell surface of the target cells, which leads to the internalization of DS-6157a into the cells. Following internalization, MAAA-1181a is released from DS-6157a in the target cells and inhibits cell replication and induces cell apoptosis. In nonclinical pharmacology studies, DS-6157a specifically inhibited the growth of GPR20-expressing tumor cells in vitro. In addition, DS-6157a inhibited tumor growth and induced tumor regression in mice bearing GPR20-expressing tumors. Taken together, these data suggest that DS-6157a may be effective in the treatment of patients with GPR20-expressing GIST.

In vivo Antitumor Activity of DS-6157a against Human Gastrointestinal Stromal Tumor Cell Line GIST-T1/GPR20 in Xenografted Nude Mice

DS-6157a was administered intravenously to female CAnN.Cg-*Foxn1nu*/CrlCrlj mice at 0, 0.1, 0.3, 1, 3, or 10 mg/kg on Day 0. The tumor length and width were measured on Days 0, 4, 7, 11, 14, 18, and 21. Plasma samples were collected on Day 21 to assess the plasma concentration of DS-6157a and total antibody. DS-6157a demonstrated significant dose-dependent antitumor activity at 0.3, 1, 3, or 10 mg/kg and inhibited tumor growth by 26.5%, 53.3%, 89.7%, and 92.9%, respectively, compared with the control group on Day 21 ($P < 0.001$ in each group). The mean plasma concentrations of DS-6157a and total antibody in plasma on Day 21 increased in a dose-dependent manner. Further details are provided in the DS-6157a Investigator's Brochure.

Pharmacokinetics of DS-6157a in Monkeys after Single Intravenous Administration

Male cynomolgus monkeys received DS-6157a IV at 0.1, 0.3, or 1 mg/kg. Pharmacokinetic (PK) parameters were assessed for DS-6157a, total antibody (drug conjugated and unconjugated antibody), and MAAA-1181a. The area under the curve (AUC) of DS-6157a increased in a dose-dependent manner after single intravenous administration of DS-6157a at doses of 0.1 mg/kg to 1 mg/kg. The terminal elimination half-life (t1/2) ranged from 4.43 days to 6.67 days. The total body clearance (CL) ranged from 8.73 mL/d/kg to 11.0 mL/d/kg. No clear differences in the PK parameters were observed between DS-6157a and the total antibody. MAAA-1181a was below the lower limit of quantification (BLQ) of 0.100 ng/mL and ADA was not detected in any animal. Further details are provided in the DS-6157a IB.

Intermittent intravenous dose toxicity studies (once every 3 weeks [Q3W], three times in total, followed by a recovery period) of DS-6157a were conducted in rats and cynomolgus monkeys. The dose levels in the rat study were 20, 60, and 199 mg/kg, and dose levels in the cynomolgus monkey study were 3, 10, and 30 mg/kg. DS-6157a was tolerated at doses up to 199 mg/kg in rats and 30 mg/kg in monkeys following the intermittent intravenous administration. The target organs/tissues of DS-6157a in rats were the skin, intestine, kidney, lympho-hematopoietic system, reproductive organs, tooth, and liver. Changes observed during the dosing period showed reversibility except for the degenerative changes in the testes at 60 mg/kg or above. In monkeys, the effects of DS-6157a were observed in the intestine, skin, ovary, thymus, esophagus, lung, mammary gland, and tongue. No toxicities were observed after the recovery period.

MAAA-1181a monohydrate was administered intravenously once a week for 4 weeks to rats and monkeys. The dose levels in the rat study were 3, 10, and 30 mg/kg, and dose levels in the cynomolgus monkey study were 1, 3, and 12 mg/kg. The target organ/tissues affected by MAAA-1181a in both species were the intestines, lymphatic/hematopoietic organs, and cornea. Histopathological changes in the heart were also observed in 2 monkeys at the lethal dose of MAAA-1181a (12 mg/kg).

1.1.3 Clinical Experience

Details of the information regarding the clinical experience of DS-6157a are provided in the IB.

1.1.4 Study Rationale and Rationale for Starting Dose

GPR20 is abundantly expressed in GIST. DS-6157a is an ADC that targets GPR20 and is composed of a humanized anti-GPR20 IgG1 monoclonal antibody, an enzymatically cleavable maleimide glycine-glycine-phenylalanine-glycine (GGFG) peptide linker, and a DNA topoisomerase I inhibitor named MAAA-1181a. Nonclinical studies have demonstrated the potent antitumor activity of DS-6157a in GPR20-positive tumor-bearing mouse models. Thus, DS-6157a is expected to demonstrate efficacy in human patients.

For the first-in-human study, a dose-escalating clinical study with DS-6157a, the proposed human starting dose (HSD) is 1.6 mg/kg, which was selected based on the rationale summarized below and is expected to ensure patient safety while affording a minimum level of efficacy.

In the 6-week intermittent dose toxicity study in rats, the severely toxic dose 10% (STD10) was considered to be more than 199 mg/kg. By determining 1/10 of the 199 mg/kg per ICH guidance S9, the human equivalent dose (HED) was estimated to be 3.2 mg/kg.

In the 6-week intermittent dose toxicity studies in cynomolgus monkeys, the highest non-severely toxic dose (HNSTD) was 30 mg/kg. By determining 1/6 of the HNSTD in cynomolgus monkeys per ICH guidance S9, the HED was estimated to be 1.6 mg/kg.

Based on predicted human pharmacokinetics, DS-6157a C_{trough} at 1.6 mg/kg dose administered Q3W was estimated to be comparable to the observed C_{trough} values in mice following administration of 3 mg/kg dose (mean 2.29 µg/mL and 95% CI: 1.09 to 3.49 µg/mL), which led to tumor regression in the GIST-T1/GPR20 xenograft mouse model. These data indicate that pharmacologically active exposures of DS-6157a are expected to be maintained in humans at DS-6157a doses of 1.6 mg/kg and above.

In the interest of benefit and risk balance, 1.6 mg/kg is considered to be sufficient as HSD for the cancer therapy.

1.2 Potential Risks and Benefits of the Treatment Regimen

DS-6157a is being developed for the treatment of GIST, which is characterized by high expression of GPR20.

Nonclinical studies have demonstrated the potent antitumor activity of DS-6157a in GPR20 positive tumor-bearing mouse models. Thus, DS-6157a is expected to demonstrate efficacy in GIST patients.

Nonclinical toxicology studies for DS-6157a and MAAA-1181a indicated potential risks of gastrointestinal toxicity, skin toxicity, lymphatic/hematopoietic organ toxicity, nephrotoxicity, hepatotoxicity, pulmonary toxicity, corneal toxicity, and reproductive organ toxicity in humans. As with any therapeutic antibody, there is a possibility of infusion-related reaction (IRR) and immune responses causing allergic or anaphylactic reactions to DS-6157a.

As of 04 August 2021, 34 subjects have received at least one dose of DS-6157a in the DS6157-A-U101 clinical study. Of these 34 subjects, 4 had dose-limiting toxicities (DLTs) (1 subject with intolerable intermittent diarrhea, nausea and vomiting [Grade 2 for each event] at 12.8 mg/kg; 1 subject with Grade 3 febrile neutropenia at 12.8 mg/kg; 1 subject with Grade 4 hepatic function abnormal, Grade 4 platelet count decreased, and Grade 3 renal disorder at 9.6 mg/kg; and 1 subject with Grade 5 hepatic function abnormal at 6.4 mg/kg).

Among the 4 subjects with DLTs, 2 experienced serious hepatic events that were considered by the Investigator as related to DS-6157a. One subject developed an SAE of Grade 5 hepatic function abnormal (Cycle 1 Day 8) after 1 dose of DS-6157a 6.4 mg/kg IV. Another subject had SAEs of Grade 4 hepatic function abnormal (Cycle 1 Day 8), Grade 4 platelet count decreased (Cycle 1 Day 8), and Grade 3 renal disorder (Cycle 1 Day 10) and a decrease in hemoglobin (Grade 4, not reported as AE/SAE) (Cycle 1 Day 9) after 1 dose of DS-6157a 9.6 mg/kg IV. There have been no other severe hepatotoxicity events observed in subjects treated with DS-6157a. These hepatic SAEs are being further evaluated. No interstitial lung disease (ILD)/pneumonitis events have been reported.

Based on the safety data from the nonclinical studies and the ongoing study, ILD/pneumonitis and hepatotoxicity are important potential risks. Nausea and vomiting are classified as identified risks or adverse drug reactions. Other potential risks include IRR, other gastrointestinal events (i.e., diarrhea and colitis), hematological events (i.e., anemia, neutropenia, and thrombocytopenia), dermatological events, left ventricular ejection fraction (LVEF) decreased, renal events, and corneal events. These risks will be monitored closely in the DS-6157a clinical development program.

Although DS-6157a exhibits an acceptable safety profile, with close monitoring strategies in place, Daiichi Sankyo is further conducting a full analysis of all available dose escalation trial data to determine a dose level with a positive benefit-risk ratio. Further details are provided in the IB.

2. STUDY OBJECTIVES AND ENDPOINTS

2.1 Primary Objectives

The primary objectives of this study are:

- Dose Escalation (Part 1): Investigate the safety and tolerability of DS-6157a, determine the maximum tolerated dose (MTD), and/or the recommended dose for expansion (RDE)
- Dose Expansion (Part 2): Investigate the safety, tolerability, and efficacy of DS-6157a at RDE

2.2 Secondary Objectives

The secondary objectives for both Part 1 and Part 2 of this study are to:

- Characterize the pharmacokinetic (PK) properties of DS-6157a, total anti-GPR20 antibody and drug component (MAAA-1181a)
- Evaluate the efficacy of DS-6157a (Part 1 only)
- Assess the incidence of anti-drug antibodies (ADAs) against DS-6157a

2.3 Exploratory Objective

The exploratory objective of this study is to:

- Identify biomarkers that correlate with efficacy, toxicity and mechanism of action of DS-6157a

2.4 Endpoints

Table 1 Study Objectives and Corresponding Endpoints

Primary Objectives:	Endpoint/Variable:
• Dose Escalation: To investigate the safety and tolerability and to determine MTD and RDE of DS-6157a • Dose Expansion: To investigate the safety, tolerability, and efficacy of DS-6157a at RDE	Dose-limiting toxicities (DLTs) Serious adverse events (SAEs) Treatment-emergent adverse events (TEAEs) Adverse event (AE) of special interest (AESIs) Chemistry/hematology laboratory parameters Physical examination Vital signs Electrocardiograms (ECGs) LVEF by echocardiogram (ECHO)/multi-gated acquisition scan (MUGA) Ophthalmologic findings **Dose Expansion only:** Objective response rate (ORR), duration of response (DoR), disease control rate (DCR), clinical benefit rate (CBR), time to response (TTR), progression-free survival (PFS), and best percent change in target lesion by RECIST Version 1.1

Secondary Objectives:	Endpoint/Variable:
Pharmacokinetic (PK) properties of DS-6157a, total anti-GPR20 antibody and drug component (MAAA-1181a)	Plasma PK parameters such as (AUC_{last}, AUC_{tau}, C_{max}, T_{max}, C_{trough}, and $t_{1/2}$) of DS-6157a, total anti-GPR20 antibody, and MAAA-1181a
Evaluate the efficacy of DS-6157a (Part 1 only)	ORR, DoR, DCR, CBR, TTR, PFS, and best percent change in target lesion by RECIST Version 1.1
Assess the incidence of anti-drug antibodies (ADAs) against DS-6157a	ADA for DS-6157a will be measured in plasma
Exploratory Objectives:	**Endpoint/Variable:**
To identify biomarkers that correlate with efficacy, toxicity, and mechanism of action of DS-6157a	Immunohistochemical (IHC) expression of GPR20, KIT, and markers of response to topoisomerase I inhibition. IHC analysis of DS-6157a in tumor biopsies. Mutation analysis of GIST markers (e.g. KIT, PDGFRA) in tumor biopsies. Gene expression analysis in tumor pre- vs on-treatment, and characterization of treatment dependent changes in soluble markers.

3. STUDY SUBJECT POPULATION AND DISCONTINUATION

3.1 Inclusion Criteria

Patients must meet the following criteria in order to be included in the research study:

1. Is able to provide written informed consent, signed by the patient or by a legal guardian prior to the performance of any study-related procedures, and is willing and able to comply with the protocol. Patient or his/her legal guardian must be fully informed about their illness and the investigational nature of the study protocol (including foreseeable risks and possible toxicities) and must sign and date an Institutional Review Board (IRB)/Independent Ethics Committee (IEC) approved informed consent form (ICF)(including Health Insurance Portability and Accountability Act authorization [HIPAA], if applicable) before performance of any study-specific procedures or examinations.
2. At least 20 years old in Japan or 18 years old in other countries at the time of signature of the informed consent form (ICF), following local regulatory requirements.
3. Eastern Cooperative Oncology Group (ECOG) Performance Status score of 0 or 1 (Appendix A).
4. Has a histopathologically documented unresectable and/or metastatic GIST meeting the criteria below:

- **Dose Escalation (Part 1)**: patients should meet one of the following criteria:
  a. **(For US sites only)** Patients with GIST who have progressed on, or are intolerant to, imatinib (IM) and at least one post-IM treatment, or who are not candidates for post-IM standard of care treatment
  b. **(For Japan sites only)** Patients with GIST who have received all the existing standard of care treatments or who are not candidates for one or more available post-IM standard of care treatments
  c. Patients with GIST who are not candidates for IM or curative intent surgical treatment (i.e., patients without activating KIT or PDGFRa mutations, with PDGFRa D842V mutations, or are KIT negative by local results)
- **Dose Expansion (Part 2) Cohort 1:** patients with GIST who have progressed on or are intolerant to IM and at least one post-IM treatment
- **Dose Expansion (Part 2) Cohort 2:** patients with GIST who have progressed on IM and had not received a post-IM treatment (2nd line)

5. Consents to provide fresh tumor biopsy tissue samples both before and on DS-6157a treatment for the measurement of GPR20 levels by immunohistochemistry and other biomarkers. Evidence of GPR20 expression is not required for participation in the study unless the biomarker assessments in Part 1 suggest that patient selection in Part 2 should be enriched by biomarker confirmation.
6. Has a left ventricular ejection fraction (LVEF) ≥50% by either ECHO or MUGA within 28 days before study treatment.
7. Has at least 1 measurable lesion based on Response Evaluation Criteria in Solids Tumors (RECIST) Version 1.1 as assessed by the Investigator (Appendix B).
8. Has adequate organ function within 7 days before the start of study treatment, defined as:
   - Platelet count ≥100,000/mm^3
   - Hemoglobin ≥8.5 g/dL
   - Absolute neutrophil count ≥1,500/mm^3
   - Creatinine clearance ≥50 mL/min as calculated using the Cockcroft-Gault equation
   - Aspartate aminotransferase ≤3 × ULN (if liver metastases are present, ≤5 × ULN)
   - Alanine aminotransferase ≤3 × ULN (if liver metastases are present, ≤5 × ULN)
   - Total bilirubin ≤1.5 × ULN or ≤3.0 × ULN for patients with documented history of Gilbert's Syndrome
   - International Normalization Ratio (INR)/prothrombin time (PT) and either partial thromboplastin time (PTT) or activated partial thromboplastin time (aPTT) ≤ 1.5 x ULN
9. Has an adequate treatment washout period prior to start of study treatment, defined as:

- Major surgery: ≥4 weeks (or 2 weeks for minor surgeries).
- Radiation therapy: ≥3 weeks (or 2 weeks for palliative radiation excluding pelvic radiation).
- Systemic anti-cancer therapy (except for anti-androgen for prostate cancer and bisphosphonate, denosumab, or medroxyprogesterone acetate for bone metastases):
    - Cytotoxic chemotherapy: ≥3 weeks or 5 times the terminal elimination half-life ($t_{½}$) of the chemotherapeutic agent, whichever is shorter.
    - Antibody and ADC therapy: ≥3 weeks or 5 times the $t_{½}$, whichever is longer.
    - Prior TKIs: washout period as listed inAppendix F.
    - Immunotherapy: ≥4 weeks.
    - Chloroquine/Hydroxychloroquine >14 days.

10. Male patients with female partners of childbearing potential and female patients of child-bearing potential must agree to use a highly effective form of contraception (Appendix C), or avoid intercourse during and upon completion of the study and for at least 4 months (for males) and for at least 7 months (for females) after the last dose of study drug. Male patients must agree not to freeze or donate sperm starting at screening and throughout the study period, and at least 4 months after the final study drug administration. Female patients must agree not to donate, or retrieve for their own use, ova from the time of screening and throughout the study treatment period, and for at least 7 months after the final study drug administration.

3.2 Exclusion Criteria

Patients who meet any of the following criteria will be excluded from study entry:

1. Treatment with any of the following:
    - History of an allogeneic bone marrow or solid organ transplant within 3 months before the start of study treatment
    - Concomitant treatment with any medication that is classified as having a known or possible risk of Torsades de pointes should be avoided from the start of study treatment through the end of Cycle 3 (see www.crediblemeds.org and Appendix E). Consult with Medical Monitor if such medication is needed during the study.
    - Prophylactic administration of G-CSF, filgrastim, pegfilgrastim, erythropoietin, or the transfusion of blood, red blood cells (RBC), or platelets within 14 days before the start of treatment and during Cycle 1. Chronic therapy with erythropoietin at stable dose that started at least >14 days before the first dose of DS-6157a may continue.

2. Has unresolved toxicities from previous anticancer therapy, defined as toxicities (other than alopecia) not yet resolved to NCI CTCAE version 5.0, Grade ≤1.

   Patients with chronic Grade 2 toxicities may be eligible following discussion with the Medical Monitor.

3. Has spinal cord compression or clinically active CNS metastases (including brain metastases), defined as untreated and symptomatic, or requiring therapy with steroids or anticonvulsants to control associated symptoms. Patients with treated brain metastases that are no longer symptomatic and who require no treatment with steroids may be included in the study if they have recovered from the acute toxic effect of radiotherapy.
4. Has known hypersensitivity to either the drug substances or inactive ingredients in the drug product.
5. Has a prior or concurrent malignancy whose natural history or treatment has the potential to interfere with the safety, efficacy, or any other assessments of the investigational regimen based on consultation with the Medical Monitor.
6. Has a documented history of myocardial infarction or unstable angina within 6 months before study treatment.
7. Has a medical history of symptomatic congestive heart failure (New York Heart Association classes II–IV; Appendix D) or a serious cardiac arrhythmia requiring treatment.
8. Has a corrected QT by Fridericia's formula (QTcF), of >470 ms based on the average of triplicate 12-lead electrocardiogram (ECG) per local read.
9. Has a documented history of (non-infectious) interstitial lung disease (ILD)/pneumonitis that required corticosteroids, has current ILD/pneumonitis, or where suspected ILD/pneumonitis cannot be ruled out by imaging at screening.
10. Has a history of underlying pulmonary disorder, including but not limited to, pulmonary emboli within 3 months of the study randomization, severe asthma, severe COPD, restrictive lung disease, pleural effusion.
11. Has any autoimmune, connective tissue or inflammatory disorders (e.g., rheumatoid arthritis, Sjogren's, sarcoidosis) where there is documented, or a suspicion of pulmonary involvement at the time of screening.
12. Prior pneumonectomy
13. Has clinically significant pulmonary compromise or requirement for supplemental oxygen.
14. Has clinically significant corneal disease.
15. Has an uncontrolled infection requiring IV antibiotics, antivirals, or antifungals.
16. Has active human immunodeficiency virus (HIV) infection as determined by plasma HIV RNA viral load.
17. Has evidence of active hepatitis B virus (HBV) or hepatitis C virus (HCV) infection, as manifested by the detectable viral load (HBV-DNA or HCV-RNA, respectively).
18. Has received a live vaccine within 30 days prior to the first dose of study drug. Examples of live vaccines include, but are not limited to, the following: measles, mumps, rubella, varicella/zoster (chicken pox), yellow fever, rabies, Bacillus Calmette-Guérin (BCG), and

typhoid vaccine. Seasonal influenza vaccines for injection are generally killed virus vaccines and are allowed; however, intranasal influenza vaccines (eg, FluMist®) are live attenuated vaccines and are not allowed.

19. Is a lactating mother (women who are willing to temporarily interrupt breastfeeding will also be excluded), or pregnant as confirmed by pregnancy tests performed within 7 days before the start of study treatment.
20. Women who plan to become pregnant while in the study and for at least 7 months after the last administration of study treatment.
21. Men who plan to father a child while in the study and for at least 4 months after the last administration of study treatment.
22. As judged by the Investigator, any evidence of severe or uncontrolled systemic diseases, including uncontrolled hypertension, uncontrolled diabetes mellitus, active bleeding or severe bleeding diatheses, substance abuse, or other medical condition that would increase the risk of toxicity or interfere with participation of the patient or evaluation of the clinical study.

3.3 Discontinuation from Study Treatment

Patients may be withdrawn from study treatment for any of the following reasons:

- Disease progression (PD) based on RECIST Version 1.1 criteria, where the patient is no longer receiving benefit in the opinion of the treating Investigator.
    - However, patients who are receiving benefit in the opinion of the treating Investigator may be allowed to stay on study on a case-by-case basis with agreement from the Medical Monitor and if the patient re-consents to continue receiving the study drug and meet the criteria listed in Section 5.2.

Clinical progression (definitive clinical signs of PD), but a recent radiographic assessment did not meet the criteria for PD according to RECIST Version 1.1

- Adverse event
- Death
- Pregnancy
- Withdrawal of consent by patient
- Lost to follow-up
- Physician decision
- Study terminated by Sponsor
- Other

After discontinuation from protocol treatment, patients must be followed for AEs for at least 30 days after their last dose of study drug. All new AEs occurring during this period must be reported and followed until resolution, unless, in the opinion of the Investigator, these values are

not likely to improve because of the underlying disease. In this case, the Investigator must record his or her reasoning for this decision in the patient's medical records and indicate on the AE pages that the outcome is not resolved on the electronic case report form (eCRF).

All patients who have Grade 3 or 4 laboratory abnormalities (per National Cancer Institute Common Terminology Criteria for Adverse Events [NCI CTCAE Version 5.0]) at the time of discontinuation must be followed until the laboratory values have returned to Grade 1 or 2, unless it is, in the opinion of the Investigator, not likely that these values are to improve. In this case, the Investigator must record his or her reasoning for making this decision in the patient's medical records and indicate on the AE pages that the outcome is not resolved on the eCRF.

4. STUDY REGISTRATION

The patient must willingly consent after being informed of the procedures to be followed, the experimental nature of the treatment, potential benefits, alternatives, side-effects, risks, and discomforts. Human protection committee (IRB/IEC) approval of this protocol and any associated ICFs is required. Eligible patients who wish to participate in the study will be enrolled into the study.

Registration must occur prior to the initiation of study treatment. Patient registration and dose level assignment will be performed by Sarah Cannon Development Innovations (Innovations). The study site will document the patient identification number, dose level, and date of enrollment on the Patient Enrollment Form.

For additional information regarding study registration, please refer to the Study Reference Manual.

5. STUDY DESIGN

This study is a Phase I, two-part, multicenter, open-label, multiple-dose, first-in-human study of the antibody-drug conjugate, DS-6157a, given as a single agent to patients with GIST. Patients will be enrolled in this study in the United States (US), Japan, and other country(ies).

In Dose Escalation (Part 1), approximately 40 patients may be enrolled. Once the MTD and RDE are established for DS-6157a in Part 1, enrollment in Dose Expansion (Part 2) will commence in two cohorts. Up to approximately 30 patients with GIST who have been previously treated with IM and at least one other post-IM treatment will be enrolled in Cohort 1, and up to approximately 30 patients with GIST who progressed on IM or who are intolerant to IM but have not received post-IM treatment (2nd line) will be enrolled in Cohort 2. Enrollment into Dose Escalation will not be restricted to patients with evidence of GPR20 expression. Patient selection may be considered for Part 2 based on the biomarker assessments and its correlation with safety/efficacy signals in Part 1.

