CLINICAL TRIAL PROTOCOL

Trial Title:	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
Short Title:	Sym015 (Anti-MET) in Patients with Advanced Solid Tumor Malignancies
Sponsor:	Symphogen A/S Pederstrupvej 93 DK-2750 Ballerup Denmark
Sponsor's Medical Expert:	[redacted]
Coordinating Investigator Part 1/Part 2 Basket Cohort:	[redacted]
Coordinating Investigator NSCLC Cohorts:	[redacted]
Trial ID:	Sym015-01
Trial Phase:	Phase 1a/2a
EudraCT Number:	2016-003912-11
IND Number:	129286
Protocol Version/Date:	8.0 / 07-Dec-2018 (Amendment 7)
Previous Protocol Versions/Dates:	7.0 / 20-Nov-2017 (Amendment 6) 6.0 / 11-May-2017 (Amendment 5) 5.0 / 04-Nov-2016 (Amendment 4) 4.0 / 02-May-2016 (Amendment 3) 3.0 / 22-Feb-2016 (Amendment 2) 2.0 / 17-Feb-2016 (Amendment 1) 1.0 / 01-Dec-2015

Sponsor Declarations

The trial will be conducted in compliance with this clinical trial protocol, International Council for Harmonisation (ICH) of Technical Requirements for Pharmaceuticals for Human Use E6(R2): Guideline for Good Clinical Practice (GCP) (EMA/CHMP/ICH/135/1995), the Declaration of Helsinki, and applicable regulations.

The Sponsor has appointed a Coordinating Investigator for the trial. This Coordinating Investigator will provide input to the trial design and act as overall coordinator for Investigators across all sites. The Coordinating Investigator will furthermore sign off the Clinical Trial Report on behalf of all Investigators.

Lists of Investigators responsible for conducting the trial, medically qualified physicians responsible for all site-related medical decisions (if other than the Investigators), monitors, clinical laboratories, and other medical and/or technical departments and/or institutions involved in the trial are provided as separate documents.

Principal Investigator Signature Page

I, the undersigned, am responsible for the conduct of the trial at this site and agree:

- To assume responsibility for the proper conduct of the clinical trial at this Investigational Site.
- Not to implement any changes to the clinical trial protocol without agreement from the Sponsor and prior review and written approval from the appropriate Healthy Authority (as indicated) and the Institutional Review Board/Ethics Committee, except where necessary to eliminate an immediate hazard to the patients.
- That I am aware of, and will comply with "Good Clinical Practice" (ICH E6(R2) GCP) (EMA/CHMP/ICH/135/1995), the Declaration of Helsinki, and all applicable regulatory requirements.
- That all site staff to which I have delegated tasks for this clinical trial are appropriately selected and adequately informed about the investigational product(s) and of their trial-related duties and functions as described in the clinical trial protocol.

_____ _____

Signature Date of Signature

Name: _____

Academic Degree: _____

Function: _____

Institution: _____

TABLE OF CONTENTS

LIST OF FIGURES

LIST OF TABLES

1. SYNOPSIS

Item	Summary
Trial Title	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
Trial ID	Sym015-01
Trial Phases	This is an open-label, multicenter trial composed of 2 parts: • Part 1 is a Phase 1a dose-escalation in patients with *KRAS* proto-oncogene (*KRAS*) wild-type (WT) advanced solid tumor malignancies without available therapeutic options • Part 2 is a Phase 2a dose-expansion in which dosing will be at the recommended Phase 2 dose (RP2D) on an every second week (Q2W) schedule. Three cohorts will be included: o 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 tyrosine kinase inhibitor (TKI). Note: Effective with protocol version 8.0 (December 2018), accrual to the Basket Cohort is suspended. o NSCLC *MET*-Amplified Cohort: A cohort of approximately 20 patients with advanced non-small cell lung carcinoma (NSCLC) with *MET*-amplification, and without available therapeutic options. Patients may have received prior therapy with MET-targeting and/or epidermal growth factor receptor (EGFR)-targeting agents. o NSCLC $MET^{Ex14Del}$ Cohort: A cohort of approximately 6-12 patients with advanced NSCLC with *MET* exon 14 skipping alteration ($MET^{Ex14Del}$), 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. *A basket cohort is designed to evaluate the potential antitumor effects of a targeted therapy by enriching for patients with a defined genetic alteration (e.g., mutations in or overexpression of a specific gene(s)) regardless of the histotype of the enrolled patients' tumors.
Trial Sites and Countries	Part 1, Dose-Escalation: 2 to 3 investigational trial sites, located within the United States (USA). Part 2: 15 to 27 investigational trial sites, located within the USA, Asia Pacific, and Europe.
Planned Trial Period	Part 1 of the trial is expected to begin Q1 2016. Patients will be enrolled in dose-escalation cohorts until establishment of a maximum tolerated dose (MTD) or until 24 mg/kg has been evaluated, whichever comes first, expected by Q1 2017. Enrollment to Part 2 of the trial will commence upon establishment of the Q2W RP2D. Enrollment is expected to complete by Q4 2019. The end of trial will be reached at the latest 1 month (30 +7 days) after the last patient has been withdrawn from Sym015. Patients will continue to be followed to assess duration of disease stabilization, response, and overall survival (OS).

