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Symphogen A/S

Sym015-01

An Open-label, Multicenter Phase 1a/2a Trial Investigating the Safety, Tolerability and Antitumor Activity of Multiple Doses of Sym015, a Monoclonal Antibody Mixture Targeting MET, in Patients with Advanced Solid Tumor Malignancies

Statistical Analysis Plan

Version: Final

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Signatures below confirm that the Statistical Analysis Plan was developed in accordance with SOP-GDO-WW-019 and that it is approved for release.

This document has been approved and signed electronically on the final page by the following:

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REVISION HISTORY

Version No.	Effective Date	Summary of Change(s)
Draft 0.1	25 May 2016	New document
Draft 1.0	12 Aug 2016	Document Review
Draft 2.0	Feb 2017	Document Review
Draft 0.3	22 Feb 2019	Use of new template and Document Review
Draft 0.4	23 Apr 2019	Document Review
Draft 0.5	22 May 2019	Comment Resolution
1.0	05 Jun 2019	Final

LIST OF ABBREVIATIONS

List and define all acronyms and abbreviations used in the document here. Abbreviations should be spelled out in full and the abbreviation indicated in parentheses at first appearance in the text. Abbreviations should appear in alphabetical order.

Abbreviation / Acronym	Definition / Expansion
1M FUP	One-Month Follow-up
ADA	Anti-Drug Antibody
ADCC	Antibody-Dependent Cellular Cytotoxicity
AE	Adverse event
ALP	Alkaline Phosphatase
ALT	Alanine Aminotransferase
ANC	Absolute Neutrophil Count
ASCO	American Society of Clinical Oncology
AST	Aspartate Aminotransferase
ATC	Anatomical therapeutic chemical
AUC	Area under the concentration-time curve
AUC_{τ}	Area under the concentration-time curve in a dosing interval
$AUC_{Norm,\tau}$	Dose-normalized area under the concentration-time curve in a dosing interval
BLQ	Below the lower limit of quantification
BMI	Body Mass Index
BUN	Blood Urea Nitrogen
C#/D#	Cycle # / Day #
CAP	College of American Pathologists
CEC	Central Ethical Committee
CI	Confidence Interval
CISH	Chromogenic In Situ Hybridization
CL	Clearance
CNS	Central Nervous System
C_{max}	Maximum Concentration

Abbreviation / Acronym	Definition / Expansion
CR	Complete Response
CRF	Case Report Form
CSP	Clinical Study Protocol
CSR	Clinical Study Report
CT	Computed Tomography
CTAE	Common Terminology Criteria for Adverse Events
C_{trough}	Trough Concentration
CV	Coefficient of variation
C_z	Last Quantifiable Concentration
DLT	Dose-Limiting Toxicity
DRM	Data Review Meeting
DSUR	Development Safety Update Report
ECG	Electrocardiogram
ECHO	Echocardiogram
ECOG	Eastern Cooperative Oncology Group
eCRF	Electronic Case Report Form
EOI	End of Infusion
EOT	End of Treatment
FAS	Full Analysis Set
FISH	Fluorescence In Situ Hybridization
FUP	Follow-up
GCP	Good Clinical Practice
HA	Health Authority
hCG	Human Chorionic Gonadotropin
HGF	Hepatocyte Growth Factor
HIV	Human immunodeficiency virus
ICH	International Council for Harmonisation
ICMJE	International Committee of Medical Journal Editors
IEC	Independent Ethics Committee
IgG1	Immunoglobulin G1

Abbreviation / Acronym	Definition / Expansion
IHC	Immunohistochemistry
IMP	Investigational Medicinal Product
INR	International Normalized Ratio
IRB	Institutional Review Board
IRR	Infusion-Related Reaction
ISF	Investigator Site File
IV	Intravenous
KRAS	Kirsten Rat Sarcoma
LLN	Lower Limit of Normal
LLOQ	Lower limit of quantification
LOQ	Limit of quantification
mAb	Monoclonal Antibody
MedDRA	Medical Dictionary for Regulatory Activities
MET	MET proto-oncogene, hepatocyte growth factor receptor gene
$MET^{Ex14Del}$	MET exon 14 skipping alteration
MRI	Magnetic Resonance Image/Imaging
MTD	Maximum tolerated dose
MUGA	Multi-Gated Acquisition
NA	Not available
NCS	Not clinically significant
NE	Not Evaluable
NGS	Next-Generation Sequencing
NK	Not known
NOAEL	No Observed Adverse Effect Level
NSAID	Nonsteroidal Anti-Inflammatory Drug
NSCLC	Non-Small Cell Lung Cancer
NYHA	New York Heart Association
OR	Objective Response
OTC	Over the counter
PD	Progressive Disease

Abbreviation / Acronym	Definition / Expansion
PDX	Patient-Derived Xenograft
PK	Pharmacokinetic
PR	Partial Response
PS	Performance Status
PSA	Prostate-Specific Antigen
PT	Preferred Term
PTT	Partial Thromboplastin Time
Q2W	Every Second Week
qPCR	Quantitative PCR
QT	The QT interval is measured from the beginning of the QRS complex to the end of the T wave
QTc	corrected QT interval
QTcB	QT corrected using Bazzett's formula
QTcF	QT corrected using Fridericia's formula
RECIST	Response Evaluation Criteria in Solid Tumors
RP2D	Recommended Phase 2 Dose
RTK	Receptor Tyrosine Kinase
SAE	Serious adverse event
SAP	Statistical Analysis Plan
SD	Standard Deviation or Stable Disease (meaning to be extrapolated by the context)
SISH	Silver In Situ Hybridization
SMC	Safety Monitoring Committee
SOC	System Organ Class
SOI	Start of Infusion
SOP	Standard Operating Procedure(s)
SUSAR	Suspected Unexpected Serious Adverse Reactions
$T_{½}$	Terminal elimination half-life
TEAE	Treatment-emergent adverse event
T_{max}	Time of Maximum Concentration

Abbreviation / Acronym	Definition / Expansion
ULN	Upper Limit of Normal
V_z	Volume of distribution during the terminal phase
WHO-DD	World Health Organisation - Drug Dictionary
WT	Wild-Type
λ_z	Terminal Rate Constant

1 INTRODUCTION

Cancers are malignant tumors formed by an abnormal growth of cells and tissue leading to organ failure. They fall into two categories: solid and hematological cancers. Solid tumors are formed by an abnormal growth of body tissue cells other than blood, bone marrow or lymphatic cells. A solid tumor consists of an abnormal mass of cells, which may stem from different tissue types such as lung, breast, colon, prostate, stomach and liver, and which initially grows in the organ of its cellular origin. In advanced stages of the disease, solid tumors may spread to other organs through metastatic tumor growth. Cancer is the second-leading cause of death and disability in the world. Lung, breast, colorectal, prostate and stomach cancer are the most common malignancies [1]. Non-small cell lung cancer (NSCLC) is the leading cause of death due to malignancy globally [2].

MET (MET proto-oncogene tyrosine kinase, hepatocyte growth factor receptor, also known as c-MET) is a receptor tyrosine kinase (RTK) containing an extracellular ligand-binding domain, a transmembrane domain, and an intracellular domain with tyrosine kinase activity. The hepatocyte growth factor (HGF), also known as scatter factor, is the only known ligand for MET. Binding of HGF to MET leads to receptor dimerization and autophosphorylation, which activates downstream signaling pathways and ultimately leads to increased cell proliferation, survival, and motility.

Dysregulation of MET or HGF activity plays a role in many cancers by facilitating cancer invasiveness, angiogenesis, metastasis, and tumor growth, thus leading to a more aggressive cancer phenotype and a poorer prognosis.

Recent preclinical and clinical results have indicated that MET (MET proto-oncogene, hepatocyte growth factor receptor gene)-amplification confers addiction to this receptor in cancer cells and make them susceptible to treatment with MET-targeted therapeutics [4][5].

Sym015 is a recombinant antibody mixture containing 2 humanized IgG1 mAbs, designated Hu9006 and Hu9338, which bind specifically to MET, the receptor for HGF. Preclinical studies have shown that Sym015 effectively down-regulates the target and has superior tumor growth inhibitory activity compared to other antibodies targeting this receptor. Sym015 is intended for the treatment of solid tumor malignancies with amplification of the gene encoding MET.

The investigational medicinal product (IMP) tested in this trial is Sym015. This is the first clinical trial to study Sym015.

The Statistical Analysis Plan (SAP) details the statistical methodology to be used in analyzing study data and outlines the statistical programming specifications, tables, figures, and listings. It describes the variables and populations, anticipated data transformations and manipulations, and other details of the analyses not provided in the clinical study protocol. This SAP covers the planned analysis of all data collected on paper (source documents /case report forms [CRFs]), captured electronically in Data Labs, and provided by external vendors. PKand immunogenicity blood samples are analyzed by externa[redacted] Tissue samples are analyzed by externa[redacted]. Biomarker blood samples are analyzed by external laboratory [redacted]

The analyses described are based on the Clinical Study Protocol (CSP) Version 8.0 (07-Dec-2018): Sym015 (Anti-MET) in Patients with Advanced Solid Tumor Malignancies, incorporating Amendment No.6, dated 20 November 2017, Amendment No. 5, dated 11 May 2017, Amendment No.4, dated 04 November 2016, Amendment No.3, dated 02 May 2016, Amendment No.2, dated 02 Feb 2016, Amendment No.1, dated 17 December 2016, and original CSP Version Final 1.0, dated 01 December 2015.

The SAP will be finalized prior to database lock and describes the statistical analysis as it is foreseen when the study is being planned. If circumstances should arise during the study rendering this analysis inappropriate, or if in the meantime improved methods of analysis should come to light, different analyses may be made. If this occurs, the sponsor will determine how the revision impacts the study and how the SAP revision should be implemented. The details of the revision will be documented and described in the clinical study report (CSR)

The structure and content are based upon ICH requirements as detailed in ICH E3 Structure and Content of Clinical Study Reports [8].

2 STUDY OBJECTIVES

2.1 Objectives of Part 1, Dose-Escalation

Part 1 is the Phase 1a dose-escalation portion of the study, conducted in patients with Kirsten Rat Sarcoma proto-oncogene (KRAS) wild-type (WT) advanced solid tumor malignancies without available therapeutic options.

2.1.1 Primary Objective

To assess the safety and tolerability of Sym015 when administered by IV infusion on a Every Second Week (Q2W) schedule to patients with KRAS wild-type (WT) advanced solid tumor malignancies without available therapeutic options.

2.1.2 Secondary Objective(s)

1. To determine a Q2W Recommended Phase 2 Dose (RP2D) of Sym015
2. To evaluate the PK profile of Sym015
3. To evaluate target-engagement in skin biopsy tissue
4. To evaluate the immunogenicity of Sym015
5. To evaluate potential pharmacodynamic biomarkers of Sym015 action, and estimate, if feasible, the magnitude of biological activity
6. To make a preliminary evaluation of the antitumor activity of Sym015

2.2 Objectives of Part 2

Part 2 is the Phase 2a dose-expansion portion of the study in which dosing will be at the recommended Phase 2 dose (RP2D) on a biweekly (Q2W) schedule. Three patient cohorts, as defined later in section 3.1, will be included.

2.2.1 Primary Objective

To evaluate the antitumor activity of Sym015 when administered at the Q2W RP2D to patients in the following cohorts:

1. Basket Cohort
2. NSCLC MET-Amplified Cohort
3. NSCLC $MET^{Ex14Del}$ Cohort

2.2.2 Secondary Objective(s)

1. To further evaluate the safety and tolerability of Sym015 when administered at the Q2W RP2D
2. To further evaluate the PK profile of Sym015 when administered at the Q2W RP2D
3. To further evaluate the immunogenicity of Sym015 when administered at the Q2W RP2D
4. To further evaluate potential pharmacodynamic biomarkers of Sym015 action, and estimate, if feasible, the magnitude of biological activity when administered at the Q2W RP2D

   Above secondary efficacy objectives at points 1 to 4 will be studied in the three Part 2 cohorts. Additionally, these will also be assessed on a subset of the Basket cohort as detailed in below point 5.

5. Basket Cohort: To make a preliminary assessment of the antitumor activity of Sym015, and to evaluate all of the above secondary objectives, in a subset of approximately 6 patients with solid tumor malignancies administered Sym015 at the Q2W RP2D after having received prior therapy with a MET-targeting TKI.

3 INVESTIGATIONAL PLAN

3.1 Overall Study Design and Plan

This is an open-label, multicenter trial composed of 2 parts:

Dose-Escalation Phase

Part 1 is the Phase 1a dose-escalation portion of the study conducted in patients with KRAS wild-type (WT) advanced solid tumor malignancies without available therapeutic options. During Part 1, dose-escalation, cohorts of patients with KRAS WT advanced solid tumor malignancies will receive increasing doses of Sym015 on a Q2W schedule until establishment of the MTD or until [redacted]has been evaluated. Dose-escalation will follow a standard 3+3 design with escalation dependent upon the occurrence of DLTs. The following dose levels of Sym015 will potentially be evaluated:

- Dose Level 1[redacted]
- Dose Level 2[redacted]
- Dose Level 3[redacted]
- Dose Level 4[redacted]

An MTD may or may not be reached in the range of doses tested.