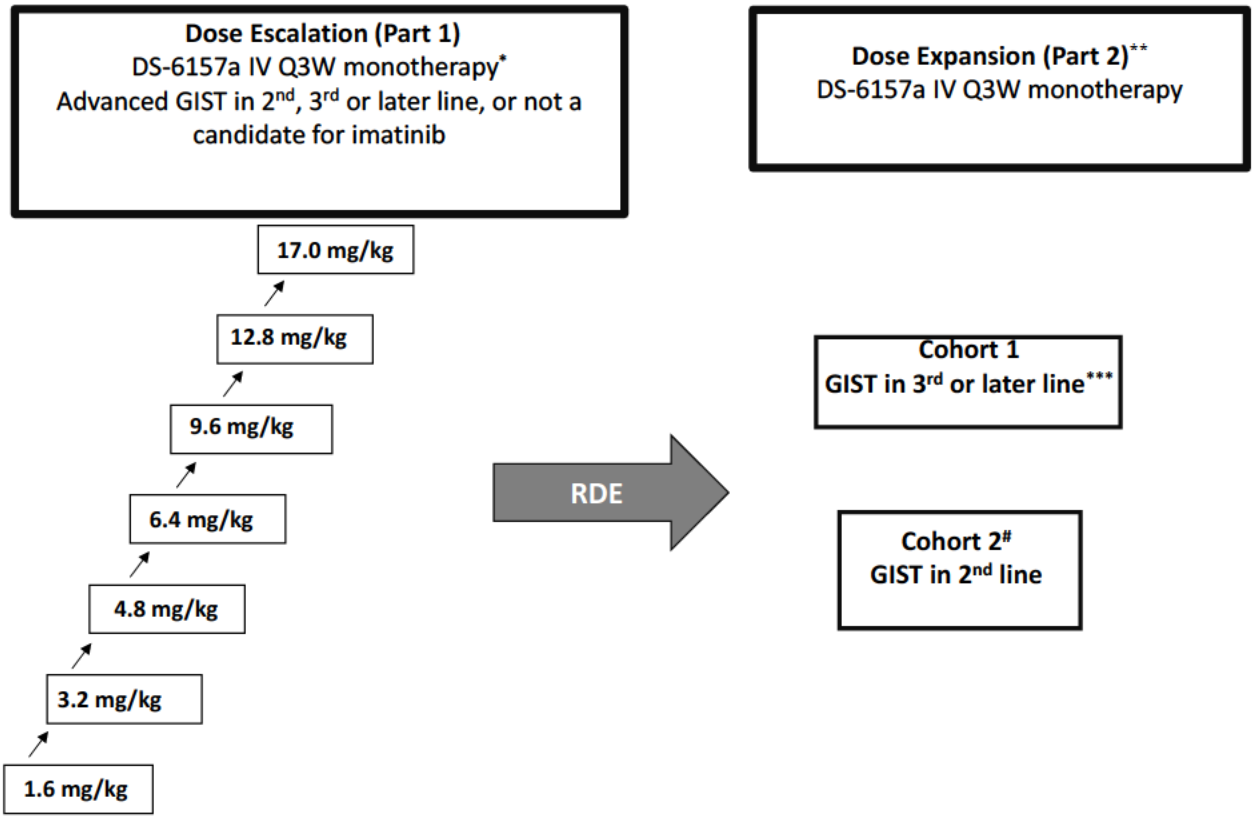
Based on all available data collected in Dose Escalation (e.g., PK, safety, efficacy, and biomarker data), multiple doses or regimens less than or at the MTD (if attained, or the highest dose evaluated) may be selected as RDEs for further evaluation in Dose Expansion. If this is the

case, up to approximately 30 patients may be randomized into each dose or regimen in one or more cohorts during Dose Expansion.

DS-6157a will be administered intravenously (IV) on Day 1 of each cycle on a 21-day schedule. The study will identify an MTD (see Section 5.1.3) and an RDE (see Section 5.1.4) for DS-6157a.

The study schema is presented in Figure 1.

Figure 1 Study Schema



GIST: gastrointestinal stromal tumors, RDE: recommended dose for expansion

*These are provisional doses. Actual dose levels will be determined by clinical toxicity findings in each dose cohort and the Bayesian logistic regression model (BLRM). Higher or intermediate doses may also be considered.

**DS-6157a dose will be determined in Dose Escalation (Part 1).

***Cohort 1 includes patients who have been previously treated with imatinib and at least one post-imatinib treatment.

#Cohort 2 will be initiated after acceptable efficacy is demonstrated objective responses or SD for a minimum of 6 months in ≥20% of 10 or more patients treated with DS-6157a at RDE) in Dose Escalation and Dose Expansion Cohort 1.

5.1 Treatment Plan

DS-6157a will be prepared and administered via intravenous (IV) infusion according to the details in the Pharmacy Manual.

For Dose Escalation (Part 1), on Cycle 1 Day 1 DS-6157a will be infused for 90 ±10 minutes. A 21-day observation period (Cycle 1) will then occur, at the end of which all relevant safety data will be reviewed. Patients will continue to receive DS-6157a (Q3W) until unacceptable toxicity, progressive disease (PD), death, or withdrawal of consent (Section 3.3). If there is no infusion-related reaction on Cycle 1 Day 1, the subsequent dose of DS-6157a may be infused for 30 ± 5 minutes based on the clinical judgment of the Investigator and/or Medical Monitor, but this reduced infusion rate is not mandatory.

For Dose Expansion (Part 2), on Cycle 1 Day 1 the RDE of DS-6157a will be infused for 90 ± 10 minutes. Patients will then continue to receive DS-6157a (Q3W) until unacceptable toxicity, PD, death, or withdrawal of consent (Section 3.3). If there is no infusion-related reaction after the initial dose, the subsequent dose of DS-6157a may be infused for 30 ± 5 minutes based on the clinical judgment of the Investigator and/or Medical Monitor, but this reduced infusion rate is not mandatory.

For both Dose Escalation and Dose Expansion, the patient's weight at screening (baseline) will be used to calculate the initial dose. The dose will be recalculated if the patient's weight changes by more than 10% from baseline, or per institutional standard even if the weight change is less than ±10%. This new body weight will be used to calculate the dose for subsequent cycles of DS-6157 infusion.

5.1.1 Dose Escalation Procedure

Dose escalation of DS-6157a will be guided by a Bayesian logistic regression model (BLRM) (Neuenschwander et al. 2008) following the escalation with overdose control (EWOC) principle (Babb et al. 1998, Rogatko et al. 2005). The details of the methodology are described in Section 10.7.

Cohorts of 3 to 6 patients will be enrolled and assessed for DLT during Dose Escalation. The first two patients at each dose level in Dose Escalation will start the study treatment (first dose) at least 24 hours apart. Dose escalation decision and enrollment of patients to a new cohort requires completion of DLT evaluation of at least 3 patients treated in the current cohort. Patients who have neither completed the DLT evaluation period with full dose nor experienced a DLT will not be included in the BLRM update. In the event that additional patients in the previous cohort experience a DLT after the enrollment of patients to a new cohort has begun, dose level assignment of the next patient in the study will be based on an updated BLRM using DLT outcome data from all assessed doses thus far, and clinical assessment of the overall safety data by the Sponsor and Investigator(s). The model will also be re-evaluated before enrolment of any additional patients to a cohort if 2 evaluable patients in the cohort experience DLT before the enrollment of the next patient.

The next dose level will be chosen by the Sponsor and Investigator(s) based on the dose recommendation by the BLRM as outlined in Section 10.7.3, and clinical assessment of the overall safety data. In addition, any available PK, pharmacodynamics, and efficacy data may be considered for dose escalation decisions. The dose level increase will not be greater than 100% even if the BLRM suggests a dose higher than 100% for next cohort.

The actual number of dose cohorts to be explored in this study will depend on determination of the MTD based on DLTs reported during the DLT evaluation period (Day 1 to Day 21 of Cycle 1 in Dose Escalation). Additional patients may be enrolled at the MTD or any dose levels below the MTD in order to collect sufficient safety and PK data or to characterize safety and PK in specific ethnicities.

For MTD (or RDE if MTD is not observed) determination, the following stopping rules will be implemented for Dose Escalation:

- At least 6 evaluable patients at MTD/RDE level with at least 15 evaluable patients in total enrolled in Dose Escalation, or
- At least 9 evaluable patients have been enrolled at a dose level which is the model's recommendation for the next dose cohort and for which the posterior probability of target DLT rate interval (16%, 33%] is at least 50%, or
- DLT assessment with at least 3 evaluable patients at the maximum tolerated dose level with 95% credible interval for posterior probability of DLT rate is within (5%, 33%), or
- Initial dose level is too toxic.

In order to refine the RDE, additional patients may be enrolled into selected dose levels. These added patients will also be used to generate data on safety, tolerability, PK, potential efficacy, and the correlation with biomarker expression levels. The RDE will be decided based on considerations of the MTD and on an overall assessment of the dose escalation part that will include safety data, efficacy, PK, and biomarker data collected at all doses tested.

For subjects in Japan only: Patients in Dose Escalation will be hospitalized during the DLT evaluation period (i.e., Day 1 to Day 21 of Cycle 1 in Dose Escalation). However, temporary stays outside the hospital are permitted at the Investigator's discretion. The Investigator should examine the patient carefully before granting permission for the patient to temporarily leave the clinic. The study site should provide the patient with emergency contact information. Additional safety assessments should be conducted as needed, at the Investigator's discretion.

5.1.2 Dose-Limiting Toxicity

Toxicity will be assessed using the NCI CTCAE Version 5.0.

A DLT is defined as any TEAE that occurs during the DLT evaluation period (21 days starting from Cycle 1 Day 1), excluding toxicities clearly related to disease progression or intercurrent illness, that are Grade ≥3 according to the NCI CTCAE Version 5.0, with the exceptions defined below.

For Hematologic Toxicities, a DLT is defined as follows:

- Grade 4 neutrophil count decreased lasting >7 days
- Grade ≥3 febrile neutropenia
- Grade ≥3 anemia requiring transfusion
- Grade 4 anemia
- Grade 4 platelet count decreased, or
- Grade ≥3 platelet count decreased lasting >7 days
- Grade ≥3 platelet count decreased associated with clinically significant hemorrhage and/or requiring transfusion
- Grade 4 lymphocyte count decreased lasting ≥14 days (lymphocyte count decrease of Grade 3 will not be a DLT)

For Hepatic Organ Toxicities, a DLT is defined as follows:

- Grade 4 aspartate aminotransferase (AST) or alanine aminotransferase (ALT) increased
- AST or ALT >3 × ULN if accompanied by Grade ≥2 blood total bilirubin increased with serum alkaline phosphatase <2 × ULN (based on Hy's law definition)
- In patients without liver metastases, AST or ALT >5 × ULN
- In patients with liver metastases, AST or ALT >5 × ULN, if the baseline level was ≤3 × ULN
- In patients with liver metastases, AST or ALT >8 × ULN, if the baseline level was >3 × ULN

For Non-Hematologic, Non-Hepatic Major Organ Toxicities, a DLT is defined as all TEAEs of Grade ≥3 with the following exceptions:

The following AEs will not be considered DLTs:

- Grade 3 fatigue lasting <7 days
- Grade 3 nausea, vomiting, diarrhea, or anorexia that has resolved to Grade ≤2 within 3 days with maximal medical management
- Grade 3 isolated laboratory findings not associated with signs or symptoms including alkaline phosphatase (ALP) increased, hyperuricemia, serum amylase increased, and lipase increased, and Grade 3 hyponatremia lasting <72 hours developed from Grade 1 at baseline. Symptomatic Grade 4 events will be considered DLTs unless there is documented evidence that the abnormality is associated with disease progression.

For the following non-hematologic, non-hepatic major organ toxicities, a DLT is defined as:

- Symptomatic congestive heart failure

- Any LVEF decline from baseline leading to discontinuation of study treatment
- Grade ≥2 ILD or pneumonitis
- Grade 3 skin toxicity lasting >7 days or Grade 4 for any duration
- All other Grade ≥3 non-hematologic, non-hepatic major organ toxicities will be a DLT

If any of the toxicities listed directly above are observed during the DLT evaluation period, the Investigator, Medical Monitor, and Sponsor will discuss if they are to be classified as DLTs.

Premedication (any treatment administered prior to study drug administration to avoid TEAEs), is prohibited during the DLT evaluation period. However, supportive therapy for the treatment of TEAEs is permitted after DS-6157a infusion (e.g., antiemetics are permitted if nausea and vomiting are observed post-dose but will not be administered prior to dosing to prevent nausea and vomiting during the DLT evaluation period).

Determination of Dose-Limiting Toxicities

The patient population (DLT-Evaluable Set) used for determination of DLTs will consist of all patients enrolled in Dose Escalation who had a DLT, or who received the full dose of DS-6157a in Cycle 1 and completed the DLT evaluation period. Minimum safety requirements will be met if, during Cycle 1 of treatment, the patient receives the planned total dose of DS-6157a, completes all required safety evaluations, and is observed for at least 21 days following the first dose of DS-6157a. Dose escalation to the next dose level will take into account all the safety data as detailed in Section 5.1.1.

Patients who discontinue treatment early due to PD or withdrawal will be asked to have all end-of-treatment safety evaluations performed as described in the protocol (see Section 7.4). If a patient withdraws from treatment during Cycle 1 due to any reason other than a DLT and does not meet the minimum requirements for inclusion in the DLT-Evaluable Set described above, that patient will be replaced.

5.1.3 Maximum-Tolerated Dose

Once the dose escalation stopping criteria are met, the Sponsor will estimate the MTD using a Bayesian logistic regression model (BLRM) and following the escalation with overdose control (EWOC) principle, where the estimated MTD is the dose with the highest posterior probability of the target DLT rate interval of 16% <DLT rate ≤33% fulfilling the overdose control constraint, i.e. probability of a DLT rate >33% (sum of probabilities for excessive and unacceptable toxicity) should be less than 25%. The final MTD will be decided based on considerations of the estimated MTD and on an overall assessment of safety data from subsequent cycles and PK information collected at all different doses tested.

5.1.4 Recommended Dose for Expansion

Based on all available data collected in Dose Escalation (e.g., PK, safety, efficacy, and biomarker data), one dose or regimen, or multiple doses or regimens less than or at the MTD (if attained, or the highest dose evaluated) may be selected as RDE(s) for further evaluation in one

or more cohort(s) in Dose Expansion. If multiple doses or regimens are selected for Dose Expansion, up to approximately 30 eligible patients may be randomized into each dose or regimen in one or more cohort(s) in Dose Expansion. Alternatively, if a selected RDE is found to be not suitable due to safety or efficacy related reasons during evaluation in Dose Expansion, further enrollment may be continued at a different dose level not exceeding MTD as the new RDE.

Dose Expansion cohorts (Part 2) will then begin at the RDE to further characterize safety and tolerability, the PK profile, and efficacy of DS-6157a. Based on evolving efficacy data from Part 1, additional disease cohorts may be included in Part 2. As one of the options, if there is an objective response in at least one of the patients with GIST who are not candidates for IM or curative intent surgical treatment (e.g., patients without activating KIT or PDGFRa mutations, with PDGRFa D842V mutations, or are KIT negative), an additional Dose Expansion cohort (Cohort 3) of approximately 12 patients of this population may be evaluated at the RDE.

5.2 Treatment Duration

DS-6157a will be administered IV on Day 1 of each cycle Q3W. Patients will continue to receive DS-6157a Q3W as long as the patient is deriving benefit from the treatment, until progression of disease (PD) according to RECIST Version 1.1 as assessed by the Investigator, unacceptable toxicity, death, or withdrawal of consent (Section 3.3). Patients may be treated beyond initial radiological progression (according to RECIST Version 1.1) on a case-by-case basis (with agreement from the Medical Monitor), if the Investigator feels that it is in the patient's best interest, the patient re-consents to continue receiving study treatment in a separate consent form, and as long as the patient is deriving benefit from the treatment and all the following criteria are met:

- Absence of clinical symptoms or signs indicating clinically significant disease progression
- No decline in performance status
- Absence of rapid disease progression or threat to vital organs or critical anatomical sites (e.g., CNS metastasis, respiratory failure due to tumor compression, spinal cord compression) requiring urgent alternative medical intervention
- No significant, unacceptable or irreversible toxicities related to study treatment
- Patient agrees to continue protocol-specified assessments and monitoring

Assessments will be performed by the Investigator at screening and every 6 weeks (±7 days) during the first 36 weeks of treatment and every 9 weeks (±7 days) thereafter, as described in the Assessment Schedule and in Section 7.3. After treatment discontinuation, patients will be evaluated according to follow-up procedures described in Section 7.4.

The **start of the study** is defined as the date when the first patient in the study signs informed consent.

The **end of the study** is defined as the date of the last visit (including all follow-up visits) of the last patient in the whole study.

5.3 Concomitant Medications

Patients will be asked about prior medications during screening and instructed not to take any additional medications during the course of the study without prior consultation with the study team. At each visit, the patient will be asked about any new medications he or she is taking or has taken after the start of the study drug.

5.3.1 Permitted Concomitant Medications

Premedication with antiemetics is allowed according to standard practice guidelines after the DLT evaluation period in Part 1 if nausea and vomiting are observed post-dose during the DLT evaluation period.

Hematopoietic growth factors (G-CSF, GM-CSF) for treatment of neutropenia or transfusion of blood, red blood cells, and platelets may be used for prophylaxis after the DLT evaluation period (Day 1 to Day 21 in Cycle 1 [Part 1]) or for treatment based on the clinical judgment of the Investigator and as per local guidelines. (Note: GM-CSF is not approved in Japan).

Concomitant use of dietary supplements, medications not prescribed by the Investigator, and alternative/complementary treatments must be discussed with the Investigator.

Medical marijuana or other types of legally available cannabis products (e.g., CBD) are permitted as concomitant herbal medicines throughout screening, the treatment phase, and during the post-study follow up. If its use for palliative care began within a 7-day timeframe of study initiation, please discuss with the Medical Monitor.

Supportive care and other medications considered necessary for the patient's safety and well-being may be given at the discretion of the Investigator with the exception of those listed in Section 5.3.2.

5.3.2 Prohibited Concomitant Treatments

The following treatments are prohibited while in this study:

- Other investigational therapy
- Radiation therapy, except palliative radiotherapy on non-target lesions if deemed essential for symptomatic management at the Investigator's discretion.
- Anticancer surgery
- Other anticancer systemic therapy, including cytotoxic drugs, targeted agents, immunotherapy or endocrine therapy
- Prophylactic antiemetics and anti-diarrheal agents, or premedication for the prophylaxis of nausea, vomiting, and diarrhea are prohibited during DLT evaluation period (Day 1 to Day 21 of Cycle 1 [of Dose Escalation]).
    - Exception #1: patients, who at baseline, report their chronic and stable use of antiemetics or anti-diarrheal agents may continue use throughout the study. Changes in dose or frequency of use should be monitored and discussed with the Medical Monitor to determine if the change constitutes an adverse event

  - Exception #2: these medications may be administered for remedial therapy of symptoms after they have occurred at any time during the study, as well as for the prophylaxis of nausea, vomiting, and diarrhea after DLT evaluation period.
- Prophylactic administration of G-CSF (i.e., filgrastim, pegfilgrastim) or erythropoietin and transfusion of blood, RBCs, or platelets is prohibited within 14 days before the start of DS-6157a. Chronic therapy with erythropoietin at a stable dose that started at least 14 days before the first dose of DS-6157a may continue.
- The live flu vaccine (including the nasal mist version)
- Concomitant use of chronic systemic (IV or oral) corticosteroids or other immunosuppressive medications except for managing AEs (inhaled steroids or intra-articular steroid injections are permitted in this study).
  - Patients with bronchopulmonary disorders who require intermittent use of bronchodilators (such as albuterol) will not be excluded from this study.
- Concomitant treatment with any medication that is classified as having a known risk or possible risk of Torsades de pointes should be avoided from the start of study treatment through the end of Cycle 3 (see www.crediblemeds.org and Appendix E). Consult with Medical Monitor if such medication is needed during the study.
- Concomitant treatment with chloroquine or hydroxychloroquine is not allowed during the study treatment. Refer to Appendix H for further details.

5.3.3 Restricted Concomitant Treatments

Use of tobacco products, e-cigarettes and vaping is strongly discouraged but not prohibited.

6. DOSE MODIFICATIONS

If toxicity occurs, the toxicity will be graded using the NCI CTCAE Version 5.0, and appropriate supportive care treatment will be administered to decrease the signs and symptoms thereof. Dose adjustments will be based on the organ system exhibiting the greatest degree of toxicity.

The Investigator will evaluate which toxicities are attributed to the study drug and adjust the dose of the drug as recommended below. All dose modifications must be based on the worst preceding toxicity (CTCAE version 5.0).

Specific criteria for interruption, re-initiation, dose reduction, and/or discontinuation of DS-6157a are listed in Table 2. All interruptions or modifications must be recorded on the AE and drug administration CRFs. Appropriate clinical experts must be consulted as deemed necessary.

There will be no dose modifications for Grade 1 or Grade 2 AEs unless specified below in Table 2. For a recurrent Grade ≥3 AE, the patient will be permanently discontinued from study treatment based on Investigator discretion.

Prophylactic or supportive treatment for expected toxicities, including management of TEAEs, will be at the treating physician's discretion and per institutional guidelines, except for prophylactic treatment prior to the DLT evaluation period.

Two dose reductions will be permitted (the dose cannot be reduced to <1.6 mg/kg) in any patient. Once the dose of DS-6157a has been reduced because of toxicity, all subsequent cycles must be administered at that lower dose level unless further dose reduction is required. More than 2 dose reductions are not allowed and the patient will be withdrawn from the study treatment if further toxicity meeting the requirement for dose reduction occurs.

During the dose escalation part of the trial, intra-patient dose escalation (IPDE) of DS-6157a may be allowed on a case by case basis in patients who may benefit from IPDE based on the clinical judgement of the investigator and in agreement with the Medical Monitor and Sponsor. The eligibility criteria for consideration of patients for IPDE are the following:

- Patient must provide consent for IPDE.
- A minimum of 4 cycles of treatment and evaluations must be completed before IPDE
- Patient must meet inclusion criteria of #1-3, 6 and 8 based on the most recent data, and 9 (except for DS-6157 treatment) again. Any criteria that did not meet the eligibility can be re-tested.
- Patient who meets any of exclusion criteria based on the most recent data, or who experienced ILD of any grade or any other dose modification toxicity event during DS-6157a treatment will not be eligible for IPDE.

IPDE may be conducted up to a dose that is 1 dose level below the dose already established to be safe and tolerable. Dose escalation should not be more than 3 dose levels at a time. The actual dose level will be decided based on the overall individual clinical status and PK profile. A patient may be allowed further IPDE after completing a minimum of another 4 cycles after the first IPDE, as long as the conditions for IPDE are met. AEs arising after IPDE should follow dose modifications/reductions per Table 2, but further re-escalations will be prohibited after such events.

Dose can be delayed for up to 28 days from the planned date of administration. If a patient has a persisting AE/SAE that requires a longer dose delay, then patient will be withdrawn from the study after consulting with Medical Monitor.

Treatment cycles for a patient for whom DS-6157a dosing was temporarily withheld for any reason may have future cycles scheduled based on the date of the last DS-6157a dose. However, the tumor assessments will follow the pre-specified schedules relative to the start of the study treatment (Cycle 1 Day 1).

Investigators may contact the Medical Monitor or designee to discuss questions regarding dose modification or discontinuation of study drug.