Primary Objectives	Primary objective of Part 1, Dose-Escalation: To assess the safety and tolerability of Sym015 when administered by intravenous (IV) infusion on a Q2W schedule to patients with *KRAS* WT advanced solid tumor malignancies without available therapeutic options. Primary objective of Part 2: To evaluate the antitumor activity of Sym015 when administered at the Q2W RP2D to patients in the following cohorts: • Basket Cohort: *MET*-amplified, *KRAS* WT solid tumor malignancies without available therapeutic options. • NSCLC *MET*-Amplified Cohort: *MET*-amplified advanced NSCLC without available therapeutic options. • NSCLC $MET^{Ex14Del}$ Cohort: $MET^{Ex14Del}$ advanced NSCLC without available therapeutic options.
Primary Endpoints	Primary Endpoint of Part 1, Dose-Escalation: The occurrence of dose-limiting toxicities (DLT) measured during Cycle 1 of Sym015 administration on a Q2W (28 days equals 1 cycle) dosing schedule. Primary Endpoint of Part 2: Documented, confirmed objective response (OR) (defined as partial response [PR] or complete response [CR]), assessed by the Response Evaluation Criteria in Solid Tumors (Version 1.1) (RECIST v1.1) at any time during trial participation by Investigator assessment.
Overall Trial Design	During Part 1 of the trial, 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 24 mg/kg has been evaluated. Dose-escalation will follow a standard 3+3 design with dose-escalation guided by DLTs. Patients in Part 1 will receive infusions of Sym015 on a Q2W schedule at the specified dose level until the highest planned dose has been evaluated and/or an MTD is identified. A safety monitoring committee (SMC) will be established and will include Investigator(s), Medical Monitor(s), and Sponsor's medical representatives. The SMC will review clinical and laboratory safety data regularly throughout the trial. The SMC will select the Q2W RP2D to be used in Part 2 based on safety data and available pharmacokinetic (PK) results. During Part 2, three cohorts will receive Sym015 at the RP2D on a Q2W dosing schedule: • Basket Cohort: A basket cohort of *KRAS* WT, advanced solid tumor malignancy patients with *MET*-amplification will be evaluated. Patients must be MET-targeting TKI-naïve; an exception will be a subset of approximately 6 patients who have received prior therapy with a MET-targeting TKI. Note: Effective with protocol version 8.0 (December 2018), accrual to the Basket Cohort is suspended. • NSCLC *MET*-Amplified Cohort: A cohort of advanced NSCLC patients with *MET*-amplification will be evaluated. Patients may have received prior therapy with MET-targeting and/or EGFR-targeting agents. • NSCLC $MET^{Ex14Del}$ Cohort: A cohort of advanced NSCLC patients with $MET^{Ex14Del}$ will be evaluated. Tumors need not be *MET*-amplified, and patients may have received prior therapy with MET-targeting and/or EGFR-targeting agents.
Trial Periods	Prescreening: Sites may choose to prescreen patients utilizing genomic analysis