Note: Effective with protocol version 5.0 (November 2016), following review of available safety and PK data, the decision has been made to choose the following as the Q2W RP2D of Sym015: Loading dose o[redacted]infused over 1.5 hours on C1/D1, followed by Q2W maintenance doses of[redacted]infused over 1 hour beginning on C1/D15. As the MTD has not yet been reached, dose-escalation will continue in Part 1 of the trial to[redacted]

Dos-Expansion Phase:

Part 2 is the Phase 2a dose-expansion portion of the study in which dosing will be at the RP2D on a biweekly (Q2W) schedule. Three cohorts will be included:

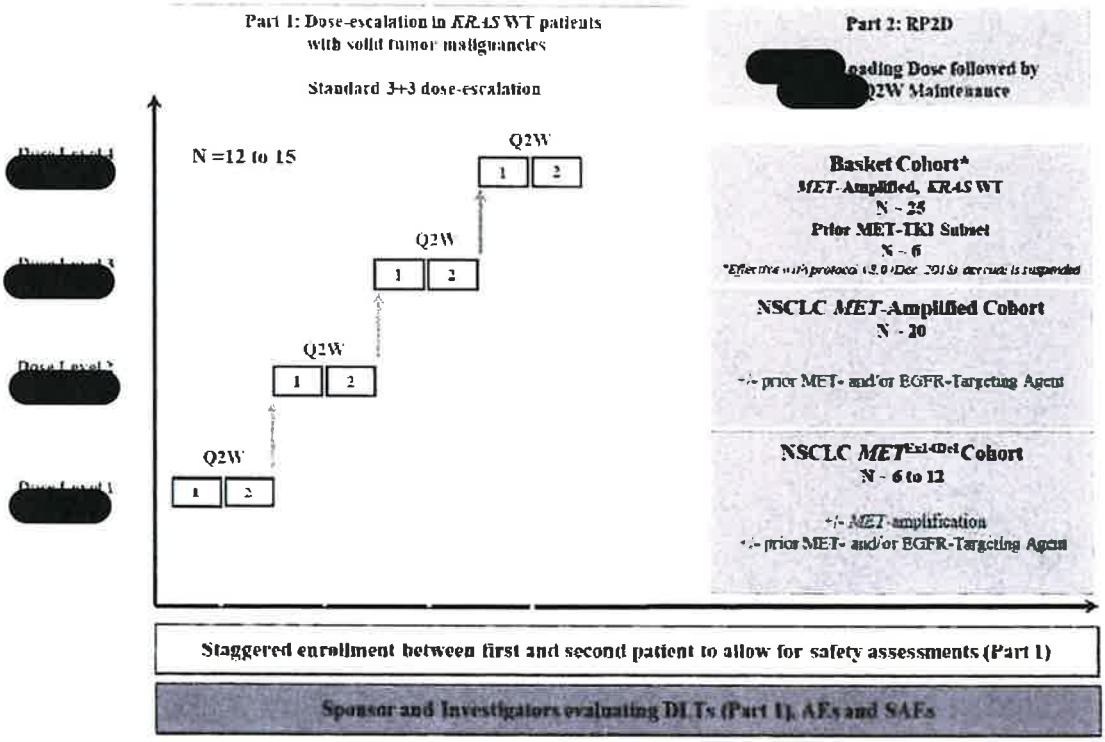
- Basket Cohort: A cohort of approximately 25 patients with KRAS WT advanced solid tumor malignancies with MET-amplification, and without available therapeutic options. Included in this group will be a subset of approximately 6 patients who have received prior therapy with a MET-targeting TKI.

- NSCLC MET-Amplified Cohort: A cohort of approximately 20 patients with advanced NSCLC with MET-amplification, and without available therapeutic options. Patients may have received prior therapy with MET-targeting and/or EGFR-targeting agents.
- NSCLC $MET^{Ex14Del}$ Cohort: A cohort of approximately 6-12 patients with advanced NSCLC with $MET^{Ex14Del}$, and without available therapeutic options. Tumors need not be MET-amplified, and patients may have received prior therapy with MET-targeting and/or EGFR-targeting agents.

During Part 2, these three cohorts will receive Sym015 at the RP2D on a Q2W dosing schedule.

The trial design is shown in Figure 1.

Figure 1 Overall Trial Design



Abbreviations: EGFR, epidermal growth factor receptor; Dec, December; *KRAS*, *KRAS* proto-oncogene; *MET*, *MET* proto-oncogene; $MET^{Ex14-Del}$, *MET* exon 14 skipping alteration; N, number of patients; NSCLC, non-small cell lung carcinoma; Q2W, dosing every second week; RP2D, recommended Phase 2 dose; TKI, tyrosine kinase inhibitor; WT, wild-type

Part 1 will be conducted in the United States (USA). Part 2 will be conducted in the USA and countries within the Asia Pacific and European regions. The number of investigational trial sites expected to participate, will be approximately 2 to 3 in Part 1 and 15 to 27 in Part 2.

3.2 Endpoints and Associated Variables

Primary Endpoint - Part 1, Dose-Escalation

The primary objective of the dose-escalation part is to assess the safety and tolerability of Sym015. This will be assessed by the primary endpoint for Part 1, occurrence of DLTs during Cycle 1 of Sym015 administration.

Primary Endpoint - Part 2

The primary objective of Part 2 is to evaluate the antitumor activity of Sym015 when administered at the Q2W RP2D. The primary endpoint is documented, confirmed OR, defined as documented PR or CR and assessed by RECIST v1.1 at any time during trial participation by Investigator assessment. The assessment will be performed after completion of Part 2 of the trial.

Secondary Endpoints

The following anti-tumor response endpoints will be measured in Part 1:

- Documented OR, defined as documented PR or CR and assessed by RECIST v1.1 at any time during trial participation by Investigator assessment.

Additionally, the following anti-tumor response endpoints will be measured in both Part 1 and 2:

  - Duration of response (DR)
  - Best overall response (BOR)
  - SD for ≥4 months and SD for ≥6 months
  - Disease Control Rate (DCR)

- Changes in sum of diameters of target lesions from baseline to end of trial participation
- Time to disease progression (TTP) as determined based on radiological evidence
- Progression-free survival (PFS)
- Overall survival (OS)

3.2.1 Efficacy Variables

3.2.1.1 Tumor evaluation and time to event variables

The anti-tumor activity of Sym015 will be assessed by the Investigator, or qualified designee, according to RECIST v1.1 [6].

Patients will undergo imaging by CT or MRI of neck, chest, abdomen and pelvis as indicated based on tumor type and clinical judgment in order to follow the underlying malignancy. The use of CT or MRI must be consistent per patient throughout the trial.

- Screening

Note: A CT/MRI performed within 28 days prior to Day 1 may be used for evaluation of eligibility and as baseline scan, provided that the CT/MRI has been performed according to the protocol requirements

- EOC2 and end of every second cycle thereafter, i.e., EOC4, EOC6, EOC8, etc.

Note: May be performed at any time during the week prior to Day 1 of the next cycle, including Day 1 of the next cycle, prior to dosing (provided results are available prior to study drug administration)

- Suspected PD (as soon as possible)
- At least 28 days following an OR (PR, CR)

- EOT (if >3 weeks since previous CT/MRI)
- At 1M FUP (if PD was not documented before or at EOT)

If PD is documented at any time, no further disease assessments will be required. Patients with documented PD will be discontinued from Sym015 so that alternative management of their malignancy may be considered.

For all imaging time points, the following will be recorded as per RECIST v1.1: 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); final response assessment at each visit (PD, SD, PR, CR or Not Evaluable [NE]), per investigators evaluation.

Tumor evaluation according to RECIST 1.1 will be the basis for the derivation of all efficacy endpoints.

To be assigned a status of PR or CR, changes in disease status must be confirmed by repeat imaging studies performed no less than 28 days (4 weeks) after the criteria for response are first met. In the case of SD, follow-up measurements must have met the SD criteria at least once after trial entry at a minimal interval in general no less than 6-8 weeks from first dose of Sym015; for the scope of derivation of SD as BOR, a minimal SD duration of 6 week will be required.

The following anti-tumor response endpoints will be derived based on Tumor evaluation according to RECIST 1.1:

- Target and Non-target Response at each timepoint will be derived according to RECIST 1.1 **[6]**.
    - Evaluation of target lesions will be derived based on sum of diameters as follow:
        - *'Complete Response (CR): Disappearance of all target lesions. Any pathological lymph nodes (whether target or non-target) must have reduction in short axis to <10 mm.*

- *Partial Response (PR): At least a 30% decrease in the sum of diameters of target lesions, taking as reference the baseline sum diameters.*
- *Progressive Disease (PD): At least a 20% increase in the sum of diameters of target lesions, taking as reference the smallest sum on study (this includes the baseline sum if that is the smallest on study). In addition to the relative increase of 20%, the sum must also demonstrate an absolute increase of at least 5 mm. (Note: the appearance of one or more new lesions is also considered progression).*
- *Stable Disease (SD): Neither sufficient shrinkage to qualify for PR nor sufficient increase to qualify for PD, taking as reference the smallest sum of diameters while on study.'*

o Evaluation of non-target lesions: non-target lesions response will be reported in CRF as CR, NON-CR/NON-PD, PD, Not Evaluated; worst response will be taken as the Non-Target Lesion response for the correspondent timepoint; for assessment of worst response the following order will be followed: PD, Not Evaluated, NON-CR/NON-PD, CR.

Target and Non-Target Response at each timepoint, derived as described, will be reviewed by Symphogen an[redacted]n a patient by patient basis across time.

At each timepoint Overall Responses will be captured in CRF; as well Overall Responses will also be derived according to RECIST 1.1 **[6]**:Table 1 of above-mentioned paper **[6]** reported below is reflected in CSP Table 14 'Overall Response Status for Patients with Baseline Measurable Disease' and will be used to derive overall response at each time point for patients who have measurable disease at baseline. When patients have non-measurable (therefore non-target) disease only, Table 2 is to be used.

Overall responses derived as described are supposed to coincide with overall responses collected in CRF; cases of mismatch will be queried; any unsolved case of mismatch will be reviewed by Symphogen an[redacted]n a patient by patient basis across time.

Table 1 – Time point response: patients with target (+/– non-target) disease.

Target lesions	Non-target lesions	New lesions	Overall response
CR	CR	No	CR
CR	Non-CR/non-PD	No	PR
CR	Not evaluated	No	PR
PR	Non-PD or not all evaluated	No	PR
SD	Non-PD or not all evaluated	No	SD
Not all evaluated	Non-PD	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, and NE = inevaluable.

Eisenhauer EA, Therasse P, Bogaerts J, et al: New response evaluation criteria in solid tumors: Revised RECIST guideline (version 1.1). Eur J Cancer 2009; 45:228–247

Table 2 – Time point response: patients with non-target disease only.

Non-target lesions	New lesions	Overall response
CR	No	CR
Non-CR/non-PD	No	Non-CR/non-PD[a]
Not all evaluated	No	NE
Unequivocal PD	Yes or No	PD
Any	Yes	PD

CR = complete response, PD = progressive disease, and NE = inevaluable.

a 'Non-CR/non-PD' is preferred over 'stable disease' for non-target disease since SD is increasingly used as endpoint for assessment of efficacy in some trials so to assign this category when no lesions can be measured is not advised.

Eisenhauer EA, Therasse P, Bogaerts J, et al: New response evaluation criteria in solid tumors: Revised RECIST guideline (version 1.1). Eur J Cancer 2009; 45:228–247

- Best overall response (BOR)

The best overall response is determined once all the data for the patient is known. Patients with non-target disease only, may have a time point response of NON-CR/NON-PD, these responses will be considered as SD for derivation of BOR.

Determinations of BORs derived as here described will be reviewed by Symphogen and [redacted] on a patient by patient basis across time.

The best overall response is the best response recorded from the start of the study treatment until the end of treatment taking into account any requirement for confirmation. Specifically, in non-randomised trials where response is the primary endpoint, confirmation of PR or CR is needed to deem either one the 'best overall response'. [6]

When a CR or PR is achieved but is not confirmed at subsequent assessment time point, the BOR will be reported as unconfirmed CR or PR.

Best response determination in trials where confirmation of complete or partial response is required: Complete or partial responses may be claimed only if the criteria for each are met at a subsequent time point as specified in the protocol. [6]

Employed rules for CR/PR BOR derivation are schematically reported in below Table 3.

Table 3 – Rules for Complete and Partial Response BOR derivation

Overall response at timepoint	Overall response Subsequent timepoint	BOR
CR	CR	Confirmed CR
CR	PR	Unconfirmed CR
CR	SD	Unconfirmed CR
CR	PD	Unconfirmed CR
CR	NE	Unconfirmed CR
PR	CR	If subsequent overall response is CR: Confirmed CR If subsequent overall response is not CR: Confirmed PR
PR	PR	Confirmed PR
PR	SD	Unconfirmed PR
PR	PD	Unconfirmed PR
PR	NE	Unconfirmed PR

Should a patient have responses of unconfirmed CR and confirmed PR, BOR will be defined as confirmed PR for that patient.

When SD is believed to be best response, it must also meet the protocol specified minimum time from baseline (specified as 6 weeks in this trial). If the minimum time is not met when SD is otherwise the best time point response, the patient's best response depends on the subsequent assessments. For example, a patient who has SD at first assessment, PD at second and does not meet minimum duration for SD, will have a best response of PD. The same patient lost to follow-up after the first SD assessment would be considered NE.

- Documented Objective Response (OR), is defined as confirmed CR or PR, based on determination of confirmed BOR.

- Duration of response (DR)

'The duration of overall response is measured from the time measurement criteria are first met for CR/PR (whichever is first recorded) until the first date that recurrent or progressive disease is objectively documented (taking as reference for progressive disease the smallest measurements recorded on study).' [6].

Duration of Response (weeks) = (Date of PD or Death [whichever is first recorded] – Date of first CR/PR [whichever is first recorded] + 1) / 7

Duration of Response will be presented at one decimal place precision.

In case of patients out of study before experiencing PD or death, the duration of response will be measured up to the last available valid tumor assessment per RECIST v1.1.

Changes in sum of diameters of target lesions from baseline For patients with measurable disease (i.e., with target lesions), absolute and percent changes in the sum of diameters of target lesions from baseline will be calculated, the best change will be identified as the nadir, i.e. largest reduction or smallest increase. This endpoint will not be derived for patients who do not have a baseline tumor assessment or who do not have any post-baseline tumor assessments.

- Time to disease progression (TTP) as determined based on radiological evidence

  Time to documented PD (based on radiological assessments) will be derived and expressed in the unit of weeks. TTP is defined as the time from first dose of study drug until objective tumor progression; TTP does not include deaths [7]. Based on this definition, PD will be counted as outcome; patients with last tumor assessment showing CR or PR or SD will be censored at the time of last available tumor assessment per RECIST v1.1; patients who died for any causes (including deaths of disease but with no documented PD) will be censored at the time of last available tumor assessment per RECIST v1.1.