All confirmed or suspected coronavirus disease 2019 (COVID-19) infection events must be recorded in the eCRF. Please refer to Appendix H for additional information on dose modifications.

Table 2 Dose Modifications for DS-6157a

Worst toxicity CTCAE v5.0 Grade (unless otherwise specified)	Dose or schedule modification for DS-6157a
No toxicity	Maintain dose and schedule
Infusion-Related Reaction	
Grade 1 (Mild transient reaction; infusion interruption not indicated; intervention not indicated)	No interruption or change in the infusion rate is indicated.
Grade 2 (Therapy or infusion interruption indicated but responds promptly to symptomatic treatment (e.g., antihistamines, nonsteroidal anti-inflammatory drugs (NSAIDs), narcotics, IV fluids); prophylactic medications indicated for ≤24 hrs)	Grade 2 IRR occurring **during** infusion of DS-6157a: • Administration of DS-6157a must be interrupted and symptomatic treatment started (e.g. antihistamines, NSAIDs, narcotics, IV fluids). • If the event resolves or improves to Grade 1, infusion can be re-started at a 50% reduced infusion rate. Grade 2 IRR occurring **post** infusion of DS-6157a: • Symptomatic treatment must be started (e.g., antihistamines, antiemetics, NSAIDs, IV fluids) until the event resolves or improves to Grade 1. Subsequent administrations of DS-6157a after any Grade 2 IRR occurring **during or post** infusion of DS-6157a : • Premedication (e.g., acetaminophen, diphenhydramine, and/or corticosteroids or equivalents) should be considered at the Investigator's discretion. If the Grade 2 event recurs despite pre-medication, then all subsequent administrations of DS-6157a must be conducted at the 50% reduced infusion rate and/or with pre-medication. • If the infusion rate is reduced by 50% (regardless of pre-medication) and the Grade 2 event does not recur at a given cycle, then administrations of DS-6157a at subsequent cycles can be conducted at the initial infusion rate at the investigator's discretion. If the Grade 2 event recurs at the initial infusion rate, then all subsequent administrations of DS-6157a must be conducted at the 50% reduced infusion rate and with pre-medication.

Grade 3 or 4 (Prolonged or life-threatening consequences, urgent intervention indicated)	Administration of DS-6157a must be discontinued immediately and permanently. Urgent intervention indicated. Antihistamines, steroids, epinephrine, bronchodilators, vasopressors, intravenous fluid therapy, oxygen inhalation etc., must be administered.
Hematologic Toxicity	
Neutrophil Count Decreased and/or White Blood Cell Count Decreased	
Grade 3	Delay dose until resolved to ≤Grade 2, then maintain dose
Grade 4	Delay dose until resolved to ≤Grade 2, Reduce dose by 1 level
Febrile Neutropenia (Absolute neutrophil count <1 × 10^9/L, fever >38.3°C or a sustained temperature of ≥38 °C for more than one hour)	Delay dose until resolved, Reduce dose by 1 level
Lymphocyte Count Decreased[a]	
Grade 1 to Grade 3	No dose modification
Grade 4 (<0.2 × 10^9/L)	Delay dose until resolved to ≤ Grade 2: - If resolved in ≤14 days from day of onset, maintain dose - If resolved in >14 days from day of onset, reduce dose 1 level
Anemia	
Grade 3 (Hemoglobin (Hb) <8.0 g/dL); transfusion indicated	Delay dose until resolved to ≤ Grade 2, then maintain dose
Grade 4 Life threatening consequences; urgent intervention indicated	Delay dose until resolved to ≤ Grade 2, then reduce dose 1 level
Platelet Count Decreased	
Grade 3 (Platelets <50 – 25 × 10^9/L)	Delay dose until resolved to ≤ Grade 1: - If resolved in ≤7 days from day of onset, maintain dose - If resolved in >7 days from day of onset, reduce dose 1 level
Grade 4 (Platelets <25 × 10^9/L)	Delay dose until resolved to ≤ Grade 1, then reduce dose 1 level
Cardiac Toxicity	
Symptomatic congestive heart failure (CHF)	Discontinue patient from study treatment

Decrease in left ventricle ejection fraction (LVEF) 10-20% (absolute value), but LVEF >45%	Continue treatment with DS-6157a
LVEF 40% to 45% and decrease is <10% (absolute value) from baseline	Continue treatment with DS-6157a Repeat LVEF assessment within 3 weeks
LVEF 40% to 45% and decrease is 10% - 20% (absolute value) from baseline	Interrupt DS-6157a dosing Repeat LVEF assessment within 3 weeks If LVEF has not recovered to within 10% (absolute value) from baseline, discontinue patient from study treatment. If LVEF recovers to within 10% from baseline, resume treatment with study drug.
LVEF <40% or >20% (absolute value) drop from baseline	Permanently discontinue from study treatment
Electrocardiogram QT prolonged	
Grade 3 (Average QTcF >500 ms or >60 ms change from baseline)	Repeat the ECG in triplicate within 1 hour and then monitor at the frequency determined by the Investigator's discretion. Delay dose until resolved to ≤ Grade 1 (QTcF ≤480 ms or change from baseline ≤30 msec), determine if another medication the patient was taking may be responsible and can be adjusted or if there are any changes in serum electrolytes that can be corrected, then if attributed to DS-6157a and confirmed on repeat ECG triplicate, reduce dose 1 level.
Grade 4 (Torsade de pointes or polymorphic ventricular tachycardia or signs/symptoms of serious arrhythmia)	Discontinue patient from study treatment
Interstitial lung disease **(ILD)/pneumonitis**	If a patient develops radiologic changes potentially consistent with ILD/pneumonitis or an acute onset of new or worsening pulmonary function or other related signs/symptoms such as dyspnea, cough, or fever, rule out ILD/pneumonitis. If the AE is confirmed to have an etiology other than ILD/pneumonitis, follow the management guidance outlined in the "Other Non-Laboratory Adverse Events" dose modification section below. If the AE is suspected to be ILD/pneumonitis, treatment with study drug should be interrupted pending further evaluations.

	Evaluations should include: • high resolution CT • pulmonologist consultation (infectious Disease consultation as clinically indicated) • blood culture and CBC. Other blood tests could be considered as needed • Consider bronchoscopy and bronchoalveolar lavage if clinically indicated and feasible. • pulmonary function tests and pulse oximetry (SpO_2) • arterial blood gases if clinically indicated • one blood sample collection for PK and exploratory biomarker analysis as soon as ILD/pneumonitis is suspected, if feasible. Other tests could be considered, as needed. If the AE is confirmed to be ILD/pneumonitis, follow the management guidance as outlined below. All events of ILD/pneumonitis regardless of severity or seriousness will be followed until resolution including after drug discontinuation.
Grade 1	The administration of DS-6157a must be interrupted for any ILD/pneumonitis events regardless of grade. • Monitor and closely follow-up in 2 to 7 days for onset of clinical symptoms and pulse oximetry • Consider follow-up imaging in 1-2 weeks (or as clinically indicated). • Consider starting systemic steroids (e.g. at least 0.5 mg/kg/day prednisone or equivalent) until improvement, followed by gradual taper over at least 4 weeks. • If worsening of diagnostic observations despite initiation of corticosteroids, then follow Grade 2 guidelines.* For Grade 1 events, DS-6157a can be restarted only if the event is fully resolved to Grade 0: - If resolved in ≤28 days from day of onset, maintain dose - If resolved in >28 days from day of onset, reduce dose

	1 level However, if the event Grade 1 ILD occurs beyond cycle Day 22 and has not resolved within 49 days from the last infusion, the drug should be discontinued. * If patient is asymptomatic, then patient should still be considered as Grade 1 even if steroid treatment is given.

Grade 2	Permanently discontinue patient from study treatment.
	• Promptly start and treat with systemic steroids (e.g., at least 1mg/kg/day prednisone or equivalent) for at least 14 days or until complete resolution of clinical and chest CT findings, then followed by a gradual taper over at least 4 weeks.
	• Monitor symptoms closely.
	• Re-image as clinically indicated.
	• If worsening or no improvement in clinical or diagnostic observations in 5 days,
	  • Consider increasing dose of steroids (e.g., 2 mg/kg/day prednisone or equivalent) and administration may be switched to intravenous (e.g. methylprednisolone).
	  • Re-consider additional work-up for alternative etiologies as described above.
	  • Escalate care as clinically indicated.

Grade 3 or 4	Permanently discontinue patient from study treatment. • Hospitalization required. • Promptly initiate empiric high-dose methylprednisolone IV treatment (e.g., 500-1000 mg/day for 3 days), followed by at least 1.0 mg/kg/day of prednisone (or equivalent) for at least 14 days or until complete resolution of clinical and chest CT findings, then followed by a gradual taper over at least 4 weeks. • Re-image as clinically indicated. • If still no improvement within 3 to 5 days,

	• Re-consider additional work-up for alternative etiologies as described above. Consider other immuno-suppressants and/or treat per local practice.
Ocular Toxicity	
Grade 3	Delay dose until resolved to ≤Grade 1: If resolved in ≤7 days from day of onset, maintain dose If resolved in >7 days from day of onset, reduce dose 1 level
Grade 4	Discontinue patient from study treatment
Blood creatinine increased	
Grade 3 (>3.0 x baseline or >3.0 to 6.0 × upper limit of normal [ULN])	Delay dose until resolved to ≤Grade 1 or baseline, then reduce dose 1 level
Grade 4 (>6.0 × ULN)	Discontinue patient from study treatment
Hepatic Toxicity	
Aspartate aminotransferase (AST) or alanine aminotransferase (ALT) with simultaneous total bilirubin (TBL)	
AST/ALT ≥3.0 × ULN with simultaneous TBL >2.0 × ULN	Delay study medication until drug-induced liver injury can be ruled out. If drug-induced liver injury is ruled out, the patient should be treated accordingly, and resumption of study drug may occur after discussion between the Investigator and Sponsor. If drug-induced liver injury cannot be ruled out from diagnostic workup, permanently discontinue study treatment. Monitor AST/ALT and TBL twice weekly until resolution or return to baseline.
Aspartate aminotransferase (AST) or alanine aminotransferase (ALT)	
Grade 2 (>3.0 - 5.0 × ULN if baseline was normal; >3.0 - 5.0 × baseline if baseline was abnormal)	No action for Grade 2 AST/ALT
Grade 3 (>5.0 - 20.0 × ULN if baseline was normal; >5.0 - 20.0 × baseline if baseline was abnormal) In patients without liver metastases and patients with liver metastases and	Repeat testing within 3 days. Delay dose until resolved to ≤ Grade 1 if baseline ≤ 3 x ULN, otherwise delay dose until resolved to ≤ baseline, then: If resolved in ≤7 days from day of onset, maintain dose If resolved in >7 days from day of onset, reduce dose 1

baseline level ≤3 × ULN	level
Grade 3 (>8.0 - 20.0 × ULN if baseline was normal; >8.0 - 20.0 × baseline if baseline was abnormal) In patients with liver metastases, if the baseline level was >3 × ULN	Repeat testing within 3 days. Delay dose until resolved to ≤baseline level, then: If resolved in ≤7 days from day of onset, maintain dose If resolved in >7 days from day of onset, reduce dose 1 level
Grade 4 (>20.0 × ULN if baseline was normal; >20.0 × baseline if baseline was abnormal)	Discontinue patient from study treatment
Total Bilirubin	
Grade 2 (>1.5 - 3.0 × ULN if baseline was normal; >1.5 - 3.0 × baseline if baseline was abnormal)	If no documented Gilbert's syndrome or liver metastases at baseline, delay dose until resolved to ≤Grade 1: - If resolved in ≤7 days from day of onset, maintain dose - If resolved in >7 days from day of onset, reduce dose 1 level If documented Gilbert's syndrome or liver metastases at baseline, continue study treatment
Grade 3 (>3.0 - 10.0 × ULN if baseline was normal; >3.0 - 10.0 × baseline if baseline was abnormal)	If no documented Gilbert's syndrome or liver metastases at baseline, repeat testing within 3 days. Delay dose until resolved to ≤Grade 1: - If resolved in ≤7 days from day of onset, reduce dose 1 level - If resolved in >7 days from day of onset, discontinue DS-6157a If documented Gilbert's syndrome or liver metastases at baseline, repeat testing within 3 days. Delay dose until resolved to ≤ Grade 2: - If resolved in ≤7 days from day of onset, reduce dose 1 level - If resolved in >7 days from day of onset, discontinue DS-6157a
Grade 4 (>10.0 × ULN if baseline was normal; >10.0 × baseline if baseline was abnormal)	Discontinue patient from study treatment
Blood Alkaline Phosphatase Increased	
Grade 3 (>5.0 - 20.0 × ULN if baseline was normal; >5.0 - 20.0 × baseline if baseline was abnormal) or	No modification unless determined by the Investigator to be clinically significant or life-threatening.

Grade 4 (>20.0 × ULN if baseline was normal; >20.0 × baseline if baseline was abnormal)	
Gastrointestinal	
Nausea	
Grade 3	Delay dose until resolved to ≤ Grade 1 If resolved in ≤7 days from day of onset, maintain dose If resolved in >7 days from day of onset, reduce dose 1 level
Vomiting	
Grade 3	Delay dose until resolved to ≤ Grade 1 If resolved in ≤7 days from day of onset, maintain dose If resolved in >7 days from day of onset, reduce dose 1 level
Grade 4	Discontinue patient from study treatment
Diarrhea/Colitis	
Grade 3	Delay dose until resolved to ≤ Grade 1 If resolved in ≤3 days from day of onset, maintain dose If resolved in >3 days from day of onset, reduce dose 1 level
Grade 4	Discontinue patient from study treatment
Other Laboratory Adverse Events	
Grade 3	Delay dose until resolved to ≤ Grade 1 or baseline level: If resolved in ≤7 days from day of onset, maintain dose If resolved in >7 days from day of onset, reduce dose 1 level
Grade 4	Discontinue patient from study treatment
Other Non-Laboratory Adverse Events	
Grade 3	Delay dose until resolved to ≤ Grade 1 or baseline: If resolved in ≤7 days from day of onset, maintain dose If resolved in >7 days from day of onset, reduce dose 1 level
Grade 4	Discontinue patient from study treatment

a There will be no dose modifications for Grade 1 to Grade 3 lymphopenia
All dose modifications must be based on the worst preceding toxicity.
CTCAE = Common Terminology Criteria for Adverse Events

6.1 Other Risks Associated with Drugs of the Same Class

MAAA-1181a is a derivative of exatecan (DX-8951f), a topoisomerase I inhibitor. Other products of the same class include irinotecan (Irinotecan package inserts. 2016) and topotecan (Topotecan package inserts. 2015). Exatecan is a camptothecin derivative, which has previously been developed by the former Daiichi Pharmaceuticals Co., Ltd. as an anti-cancer therapy.

The main risks associated with the use of topoisomerase I inhibitors include hematological toxicities and gastrointestinal toxicities. Hematological toxicities, manifesting as neutropenia, febrile neutropenia, anemia, thrombocytopenia, and pancytopenia are commonly observed. An increased risk of infections, including neutropenic colitis, neutropenic sepsis, and disseminated intravascular coagulopathy has been reported with these agents.

Diarrhea and delayed onset diarrhea, which can be severe and lead to dehydration, have been associated with topoisomerase I inhibitors. Other gastrointestinal toxicities include nausea, vomiting, ileus, and intestinal perforation. Acute cholinergic syndrome, manifesting as diarrhea and other cholinergic symptoms have been reported with irinotecan. Other significant risks include ILD, liver impairment, renal impairment, anaphylaxis, myocardial ischemic events, and thromboembolic events.

The safety profile of exatecan is broadly similar to the safety profile of other topoisomerase I inhibitors, with hematological toxicities and gastrointestinal toxicities being the most significant groups of events (Cheverton et al. 2004, Deciphera 2019, De Jager et al. 2000).

7. STUDY ASSESSMENTS AND EVALUATIONS

7.1 Overview

All patients should visit the study center on the days specified within this protocol. The complete Schedule of Assessments for this study is presented at the beginning of this protocol (see Assessment Schedule). The key procedures required in this study include:

- All AEs regardless of seriousness or relationship to DS-6157a treatment (called study treatment) spanning from the signing of the ICF until at least 30 calendar days after the patient's last dose of study drug, or the patient's start of another cancer treatment are to be recorded on the corresponding screen(s) included in the eCRF.
- PK samples throughout the study
- Baseline and on-treatment blood biomarker and immunogenicity assessments
- Tumor biopsy biomarker assessments
- Tumor assessments (based on computed tomography [CT]/positron emission tomography [PET]/ and/or magnetic resonance imaging [MRI] scan) according to RECIST Version 1.1 (Appendix B).

A cycle of treatment is scheduled to last 3 weeks (21 calendar days). Multiple procedures may be scheduled at the same time point relative to DS-6157a dosing. Priority must be given to PK collection at the time specified. Vital signs and ECG assessments must be performed prior to PK sample collections when these assessments are scheduled for the same timepoints.

7.2 Screening

At enrollment, each potential research patient will provide written informed consent ≤28 days prior to initiation of treatment and prior to starting any study-specific procedures. Upon signature of the ICF, patients will be assigned a unique patient number as enrollment (screening) occurs.

The study will allow re-screening for any patient who failed to meet eligibility criteria upon initial screening. The failed screening test(s) and the other screening results that are out of window relative to the start of the study treatment, and any other protocol-specified screening tests per the Medical Monitor's guidance, will be re-tested during re-screening. The initial screening information and the reason why the patient was ineligible for the initial evaluation will be recorded in the Screening Log.

The screening assessments described in the Assessment Schedule will be collected, reviewed, and determined whether acceptable by the site Principal Investigator or designee after obtaining informed consent prior to the initiation of treatment.

The following screening parameters should be recorded ≤7 days prior to initiation of treatment:

- Medical history and demographics
- Cancer history and prior cancer therapies
- Smoking history
- Physical examination (including height and weight) and skin assessments
- ECOG performance status
- Vital signs (blood pressure, SpO_2, body temperature, and pulse rate)
- Triplicate ECGs
- Hematology (red blood cell [RBC] count, hemoglobin [Hb], hematocrit, reticulocytes, total white blood cell [WBC] count, absolute neutrophil count [ANC], absolute lymphocyte count, 5-part % differential [neutrophils, lymphocytes, monocytes, basophils, eosinophils], and platelet count)
- Biochemistry (sodium, potassium, phosphate, chloride, creatinine, calcium, venous bicarbonate HCO_3 or carbon dioxide (CO_2), albumin, total protein, AST, ALT, alkaline phosphatase [ALP], bilirubin [total {required}/fractionated {direct/indirect} bilirubin, if available], lactate dehydrogenase, serum glucose, creatinine kinase [CK: if CK is elevated, then CK-MB, CK-MM, troponin I, and myoglobin should be reactively tested, with further follow-up as clinically warranted], blood urea nitrogen [BUN] or urea, and serum uric acid)
- Urinalysis (Dipstick); if abnormal and clinically significant, the Investigator must order a microscopic analysis of the urine sediment
- Screening pregnancy test (serum)
- Coagulation (PT, aPTT or PTT and INR)

If these assessments are performed within 72 hours of initiation of treatment, they do not need to be repeated on Cycle 1 Day 1 with the exception of the ECOG performance status, an

abbreviated physical examination, vital signs, and triplicate ECGs. ECHO or MUGA, and tumor assessments (scans) should be performed ≤28 days prior to initiation of treatment. Tests for HIV infection, hepatitis B, and hepatitis C must be performed at screening. For subsequent cycles, all Day 1 assessments will have a 48-hour window except for ECHO/MUGA, which will have a 3-day window at Cycle 2 and a 7-day window for subsequent cycles.

Relevant medical history and concomitant medications present at study entry and/or during screening that are relevant to the patient's safety during the study as judged by the Investigator will be recorded in the electronic case report form (eCRF) (see Section 5.3 for details on concomitant medications).

7.2.1 Screen Failures and Rescreening

Screen failures are defined as patients who signed the informed consent form to participate in the clinical study but are not subsequently entered in the study. Individuals who do not meet the criteria for participation in this study (screen failure) may be rescreened. Rescreened patients should be assigned a new patient number that is different from the initial screening. Rescreening of a patient should be documented by recording the previous patient number on the eCRF so that its effect on study results, if any, can be assessed.

7.2.2 Tumor Imaging During Screening

Baseline tumor assessments must be performed within 28 days before first drug administration. Tumor responses must be assessed according to RECIST Version 1.1 (see Appendix B) and must include computed tomography (CT) scans or magnetic resonance imaging (MRI) of **the chest** and **abdominopelvic cavity** and, if clinically indicated, imaging of any other known or suspected sites of disease (e.g., brain) using an appropriate method (CT scan or MRI). If there is a history of CNS metastasis, a CT scan of the head or MRI of the brain must be performed. The same radiographic procedure must be used throughout the study. In case of suspected (but not otherwise confirmed) bone metastasis at screening or in subsequent cycles, tumor assessment must include a bone scan. Correlative imaging must then be repeated at each tumor assessment. Assessments will be performed by the Investigator.

Additionally, all images including CT and MRI may be submitted to a central imaging CRO for independent retrospective review.

7.3 Tumor Assessments During Study Treatment

Patient will remain on treatment as long as, in the opinion of the Investigator, they are deriving benefit and the criteria for withdrawal listed in Section 3.3 are not met. Please refer to the Assessment Schedule for detailed outlines of each visit during the treatment period for each part of the study.

Response will be assessed by CT scans or MRI of **the abdominopelvic cavity** (and chest ONLY if the screening imaging documented sites of disease in the chest) at 6-week intervals (±7 days) during the first 36 weeks and every 9 weeks (±7 days) thereafter, taking as reference the first dose date for non-randomized patients and the randomization date for randomized patients. Then, patients will be assessed at the EOT visit by CT scans or MRI of **the chest** and

abdominopelvic cavity, and at the discretion of the Investigator. Patients will continue treatment with DS-6157a, until progression of disease (PD) according to RECIST Version 1.1 as assessed by the Investigator, initiation of new anti-cancer treatment, unacceptable toxicity, death, lost to follow up, or withdrawal of consent. However, patients may be treated beyond initial radiological progression (according to RECIST Version 1.1) on a case-by-case basis (with agreement from the Medical Monitor), if the Investigator feels that it is in the patient's best interest, the patient re-consents to continue receiving study treatment in a separate consent form, and as long as the patient is deriving benefit from the treatment, and no other criterion listed in Section 3.3 is fulfilled.

The assessments to be performed at this time are specified in Appendix B and will occur regardless of dose interruptions/delays. Please refer to Section 9 for further instructions on evaluating response (e.g., PD, SD).

The following assessments will be performed if abnormal at baseline or if clinically indicated:

- CT scan or MRI of the chest, abdomen, and pelvis/lower abdomen
- CT scan of the head/MRI of the brain if history of CNS metastasis
- Bone scan in case of suspected (but not confirmed) bone metastasis

Additionally, all images including CT and MRI may be submitted to a central imaging vendor for independent retrospective review.

7.3.1 Tumor Imaging by RECIST Version 1.1

For RECIST Version 1.1 (Appendix B), the overall responses will be categorized as Complete Response (CR), Partial Response (PR), Stable Disease (SD), Progressive Disease (PD), or Not Evaluable (NE). For patients who experience an objective response of CR or PR, responses will be considered unconfirmed until the response has been documented by a subsequent confirmatory scan obtained no less than 4 weeks after the initial scan demonstrating an objective response.

7.4 Follow-up Periods and Study Completion

7.4.1 End-of-Treatment Visit

The end-of-treatment (EOT) visit will be performed after the Investigator decides with the patient to permanently discontinue the study treatment for any reason, as soon as possible but within 30 days of the last dose of treatment or before the patient starts another therapy, whichever occurs sooner.

