STATISTICAL ANALYSIS PLAN

Trial Sponsor:	Symphogen
Protocol Number:	Sym023-01
IND Number:	137066
EUDRACT Number:	N/A
Investigational Drug:	Sym023
Indication:	Advanced Solid Tumors or Lymphomas
Drug Number:	N/A
Dosage Form/Strength:	Liquid (IV) – 0.03 mg/kg, 0.1 mg/kg, 0.3 mg/kg, 1.0 mg/kg, 3.0 mg/kg, 10.0 mg/kg, 20 mg/kg

Protocol Title:

A Phase 1, Open-Label, Multicenter Trial Investigating the Safety, Tolerability, and Preliminary Antineoplastic Activity of Sym023 (Anti-TIM-3) in Patients with Advanced Solid Tumor Malignancies or Lymphomas

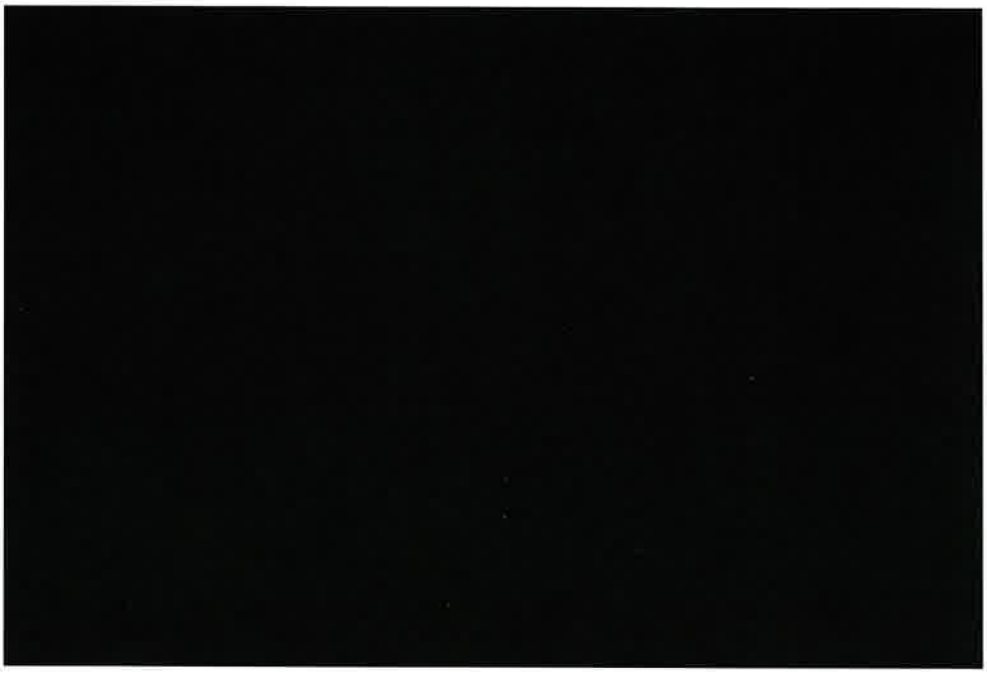
First Sign-off Date:	08May2019
Final Sign-off Date:	26Jun2020

FIRST SIGN-OFF SIGNATURES

Study Biostatistician:

Peer Review Biostatistician:

Approved by:



CHANGE LOG FOR CHANGES MADE AFTER THE INITIAL APPROVAL

Revision Date**	Section(s) Modified	Brief Description of Revision(s) or Reason(s) for Revision	Modifications Reviewed and Approved by*
			Sponsor
08May2019	N/A	Original document creation	[redacted]
26Jun2020	1	Updated protocol CRF versions and dates	
26Jun2020	6.1, 7.4	Added BMI to baseline characteristics	
26Jun2020	6.2.1, 6.3.1	Clarification added to visit windows	
26Jun2020	6.2.4	Details added regarding change from CTCAE v4.03 to CTCAE v5.0	
26Jun2020	6.2.4	Adverse Events incidence counting rules clarified	
26Jun2020	7.5.3	List of AE summaries updated to remove reflect CTCAE v5.0 and add summary by relationship to study treatment and non-serious events with incidence rate of at least 5%	
26Jun2020	7.5.4	Removal of shift tables by visit and box plots	
26Jun2020	7.6.1	Removal of summary of tumor markers	
26Jun2020	7.6.2	Removal of waterfall plot at end of Cycle 2	
26Jun2020	7.7	Clarification of descriptive statistics for PK analysis; removal of geometric mean plots	
26Jun2020	7.8	Removal of three ADA summaries and clarification about plot	
26Jun2020	12	Grading details updated from CTCAE v4.03 to CTCAE v5.0	

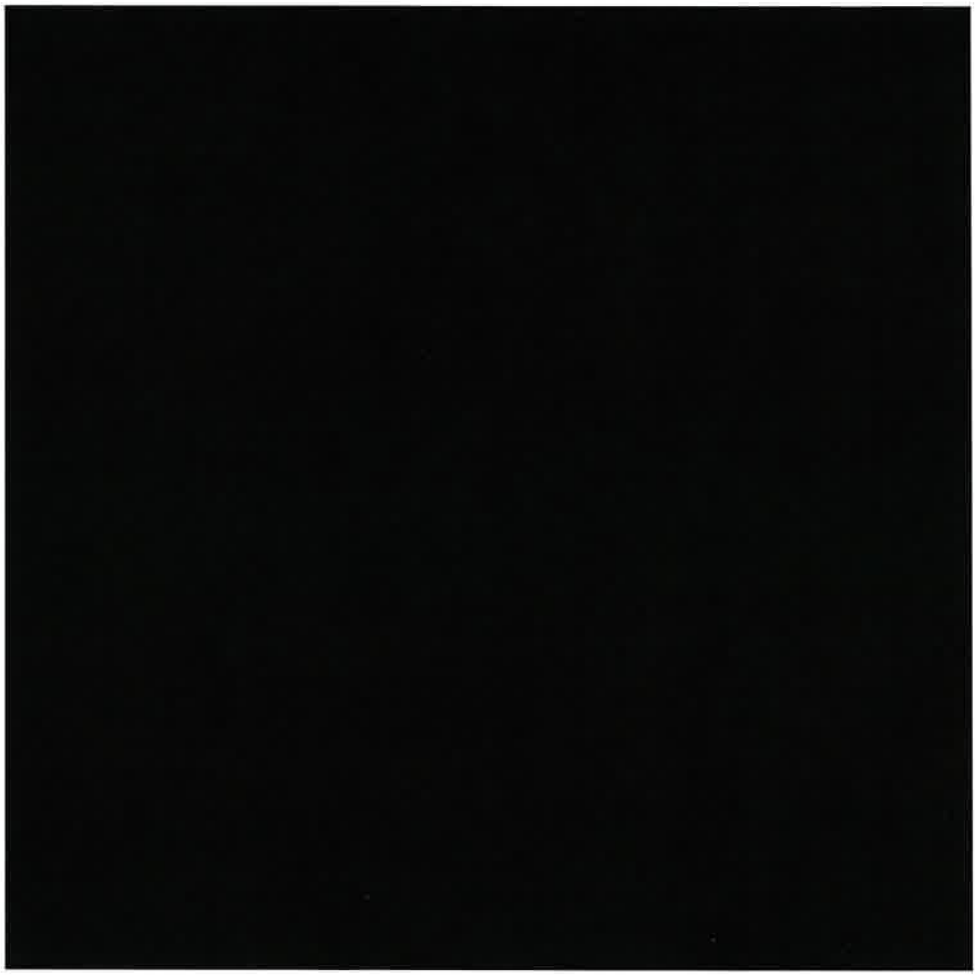
* Provide person's initial and last name.
** Update the Last Revision Dates on the cover page and the document header.

FINAL SIGN-OFF SIGNATURES

Study Biostatistician:

Peer Review Biostatistician:

Approved by:



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GLOSSARY OF ABBREVIATIONS

Abbreviation	Term
ADaM	Analysis Data Model
AE	Adverse Event
BMI	Body Mass Index
BOR	Best Overall Response
C1D1	Cycle 1 Day 1
CHF	Congestive Heart Failure
CR	Complete Response
CRF	Case Report Form
ctDNA	Circulating Tumor DNA
DLT	Dose-Limiting Toxicities
DOR	Duration of Objective Response
DNA	Deoxyribonucleic Acid
ECHO	Echocardiogram
ECOG	Eastern Cooperative Oncology Group
EOI	End of Infusion
EOT	End of Treatment
FAS	Full Analysis Set
1M FUP	1-Month Follow up
IgG2	Immunoglobulin G2
IHC	Immunohistochemistry
IRB	Institutional Review Board
iRECIST	Immunotherapeutics Response Evaluation Criteria in Solid Tumors
IV	Intravenous

GLOSSARY OF ABBREVIATIONS

mAb	Monoclonal Antibody
MAD	Maximum Administered Dose
MedDRA	Medical Dictionary for Regulatory Activities
MHC	Major Histocompatibility Complex
MTD	Maximum Tolerated Dose
MUGA	Multi-Gated Acquisition
NE	Non-evaluable
OR	Objective Response
ORR	Overall Response Rate
PBMC	Peripheral Blood Mononuclear Cell
PD	Progressive Disease
PD-1	Programmed Cell Death Protein 1
PFS	Progression-free survival
PR	Partial Response
PK	Pharmacokinetics
PtdS	Phosphatidylserine
Q2W	Every 2 Weeks
RECIST	Response Evaluation Criteria in Solid Tumors
RECIL	Response Evaluation Criteria in Lymphoma
RNA	Ribonucleic Acid
RP2D	Recommended Phase 2 Dose
SAP	Statistical Analysis Plan
SD	Stable Disease
SDTM	Study Data Tabulation Model
SOI	Start of Infusion

GLOSSARY OF ABBREVIATIONS

TIM-3	T-cell Immunoglobulin and Mucin-domain Containing-3
TTP	Time to Progression
WES	Whole Exome Sequencing

1 INTRODUCTION

This Statistical Analysis Plan (SAP) outlines the statistical methods for the display, summary and analysis of data collected within the scope of Sym023-01 Version 5 dated 02May2019. As with any SAP, the proposed methods and approaches to the data analysis should be deemed as flexible. The analysis of the data should allow changes in the plan to the extent that deviations from the original plan would provide a more reliable and valid analysis of the data. As such, the statistical analysis to a certain degree is iterative since much of the planning is based on assumptions that require verification. The purpose of this plan is to provide general guidelines from which the analysis will proceed. Nevertheless, deviations from these guidelines must be substantiated by a sound statistical rationale.

The SAP should be read in conjunction with the study protocol and the Case Report Forms (CRFs). This version of the SAP has been developed using the version of the protocol mentioned above and revision 2 of the annotated CRFs dated 29Aug2019.