  TTP (weeks) = (Date of PD – Date of first IMP infusion + 1) / 7

- SD for ≥ months and SD for ≥6 months

  'Stable disease is measured from the start of the treatment (in randomised trials, from date of randomisation) until the criteria for progression are met, taking as reference the smallest sum on study (if the baseline sum is the smallest, this is the reference for calculation of PD).' [6].

  Therefore, determination of SD duration ≥4 months and ≥6 months will be based on the calculated value of TTP regardless of censoring. If a month corresponds to 4.34524 weeks, a TTP of 17.381 will be needed to claim an SD duration ≥4 months; as well, a TTP of 26.0715 will be needed to claim an SD duration ≥6 months

- Disease control rate (DCR)

  The DCR is defined as the percentage of patients who had BOR of confirmed CR or confirmed PR or SD (including unconfirmed CR/PR, provided 6 weeks minimum criteria for SD duration is met).

- Progression Free Survival (PFS)

  PFS is defined as the time from first dose of study drug until objective tumor progression as determined based on radiological evidence or death, whichever occurs first [7]. PFS data will be censored on the date of the last adequate tumor assessment for patients who do not

have an event (PD or death) at data cutoff, or for patients who died after two or more subsequent missing response assessments (which correspond to 63 days considering 2 times the 28-days scheduled time interval between two subsequent response assessments, plus 7 days' time window). Patients who do not have a baseline tumor assessment or who do not have any post-baseline tumor assessments will be censored at start of treatment unless death occurred, in which case the death will be considered an event.

PFS (months) = (Date of PD or Death [whichever is first recorded] – Date of first IMP infusion + 1) / 30.4375.

Moreover, for the scope of an additional sensitivity analysis, non-radiological clinical progression will also be considered as an outcome; date of clinical progression is available in CRF at end of treatment page.

- Overall Survival (OS)

Overall survival is defined as the time from first dose of study drug until death from any cause. After the 1M FUP Visit, the Investigator will make every effort to obtain follow-up information on response assessment and/or overall survival (OS) about once every 2 months. Survival follow-up is required until death, withdrawal of consent, trial site closure, or termination/end of the trial. Occurrence of one of these events constitutes the EOS for the patient. Patients alive at EOS will be censored at the time of last contact when patient is known to be alive.

OS (months) = (Date of Death – Date of first IMP infusion + 1) / 30.4375

3.2.1.2 Pharmacodynamic Variables

These variables include:

- Tumor Markers Evaluation (Part 1 and Part 2 Basket Cohort) recommended to be evaluated at timepoints coinciding with the CT/MRI
- Archival Tumor Tissue for MET and KRAS assessment (Part 1 and Part 2 Basket Cohort) collected at Screening; if archival tissue is not available, tissue from a tumor biopsy

performed during screening is used; assessment of MET-amplification status is optional in Part1.

- Tumor Biopsy for Eligibility Assessment (Part 1 and Part 2 Basket Cohort) collected at Screening
- Tumor Biopsy for Biomarkers Analysis
  - Part 1: only applicable for patients with known MET-amplification who consent to this optional procedure. Collected at Screening, at End of Cycle (EOC) 2 (i.e., coinciding with time of first response assessment) or upon PD, whichever occurs first
  - Part 2 Basket Cohort: Required at Screening if archival tissue is unavailable or insufficient for central analysis (to be performed after confirmation of eligibility); Required at End of Cycle 2 (i.e., coinciding with time of first response assessment) or upon PD, whichever occurs first
  - Part 2 NSCLC^{Ex14Del} Cohort: optional at Screening and at EOC 2 (i.e., coinciding with time of first response assessment) or upon PD, whichever occurs first
  - Part 2 NSCLC MET-Amplified Cohort: required at Screening; Optional at EOC 2 (i.e., coinciding with time of first response assessment) or upon PD, whichever occurs first
- Tumor Biopsy for MET Status
  - Part 2 NSCLC MET-Amplified Cohort: Required at Screening, tissue from a newly performed pre-dosing tumor biopsy must be submitted for central confirmation of MET-amplification; Optional at EOC 2 (i.e., coinciding with time of first response assessment) or upon PD, whichever occurs first
  - Part 2 NSCLC^{Ex14Del} Cohort: Required at Screening, tissue from a recent or newly performed pre-dosing tumor biopsy must be submitted for central assessment of METEx14Del; Optional at EOC 2 (i.e., coinciding with time of first response assessment) or upon PD, whichever occurs first

- Blood Sample for Genomic and Biomarker Analyses: Screening (it will be permissible to perform this procedure outside the 14-day screening period, provided informed consent for the trial has been obtained); EOC 2 (coinciding with time of first response assessment or upon PD, whichever occurs first); End of Treatment (if after EOC 2; need not repeat if patient is discontinuing at the EOC 2 or if a sample was obtained upon PD)
- Skin biopsy (Part 1 only): Screening, EOC2 (i.e., coinciding with time of first response assessment) or upon PD, whichever occurs first

3.2.1.3 Immunogenicity Variables

Anti-drug antibody (ADA) Testing: all samples must be taken prior to the Sym015 infusion of that visit. Analysis of ADA and residual serum levels of Sym015 will be performed at a specialty laboratory. ADA samples are collected are C1/D1, C2/D1 (Part 2 only), Day 1 of every second cycle thereafter, i.e., Cycle 3, 5, 7 etc. (prior to dosing), EOT, 1M FUP.

3.2.2 Pharmacokinetic Variables

Derivation of PK parameters will be the responsibility of Symphogen A/S.

PK samples will be taken according to the schedules shown in CSP Table 9. The serum concentration of Sym015 is defined as the sum of the serum concentration of the two constituent antibodies of Sym015, Hu9006 and Hu9038-

The PK endpoints will be derived based on the serum concentration versus time curves of Sym015, and the first infusion of Sym015 in both parts of the trial. Refer to CSP Table 11.

C_{max}, C_{trough} and T_{max} will be derived from observed data while AUC_{τ}, $AUC_{norm,\tau}$, CL, V_z, and $T_{½}$ will be estimated using non-compartmental methods and actual time points.

Table 9 Schedule of Pharmacokinetic Assessments

		Cycle 1			Cycles Thereafter		EOT	IM FUP
Sampling Time	**Window**	**D1-D3**	**D8**	**D15**	**D1**	**D15**		
Part 1 / Part 2 Basket Cohort								
Prior to SOI	- 4 h	X		X[1]	X[1]	X[1]		
EOI	− 10 min	X		X[1]	X[1]	X[1]		
EOI + 1 h	±15 min	X						
EOI + 2 h	±30 min	X						
EOI + 4 h	±30 min	X						
EOI + 8 h	±90 min	X						
EOI + 24 h	±6 h	X						
EOI + 48 h	±12 h	X						
During Visit	NA		X				X	X
Part 2 NSCLC Cohorts (effective with protocol v8.0; December 2018)								
Prior to SOI	- 4 h	X		X[1]	X[1]	X[1]		
EOI	− 10 min	X		X[1]	X[1]	X[1]		
EOI + 4 h	±30 min	X						
EOI + 48 h	±12 h	X						
During Visit	NA		X				X	X

Abbreviations (in alphabetical order): D, day; EOI, End of Infusion; EOT, End of Treatment Visit; NA, Not Applicable; h, hour; min, minutes; IM FUP, 1-Month Follow-up Visit; SOI, Start of Infusion

1) If Sym015 is pursued, only one PK sample should be taken during the visit

Table 11 PK Endpoints Definitions and Derivations

Symbol	Definition and derivation
C_{trough}	Trough concentration (i.e., concentration of Sym015 measured pre-infusion)
AUC_τ	Area under the concentration-time curve in a dosing interval (i.e., from time zero (end of infusion) up to 336 hours or 504 hours depending on regimes). AUC_τ will be calculated using the linear trapezoidal method and interpolated in case of measurements after 336/504 hours, or extrapolated using terminal rate constant and the last quantifiable concentration. C_z
C_z	Last quantifiable concentration. C_z is not an endpoint, but is used for derivation of endpoints
$AUC_{norm,\tau}$	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 reach maximum concentration
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
$T_{\frac{1}{2}}$	Terminal elimination half-life, calculated as $\ln(2)/\lambda_z$
CL	Clearance (Dose/AUC_τ)
V_z	Volume of distribution during the terminal phase (CL/λ_z)

3.2.3 Safety Variables

- Medication/Procedure Survey
- Adverse Events (AE) Survey
- Dose-Limiting Toxicities Evaluation (Part 1 Only)
- Vital Signs and Body Weight
- Performance Status
- Physical Examinations
- Electrocardiograms (ECG)
- Echocardiogram (ECHO) or Multi-Gated Acquisition Scan (MUGA)
- Clinical Laboratory Assessments and Pregnancy Test

3.2.3.1 Medication/Procedure Survey

To include all medications taken other than Sym015 and all procedures performed during trial. For medications the following are collected: generic name or brand name, indication for use, dose and frequency, route of administration, start and stop dates or if ongoing at 1M FUP Visit. For procedures the following are collected: date and reason for procedure.

Collected starting from the date of Screening and until the date of the 1M FUP.

Full description and analysis are detailed in section 4.8.

3.2.3.2 Adverse Events (AE) Survey

All AEs will be recorded from signing of informed consent for participation in the trial. The recording period ends at the time of the 1M FUP Visit. All AEs should be followed until they are resolved or until the 1M FUP Visit, whichever comes first.

Definition of AE

An AE is any untoward medical occurrence in a patient or a clinical investigation Patient administered a pharmaceutical product, and which does not necessarily have a causal relationship with this treatment. An AE can therefore be any unfavorable and unintended sign (including an abnormal laboratory finding), symptom, or disease temporally associated with the use of an IMP, whether or not considered related to the IMP.

Causality for the above-mentioned AE will be assessed appropriately by the investigator as detailed below in this paragraph.

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

PD will not be captured as an AE unless the nature of the PD is different than expected (i.e., other diagnosis and/or signs/symptoms that are not typical of PD) as assessed by the Investigator.

Definition of Treatment-emergent AE (TEAE)

Treatment-emergent AEs (TEAEs) are events that occur on or after first dose of the study medication or a worsening in severity of a pre-existing condition occurring after first dose of the study medication.

Definition of Infusion Related Reaction (IRR)

An IRR is defined as an AE occurring during the Sym015 infusion and up to 2 hours after the end of infusion (EOI), which is assessed by the Investigator to be related to the infusion of Sym015. Signs of IRRs may include but are not limited to facial flushing and swelling, shortness of breath, headache, diaphoresis, tachycardia, hypotension, chills, rigors, chest and throat tightness, as well as chest, back and/or abdominal discomfort. If an IRR occurs, it should be classified according to the Common Terminology Criteria for Adverse Events (Version 4.03) (CTCAE v4.03). In all cases, the Investigator should use best clinical judgment in managing such reactions.

All IRRs must be reported in the CRF as an AE with the term "Infusion-related Reaction" followed by a specification of symptoms (e.g., "Infusion-related Reaction with dyspnea and flushing").

Definition of AE duration

AE duration will be derived as AE duration = (AE end date - AE onset date +1); in case of AE ongoing, the date of last contact with the patient will be used as AE for the scope of derive the AE duration.

Definition of Serious AE (SAE)

An SAE is an AE that meets one or more of the following outcome criteria:

- Results in death
- Is life-threatening (patient is at immediate risk of death at the time of the event; it does not refer to an event which hypothetically might cause death if it was more severe)
- Requires inpatient hospitalization or prolongation of existing hospitalization
- Results in persistent or significant disability/incapacity
- Is a congenital anomaly/birth defect
- Is medically important (Medically important events may not be immediately life-threatening or result in death or hospitalization but may jeopardize the patient or may require intervention to prevent one of the other outcomes listed in the definition above).

AE Severity

The Investigator will use the CTCAE v4.03 to describe the severity of an AE. If the severity of an AE is not specifically graded by the CTCAE guidance document, the Investigator should use the general definitions of Grades 1 to 5 as per the following, and use his/her best medical judgment to describe the severity of the AE:

- Grade 1: Mild
- Grade 2: Moderate
- Grade 3: Severe

- Grade 4: Life-threatening or disabling
- Grade 5: Death caused by the event

Changes in severity of AEs will be recorded.

AE Relationship to IMP

The Investigator must assess causal relationship to the IMP, Sym015. The causal relationship is an assessment of whether or not the event is related to the use of the IMP. It is not an evaluation of whether or not the event could hypothetically occur in the investigational patient population.

The causal relationship of an AE to the IMP, Sym015, will be rated as follows:

- Not Related: The AE is not related to the IMP, which means the event:
  - Does not follow a reasonable temporal sequence from drug administration
  - Is readily explained by the patient's clinical state or by other modes of therapy administered to the patient
  - The AE is clearly NOT related to the IMP
- Unlikely Related: The AE is considered not related to the IMP based on the following:
  - Does not follow a reasonable temporal sequence from administration of drug
  - Could readily be a result of the patient's clinical state, environmental, or toxic factors, or other modes of therapy
  - Does not follow a known response pattern to the suspected drug
  - Does not reappear or worsen when the drug is re-administered
- Possibly Related: The AE might not be related, but possibility cannot be ruled out with certainty and therefore would be considered related based on:
  - Follows a reasonable temporal sequence from administration of drug

- Could readily have been a result of the patient's clinical state, environmental or toxic factors, or other modes of therapy
- Follows a known response pattern to the suspected drug

- Probably Related: It has been determined with a high degree of certainty that the AE is associated with administration of IMP based on:
  - Follows a reasonable, temporal sequence
  - Cannot be reasonably explained by known characteristics of the patient's clinical state, environmental, or toxic factors, or other modes of administered therapy
  - The AE disappears or decreases in severity upon cessation of drug, or reduction in dose.
  - Follows a known response pattern to the suspected drug
- Related: The AE is related to the IMP, which means the event:
  - Follows a reasonable temporal sequence from drug administration
  - Abates upon discontinuation of the IMP (de-challenge)
  - Is confirmed by reappearance of the reaction on repeat exposure (re-challenge)
  - Cannot be reasonably explained by the known characteristics of the patient's clinical state
  - Is not likely to have been produced by the patient's clinical state or by other modes of therapy administered to the patient

Outcome

Outcome of the AE must be assessed by the Investigator utilizing one of the following terms:

- Recovered
- Recovered with sequelae (if recovered with sequelae, specify sequelae)

- Not recovered
- Fatal
- Unknown

Instructions for reporting changes in an ongoing AE during a patient's participation in the trial are provided in the instructions that accompany the AE CRF pages.