The assessments of the EOT visit will then be performed instead of the next planned visit. If the patient discontinues treatment without having PD, the patient will be followed until the start of the next anti-cancer therapy, PD, death, lost to follow-up, withdrawn consent, or end of study, whichever occurs sooner.

7.4.2 30-day Safety Follow-up

All patients will be followed for at least 30 days after the last dose of study treatment during the off-treatment period until all treatment-related toxicity resolves, or before the start of another anti-cancer treatment. Any concomitant medications and procedures received up to 30 days after the last dose of study treatment must be recorded.

During this period, SAEs and AESIs occurring during the study that are considered to be related to study treatment or procedures will be followed for at least 30 days after the patient's last dose of DS-6157a. All new AEs occurring during this period must be reported and followed, unless, in the opinion of the Investigator, they are not likely to improve because of the underlying disease (see Section 3.3). In these cases, the Investigator must record his or her reasoning for this decision in the patient's medical records and indicate on the AE pages that the outcome is not resolved on the eCRF.

7.4.3 Long-term Follow-up

Patients who did not experience progressive disease or death during the 30-day safety follow-up will be followed until the start of a new anti-cancer treatment, progressive disease, death, lost to follow up, withdrawal of consent, or at the discretion of the Investigator. Tumor assessment will be performed per RECIST v1.1 at the same frequency specified in Section 7.3 (i.e., every 6 weeks [±7 days] for the first 36 weeks and, every 9 weeks [±7 days] thereafter). If a new anticancer therapy is planned to start before the next planned tumor assessment, the tumor assessment may be performed just before starting the new therapy.

7.4.4 Early Patient Termination/Patient Withdrawal

Patients who discontinue study treatment will be asked to have all end-of-treatment assessments performed as described in the protocol (see Assessment Schedule). If a patient discontinues treatment during Cycle 1 due to any reason other than a DLT and does not meet the minimum requirements for inclusion in the MTD determining population described in Section 5.1.3, that patient will be replaced.

7.5 ECG Measurements

For each set of triplicate ECGs, three standard resting 12-lead ECGs will be obtained not more than 3 minutes apart each from the previous ECG. ECGs will be obtained after the patient has been resting quietly in semi-supine or supine position for at least 5 minutes before the first ECG and during the triplicate. When ECG and PK assessments coincide, ECGs must be done **within** 10 minutes **before** the scheduled PK sample. When ECG and blood draws other than PK coincide, ECGs should be done before these blood draws, however these blood draws (other than PK) may be taken more than 10 minutes after ECGs, or ECGs may be done more than 10 minutes after these blood draws (other than PK). . ECG parameters to be recorded are: Heart rate; RR, PR, and QT intervals; QRS duration; ECG body position; interpretation of ECG. Depending on the emerging ECG data during dose escalation, ECGs may be transmitted to a central reading vendor, as an option.

Triplicate ECG measurements will be collected at the following time points:

- Screening
- Cycle 1 Day 1: Pre-dose and after end of infusion (EOI), and 2, 4, and 7 hours (±15 minutes) after EOI
- Cycle 1 Day 2: 24 hours (±2 hours) after the start of Day 1 infusion
- Cycle 1 Days 4, 8, and 15 (±1 day)
- Cycle 1 Day 22: only in patients with planned PK assessment
- Cycle 2 Day 1: Pre-dose and after EOI
- Cycle 2 Days 8 and 15 (±2 days)
- Cycle 2 Day 22: only in patients with planned PK assessment
- Cycle 3 Day 1: Pre-dose and after EOI, and 2, 4, and 7 hours (±15 minutes) after EOI
- Cycle 3 Day 2: 24 hours (±2 hours) after the start of Day 1 infusion
- Cycle 3 Days 4 (±1 day), 8 and 15 (±2 days)
- Cycle 3 Day 22: Pre-dose (only in patients with planned PK assessment)
- Cycle 4 and beyond: Pre-dose on Day 1

A single ECG will be obtained at the EOT visit.

7.6 Pharmacokinetic Assessments

Blood samples for PK assessments will be taken at approximately the following time points:

- Cycle 1 Day 1: Pre-dose (within 8 hours before treatment), within 15 minutes after EOI, and 2, 4, and 7 hours (±15 minutes) after EOI
- Cycle 1 Day 2: 24 hours (±2 hours) after the start of Day 1 infusion
- Cycle 1 Days 4, 8, and 15 (±1 day)
- Cycle 1 Day 22: Only applicable to patients whose scheduled Day 1 dose of the next cycle is delayed for ≥3 days or who cannot continue the next cycle of study treatment.
- Cycle 2 Day 1: Pre-dose (within 8 hours before treatment) and within 15 minutes after EOI
- Cycle 2 Days 8 and 15 (±2 days)
- Cycle 2 Day 22: Only applicable to patients whose scheduled Day 1 dose of the next cycle is delayed for ≥3 days or who cannot continue the next cycle of study treatment.
- Cycle 3 Day 1: Pre-dose (within 8 hours before treatment), within 15 minutes after EOI, and 2, 4, and 7 hours (±15 minutes) after EOI
- Cycle 3 Day 2: 24 hours (±2 hours) after the start of Day 1 infusion
- Cycle 3 Day 4 (±1 day), Days 8 and 15 (±2 days)
- Cycle 3 Day 22: Only applicable to patients whose scheduled Day 1 dose of the next cycle is delayed for ≥3 days or who cannot continue the next cycle of study treatment.
- Cycle 4 Day 1, Cycle 6 Day 1, and Cycle 8 Day 1: Pre-dose (within 8 hours before treatment)

Additional blood samples will be taken from patients who undergo IPDE.

- Day 1 of the first 4 cycles of IPDE: Pre-dose (within 8 hours before treatment) and within 15 minutes after EOI

When ECG and PK assessments coincide, ECGs must be done **within** 10 minutes **before** the scheduled PK sample. When ECG and blood draws other than PK coincide, ECGs should be done before these blood draws, however these blood draws (other than PK) may be taken more than 10 minutes after ECGs, or ECGs may be done more than 10 minutes after these blood draws (other than PK).. Additionally, a random PK sample may be drawn at any time during the study based on safety assessments of the patient.

At each PK time point, approximately 5 mL of blood will be collected. Instructions for the handling of blood samples and shipping of plasma samples for DS-6157a PK analyses are included in the Laboratory Manual. The actual time of DS-6157a administration (start of infusion and end of infusion) and the exact time of blood collection must be recorded on the eCRF.

The plasma PK parameters for DS-6157a, total anti-GPR20 antibody, and MAAA-1181a for each patient will be estimated using standard noncompartmental methods. The following PK parameters will be calculated: area under the plasma concentration-time curve up to the last quantifiable time (AUC_{last}), area under the plasma concentration-time curve in the dosing interval (AUC_{tau}), C_{max}, T_{max}, and C_{trough} after the Cycle 1 and Cycle 3 doses. If data permit, the terminal elimination rate constant (K_{el}), the $t_{½}$, elimination clearance (CL), the apparent volume of distribution at steady-state during terminal phase (V_z), the apparent volume of distribution at steady-state (V_{ss}), and area under the plasma concentration-time curve up to time infinity (AUC_{inf}) will also be calculated.

Population PK and exploratory exposure-response analyses may be performed to further characterize the PK of DS-6157a, total anti-GPR20 antibody and MAAA-1181a, and the relationship between exposure and efficacy and/or safety endpoints. If performed, results of population PK or exposure-response analyses will be reported separately from the Clinical Study Report.

For the COVID-19 PK sampling schedule for chloroquine and hydroxychloroquine administration, see the Assessment Schedule.

7.7 Anti-Drug Antibody Assessments

Blood samples (5 mL) for determination of potential anti-drug antibody against DS-6157a will be collected pre-dose from all patients treated with DS-6157a on Day 1 and Day 8 of Cycle 1, pre-dose on Day 1 of Cycle 2 to Cycle 4, and thereafter every 2 cycles from Cycle 4 through the EOT visit, and 30-day safety follow-up visit. Additional blood samples will be collected at pre-dose of the first 4 dosing cycles from patients who undergo IPDE. For patients with a positive ADA at the 30-day safety follow-up visit, an additional blood ADA sample should be collected every 3 months (±1 month) up to 1 year from the last dose of DS-6157a, or if the ADA becomes negative, or if ADA titer is equal to or less than baseline (applicable when pre-existing ADA is observed), or if the patient starts another therapy for cancer, or withdraws consent from the study, whichever occurs first.

Samples will be measured for the presence of ADAs using a validated bridging immunoassay. Tiered analysis will be performed to include screening, confirmatory, and titer assay steps and

positive-negative cut points will be employed that were statistically determined from drug-naïve validation samples.

Immunogenicity will be assessed through characterization of incidence and titer of ADAs. The number and percentage of patients will be calculated for the presence or absence of ADAs before and after the start of study drug administration. Positive ADA samples will be stored for further assessments, and may include neutralizing antibody measurement when the assay becomes available.

Instructions regarding sample collection, sample handling/processing and sample shipping are provided in the Laboratory Manual in the Investigator Site File.

7.8 COVID-19 Antibody Testing

If patient provides consent, samples should be collected prior to study drug infusion at Cycle 1 Day 1, Cycle 5 Day 1, every 4 cycles thereafter (Cycle 9, Cycle 13, etc.), and at the EOT visit. For patients with suspected or confirmed COVID-19 infections, follow the dose modifications in Appendix H.

7.9 Biomarker Assessments

7.9.1 Archival Tumor Samples

Archival tumor samples, if available, will be collected at screening with the purpose of retrospectively identifying GPR20 expression status. Archival sample collection is recommended, but not mandated, and every effort should be made to obtain a sample. If the patient only has bone lesions that can be biopsied at the screening time, archival tumor sample taken from a non-bone lesion must be submitted. This material must be provided as a formalin-fixed paraffin embedded (FFPE) tissue block or 15 paraffin-dipped unstained slides. The status of GPR20 expression will be analyzed to explore whether these are correlated with the response to treatment.

7.9.2 Fresh Biopsies

All patients will be required to undergo mandatory pre-treatment and on-treatment biopsies if the patient is clinically stable as judged by the Investigator. In addition, consenting patients may undergo an optional EOT tumor biopsy. If the patient agrees to the optional EOT biopsy, that biopsy must be obtained prior to the start of a new anticancer treatment. If IPDE is conducted, it is highly recommended to collect additional fresh biopsies after IPDE, if clinically feasible.

If the patient has multiple lesions suitable for biopsy, bone biopsy is to be avoided. However, if the patient only has bone lesions that can be biopsied, bone biopsy is still required for exploratory biomarkers assays.

Fresh biopsies will be used to retrospectively determine GPR20 expression status by protein and RNA level, if evaluable. Evaluable pre-treatment, on-treatment, and disease progression samples will be used for exploratory biomarker research such as topoisomerase relevant pathway markers and tumor microenvironment with protein and gene expression analyses. If possible, sites must collect pre- and on-treatment biopsies from the same tumor lesion. Failure to obtain sufficient

tumor sample after making best efforts to biopsy the tumor will not be considered a protocol deviation. When feasible, collection of an optional tumor biopsy at EOT is encouraged, but will not be considered to be a protocol deviation if the patient declines the EOT biopsy. These samples will be used to investigate changes in pathway signaling and potential mechanisms of resistance (i.e., genetic alterations, or evidence of alternative pathway activation).

Fresh pre-treatment and on-treatment tumor biopsies are mandatory. All fresh biopsies will be processed according to the laboratory manual.

Core needle biopsies must be freshly taken after determination that the patient is eligible and before the first study drug treatment. If a pre-treatment biopsy during screening is not feasible or is unsafe, a pre-existing biopsy with equivalent quality collected after the termination of the most recent prior therapy and within 6 months of starting the first dose of DS-6157a will be acceptable. If a pre-existing biopsy collected within 6 months of starting DS- 6157a is provided at screening (i.e., if the fresh pre-treatment tumor biopsy is not feasible or unsafe), the cfRNA and cfDNA samples will be collected at screening (within -28 to 0 days) and prior to DS-6157a infusion on Cycle 1 Day 1.

Another equivalent of four core needle biopsies must be collected at Cycle 2 between Day 8 and Day 15. Thereafter, collection of additional tumor biopsies is optional and can be performed between the EOT and follow-up visits prior to starting new treatments.

If IPDE is conducted, it is highly recommended to collect additional four core needle biopsies in the second cycle after IPDE, if clinically feasible. It should be collected between Day 8 and Day 15 of the cycle.

Sampling must be undertaken by experienced physicians in appropriate settings. The on-treatment biopsy can be omitted if clinically contraindicated or if the risk of the procedure for the individual patient has increased to a significant level.

Instructions regarding sample collection, sample handling/processing and sample shipping are provided in the Laboratory Manual in the Investigator Site File.

7.9.3 Blood Samples for cfDNA and cfRNA Analysis

Two blood samples (2 × 10 mL) will be collected to provide plasma for cell-free (cf)DNA and one sample (1 × 10 mL) will be collected for cfRNA analysis to explore markers associated with response and/or resistance to DS-6157a and other exploratory biomarker research purpose. Each blood sample is to be collected at the following time points:

cfDNA

- Screening: within 7 days after the screening tumor biopsy but prior to the first infusion of DS-6157a on Cycle 1 Day 1
- Cycle 2 between Day 8 and 15, irrespective of biopsy date. However, collection on the same day as the tumor biopsy is recommended.
- Every 3 cycles thereafter (i.e., Cycle 5 Day 1, Cycle 8 Day 1, Cycle 11 Day 1 …)
- EOT visit

cfRNA

- Screening: within 7 days after the screening tumor biopsy but prior to the first infusion of DS-6157a on Cycle 1 Day 1
- Cycle 2 between Day 8 and 15, irrespective of biopsy date. However, collection on the same day as the tumor biopsy is recommended.
- Cycle 5 Day 1: at the 12 week (±7 days) tumor assessment
- EOT visit

7.9.4 Exploratory Blood Biomarker Samples

Blood sample for peripheral blood mononuclear cell (PBMC) and serum will be collected for exploratory analysis of biomarkers to assess the effect of DS-6157a on cytokines and chemokines, and on immune cells using methods such as flow cytometry and gene expression profiling. Biomarker blood samples will be taken at the following time points:

- Cycle 1 Day 1: Pre-dose
- Cycle 1 Day 8
- Cycle 2 Day 1: Pre-dose
- Cycle 3 Day 1: Pre-dose
- Any time that ILD is suspected

If IPDE is conducted, it's recommended to collect additional blood biomarker samples at the following time points:

- Pre-dose on Day 1 of first cycle of IPDE
- Day 8 of first cycle of IPDE
- Pre-dose on Day 1 of second cycle of IPDE

Pre-dose on Day 1 of third cycle of IPDE

Instructions regarding sample collection, sample handling/processing and sample shipping are provided in the Laboratory Manual.

7.9.5 Additional Biomarker Assessment

In addition to the biomarkers specified above, exploratory biomarker research may be conducted on any samples. These studies would extend the search for other potential biomarkers relevant to the effects of DS-6157a, a malignancy and/or the resistance to the treatment. This may include the development of ways to detect, monitor, or treat malignancies. These additional investigations would be dependent upon clinical outcome, reagent and sample availability.

If the patient agrees, samples may be stored for a maximum of 15 years (or according to local regulations) following the last patient's last visit for the study at a facility selected by the sponsor to enable further analysis and address scientific questions of biomarker responses to DS-6157a and/or malignancies. Such analyses including genetic and genomic testing are exploratory in nature, and will not be performed using clinically approved diagnostic assays. Results from

these exploratory assays have not been validated as appropriate for making treatment decisions for patients, and therefore the results will not be returned to patients or Investigators.

7.9.6 Withdrawal of Consent for Use of Tissue Samples and Blood During the Study Period

Patients have the right to withdraw permission for storage of biological samples for future research and the optional end-of-treatment biopsies, even if previously consented, and still continue on the study. Upon study withdrawal, if the patient exercises his/her right to withdraw permission for sample storage, any remaining specimens will be disposed of according to one of the procedures described below:

1. If specimens are temporarily stored at the study site, the Investigators will dispose of specimens from the withdrawing patient.

2. If specimens are stored at a specimen collection agency or analysis laboratories, the Investigators will report the site patient identifier or number to the Sponsor, and the Sponsor will direct the agency to dispose of the specimens.

If samples are already analyzed, Daiichi Sankyo is not obliged to destroy the results of this research.

8. DRUG FORMULATION, AVAILABILITY, ADMINISTRATION, AND TOXICITY INFORMATION

8.1 DS-6157a

Investigational Product	Dosage Form and Strength	Manufacturer
DS-6157a	100 mg lyophilized powder	Daiichi Sankyo

8.1.1 Labeling, Packaging, and Supply

DS-6157a will be supplied in an amber glass vial by Daiichi Sankyo as lyophilized powder.

Every 3 weeks, patients will receive DS-6157a intravenously by trained research staff. The research staff will document the amount of study drug administered. The batch number of the study drug dispensed to the patient must be entered on the eCRF, if applicable.

The immediate packaging will contain a statement to conform with FDA IND requirements as follows: "Caution: New Drug - Limited by federal (or US) law to investigational use."

All study drugs must be kept in a secure place under appropriate storage conditions. Storage conditions for DS-6157a are included on the investigational product label.

The Sponsor or its representative must be granted access on reasonable request to check drug storage, dispensing procedures, and accountability records.

8.1.2 Preparation and Administration of DS-6157a

The first dose of DS-6157a in each patient will be infused for 90 ± 10 minutes. If there is no infusion-related reaction after the initial dose, the subsequent dose of DS-6157a may be infused for 30 ± 5 minutes based on the clinical judgment of the Investigator and/or Medical Monitor, but this reduced infusion rate is not mandatory.

Preparation and administration instructions will be provided in the pharmacy manual.

8.1.3 Precautions and Risks Associated with DS-6157a

Precautions and risks are located in the IB.

8.2 Accountability for All Study Drugs

The Principal Investigator (or designee) is responsible for accountability of all used and unused study drug supplies at the site.

All study drug inventories must be made available for inspection by the Sponsor or its representative (e.g., Innovations), and regulatory agency inspectors upon request.

Throughout the study and at its completion, Innovations Drug Accountability Record Form(s) or site inventory forms (if approved by Innovations) will be completed by the site and sent to the Innovations Regulatory Department. Study drug supplies must not be destroyed unless prior approval has been granted by the Sponsor or its representative. Please contact the Sponsor or its representative regarding disposal of any study drug.

9. RESPONSE EVALUATIONS AND MEASUREMENTS

Response and progression will be evaluated in this study using RECIST Version 1.1 (see Appendix B). Lesions are either measurable or non-measurable according to the criteria. The term "evaluable" in reference to measurability will not be used, as it does not provide additional meaning or accuracy.

10. STATISTICAL CONSIDERATIONS

10.1 Statistical Design

This is a Phase I, two-part, multicenter, open-label, multiple dose first-in-human study of DS-6157a in patients with GIST. The primary objectives are to evaluate the safety, tolerability, MTD, RDE, and to investigate efficacy of DS-6157a.

10.2 General Statistical Considerations

The data cut-off for the primary analysis will occur after all patients have either discontinued the study or have been followed for at least 6 months, whichever is earlier.

Data will be summarized by cohort and dose level, and overall when appropriate.

Descriptive statistics on continuous data will include mean, median, standard deviation, and range (as well as geometric mean and geometric coefficient of variation for PK data), while

categorical data will be summarized using frequency counts and percentages. Graphical summaries of the data may be presented. Time to events endpoints will be reported using Kaplan-Meier estimates.

No statistical testing is planned for this study. If multiple doses or regimens are selected for Dose Expansion (Part 2), then no statistical comparison among the doses or regimens is planned.

Assessments of change from baseline to post-treatment or the ratio of post-treatment to baseline will include only those patients with both baseline and post-treatment measurements. The last non-missing value of a variable taken before the first dose of study drug will be used as the baseline value, unless otherwise specified. In general, missing data will not be imputed for the purpose of data analysis, unless otherwise specified.

A detailed statistical analysis plan (SAP) describing the methodology to be used in analysis will be prepared and finalized before database lock. Statistical methods described within this document may be changed based on advances in research.

10.3 Sample Size Considerations

In Dose Escalation, this study will utilize the BLRM (Neuenschwander et al. 2008) and following the escalation with overdose control (EWOC) principle (Babb et al. 1998, Rogatko et al. 2005) to guide dose finding with at least 3 DLT-evaluable patients per dose level. The number of patients enrolled will depend on actual data. The average sample size is 18 based on the simulation with the assumption of 8.0% and 24.5% at 1.6 mg/kg and at 9.6 mg/kg, respectively, with 9.6 mg/kg as the highest dose tested. In addition, to refine the RDE, additional patients may be enrolled into selected dose levels.

In Dose Expansion, up to approximately 30 patients will be enrolled in each cohort. The sample size is determined such that sufficient precision is achieved to exclude a clinically non-interesting ORR associated with the current standards of care. The exact 95% and 90% confidence intervals at various ORR are provided in Table 3. Assuming the ORR is approximately 20% in current standard of care (Deciphera 2019, Heinrich et al. 2018, Heinrich et al. 2019), the efficacy of DS-6157a over the standard of care can be concluded if observed ORR in the cohort is greater than or equal to 36.7%.

Table 3 Exact CI for sample size of 30 at various observed ORR

Sample size	Observed ORR	Exact 95% CI	Exact 90% CI
N=30	30.0%	[14.7, 49.4]	[16.6, 46.5]
	33.3%	[17.3, 52.8]	[19.3, 49.9]
	36.7%	[19.9, 56.1]	[22.1, 53.3]
	40.0%	[22.7, 59.4]	[25.0, 56.6]
	43.3%	[25.5, 62.6]	[27.9, 59.8]
	46.7%	[28.3, 65.7]	[30.8, 63.0]
	50.0%	[31.3, 68.7]	[33.9, 66.1]

The confidence intervals are calculated based on the binomial distribution using Clopper-Pearson method using SAS® version 9.4.

If multiple doses or regimens are selected in one or more cohorts for Dose Expansion (Part 2), then up to approximately 30 patients may be randomized into each dose or regimen in one or more cohorts. Intra-patient dose escalation (IPDE) may be allowed for selected patients (Section 6).

10.4 Analysis Populations

The following analysis populations will be used:

- **Safety Analysis Set** will include all patients who received any DS-6157a. For this study, the Full Analysis Set and the Safety Analysis Set are identical for patients enrolled in the nonrandomized portion of the study.

  Patient data will be analyzed according to the study treatment received, where treatment received is the randomized/assigned study drug treatment if the patient took at least one dose of the randomized/assigned study drug treatment; otherwise the first treatment received will be used.

- **DLT-Evaluable Set** will include all patients enrolled in Dose Escalation (Part 1) of the study who had a DLT, or who received the full dose of DS-6157a in Cycle 1 and completed the DLT evaluation period.
- **Full Analysis Set (FAS)** will include all patients who received any DS-6157a.
- **PK Analysis Set** will include all patients in safety analysis set who had at least one PK sample with measurable concentration.

Demographic and baseline characteristics, disposition, and safety analyses will be presented for the Safety Analysis Set. In addition, for randomized patients, disposition will also be presented for FAS. Efficacy analyses will be presented for FAS. Analysis of PK parameters will be based on the PK analysis set.

Efficacy and safety endpoints observed after IPDE will be summarized separately from the rest of the results; these summaries may include tables, listings, or figures as appropriated depending on the number of patients and amount of data observed post-IPDE. Further details on this will be given in the SAP.