This is a Phase 1, multicenter, open-label, uncontrolled, non-randomized, dose-escalation study with one study drug. The trial is designed to evaluate safety, tolerability and dose-limiting-toxicities (DLTs) to establish the maximum tolerated dose (MTD) or maximum administered dose (MAD), and select the recommended Phase 2 dose (RP2D) of sequential escalating doses of Sym023 (anti-TIM-3 mAb) when administered every 2 weeks (Q2W) in 4-week cycles, to patients with locally advanced/unresectable or metastatic solid tumor malignancies or lymphomas that are refractory to available therapy or for which no standard therapy is available.

TIM3 (T-cell immunoglobulin and mucin-domain containing-3) is an immune checkpoint receptor expressed by a range of different immune cells. The role of TIM-3 in regulating immune cell function is complex and appears context-dependent. Antibody-mediated engagement of TIM-3 has been shown to induce increased proliferation and cytokine production by T-cells *in vitro*, as well as tumor growth inhibition in tumor xenograft models, especially in combination with Programmed Cell Death Protein 1 (PD-1). Multiple anti-TIM-3 antibodies are in early clinical development for use as cancer immunotherapy in solid and hematologic malignancies. Clinical activity in the form of disease stabilization across a variety of cancer types has been observed, as well as one partial response.

Sym023 is a recombinant, fully human, IgG2 antibody that binds human TIM-3 with nanomolar affinity and cynomolgus TIM-3 with 100-fold reduced affinity. Sym023 does not cross-react with mouse or rat TIM-3. Sym023 blocks PtdS binding to TIM-3 and induces cytokine secretion and activation of immune cells *in vitro*.

2 STUDY OBJECTIVES

2.1 Primary Objective

The primary objective is the evaluation of the safety, tolerability, and DLTs to establish the MTD and/or RP2D of sequential escalating doses of Sym023 (anti-TIM-3) when administered once Q2W by intravenous (IV) infusion to patient cohorts with locally advanced/unresectable or metastatic solid tumor malignancies or lymphomas that are refractory to available therapy or for which no standard therapy is available.

2.2 Secondary Objectives

The secondary objectives are the following:

- Evaluation of the immunogenicity of Sym023
- Characterization of the PK profile of Sym023
- Evaluation of the preliminary antineoplastic effects of Sym023, including:
    - Evidence of objective response (OR) and stable disease (SD)*
    - Duration of OR and SD*
    - Time to progression (TTP) of disease*

* As assessed by RECIST v1.1, iRECIST, and Response Criteria in Lymphoma (RECIL 2017)

2.3 Exploratory Objectives

The exploratory objectives are the following:

- Evaluation of potential pharmacodynamic markers, e.g. receptor occupancy in peripheral blood mononuclear cells (PBMCs) (peripheral blood to be collected)
- Evaluation of potential biomarkers, including but not limited to assessment of:
    - In peripheral blood: circulating tumor DNA (ctDNA), ribonucleic acid (RNA), relevant proteins/cytokines and cellular biomarkers
    - In tumor tissue: DNA, RNA, protein, and cellular biomarkers (*biopsies optional*)

Note: Assay methodology and biomarker assessments to be determined (TBD). Potential analyses may include but are not limited to: ctDNA sequencing; RNA sequencing (RNA-seq)/whole-exome sequencing (WES); measurement of relevant proteins/cytokines in the blood; cytometric analysis of cells in blood; and immunohistochemistry (IHC) of tumor material when collected (*tumor sampling is optional*).

3 STUDY DESIGN

3.1 Study Design

This is a Phase 1, multicenter, open-label, dose-escalation study designed to evaluate safety, tolerability, and DLTs to establish the MTD or MAD, and the RP2D of sequential escalating doses of Sym023 (study drug) when administered Q2W (4 weeks equals 1 cycle) by IV infusion, to patients with advanced, refractory solid tumor malignancies or lymphomas.

Initially, a modified, accelerated-titration, dose-escalation design will be used with entry of single patient cohorts for up to two dose levels, based on tolerability. Thereafter, a standard 3+3 design will be used, with a target toxicity level of less than 33.3% as determined by DLTs. The number of patients treated, the number of cohorts evaluated, and the MTD/MAD will depend upon the observed tolerability of Sym023 during Cycle 1; however, the maximum dose to be administered in the trial is not to exceed 20 mg/kg.

In the absence of documented progressive disease (PD) or unacceptable toxicity, patients may continue to receive additional 4-week cycles of study drug at the same dose, infusion duration, and schedule established for the patient.

Dose cohorts will be numbered and entered sequentially. Sym023 will be administered at up to 7 planned dose levels; anticipated dose levels include:

- Dose Level 1: 0.03 mg/kg

- Dose Level 2: 0.1 mg/kg
- Dose Level 3: 0.3 mg/kg
- Dose Level 4: 1.0 mg/kg
- Dose Level 5: 3.0 mg/kg
- Dose Level 6: 10.0 mg/kg
- Dose Level 7: 20.0 mg/kg

Once assigned to a dose cohort, patients will continue to be treated with study drug at that same dose level throughout the duration of their time on study. There will be no intra-patient dose escalation.

3.2 Randomization

Not applicable. This is an open-label, uncontrolled trial in which all patients will receive Sym023.

3.3 Hypothesis Testing

No formal hypothesis testing is planned for this trial. Safety and antineoplastic activity analyses will be descriptive in nature.

3.4 Interim Analysis

Safety evaluation will be performed prior to each dose-escalation. No other interim analyses are planned.

3.5 Sample Size

Approximately 20-48 male and female patients will be enrolled and treated, based on a modified accelerated titration Phase 1 design (more specifically, up to 2 single patient cohorts, followed by a standard 3+3 design), to allow determination of the MTD and/or RP2D. It is assumed that approximately 7 cohorts may be required during the dose escalation. However, the protocol allows for enrollment of > 7 cohorts, should this be necessary to identify the MTD and/or RP2D. Expansion of the MTD/MAD cohort to treat up to 12 patients may be considered for further evaluation of tolerability.

3.6 Study Procedures

All patients will be assessed by scheduled clinical, laboratory, and other diagnostic assessments throughout the study. All efforts should be made to perform assessments as close as possible to the scheduled timepoints. The projection of visit days within each cycle should be made from Day 1 of the respective cycle. Visit windows are provided below. Study assessments are to be performed as follows:

- Screening evaluations are to be performed within 14 days prior to first study drug dose, unless otherwise specified (for exceptions see protocol section 7.2, section 7.3, and section 7.4).
- The day of first administration of study drug will be considered Day 1 of study.
- C1/D3 evaluations may be conducted +1 day.
- On-study evaluations (including laboratory assessments) are to be performed on or about the indicated study day (i.e. ± 2 working days) (a slightly longer allowance for routine assessments is permissible in the event of scheduling difficulties associated with weekends, holidays, etc.).
- End of Cycle assessments may be conducted at any time during the week prior to Day 1 of the next cycle, including on Day 1 of the next cycle, prior to dosing.

- EOT evaluations are to be performed within approximately 10 days following the decision to discontinue treatment, or before initiation of a new treatment, whichever occurs first.
- 1M FUP evaluations are to be performed approximately 30 days (+7 days) following the last dose of study drug (i.e. as all patients are to be followed for a minimum of 30 days after study drug discontinuation to monitor for the occurrence of AEs).

3.7 Schedule of Assessments

STUDY ASSESSMENTS	Screening	CYCLE 1						CYCLE 2			SUBSEQUENT CYCLES			EOT *within 10d after treatment discontinuation*	1M FUP* *30d (+7) after last dose*	Long-Term FUP* *if OR/ SD at EOT, for new-onset or ongoing immune-mediated AEs*	As Clinically Indicated
		D1	D2	D3 (+1)	D8 (±2)	D15 (±2)	D22 (±2)	D1 (±2)	D15 (±2)	End of Cycle 2 (final week)	D1 (±2)	D15 (±2)	End of Even Numbered Cycles (final week)				
CONSENT AND MEDICAL HISTORY																	
Informed Consent[1]/ Eligibility Assessment	x																
Demography	x																
Past Medical History[2]	x	x[a]															
History of Primary Malignancy[3]	x																
SAFETY ASSESSMENTS *(screening assessments within 14 days prior to first dose of study drug unless otherwise specified)*																	
Medication/Procedure Survey[4]	from 14 days prior to 1st dose through 30 days after last dose																
AE Reporting[5]	from signing of informed consent through 30 days after last dose; through 2 months (or 4 months to 2 years) FUP if related critical AEs persist															Q2M[d]	x
DLT Assessment[6]		C1/D1 through C1/D28 (+/- 2 days)															x
ECOG PS Evaluation	x	x[a]						x			x			x	x		x
Vital Signs[7]	x	SOI; EOI; 2h, 4h, 8h after EOI	x	x		SOI, EOI		x			x			x	x		x
Physical Exam (to include weight, pulmonary and cardiac assessments)[8]	x	x[a]						x			x			x	x		x
Hematology Panel[9]	x	x[a]		x	x	x	x	x	x		x	x		x	x		x
Biochemistry Panel[10]	x	x[a]		x	x	x	x	x	x		x	x		x	x		x
Coagulation Panel[11]	x	x[a]				x		x			x			x	x		x
Thyroid Function Tests[12]	x	x[a]						x			x			x	x		x
Urinalysis[13]	x	x[a]				x		x			x			x	x		x
Pregnancy Testing[14]	x	x												x			x
ECG (12-lead)[15]	x	SOI, EOI +15 min						SOI, EOI +15 min						x			x
SAFETY ASSESSMENTS *(results from assessments previously performed as standard of care within 28 days [+2d] prior to 1st dose may be utilized provided no antineoplastic therapy has been delivered between assessment and 1st dose; otherwise within 14 days of 1st dose)*																	
MUGA Scan or ECHO[16]	x													x			x
Ophthalmology Exam[17]	x							EOC1 visual acuity only		x[b]			x[b]	x			x
Pulmonary Function Tests[18]	x													x			x