Handling of partial AE onset and end date

Any AEs with incomplete start and end dates will be treated as follows:

- Adverse events with completely unknown onset date will be considered as treatment-emergent; for the scope of AE duration derivation, these AE will be considered as occurred the day of first IMP infusion.
- Adverse events with unknown start day and month but with known start year will be considered:
  - as treatment-emergent if the start year coincides or is after the first dosing year; for the scope of AE duration derivation, these AE will be considered as occurred the day of first IMP infusion if the start year coincides with first dosing year, as occurred on 1st January otherwise (i.e. in case the start year is after the first dosing year)
  - as non-treatment emergent if start year is before the first dosing year; for the scope of AE duration derivation, these AE will be considered as occurred on 1st January.
- Adverse events with unknown start day but with known start month and year will be considered:
  - as treatment-emergent if the start month and year coincide or are after the month and year of first dosing; for the scope of AE duration derivation, these AE will be considered as occurred the day of first IMP infusion if the start month and year coincides with first dosing month and year, as occurred on 1st day of the month otherwise (i.e. in case the month and year is after the month and year of first dosing)

- as non-treatment emergent if start month and year is before the month and year of first dosing; for the scope of AE duration derivation, these AE will be considered as occurred on 1st day of the month.

- Adverse events with completely unknown end date will be considered as ended on the day of last contact with the patient).

- Adverse events with unknown end day and month but with known end year:
  - if the AE end year if before the year of last contact with the patient, AE will be considered as ended on 31th December.
  - if the AE end year coincide with the year of last contact with the patient, AE will be considered as ended on day of last contact with the patient.
  - If AE end year is after the year of last contact with the patient, for the scope of derive the AE duration the date of last contact with the patient will be used as AE end date.

- Adverse events with unknown end day but known end month and end year:
  - if the AE end month and year are before the month and year of last contact with the patient, AE will be considered as ended on last day of the month.
  - if the AE end month and year are coinciding with the month and year of last contact with the patient, AE will be considered as ended on last day of last contact with the patient.
  - If AE end month and year are after the month and year of last contact with the patient, for the scope of derive the AE duration the date of last contact with the patient as AE end date.

Adverse events with completely or partial unknown start and end dates will be shown as not known (NK), for the respective unknown part, in the listings.

3.2.3.3 Dose-Limiting Toxicities Evaluation (Part 1 Only)

A DLT is defined as any of the following toxicities that occur during the DLT observation period, if considered related (causality rating of possibly, probably, or related) to Sym015:

1. Grade 3 non-hematologic toxicity regardless of duration, with the exceptions of:
   a. Grade 3 nausea, vomiting, diarrhea, or fatigue lasting ≤ 2 days with best supportive care
   b. Grade 3 asymptomatic electrolyte abnormalities lasting ≤ 3 days that are not considered clinically relevant by the Investigator and that resolve with medical therapy
2. Any Grade 4 non-hematologic toxicity, with the exception of:
   a. Grade 4 asymptomatic electrolyte abnormalities lasting < 3 days that are not considered clinically relevant by the Investigator and that resolve with medical therapy.
3. Neutropenia that is:
   a. Grade 3-4 febrile neutropenia
   b. Grade 4 and sustained (i.e., ANC <500 per mm3, duration >5 days)
4. Thrombocytopenia that is:
   a. Grade 3 with clinically significant hemorrhage
   b. Grade 4 (platelets < 25,000 per mm3)
5. AST/ALT elevation > 3xULN with bilirubin elevation > 2xULN that cannot be explained by factors not related to study drug
6. Inability to complete Cycle 1 at the assigned dose due to ≥ Grade 3 toxicity
7. Treatment delays >2 weeks from the scheduled "next dose" due to ≥ Grade 3 toxicity

DLT events (Yes / No) are collected in CRF as well as date of assessment, DLT description and AE Reference.

The observation period for DLTs is defined as Cycle 1 with a final assessment 14 (±2) days after the last dose of Cycle 1 or prior to dosing on C2/D1.

Cycle 1 must have been completed at the assigned dose of Sym015 for a patient to complete the DLT observation period.

3.2.3.4 Vital Signs and Body Weight

To include temperature, heart rate, blood pressure, and body weight. Collected at Screening, Prior to each dosing, at EOT, at 1M FUP and as clinically indicated

3.2.3.5 Performance Status

To be assessed by Eastern Cooperative Oncology Group (ECOG) performance Status (PS) score. Collected at Screening, at Day 1 of each cycle (prior to dosing; does not need to be assessed prior to C1/D1 if assessed during screening ≤ 7 days from C1/D1), at EOT, at 1M FUP and as clinically indicated.

ECOG PS Score:

- 0=Fully active, able to carry on all pre-disease activities without restrictions
- 1=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=Ambulatory and capable of self-care, but unable to carry out any work activities. Up and about more than 50% of waking hours
- 3=Capable of only limited self-care, confined to bed or chair more than 50% of waking hours
- 4=Completely disabled. Cannot carry on self-care. Totally confined to bed or chair
- 5=Dead

3.2.3.6 Physical Examination

To include evaluation of the following at Screening: General appearance, skin, head, ears, eyes, nose, throat, neck/thyroid, chest, cardiovascular system, abdomen, musculoskeletal system, lymph nodes, neurologic status, and mental status; include height (without shoes, rounded to nearest centimeter). Thereafter, a targeted physical examination may be performed as indicated.

To be assessed at Screening, at Day 1 of each cycle (prior to dosing; does not need to be performed prior to C1/D1 if performed during screening ≤ 7 days from C1/D1), at EOT, at 1M FUP, and as clinically indicated.

3.2.3.7 Electrocardiograms (ECG)

A 12-lead ECG will be performed on Screening, EOT, and as clinically indicated.

Parameters measured will include heart rate, PR, R-R, QRS, QT, and QTc intervals (calculated by the Fridericia [QTcF] or Bazzett's [QTcB] correction formula). Clinical assessment (abnormality as clinically significant or not clinically significant) will be performed.

3.2.3.8 Echocardiogram (ECHO) or Multi-Gated Acquisition Scan (MUGA)

ECHO or MUGA scan will be performed at Screening, in the event of cardiac symptoms (e.g., shortness of breath, edema) and as otherwise clinically indicated.

3.2.3.9 Clinical Laboratory Assessments and Pregnancy Test

Blood samples will be taken at all scheduled visits and will be analyzed for the following parameters as per CSP Table 8 and as clinically indicated:

Table 8 Schedule of Safety Blood and Urine Samples

Sample Analysis	Screening	Cycle 1				Cycles Thereafter		EOT	1M FUP
Day within Cycle		D1	D3 D8	D15	D22	D1	D15		
Hematology Panel	X	X[1]	X	X	X	X	X	X	X
Biochemistry Panel	X	X[1]	X	X	X	X	X	X	X
Coagulation Panel	X	X[1]	X	X	X	X	X	X	X
Urinalysis	X	X[1]		X		X		X	X
Pregnancy Test	X							X	

Abbreviations (in alphabetical order): D, day; EOT, End of Treatment Visit; 1M FUP, 1-Month Follow-up Visit

1) Does not need to be performed prior to C1/D1 if performed during screening ≤7 days from C1/D1

- Hematology panel (complete blood count with differential, ANC, and platelet count): at Screening, Cycle 1 (weekly prior to dosing if on dosing day, Day 3. Note: Does not need to be performed prior to C1/D1, if performed during screening ≤7 days from C1/D1), each cycle thereafter (Day 1 and 15 prior to dosing), EOT, 1M FUP, and as clinically indicated.

- Biochemistry panel (sodium, potassium, chloride, bicarbonate or carbon dioxide, blood urea nitrogen (BUN), creatinine, glucose, bilirubin [total and direct], AST, ALT, ALP, calcium, magnesium, phosphorus, albumin, total protein, uric acid, amylase, lipase, and creatine kinase): at Screening, Cycle 1 (weekly prior to dosing if on dosing days, Day 3. Note: Does not need to be performed prior to C1/D1, if performed during screening ≤7 days from C1/D1), each cycle thereafter (Day 1 and 15 prior to dosing), EOT, 1M FUP, and as clinically indicated.

- Coagulation panel (PT, PTT and INR): at Screening, Cycle 1 (Day 1 and 15 prior to dosing. Note: Does not need to be performed prior to C1/D1, if performed during screening ≤7 days from C1/D1), each cycle thereafter (Day 1 prior to dosing), EOT, 1M FUP, and as clinically indicated.

- Urinalysis (specific gravity, pH, protein, glucose, ketones, occult blood, leukocyte esterase, nitrite, bilirubin, and urobilinogen): at Screening, Cycle 1 (Day 1 and 15 prior to dosing. Note: Does not need to be performed prior to C1/D1, if performed during screening ≤7 days from C1/D1), each cycle thereafter (Day 1 prior to dosing), EOT, 1M FUP, and as clinically indicated.

- Pregnancy test (serum human Chorionic Gonadotropin (β-hCG) at screening, urine β-hCG thereafter, in women of childbearing potential): at Screening, EOT and as clinically indicated.

All clinical laboratory test results will be graded per NCI CTCAE v4.03 if applicable, as well as high (higher than the normal range), normal (in the normal range) and low (lower than normal range).

4 STATISTICAL METHODS

4.1 Data Quality Assurance

All tables, figures and data listings to be included in the report will be independently checked for consistency, integrity and in accordance with standard [redacted] procedures.

4.2 General Presentation Considerations

4.2.1 Baseline

'Baseline' is defined as the last available pre-treatment assessment, considering both scheduled and unscheduled assessments.

Safety assessments at Cycle 1 Day 1 with no time of assessment (i.e. Vital Signs and Body Weight, ECOG PS, Physical Examination) are assumed to be taken pre-treatment.

4.2.2 End of Treatment (EOT)

'End of Treatment' is defined as the first assessment obtained on or after the last dose of study treatment, considering both scheduled and unscheduled assessments.

4.2.3 Unscheduled assessments

Unscheduled assessments will be presented in listings in chronological order.

By-visit summaries of each test/exam will be tabulated according to the protocol defined visit schedule.

Post Baseline safety unscheduled assessments (for Clinical Laboratory, ECG QTc, etc.) will be used for determination of worst result (i.e. Maximum and Minimum post Baseline result) as well as the maximal laboratory CTCAE grade if applicable; also, all post baseline tumor evaluation assessments will be used to derive BOR.

Moreover, post baseline, worst by-visit result will be used in by-visit summaries of Clinical Laboratory. In this case, both scheduled and unscheduled results will be used to determinate worst by-visit result. Each unscheduled result will be bracketed into scheduled visits. Sites should define which scheduled timepoint each unscheduled laboratory assessments belongs to; this information is captured in CRF. In the case such information will not be available, following rules will apply:

- safety blood laboratories obtained after first dosing and up to C1D5 will be bracketed in C1D3;
- safety blood laboratories obtained from C1D6 up to C1D10 will be bracketed in C1D8;
- safety blood laboratories obtained from C1D11 up to pre-dose on the day of Cycle 1 second infusion will be bracketed in C1D15;
- safety blood laboratories obtained from post-dose on the day of Cycle 1 second infusion up C1D24 will be bracketed in C1D22
- safety blood laboratories obtained from C1D25 to pre-dose on the day of Cycle 2 first infusion will be bracketed in C2D1;
- safety blood laboratories obtained from post-dose on the day of Cycle 2 first infusion up to pre-dose on the day of Cycle 2 second infusion will be bracketed in C2D15;
- safety blood laboratories obtained from post-dose on the day of Cycle 2 second infusion up to pre-dose on the day of Cycle 3 first infusion will be bracketed in C3D1;
- Starting from C3, safety blood laboratories obtained from post-dose on the day of the previous Cycle second infusion up to pre-dose on the day of the current Cycle first infusion will be bracketed in the current Cycle D1;

- Starting from C3, safety blood laboratories obtained from post-dose on the day of the current Cycle first infusion up to pre-dose on the day of current Cycle second infusion will be bracketed in the current Cycle D15;

Safety blood laboratory result associated with higher CTCAE grade by visit, will be flagged as worst by visit result and used in by visit summary tables; if multiple within visit unscheduled results are associated with the same CTCAE grade, the most extreme value in the direction used for CTCAE grade derivation will be flagged as the worst. Safety blood laboratory test for which a CTCAE grade derivation rule is not available, the by visit result farthest to the normal range limit will be flagged as worst by visit result and used in by visit summary tables; results above normal ranges will be compared with upper limit of normality, while results below normal ranges will be compared with lower limit of normality; it is not expected to observe in the same visit abnormal high and low results, should this occur the worst within visit will be manually flagged after data review from medical perspective. In case all by visit results are within normal ranges and not associated with a CTCAE grade, or in case no CTCAE and no normal ranges are available for a specific parameter, result obtained at the scheduled assessment will be used in the by visit summary tables and if no scheduled assessment is available the by visit unscheduled closest to the scheduled timepoint will be considered.

Except considered as Baseline, EOT or worst result or worst by visit result for safety blood laboratories, unscheduled assessments will not be included in summaries.

4.2.4 Treatment Day

'Treatment Day' will be calculated relative to the date of C1/D1 as follow:

- assessments taken before the first infusion of IMP

  Treatment Day = Assessment Date - First IMP infusion Date

- assessments after the first infusion of IMP

  Treatment Day = Assessment Date - First IMP infusion Date + 1.

4.2.5 Missing Data

In case of partially missing date of birth or date of diagnosis, the following rule will be applied: if year and months are known but day is missing, then the day will be imputed as 15th; in case of only year known, the day and month will be imputed as 15th June.