10.5 Data Analysis

10.5.1 Study Population Data

Disposition and reasons for discontinuing the study treatment and discontinuing from the study will be summarized and listed for the FAS and Safety Analysis Set. Demographic and baseline characteristics such as age, sex, race, ethnicity, baseline ECOG performance status, histology, cancer stage, best response to prior chemotherapy, lines of prior regimens, and prior treatment type will be summarized for the Safety Analysis Set.

10.5.2 Efficacy Analysis

Efficacy analyses will be based on FAS. If multiple doses or regimens were selected for Dose Expansion (Part 2) and not all randomized patients receive at least one dose of DS-6157a dose/regimen as randomized, sensitivity analyses will be performed for the Safety Analysis Set.

Efficacy variables will include BOR, ORR, DCR, CBR, DoR, TTR, and PFS using RECIST Version 1.1. In this study, best response determination using RECIST Version 1.1 requires confirmation of CR or PR.

A brief description of each endpoint is provided below.

- The BOR will be determined using tumor assessments performed before the start of any follow-up anticancer therapies (i.e. anticancer drug, radiotherapy, or surgery).
    - CR = at least two determinations of CR at least 4 weeks apart before progression.
    - PR = at least two determinations of PR or better at least 4 weeks apart before progression (and not qualifying for a CR).
    - SD = at least one SD assessment (or better) >6 weeks after randomization/starting treatment and before progression (and not qualifying for CR or PR).
    - PD = progression ≤12 weeks from randomization/start of study treatment (and not qualifying for CR, PR, or SD).
    - NE = all other cases
- ORR is defined as the proportion of patients with BOR of CR or PR.
- DCR is defined as the proportion of patients with BOR of CR, PR, or SD.
- CBR is defined as the proportion of patients with BOR of CR or PR, or patients with SD lasting at least 180 days.
- DoR is defined as the duration from the first documented response to the date of progression or death due to any cause. In case a patient does not have progression or death, DoR is censored at the date of last adequate tumor assessment (defined as an assessment of CR, PR, or SD). DoR analysis will include only responders.
- TTR is defined as the time from randomization/start of study treatment to the date of first documented response. TTR analysis will include only responders.
- PFS is defined as the time from randomization/start of study treatment to the date of event defined as the first documented radiological progression or death due to any cause. If a patient has not had an event, PFS is censored at the date of last adequate tumor assessment.

The efficacy variables will be listed and summarized. Objective response rate, DCR, and CBR will be summarized with the 90% and 95% confidence intervals using the Clopper-Pearson method. For DoR and PFS, the survival distribution of these endpoints will be summarized and presented graphically using the Kaplan-Meier method, and median event times and their 2-sided 95% CI using Brookmeyer and Crowley methods will be presented. Time to response will be summarized descriptively.

Descriptive statistics for the best percentage change from baseline in the sum of dimensions (SoD) of measurable tumors will be provided. A waterfall plot of the best percent change in the SoD for each patient will be presented.

10.5.3 Safety Analysis

Safety analyses in general will be descriptive and will be presented in tabular format with the appropriate summary statistics. Safety analyses will be presented using the Safety Analysis Set, except for the presentation of DLTs, which will use the DLT-Evaluable Set.

The on-treatment period is defined as:

From the start of study treatment, to earlier of (30 days after the last dose of the study treatment, date of first follow-up anticancer therapy -1), inclusive.

10.5.3.1 Adverse Events and DLTs

Safety will be assessed through the analysis of the reported incidence of treatment-emergent AEs (TEAEs). Treatment-emergent AEs are those with an onset date during the on-treatment period.

Adverse events will be graded according to NCI CTCAE Version 5.0 and coded using the current version of Medical Dictionary for Regulatory Activities (MedDRA; https://www.meddra.org/).

DLTs in the DLT Evaluable Set will be listed and summarized.

Treatment-emergent AEs will be summarized using system organ class (SOC) and preferred term. In addition, treatment-emergent SAEs, TEAEs by maximum NCI CTCAE grade, and TEAEs associated with study treatment discontinuation, reduction or interruption will also be presented.

All AEs will be listed including, but not limited to, verbatim term, preferred term, SOC, NCI CTCAE grade, and relationship to study drug.

Deaths will be listed and summary tables will be generated.

SAEs starting or worsening after the on-treatment period, if reported as related to study treatment, will be summarized.

Adverse events of special interest (AESIs) once defined based on continued review of the safety profile of DS-6157a will also be summarized.

10.5.3.2 Clinical Laboratory Evaluation Analyses

Descriptive statistics will be provided for clinical laboratory test results (hematology and chemistry) and changes from baseline by scheduled time of evaluation, including the EOT visit.

Abnormal laboratory results will be graded according to NCI CTCAE Version 5.0, if applicable. A shift table, presenting the 2-way frequency tabulation for baseline and the worst on-treatment value according to the NCI CTCAE grade, will be provided for clinical laboratory tests. Abnormal clinical laboratory test results ≥Grade 3 will be listed.

10.5.3.3 Vital Sign Analyses

Descriptive statistics will be provided for the vital sign measurements and changes from baseline by scheduled time of evaluation, including the EOT visit.

10.5.3.4 Electrocardiogram Analyses

Descriptive statistics will be provided for ECG parameters and changes from baseline, including the EOT visit. In addition, the number and percentage of patients meeting the following criteria will be tabulated for QT and QTcF: ≤450 msec, >450 to ≤480 msec, >480 msec to ≤500 msec, and >500 msec, and change from baseline ≥30 msec and ≥60 msec.

The QT intervals will be corrected for heart rate by Fridericia's formula ($QTcF = QT/[RR]^{1/3}$).

10.5.3.5 Other Safety Analyses

All other safety variables (e.g., physical examination findings, ECOG performance status, ECHO/MUGA and ophthalmologic and skin findings) will be listed and summary tables will be generated.

10.5.4 Pharmacokinetics/Pharmacodynamics

Plasma concentration data of DS-6157a, total anti-GPR20 antibody, and MAAA-1181a will be listed, plotted, and summarized using descriptive statistics at each time point.

PK parameters of DS-6157a, total anti-GPR20 antibody, and MAAA-1181a will be listed and summarized using descriptive statistics. Dose proportionality will be assessed using data from Part 1.

Population PK and exploratory exposure-response analyses may be performed to further characterize the PK of DS-6157a, total anti-GPR20 antibody, and MAAA-1181a, and the relationships between exposure and efficacy and/or safety endpoints. If performed, results of population PK or exposure-response analyses will be reported separately from the Clinical Study Report.

10.5.5 Anti-drug Antibody

ADA status will be determined (e.g., negative or positive) at the scheduled protocol time points for all patients. Titer and neutralizing antibodies will be determined for ADA positive time points only.

The treatment-emergent ADA incidence will be calculated by dose cohort, which is the proportion of patients having ADA positive during study period. Treatment-emergent ADA-positive patients will include the following:

- patients who are ADA negative at baseline and become ADA positive post-treatment (treatment-induced ADA); and
- patients who are ADA positive at baseline and post-treatment but also have a two-fold increase in ADA titer from baseline to post-treatment (treatment-boosted ADA); and
- patients who have missing ADA data at baseline but are ADA positive post-treatment.

Individual ADA status and titer data will be reported in data listings. Neutralizing antibodies will be tabulated by dose cohort.

10.6 Statistical Analysis Process

The clinical study will be analyzed by Sarah Cannon Development Innovations according to this protocol and the SAP, which will detail all methodologies and displays/shells for statistical analyses.

The SAP will provide the statistical methods and definitions for the statistical analysis of the efficacy, safety, PK and other data, as well as describe the approaches to be taken for summarizing other clinical study information such as patient disposition, demographic and baseline characteristics, study drug exposure, and prior and concomitant medications. The SAP will also include a description of how missing, unused, and spurious data will be addressed. The pharmacokinetic modeling of the concentration data, and the exposure/response analysis will be outside the scope of the SAP.

To preserve the integrity of the statistical analysis and clinical study conclusions, the SAP will be finalized prior to database lock for primary analysis.

All statistical analyses will be performed using SAS® Version 9.3 or higher (SAS Institute, Cary, NC 27513), unless specified otherwise in this protocol or in the SAP. The BLRM will be implemented using East® (Versions 6.5, Cytel, Inc.) with the BLRM module.

10.7 Specification of Bayesian Logistic Regression Model with Escalation with Overdose Control

The critical aspects of dose escalation are outlined in Section 10.7.1 to Section 10.7.4. The operating characteristics of BLRM with EWOC is provided in Appendix G.

10.7.1 Bayesian Logistic Regression Model

In this study, a 2-parameter Bayesian logistic regression model (BLRM), as defined below, will be used:

$$\text{logit}(\pi(d_i)) = \log(\alpha) + \beta \log(d_i/d^*), \quad \alpha>0, \beta>0$$

where $\text{logit}(\pi(d_i)) = \ln(\pi(di)/(1-\pi(di)))$, $\pi(di)$ is the DLT rate at i^{th} dose level d_i. Doses are rescaled as d_i/d^* with the reference dose $d^* = 9.6$ mg/kg. As a consequence $\log(\alpha)$ is equal to $\text{logit}(\pi(d^*))$ at dose d^*. Note that for a dose equal to zero, the probability of toxicity is zero.

10.7.2 Prior Specification for Bayesian Logistic Regression Model Parameters

The Bayesian approach requires the specification of a prior distribution for the BLRM parameters. A minimally informative bivariate normal prior for the model parameters (α, β) is obtained as follows:

- Based on extrapolation of nonclinical toxicology studies in monkeys, the MTD is projected to be greater than 9.6 mg/kg in humans (the highest nonseverely toxic dose [HNSTD] of monkeys is 30 mg/kg and assuming humans and monkeys are equally

sensitive, the MTD is projected to be greater than 9.6 mg/kg in humans). The median prior probabilities of DLT are set to be approximately 8.0% and 24.5% at 1.6 mg/kg (projected starting dose for dose escalation) and at 9.6 mg/kg, respectively.

- For the remaining doses, the prior medians of probability of DLT are assumed linear in log-dose on the logit-scale.
- Set Prob($\pi(d1) \leq 0.25$) = 0.90 and Prob($\pi(d^*) \leq 0.4$) = 0.70, which yields wide prior credible intervals (obtained from minimally informative Beta distributions1), the optimal parameters of the bivariate normal distribution can be obtained using EAST® (Version 6.5, Cytel Inc.) with BLRM module as follows:

Prior parameters for bivariate normal distribution of model parameters

Parameters	Means	Standard deviations	Correlation
ln(α), ln(β)	(-1.125, -0.308)	(1.373, 0.778)	0

10.7.3 Dose-Escalation Following EWOC Principle

Dose recommendation for the next cohort will be based on summaries of the posterior probability of DLT across the postulated dose range. After patients of each cohort complete DLT evaluation during Cycle 1, the joint posterior distribution of the BLRM parameters will be generated according to Bayes' theorem based on the likelihood function of the accumulated DLT data from Cycle 1 and the prior distribution.

Posterior probabilities of DLT rate at different dose levels will then be obtained from updated BLRM, and summarized for DLT rate in 4 different ranges:

- [0%, 16%] as DLT rate interval for 'under-dosing'
- (16%, 33%] as 'target' DLT rate interval
- (33%, 60%] as DLT rate interval for 'excessive toxicity'
- (60%, 100%] as DLT rate interval for 'unacceptable toxicity'

The dose level recommended for next dose cohort will be based on these probabilities according to the EWOC principle. The EWOC principle requires that the recommended dose for the next dose cohort is the one with:

- The highest posterior probability of the DLT rate in the target DLT rate range of (16%, 33%]
- Less than 25% of probability for DLT rate >33% (probability for excessive or unacceptable toxicity).

10.7.4 Dose Increment During Dose Escalation

- The dose level increment must not be greater than 100% even if the model suggests a higher dose than 100% for next cohort.

10.8 Analysis Time Points

10.8.1 Primary Analysis

The primary analysis of the study will occur after all patients have either discontinued the study or been followed for at least 6 months, whichever is earlier.

10.8.2 Final Analysis

The final analysis of the study will occur after all patients have discontinued the study. Data collected beyond the primary analysis cut-off will be presented as appropriate in a Clinical Study Report addendum.

10.8.3 Planned Interim Analysis

A formal interim analysis is not planned.

10.9 Safety Management

In accordance with the FDA guidance, the Sponsor has in place a multilayered process for ensuring patient safety through close collaboration of study site investigators, Sponsor's and CRO's study teams, CRO's safety team, and Sponsor's Clinical Safety and Pharmacovigilance (CSPV)-led Joint Safety Management Team (JSMT). This collaborative process constitutes the Data Safety Monitoring Plan for the study as detailed below:

Study safety is evaluated continuously by representatives of the Sponsor's CSPV and the CRO's safety team. Signal detection is performed at least monthly and ad hoc throughout the study by the JSMT composed, at a minimum, of Sponsor's CSPV safety physician (chairman of the JSMT) and CSPV single case review physician; CRO's safety team; and Sponsor's and CRO's study Medical Monitors and study biostatisticians. The JSMT monitors actual or potential issues related to patient safety that could result in a significant change in the medical risk-benefit balance associated with the use of study drug. Furthermore, the Sponsor and CRO will keep the Investigators updated on important safety information. If appropriate, selected safety issues may be escalated to a senior level, multidisciplinary, Sponsor-wide Global Safety Board for further evaluation and action.

To support safety oversight, Sponsor has established ongoing processes for collection, review, analysis, and submission of individual AE reports and their aggregate analyses. Because this is an open-label study, the Sponsor's and CRO's Medical Monitors and the investigators will have access to all data necessary for safety evaluation.

All participants in this study represent individuals with high unmet medical need as the prognosis for advanced/metastatic solid tumors is generally very poor. Sponsor has elected not to use a Data Monitoring Committee for this study. In addition to the comprehensive safety monitoring plan outlined above, the following key points were considered for this decision:

- This is an open-label study.
- Patients will be observed frequently for clinical evaluation and blood counts during dose escalation.

- The eligibility criteria exclude patients with disease characteristics that could predispose to higher risk of morbidity, including: patients with pre-existing cardiac, lung, and autoimmune diseases as specified.
- Well-defined discontinuation criteria are established in the protocol for individual patients for both safety and treatment futility with clear criteria for treatment discontinuation, dose delay, and toxicity management.

10.10 Steering Committee

The Steering Committee will be chaired by the Principal Investigator.

The specific roles and responsibilities of the Steering Committee and its members will be documented and described in a separate document.

11. SAFETY REPORTING AND ANALYSES

Safety assessments will consist of monitoring and recording protocol-defined AEs and SAEs, and measurement of protocol-specified hematology, clinical chemistry, and urinalysis variables, measurement of protocol-specified vital signs, and other protocol-specified tests that are deemed critical to the safety evaluation of the study drug.

The Principal Investigator is responsible for recognizing and reporting SAEs to the Innovations Safety Department (see Section 11.4) and the Innovations Safety Department in turn notifies the Sponsor (see Section 11.4). It is the Sponsor's responsibility to report relevant SAEs to the applicable local, national, or international regulatory bodies. In addition, Investigators must report SAEs and follow-up information to their responsible IRBs according to the policies of each IRB.

The Principal Investigator is also responsible for ensuring that every staff member involved in the study is familiar with the content of this section.

11.1 Definitions

11.1.1 Adverse Events

Adverse event means any untoward medical occurrence associated with the use of a drug in humans, whether or not considered drug-related. An AE can be any unfavorable and unintended sign (e.g., an abnormal laboratory finding), symptom, or disease temporarily associated with the use of a drug, without any judgment about causality. An AE can arise with any use of the drug (e.g., off-label use, use in combination with another drug) and with any route of administration, formulation, or dose, including overdose.

11.1.2 Serious Adverse Event

An AE or a suspected adverse reaction (SAR) is considered "serious" if it results in any of the following outcomes:

- Death
- Is life-threatening

- Requires inpatient hospitalization or prolongation of existing hospitalization
- A persistent or significant disability/incapacity
- A congenital anomaly/birth defect
- An important medical event

Important medical events that may not result in death, be life-threatening, or require hospitalization may be considered serious when, based upon appropriate medical judgment, they may jeopardize the patient and may require medical or surgical intervention to prevent one of the outcomes listed in this definition. 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 hospitalization, or development of drug dependency or drug abuse.

It is important to distinguish between "serious" and "severe" AEs, as the terms are not synonymous. Severity is a measure of intensity; however, an AE of severe intensity need not necessarily be considered "serious." Seriousness serves as the guide for defining regulatory reporting obligations and is based on patient/event outcome or action usually associated with events that pose a threat to a patient's life or vital functions. For example, nausea which persists for several hours may be considered "severe" nausea but may not be considered an SAE. On the other hand, a stroke which results in only a limited degree of disability may be considered only a mild stroke but would be considered an SAE. "Severity" and "seriousness" should be independently assessed when recording AEs and SAEs on the eCRF screen.

Note:

- Procedures are not AEs or SAEs, but the reason for the procedure may be an AE or SAE.
- Pre-planned (prior to signing the ICF) procedures or treatments requiring hospitalizations or pre-existing conditions that do not worsen in severity are not SAEs.

11.1.3 Adverse Reaction

An adverse reaction (AR) means any AE caused by a drug. Adverse reactions are a subset of all SARs where there is a reason to conclude that the drug caused the event.

11.1.4 Suspected Adverse Reaction

Suspected adverse reaction means any AE for which there is a reasonable possibility that the drug caused the AE. "Reasonable possibility" means that there is evidence to suggest a causal relationship between the drug and the AE. An SAR implies a lesser degree of certainty about causality than AR, which means any AE caused by a drug.

11.2 Recording and Reporting of Adverse Events

11.2.1 Recording of Adverse Events

All AEs, SAEs, and AESIs will be reported in the eCRF.

All events (serious and non-serious) must be reported with Investigator's assessment of the event's seriousness, severity, and causality to the study drug. A detailed narrative summarizing

the course of the event, including its evaluation, treatment, and outcome must be provided. Specific or estimated dates of event onset, treatment, and resolution must be included when available. Medical history, concomitant medications, and laboratory data that are relevant to the event will also be summarized in the narrative. For fatal events, the narrative will state whether an autopsy was or will be performed and include the results if available. Source documents (including medical reports) will be retained at the study site and must not be submitted to the Sponsor for SAE reporting purposes.

Grade 3 or Grade 4 AEs ongoing at the discontinuation of the study drug will be monitored (including local laboratory tests when appropriate, see Section 3.3) until the AE is determined to be resolving or back to baseline.

Additional relevant information regarding the AESIs ILD/pneumonitis (Section 11.11), regardless of seriousness, is to be collected through the targeted questionnaires within the eCRF. Additional relevant information regarding the AESI infusion-related reaction (Section 11.11) is to be collected through the narrative form within the eCRF.

For broad surveillance of ILD/pneumonitis, a set of pre-defined list of preferred term s eligible for adjudication as described in the Event Adjudication Site Manual, is utilized for enhanced data collection.

Disease progression/worsening of the cancer will not be recorded as an AE on the Adverse Event eCRF. However, events associated with disease progression, such as clinical symptoms, may be recorded as AEs. Death due to disease progression should be recorded on the Death eCRF.

If the AE is serious, it must be reported immediately to Innovations Safety Department via electronic data capture (EDC). Other untoward events occurring in the framework of a clinical study are to be recorded as AEs (i.e., AEs that occur prior to assignment of study treatment that are related to a protocol-mandated intervention, including invasive procedures such as biopsies, medication washout, or no treatment run-in).

Any clinically significant signs and symptoms, abnormal test findings, changes in physical examination, hypersensitivity, and other measurements that occur will be reported as AEs, and reported on the relevant eCRF screen.

Test findings will be reported as an AE if the test result requires an adjustment in the study drug(s) or discontinuation of treatment; and/or test findings require additional testing or surgical intervention; a test result or finding is associated with accompanying symptoms; or a test result is considered to be an AE by the Investigator.

All AEs should be recorded individually in the patient's own words (verbatim) unless, in the opinion of the Principal Investigator or designated physician, the AEs constitute components of a recognized condition, disease, or syndrome. In the latter case, the condition, disease, or syndrome should be named rather than each individual sign or symptom. If a constellation of signs and/or symptoms cannot be medically characterized as a single diagnosis or syndrome at the time of reporting, each individual event should be recorded as an AE or SAE as appropriate on the relevant form(s) (eCRF screen). If a diagnosis is subsequently established, it must be

reported as follow-up information is available. If a diagnosis is determined subsequent to the reporting of the constellation of symptoms, the signs/symptoms should be updated to reflect the diagnosis.

A persistent AE is one that extends continuously, without resolution, between patient evaluation time points. All persistent AEs that meet the SAE criteria must be recorded on the eCRF.

A recurrent AE is one that occurs and resolves between patient evaluation time points and subsequently recurs. All recurrent AEs that meet the SAE criteria must be recorded on the eCRF.

Infusion-related reactions should be recorded and reported under the AE term "Infusion related reaction." All applicable symptoms or signs of IRR (e.g. flushing, tachycardia, nausea, and bronchospasm) can be described in the narrative form on the eCRF.

11.2.2 Reporting of Adverse Events

All AEs regardless of seriousness or relationship to DS-6157a treatment (called study treatment), spanning from the signing of the ICF until 30 calendar days after discontinuation or completion of study treatment as defined by the study for that patient after his/her last dose of study drug, are to be recorded on the corresponding screen(s) included in the eCRF.

All AEs resulting in discontinuation from the study should be followed until resolution or stabilization. All new AEs occurring during this period must be reported and followed until resolution unless, in the opinion of the Investigator, the AE or laboratory abnormality/ies is/are not likely to improve because of the underlying disease. In this case, the Investigator must record his or her reasoning for this decision in the patient's medical record.

After 30 days after completion of protocol-specific treatment or discontinuation, only AEs, SAEs, or deaths assessed by the Investigator as treatment-related are to be reported.

11.2.2.1 Safety Reporting for COVID-19

The following guidance is for reporting COVID-19 cases that have occurred in the context of a clinical trial with a Daiichi Sankyo product or compound:

- All confirmed or suspected COVID-19 events must be recorded in the eCRF.
  - Patients who test positive for COVID-19 should be reported as "Confirmed COVID-19," either as an adverse event (AE) or serious adverse event (SAE).
  - Patients whose medical history and clinical manifestations, signs, and possible exposure are consistent with COVID-19 but for whom no PCR or antibody test for COVID-19 is available, should be reported as "Suspected COVID-19", either as an AE or SAE.
- The usual protocol mandated SAE reporting requirements should be followed for confirmed or suspected COVID-19 (or SARS-CoV-2) as done for any other AE, i.e. the investigator should assess whether any seriousness criteria are met per protocol, and appropriate protocol reporting requirements should be followed.

  - In the event that the Investigator assesses that a COVID-19 case does not meet any seriousness criteria as outlined in the protocol, it should be reported as a non-serious adverse event in the case report form (CRF).
- When assessing the severity of the COVID-19 adverse event, please use the severity grading criteria in the appropriate protocol.
- All study drug interruption or dose reduction or discontinuation due to the COVID-19 event must be recorded on the AE and drug administration eCRFs.
- For both serious or non-serious COVID-related AEs, the following information should be provided as a minimum:
  - Date and laboratory results confirming the COVID-19 diagnosis (including viral antigen test and/or antiviral antibody serological test) in the lab eCRF, if available.
  - Clinical course of the case including presenting signs, symptoms, exposure, actions taken with the investigational products, medications used for treatment or prophylaxis of COVID- 19, and outcome in relevant eCRF (e.g., concomitant medication, AE).
- Findings from diagnostic imaging (including CT scan or other chest imaging).

11.3 Assessment of Adverse Events

The Investigator must assess causal the relationship between an AE and the study drug on the basis of his/her clinical judgment and the following definitions. The causality assessment must be made based on the available information and can be updated as new information becomes available.