	(e.g., Guardant360 or other similar liquid biopsy methodology) or tumor tissue (archival, or recently obtained if acquired outside of the screening process as part of the site's usual practice) to assess *MET*-amplification status and *MET*^{Ex14Del} status before entering patients into screening for the treatment portion of the trial. In this case, the site will use a separate pre-screening informed consent form. Screening Period: After providing informed consent, the eligibility of patients will be established according to the protocol-defined inclusion and exclusion criteria. Treatment Period: Patients in the trial will receive IV infusions of Sym015 on a Q2W schedule until occurrence of any of the following: Unacceptable toxicity or other conditions preventing further administration, progressive disease (PD), termination of the trial, or patient's decision to withdraw. End of Treatment/Follow-up: Once Sym015 has been discontinued, an End of Treatment (EOT) Visit will be performed within 10 days following the decision to withdraw treatment. A follow-up visit will be performed 1 month after the last administration of Sym015. After the 1-Month Follow-up (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 stable disease (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. Occurrence of one of these events constitutes the end of trial for the patient.
Number of Patients	It is planned to enroll approximately 63-72 patients in total. Approximately 12-15 patients will receive increasing doses of Sym015 during Part 1. Approximately 51-57 patients will receive Sym015 at the RP2D on a Q2W schedule during Part 2. Three cohorts will be included: • Basket Cohort: Approximately 25 patients with *KRAS* WT, advanced solid tumor malignancies with documented *MET*-amplification will be enrolled and treated. A subset of approximately 6 patients will have received prior therapy with a MET-targeting TKI. Note: Effective with protocol version 8.0 (December 2018), accrual to the Basket Cohort is suspended. NSCLC *MET*-Amplified patients entered to the Basket Cohort will be counted toward the NSCLC *MET*-Amplified Cohort; NSCLC *MET*^{Ex14Del} patients entered to the Basket Cohort will be counted toward the NSCLC *MET*^{Ex14Del} Cohort; patients with both will be counted as *MET*-Amplified. • NSCLC *MET*-Amplified Cohort: approximately 20 patients with advanced NSCLC with documented *MET*-amplification will be enrolled and treated. Patients may have received prior therapy with MET-targeting and/or EGFR-targeting agents. • NSCLC *MET*^{Ex14Del} Cohort: approximately 6-12 patients with advanced NSCLC with documented *MET*^{Ex14Del} will be enrolled and treated. Tumors need not be *MET*-amplified, and patients may have received prior therapy with MET-targeting and/or EGFR-targeting agents. Note: NSCLC patients with tumors identified as both *MET*-Amplified and *MET*^{Ex14Del} will be enrolled to the *MET*-Amplified cohort.
Main Inclusion	**Main inclusion criteria all patients, Part 1 and Part 2:**

and Exclusion Criteria	• Male or female, at least 18 years of age at the time of informed consent • Eastern Cooperative Oncology Group (ECOG) performance status (PS) of 0 or 1 • Life expectancy >3 months assessed during Screening • Documented (histologically- or cytologically-proven) solid tumor malignancy that is locally advanced or metastatic, and that is refractory to standard therapy or for which no standard therapy is available or accessible (i.e., patients must have recurrent and/or progressive disease and be without available therapeutic options) **Additional main inclusion criteria applicable to Part 1 patients ONLY:** • Tumor documented to be *KRAS* WT by local assessment according to institutional standards. If *KRAS* WT is not previously documented and if archival tissue is not available for pretrial assessment, patient must be willing to undergo a tumor biopsy to confirm eligibility **Additional main inclusion criteria applicable to Part 2 patients ONLY:** • Measurable disease according to RECIST v1.1 that has been confirmed by computed tomography (CT) or magnetic resonance imaging (MRI) within 4 weeks prior to Cycle 1/Day 1 (C1/D1) Note: Measurable disease is defined as 1 or more target lesions assessed by CT or MRI. A tumor lesion situated in a previously irradiated area is considered measurable only if subsequent PD has been documented in the lesion • Basket Cohort ONLY: o Confirmed *MET*-amplification by local assessment; i.e., *MET* gene copy number to control probe ratio [G:CN] >2.2 scored in 50 tumor nuclei by fluorescence *in situ* hybridization (FISH), chromogenic *in situ* hybridization (CISH), silver *in situ* hybridization (SISH) or similar, or a copy number >5 by next-generation sequencing (NGS) or quantitative polymerase chain reaction (qPCR) Note: Peripheral blood collection for *MET*-amplification assessment in ctDNA will be allowed as a local pre-screening methodology provided results are 3+ by Guardant360* analysis (or equivalent to 3+ by Guardant360 if an alternative Sponsor-approved methodology is used), and provided subsequent required confirmatory tumor tissue evaluation meets the above inclusion criterion. *http://guardanthealth.com/ o Tumor documented to be *KRAS* WT by local assessment according to institutional standards. If *KRAS* WT is not previously documented and if archival tissue is not available for pretrial assessment, patient must be willing to undergo a tumor biopsy to confirm eligibility Note: Peripheral blood collection for *KRAS*-mutation assessment in circulating tumor deoxyribonucleic acid (ctDNA) (also referred to as "liquid biopsy") will be allowed as a local pre-screening methodology by Guardant360* analysis. Other liquid biopsy methodologies, except if used to detect $MET^{Ex14Del}$, will only be allowed if previously approved by the Sponsor. o No prior therapy with MET-targeting agents Note: An exception will be a subset of approximately 6 patients entered to the

Basket Cohort after having received prior therapy with a MET-targeting TKI.