Specific rules for handling for missing efficacy assessments are detailed in section 4.11.1.3.

Methods for handling missing concomitant medication and adverse events dates are detailed in sections 4.8 and 3.2.3.2 respectively.

Imputations will be used to derive parameters, in listings original data will be presented as collected.

4.2.6 Data Listing

All original and derived parameters will be listed.

All listings will include scheduled and unscheduled measurements.

Unless specified otherwise, data in listings will be presented by Study Part (Part 1 and Part 2), Cohort (dose group in Part 1), patient, and visit (ordered by date and time within patient).

All listings will display the same number of decimals as in the source data. All raw data will be reported exactly as provided.

The data for the patients who consented but for any reason did not receive any dose of study drug (including screening failures) will be also listed but with a label of '*'and a footnote to flag these.

Populations used to produce listings are defined in section 4.5.

4.2.7 Tables and Descriptive Statistics

Unless specified otherwise summary tables and figures will be presented by Study Part (Part 1 and Part 2), Cohort (dose group in Part 1) and visit (as applicable); also, overall summaries will be shown for the two study parts and for all patients pooled together. In general, summary tables will be structured in three panels: first panel will summarize overall results obtained in the study parts

and in all patients pooled together; second panel will display all dose groups within the Study Part 1; third panel will display all cohorts within the Study Part 2. Changes from baseline in categorical data may be summarized using shift tables where appropriate; in shift table each study Part and Cohort will be appear in a different panel, i.e. first panel will be for 'Overall Part 1 + Part 2', second panel will be for 'Overall Part 1', third panel will be for 'Overall Part 2', then a panel for each dose groups within Part 1, finally a panel for each cohort within Part 2.

In general, for variables showing multiple possible categories, these will be displayed following the within variable logic criteria, for example: ECOG categories will be displayed from 0 and going to grow; where such a logic criterium does not exist (example: gender, ethnicity, SOC, PT), categories will be displayed by descending frequencies based on the overall all patients pooled together. In the end, the order used to show categories within variables should be the same in the three parts of each table.

Unless otherwise stated, continuous data will be summarized using descriptive statistics including: number of non-missing observations (n), arithmetic mean, standard deviation (SD), median, minimum, and maximum.

Categorical data will be summarized in terms of the number of patients providing data at the relevant time point, frequency counts and percentages. Any planned collapsing of categories will be detailed in the SAP text and the data displays. Unless otherwise specified, percentages will be calculated using number of patients providing data at the relevant time point as the denominator.

For visits at which less than 10 patients in the expansion cohorts remain on study treatment, statistical summaries will no longer be produced.

The following rules will apply to all descriptive statistic displays, except the PK concentrations, and parameters that are reported in significant digits as described below, where 'd' denotes the decimal places in the original reported value:

- n: 0 decimal places (d.p.)
- Mean: d + 1 d.p.

- Confidence Interval: d + 1 d.p.
- SD: d + 2 d.p.
- Median: d + 1 d.p..
- Minimum: d.
- Maximum: d.
- Statistics in percentage: 1 d.p.
- p-value: 4 d.p.
- Except for p-value, a maximum of 3 decimal places will be displayed.

P-values greater than or equal to 0.001, in general, will be presented to three decimal places. P-values less than 0.001 will be presented as "<0.001".

Details for reporting of statistical summaries specific to PK are detailed in section 4.11.4.4.

All tables, listings, and graphs will be produced to landscape orientation using Courier New 9pt font and will be incorporated into a MS Word document as a (RTF) rich text file (margins on standard A4: Margins (top, left, right, and bottom) 2.54 cm.

4.2.8 Figures

If not otherwise specified, each figure will be presented separately for the two study parts with differentiate legend to discriminate the dose groups within the regimen, e.g. different line types can be used for each group; moreover, an overall figure will also be presented with differentiate legend to discriminate the two study parts. In the end, there will be three panel for each figure: first panel will show all patients, second panel patients in study part 1, third panel patients in study part 1.

All figures will be produced in black and white.

4.3 Software

The tables, listings, figures and any non-descriptive statistical analysis will be produced using SAS® Software (Version 9.3 or higher). The REPORT procedure (SAS PROC Report) will be used to produce all tables and listings; SAS/GRAPH will be used to produce all figures.

4.4 Study Patients

4.4.1 Disposition of Patients

The patient disposition including the date the informed consent was signed, date of last infusion of study drug and the primary reason for End of Treatment will be listed. Moreover, the number of patients who consented to the study, were exposed to study treatment and primary reason for end of treatment will be summarized.

Those patients who did not meet the eligibility criteria or were screen failures will be listed.

A listing of patients included into each of the analysis set will be presented, related summary statistics will be provided.

A clear accounting of the disposition of all patients who enter the study will be provided, from screening to study completion.

4.4.2 Protocol Deviations

A protocol deviation is any change, divergence, or departure from the study design or procedures of a study protocol. All protocol deviations will be listed by patient. All protocol deviations will be discussed during Data Review Meeting (DRM) and addressed with the "final" classification together their overall effect on a patient, as well, assignment of each patient to the analysis sets will be decided. During DRM, all protocol deviations and their possible impacts will be discussed between [redacted] and the Sponsor and will be assessed as "minor" or "major". Major protocol deviations and protocol deviations affecting primary analyses can lead to the exclusion of a patient from the analysis sets. Reasons for excluding patients from any analysis set will be reported and described in the DRM Report that will be finalized before database hard lock and signed off by all relevant scientific experts.

4.5 Analysis Sets

Analysis sets are defined in accordance with the consolidated ICH E9 GCP guidelines.

The Full Analysis Set (FAS) will comprise all enrolled patients who have received at least one dose of Sym015. 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. For the evaluation of PK endpoints; patients, full profiles, or single measurements can be excluded from the analyses. The decision of excluding patients, full profiles, or part of profiles will be described in the clinical trial report (CTR).

The DLT Analysis Set will comprise all patients in the FAS enrolled in Part 1, except patients who did not complete Cycle 1 (i.e., the initial 28-day period of Q2W dosing) for reasons other than drug toxicity. The DLT Analysis Set will be used for evaluation of DLTs.

Demographic and Baseline Characteristics and Safety variables will be listed based on all consented patients, not treated patients will be flagged as specified in section4.2.6.

Efficacy, Immunology, Pharmacodynamic and Pharmacokinetic variables will be listed based on FAS.

In general, all summary tables will be produced based on FAS.

DLT listing and DLT event evaluation will be based on DLT Analysis Set.

4.6 Demographics and Baseline Characteristics, Disease History and Prior Cancer Therapies

The following demographic and baseline variables will be recorded:

- Date of informed consent
- Date of Birth
- Gender, Race and Ethnicity
- Height

- Weight at screening and baseline
- Stage at initial diagnosis and current stage
- Screening and baseline ECOG PS (categories)
- Disease history and diagnosis, including:
  - Site of primary tumor
  - Date of initial diagnosis
  - Histopathologic diagnosis
  - Sites of metastases
  - MET-amplification Status: Amplified [yes, no, unknown]
  - Fluorescence In Situ Hybridization (FISH)
  - Chromogenic In Situ Hybridization (CISH)
  - Silver In Situ Hybridization (SISH)
  - Next-Generation Sequencing (NGS)
  - Quantitative PCR (qPCR)
  - KRAS Mutation Status [Wild Type, Mutated]
  - METex14 Mutation Status [Yes, No, Not Applicable] (only collected from Protocol version 7)
  - Debulking surgery performed [yes, no], if yes date of debulking
  - Date of most recent progression
- Prior cancer therapies (surgical procedure and prior radiation and systemic therapy including dates of the treatments and, as applicable, body site or location, dose, best response, reason for discontinuation and progression date).

Age at consent in years will be derived as (Year of informed consent signed – Year of date of birth) + 0 if the month and day of informed consent signed >= the month and day of date of birth, else + 1. The following age classes will be as well derived: < 65 years; 65 - <75 years; 75 - <85 years; 85 years or older.

BMI at baseline will be calculated as Weight [kg] / (Height [m])^2

Time since initial diagnosis will be derived as (Year of informed consent signed – Year of initial diagnosis) + 0 if the month and day of informed consent signed >= the month and day of initial diagnosis, else + 1.

Number of sites with metastases will be derived by counting all sites with metastases.

Prior systemic therapies for cancer will be counted by patient and summarized as 0, 1, 2, 3, 4+ for each patient.

Regimens containing MET targeting, EGFR targeting, as well as PD1/PDL1 targeting agents will be manually identified and flagged in the list of the prior systemic therapies.

Anatomic based cancer type categorization will be manually defined for each patient based on primary tumor site which may also be combined with tumor histology.

Demographic and baseline characteristics, Disease History and Prior Cancer Therapies will be listed.

Descriptive continuous statistics will be presented for:

- Demographic and baseline characteristics (including age in years, height, weight and baseline BMI)
- Disease History information (including Time since initial diagnosis [years]).
- Cancer Gene Mutation as part of Disease History (including FISH, CISH, SISH, NGS and Quantitative PCR)

The frequency and percentage of patients will be tabulated for:

- Demographic and baseline characteristics categorical variables (including age classes, gender, race, and ethnicity);
- Disease History information includes Cancer Baseline Characteristics (Site of primary tumor, Histopathologic Diagnosis, Anatomic based cancer type, prior debulking surgery [yes, no], sites of metastases and number of sites with metastasis, baseline ECOG PS) and Cancer Gene Mutation -(MET amplification Status [Amplified, Non-Amplified], KRAS Mutation Status [Wild Type, Mutated], METex14 Mutation Status [Yes, No, Not Applicable]);
- Prior Cancer Therapies (including prior surgical treatment [yes/no], prior radiation therapy [yes/no], number of prior systemic therapies [0, 1, 2, 3, More than 3]), Prior MET targeting therapies [yes/no], Prior EGFR targeting therapies [yes/no], Prior PD1/PDL1 targeting therapies [yes/no].

Date of informed consent, date of birth, weight at screening, Stage at initial diagnosis and current stage, ECOG at screening, date of initial diagnosis and date of most recent progression will only be listed.

4.7 Medical History

Medical history is assessed at screening and include prior and ongoing medical illnesses and conditions and prior surgical procedures not related to the primary diagnosis.

Medical History terms will be coded using Medical Dictionary for Regulatory Activities (MedDRA) version 22.0 or later version. Medical History terms will be listed only.

4.8 Prior and Concomitant Medications and Concomitant Procedures

Medications are all prescription medications, over-the-counter medications, or alternative therapies registered from screening through 30 days after the last dose of study drug. Medications will be listed (excluding Premedication for Sym015 Infusions which will be listed separately).

Medications will be coded using the World Health Organization Drug Dictionary (WHODD), version global 2019 March B3 or later version and will be presented by WHODD Anatomical-Therapeutic-Chemical (ATC) therapeutic classification and preferred term (PT).

Medications and treatments administered prior to the first infusion of study drug which stopped prior to first infusion of study drug will be considered as prior medications and flagged in the listing.

Medications and treatments which started before, on or after the first infusion of study drug and which stopped after first infusion of study drug (including medications and treatments which stopped the day of first infusion) will be considered as concomitant medications.

If medication start and/or stop dates are missing or partial, the dates will be compared as far as possible with the date of first dose of study medication. Medications will be assumed to be concomitant, unless there is clear evidence (through comparison of partial dates) to suggest that the medication stopped prior to the first dose of study medication. If there is clear evidence to suggest that the medication stopped prior to the first dose of study medication, the medication will be assumed to be Prior.

Concomitant procedures performed during the study will be collected and listed.

4.9 Pre-medications for Sym015

A premedication schedule is implemented for all patients treated.

For Part 1 of the trial, premedication is mandatory prior to each dose of Sym015.

For Part 2 of the trial, premedication is mandatory prior to each dose of Sym015 during Cycle 1; if a patient is without evidence of IRRs after Cycle 1, the Investigator may opt to withdraw premedication on a patient-by-patient basis with subsequent dosing.

All pre-medications will be listed. Study drug administrations proceeded by premedication will be flagged in the corresponding listing.

4.10 Treatment Exposure and Compliance

Data of study drug infusion including dose reduction and interruption information, patient drug administration irregularities (dose reduction and interruption) and infusion related reaction will be listed.

Duration of the Sym015 exposure, treatment duration, actual number of doses, planned total dose, actual total dose and Relative Dose Intensity (RDI) will be derived as follow:

- Duration of exposure (days) = (last dose date - first dose date + 1)
- Actual Treatment duration (days) = (last dose date - first dose date + 14)
- Actual Treatment duration (weeks) = (last dose date - first dose date + 14) / 7

  Actual Treatment duration (week) will be presented at one decimal place precision.
- Number of treatment cycles initiated (i.e. at least one infusion for the cycle)
- Number of treatment cycles completed (i.e. all cycle infusions were received by the patient)
- Planned total number of doses = (Date of last dose – Date of first dose + 1) / 14 rounded up to integer
- Planned total dose = Planned dose * Actual total number of doses received
- Planned treatment duration (weeks) = Actual total number of doses × 2
- Planned treatment duration (days) = Actual total number of doses × 14
- Relative dose intensity (RDI)

$$RDI\ (\%) = 100 \times \frac{\text{Sum of all received dose/Actual treatment duration (days)}}{\text{Total planned dose / Planned treatment duration (days)}}$$

  whereas the total planned dose (mg/kg) and planned dose duration are calculated based on the number of doses of the study medication a patient had received at the initially planned dose (mg/kg) for the cycle according to the planned dosing schedule.

Example, if a patient received 8 bi-weekly (i.e. dose regimen Q2W) doses of a study medication with a loading dose of 12 mg/kg and rest 9 mg/kg, with 1 dose reduction from 9 mg/kg to 6 mg/kg starting at week 14 and 1 week delay and at week 16, then

$$RDI\ (\%) = 100\ \times \frac{(12 + 5 \times 9 + 2 \times 6)\ /\ 119}{(12 + 7 \times 9)\ /\ 112} = 86.6\%$$

The number of initiated and completed cycles of taking Sym015 will be summarized both as categoric (0, 1, 2, 3, 4, 5, 6, >6) and continuous parameter.