STUDY ASSESSMENTS	Screening	CYCLE 1						CYCLE 2			SUBSEQUENT CYCLES			EOT *within 10d after treatment discontinuation*	1M FUP* *30d (+7) after last dose*	Long-Term FUP* *if OR/ SD at EOT, for new-onset or ongoing immune-mediated AEs*	As Clinically Indicated
		D1	D2	D3 (+1)	D8 (±2)	D15 (±2)	D22 (±2)	D1 (±2)	D15 (±2)	End of Cycle 2 (final week)	D1 (±2)	D15 (±2)	End of Even Numbered Cycles (final week)				
DISEASE ASSESSMENTS *(screening assessments within 28 days [+2d] prior to first dose of study drug)*																	
Tumor Marker Measurement[19]	x									x[b]			x[b]	x[c]	If no prior PD	Q2M[d]	
Imaging for Disease (and Pulmonary Status)[20]	x									x[b]			x[b]	x[c]	If no prior PD	Q2M[d]	
Lymphoma patients: FDG-PET, X-ray, U/S, BM aspiration/Bx	As indicated									As indicated[b]			As indicated[b]	As indicated	As indicated	Q2M[e]	
Response Assessment (in event of OR or SD)[21]										x[b]			x[b]	x[c]	If no prior PD	Q2M[e]	
ADDITIONAL ASSESSMENTS																	
ADAAssessment[22]		x				x		x			Odd # Cs			x	x	Q2M for 6 months[f]	x
PK Assessment[23]		SOI; EOI; 2h, 4h, 8h after EOI	24h after EOI	-12h to +24h	x	SOI, EOI	x	SOI, EOI	SOI, EOI		SOI, EOI	SOI, EOI		x	x	Q2M for 6 months[f]	
Peripheral Blood for Pharmacodynamic Studies (receptor occupancy)[24]		x	24h			x		x	D15 (+ 0-7)	EOC2 or C3/D1[b]			Q4C (C6, C10, etc.)[b]	x	x		
Peripheral Blood for Biomarker Studies[25]	upon eligibility								D15 (+ 0-7)					x			
Tumor Biopsy for Biomarker Studies (optional)[26]	upon eligibility								D15 (+ 0-7)					Upon PD if prior OR or SD > 16wks			
TRIAL TREATMENT																	
Premedication Administration (if indicated)		x				x		x	x		x	x					
Study Drug Infusion (30 minutes) (+10 min)		x				x		x	x		x	x					
Post-Infusion Monitoring		2h				1h		1h	1h		1h	1h					

Abbreviations (in alphabetical order): 1M FUP, 1-month follow-up; ADA, anti-drug antibody; AE, adverse event; BM, bone marrow; Bx, biopsy; C, cycle: D/d, day; DLT, dose-limiting toxicity; h, hour; ECG, electrocardiogram; ECHO, echocardiogram; ECOG, Eastern Cooperative Oncology Group; EOC, end of cycle; EOI, end of infusion; EOT, end of treatment; FDG, fluorodeoxyglucose; FUP, follow-up; MUGA, multi-gated acquisition; OR, objective response; PET, positron emission tomography; PK, pharmacokinetic; PS, performance status; Q2M, every 2 months; Q4C, every 4 cycles; SD, stable disease; SOI, start of infusion; U/S, ultrasound

[a] Need not be assessed prior to Cycle 1 if ≤ 7 days since screening
[b] End of Cycle assessments may be conducted at any time during the week prior to Day 1 of the next cycle, including on Day 1 of the next cycle, prior to dosing
[c] Conduct only if > 6 weeks since the previous assessment
[d] To be conducted to assess for delayed onset of any post-therapy immune-mediated AE (up to 6 months following last dose), and in the event of an immune-mediated toxicity ongoing at the 1M FUP or noted during the 6-month post-therapy FUP period (up to 2 years). Clinical events may be followed in writing or by telephone; an in-person visit will not be required.
[e] To be conducted in the event of ongoing OR or SD at the end of treatment; continue until confirmed PD or another therapeutic intervention is initiated, or until the end of trial. Documentation may be submitted in writing or by e-mail; an in-person visit will not be required.
[f] Samples to be obtained if patient is available for blood collection

1. Informed Consent: To be signed prior to enrollment and prior to performing any protocol-related procedure, unless such testing was performed previously as part of the routine clinical management of the patient.
2. Past Medical History: To include history of prior/ongoing diseases or conditions as well as prior surgical procedures not related to the underlying malignancy.
3. History of Primary Malignancy: To include details of the primary malignancy, including: diagnosis and histological/cytological classification; date of initial diagnosis; stage of disease at diagnosis and at entry; current sites of metastases; prior surgical procedures for the malignancy and dates; prior antineoplastic therapy, prior radiation therapy, as well as dates of treatments, numbers of cycles, and best response to each therapy; date of most recent disease progression.
4. Medication/Procedure Survey: To include period within 14 days prior to first study drug dose and throughout study for a period of 30 days following last study drug dose.
5. AE Reporting: To detail symptoms that may be present prior to/at the time of first administration. AEs to be assessed from signing of informed consent, throughout study, and for the 1-month period (30 days) following last study drug dose; AEs to continue to be assessed for 2 months (and if necessary 4 months) following last study drug dose if events associated with study drug persist (to confirm that events have resolved, returned to baseline status, or been adequately explained. Investigator discretion may be used with respect to the method of contact for this AE assessment; clinical events may be followed in writing or by telephone, an in-person visit will not be required). Any patient who develops an immune-related toxicity (e.g., pulmonary fibrosis, myocarditis, ocular toxicity, drug-induced hepatotoxicity, etc.) will be followed at approximately 2-month intervals for up to 2 years to assess the course of the condition and evaluate potential reversibility of the finding.
6. DLT Assessment: Beginning on C1/D1 and ending at EOC1 (C1/D28 ± 2 days). To include evaluation for the occurrence of events meeting the trial DLT criteria. Only DLTs occurring during Cycle 1 will be used to make decisions regarding dose-escalation and tolerability. Events occurring after Cycle 1 will also be evaluated and taken into consideration when deciding upon further doses to be assessed as well as establishment of the RP2D.
7. Vital Signs: To include temperature, pulse, respiratory rate, blood pressure, and pulse oximetry. C1/D1 through C1/D3 window allowances align with PK timepoints windows
8. Physical Examination: Complete at screening including height, weight, general appearance, skin, head, eyes, ears, nose, throat, neck/thyroid, chest [includes pulmonary assessment, breasts], cardiovascular [includes heart, peripheral pulses] abdomen, musculoskeletal system, lymph nodes, neurologic and mental status; directed thereafter, must include weight as well as pulmonary and cardiac assessments. Dose adjustments should be made in the event of noted weight change (± 10% [less at the site's discretion or if required by institution procedures]). Pulmonary findings will be evaluated in detail at each visit by the Investigator (or physician designee). Evaluation to include review of pulmonary symptoms including but not limited to: cough, sputum production, hemoptysis, wheezing, dyspnea, dyspnea on exertion, chest pain, and/or chest pain associated with respirations, as well as review of cardiac symptoms including but not limited to chest pain, orthopnea, nocturia, edema, and palpitations.
9. Hematology Panel: To include CBC with hemoglobin, hematocrit, differential, ANC, and platelet count. Evaluation frequency should be increased in the event of hematologic toxicity.
10. Biochemistry Panel (fasting not required): To include Na, K, Cl, bicarbonate or carbon dioxide, BUN or equivalent, creatinine, glucose, bilirubin [total and direct], AST, ALT, ALP, Ca, Mg, phosphorous, albumin, total protein, uric acid, amylase, lipase, and CK (if abnormal, perform isoenzyme analysis to include at minimum CK-MB), serial troponins,

and measurement of BNP. Evaluation frequency should be increased in the event of significant serum chemistry abnormalities. Clinically significant electrolyte abnormalities should be corrected prior to dosing.

11. Coagulation Panel: To include PTT (or aPTT), PT/INR.
12. Thyroid Function Tests: To include measurement of TSH, fT3, and fT4.
13. Urinalysis: Multi-panel chemical test strips are acceptable and should include assessment of specific gravity, pH, protein, glucose, ketones, leukocytes, nitrite, bilirubin, urobilinogen, and blood. Microscopic examination of sediment, if clinically indicated, to include assessment of cells (WBC and RBC per HPF, and casts).
14. Pregnancy Testing: β-hCG in WOCBP; serum at Screening, serum or urine thereafter; negative test must be confirmed within 2 working days prior to first dose of study drug.
15. ECG (12-Lead): To include measurement of PR interval, QRS duration, QT interval, and QTc interval (msec), as well as HR (BPM); to be performed after patient has been supine or semi-recumbent for ≥ 10 minutes; repeat subsequent timepoints in triplicate separated by 5 minutes for 4 cycles (Day 1, SOI and EOI) in patients with a Cycle 1 or Cycle 2 QTc that is either: a) > 500 msec; b), increased by 60 msec over baseline; or c) decreased by 20 msec below baseline. If abnormities suggest new evidence of myocardial ischemia, perform isoenzyme analysis (to include at minimum CK-MB), serial troponins, and measurement of BNP.
16. MUGA Scan or ECHO: For measurement of LVEF; to be performed ONLY in patients with a history of CHF, individual patients should be followed with the same testing procedure throughout the study.
17. Ophthalmology Examination: To include funduscopic and slit lamp evaluations for assessment of retinal and corneal integrity, visual acuity as assessed by standardized chart or other appropriate measurement tool (e.g., Snellen chart), and any other noted ocular abnormality. If changes in visual acuity are noted, a thorough ophthalmologic evaluation should be performed within 48 hours (if feasible, based on weekends or holidays) of the initial observation in order to confirm the finding and determine if there is evidence of an immune-mediated AE, or other event that would preclude further treatment with study drug.
18. Pulmonary Function Tests: To include spirometry and diffusing capacity of carbon monoxide [DL_{CO}] to assess for evidence of pulmonary fibrosis. Spirometry assessments to include at minimum: FVC, FEV1, FRC, RV, and TLC. To be repeated if evidence of interstitial pneumonitis, pulmonary fibrosis or other potential evidence of drug-related pulmonary toxicity is documented on imaging studies or if pulmonary symptomatology indicates.
19. Tumor Marker Measurement: As indicated by tumor type.
20. Imaging for Assessment of Disease (and Pulmonary Status): To include diagnostic imaging by CT or MRI of the chest with each evaluation (for disease evaluation where indicated, and to assess for evidence of pulmonary fibrosis) plus abdomen and pelvis, and other sites as indicated based on tumor type and clinical judgment to assess the status of the underlying malignancy. Use of contrast is preferred but is at the discretion of the Investigator, as medically indicated. The same method(s) of disease evaluation and the same technique should be used throughout the study. For all imaging timepoints, the following will be recorded as per RECIST v1.1 (or other response criteria, as indicated): target lesions including size, location, and type (nodal/non-nodal); sum of diameters of target lesions; any new lesions noted during trial, including size, location, and type (nodal/non-nodal).
21. Response Assessment: To be assessed by the Investigator or qualified designee as per RECIST v1.1 (or other response criteria, as indicated).
22. ADA **(Specialty Lab)**: To assess immunogenicity; whole blood (~5 mL at each timepoint) will be collected for serum acquisition. If sampling is on a dosing day, collect prior to infusion. If a collected serum sample is inadequate or insufficient for ADA analysis, the analysis of ADA can be done using a PK serum sample from the same timepoint, if available. A detailed laboratory manual specifying sample collection, handling, storage, and shipment will be provided to the trial sites.
23. PK Sampling **(Specialty Lab)**: See protocol **Section 7.6.1** for window allowances. Whole blood (~5 mL at each timepoint) will be collected for serum acquisition. If a collected serum sample is inadequate or insufficient for PK analysis, the analysis of PK can be done using an ADA serum sample from the same timepoint, if available. A detailed laboratory manual specifying sample collection, handling, storage, and shipment will be provided to the trial sites. PK sampling times may be adjusted according to early trial results to optimize evaluation.
24. Peripheral Blood for Pharmacodynamic Studies (Receptor Occupancy) **(Specialty Lab):** Whole blood (~10 mL at each timepoint) will be collected for assessment of receptor

occupancy. C2D15 (+ 0 to 7 days) after dosing; to be collected on the day of tumor biopsy, if performed. End of Cycle sampling may be combined with EOT if patient discontinues treatment. A detailed laboratory manual specifying sample collection, handling, storage, and shipment will be provided to the trial sites.