- Related:
  - The AE follows a reasonable temporal sequence from study drug administration, and cannot be reasonably explained by the patient's clinical state or other factors (e.g., disease under study, concurrent diseases, and concomitant medications).

  or

  - The AE follows a reasonable temporal sequence from study drug administration, and is a known reaction to the drug under study or its chemical group, or is predicted by known pharmacology.
- Unrelated:
  - The AE does not follow a reasonable sequence from study drug administration, or can be reasonably explained by the patient's clinical state or other factors (e.g., disease under study, concurrent diseases, and concomitant medications).

11.4 Expedited Reporting by Investigators

The following types of events must be reported by the Investigator in the eCRF within 24 hours of awareness:

- SAEs (See Section 11.1.2 for definition) occurring at any time from the signing of the ICF through the 30-day follow-up period after the last dose of study drug must be reported as SAEs on the eCRF and followed until resolution (with autopsy report if

applicable). Adverse events classified by the treating Investigator as "serious" require expeditious handling and reporting to the Innovations Safety Department in order to comply with regulatory requirements. Determination of "life-threatening" or "serious" is based on the opinion of either the Sponsor or the Investigator. Additionally, any SAE brought to the attention of an Investigator at any time outside of the time period specified above must be reported immediately to the Sponsor if the event is considered to be drug related.

- All potential ILD/pneumonitis cases should be reported within 24 hours: including both serious and non-serious potential ILD cases (potential ILD is described by the Event Adjudication Site Manual).
- Hepatic events (both serious and non-serious, and clinical laboratory result) which meet the potential Hy's Law criteria defined as an elevated [ALT or AST] ≥3 × ULN and an elevated total bilirubin >2 × ULN that may occur simultaneously or at different time points during the study, regardless of whether these hepatic events are symptomatic, lead to study drug discontinuation, dose reduction or dose interruption, require corrective treatment, constitute an AE in the Investigator's clinical judgment. A targeted questionnaire is built within the eCRF to collect relevant additional information for these potential cases. For broad surveillance of hepatotoxicity, hepatic events that meet the biochemical criteria (AST or ALT ≥ 3 x ULN, TBL > 2 x ULN) are included for enhanced data collection.
- Overdose is always serious. By definition an overdose is medically important, which meets the seriousness criterion of important medical event. An overdose can occur with or without an AE. AEs can either be serious or non-serious. Details of the overdose including DS-6157a dosage, clinical course, associated AEs, and outcome must be captured in the narrative form of the eCRF.

All events (serious and non-serious) must be reported with Investigator's assessment of the event's seriousness, severity, and causality to the study drug. A detailed narrative summarizing the course of the event, including its evaluation, treatment, and outcome must be provided. Specific or estimated dates of event onset, treatment, and resolution must be included when available. Medical history, concomitant medications, and laboratory data that are relevant to the event must also be summarized in the narrative. For fatal events, the narrative must state whether an autopsy was or will be performed, and include the results if available. Source documents (including medical reports) will be retained at the study site and will not be submitted to the Sponsor for SAE reporting purposes.

Urgent safety queries must be followed up and addressed promptly. Follow-up information and response to non-urgent safety queries must be combined for reporting to provide the most complete data possible within each follow-up.

In the event that eCRF is unavailable, report SAEs on a Serious Adverse Event Report (SAVER) form. All completed SAVER forms must be signed by the Investigator, and e-mailed to the sponsor and CRO using the following contact information (during both business and non-business hours):

Daiichi Sankyo Safety Department

Safety Dept. Email: clinicalsafety@daiichisankyo.co.jp

DS-6157a Safety email: DSJ_DS-6157@daiichisankyo.co.jp

Sarah Cannon Innovations Safety Department

Safety Dept. Email: CANN.SAE@SCRI-Innovations.com

Once the eCRF becomes available, please enter SAEs reported on the SAVER Form into eCRF as soon as possible. Please call the local SAE Hotline (see Study Manual) or your study monitor for any questions on SAE reporting.

11.4.1 Investigator Reporting After Study Discontinuation

During the 30 days after completing protocol-specific treatment or study discontinuation, treatment-related AEs, SAEs, or deaths determined by the Investigator as treatment-related are to be reported directly to the Sponsor or Innovations Safety.

11.5 Abnormal Laboratory Values

All clinical laboratory results, vital signs, and ECG results or findings must be appraised by the Investigator to determine their clinical significance. If an abnormal laboratory value or vital sign is associated with clinical signs and/or symptoms, the sign or symptom should be reported as an AE or SAE, and the associated laboratory value or vital sign should be considered additional information that must be collected on the relevant eCRF screen. If the laboratory abnormality is a sign of a disease or syndrome, only the diagnosis needs to be recorded on the eCRF screen.

Abnormal laboratory values will be reported as an AE if the laboratory result requires an adjustment in the study drug(s) or discontinuation of treatment; and/or laboratory findings require additional testing or surgical intervention; a laboratory result or finding is associated with accompanying symptoms; or a laboratory result is considered to be an AE by the Investigator.

11.6 Deaths

Deaths that occur during the protocol-specified AE reporting period that are attributed by the Investigator solely to progression of disease will be recorded on the "End of Study" eCRF screen. However, when a patient dies from disease progression with no other immediate cause, disease progression will be recorded on the eCRF as AE term "disease progression" as well as the outcome, and serious criteria of death, and expeditiously reported to the Innovations Safety Department. All other on-study deaths, regardless of attribution, will be recorded on the eCRF screen and expeditiously reported to the Innovations Safety Department.

When recording a SAE with an outcome of death, the event or condition that caused or contributed to the fatal outcome should be recorded as the single medical concept on the eCRF screen. If the cause of death is unknown and cannot be ascertained at the time of reporting, record "Death" on the eCRF. During post-treatment follow-up, deaths attributed to progression of disease will be recorded on the "Follow-up Summary" and "Death Page" eCRFs.

11.7 Pre-Existing Medical Conditions

A pre-existing medical condition is one that is present at the start of the study. Such conditions should be recorded on the General Medical History of the eCRF screen. A pre-existing medical condition should be recorded as an AE or SAE only if the frequency, severity, or character of the condition worsens during the study. When recording such events on the eCRF screen, it is important to convey the concept that the pre-existing condition has changed by including applicable descriptors.

11.8 New Cancers

The development of a new primary cancer should be regarded as an AE and will generally meet at least one of the seriousness criteria (see Section 11.1.2). New primary cancers are those that are not the primary reason for the administration of the study treatment and have developed after the inclusion of the patient into the study. They do not include metastases of the original cancer. Symptoms of metastasis or the metastasis itself should not be reported as an AE/SAE, as they are considered to be disease progression.

11.9 Pregnancy, Abortion, Birth Defects/Congenital Anomalies

If a patient becomes pregnant while enrolled in the study, EIU Reporting Form (a paper report form, not available within the eCRF) must be completed and Faxed (866.807.4325)/Emailed (CANN.SAE@scri-innovations.com to the Innovations Safety Department. The Innovations Safety Department should be notified expeditiously, irrespective of whether or not it meets the criteria for expedited reporting. Abortions (spontaneous, accidental, or therapeutic) must also be reported to the Innovations Safety Department.

If a female partner of a male patient becomes pregnant during the male patient's participation in this study, this must be reported to the Innovations Safety Department immediately. Every effort should be made to follow the pregnancy for the final pregnancy outcome.

Congenital anomalies/birth defects always meet SAE criteria, and should therefore be expeditiously reported as an SAE, using the previously described process for SAE reporting. An EIU Report Form should also have been previously completed, and will need to be updated to reflect the outcome of the pregnancy.

11.10 DS-6157a Overdose

Symptomatic and non-symptomatic overdose must be reported in the eCRF system. Any accidental or intentional overdose is to be reported to the Innovations Safety Department no greater than 24 hours from first knowledge of the event using the corresponding screens in the eCRF and following the same process described for SAE reporting (see Section 11.4) if the overdose is symptomatic.

For information on how to manage an overdose of DS-6157a, see the IB.

11.11 Adverse Events of Special Interest

For the DS-6157a clinical program, based on the currently available nonclinical safety findings and relevant literature including safety data on the drugs of same class, the following events are considered as AESIs:

- Interstitial lung disease (ILD)/Pneumonitis
- IRR

Relevant information regarding the AESIs ILD/pneumonitis, regardless of seriousness, is to be collected through the targeted questionnaires and narrative forms within the eCRFs in the clinical study database.

Relevant information regarding the AESI IRR is to be collected through the narrative form within the clinical study database.

11.11.1 Interstitial Lung Disease Adjudication Committee

An independent ILD Adjudication Committee for the DS-6157a program is responsible for reviewing all cases of potential ILD/pneumonitis. To ensure adequate and relevant independent evaluation, systematic additional data collection will be conducted for all cases that will be brought for adjudication. These additional data collections will cover a more in-depth relevant medical history (e.g., smoking, radiation, chronic obstructive pulmonary disease, and other chronic lung conditions), diagnostic evaluation, treatment, and outcome of the event. This data collection will be triggered based on a set of pre-defined list of preferred term s eligible for adjudication as described in the Event Adjudication Site Manual.

11.12 Regulatory Authorities, Investigators, and Institutional Review Board/Ethics Committee

Sponsor and/or the Innovations Safety Department will inform Investigators, Institutional Review Boards (IRBs)/Independent Ethics Committees (IECs), and regulatory authorities of any suspected unexpected serious adverse reactions (SUSARs) occurring at other study sites or in other studies of the investigational drug, as appropriate per local reporting requirements. Sponsor and/or the Innovations Safety Department will comply with any additional local safety reporting requirements.

In the US, upon receipt of the Sponsor's notification of SUSARs that occurred with the study drug, unless delegated to the Sponsor, it is the Investigator's responsibility to inform the IRB per Sponsor's instruction.

12. QUALITY ASSURANCE AND QUALITY CONTROL

12.1 Monitoring

Site monitoring shall be conducted to ensure that patient protection, study procedures, laboratory, study intervention administration, and data collection processes are of high quality and meet Sponsor, Good Clinical Practice, ICH and, when appropriate, regulatory guidelines.

12.2 Audits and Inspections

The Investigator will permit study-related quality audits and inspections by Innovations or its representative(s), the Sponsor, government regulatory authorities, and the IRB(s) of all study-related documents (e.g., source documents, regulatory documents, data collection instruments, case report forms). The Investigator will ensure the capability for review of applicable study-related facilities. The Investigator will ensure that the auditor or inspector or any other compliance or Quality Assurance reviewer is given access to all study-related documents and study-related facilities.

At the discretion of the Sponsor or its delegate, Source Document Verification may be performed on partial or all data items as defined in study documents and/or plans.

Participation as an Investigator in this study implies the acceptance of potential inspection by the Sponsor or its representative, government regulatory authorities, and IRB(s)/IEC(s).

13. ETHICAL, FINANCIAL, AND REGULATORY CONSIDERATIONS

This research study will be conducted according to the standards of Good Clinical Practice outlined in the ICH E6 Tripartite Guideline and CFR Title 21 part 312, applicable government regulations, institutional research policies and procedures, and any other local applicable regulatory requirement(s).

13.1 Institutional Review Board Approval

The clinical study protocol, ICF, IB, available safety information, patient documents (e.g., study diary), patient recruitment procedures (e.g., advertisements), information about payments (i.e., Principal Investigator payments) and compensation available to the patients, and documentation evidencing the Principal Investigator's qualifications should be submitted to the IRB for ethical review and approval if required by local regulations, prior to the study start.

The Principal Investigator/Sponsor and/or designee will follow all necessary regulations to ensure appropriate, initial, and on-going IRB study review. The Principal Investigator/Sponsor (as appropriate) must submit to and, where necessary, obtain approval from the IRB for all subsequent protocol amendments and changes to the ICF. Investigators will be advised by the Sponsor or designee whether an amendment is considered substantial or non-substantial and whether it requires submission for approval or notification only to an IRB.

Safety updates for DS-6157a will be prepared by the Sponsor or its representative as required, for distribution to the Investigator(s) and submission to the relevant IRB.

13.2 Regulatory Approval

As required by local regulations, the Sponsor will ensure all legal aspects are covered, and approval of the appropriate regulatory bodies obtained, prior to study initiation. If required, the Sponsor will also ensure that the implementation of substantial amendments to the protocol and other relevant study documents happen only after approval by the relevant regulatory authorities.

13.3 Informed Consent

Informed consent is a process by which a patient voluntarily confirms his or her willingness to participate in a particular study after having been informed of all aspects of the study that are relevant to the patient's decision to participate. Informed consent is documented by means of a written, signed, and dated ICF.

The ICF will be submitted for approval to the IRB that is responsible for review and approval of the study. Each ICF must include all of the relevant elements currently required by the FDA, as well as local county authority or state regulations and national requirements.

Before recruitment and enrollment into the study, each prospective candidate will be given a full explanation of the research study. Once the essential information has been provided to the prospective candidate, and the Investigator is sure that the individual candidate understands the implications of participating in this research study, the candidate will be asked to give consent to participate in the study by signing an ICF. A notation that written informed consent has been obtained will be made in the patient's medical record. A copy of the ICF, to include the patient's signature, will be provided by the Investigator to the patient.

If an IRB/IEC approved amendment to the protocol substantially alters the study design or the potential risks to the patient, the patient's consent to the most recent version of the approved ICF to continue participation in the study should be obtained.

13.3.1 Confidentiality

13.3.1.1 Patient Confidentiality

Confidentiality of patients' personal data will be protected in accordance with the Health Insurance Portability and Accountability Act of 1996 (HIPAA). HIPAA regulations require that, in order to participate in the study, a patient must sign an authorization form for the study that he or she has been informed of the following:

- What protected health information (PHI) will be collected from patients in this study
- Who will have access to that information and why
- Who will use or disclose that information
- That health information may be further disclosed by the recipients of the information, and that if the information is disclosed the information may no longer be protected by federal or state privacy laws
- That the information collected about the research study will be kept separate from the patient's medical records, but the patient will be able to obtain the research records after the conclusion of the study
- Whether the authorization contains an expiration date
- The rights of a research patient to revoke his or her authorization.

In the event that a patient revokes authorization to collect or use his or her PHI, the Investigator, by regulation, retains the ability to use all information collected prior to the revocation of patient authorization. For patients that have revoked authorization to collect or use PHI, attempts should

be made to obtain permission to collect at least vital status (i.e., that the patient is alive) at the end of their scheduled study period.

In compliance with ICH GCP guidelines and applicable parts of 21 CFR it is a requirement that the Investigator and institution permit authorized representatives of the Sponsor, Innovations, the regulatory authorities, and the IRB direct access to review the patient's original medical records at the site for verification of study-related procedures and data.

One measure to protect confidentiality is that only a unique study number will identify patients in the eCRF database system or other documents submitted to the Sponsor or delegate and Innovations. This information, together with the patient's year of birth, will be used in the database for patient identification. Patient names or addresses will not be entered in the eCRF database system. No material bearing a patient's name will be kept on file by the Sponsor or Innovations. Patients will be informed of their rights within the ICF.

13.3.1.2 Investigator and Staff Information

Personal data of the Investigators and sub-Investigators may be included in the Sponsor and/or Innovations databases, and shall be treated in compliance with all applicable laws and regulations. When archiving or processing personal data pertaining to the Investigator or sub-Investigator, the Sponsor and/or Innovations shall take all appropriate measures to safeguard and prevent access to this data by any unauthorized party.

13.4 Financial Information

The finances for this clinical study will be patient to a separate written agreement between the Sponsor and applicable parties. Any Investigator financial disclosures as applicable to 21CFR Part 54 shall be appropriately provided.

14. RESEARCH RETENTION AND DOCUMENTATION OF THE STUDY

14.1 Amendments to the Protocol

Amendments to the protocol shall be planned, documented, approved by the IRB/IEC, and signature-authorized prior to implementation.

If an amendment to the protocol is required, the amendment will be originated and documented by the Sponsor or its representative. All amendments require review and approval of all pharmaceutical companies and the Principal Investigator supporting the study. The written amendment must be reviewed and approved by the Sponsor, and submitted to the IRB/IEC at the Investigator's facility for the board's approval.

Amendments specifically involving change to study design, risk to patient, increase to dosing or exposure, patient number increase, or addition or removal of new tests or procedures shall be reviewed and approved by the IRB/IEC of record for the Investigator's facility.

The amendment will be submitted formally to the FDA or other regulatory authorities by the Sponsor as applicable, and IRB/IEC approval obtained, specifically when an increase to dosing

or patient exposure and/or patient number has been proposed; or, when the addition or removal of an Investigator is necessitated.

Items requiring a protocol amendment with the IRB/IEC and/or the FDA or other regulatory authorities' approval include, but are not limited to, the following:

- Change to study design
- Risk to patients
- Increase to dose or patient exposure to drug
- Patient number increase
- Addition or removal of tests and/or procedures
- Addition/removal of an Investigator.

It should be further noted that, if an amendment to the protocol substantially alters the study design or the potential risks to the patients, their consent to continue participation in the study should be obtained.

14.2 Documentation Required to Initiate the Study

Before the study can begin, certain documentation required by FDA regulations and ICH GCP must be provided by the Investigator. The required documentation should be submitted to:

Sarah Cannon Development Innovations
Regulatory Department
1100 Dr. Martin L. King Jr. Blvd. Suite 800
Nashville, TN 37203
Email: SCRIRegulatory@SCRI-Innovations.com

Documents required at a minimum to begin a study include, but are not limited to, the following:

- A signature-authorized protocol and contract
- A copy of the official IRB approval of the study and the IRB members list
- Current curricula vita for the Principal Investigator and any associate Investigator(s) who will be involved in the study
- Indication of appropriate accreditation for laboratories (as required per local laws and regulations) to be used in the study and the normal ranges for tests to be performed by those laboratories
- Original Form FDA 1572 (Statement of Investigator), appropriately completed and signed
- A copy of the IRB/IEC-approved ICF containing permission for audit by representatives of the Sponsor, Innovations, the IRB, and the FDA and other regulatory agencies (as applicable)
- Financial disclosure forms for all Investigators listed on Form FDA 1572 (if applicable, i.e., for covered trials)
- Verification of Principal Investigator acceptability from local and/or national debarment list(s).

14.3 Study Documentation and Storage

The Principal Investigator must maintain a list of appropriately qualified persons to whom he/she has delegated study duties and should ensure that all persons assisting in the conduct of the study are informed of their obligations. All persons authorized to make entries and/or corrections on the eCRFs are to be included on this document. All entries in the patients' eCRFs are to be supported by source documentation where appropriate.

Source documents are the original documents, data, records, and certified copies of original records of clinical findings, observations, and activities from which the patients' eCRF data are obtained. These can include, but are not limited to, hospital records, clinical and office charts, laboratory, medico-technical department and pharmacy records, diaries, microfiches, ECG traces, copies or transcriptions certified after verification as being accurate and complete, photographic negatives, microfilm or magnetic media, x-rays, and correspondence.

The Principal Investigator and study staff members are responsible for maintaining a comprehensive and centralized filing system (e.g., regulatory binder or Investigator study file [ISF]) of all essential study-related documentation, suitable for inspection at any time by representatives from the Sponsor and/or applicable regulatory authorities. The ISF must consist of those documents that individually or collectively permit evaluation of the conduct of the study and the quality of the data produced. The ISF should contain at a minimum all relevant documents and correspondence as outlined in ICH GCP Section 8 and 21 CFR Part 312.57, including key documents such as the IB and any amendments, the protocol and any amendments, signed ICFs, patient information sheet (PIS), copies of completed eCRFs, IRB/IEC approval documents, Financial Disclosure forms, patient identification lists, enrollment logs, delegation of authority log, staff qualification documents, laboratory normal ranges, and records relating to the study drug including accountability records. Drug accountability records should, at a minimum, contain information regarding receipt, shipment, and disposition. Each form of drug accountability record, at a minimum, should contain Principal Investigator name, date drug shipped/received, and the date, quantity, and batch/code or lot number for the identity of each shipment. In addition, all original source documents supporting entries in the eCRF must be maintained and readily available.

The Sponsor shall maintain adequate investigational product and financial interest records as per 21 CFR Part 54.6 and Part 312.57 for no less than 2 years after the last marketing application has been approved by FDA; or, in the event that the marketing application has not been approved by FDA, for no less than 2 years after the last shipment/delivery of the drug for investigational use or the drug is discontinued and the FDA has been notified of the discontinuation.

The IRB shall maintain adequate documentation/records of IRB activities as per 21 CFR Part 56.115 for at least 3 years after completion of the research.

The Investigator shall maintain adequate records of drug disposition, case histories, and any other study-related records as per 21 CFR Part 312.62 for no less than 2 years after the last marketing application has been approved by FDA; or, in the event that the marketing application has not been approved by FDA, for no less than 2 years after the last shipment/delivery of the

drug for investigational use or the drug is discontinued and FDA has been notified of the discontinuation.

To enable evaluations and/or audits from regulatory authorities or from the Sponsor or its representative, the Investigator additionally agrees to keep records, including the identity of all participating patients (sufficient information to link records, e.g., eCRF and medical records), all original signed ICFs, copies of all eCRF records, SAE Reporting forms, source documents, detailed records of treatment disposition, and related essential regulatory documents. The documents listed above must be retained by the Investigator for as long as needed to comply with national and international regulations (generally 2 years after discontinuing clinical development or after the last marketing approval). Sponsor or its representative will notify the Investigator(s)/institutions(s) when the study-related records are no longer required.

If the Investigator relocates, retires, or for any reason withdraws from the study, the Sponsor or its representative must be prospectively notified. The study records must be transferred to an acceptable designee, such as another Investigator, another institution, or to Innovations. The Investigator must obtain the Sponsor's written permission before disposing of any records, even if retention requirements have been met. All study files will be maintained by the Sponsor or its representative throughout the study, and will be transferred to the Sponsor at the conclusion of the study, if applicable.

14.4 Data Collection

The study eCRF is the primary data collection instrument for the study. Case report forms will be completed using the English language except for patient questionnaires for non-English speaking patients and should be kept current to enable the Sponsor to review the patients' status throughout the course of the study.

In order to maintain confidentiality, only study number, patient number, and year of birth will identify the patient in the eCRF system. If the patient's name appears on any other document (e.g., laboratory report), it must be anonymized on the copy of the document to be supplied to Innovations and be replaced instead with the patient number and other identifier (i.e., patient initials) as allowed per institutional policy. The Investigator will maintain a personal patient identification list (patient numbers with corresponding patient identifiers) to enable records to be identified and verified as authentic. Patient data/information will be kept confidential, and will be managed according to applicable local, state, and federal regulations.

All data requested by the eCRF system must be supported by and be consistent with the patient's source documentation. All missing data must be explained. When a required laboratory test, assessment, or evaluation has not been done or an "Unknown" box is not an option on the eCRF, a note in the eCRF system should be created by the site personnel entering the patient's data verifying that the test was "Not Done" or the result was "Unknown." For any entry errors made, the error(s) must be corrected, and a note explaining the reason for change should be provided.

The Investigator will electronically sign and date the patient eCRF indicating that the data in the eCRF has been assessed. Each completed eCRF will be signed and dated by the Principal Investigator, once all data for that patient is final.

14.5 Disclosure and Publication Policy

The Sponsor is committed to meeting the highest standards of publication and public disclosure of information arising from clinical studies sponsored by the company. We will comply with US, European Union, and Japanese policies for public disclosure of the clinical study protocol and clinical study results, and for sharing of clinical study data. We follow the principles set forward in "Good Publication Practice for Communicating Company-Sponsored Medical Research (GPP3)", and publications will adhere to the "Recommendations for the Conduct, Reporting, Editing, and Publication of Scholarly Work in Medical Journals" established by the International Council of Medical Journal Editors.