Duration of the Sym015 exposure, treatment duration, actual number of doses will be summarized as continuous variables. RDI will be summarized both as categoric (> 100%; 90 % - 100 %; 80 % - < 90%; 70 % - < 80%) and continuous parameter. Swimmer Plot will be presented showing Treatment Duration together with Tumor Response data.

Number of patients who had dose reduction (Any, 1, 2, 3+ times) and dose interruption (Any, 1, 2, 3+ times) will be summarized.

In this section, percentages are intended to be calculated using the number of patients dosed in each group, or the Full Analysis Set for the overall study group, as denominator.

4.11 Efficacy Evaluation

4.11.1 Analysis and Data Conventions

No formal testing of hypotheses has been planned in this study. Therefore, no formal sample size calculations were performed.

4.11.1.1 Multi-center Studies

There will not be any adjustment for study centers, subgroup analysis based on study centers are not planned.

4.11.1.2 Adjustments for Covariates

No statistical models will be provided for the analysis of Study Endpoints. All study analyses will be descriptive and will be seen from an exploratory perspective. No adjustment for covariates is expected.

4.11.1.3 Handling of Dropouts or Missing Data

Efficacy data that are reported as missing will be excluded from all descriptive and non-descriptive data analysis. There will be no imputation of missing efficacy data.

For general rules about handling of missing data refer to section 4.2.

4.11.1.4 Multiple Comparisons/Multiplicity

Not Applicable.

4.11.1.5 Interim Analyses

No interim analysis is planned other than evaluations for dose escalations. No statistical adjustments will be made for the interim look of the data during the study.

All relevant safety and toxicity data will be reviewed on an ongoing basis throughout the trial.

4.11.1.6 Examination of Subgroups

Anatomic based cancer type will be used as a subgroup to summarize some study endpoints or as stratification factor in certain graphics as appropriately described in the text of this SAP. Anatomic based cancer type categorization is derived as described in section 4.6.

4.11.2 Analysis of Efficacy Variable

All statistical analysis of the efficacy endpoints will be presented using the FAS.

All Efficacy Endpoints will be listed.

Time to Event endpoints (TTP, PFS, OS) will be listed at 1 d.p. precision.

In this section, percentages are intended to be calculated using the number of patients dosed in each group, or the Full Analysis Set for the overall study group, as denominator.

4.11.2.1 Anti-Tumor Response according to RECIST v1.1

The following anti-tumor response endpoints will be measured:

- Number and percentage of patients with documented confirmed OR will be summarized by Study Part and Cohort (dose group in Part 1) using frequency distribution with the corresponding 90% exact Clopper-Pearson Confidence Intervals (CI) for binomial proportion. All documented confirmed ORs will be listed.

- Duration of response (DR) will be listed and summarized as a continuous variable by Study Part and Cohorts (dose group in Part1)

- Best overall response (BOR) will be listed and summarized by Study Part and Cohorts (dose group in Part1) using frequency distribution for the categories Confirmed/Unconfirmed CR, Confirmed/Unconfirmed PR, SD, PD, and Not Evaluable.

- Patients in DCR will be listed and summarized by Study Part and Cohorts (dose group in Part1) using frequency distribution with the corresponding 90% exact Clopper-Pearson Confidence Intervals (CI) for binomial proportion.

- Stable Disease (SD)

  Number and percentage of patients with SD duration $\geq$ 4 months and SD $\geq$ 6 months will be presented summarized by Study Part and Cohorts (dose group in Part1).

- Changes in sum of diameters of target lesions from baseline

  Changes in the sum of diameters of target lesions from baseline will be listed as percentage and absolute value, the best change (i.e. the nadir, largest reduction or smallest increase) will be identified and presented using summary table and plotted with a waterfall plot. Change in sum of diameters will also be presented by anatomic based cancer type.

- Time to Progression (TTP)

  TTP will be analyzed with Kaplan Meier product-limit method. The median TTP, as well as 6-month and 12-month progression rates and the corresponding 90% CIs will be estimated using the product-limit method and presented using a Kaplan-Meier plot with median TTP rate marked, and the number of patients at-risk presented at 2, 4, 6, 8, 10 and 12 months, and each two months going forward, as applicable.

- Progression Free Survival (PFS)

  PFS, including PFS per additional sensitivity analysis, will be analyzed with Kaplan Meier product-limit method. The median PFS, as well as 6-month and 12-month progression rates and the corresponding 90% CIs will be estimated using the product-limit method and presented using a Kaplan-Meier plot with median PFS rate marked, and the number of patients at-risk presented at 2, 4, 6, 8, 10 and 12 months, and each two months going forward, as applicable.

- Overall Survival (OS)

  OS will be analyzed with Kaplan Meier product-limit method. The median OS, as well as 6-month and 12-month progression rates and the corresponding 90% CIs will be estimated using the product-limit method and presented using a Kaplan-Meier plot with median OS rate marked, and the number of patients at-risk presented at 6, 12, 18, and 24 months, and each six months going forward, as applicable.

- Results of the tumor evaluation by CT/MRI for target lesions, non-target lesions and tumor response will be listed.

4.11.3 Pharmacodynamic and Immunogenicity

These variables include:

- Tumor markers: Evaluated at timepoints coinciding with the CT/MRI imaging studies
- Archival Tumor Tissue for MET and KRAS

- Tumor Biopsy for MET Status
- Tumor Biopsy for Eligibility and Biomarkers Analysis
- Blood Sample for Genomic and Biomarker Analyses. Potential biomarkers of interest include genes, gene transcripts and proteins of the RTKs and molecules of the MET signalling pathway, including MET, HGF, EGFR, HER2, HER3, IGF1R, ROS1, RET, PIK3CA, PTEN, cMYC, KRAS, NRAS, BRAF, AKT1, FGFR, and RON. Analysis of biomarker blood samples may include genes and/or proteins that are unknown or have not been included in the scientific hypotheses of this trial, but that, during the collection of data from this trial, may evolve as new candidate genes and markers related to Sym015 safety, efficacy, or mechanism of action.
- Skin Biopsy results (Part 1 only).
- Anti-drug antibody (ADA) Testing.

All these data will be listed.

Data driven exploratory analysis may be conducted according to the study exploratory objectives based on the available Pharmacodynamic data.

Percentage and nominal change in target expression (parameters) from baseline to end of Cycle 2 or PD (whichever comes first) in skin biopsy samples will be presented in study part 1. Descriptive statistics will be used, including scatter plots of values at end of Cycle 2 versus baseline.

4.11.4 Pharmacokinetics

4.11.4.1 Pharmacokinetic Concentrations

The serum concentration of Sym015 is defined as the sum of the serum concentration of the constituent antibodies, Hu9006 and Hu9338. Serum concentrations for Sym015 and each of the constituent antibodies, Hu9006 and Hu9338 will be listed by Study Part, cohort (dose group in Part 1), patient, including actual time relative to dosing (minutes), scheduled time (derived based

on datetime of dosing and schedule of PK assessments) and time deviation from scheduled time (minutes).

The following definitions are used for PK plots and tables:

- First profile: all PK data points from Cycle 1 Day 1 to Cycle 1 Day 15 (pre-dose)
- Dosing/sampling occasions: Week 1, 3, 5, 7, 9 etc., EOT, 1MFUP
- Peaks: serum concentration assessed at EOI for each dosing occasion
- Troughs: serum concentrations assessed prior to SOI for each dosing occasion

Violations of scheduled sampling will be reviewed on a patient by patient basis by Symphogen and [redacted] Following data review by Symphogen's pharmacokinetic expert, data points may be excluded from mean calculations and parameter calculation based on the below criteria:

- Individual outlying data points which are markedly deviating from the preceding and following time points
- Data points or PK profiles which are not compatible with known physiological processes underlying the PK properties
- Unexpected events or protocol deviations documented in e.g. laboratory notes or in protocol deviation reviews

Exclusions will be documented in the study files and the PC/PP files.

Patient profiles of Sym015 plasma concentrations vs. time points will be plotted by Study Part and cohort (dose group in Part 1) and analyte (Hu9006, Hu9038 or Sym015). Following plots will be produced:

- Patient Profiles (one panel for each patient) with overlays of Sym015, Hu9006, and Hu9038 concentration vs. actual time by Study Part and Cohort (First profile) – Linear
- Patient Profiles (one panel for each patient) with overlays of Sym015, Hu9006, and Hu9038 concentration vs. actual time by Study Part and Cohort (First profiles) – Semi-log

- Patient Profiles (one panel for each patient) with overlay of Sym015, Hu9006, and Hu9038 concentration vs. actual time by Study Part and Cohort (peak and trough for each dosing occasion) – Linear

- Patient Profiles (one panel for each patient) with overlay of Sym015, Hu9006, and Hu9038 concentration vs. actual time by Study Part and Cohort (peak and trough for each dosing occasion) – Semi-log

Descriptive summary (n, arithmetic mean, SD, median, minimum, maximum, geometric means, and geometric CV%) of serum concentrations of Sym015, Hu9006, and Hu9038 and fraction Hu9006 (concentration of Hu9006/concentration of Sym015) will be tabulated by dose schedule, dose group and nominal sampling time. Following tables will be produced:

- Summary of Sym015, Hu9006, and Hu9038 concentration, and fraction Hu9006 by Cohort and Time Point (First profile)
- Summary of Sym015, Hu9006, and Hu9038 concentration, and fraction Hu9006 by Cohort and Time Point (Peak and trough for each dosing occasion)

The arithmetic and geometric means of the plasma concentrations of Sym015 vs. nominal time points will be plotted by dose group with +/-1 standard deviation (for arithmetic means). In figures of geometric means, error bars will be calculated using the following formula: Exp (mean_Ln +/- sd_Ln) where 'sd_Ln' denotes the standard deviation of the concentration values on the log base 10 scale and 'mean_Ln' denotes the arithmetic mean of the concentration values on the log base 10 scale.The following mean concentration vs. time plots will be produced for each analyte (Sym015, Hu9006 and Hu9038):

- Arithmetic Mean Concentration of <Analyte> vs. planned time point by cohort (First profile) – Linear
- Geometric Mean Concentration of <Analyte> vs. planned time point by cohort (First profile) – Semi-log
- Arithmetic Mean Peak and Trough Concentrations of <Analyte> vs. planned time point by cohort (peaks and troughs at all dosing occasions) – Linear

- Geometric Mean Peak and Trough Concentrations of <Analyte> vs. planned time point by cohort (peaks and troughs at all dosing occasions) – Semi-log

4.11.4.2 Handling of Values Below the Limit of Quantification (BLQ)

In summary tables, values below the LLOQ (BLQ) will be handled as follows:

- At a time point where less than or equal to 50% of the values are BLQ, all BLQ values will be set to the ½*lower limit of quantification (LLOQ), and all descriptive statistics will be calculated.
- At a time point where more than 50% of the values are BLQ, the mean, SD, geometric mean and CV% will be set to Not Determined (ND). The max value will be reported from the individual data, and the min and median will be set to BLQ.
- If all values are BLQ at a time point, no descriptive statistics will be calculated for that time point. Not Applicable (NA) will be written in the field for SD and CV% and BLQ will be written in fields for mean, geometric mean, min, median, and max.
- The number of BLQ values (n below LLOQ) will be reported for each time point.

In figures, all BLQ values will be set to the ½*LLOQ.

4.11.4.3 Pharmacokinetic Parameters

Pharmacokinetic parameters for the first profile for each patient and analyte (Sym015, Hu9006, Hu9038) will be derived by model-independent, non-compartmental analysis (NCA) according to Symphogen's local procedures.

All derived serum PK parameters will be listed by Study Part and Cohort (dose group in Part 1), patient, and Day, and summarized descriptively by Study Part and Cohort (dose group in Part 1) and Day. The following descriptive statistics will be presented for PK parameters: n, arithmetic mean, SD, geometric mean, geometric CV% (calculated as: gCV%=SQRT(exp(s^2)-1)*100; where s is the standard deviation of the log-transformed values), median, minimum and maximum values.

4.11.4.4 Pharmacokinetic Analysis

Descriptive statistics of plasma concentrations will be reported with the same precision as the source data and plasma concentrations.

In addition to general continuous summary statistics presented in section 4.2, for PK parameters, geometric means with coefficient of variation (CV %) will be also summarized.

For drug concentrations and concentration-dependent pharmacokinetic parameters, the rules of data presentation are described in table below.

Presentation of PK Parameters and Summary Statistics

Typical Variable	N	Digit rule	Minimum/ Maximum	Mean Median	SD	Geometric Mean	CV (%)
concentration	X	Significant digits	3	4	4	3	3
C_{max}	X	Significant digits	3	4	4	4	4
t_{max}*	X	Fixed decimal places	as raw data	as raw data	-	-	-
λ_z	X	Significant digits	4	3	5	5	5
$t_{1/2}$	X	Significant digits	3	3	4	4	4
$AUC_{(0-xx)}$	X	Significant digits	3	3	4	4	4
$AUC_{(0-\tau)}$	X	Significant digits	3	3	4	4	4

* Mean and SD, geometric mean and CV will not be calculated for t_{max}.

4.12 Safety Evaluation

4.12.1 Dose Limiting Toxicities (DLT)

All DLT events occurred in Cycle 1 will be listed in DLT analysis set. Presence and absence of DLTs will be presented for patients in DLT analysis set.

4.12.2 Adverse Events

The AEs will be coded using MedDRA version22.0 or later version.

In AE summary tables, percentages will be calculated using the number of patients dosed in each group, or the Full Analysis Set for the overall study group, as denominator.

TEAEs will be presented by MedDRA System Organ Class (SOC) and Preferred Term (PT). In all AE summary tables, SOCs and PTs will be presented in the order of descending frequencies as detailed in section 4.2. AE frequency accounts for number and percent of patients who have a specific SOC and PT as well as the worst grade, if there were multiple occurrences at different toxicity grade, which was determined using CTCAE v4.03.