25. Peripheral Blood for Biomarker Studies **(Specialty Lab):** *To be obtained only after eligibility has been confirmed. (May be collected C1/D1 prior to dosing.)* Whole blood (~30 mL at each timepoint) to be collected. C2D15 (+ 0 to 7 days) after dosing; to be collected on the day of tumor biopsy, if performed. For those timepoints where both a blood sample and a tumor biopsy are to be obtained, the blood sample must be collected first. A detailed laboratory manual specifying sample collection, handling, storage, and shipment will be provided to the trial sites.
26. Tumor Biopsy for Biomarker Studies (optional) (**Specialty Lab**): *To be obtained only after eligibility has been confirmed. (May be collected C1/D1 prior to dosing.)* Tissue for FFPE to be collected. C2D15 (+ 0 to 7 days) after dosing; to be collected with paired peripheral blood for biomarker studies. For those timepoints where both a blood sample and a tumor biopsy are to be obtained, the blood sample must be collected first. EOT sample upon PD only in patients with a prior OR or prolonged SD (> 16 weeks). A detailed laboratory manual specifying sample collection, handling, storage, and shipment will be provided to the trial sites

4 DATA AND ANALYTICAL QUALITY ASSURANCE

The overall quality assurance procedures for the study data, statistical programming and analyses are described in [redacted]'s Standard Operating Procedures. Detailed data management procedures are documented in the Data Management Plan, Data Validation Check Specifications, and Data Review Plan. Detailed statistical and programming quality control and quality assurance procedures are documented in the Statistical Analysis and Programming QC/QA Plan.

The study endpoints and analytic approaches are both prospectively defined and documented in the protocol and in this SAP. The SAP will be finalized prior to the database lock and data analysis.

5 ANALYSIS SETS

5.1 Full Analysis Set (FAS)

The Full Analysis Set (FAS) will comprise all consented patients who have received at least a fraction of one dose of study drug. The FAS will be used for evaluation of all endpoints except evaluation of DLTs. The patients in the FAS will contribute to the analyses as allocated to treatment.

5.2 DLT Analysis Set

The DLT Analysis Set will comprise all patients in the FAS enrolled in the dose-escalation, except patients who did not complete Cycle 1 for reasons other than drug toxicity. The DLT Analysis Set will be used for summarizing DLTs and the process of MTD determination.

5.3 PK Analysis Set

The PK Analysis Set will comprise all patients in the FAS with evaluable PK parameter data and no major protocol deviations with an impact on PK data.

5.4 ADA Analysis Set

The ADA Analysis Set will comprise all patients in the FAS from whom one or more anti-drug antibody (ADA) samples has been collected.

6 SPECIFICATION OF ENDPOINTS AND VARIABLES

6.1 Demographic and Baseline Characteristics

Demographics, baseline characteristics, medical history, surgical history and prior cancer treatments will be collected at the screening visit within 14 days of Cycle 1 Day 1 and will be confirmed (and updated as needed) at the Cycle 1 Day 1 visit.

- Demographics variables include age at informed consent, sex, race and ethnicity. Age will be calculated based on the date of birth and date of consent when age is missing on the CRF. In these

cases, the following imputation rules will be applied to estimate date of birth for the purpose of calculating age when only partial information is known: if day and month are missing, December 31 will be assigned to the missing fields; if day is missing, the last day of the month will be assigned to the missing day. Imputed values will not be listed in data listings.

- Baseline characteristics include ECOG performance status, height, weight and BMI.
- Medical history includes diagnosis or symptoms entered on the Medical History form. Verbatim descriptions of diagnoses or symptoms will be coded using the Medical Dictionary for Regulatory Activities (MedDRA version 21.0 or later).
- Surgical history includes surgical procedures entered on the General Surgical History form.
- Cancer history includes:
    - cancer type (solid tumor malignancy or lymphoma)
    - primary tumor site (for solid tumors)
    - histological type
    - tumor grade
    - presence of metastases (yes, no)
    - sites of metastatic disease (for metastatic solid tumors)
    - lymphoma type
    - stage at initial diagnosis
    - stage at enrollment
    - date of most recent disease progression
    - time since initial diagnosis in months, defined as: (date of first treatment – date of initial diagnosis + 1)/30.4375
    - time since diagnosis of metastatic disease in months, defined as (date of first treatment – date of metastatic diagnosis + 1)/30.4375
- Prior cancer treatments include radiotherapies entered on the prior radiotherapy for cancer form, prior cancer surgeries entered on the prior surgical procedures for cancer treatment form and prior treatments (intent, regimen, drug, start and end dates, best response, reason for discontinuation) entered on the prior antineoplastic/systemic drug therapies for cancer treatment form:
    - prior radiotherapies will be categorized by intent (Curative, Palliative, Other)
    - prior surgeries will be categorized by type (Biopsy, Resection of primary lesion, Resection of metastatic lesion, Other)
    - number of antineoplastic/systemic drug therapies/regimens (1, 2, 3, 4 or more) will be calculated for each patient
    - number of antineoplastic/systemic drug therapies/regimens for advanced/metastatic disease (excluding neoadjuvant and adjuvant therapies) will be calculated for each patient
    - prior exposure to checkpoint inhibitors (yes/no) will be determined for each patient
    - prior exposure to anti-TIM-3 agent (yes/no) will be determined for each patient

6.2 Safety

Safety parameters that will be measured in the study are:

1. Adverse events
2. Laboratory measurements
3. Vital signs
4. ECG
5. Physical examination

6. ECOG performance status
7. Pregnancy test
8. Concomitant medications/treatments
9. Ophthalmology exam
10. Pulmonary function tests
11. MUGA Scan or ECHO (to be performed only in patients with a history of congestive heart failure)

Unless stated otherwise, safety endpoints will all be presented for the FAS by cohort and tumor type. Safety data will be presented descriptively; no formal statistical analyses will be performed.

6.2.1 Safety Study Day and Visit Window Definitions

The study visit windows listed in Table 1 (based on visit dates) will be used to analyze laboratory, vital signs, ECG, physical examination, ECOG performance status, ophthalmology exam, and pulmonary function tests.

Table 1 - Safety Study Visit Windows

Visit	Safety Parameters	Target Day	Window
Baseline	ECOG Performance Status, Vital Signs, Physical Examination, Hematology, Biochemistry, Coagulation, Thyroid Function Tests, Urinalysis, Ophthalmology Examination, Pulmonary Function Tests	Day -14 to Day 1	Day -14 to 1
Cycle 1 Day 2	Vital Signs	Day 2 of Cycle 1	No window will be used
Cycle 1 Day 3	Vital Signs, Hematology, Biochemistry	Day 3 of Cycle 1	Day 3 to 4 of Cycle 1
Cycle 1 Day 8	Hematology, Biochemistry	Day 8 of Cycle 1	Day 5 to 11 of Cycle 1
Cycle 1 Day 15	Vital Signs, Hematology, Biochemistry, Coagulation, Urinalysis	Day 15 of Cycle 1	Day 12 of Cycle 1 to Day of 2nd infusion of Cycle 1
Cycle 1 Day 22	Hematology, Biochemistry	Day 22 of Cycle 1	Day of 2nd infusion of Cycle 1 + 1 to Day -3 of Cycle 2

Visit	Safety Parameters	Target Day	Window
Cycle n Day 1 (Cycle 2 and up)	ECOG Performance Status, Vital Signs, Physical Examination, Hematology, Biochemistry, Coagulation, Thyroid Function Tests, Urinalysis, ECG	Day 1 of Cycle n	For Cycle 2: Day -2 of Cycle 2 to Day 1 of Cycle 2 For Cycle 3 and later: Day of 2nd infusion of Cycle (n – 1) (i.e. Day of previous dose) + 1 to Day 1 of Cycle n
Cycle n Day 15 (Cycle 2 and up)	Hematology, Biochemistry	Day 15 of Cycle n	Day 2 of Cycle n to Day of 2nd infusion of Cycle n
End of Cycle n	Ophthalmology Examination	Day 28 of Cycle n	Day of 2nd infusion of Cycle n + 1 to Day 1 of Cycle (n + 1), prior to dosing
End of Treatment	ECOG Performance Status, Vital Signs, Physical Examination, Hematology, Biochemistry, Coagulation, Thyroid Function Tests, Urinalysis, ECG, Ophthalmology Examination	Within 7-10 days after date of treatment discontinuation, and before initiation of a new antineoplastic treatment	Date of treatment discontinuation to date of treatment discontinuation + 10 or date of new antineoplastic treatment, whichever occurs first
One-Month Follow-up	ECOG performance status, vital signs, physical examination, Hematology, Biochemistry, Coagulation, Thyroid Function Tests, Urinalysis	30 days after last dose of study medication	Last dose of study medication + 23 to last dose of study medication + 37 (i.e. +/-7 days)

Baseline is defined as the last available observation prior to the first administration of study drug on Cycle 1 Day 1.

6.2.2 Primary Endpoint and Analysis

The primary objective is to evaluate the safety and tolerability and to establish the maximum tolerated dose (MTD) and/or recommended Phase 2 dose (RP2D) of sequential escalating doses of Sym023. This will be assessed by the primary endpoint of occurrence of DLTs during Cycle 1.

The MTD is defined as the highest dose with a maximum of 1 out of 6 patients experiencing a DLT. The MTD may or may not be determined within the dose levels tested. Based on an overall evaluation of the dose-escalation, the RP2D will be selected. The RP2D may be equal to or lower than the MTD.

6.2.3 Extent of Exposure to Study Medication

The number of treatment cycles received, the total dose received, the exposure to study treatment and the treatment duration will be derived using data from the study drug infusion form. The percentage volume infused (%) by cycle will be based on the data from the CRF.

The **number of treatment cycles initiated** is the number of cycles with at least a fraction of one dose taken during a cycle.

The **total dose received** (mg/kg) for Sym023 is the sum of dose received at each cycle. The dose received for each cycle is defined as the planned study drug dose (mg/kg) multiplied by percentage volume infused (%)/100.

The **exposure to study treatment** (in days) is calculated as the date of last dose – date of first dose + 1.

The **treatment duration** (in days) is calculated from the date of first dose to the date of last dose + 14.