In order to ensure that we are in compliance with the public disclosure policies and the International Council of Medical Journal Editors recommendations, and to protect proprietary information generated during the study, all publications (manuscripts, abstracts, or other public disclosure) based on data generated in this study must be accepted, reviewed, and approved in writing by the Sponsor prior to submission.

15. REFERENCES

Allander et al. 2001

Allander SV, Nupponen NN, Ringnér M, Hostetter G, Maher GW, Goldberger N, et al. Gastrointestinal stromal tumors with KIT mutations exhibit a remarkably homogeneous gene expression profile. Cancer Res. 2001;61(24):8624-8.

Babb et al. 1998

Babb J, Rogatko A, Zacks S. Cancer phase I clinical trials: efficient dose escalation with overdose control. Stat Med. 1998;17(10):1103-20.

Brennan et al. 2002

Brennan TJ, Matthews W, Moore M, inventors; DELTAGEN, INC., assignee. Transgenic mice containing GPCR5-1 Gene Disruptions. International Publication No. WO/2002/079440. 29 Mar 2002.

Cheverton et al. 2004

Cheverton P, Friess H, Andras C, Salek T, Geddes C, Bodoky G, et al. Phase III results of exatecan (DX-8951f) versus gemcitabine (Gem) in chemotherapy-naïve patients with advanced pancreatic cancer (APC). J Clin Oncol. 2004;22:14(Suppl.2):abstract 4005.

Chi et al. 2010

Chi P, Chen Y, Zhang L, Guo X, Wongvipat J, Shamu T, et al. ETV1 is a lineage survival factor that cooperates with KIT in gastrointestinal stromal tumours. Nature. 2010;467(7317):849-53.

Corless et al. 2011

Corless CL, Barnett CM, Heinrich MC. Gastrointestinal stromal tumours: origin and molecular oncology. Nat Rev Cancer. 2011;11(12):865-78.

CTCAE Version 5.0

Common terminology criteria for adverse events (CTCAE): Version 5.0 (v5.0: Published 27 November 2017). Available from: https://ctep.cancer.gov/protocolDevelopment/electronic_applications/docs/CTCAE_v5_Quick_Reference_5x7.pdf

Deciphera 2019

https://investors.deciphera.com/static-files/9134e04e-d75a-40b2-8e56-2b9876c20997 (Accessed 10 September 2019)

De Jager et al. 2000

De Jager R, Cheverton P, Tamanoi K, Coyle J, Ducharme M, Sakamoto N, et al. DX-8951f: summary of phase I clinical trials. Ann N Y Acad Sci. 2000;922:260-73.

DS-6157a Investigator's Brochure

DS-6157a Investigator's Brochure version 1.0, Daiichi Sankyo, Inc. 23 August 2019

Eisenhauer et al. 2009

Eisenhauer EA, Therasse P, Bogaerts J, Schwartz LH, Sargent D, Ford R, et al. New response evaluation criteria in solid tumours: revised RECIST guideline (Version 1.1). Eur J Cancer. 2009;45(2):228-47.

Hase et al. 2008

Hase M, Yokomizo T, Shimizu T, Nakamura M. Characterization of an orphan G protein-coupled receptor, GPR20, that constitutively activates Gi proteins. J Biol Chem. 2008;283(19):12747-55.

Heinrich et al. 2018

Heinrich M, von Mehren M, Jones RL, Bauer S, Kang Y-K, Schöffski P, et al. Avapritinib is highly active and well-tolerated in patients with advanced GIST driven by a diverse variety of oncogenic mutations in KIT and PDGFRa. Presented at Connective Tissue Oncology Society 2018 Annual Meeting (15 November 2018; Abstract 3027631).

Heinrich et al. 2019

Heinrich M, Jones RL, von Mehren M, Bauer S, Kang Y-K, Schöffski P, et al. Clinical activity of avapritinib in ≥4th line (4L+) and PDGFRa exon 18 gastrointestinal stromal tumors (GIST). Presented at 2019 American Society of Clinical Oncology Annual Meeting (31 May- 4 June 2019; Poster 11022).

Iida et al. 2021

Iida K, Ahmed AHA, Nagatsuma AK, Shibutani T, Yasuda S, Kitamura M, et al. Identification and therapeutic targeting of GPR20, selectively expressed in gastrointestinal stromal tumors, with DS-6157a, a first-in-class antibody-drug conjugate. Cancer Discov. February 12 2021 DOI: 10.1158/2159-8290.CD-20-1434.

Irinotecan package inserts. 2016

CAMPTOSAR® (Irinotecan) Injection, intravenous infusion [package insert]. New York, USA: Pfizer Inc.; 2016

CAMPTO® (Irinotecan) 20 mg/ml, concentrate for solution for injection [SmPC]. UK: Pfizer Limited.; 2016.

TOPOTECIN® (Irinotecan) intravenous drip infusion [package insert]. JP: DaiichiSankyo Company Ltd.; 2016.

Kubo et al. 2013

Kubo K, Azuma A, Kanazawa M, Kameda H, Kusumoto M, Genma A, et al. Consensus statement for the diagnosis and treatment of drug-induced lung injuries. Respir Investig. 2013;51(4):260-77.

Neuenschwander et al. 2008

Neuenschwander B, Branson M, Gsponer, T. Critical aspects of the Bayesian approach to phase I cancer trials. Stat Med. 2008;27(13):2420-39.

Pommier Y. 2006

Pommier Y. Topoisomerase I inhibitors: Camptothecins and beyond. Nat Rev Cancer. 2006;6(10):789-802.

Ran et al. 2018

Ran L, Chen Y, Sher J, Wong EWP, Murphy D, Zhang JQ, et al. FOXF1 defines the core-regulatory circuitry in gastrointestinal stromal tumor. Cancer Discov. 2018;8(2):234-51.

Rogatko et al. 2005

Rogatko A, Babb JS, Tighiouart M, Khuri FR, Hudes G. New paradigm in dose-finding trials: patient-specific dosing and beyond phase I. Clin Cancer Res. 2005;11(15):5342-6.

Topotecan package inserts. 2015

HYCAMTIN® (Topotecan) for injection [package insert]. New Jersey, USA: Novartis Pharmaceuticals Corporation; 2015.

HYCAMTIN® (Topotecan) 1mg and 4mg powder for concentrate for solution for injection [SmPC]. UK: Novartis Pharmaceuticals UK Ltd.; 2015.

16. APPENDICES

Appendix A: Eastern Cooperative Oncology Group (ECOG) Performance Status Criteria

ECOG Performance Status Scale	
Grade	**Descriptions**
0	Normal activity. Fully active, able to carry on all pre-disease performance without restriction.
1	Symptoms, but ambulatory. Restricted in physically strenuous activity, but ambulatory and able to carry out work of a light or sedentary nature (e.g., 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

Appendix B: Response Evaluation Criteria in Solid Tumors (RECIST) Version 1.1

Introduction

This appendix details the general implementation of RECIST Version 1.1 Guidelines (Eisenhauer et al. 2009) for the study with regard to Investigator assessment of tumor burden including protocol-specific requirements for this study.

Definition of measurable, non-measurable, target and non-target lesions

Only subjects with at least one measurable tumor lesion or malignant /lymph node that can be accurately assessed at baseline must be included in the study. At baseline, tumor lesions/lymph nodes will be categorized as measurable or non-measurable as follows:

Measurable:

Tumor lesions: To be considered measurable disease, tumor lesions must be accurately measured in at least one dimension (longest diameter in the plane of measurement is to be recorded) with a minimum size of:

- 10 mm by computed tomography CT (CT scan slice thickness/interval no greater than 5 mm).
- 10 mm caliper measurement by clinical exam (lesions which cannot be accurately measured with calipers must be recorded as non-measurable).
- 20 mm by chest X-ray.

Malignant lymph nodes: To be considered pathologically enlarged and measurable, a lymph node must be ≥15 mm in short axis when assessed by CT scan (CT scan slice thickness recommended to be no greater than 5 mm). At baseline and in follow-up, only the short axis will be measured and followed.

Non-measurable:

- All other lesions, including small lesions (longest diameter <10 mm or pathological lymph nodes with ≥10 to <15mm short axis at baseline).
- Truly non-measurable lesions include the following: leptomeningeal disease, ascites, pleural / pericardial effusion, inflammatory breast disease, lymphangitic involvement of skin or lung, and abdominal masses/abdominal organomegaly identified by physical examination that is not measurable by CT or MRI.
- Previously irradiated lesions or lesions subjected to other local-regional therapy. **Note:** These lesions may be considered measurable disease if there has been demonstrated progression, per Investigator assessment.

Special Consideration Regarding Lesion Measurability:

Bone lesions

- Bone scan, PET scan, or plain films are not considered adequate imaging techniques to measure bone lesions. However, these techniques can be used to confirm the presence or

disappearance of bone lesions.

- Lytic bone lesions or mixed lytic-blastic lesions, with identifiable soft tissue components, can be considered measurable if the soft tissue component meets the definition of measurability described above.
- Blastic bone lesions are considered non-measurable.

Cystic lesions

Cystic lesions thought to represent cystic metastases can be considered measurable lesions if they meet the criteria for measurability from a radiological point of view, but if non-cystic lesions are present in the same subject, these must be selected as target lesions.

Definition of Target and Non-Target Lesions

Target lesions:

A maximum of 5 measurable lesions (with a maximum of 2 lesions per organ), representative of all involved organs must be identified as target lesions at baseline. Pathological lymph nodes which are defined as measurable and may be identified as target lesions must meet the criterion of a short axis of ≥ 15 mm by CT scan. Target lesions must be selected on the basis of their size (longest diameter for non-nodal lesions or short axis for nodal lesions), but in addition must be those that lend themselves to reproducible repeated measurements. It may be the case that, on occasion, the largest lesion does not lend itself to reproducible measurement in which circumstance the next largest lesion, which can be measured reproducibly, must be selected.

A *sum of the diameters* (longest for non-nodal lesions, short axis for nodal lesions) for all target lesions will be calculated and reported as the baseline sum of diameters. If lymph nodes are selected as measurable lesions, only the short axis is added into the sum, even if the nodes regress to below 10 mm in the study. The baseline sum of diameters will be used as reference to further characterize any objective tumor response with regards to measurable disease.

Special cases:

- If a target lesion has completely disappeared, the longest diameter must be recorded as 0 mm.
- If a target lesion is believed to be present and is faintly seen but too small to measure, a default value of 5 mm must be assigned. If an accurate measure can be given, this must be recorded, even if it is below 5 mm.
- When nodal disease is included in the sum of target lesions and the nodes decrease to 'normal' size (<10 mm), they may still have a measurement reported on scans. This measurement must be recorded even though the nodes are normal in order to not to overstate progression if it be based on increase in size of the nodes.
- If a target lesion splits into two or more parts, then record the sum of the diameters of those parts. If two or more target lesions merge then the sum of the diameters of the combined lesion must be recorded for one of the lesions and 0 mm recorded for the other lesion(s).

Non-target lesions:

All other lesions (or sites of disease) including pathological lymph nodes (those with short axis ≥10mm but <15mm) must be identified as non-target lesions (NTLs) and should also be recorded at baseline. Nodes that have a short axis <10 mm are considered non-pathological and should not be recorded or followed. In addition, it is possible to record multiple NTLs involving the same organ as a single item on the case record form (e.g., 'multiple enlarged pelvic lymph nodes' or 'multiple liver metastases').

Methods of Assessment

The same method of assessment and the same technique should be used to characterize each identified and recorded lesion at baseline and during follow-up visits. All baseline evaluations should be performed as close as possible to the treatment start and never more than 4 weeks before the beginning of the treatment. Additionally, all images including CT and MRI may be submitted to a central imaging CRO for independent retrospective review.

CT, MRI: CT scanning with IV contrast is the best currently available and reproducible method to measure lesions selected for response assessment. This guideline has defined measurability of lesions on CT scan based on the assumption that CT slice thickness is 5 mm or less. When CT scans have slice thickness greater than 5 mm, the minimum size for a measurable lesion should be twice the slice thickness. If IV contrast cannot be administered (for example, in the situation of allergy to contrast), a non-contrast CT of the chest is still preferred over MRI or chest X-ray. MRI is also acceptable and can be used when CT is not feasible or is medically contra-indicated.

Clinical lesions: Clinical lesions will only be considered measurable when they are superficial and ≥ 10 mm diameter as assessed using calipers (e.g., skin nodules). For the case of skin lesions, documentation by color photography including a ruler to estimate the size of the lesion is suggested.

X-ray: Chest CT is preferred over chest X-ray, particularly when progression is an important endpoint, since CT is more sensitive than X-ray, particularly in identifying new lesions. However, lesions on chest X-ray may be considered measurable if they are clearly defined and surrounded by aerated lung.

Ultrasound: Ultrasound is not useful in assessment of lesion size and should not be used as a method of measurement. Ultrasound examination can, however, be used to identify the presence of new lesions. If new lesions are identified by ultrasound in the course of the study, confirmation by CT or MRI is advised.

Endoscopy, Laparoscopy, Tumor markers, Cytology, Histology: The utilization of these techniques alone will not be used for objective tumor response measurements.

FDG-PET: FDG-PET scans may be used as a method for identifying new lesions in the assessment of progression, according with the following algorithm: New lesions will be recorded where there is positive FDG uptake (defined as when an uptake greater than twice that of the surrounding tissue is observed) not present on baseline FDG-PET scan or in a location corresponding to a new lesion by CT/MRI at the same visit. If there is no baseline FDG-PET

scan available, and no evidence of new lesions by CT/MRI then follow-up CT/MRI assessments should be continued, scheduled as per protocol or clinical indicated, in order to confirm new lesions.

Tumor response evaluation

This section provides the definitions of the criteria used to determine objective tumor response.

Evaluation of target lesions:

Complete Response (CR)	Disappearance of all target lesions since baseline. Any pathological lymph nodes must have a reduction in short axis to <10 mm.
Partial Response (PR)	At least a 30% decrease in the sum of the diameters of target lesions, taking as reference the baseline sum of diameters.
Stable Disease (SD)	Neither sufficient shrinkage to qualify for PR nor sufficient increase to qualify for PD.
Progressive Disease (PD)	At least a 20% increase in the sum of diameters of target lesions, taking as reference the smallest sum on study or nadir (this includes the baseline sum if that is the smallest on study). In addition to the relative increase of 20%, the sum must also demonstrate an absolute increase of at least 5 mm.
Not Evaluable (NE)	Only relevant if any of the target lesions were not assessed or not evaluable. Note: If the sum of diameters of assessed lesions meets the progressive disease criteria, progressive disease overrides not evaluable as a target lesion response.

Evaluation of non-target lesions

Complete Response (CR)	Disappearance of all non-target lesions since baseline. All lymph nodes must be non-pathological in size (<10 mm short axis).
Non-CR/Non-PD	Persistence of one or more non-target lesion(s) and/or maintenance of tumor marker level above normal limits and no lesions considered to have unequivocal progression (PD).
Progression (PD)	Unequivocal progression of existing non-target lesions indicative of a substantial worsening in non-target disease. Unequivocal progression may be due to an important progression in one lesion only or in several lesions. In all cases the progression MUST be clinically significant for the physician to consider changing (or stopping) therapy.
Not Evaluable (NE)	Only relevant when one or some of the non-target lesions were not assessed and, in the Investigator's opinion, they are not able to provide an evaluable overall non-target lesion assessment at this visit. Note: For patients without target lesions at baseline, this is relevant if any of the non-target lesions were not assessed at this visit and the progression criteria have not been met.

To achieve 'unequivocal progression' on the basis of non-target lesions, there must be an overall level of substantial worsening in non-target disease such that, even in presence of SD, PR or CR in target lesions, the overall tumor burden has increased sufficiently to merit discontinuation of therapy. A modest 'increase' in the size of one or more non-target lesions is usually not sufficient to qualify for unequivocal progression status.

New lesions: The presence of one or more new lesions is assessed as disease progression. A lesion identified at a follow-up assessment in an anatomical location that was not scanned at baseline is considered a new lesion and will indicate disease progression. The finding of a new lesion should be unequivocal: i.e. not attributable to differences in scanning technique, change in imaging modality or findings thought to represent something other than tumor. If a new lesion is equivocal, for example because of its small size, the treatment and tumor assessments should be continued until the new lesion has been confirmed. If repeat scans confirm there is a new lesion, then the progression date should be declared using the date of the initial scan.

Evaluation of overall response

Target lesions	Non-Target lesions	New Lesions	Overall response
CR	CR	No	CR
CR	NA	No	CR
NA	CR	No	CR
CR	Non-CR/Non-PD	No	PR
CR	NE	No	PR
PR	Non-PD or NE	No	PR
SD	Non-PD or NE	No	SD
NA	Non-CR/Non-PD	No	Non-CR/Non-PD
NE	Non-PD or NE	No	NE
NA	NE	No	NE
PD	Any	Yes or No	PD
Any	PD	Yes or No	PD
Any	Any	Yes	PD

CR = complete response, PR = partial response, SD = stable disease, PD = progressive disease, NE = not evaluable, NA = not applicable (relevant when no target lesions/non-target lesions at baseline).

Special notes on response evaluation

Missing assessments and non-evaluable designation: When no imaging/measurement is done at all at a particular time point, the patient is not evaluable (NE) at that time point. If only a subset of lesion measurements are made at an assessment, usually the case is also considered NE at that time point, unless a convincing argument can be made that the contribution of the individual

missing lesion(s) would not change the assigned time point response. This would be most likely to happen in the case of PD.

Symptomatic progression: Patients with a global deterioration of health status requiring discontinuation of treatment without objective evidence of PD at that time should be reported as "symptomatic deterioration." Every effort should be made to document objective progression even after discontinuation of treatment. Symptomatic deterioration is not a descriptor of an objective response: it is a reason for stopping study treatment.

Confirmation of response: Confirmation of response (by repeat scans after 4 weeks or as specified in the protocol) is required.

Appendix C: Guidelines for Women of Childbearing Potential and Fertile Male Patients

Acceptable Contraception Methods:

Women of childbearing potential, defined as all women physiologically capable of becoming pregnant, must use highly-effective contraception during the study and until 7 months following the last dose of DS-6157a. For male patients with a pregnant or non-pregnant partner of child-bearing potential, highly-effective contraception measures are required for at least 4 months following the last dose of DS-6157a.

Highly effective contraception is defined as either:

True Abstinence	When this is in line with the preferred and usual lifestyle of the patient during the entire period of risk associated with the study drug. Periodic abstinence (e.g., calendar, ovulation, symptothermal, post-ovulation methods) and withdrawal are not acceptable methods of contraception.
Sterilization	When a woman of childbearing potential has had surgical bilateral oophorectomy (with or without hysterectomy) or tubal ligation at least six weeks prior to study entry. In case of oophorectomy alone, only when the reproductive status of the woman has been confirmed by follow-up hormone level assessment.
Female condom	Barrier methods of contraception: condom or an occlusive cap (diaphragm or cervical/vault caps) with spermicidal* foam/gel/film/cream/vaginal suppository. *Spermicidal agents are not approved in Japan.
Male Partner Sterilization	With the appropriate post-vasectomy documentation of the absence of sperm in the ejaculate.
Intrauterine device	Placement of an intrauterine device (IUD) or intrauterine system (IUS)
Hormonal contraception	Combined (estrogen and progestogen containing) hormonal contraception associated with inhibition of ovulation, which may be oral, intravaginal, or transdermal. Progestogen-only hormonal contraception associated with inhibition of ovulation, which may be oral, injectable, or implantable.

Hormonal contraception may be susceptible to interaction with the study drug or other drugs, which may reduce the efficacy of the contraception method.

If a contraceptive method is restricted by local regulations/guidelines, then it does not qualify as an acceptable highly effective method of contraception for patients participating at sites in the relevant country/region.

Patients should promptly notify the Investigator if they, or for male patients their partner, become pregnant during this study or within 7 months after the last dose of DS-6157a. If a

female patient becomes pregnant during the treatment period, she must discontinue DS-6157a immediately. Pregnancy in a female patient or a male patient's partner must be reported as outlined in Section 11.9.

The following are acceptable forms of barrier contraception:

- Latex condom, diaphragm or cervical/vault cap when used with spermicidal foam/gel/film/cream/suppository

Unacceptable Contraception Methods: for women of childbearing potential include:

- Periodic abstinence
- Natural family planning (rhythm method) or breastfeeding
- Fertility awareness
- Withdrawal
- Triphasic combined oral contraceptives
- All progesterone only pills, except Cerazette™
- All barrier methods, if intended to be used alone
- Non-copper containing intrauterine devices

Women Not of Childbearing Potential are Defined as Follows:

- Women are considered post-menopausal and not of childbearing potential if they have had 12 months of natural (spontaneous) amenorrhea with an appropriate clinical profile (i.e., age appropriate, history of vasomotor symptoms).
- Women <45 years of age a high follicle stimulating hormone (FSH) level (>40 mIU/mL) in the postmenopausal range, with no other associated medical reason, may be used to confirm a post-menopausal state in women not using hormonal contraception or hormonal replacement therapy. In the absence of 12 months of amenorrhea, a single FSH measurement is insufficient.
- Women who are permanently sterilized at least 6 weeks before screening (e.g., bilateral tubal ligation/occlusion, hysterectomy, bilateral salpingectomy, bilateral oophorectomy).
- Women who are >45 years-of-age, not using hormone-replacement therapy and who have experienced total cessation of menses for at least 1 year OR who have a FSH value >40 mIU/mL and an estradiol value <40 pg/mL (140 pmol/L).
- Women who are >45 years-of-age, using hormone-replacement therapy and who have experienced total cessation of menses for at least 1 year OR who have had documented evidence of menopause based on FSH >40 mIU/mL and estradiol <40 pg/mL prior to initiation of hormone-replacement therapy.
- Women who had have a congenital or acquired condition that prevents childbearing.

Appendix D: New York Heart Association Classification of Cardiac Disease

The following table presents the New York Heart Association classification of cardiac disease.

Class	Functional Capacity	Objective Assessment
I	Patients with cardiac disease but without resulting limitations of physical activity. Ordinary physical activity does not cause undue fatigue, palpitation, dyspnea, or anginal pain.	No objective evidence of cardiovascular disease.
II	Patients with cardiac disease resulting in slight limitation of physical activity. They are comfortable at rest. Ordinary physical activity results in fatigue, palpitation, dyspnea, or anginal pain.	Objective evidence of minimal cardiovascular disease.
III	Patients with cardiac disease resulting in marked limitation of physical activity. They are comfortable at rest. Less than ordinary activity causes fatigue, palpitation, dyspnea, or anginal pain.	Objective evidence of moderately severe cardiovascular disease.
IV	Patients with cardiac disease resulting in inability to carry on any physical activity without discomfort. Symptoms of heart failure or the anginal syndrome may be present even at rest. If any physical activity is undertaken, discomfort is increased.	Objective evidence of severe cardiovascular disease.

Source: The Criteria Committee of New York Heart Association. Nomenclature and Criteria for Diagnosis of Diseases of the Heart and Great Vessels. 9th Ed. Boston, MA: Little, Brown & Co; 1994:253-256.

Appendix E: Drugs That Prolong QT Interval and/or Induce Torsades De Pointes

Drugs with known or possible risk of QT prolongation and/or Torsades de pointes should be avoided for all patients from the start of study treatment through end of Cycle 3. Please note that the list below was derived from www.crediblemeds.org on 15 March 2019 and serves only as guidance. Since CredibleMeds® constantly assesses new drug information and updates its lists, sites should go directly to the crediblemeds.org website in real-time for reference.