For purposes of the summary tables, AEs will be classified as either being related to study drug or not related. AEs related to study drug will include AEs classified as 'Related', 'Probably Related' or 'Possibly Related'. AEs not related to study drug will include AEs that are 'Unlikely Related' or 'Not Related'.

All AEs will be listed. The AEs will be presented using summary tables including:

- Patient Overall Summary of TEAEs. This table will include following summaries:
    - Any TEAEs
    - Any related TEAEs
    - Any Serious TEAEs
    - Any related Serious TEAEs
    - Grade 3 or higher TEAEs
    - Any Related Grade 3 or higher TEAEs
    - Any TEAEs leading to Permanent Discontinuation of IMP
    - Any Related TEAEs leading to Permanent Discontinuation of IMP

- Any TEAEs leading to interruption or Stop of study drug
- Any Related TEAEs leading to interruption or Stop of study drug
- Any TEAEs with an outcome of reduction or delay of study drug
- Any Relate TEAEs with an outcome of reduction or delay of study drug
- Any FATAL TEAEs
    - Fatal TEAEs within 30 days from last IMP infusion
    - Fatal TEAEs at more than 30 days from last IMP infusion

- TEAEs by SOC and PT
- Related TEAEs by SOC and PT
- TEAEs by SOC and PT and Worst CTCAE Grade
- Related TEAEs by SOC and PT and Worst CTCAE Grade
- Serious TEAEs by SOC and PT
- Related Serious TEAEs by SOC and PT
- TEAEs Leading to Permanent Discontinuation of IMP by SOC and PT
- Related TEAEs Leading to Permanent Discontinuation of IMP by SOC and PT
- Serious Adverse Events - Key Patient Information
- Adverse Events with Outcome of Death - Key Patient Information (non TEAEs will be flagged)
- Adverse Events Leading to Permanent Discontinuation of IMP - Key Patient Information
- Adverse Events Leading to Dose Reduction - Key Patient Information
- Adverse Events Leading to Dose Interruption or Stop- Key Patient Information

- Listing of Death (Deaths occurring within 30 days from last infusion of IMP will be identified; non TEAEs will be flagged)

Key Patients Information will include Patient number, gender and age, AE SOC, PT and Reported Term, AE Serious (Yes / No), AE start and end date and AE duration (days), AE Relationship to Study Drug, TEAE (Yes / No); additional information may also be reported in different listing.

4.12.3 Deaths, Serious Adverse Events, and Other Significant Adverse Events

Reporting of Deaths, Serious Adverse Events and other significant Adverse Events is described in the above section 4.12.2.

4.12.4 Clinical Laboratory Evaluation

All clinical laboratory test results will be presented and summarized using the International System of Units (SI units; Système International d'Unités). The original lab test units will be converted to SI according to *Young, D.S and Huth, E.J; 1998; SI Units for Clinical Measurement; American College of Physicians; Philadelphia* and *Burtis, C.A, Ashwood, E.R and Bruns, D.E; 2008; Fundamentals of Clinical Chemistry; Saunders Elsevier; Missouri* [Laboratory test converted to SI will be stored in SDTM LB domain as LBSTRESU and LBSTRESC].

Descriptive statistics (n, mean, standard deviation, median, and range) of the lab parameters and changes from baseline will be presented in SI units for biochemistry, hematology, and coagulation. Such descriptive statistics will be presented by Visit and at End of Study; by Visit summaries will be presented based on worst by-visit result as detailed in section 4.12.4. Worst Result during Treatment (i.e. Maximum and Minimum observed result post Baseline and corresponding change from baseline including results from unscheduled and repeated assessments) will be presented as well.

Shift in biochemistry, hematology, and coagulation result CTCAE grading from baseline to visit maximal grade will be tabulated by each visit and at the end of treatment, as well as from baseline to the maximal grade during the whole study (maximal grade will also include results from unscheduled and repeated assessments).

All clinical laboratory test results will be listed in the original and SI units, for biochemistry, hematology, coagulation, and urinalysis. Listing of abnormal values will be provided as well.

Individual patient biochemistry, hematology, and coagulation parameters during the trial can be presented graphically using longitudinal spaghetti plots. Specific lab parameters to be plotted will be decided by Symphogen from clinical meaning perspective after examination of corresponding listings.

Selected biochemistry, hematology, and coagulation parameters will be presented using box plots by visits and Anatomic based cancer type. Specific lab parameters to be plotted will be decided by Symphogen from clinical meaning perspective after examination of corresponding listings.

Results from the pregnancy tests will be listed.

4.12.5 Echocardiogram (ECHO) or Multi-Gated (MUGA) Scan

ECHO/MUGA data will be listed.

4.12.6 Vital Signs

Data for vital signs (weight, blood pressure, heart rate, temperature) will be listed.

Descriptive summary statistics (for observed values and changes from baseline) for vital sign parameters will be provided.

4.12.7 Electrocardiograms (ECG)

ECG parameter data will be listed.

Normal, abnormal, or abnormal clinically significant ECG will be presented in a summary table. A shift from baseline table will be presented as well. Number and percentage of patients with maximum postdose QTcF values of <=450, >450 ms and <=480, >480 ms and <=500, and >500 ms, and maximal change from baseline values of <=30, >30 and <=60ms, and >60 ms will be at each scheduled timepoint as well as the highest measurement during the study and at end of treatment. (highest QTcF Prolongations measurement will also include results from unscheduled and repeated assessments). Above categories of QTcF are based on ICH E14 [9].

4.12.8 Physical Examination

All results from the physical examination will be listed.

Normal, abnormal not clinically significant, or abnormal clinically significant physical examination will be summarized by Body System. A shift table from baseline of normal and abnormal findings in physical examination will be presented.

4.12.9 Eastern Cooperative of Oncology Group (ECOG) Performance Status (PS)

ECOG performance status will be listed.

Number of patients reporting each ECOG score will be presented; a shift table will also be presented to show changes from Baseline.

4.13 Safety Monitoring

A safety monitoring committee (SMC) is established and includes Investigator(s), Medical Monitor(s), and Sponsor's medical representatives. The SMC reviewed clinical and laboratory safety data regularly throughout the trial. The SMC selected the Q2W RP2D to be used in Part 2 based on safety data and available PK results.

The annual Development Safety Update Report (DSUR) was submitted by the Sponsor or designee to all appropriate Health Authorities and central IRBs/ECs as per ICH Guidelines. Submission of the DSUR to local IRBs/ECs was handled as per local regulations and/or requests.

4.14 Other Analyses

No other analyses planned.

4.15 Determination of Sample Size

The primary endpoint of Part 1 of the trial is the occurrence of DLTs measured during Cycle 1 of Sym015 administration. The number of enrolled patients will depend on the extent of observed DLTs independently in each cohort. Based on a 3+3 design, it is planned to enroll between 12 and 15 patients during dose-escalation, however the actual number of patients will depend on observed DLTs.

In Part 2 of the trial, the primary endpoint is documented, confirmed OR assessed by RECIST v1.1, at any time during trial participation by Investigator assessment. It is planned to include 25 patients with various advanced solid tumor malignancies, documented and confirmed as MET-amplified in the Basket Cohort, 20 patients in the NSCLC MET-Amplified Cohort, and 6-12 patients in the NSCLC $MET^{Ex14Del}$ Cohort, for the total of approximately 51-57 patients in Part 2.

No power and type I error considerations were used to determine the sample size in each cohort. Proposed sample sizes in Basket and NSCLC Cohorts should allow to obtain preliminary safety, PK, response, and pharmacodynamic information of Sym015 in the respective patient populations. The expected (target) range of OR in any of these three cohorts is in the range of 20%-50%, depending on histology, previous therapies, and other prognostic factors defining the enrolled patient population.

4.16 Changes in the Conduct of the Study or Planned Analysis

- DCR analysis was not included as part of study endpoints in the Protocol, such analysis has been added in this SAP.
- Protocol defines SD for >4 months as a secondary endpoint, this has been changed to SD for ≥4 months, moreover SD for SD for ≥6 months has been added as well.
- Analysis of Changes in sum of diameters of target lesions from baseline to end of trial participation was not included as part of study endpoints in the Protocol, such analysis has been added in this SAP.
- Additional sensitivity analysis has been added for PFS as described is sections 3.2.1.1 and 4.11.2.1.

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7 APPENDICES

7.1 Derivation of CTCAE Grade - Hematological Tests

Tests	Direction	Grade			
		1	2	3	4
Hemoglobin (g/dl, mmol/L or g/L)	↓	<LLN - 10.0 g/dL; <LLN - 6.2 mmol/L; <LLN -100 g/L	<10.0 - 8.0 g/dL; <6.2 - 4.9 mmol/L; <100 - 80g/L	<8.0 g/dL; <4.9 mmol/L; <80 g/L;	Life-threatening consequences;
Platelet (/mm3 or /L)	↓	<LLN - 75,000/mm3; <LLN - 75.0 x 10e9 /L	<75,000 - 50,000/mm3; <75.0 -50.0 x 10e9 /L	<50,000 - 25,000/mm3; <50.0 - 25.0 x 10e9 /L	<25,000/mm3; <25.0 x 10e9 /L
Neutrophils (/mm3 or /L)	↓	<LLN - 1500/mm3; <LLN - 1.5 x109 /L	<1500 - 1000/mm3; <1.5 - 1.0 x10e9 /L	<1000 - 500/mm3; <1.0 - 0.5 x10e9 /L	<500/mm3; <0.5 x 10e9 /L
Lymphocyte (/mm3 or /L)	↓	<LLN - 800/mm3; <LLN - 0.8 x10e9 /L	<800 - 500/mm3; <0.8 - 0.5 x10e9 /L	<500 - 200/mm3; <0.5 - 0.2 x10e9 /L	<200/mm3; <0.2 x 10e9 /L
Note: 10e9 = 10^9; LLN = Lower Limit of Normal; ULN = Upper Limit of Normal					

7.2 Derivation of CTCAE Grade - Clinical Chemistry Tests

Tests	Direction	Grade			
		1	2	3	4
Sodium (mmol/L)	↓	<LLN - 130 mmol/L	-	<130 - 120 mmol/L	<120 mmol/L
Sodium (mmol/L)	↑	>ULN - 150 mmol/L	>150 - 155 mmol/L	>155 - 160 mmol/L	>160 mmol/L
Potassium (mmol/L)	↓	<LLN - 3.0 mmol/L	-	<3.0 - 2.5 mmol/L	<2.5 mmol/L
Potassium (mmol/L)	↑	>ULN - 5.5 mmol/L	>5.5 - 6.0 mmol/L	>5.5 - 6.0 mmol/L	>7.0 mmol/L
Glucose	↓	<LLN - 55 mg/dL; <LLN - 3.0 mmol/L	<55 - 40 mg/dL; <3.0 - 2.2 mmol/L	<40 - 30 mg/dL; <2.2 - 1.7 mmol/L	<30 mg/dL; <1.7 mmol/L
Glucose	↑	Fasting glucose value >ULN - 160 mg/dL; Fasting glucose value >ULN - 8.9 mmol/L	Fasting glucose value >160 - 250 mg/dL; Fasting glucose value >8.9 - 13.9 mmol/L	>250 - 500 mg/dL; >13.9 - 27.8mmol/L	>500 mg/dL; >27.8 mmol/L
Creatinine	↑	>1 - 1.5 x baseline; >ULN - 1.5 x ULN	>1.5 - 3.0 x baseline; >1.5 - 3.0 x ULN	>3.0 baseline; >3.0 - 6.0 x ULN	>6.0 x ULN
Bilirubin	↑	>ULN - 1.5 x ULN	>1.5 - 3.0 x ULN	>3.0 - 10.0 x ULN	>10.0 x ULN
Alkaline phosphatase (AKP)	↑	>ULN - 2.5 x ULN	>2.5 - 5.0 x ULN	>5.0 - 20.0 x ULN	>20.0 x ULN
AST (SGOT)	↑	>ULN - 3.0 x ULN	>3.0 - 5.0 x ULN	>5.0 - 20.0 x ULN	>20.0 x ULN
ALT (SGPT)	↑	>ULN - 3.0 x ULN	>3.0 - 5.0 x ULN	>5.0 - 20.0 x ULN	>20.0 x ULN
Uric Acid	↑	>ULN - 10 mg/dL (0.59 mmol/L)	-	-	>10 mg/dL; >0.59 mmol/L

Tests	Direction	Grade			
		1	2	3	4
Calcium	↑	Corrected serum calcium of Hypercalcemia >ULN - 11.5 mg/dL; >ULN - 2.9 mmol/L; Ionized calcium >ULN - 1.5 mmol/L	Corrected serum calcium of >11.5 - 12.5 mg/dL; >2.9 - 3.1mmol/L; Ionized calcium >1.5 -1.6 mmol/L	Corrected serum calcium of >12.5 - 13.5 mg/dL; >3.1 - 3.4 mmol/L; Ionized calcium >1.6 - 1.8 mmol/L	Corrected serum calcium of >13.5 mg/dL; >3.4 mmol/L; Ionized calcium >1.8 mmol/L
Calcium	↓	Corrected serum calcium of <LLN - 8.0 mg/dL; <LLN - 2.0 mmol/L; Ionized calcium <LLN -1.0 mmol/L	Corrected serum calcium of <8.0 - 7.0 mg/dL; <2.0 - 1.75 mmol/L; Ionized calcium <1.0 - 0.9 mmol/L;	Corrected serum calcium of <8.0 - 7.0 mg/dL; <2.0 - 1.75 mmol/L; Ionized calcium <1.0 - 0.9 mmol/L;	Corrected serum calcium of <6.0 mg/dL; <1.5 mmol/L; Ionized calcium <0.8 mmol/L;
Phosphate	↓	<LLN - 2.5 mg/dL; <LLN - 0.8 mmol/L	<2.5 - 2.0 mg/dL; <0.8 - 0.6 mmol/L	<2.0 - 1.0 mg/dL; <0.6 - 0.3 mmol/L	<1.0 mg/dL; <0.3 mmol/L
Note: 10e9 = 10^9; **LLN** = Lower Limit of Normal; **ULN** = Upper Limit of Normal					