The **relative dose intensity (RDI)** is the ratio of the actual dose intensity to the planned dose intensity, more specifically:

$$\text{RDI} = 100\% \times \frac{\text{Actual Total Received (mg/kg)}}{\text{Planned Dose (mg/kg)} \times \text{Number of 2-week intervals in Treatment Duration}}$$

The relative dose intensity will be categorized as follows:

- > 110%
- > 100% - 110%
- > 90% - 100%
- > 80% - 90%
- >70% - 80%
- >60% - 70%
- ≤ 60%

The **mean number of days between infusions** will be calculated as treatment duration (days) / number of infusions.

A **treatment delay** is defined as a period of more than 16 days between two consecutive infusions. The number of days will be calculated for each delay as [date of infusion (i) – date of infusion (i – 1)] – 14 days, where i = 2, 3,…,j and j is the last infusion received. If the value is > 2 days, then the infusion will be considered to be delayed. The number of weeks delay will also be classified as follows (a patient may have more than one treatment delay throughout the course of the study):

- < 1 week delay (more than 16 days and less than 21 days between 2 consecutive infusions)
- ≥ 1 week delay (21 days or more and less than 28 days between 2 consecutive infusions)
- ≥ 2 weeks delay (28 days or more between 2 consecutive infusions)

The **maximum number of days delay between 2 consecutive infusions** will be calculated for each patient requiring a treatment delay, defined as the maximum treatment delay.

The reasons for any treatment delay and maximum number of days delay between 2 consecutive infusions will be categorized as adverse event or other.

A **dose modification** is defined as any infusion that is not completed as planned, according to the eCRF, and identified as having been delayed, prolonged, temporarily interrupted or stopped prematurely.

The **number of dose modifications** will be calculated and categorized (0, 1, 2, ≥ 3) for each type of modification (dose delays, prolonged infusions, infusion interruptions, infusions stopped prematurely).

The **reasons for dose modifications** will be categorized (Adverse Event, Other) for each type of modification.

6.2.4 Adverse Events

Adverse Events will be recorded from signing of informed consent for participation in the trial. The recording period ends 30 days after receiving the final dose of study drug (at the time of the one-month follow-up visit), unless extended follow-up is indicated, per the clinical trial protocol.

Adverse events will be coded using version 21.0 or later of the Medical Dictionary for Regulatory Activities and the severity of the toxicities will be graded according to the NCI CTCAE. Analysis of adverse events will be carried out on the FAS.

Only treatment emergent adverse events will be included in summary tabulations; all adverse events will be included in individual patient data listings. Treatment-emergent adverse events will be defined as adverse events with onset dates on or after the first dose of study medication or that occurred before the first dose of study medication and increased in severity after the first dose of study medication, up to the last dose of study drug plus 30 days. Treatment-related adverse events will be defined as adverse events with relationship to study drug of: possibly related, probably related, related, or not determined (missing relationship). Fatal adverse events will be defined as adverse events with toxicity grade 5.

NCI CTCAE Version:

Protocol version 1 through 3 were using the NCI CTCAE version 4.03. Beginning with protocol version 4.0 (18Mar2019), the NCI CTCAE version used for adverse event reporting was updated from version 4.03 to version 5.0. Within each research site, the applicable criteria version will be inferred based upon the event start date and the protocol version 4.0 approval date (the presumed start date of use of CTCAE v5.0.). The effective dates for CTCAE v5.0 for each site are shown in Table 2.

Table 2 - CTCAE v5.0 Effective Dates by Site

Site ID	CTCAE v5.0 Effective Date
12401	03May2019
84001	29Mar2019
84002	10Apr2019
84003	27Mar2019

For adverse events reported with start date prior to the CTCAE v5.0 approval date, the original reported toxicity grade based on CTCAE v4.03 will be stored in a supplemental variable. The toxicity grade based on CTCAE v5.0 will be determined, with clinical input where necessary, for purposes of analysis and listing. The CTCAE v5.0 Clean, Tracked, and Mapping Document (7) will be used to determine which preferred terms has definition or grade updates from CTCAE v4.03 to CTCAE v5.0. Adverse events

reported with start date on or after the CTCAE v5.0 effective date will be listed and summarized based on the original reported toxicity grade.

All adverse events summaries and listings will report toxicity grade based on CTCAE v5.0.

Adverse Events Incidence Counting Rules:

1. Adverse Events reported with identical verbatim terms and contiguous dates (i.e., end date of the first reported record is equal to or 1 day prior to the start date of the next reported record within the same reported term) will be considered to be the same event, and will therefore be grouped and categorized based upon the following conservative criteria (within identical verbatim term with contiguous dates):
    a. Worst (maximum) toxicity grade
    b. Worst seriousness
    c. Worst (most related) degree of relationship (possible causal relationships, in order from least related to most related are: not related, unlikely related, possibly related, probably related, and related)
    d. First start date
    e. Last end date
    f. Last outcome
    g. Any reported action taken of delay
    h. Any reported action taken of interruption
    i. Any reported action taken of discontinuation
    j. Any reported DLT during Cycle 1
    k. Any reported DLT after Cycle 1
    l. Any reported infusion related reaction
2. When summarizing number of events, AEs will be counted after being grouped as described above
3. When summarizing number of patients, patients will be summarized within system organ class or preferred term conservatively as applicable:
    a. Maximum grade
    b. Worst seriousness

Missing Grade:

Missing grades will not be imputed. AEs with missing grade will be reported as 'No Grade'.

Missing Relationship to Study Drug

An AE with a missing relationship to study drug will be categorized as 'Not determined' and will be included in summaries of related AEs. Imputed values will not be listed in data listings.

Adverse Events with Incomplete Dates

Imputation of dates for adverse events with incomplete dates will be performed only for determination of treatment emergent categorization. Imputed dates will not be presented in data listings. The following algorithm should be used to estimate adverse event start dates for which only partial information is known:

- Missing day and month
    - If the year is same as the year of first day on drug, then the day and month of the start date of drug will be assigned to the missing fields.
    - If the year is prior to the year of first day on drug, then December 31 will be assigned to the missing fields.

  - If the year is after the year of first day on drug, then January 1 will be assigned to the missing fields.
- Missing month only
  - Treat day as missing and replace both month and day according to the above procedure.
- Missing day only
  - If the month and year are same as the year and month of first day on drug, then the start date of drug will be assigned to the missing day.
  - If the month and year are before the year and month of first day on drug, then the last day of the month will be assigned to the missing day.
  - If the month and year are after the year and month of first day on drug, then the first day of the month will be assigned to the missing day.

If the AE stop date is complete and the imputed start date as above is after the stop date, the start date will be imputed using the stop date.

Adverse events with partially missing stop dates will be imputed a stop date as follows:

- *year is missing* - date left missing.
- *month is missing* - impute 'December'.
- *day is missing* - impute 'last day of that month'.

6.2.5 Deaths

All deaths occurring within 30 days of the last dose of study medication are to be reported on the Death form. All deaths reported are to be categorized as within 30 days of last dose of study medication or beyond.

6.2.6 Laboratory Data

Laboratory assessments include:

- Hematology: red blood cell (RBC) count, hemoglobin, hematocrit, platelet count, white blood cell (WBC) count, neutrophils (ANC), lymphocytes (ALC), monocytes, eosinophils, basophils, neutrophils (%), lymphocytes (%), monocytes (%), eosinophils (%), basophils (%)
- Biochemistry: sodium, potassium, chloride, bicarbonate (carbon dioxide), blood urea nitrogen (BUN), creatinine, glucose (non-fasting), total bilirubin, direct bilirubin, aspartate aminotransferase (AST), alanine aminotransferase (ALT), alkaline phosphatase, calcium, magnesium, phosphorus, albumin, total protein, uric acid, amylase, lipase, creatine kinase (CK), creatine kinase-MB (CK-MB), brain natriuretic peptide (BNP), troponin (note: CK-MB, BNP and troponin are only performed in case of ECG abnormalities)
- Coagulation: prothrombin time, international normalized ratio (INR)
- Thyroid Function Test: thyroid stimulating hormone (TSH), free triiodothyronine (fT3), free thyroxine (fT4)
- Urinalysis: specific gravity, pH, protein, glucose, ketones, leukocyte, nitrite, bilirubin, urobilinogen, blood, whole blood cells (/HPF), red blood cells (/HPF), casts (/HPF)
- Pregnancy Test

All laboratory data will be stored in the database with the units in which they are originally reported. Laboratory data in summary tables and patient data listings will be presented in the International System of Units (SI units; Système International d'Unités). Laboratory data not reported in SI units will be converted

to SI units before further processing or data analysis, and results in both units will be displayed in data listings. The original lab test units will be converted to SI units according to published reference values (4, 5). Laboratory tests will be graded using NCI-CTCAE v5.0 toxicity grading (see Appendix 1 NCI-CTCAE V5.0 Toxicity Grading).

For laboratory results entered with inequality symbols (<, ≤, >, ≥), numeric values will be imputed by ignoring the inequality symbol(s) (e.g. "<1.71" will be imputed as 1.71 for numeric analyses). Imputed values will not be listed in data listings (i.e., results will be presented as entered, with inequality symbols).

For each laboratory test, the worst (maximum) CTCAE grade during the course of the study and the grade at discontinuation will be identified for each patient.

6.2.7 Vital Signs

Vital signs include systolic/diastolic blood pressure, heart rate, respiration rate, oxygen saturation and temperature.

6.2.8 Electrocardiogram (ECG)

The electrocardiogram assessment includes heart rate (beats/min), PR interval (msec), QRS duration (msec), QT interval (msec) and QTc interval (msec).

The maximum post-baseline QTc value (msec) will be determined for each patient and categorized (≤ 450, > 450 and ≤ 480, > 480 and ≤ 500, > 500).

The maximum increase from baseline in QTc value (msec) will be determined for each patient and categorized (≤ 30, > 30 and ≤ 60, > 60).

6.2.9 Physical Examination

A physical examination will be performed at baseline, Day 1 of each cycle, at the End of Treatment and 30-day Follow-up visits and as clinically indicated; however, only the height (baseline only) and weight results will be entered in the database. The significant findings from the physical examination will be reported in the Medical History (prior to study drug administration) or the Adverse Event (after study drug administration) forms.

The height will be summarized with the baseline characteristics. The weight will be summarized with the vital signs.

6.2.10 ECOG Performance Status

An ECOG performance status assessment will be performed at baseline, Day 1 of each cycle, at the End of Treatment and 30-day Follow-up visits and as clinically indicated.

6.2.11 Pregnancy Test

A pregnancy test will be performed at the screening and end of treatment visits and as clinically indicated for females with childbearing potential.

6.2.12 Concomitant Medications/Treatments

Concomitant medications will be collected for all visits.

Verbatim descriptions of concomitant medications and therapies will be mapped to the World Health Organization (WHO) Drug Dictionary Enhanced (WHO-DDE) and Herbal Dictionary (WHO-HD) (version 1Q2018 or later).

Concomitant Medications Counting Rules:

- For each patient with multiple medications in a particular category (i.e., preferred term or drug class), that patient will be tabulated under the first occurrence of any medication within that category.