Drug	Drug	Drug
Abarelix	Flupentixol	Prothipendyl
Aclarubicin	Gatifloxacin	Quinidine
Alfuzosin	Gemifloxacin	Ribociclib
Amiodarone	Glasdegib	Rilpivirine
Anagrelide	Granisetron	Risperidone
Apalutamide	Grepafloxacin	Romidepsin
Apomorphine	Halofantrine	Roxithromycin
Aripiprazole	Haloperidol	Saquinavir
Arsenic trioxide	Hydrocodone - ER	Sertindole
Artemether + lumefantrine	Hydroquinidine dihydroquinidine	Sevoflurane
Artenimol + piperaquine	Ibogaine	Sorafenib
Asenapine	Ibutilide	Sotalol
Astemizole	Iloperidone	Sparfloxacin
Atomoxetine	Imipramine (melipramin)	Sulpiride
Azithromycin	Inotuzumab ozogamicin	Sultopride
Bedaquiline	Isradipine	Sunitinib
Bendamustine	Ketanserin	Tacrolimus
Benperidol	Lacidipine	Tamoxifen
Bepridil	Lapatinib	Telavancin
Betrixaban	Lenvatinib	Telithromycin
Bortezomib	Leuprolide	Terfenadine
Bosutinib	Levofloxacin	Terlipressin
Buprenorphine	Levomepromazine (methotrimeprazine)	Terodiline
Cabozantinib	Levomethadyl acetate	Tetrabenazine
Capecitabine	Levosulpiride	Thioridazine
Ceritinib	Lithium	Tiapride
Chloroquine	Lofexidine	Tipiracil and Trifluridine
Chlorpromazine	Lopinavir and ritonavir	Tizanidine
Cilostazol	Maprotiline	Toremifene
Ciprofloxacin	Melperone	Tramadol

Drug	Drug	Drug
Cisapride	Memantine	Trimipramine
Citalopram	Mesoridazine	Tropisetron
Clarithromycin	Methadone	Valbenazine
Clofazimine	Midostaurin	Vandetanib
Clomipramine	Mifepristone	Vardenafil
Clotiapine	Mirabegron	Vemurafenib
Clozapine	Mirtazapine	Venlafaxine
Cocaine	Moexipril/HCTZ	Vorinostat
Crizotinib	Moxifloxacin	Zotepine
Cyamemazine (cyamepromazine)	Necitumumab	Zuclopenthixol, Zuclopentixol
Dabrafenib	Nicardipine	
Dasatinib	Nilotinib	
Degarelix	Norfloxacin	
Delamanid	Nortriptyline	
Desipramine	Nusinersen	
Deutetrabenazine	Ofloxacin	
Dexmedetomidine	Ondansetron	
Dextromethorphan/Quinidine	Osimertinib	
Disopyramide	Oxaliplatin	
Dofetilide	Oxytocin	
Dolasetron	Paliperidone	
Domperidone	Palonosetron	
Donepezil	Panobinostat	
Dronedarone	Papaverine HCl (intra-coronary)	
Droperidol	Pasireotide	
Efavirenz	Pazopanib	
Eliglustat	Pentamidine	
Encorafenib	Perflutren lipid microspheres	
Epirubicin	Perphenazine	
Eribulin mesylate	Pilsicainide	
Erythromycin	Pimavanserin	
Escitalopram	Pimozide	
Ezogabine (retigabine)	Pipamperone	
Felbamate	Primaquine phosphate	
Fingolimod	Probucol	
Flecainide	Procainamide	

Drug	Drug	Drug
Fluconazole	Promethazine	
Fluorouracil (5-FU)	Propofol	

Appendix F: Washout Period for Prior TKIs

Drug	Half-life (hours)	Washout Period (Days)[1]
Imatinib[a]	18 hours (imatinib) and 40 hours (active metabolite)	5 days
Sunitinib[b]	40 to 60 hours (sunitinib) and 80 to 110 hours (active metabolite)	14 days
Regorafenib[c]	28 hours (regorafenib) and 51 hours (active metabolite)	11 days
Avapritinib[d]	24 hours	5 days
Nilotinib[e]	17 hours	4 days
Famitinib malate[f]	34 hours and 48 hours (major metabolite)	10 days
Cabozantinib[g]	99 hours	21 days
Masitinib[h]	23 hours	5 days
Crenolanib[i]	8 hours	2 days
Apatanib[j]	9 hours	2 days
Pazopanib[k]	31 hours	7 days
Ripretinib[l]	Not yet reported	10 days (based on conference presentations of PK data)

[1]Note: Washout period is at least 5 times $t_{1/2}$ of the prior TKI. The selected washout period also ensures that metabolite systemic exposures are less than 5% of parent systemic exposures at the end of the washout period.

a. US Prescribing information: Gleevec (imatinib mesylate)
b. US Prescribing information: Sutent (sunitinib malate)
c. US Prescribing information: Stivarga (regorafenib)
d. Heinrich MC, et al. *J Clin Oncol.* 35, no. 15_suppl (May 20, 2017) 11011
e. US Prescribing information: Tasigna (nilotinib)
f. Zhou A, et al. *Canc Chemother Pharmacol.* 2013 Nov;72(5):1043-53
g. US Prescribing information: Cabometyx (cabozantinib)
h. Rezai K, et al. *Canc Res.* 2014;74(19 Suppl):Abstract # 4630.
i. Wang ES, et al. *Blood* 2016; 128:1071
j. Roviello G, et al. *Canc Lett.* 372 (2016) 187–91
k. US Prescribing information: Votrient (pazopanib)
l. Janku F et al. 2017. *J Clin Oncol.* 35, no. 15_suppl (May 20, 2017) 2515

Appendix G: Operating Characteristics of Bayesian Logistic Regression Model (BLRM) with Escalation with overdose control (EWOC)

1. INTRODUCTION

This document provides the technical details of the methodology that will be used in the dose escalation part of Study DS6157-A-U101.

2. STATISTICAL MODELS AND DOSE RECOMMENDATION

In this study, the Bayesian logistic regression model (BLRM) along with Escalation With Overdose Control (EWOC) principle[1,2] will be applied in dose escalation part to help guide the determination of the maximum tolerated dose (MTD) or the recommended dose for expansion (RDE) of DS-6157.

2.1 Bayesian Logistic Regression Model

In this study, a 2-parameter Bayesian logistic regression model (BLRM), as defined below, will be used:

$$\text{logit}(\pi(d_i)) = \ln(\alpha) + \beta \ln(d_i/d^*), \qquad \alpha>0, \beta>0$$

where $\text{logit}(\pi(d_i)) = \ln(\pi(d_i)/(1-\pi(d_i)))$, $\pi(d_i)$ is the dose limiting toxicity (DLT) rate at i^{th} dose level d_i. Doses are rescaled as d_i/d^* with the reference dose $d^* = 9.6$ mg/kg. As a consequence, $\ln(\alpha)$ is equal to $\text{logit}(\pi(d^*))$ at dose d^*. Note that for a dose equal to zero, the probability of toxicity is zero.

2.2 Prior Specification for BLRM parameters

The Bayesian approach requires the specification of a prior distribution for the BLRM parameters. A minimally-informative bivariate normal prior for the model parameters (α, β) is obtained as follows:

- Based on extrapolation of nonclinical toxicology studies in monkeys, the MTD is projected to be greater than 9.6 mg/kg in humans (the highest nonseverely toxic dose [HNSTD] of monkeys is 30 mg/kg and assuming humans and monkeys are equally sensitive, the MTD is projected to be 9.7 mg/kg in humans). The median prior probabilities of DLT are set to be approximately 8.0% and 24.5% at 1.6 mg/kg (projected starting dose for dose escalation) and at 9.6 mg/kg, respectively.
- For the remaining doses, the prior medians of probability of DLT are assumed linear in log-dose on the logit-scale.
- Set $\text{Prob}(\pi(d_1) \leq 0.25) = 0.90$ and $\text{Prob}(\pi(d^*) \leq 0.4) = 0.70$, which yields wide prior credible intervals (obtained from minimally informative Beta distributions[1]), the optimal parameters of the bivariate normal distribution can be obtained using EAST (version 6.5, Cytel Inc.) with BLRM module as follows:

Table 2.1: Prior parameters for bivariate normal distribution of model parameters

Parameters	Means	Standard deviations	Correlation
$\ln(\alpha)$, $\ln(\beta)$	(-1.125, -0.308)	(1.373, 0.778)	0

Table 2.2: Prior probabilities of under, targeted and over dosing (simulated from the prior in Table 2.1)

Dose (mg/kg)	Prior probabilities of DLT rate in interval			Mean	SD	Percentile		
	0-0.16	0.16-0.33	0.33-1.0			2.5%	50.0%	97.5%
1.6	73.2%	14.5%	12.3%	13.0%	16.4%	0.0%	6.2%	58.7%
3.2	63.0%	19.9%	17.1%	17.5%	18.7%	0.2%	10.4%	67.1%
4.8	54.9%	21.6%	23.5%	21.1%	20.2%	0.6%	14.0%	73.9%
6.4	47.7%	24.1%	28.2%	24.4%	21.3%	1.1%	17.3%	77.3%
8.0	40.3%	28.0%	31.7%	27.3%	22.2%	1.5%	20.3%	81.3%
9.6	34.7%	27.7%	37.6%	30.1%	23.0%	2.1%	23.9%	84.0%

2.3 Dose Escalation Following EWOC Principle

Dose recommendation for the next cohort will be based on summaries of the posterior probability of DLT across the postulated dose range. After patients of each cohort complete DLT evaluation during Cycle 1, the joint posterior distribution of the BLRM parameters will be generated according to Bayes' theorem based on the likelihood function of the accumulated DLT data from Cycle 1 and the prior distribution.

Posterior probabilities of DLT rate at different dose levels will then be obtained from updated BLRM, and summarized for DLT rate in 4 different ranges:

- [0%, 16%] as DLT rate interval for 'under-dosing'
- (16%, 33%] as 'target' DLT rate interval
- (33%, 60%] as DLT rate interval for 'excessive toxicity'
- (60%, 100%] as DLT rate interval for 'unacceptable toxicity'

The dose level recommended for next dose cohort will be based on these probabilities according to the EWOC principle. The EWOC principle requires that the recommended dose for the next dose cohort is the one with:

- The highest posterior probability of the DLT rate in the target DLT rate range of (16%, 33%]
- Less than 25% of probability for DLT rate >33% (probability for excessive or unacceptable toxicity).

2.4 Dose Increment During Dose Escalation with EWOC

- The dose level increment must not be greater than 100% even if the model suggested a higher dose than 100% for next cohort

2.5 Stopping Rule for MTD Determination

For MTD (or RDE if MTD is not observed) determination, the following stopping rules will be implemented for the dose escalation phase:

- At least 6 evaluable patients at MTD/RDE level with at least 15 evaluable patients in total enrolled in the dose-escalation phase, or
- At least 9 evaluable patients have been enrolled at a dose level which is the model's recommendation for the next dose cohort and for which the posterior probability of targeted DLT rate interval is at least 50%, or
- DLT assessment with at least 3 evaluable patients at the maximum tolerated dose level with 95% credible interval for posterior probability of DLT rate within (5%, 33%), or
- Initial dose level d_1 is too toxic

3. HYPOTHETICAL SCENARIOS AND MODEL PERFORMANCE

3.1 Scenarios and Dose-escalation Recommendations

The BLRM following the EWOC principle, together with dose increment rules and stopping rules as specified previously should make reasonable dose escalation recommendations during a dose escalation process based on the DLT outcome data. Table 3.1 shows the recommended next dose in some scenarios for the first 4 dose levels using the prior parameters specified in Table 2.1. These scenarios assume that the starting BLRM dose is 1.6 mg/kg and each cohort has at least 3 evaluable patients for the BLRM following the EWOC principle to estimate next highest admissible dose level for next cohort. These simulations were conducted using EAST.

Table 3.1: Dose-escalation recommendations for various scenarios

Scenario ID	Assessed doses (mg/kg)	No. DLT/No. patients	Dose (mg/kg) for next cohort recommended by BLRM following EWOC
1.1	1.6	0/3	3.2
1.2	1.6, 3.2	0/3, 0/3	6.4
1.3	1.6, 3.2, 6.4	0/3, 0/3, 0/3	9.6
1.4	1.6, 3.2, 6.4	0/3, 0/3, 1/3	8.0
1.5	1.6, 3.2, 6.4, 8.0	0/3, 0/3, 1/3, 0/3	9.6
1.6	1.6, 3.2, 6.4, 8.0	0/3, 0/3, 1/3, 1/3	6.4
1.7	1.6, 3.2, 6.4, 8.0	0/3, 0/3, 1/3, 2/3	4.8
1.8	1.6, 3.2, 6.4	0/3, 0/3, 2/3	4.8
1.9	1.6, 3.2, 6.4, 4.8	0/3, 0/3, 2/3, 0/3	6.4
1.10	1.6, 3.2, 6.4, 4.8	0/3, 0/3, 2/3, 1/3	4.8
1.11	1.6, 3.2, 6.4, 4.8	0/3, 0/3, 2/3, 2/3	1.6
1.12	1.6, 3.2, 6.4	0/3, 0/3, 3/3	3.2
1.13	1.6, 3.2	0/3, 1/3	4.8
1.14	1.6, 3.2, 4.8	0/3, 1/3, 0/3	8.0
1.15	1.6, 3.2, 4.8, 8.0	0/3, 1/3, 0/3, 0/3	9.6
1.16	1.6, 3.2, 4.8, 8.0	0/3, 1/3, 0/3, 1/3	6.4
1.17	1.6, 3.2, 4.8, 8.0	0/3, 1/3, 0/3, 2/3	4.8
1.18	1.6, 3.2, 4.8, 8.0	0/3, 1/3, 0/3, 3/3	3.2
1.19	1.6, 3.2, 4.8	0/3, 1/3, 1/3	4.8
1.20	1.6, 3.2, 4.8	0/3, 1/3, 2/3	1.6
1.21	1.6, 3.2, 4.8	0/3, 1/3, 3/3	< 1.6
1.22	1.6, 3.2	0/3, 2/3	1.6
1.23	1.6, 3.2, 1.6	0/3, 2/3, 0/3	3.2
1.24	1.6, 3.2, 1.6	0/3, 2/3, 1/3	1.6
1.25	1.6, 3.2	0/3, 3/3	<1.6
2.1	1.6	1/3	1.6
2.2	1.6, 1.6	1/3, 0/3	3.2
2.3	1.6, 1.6, 3.2	1/3, 0/3, 0/3	6.4
2.4	1.6, 1.6, 3.2	1/3, 0/3, 1/3	3.2
2.5	1.6, 1.6, 3.2	1/3, 0/3, 2/3	1.6
2.6	1.6, 1.6	1/3, 1/3	<1.6
3.1	1.6	2/3	<1.6

Output highlights:

- Scenarios 1.x show different dose escalation scenarios of observing 0/3 DLT at initial dose level. The BLRM will recommend escalating to next dose level.
- Scenarios 2.x show different dose escalation scenarios of observing 1/3 DLT at initial dose level. The BLRM will recommend staying at the same dose level.

- Scenarios 1.21, 1.25, 2.6, and 3.1 are some scenarios which the BLRM will recommend to stop the trial and determine the initial dose is too toxic.

The above showed that the BLRM following the EWOC principle gives reasonable recommendations to guide dose escalation process under various situations.

As indicated in the protocol, the selection of the dose for next cohort of patients by clinical team is not solely based on BLRM recommendation, but on a clinical synthesis of all the relevant information on safety profile (both DLT and non-DLT information), PK/PD, and the BLRM recommendations.

3.2 Operating Characteristics of the BLRM

To investigate the operating characteristics of the BLRM following the EWOC principle, the probability that each does is selected as MTD and the average number of patients allocated to each dose level were assessed via simulations. Four scenarios for the dose-DLT relationship were considered: 1) the scenario based on the assumptions used to determine prior, 2) all doses are safe and the highest dose has a true DLT rate of 18.0%, 3) toxicity increase rapidly with dose escalation and true MTD is between 4.8 and 6.4 mg/kg; 4) all doses show excessive or unacceptable toxicity (i.e. DLT rate > 0.33). Table 3.2 shows the detailed assumption for each scenario.

Table 3.2: Assumptions for dose-DLT relationship

Scenario ID	True DLT rate in each dose (mg/kg)					
	1.6	3.2	4.8	6.4	8.0	9.6
1	8.0%	12.6%	16.3%	19.4%	22.1%	24.5%
2	1.0%	4.0%	6.0%	10.0%	14.0%	18.0%
3	1.0%	6.0%	21.0%	39.0%	54.0%	66.0%
4	39.0%	49.0%	60.0%	67.0%	71.0%	74.0%

For each simulation, the following settings and assumptions were applied. These simulations were conducted using EAST (version 6.4).

- The sample size for each cohort: at least 3
- The maximum sample size in total: 39
- The dose with the highest posterior probability for the target toxicity among the doses with less than 25% of probability for the excessive or unacceptable toxicity was selected as the next dose level
- The doses were selected from provisional dose (1.6, 3.2, 4.8, 6.4, 8.0, and 9.6 mg/kg) and dose skip was allowed as long as dose increment does not exceed 100%
- The stopping rules as specified in Section 2.5 were applied.

Table 3.3 shows the average probability of selecting each dose as the MTD and the average sample size over the simulations for each scenario.

Table 3.3: Simulation results for each scenario

	Dose (mg/kg)	< 1.6 *	1.6	3.2	4.8	6.4	8.0	9.6	Total
Scenario 1	True DLT rate	—	8.0%	12.6%	16.3%	19.4%	22.1%	24.5%	—
	Selected as MTD	6.5%	2.2%	7.6%	10.6%	16.2%	10.3%	46.6%	—
	Average # of patients	—	3.9	3.5	1.8	3.2	2.0	3.4	17.8
	Average # of patients with DLTs	—	0.31	0.43	0.29	0.61	0.45	0.84	2.94
Scenario 2	True DLT rate	—	1.0%	4.0%	6.0%	10.0%	14.0%	18.0%	—
	Selected as MTD	0.0%	0.0%	0.4%	1.4%	6.0%	8.2%	84.0%	—
	Average # of patients	—	3.1	3.1	0.6	3.2	1.7	5.4	17.1
	Average # of patients with DLTs	—	0.03	0.12	0.03	0.32	0.23	0.98	1.72
Scenario 3	True DLT rate	—	1.0%	6.0%	21.0%	39.0%	54.0%	66.0%	—
	Selected as MTD	0.2%	0.6%	20.4%	42.5%	31.2%	2.7%	2.4%	—
	Average # of patients	—	3.3	4.4	4.1	4.3	2.1	1.0	19.2
	Average # of patients with DLTs	—	0.03	0.26	0.86	1.67	1.14	0.66	4.63
Scenario 4	True DLT rate	—	39.0%	49.0%	60.0%	67.0%	71.0%	74.0%	—
	Selected as MTD	86.9%	8.9%	3.7%	0.5%	0.1%	0.0%	0.0%	—
	Average # of patients	—	5.3	1.4	0.4	0.2	0.0	0.0	7.3
	Average # of patients with DLTs	—	2.04	0.70	0.25	0.10	0.03	0.01	3.14

*During simulation, the initial dose (1.6 mg/kg) is considered too toxic.

The above showed that the BLRM with EWOC can give reasonable recommendations to guide dose escalation process under various situations.

4. References

1. Neuenschwander, B., Branson, M. and Gsponer, T. (2008). Critical aspects of the Bayesian approach to phase I cancer trials. Statistics in Medicine, 27: 2420–2439.
2. Babb, J., Rogatko, A., Zacks, S. (1998). Cancer phase I clinical trials: efficient dose escalation with overdose control. Stat Med; 17: 1103-1011

Appendix H: Instructions Related to COVID-19

Due to the potential impact of coronavirus disease 2019 (COVID-19, due to severe acute respiratory syndrome coronavirus 2 [SARS CoV-2]), on patient safety, the Sponsor recommends the following dose modification and management plan for patients with confirmed or suspected COVID-19 while being treated with DS-6157a. Dose modifications will be based on the worst CTCAE grade. **Use CTCAE version 5.0 general grading criteria to evaluate COVID-19.** All dose modifications (discontinuation, interruptions or reductions) must be recorded on the AE and drug administration eCRFs.

Dose modification criteria for suspected or confirmed COVID-19

If COVID-19 infection is suspected, delay DS-6157a and rule out COVID-19 per local guidance.

- If COVID-19 is ruled out, follow dose modification and management guidance as outlined in Table 2.
    - If COVID-19 is confirmed or is still suspected after evaluation follow dose modification as outlined in Table 4 below and manage COVID-19 per local guidance until recovery of COVID-19. COVID-19 recovery is defined as no signs/symptoms of COVID-19, at least 1 negative real-time reverse transcription polymerase chain reaction (RT-PCR) test result, and nearly or completely resolved chest CT findings.
        - [If PCR testing is not available at the site, to be considered recovered from COVID-19, the patient must not have any sign/symptoms for at least 2 weeks, in addition to meeting the requirement for chest CT imaging]

Table 4 COVID-19 Dose modification criteria

COVID-19 Worst Toxicity NCI-CTCAE Version 5.0 Grade (unless otherwise specified)	Schedule Modification for DS-6157a
Grade 1	Resume study drug at the same dose[a]
Grade 2	Resume study drug at the same dose if chest CT findings are completely resolved[a] Reduce by 1 dose level if chest CT findings are nearly resolved
Grade 3	Reduce by 1 dose level if chest CT findings are completely resolved[a] Discontinue study drug if chest CT findings are **not** completely resolved
Grade 4	Discontinue study drug

COVID-19 = coronavirus 2019; CT = computed tomography

[a] Closely monitor signs/symptoms after resuming DS-6157a, initially with a phone call every 3 days for the first week, and then with a weekly phone call thereafter, for a total of 6 weeks.

In addition to the recommendations outlined in Table 4, Investigators may consider dose modifications of the study drug according to the patient's condition and after discussion with the study Medical Monitor or designee.

If an event is suspected to be drug-related ILD/pneumonitis, manage per protocol ILD/pneumonitis management guideline (Table 2).

Prior and Concomitant Medications - Prohibited Therapies/Products

- Chloroquine or hydroxychloroquine;
  - Concomitant treatment is not allowed during the study treatment (Section 5.3.2).
  - If treatment is absolutely required for COVID-19 DS-6157a must be interrupted.
  - If administered, then a washout period of more than 14 days is required before resumption of DS-6157a.

PK Assessment(s) if Chloroquine or Hydroxychloroquine is Administered

Additional PK serum samples should be collected if chloroquine or hydroxychloroquine is administered for COVID-19 infection, at the time points specified in the Assessment Schedule if feasible. If possible, these PK samples should always be collected.

The chloroquine or hydroxychloroquine administration time and the exact time of blood sample collection for PK analysis must be recorded on the eCRF.

COVID-19 Assessment(s)

All confirmed or suspected COVID-19 infection events must be recorded in the eCRF. If a patient presents to the clinic with symptoms suggestive of COVID-19, but the real-time RT-PCR test is not available at the site (the participant must not have any signs or symptoms of COVID-19 infection for at least 2 weeks and nearly or completely resolved chest CT findings), a sample kit will be provided for sample collection to be tested at a central laboratory). The results will be provided to the site from the central laboratory.

Serum samples will be used for COVID-19 testing from each patient who provides consent. Samples will be collected prior to the study drug infusion at the time points specified in the Assessment Schedule, shipped to a central laboratory, and stored there until the tests become available.

If patients consent, the remaining serum samples will also be stored for future analysis.

Sample collection, preparation, handling, and storage instructions are provided in the Study Laboratory Manual.

Statistical Analysis - Assessment of the Impact of COVID-19

If deemed appropriate, analyses will be performed to explore the impact of COVID-19 infection on the safety, efficacy, and any other endpoints, as appropriate, reported for the study.

As a result of the impact of COVID-19 on study conduct, adjustments to the statistical analysis and interpretation will be made, if required. These will be described in the statistical analysis plan.