7.3 Derivation of CTCAE Grade - Coagulation Tests

Tests	Direction	Grade			
		1	2	3	4
Activated partial thromboplastin time prolonged	↑	>ULN - 1.5 x ULN	>1.5 - 2.5 x ULN	>2.5 x ULN; hemorrhage	-
Fibrinogen decreased	↓	<1.0 - 0.75 x LLN or <25% decrease from baseline	<0.75 - 0.5 x LLN or 25 - <50% decrease from baseline	<0.5 - 0.25 x LLN or 50 - <75% decrease from baseline	<0.25 x LLN or 75% decrease from baseline or absolute value <50 mg/dL

7.4 Schedule of Assessments – Part 1 and Part 2 Basket Cohort

Pre-Treatment Period		Treatment Period[1]										Post-Treatment Period[2]	
	Screening	Cycle 1					Cycle 2, 4, 6 etc.			Cycle 3, 5, 7 etc.		EOT	1M FUP[3]
Day within Cycle Visit Window (± days)	D-14 to D-1	D1	D2	D8 (±2)	D15 (±2)	D22 (±2)	D1 (±2)	D15 (±2)	End of Cycle	D1 (±2)	D15 (±2)	± 10 d following the decision of trial treatment withdrawal	1 month after last dose of trial treatment (30–7d)
Informed Consent	X												
Baseline Characteristics/Eligibility[4]	X	X											
Safety Assessments													
Medication/Procedure Survey	X	X			X		X	X		X	X	X	X
(S)AE Survey and Reporting	X	X	X	X	X	X	X	X	X	X	X	X	X
DLT Evaluation[5] **Part 1/Dose-Escalation only**		X	X	X	X	X	C2 only						
Vital Signs and Body Weight	X	X			X		X	X		X	X	X	X
ECOG PS[6]	X	X[7]					X			X		X	X
Physical Examination[7]	X	X[8]					X			X		X	X
ECG[9]	X											X	
ECHO or MUGA scan[7]	X												
Safety blood samples[7,8]	X	X[9]	X	X	X	X	X	X		X	X	X	X
Urinalysis[7,8]	X	X[9]			X		X			X		X	X
Pregnancy Test	X											X	
Disease Assessments													
Disease Status Evaluation by CT/MRI[7]	X								X			X[10]	X[10]
Tumor Marker Evaluation[11]	X								X			X	X
Archival Tumor Tissue (may include pre-screening by liquid bx)[12]	X												
Tumor Biopsy[13]	X[14]								C2 only[15]				
Additional Assessments													
PK Samples[16]		X	X	X	X		X	X		X	X	X	X
ADA Samples[17]		X					C2 only[18]			X		X	X
Skin Biopsy[19] **Part 1/Dose-Escalation only**	X								C2 only[20]				
Biomarker Blood Sample[21]	X								C2 only[22]			X	
Trial Treatment													
Sym015 Premedication[16]		X			X		X	X		X	X		
Sym015 Infusion		X			X		X	X		X	X		
Post-Infusion Monitoring		X			X		X	X		X	X		

Abbreviations (in alphabetical order): ADA, anti-drug antibody; Bx, biopsy; C, Cycle; CT, computed tomography scan; D, d, day(s); DLT, dose-limiting toxicity; EOT, End of Treatment Visit; ECG, electrocardiogram; ECHO, transthoracic echocardiogram; ECOG PS, Eastern Cooperative Oncology Group performance status; MRI, magnetic resonance imaging; MUGA, multi-gated acquisition scan; 1M FUP, 1-Month Follow-up Visit; PK, pharmacokinetic; Q2W, every second week; (S)AE, (serious) adverse event; TX, therapy

1) The treatment period continues until the patient is withdrawn from Sym015
2) After the 1M FUP Visit, the Investigator will make every effort to obtain follow-up information on response assessment and/or OS about once every 2 months. Response assessment follow-up is required in the event of an ongoing SD, PR or CR at the 1M FUP Visit, until PD or another therapeutic intervention is initiated. Survival follow-up is required until death, withdrawal of consent, trial site closure, or termination/end of the trial. This continued follow-up does not require an in-person visit at the trial site, but may be obtained by collection of data/documentation.
3) Screening assessments include demographics, medical history, tumor histology, mutation status, extent of disease, prior anti-cancer treatment, etc
4) DLT evaluation, **applicable for Part 1/dose-escalation cohorts only**: DLTs are reported during Cycle 1 with a final assessment 14 (±2) days after the last dose of Cycle 1 or prior to dosing on C2D1
5) Does not need to be performed prior to C1D1 if performed during screening ≤ 7 days from C1D1
6) In addition to the scheduled timepoints, an ECG should be performed if clinically indicated
7) In addition to the scheduled timepoints, an ECHO/MUGA should be performed in the event of cardiac symptoms and as otherwise clinically indicated
8) Local laboratory results must be available and assessed prior to each Sym015 infusion. Refer to Section 8.2.9 for details
9) CT or MRI imaging schedule and conditions, applying to all cohorts:
   - A CT/MRI performed within 28 days prior to C1D1 can be used for evaluation of eligibility and as baseline scan, provided that the CT/MRI has been performed according to the protocol requirements
   - The first CT/MRI assessment for response is done at the end of Cycle 2 and thereafter repeated at the end of every second cycle (in the week prior to Day 1 of the next cycle)
   - In the event of suspected PD, a CT/MRI is to be performed as soon as possible
   - In the event of CR/PR, a confirmatory CT/MRI is to be performed no earlier than 28 days after the first assessment of CR/PR.
10) A CT/MRI at EOT should only be performed if the previous CT/MRI has been performed ≥ 8 weeks before. A CT/MRI scan at 1M FUP should only be performed if no CT/MRI documents PD before or at EOT
11) Tumor marker evaluation to include tumor markers that are part of the trial site standard practices as indicated by tumor type, if applicable
12) Archival tumor tissue: To be assessed locally. Does not need to be repeated if *MET*-amplification and *KRAS* mutational status have been assessed previously and the pathology report is available to document findings.

    For Part 2-Basket Cohort: It is preferred that the local eligibility assessment for *MET*-amplification will be done using tissue from a tumor biopsy performed during screening, however archival tumor tissue may be used at the Investigator's discretion. If archival tissue is not available, tissue from a tumor biopsy performed during screening will be used. Peripheral blood collection for *KRAS*-mutation assessment and for MET-amplification assessment in ctDNA (liquid biopsy) is allowed as a local pre-screening methodology by Guardant360 analysis. Other liquid biopsy methodologies, except if used to detect *METex14* mutation, will only be allowed if previously approved by the Sponsor.

    For Part 2-NSCLC Cohort: Archival tissue to be submitted, if available
13) Tumor biopsy: To be assessed locally as part of eligibility assessment in Part 1 and Part 2, if applicable. **Optional for patients with known *MET*-amplification enrolled in Part 1**

    For Part 2-Basket Cohort: Required, to be assessed centrally. Tissue from a tumor biopsy performed during screening is preferred, however archival tissue may be submitted for central analysis at the **Investigator's discretion**, provided the archival tissue is suitable for central analysis. Sampling for central analysis to be repeated at the end of Cycle 2 or upon PD, whichever occurs first. Refer to Section 8.3.4 for details

    For Part 2-NSCLC Cohort: Biopsies are optional at the timepoints specified
14) Extended PK sampling for PK profiling will be done starting C1D1. Refer to Table 9 for details
15) **Only applicable for Part 2**: ADA sample on first day of Cycle 2, prior to dosing
16) **Only applicable for Part 1**: Skin biopsy is obtained during screening after patient eligibility has been confirmed. Sampling is repeated at the end of Cycle 2 or upon PD, whichever occurs first
17) Biomarker blood sample is taken during screening after patient eligibility has been confirmed. Sampling is repeated at the end of Cycle 2 or upon PD, whichever occurs first, and at EOT. If a tumor biopsy is collected at the same time point as the biomarker blood sample, the biomarker blood sample should be collected prior to collecting the tumor biopsy.
18) For Part 1 of the trial, premedication is mandatory prior to each dose of Sym015. For Part 2 of the trial, premedication is mandatory prior to each dose of Sym015 during Cycle 1. In Part 2, premedication may be withdrawn after Cycle 1 on a patient-by-patient basis if the patient is without evidence of infusion related reactions. Refer to Section 7.2.1 for details

7.5 Schedule of Assessments – Part 2 NSCLC Cohort

Pre-Treatment Period		Treatment Period[1]										Post-Treatment Period[2]	
	Screening	Cycle 1					Cycle 2, 4, 6 etc.			Cycle 3, 5, 7 etc.		EOT	1M FUP
Day within Cycle Visit Window (± days)	D-14 to D-1	D1	D3	D8 (±2)	D15 (±2)	D22 (±2)	D1 (±2)	D15 (±2)	EOC	D1 (±2)	D15 (±2)	≤ 10 d following the decision of trial treatment withdrawal	1 month after last dose of trial treatment (30–7d)
Informed Consent	X												
Baseline Characteristics Eligibility[3]	X	X											
Safety Assessments													
Medication/Procedure Survey	X	X			X		X	X		X	X	X	X
(S)AE Survey and Reporting	X	X	X	X	X	X	X	X	X	X	X	X	X
Vital Signs and Body Weight	X	X			X		X	X		X	X	X	X
ECOG PS[4]	X	X[4]					X			X		X	X
Physical Examination[5]	X	X[5]					X			X		X	X
ECG[6]	X											X	
ECHO or MUGA scan[7]	X												
Safety blood samples[8,9]	X	X[9]	X	X	X	X	X	X		X	X	X	X
Urinalysis[8,9]	X	X[9]			X		X			X		X	X
Pregnancy Test	X											X	
Disease Assessments													
Disease Status Evaluation by CT-MRI[10]	X								X			X	X
Tumor Biopsy[4]	X								EOC only *optional*				
Additional Assessments													
PK Samples[11]		X	X	X	X		X	X		X	X	X	X
ADA Sample		X					C2 only			X		X	X
Genomic Biomarker Blood Sample[11]	X								EOC only			X	
Trial Treatment													
Sym015 Premedication[12]		X			X		X	X		X	X		
Sym015 Infusion		X			X		X	X		X	X		
Post-Infusion Monitoring		X			X		X	X		X	X		

Abbreviations (in alphabetical order): ADA, anti-drug antibody; Bx, biopsy; C, Cycle; CT, computed tomography scan; D, day(s); DLT, dose-limiting toxicity; EOC, End of Cycle; EOT, End of Treatment Visit; ECG, electrocardiogram; ECHO, transthoracic echocardiogram; ECOG PS, Eastern Cooperative Oncology Group performance status; MRI, magnetic resonance imaging; MUGA, multi-gated acquisition scan; 1M FUP, 1-Month Follow-up Visit; PK, pharmacokinetic; Q2W, every second week; (S)AE, (serious) adverse event; TX, therapy

1) Treatment Period: The treatment period continues until the patient is withdrawn from Sym015
2) Post-treatment Period: After the 1M FUP Visit, the Investigator will make every effort to obtain follow-up information on response assessment and/or OS about once every 3 months. Response assessment follow-up is required in the event of an ongoing SD, PR or CR at the 1M FUP Visit, until PD or another therapeutic intervention is initiated. Survival follow-up is required until death, withdrawal of consent, trial site closure, or termination/end of the trial. This continued follow-up does not require an in-person visit at the trial site, but may be obtained by collection of data/documentation
3) Baseline Characteristics/Eligibility: Screening assessments include demographics, medical history, tumor histology, mutation status, extent of disease, prior anti-cancer treatment, etc
4) Safety Assessments: Does not need to be performed prior to C1/D1 if performed during screening (~ 7 days from C1/D1
5) ECG: In addition to the scheduled timepoints, an ECG should be performed if clinically indicated
6) ECHO/MUGA: In addition to the scheduled timepoint, an ECHO/MUGA should be performed in the event of cardiac symptoms and as otherwise clinically indicated
7) Blood Safety Samples/Urinalysis: Local laboratory results must be available and assessed prior to each Sym015 infusion. Refer to Section 8.2.9 for details
8) Disease Status Evaluation: CT or MRI imaging schedule and conditions:
   - A CT/MRI performed within 28 days prior to C1/D1 can be used for evaluation of eligibility and as baseline scan, provided that the CT/MRI has been performed according to the protocol requirements
   - The first CT/MRI assessment for response is done at the EOC2 and thereafter repeated at the end of every second cycle (EOC assessments may be performed at any time during the week prior to Day 1 of the next cycle, including Day 1 of the next cycle prior to dosing, provided results are available prior to study drug administration)
   - In the event of suspected PD, a CT/MRI is to be performed as soon as possible
   - In the event of CR/PR, a confirmatory CT/MRI is to be performed no earlier than 28 days after the first assessment of CR/PR
   - A CT/MRI at EOT should only be performed if the previous CT/MRI has been performed > 8 weeks before. A CT/MRI scan at 1M FUP should only be performed if no CT/MRI documents PD before or at EOT
9) Tumor Biopsy: Recent or newly performed biopsies are mandatory at screening; it is permissible to perform the screening procedure outside the 14-day screening period provided informed consent for the trial has been obtained. EOC2 tumor biopsies (coinciding with time of first response assessment) or upon PD, whichever occurs first, are optional.
10) PK Samples: Extended PK sampling for PK profiling will be done starting C1/D1. Refer to Table 9 for details
11) Genomic Biomarker Blood Sample: It is permissible to obtain the screening sample outside the 14-day screening period provided informed consent for the trial has been obtained. Subsequent samples to be obtained: EOC2 (coinciding with time of first response assessment) or upon PD, whichever occurs first; EOT (if after EOC2; need not repeat if patient is discontinuing at the EOC2 or if a sample was obtained upon PD). If a tumor biopsy is collected at the same time point as the biomarker blood sample, the biomarker blood sample should be collected prior to collecting the tumor biopsy
12) Premedication: Mandatory prior to each dose of Sym015 during Cycle 1; may be withdrawn after Cycle 1 on a patient-by-patient basis if the patient is without evidence of infusion related reactions. Refer to Section 7.2.1 for details

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