Partial medications dates will be imputed the same way as adverse events dates.

6.2.13 Other Safety Assessments

6.2.13.1 Ophthalmology Exam

An ophthalmology examination will be performed at the screening, end of cycle 1 (visual acuity only), end of treatment, at the end of even-numbered cycle visits and as clinically indicated. The ophthalmology examination includes visual acuity assessment, corneal integrity assessment, slit lamp evaluation and funduscopic evaluation.

6.2.13.2 Multi-Gated Acquisition Scan or Echocardiogram

A multi-gated acquisition (MUGA) scan or echocardiogram will be performed in patients with a history of CHF at the screening and end of treatment visits and as clinically indicated. The assessment includes left ventricular ejection fraction (LVEF) as well as an assessment of clinical significance.

6.2.13.3 Pulmonary Function Tests

Pulmonary function tests will be performed at the screening and end of treatment visits and as clinically indicated. The pulmonary function tests include forced vital capacity (FVC), forced expiratory volume in 1 second (FEV1), functional residual capacity (FRC), residual volume (RV), total lung capacity (TLC) and diffusing capacity of carbon monoxide (DLCO).

6.3 Efficacy

6.3.1 Efficacy Study Day and Visit Window Definitions

The study visit windows listed in Table 3 (based on visit dates) will be used to analyze the tumor marker results.

Table 3 - Efficacy Study Visit Windows

Visit	Efficacy Parameters	Target Day	Window
Baseline	All	Day -28 to Day 1	Day -30 to 1
End of Cycle n (even-numbered cycles)	All	Day 28 of Cycle n	Day of 2nd infusion of Cycle n + 1 to Day -1 of Cycle (n + 1)

Visit	Efficacy Parameters	Target Day	Window
End of Treatment	All	Within 7-10 days after date of treatment discontinuation, and before initiation of a new antineoplastic treatment	Date of treatment discontinuation to date of treatment discontinuation + 10 or date of new antineoplastic treatment, whichever comes first
One-Month Follow-up	All	30 days after last dose of study medication	Last dose of study medication + 23 to last dose of study medication + 37 (i.e. +/-7 days)
Long-Term Follow-up for Response	All	56 days after previous assessment	For assessments more than 37 days after last dose of study medication, use the visit as reported in SDTM

Baseline is defined as the last available observation prior to the first administration of study drug on Cycle 1 Day 1.

6.3.2 Tumor Marker Measurement

Tumor marker measurements will be performed at the screening, end of treatment, at the end of even-numbered cycles and as clinically indicated. The individual tumor markers assessed will be based on tumor type.

6.3.3 Tumor and Response Evaluations

Best overall response (BOR) will be derived for each patient, based on evaluation of response at each tumor assessment visit per investigator assessment using RECIST v1.1, iRECIST or RECIL, and reported in the following categories:

- CR or iCR
  - CR or iCR – Confirmed
  - CR or iCR – Unconfirmed
- PR or iPR
  - PR or iPR – Confirmed
  - PR or iPR – Unconfirmed
- SD
  - SD – > 16 weeks in duration
  - SD – ≤ 16 weeks in duration
- PD
- NE

Duration of SD for patients with best overall response = SD is defined as the time from the day of first study treatment to the start of radiologic disease progression or death. If the patient does not have a radiological disease progression or death, the duration of SD is defined as the time from the day of first

study treatment to the date of the last SD assessment. This duration will be calculated in weeks as: (end date – date of first study treatment + 1)/7, rounded to the nearest integer, then categorized as >16 or ≤ 16.

Overall Response Rate (ORR) is defined as the proportion of patients with objective evidence of complete response (CR for RECIST v1.1 and RECIL or iCR for iRECIST) or partial response (PR for RECIST v1.1 and RECIL or iPR for iRECIST) prior to the first evidence of progressive disease (PD for RECIST v1.1 and RECIL or iCPD for iRECIST)

For patients achieving a best overall response of stable disease (SD for RECIST v1.1 and RECIL or iSD for iRECIST), the duration of stable disease will be categorized as either > 16 weeks or ≤ 16 weeks.

Clinical Benefit Rate (CBR) is defined as the proportion of patients with objective evidence of complete response (CR for RECIST v1.1 and RECIL or iCR for iRECIST) or partial response (PR for RECIST v1.1 and RECIL or iPR for iRECIST) or minor response (MR for RECIL) or prolonged stable disease (SD > 16 weeks for RECIST v1.1 and RECIL or iCR > 16 weeks for iRECIST) prior to the first evidence of progressive disease (PD for RECIST v1.1 and RECIL or iCPD for iRECIST).

For further details regarding response criteria, refer to protocol Appendix 5 through 7.

6.3.4 Time to Progression

Time to progression (TTP) is defined as the time (in months) from the day of first study treatment to the start of radiologic disease progression: (date of first radiologic PD – date of first treatment +1)/30.4375.

Patients who do not have disease progression will be censored at the last known time that the patient was progression free (e.g. date of last evaluable tumor assessment) before receiving any new anti-cancer treatment. Patients without disease assessment post-baseline will be censored at the time of the first study treatment.

Refer to Table 4 for censoring rules for time to progression.

Table 4 - Censoring Rules for Time to Progression and Duration of Objective Response

Situation	End Date	Censored
1. Documented radiological PD before initiation of non-study anti-cancer treatment (for patients with missed tumor assessment, check #3)	Date of the first tumor assessment that determined PD	No
2. Death during the study with no prior PD and no prior initiation of non-study anti-cancer treatment (for patients with missed tumor assessment, check #3)	Date of death	Yes

Situation	End Date	Censored
3. Radiologic PD after a missed (or not available/not evaluable) tumor assessment	Date of last adequate tumor assessment prior to **missed** tumor assessment A response assessment is considered "missed" if more than 16 weeks (112 days) has elapsed since the last image-based response assessment. If a patient develops progressive disease or dies after this interval, the tumor response assessment will be excluded from the analysis and censored at the last evaluable assessment. However, if a response assigned as CR, PR, or SD is obtained after more than 16 weeks, then the tumor response assessment will <u>not</u> be excluded from the analysis as long as no other censoring events have occurred.	Yes
4. Non-study anti-cancer treatment initiated before radiologic PD	Date of last adequate tumor assessment prior to initiation of non-study anti-cancer treatment	Yes
5. Treatment discontinuation for other than radiologic PD or death (and not followed by radiologic PD or death) with no post-baseline tumor assessments	Date of first treatment	Yes
6. Treatment discontinuation for other than radiologic PD or death (and not followed by radiologic PD or death) with post-baseline tumor assessments	Date of last adequate tumor assessment prior to initiation of non-study anti-cancer treatment	Yes
7. Patients still followed without radiologic PD as of cut-off date	Date of last adequate tumor assessment prior to cut-off date	Yes
8. Only non-evaluable (NE) tumor assessments after CR, PR, or SD without radiologic PD	Date of last adequate tumor assessment prior to NE tumor assessments	Yes
General Considerations: Radiologic PD for RECIST v1.1 and RECIL is defined as overall response of 'PD'. For iRECIST, radiologic PD is defined as overall response of 'iCPD'. Clinical progression will not be considered for this analysis.		

Note: Tumor response assessments will be considered "adequate" for analysis if they are assigned as CR, PR, SD, or PD and are not censored (e.g., obtained within 9 weeks since the last assessment and prior to initiation of non-study anti-cancer treatment: systemic anti-cancer therapy, radiotherapy or cancer surgery).

Tumor response assessments obtained after initiation of non-study anti-cancer treatment will not be included in the efficacy analyses, but will be flagged in the data listings. Tumor response assessments obtained the same day as initiation of non-study anti-cancer treatment will not be excluded.

6.3.5 Duration of Objective Response

Duration of objective response (DOR) is derived for those patients with confirmed objective evidence of PR or CR. DOR (in months) is defined as the time from the first documentation of response (CR or PR) to the first documentation of objective tumor progression or death: (date of first radiologic PD or death – date of first CR or PR +1)/30.4375.

Patients who do not have disease progression or death will be censored at the last known time that the patient was alive with evidence of PR or CR (e.g. date of last evaluable tumor assessment of CR or PR) before receiving any new anti-cancer treatment. Patients without disease assessment post-response will be censored at the time of the initial CR or PR.

Refer to Table 4 for censoring rules for duration of objective response.

Note: Tumor response assessments will be considered "adequate" for analysis if they are assigned as CR, PR, SD, or PD and are not censored (e.g., obtained within 9 weeks since the last assessment and prior to initiation of non-study anti-cancer treatment: systemic anti-cancer therapy, radiotherapy or cancer surgery).

Tumor response assessments obtained after initiation of non-study anti-cancer treatment will not be included in the efficacy analyses, but will be flagged in the data listings. Tumor response assessments obtained the same day as initiation of non-study anti-cancer treatment will not be excluded.

6.4 Pharmacokinetic Parameters

Serum concentrations of Sym023 will be expressed in µg/mL. All concentrations below the lower limit of quantification (LLOQ) or missing data will be labelled as such in the concentration data listings. Concentrations below the LLOQ will be treated as LLOQ/2 in summary statistics for concentration data. PK samples are planned to be taken according to Table 5.

Table 5 - Planned PK Sampling Time Points

Sample	Sampling Time	Window	Cycle 1				Cycle 2		Cycle 3 onward		EOT	1M FUP	Long-Term FUP	As Clinically Indicated
			D1-D3	D8	D15	D22	D1	D15	D1	D15				
PK	Prior to SOI	- 4h	X		X		X	X	X	X				
	EOI	+ 10 min	X		X		X	X	X	X				
	EOI + 2h	±30 min	X											
	EOI + 4h	±30 min	X											
	EOI + 8h	±90 min	X											
	EOI + 24h	±6h	X											
	EOI + 48h	-12h to	X											

Sample	Sampling Time	Window	Cycle 1				Cycle 2		Cycle 3 onward		EOT	1M FUP	Long-Term FUP	As Clinically Indicated
			D1-D3	D8	D15	D22	D1	D15	D1	D15				
		+ 24h												
	During Visit	NA		X		X					X	X	X	

The PK profile for the first dosing occasion is defined as all samples from C1D1 'Prior to SOI' up until C1D15 'Prior to SOI'. This profile will be used to calculate the following pharmacokinetic parameters for each patient (data allowing) by standard model-independent, non-compartmental analysis (NCA) according to Symphogen's local procedures: AUC_{inf}, AUC_{τ}, $AUC_{norm,\tau}$, C_{max}, T_{max}, C_{EOI}, λ_z, $T_{½}$, CL, V_d. Definitions are given in Table 6.

Table 6 - Definition and Derivation of PK Parameters

Symbol	Definition and Derivation
C_{trough}	Trough concentration (i.e. concentration of study drug measured pre-infusion)
AUC_{inf}	Area under the concentration-time curve from start of infusion to infinity
AUC_{τ}	Area under the concentration-time curve from start of infusion up to 336 hours.
$AUC_{norm,\tau}$	Dose-normalized area under the concentration-time curve in a dosing interval, calculated as AUC_{τ} divided by the dose infused
C_{max}	Maximum concentration
T_{max}	Time to maximum concentration
C_{EOI}	Concentration at the end of infusion
λ_z	Terminal rate constant (negative of the slope of an ln-linear regression of the un-weighted data considering the terminal phase of the concentration-time curve ≥ limit of quantification). λ_z is not an endpoint, but is used for derivation of endpoints
$T_{½}$	Terminal elimination half-life, calculated as $\ln(2)/\lambda_z$
CL	Clearance after first dose, calculated as Dose/AUC_{inf} for C1/D1, where AUC_{inf} will be calculated as the sum of the area from time zero to time of last quantifiable concentration, t_z, and the area from t_z to infinity. The second area will be estimated using the observed concentration at t_z and the terminal rate constant
V_d	Volume of distribution during the terminal phase after first dose (CL_S/λ_z)

Furthermore, the C_{EOI} and C_{trough} concentrations will be derived for each infusion. EOT and 1MFUP are defined as C_{trough} values. The PK parameters will be reported with 3 significant digits.

6.5 Immunogenicity Data

ADA samples are planned to be taken according to Table 7. ADA analysis is performed using a validated double antigen bridging method on the MesoScale discovery platform. Sample analysis is carried out in three tiered steps: *i*) screening, *ii*) confirmation and *iii*) quantification of the ADA titer in confirmed positive samples.

Table 7 - ADA Sampling Time Points

Sampling Time	Window	Cycle 1				Cycle 2		Cycle 3 onward		EOT	1M FUP	Long-Term FUP	As Clinically Indicated
		D1-D3	D8	D15	D22	D 1	D15	D 1	D15				
Prior to SOI	-4h	X		X		X		Odd # cycles		X	X	X[1]	X

Abbreviations (in alphabetical order): 1M FUP, one-month follow-up; ADA, anti-drug antibody; D, day; EOI, end of infusion; EOT, end of treatment; FUP, follow-up; h, hour; SOI, start of infusion; X, ADA sampling

1) Collection of samples during Long-Term FUP to continue at 2-month intervals for 6 months (for patients who are available for blood collection)

ADA results will be categorized as negative (=0) and positive (>0). **ADA response** will be defined as a shift from negative at baseline to positive post-baseline result. **Onset of ADA response** will be defined as the study day of the first shift from negative baseline ADA result to positive post-baseline ADA result. For patient with ADA response, the **duration of ADA response** will be defined as study day of last positive post-baseline ADA result – onset of ADA response + 1.

6.6 Pharmacodynamic and Biomarker Analyses

The details of the pharmacodynamic and biomarker analyses are out of scope of this SAP and will be presented in a separate plan.

7 STATISTICAL ANALYSIS

7.1 General Data Handling Rules and Definitions

If any enrolled patient is found to not have valid documented informed consent, that patient's data will be excluded from the report, except as necessary to document the error.

All analyses will be conducted using SAS version 9.4 or later.

Except where specified all continuous variables will be summarized with descriptive statistics (the number of non-missing values, mean, standard deviation, median, 25th and 75th percentiles, minimum and maximum) and all ordinal and categorical variables will be summarized with frequency counts and percentages, by treatment group.

Missing data will be maintained as missing unless specified otherwise. For variables where missing data is imputed, the analysis dataset will contain one variable with the imputed value and the original variable with missing maintained as missing.

Except where specified, all results will be summarized by cohort and tumor type (solid tumor malignancy or lymphoma). Total columns will be displayed in all summary tables except where specified.

Results by visit, including at end of treatment, will be determined based on derived analysis visit, as described in Section 6.2.1 and Section 6.3.1. If multiple scheduled or unscheduled assessments fall within the same visit window, the result with a non-missing value closest to the target date (and latest, if ties exist) will be used for the visit. Both collected (SDTM) and derived (ADaM) visits will be displayed in listings. Analysis (ADaM) datasets will contain all collected (SDTM) results, and will indicate individual records flagged for use in analyses.

Worst measurements for applicable parameters will be determined using criteria defined for each parameter (maximum, minimum, etc.). Analysis (ADaM) datasets will contain all collected (SDTM) results, and will indicate individual records flagged for use in analyses.

7.2 Patient Disposition

The number of patients in each analysis set and the reasons for exclusion will be summarized. In addition, patients' status with regard to study treatment and follow-up will also be summarized, along with the reasons for study treatment discontinuation. The number of patients in each analysis set and reason for study discontinuation will also be summarized.

7.3 Protocol Deviations

Protocol deviations will be summarized by category for all patients.

7.4 Demographic and Baseline Characteristics

Demographic and baseline characteristics will be summarized for the FAS. Age, height, weight and BMI will be presented as continuous numeric variables. Age group (18-64, 65-74, 75-84, ≥ 85), sex, race, ethnicity will be presented categorically. ECOG performance status will be presented ordinally.

Cancer diagnosis and history will be summarized for the FAS and will be presented categorically, except the following variables which will be listed only: histological type, tumor grade, stage at initial diagnosis, stage at enrollment, date of most recent disease progression, time since initial diagnosis and time since diagnosis of metastatic disease.

Prior cancer treatments will be summarized for the FAS and will be presented categorically.

Medical history and surgical history will be listed. All other data fields will also be presented in patient data listings.

7.5 Safety Analyses

All safety data will be summarized by cohort and tumor type in tables and presented in patient data listings. The analysis set for all safety analyses will be the FAS.

7.5.1 DLT Analysis

A summary table of all patients will be presented, indicating the number of patients included in the DLT analysis set for each treatment group as well as the DLT status at Cycle 1 (yes, no, NE) for each patient; a total column will not be presented. All DLT events will be listed by dose cohort and patient. A summary table of DLTs across dose cohorts by SOC and preferred term will be presented, if applicable.

7.5.2 Extent of Exposure to Study Medication

The number of cycles initiated, exposure to study treatment, treatment duration, mean number of days between infusions, total dose received and relative dose intensity will be summarized overall. Additionally, maximum number of days delay between two consecutive infusions and dose modifications (dose delays, prolonged infusions, infusion interruptions, infusions prematurely stopped), and their corresponding reasons will be summarized overall.

7.5.3 Adverse Events

All treatment-emergent AEs will be summarized (incidence) by the system organ class, preferred term, toxicity/severity grade and causal relationship to study treatment. The total number of events will also be presented.

The following adverse events summaries will be reported:

- Overall summary of safety including AEs, treatment-related AEs, serious AEs, treatment-related serious AEs, fatal AEs, AEs of grade 3 and above, AEs leading to study drug delay, AEs leading to study drug interruptions/prolongation, AEs leading to study drug discontinuation, infusion-related reaction, and dose-limiting toxicities
- DLTs by dose escalation cohort (as described in Section 7.5.1)
- DLTs by System Organ Class and Preferred Term (as described in Section 7.5.1)
- Adverse Events by System Organ Class, Preferred Term and NCI-CTCAE v5.0 Grade
- Treatment-related Adverse Events by System Organ Class, Preferred Term and NCI-CTCAE v5.0 Grade
- Adverse Events by System Organ Class, Preferred Term and Relationship to Study Treatment
- Adverse Events Causing Study Drug Delay by System Organ Class, Preferred Term and NCI-CTCAE v5.0 Grade
- Adverse Events Causing Study Drug Interruption/Prolongation by System Organ Class, Preferred Term and NCI-CTCAE v5.0 Grade
- Adverse Events Causing Study Drug Discontinuation by System Organ Class, Preferred Term and NCI-CTCAE v5.0
- Non-Serious Adverse Events with an Incidence Rate of at Least 5% by System Organ Class and Preferred Term
- Serious Adverse Events by System Organ Class and Preferred Term
- Serious Treatment-related Adverse Events by System Organ Class and Preferred Term
- Fatal Adverse Events by System Organ Class and Preferred Term

7.5.3.1 Deaths

Summaries of deaths (including cause of death) will be provided. All deaths reported will also be presented in a listing.

7.5.4 Laboratory Data

Hematology, chemistry and coagulation tests will be graded using NCI CTCAE v5.0 toxicity grading (see Appendix 1 NCI-CTCAE V5.0 Toxicity Grading).For hematology tests that were converted from percentage to absolute, the percentage lower limit of normal (LLN) will be used to determine if the result is below normal range. If the value is below the normal range but is higher than the grade 2 value, toxicity grade 1 will be assigned. Local laboratory ranges will be used for grading.

Hematology, biochemistry and coagulation results will be summarized by study visit and at end of treatment (actual values and change from baseline) as well as by highest toxicity grade (using NCI CTCAE v5.0 toxicity grading). The worst (maximum) change from baseline in toxicity grade for selected laboratory parameters will be presented in shift tables: the patient's baseline grade will be cross-tabulated by the patient's maximum post-baseline grade during the treatment, including scheduled and unscheduled visits.

Individual patient hematology, biochemistry and coagulation parameters during the trial will be presented graphically using longitudinal plots.

The qualitative urinalysis results will be summarized and listed.

7.5.5 Vital Signs

Vital signs and their changes from baseline will be summarized by visit and at end of treatment.

7.5.6 Electrocardiogram (ECG)

Quantitative and qualitative results from the electrocardiogram will be summarized by scheduled visit and at end of treatment. QTc value and change from baseline will be summarized using the categories defined in ICH E14.

7.5.7 Physical Examination

The physical examination results stored in the database (i.e., weight and height) will be summarized with vital signs data (weight) and baseline characteristics (height).

7.5.8 ECOG Performance Status

ECOG performance status results and shifts from baseline will be summarized by visit and at end of treatment in shift tables. Shift tables presented by visit will include visits until there are less than 50% of the patients remaining.

7.5.9 Pregnancy Test

The pregnancy test results will be listed.

7.5.10 Concomitant Medications/Treatments

Concomitant medications will be summarized by treatment group, Anatomical-Therapeutic-Chemical classification (ATC) class and preferred drug name.

7.5.11 Other Safety Assessments

The ophthalmology examination results and pulmonary function tests will be summarized by visit. The MUGA scan and echocardiogram results will be listed.

7.6 Efficacy Analyses

Unless stated otherwise, all efficacy analyses will be based on the FAS.

7.6.1 Tumor Marker Measurement

The tumor marker measurements will be listed.

7.6.2 Disease Response

Best response will be summarized separately for each response evaluation method:

- RECIST v1.1: Best response will be summarized into four RECIST categories: complete response (CR), partial response (PR), stable disease (SD) and progressive disease (PD). The summary will also include a category for unevaluable patients if applicable.
- iRECIST: Best response will be summarized into five iRECIST categories: complete response (iCR), partial response (iPR), stable disease (iSD), unconfirmed progressive disease (iUPD), confirmed progressive disease (iCPD). The summary will also include a category for unevaluable patients if applicable.
- RECIL: Best response will be summarized into five RECIL categories: complete response (CR), partial response (PR), minor response (MR), stable disease (SD) and progressive disease (PD). The summary will also include a category for unevaluable patients if applicable.

The overall response rate (ORR) and clinical benefit rate (CBR) estimates will be presented along with the associated Clopper-Pearson 95% CIs.

A waterfall plot for best percent change from baseline of the sum of the target lesion measurements will also be presented, with primary disease site and study treatment dose indicated. If there are not many primary disease sites, waterfall plots may indicate the assigned dose by the color of the bar and the primary disease site may be shown using text annotations.

7.6.3 Time to Progression

TTP will be summarized separately for each response evaluation method (RECIST v1.1, iRECIST, RECIL). Median durations will be estimated using the Kaplan-Meier method, along with the corresponding 95% CI. Confidence intervals for the median values will be based on the methods of Brookmeyer and Crowley. The 25^{th} and 75^{th} percentiles will also be calculated. Kaplan-Meier estimates at 2, 4, 6, 8, 10 and 12 months and their confidence intervals (calculated with the log-log transformation methodology of Kalbfleisch and Prentice) will be tabulated. The TTP plot will be estimated using the Kaplan-Meier method.

7.6.4 Duration of Objective Response

If there are a sufficient number of responses, DOR will be analyzed using the same methodology as Time to Progression. DOR will also be presented in swim plots. Swim plots may include bars indicating first and last treatment date (capped with an arrow if treatment is ongoing) and follow-up period (capped with an arrow if follow-up is ongoing). Dates of first response, first objective disease progression and death will also be indicated.

7.7 Pharmacokinetic Analyses

Unless stated otherwise, all pharmacokinetic analyses will be based on the PK Analysis Set. All pharmacokinetic data will be presented in listings. PK concentration profiles will be summarized by assigned dose and over time in tabular and graphical formats.

Descriptive statistics of pharmacokinetic parameters and concentrations will include mean, SD, minimum and maximum. The descriptive statistics will be rounded to one more digit than the individual values for the mean, and SD, and to the same number of digits for the minimum and maximum values.

The concentration data may also be used for exploratory population PK modelling which is outside the scope of this SAP as the results will be reported separately from the Sym023-01 CSR.

The following descriptive summaries will be produced:

- Summary of Sym023 concentrations by visit, nominal time point
- Summary of PK Parameters for first dose of Sym023

The following figures will be produced:

- Individual concentration versus actual time for the first dose up to 336h – linear scale (overlaid for each cohort)
- Individual concentration versus actual time for the first dose up to 336h – semi-log scale (overlaid for each cohort)
- Individual concentration versus actual time for all PK sampling time points from first dose to 1MFUP – semi-log scale (overlaid for each cohort)
- Arithmetic Mean concentration versus nominal time for the first dose up to 336h – linear scale (overlaid for all cohorts)
- Arithmetic Mean concentration versus nominal time for the first dose up to 336h – semi-log scale (overlaid for all cohorts)
- Arithmetic Mean concentration versus nominal time for all PK sampling time points from first dose to 1MFUP – semi-log scale (overlaid for all cohorts)

Data points collected after 336h but within window will be included in plots identified as ‘first dose up to 336h’. This includes all samples collected from Cycle 1 Day 1 through Cycle 1 Day 8, as well as Cycle 1 Day 15 (Prior to SOI sample only).

7.8 Immunogenicity Analyses

Unless stated otherwise, all immunogenicity analyses will be based on the ADA Analysis Set. All ADA data will be presented in listings. Immunogenicity profiles will be summarized by assigned dose and over time in tabular format; graphical formats may also be presented if appropriate.

Since study drug in the ADA sample interferes with the capacity of detecting ADA against the drug, the measured serum levels of Sym023 in the PK sample drawn at the same/corresponding time point will be presented along with ADA results.

The following descriptive summaries will be produced:

- Summary of ADA categorical results (negative/positive) by visit
- Shift table of ADA categorical results from baseline to worst post-baseline result

The following figure might be produced (providing there is sufficient data):

- Sym023 concentration geometric mean over time by ADA status – semi-log scale

8 ANALYSES PERFORMED BEFORE DATABASE CLOSURE

Safety evaluation will be performed prior to each dose-escalation. No other interim analyses are planned.

9 CHANGES FROM METHODS PLANNED IN THE PROTOCOL

Any changes to methods planned in this statistical analysis plan will be documented in a revision to this statistical plan prior to database lock, or identified in the clinical study report.

10 STATISTICAL SOFTWARE

SAS Version 9.4 or later will be used for all statistical analyses.

11 REFERENCES

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12 APPENDIX 1 NCI-CTCAE V5.0 TOXICITY GRADING

12.1 Panel: Chemistry

Lab Test	Unit	Grade 1	Grade 2	Grade 3	Grade 4
Albumin, serum- low (hypoalbuminemia)	g/L	[30, LLN)	[20, 30)	<20	life-threatening consequences; urgent intervention indicated
Alkaline phosphatase (ALK) increased	U/L	(ULN, 2.5*ULN]	(2.5*ULN, 5*ULN]	(5*ULN, 20*ULN]	>20*ULN
Alanine aminotransferase (ALT) increased	U/L	(ULN, 3.0*ULN]	(3.0*ULN, 5.0*ULN]	(5*ULN, 20*ULN];	>20*ULN
Amylase increased	U/L	(ULN, 1.5*ULN]	(1.5*ULN, 2*ULN]	(2*ULN, 5*ULN]	> 5*ULN
Aspartate aminotransferase (AST) increased	U/L	(ULN, 3.0*ULN]	(3.0*ULN, 5.0*ULN]	(5*ULN, 20*ULN];	>20*ULN
Bilirubin increased	umol/L	(ULN, 1.5*ULN]	(1.5*ULN, 3*ULN]	(3*ULN, 10*ULN]	>10*ULN
Calcium high (hypercalcemia)	mmol/L	(ULN, 2.9]	(2.9, 3.1]	(3.1, 3.4]; hospitalization indicated	>3.4; life-threatening consequences
Calcium low (hypocalcemia)	mmol/L	[2.0, LLN)	[1.75, 2.0)	[1.5, 1.75) ; hospitalization indicated	[0, 1.5); life threatening consequences
Creatine phosphokinase (CPK) increased	U/L	(ULN, 2.5*ULN]	(2.5*ULN, 5*ULN]	(5*ULN, 10*ULN]	>10*ULN
Creatinine increased	umol/L	(ULN, 1.5*ULN]	(1.5 – 3.0* baseline]; (1.5*ULN, 3*ULN]	>3.0*baseline; (3*ULN, 6*ULN]	>6*ULN
Glucose low (hypoglycemia)	mmol/L	[3.0, LLN)	[2.2, 3.0)	[1.7, 2.2)	[0, 1.7); life threatening consequences; seizures
Lipase increased	U/L	(ULN, 1.5*ULN]	(1.5*ULN, 2*ULN]	(2*ULN, 5*ULN]	> 5*ULN

Lab Test	Unit	Grade 1	Grade 2	Grade 3	Grade 4
Magnesium low (hypomagnesemia)	mmol/L	[0.5, LLN)	[0.4, 0.5)	[0.3, 0.4)	<0.3
Magnesium high (hypermagnesemia)	mmol/L	(ULN, 1.23]	undefined	(1.23, 3.3]	> 3.3
Potassium high (hyperkalemia)	mmol/L	(ULN, 5.5]	(5.5, 6]; intervention initiated	(6, 7]; hospitalization indicated	>7; life-threatening consequences
Potassium low (hypokalemia)	mmol/L	[3, LLN)	[3, LLN); symptomatic; intervention indicated	[2.5, 3) ; hospitalization indicated	[0, 2.5); life-threatening consequences
Sodium high (hypernatremia)	mmol/L	(ULN, 150]	(150, 155] ; intervention initiated	(155, 160]; hospitalization indicated	>160; life-threatening consequences
Sodium low (hyponatremia)	mmol/L	[130, LLN)	(125-129] and asymptomatic	125-129 symptomatic; 120-124 regardless of symptoms	[0, 120); life-threatening consequences

12.2 Panel: Hematology

Lab Test	Unit	Grade 1	Grade 2	Grade 3	Grade 4
Hemoglobin increased	g/dL	Increase in >0 -2 g/dL	Increase in >2 -4 g/dL	Increase in >4 g/dL	undefined
Hemoglobin decreased	g/L	[100, LLN)	[80, 100)	[0, 80); transfusion indicated	Life-threatening consequences; urgent intervention indicated
Platelet count decreased	10^9/L	[75, LLN)	[50, 75)	[25, 50)	[0, 25)
WBC increased	10^9/L	undefined	undefined	>100	undefined
WBC decreased	10^9/L	[3, LLN)	[2, 3)	[1, 2)	[0, 1)
Lymphocytes increased	10^9/L	undefined	(4 ; 20]	>20	undefined
Lymphocytes decreased	10^9/L	[0.8, LLN)	[0.5, 0.8)	[0.2, 0.5)	[0, 0.2)
Neutrophil count decreased	10^9/L	[1.5, LLN)	[1, 1.5)	[0.5, 1)	[0, 0.5)

12.3 Panel: Coagulation

Lab Test	Unit	Grade 1	Grade 2	Grade 3	Grade 4

Lab Test	Unit	Grade 1	Grade 2	Grade 3	Grade 4
International normalized ratio of prothrombin time (INR) increased	N/A	>1.2 - 1.5; >1 - 1.5 x baseline if on anticoagulation; monitoring only indicated	>1.5 - 2.5; >1.5 - 2.5 x baseline if on anticoagulation; dose adjustment indicated	>2.5; >2.5 x baseline if on anticoagulation; bleeding	-
Activated partial thromboplastin time prolonged	Seconds	(ULN, 1.5xULN]	(1.5xULN, 2.5xULN]	>2.5 x ULN	-

Reference: https://ctep.cancer.gov/protocolDevelopment/electronic_applications/ctc.htm#ctc_50

13 APPENDIX 2 PROGRAMMING CODES FOR STATISTICAL ANALYSIS

Programming of the tables, listings and figures will be performed using SAS Version 9.4, running under UNIX environment. The following table presents the SAS codes for the analyses of efficacy endpoints.

Endpoint	Test	SAS Code

ORR	Clopper-Pearson (exact) 95% confidence interval	ods listing close;
		proc freq data = indata;
		ods output BinomialCLs=CI BinomialProp=prop;
		table objresp / binomial(level = 1 exact) out=freq1 (keep=objresp count);
		run;
		ods listing;

TTP, DOR	Kaplan-Meier: median, 95% CI, 25th-75th percentile	ods listing close;
		ods output Quartiles=Quartile;
		proc lifetest data=indata;
		time timevar*censvar(1);
		run;
		ods output close;
		ods listing;