- Willingness to undergo a pre- and post-dosing biopsy (maximum of 2 biopsies) from primary or metastatic tumor site(s) considered safely accessible for biopsy

- NSCLC *MET*-Amplified Cohort ONLY:
  - Documented NSCLC meeting disease criteria as defined above
  - Documented *MET*-amplification by either:
    - Local assessment in a recent* tumor biopsy; i.e., G:CN ≥3.0 scored in 50 tumor nuclei by FISH, CISH, SISH or similar assay, or a copy number >5 by NGS or qPCR (subsequent central confirmation required; however, patient may be enrolled and treated based on local assessment, before central confirmation results have been obtained)

      *Tissue for local assessment may be from a recent tumor biopsy, defined as one performed since last documented disease progression as part of the site's usual practice, and where no intervening antineoplastic therapy has been administered; otherwise tissue from a newly performed biopsy must be obtained and submitted.

    - Central confirmation** in a newly performed pre-dosing tumor biopsy; i.e., G:CN ≥3.0 scored in 50 tumor nuclei by FISH

      **If central confirmation of *MET*-amplification status cannot be assessed in tumor due to assay failure/technical error, the Sponsor may decide to enroll based on *MET*-amplification detected by Guardant360 on a case per case basis (see Note below regarding Guardant360 analysis).
  - May have received prior therapy with MET-targeting and/or EGFR-targeting agents (antibodies or TKIs)
  - Willingness to undergo a pre-dosing biopsy (mandatory unless a recent* tumor biopsy as defined above is available), and potentially a biopsy at the End of Cycle 2 (EOC2) (optional), from a primary or metastatic tumor site considered safely accessible for biopsy

  Note: Peripheral blood for ctDNA analysis by Guardant360 will be obtained for assessment of *MET*-amplification status. As data are acquired on concordance between findings in tumor tissue versus ctDNA, the Sponsor may decide to transition to screening for *MET*-amplification using Guardant360 analysis only (e.g., 2+ or 3+ amplification score) without requiring confirmation in a recent or newly performed tumor biopsy.

- NSCLC $MET^{Ex14Del}$ Cohort ONLY:
  - Documented NSCLC meeting disease criteria as defined above
  - Documented $MET^{Ex14Del}$ (tumors need not be *MET*-amplified)

    Note: $MET^{Ex14Del}$ status to be documented according to local institutional standards. Assessment in ctDNA by Guardant360 technology or equivalent is allowed. Tissue from a recent* or newly performed pre-dosing tumor biopsy must be submitted for central assessment.

    *Recent tumor biopsy, defined as one performed since last documented disease progression as part of the site's usual practice, and where no intervening antineoplastic therapy has been administered; otherwise tissue from a newly

performed biopsy must be obtained and submitted.

- May have received prior therapy with MET-targeting agents and/or EGFR-targeting agents (antibodies or TKIs)
- Willingness to undergo a pre-dosing biopsy (mandatory unless a recent* tumor biopsy as defined above is available), and potentially a biopsy at the EOC2 (optional), from a primary or metastatic tumor site considered safely accessible for biopsy

Note: Peripheral blood for ctDNA analysis by Guardant360 will be obtained for assessment of *MET*^{EX14Del} status.

Main exclusion criteria all patients, Part 1 and Part 2:

- Any antineoplastic agent for the primary malignancy (standard or investigational) without delayed toxicity within 4 weeks or 5 plasma half-lives, whichever is shortest, prior to C1/D1, except:
  - Nitrosoureas and mitomycin C within 6 weeks prior to C1/D1
- Immunosuppressive or systemic hormonal therapy within 2 weeks prior to C1/D1 with specified allowed exceptions
- Use of hematopoietic growth factors within 2 weeks prior to C1/D1
- Active second malignancy or history of another malignancy within the last 3 years, with specified allowed exceptions
- Central nervous system (CNS) malignancy including primary malignancies of the CNS and/or known, untreated CNS or leptomeningeal metastases, or spinal cord compression; patients with any of these not controlled by prior surgery or radiotherapy, or symptoms suggesting CNS involvement for which treatment is required
- Inadequate recovery from an acute toxicity associated with any prior antineoplastic therapy
- Major surgical procedure within 4 weeks prior to C1/D1 or inadequate recovery from any prior surgical procedure
- Active thrombosis, or a history of deep vein thrombosis or pulmonary embolism, within 1 month prior to C1/D1, unless adequately treated and stable
- Active uncontrolled bleeding or a known bleeding diathesis
- Significant cardiovascular disease or condition
- Abnormal hematologic, renal or hepatic function as defined by the following criteria:
  - Absolute neutrophil count (ANC) $<1.5 \times 10^9$/L ($1500/mm^3$)
  - Hemoglobin ≤9 g/dL
  - Platelet count $<75 \times 10^9$/L ($75{,}000/mm^3$)
  - Serum creatinine >1.5 × upper limit of normal (ULN) for the institution
  - Aspartate aminotransferase (AST) >3.5 × ULN for the institution or AST >5 × ULN for the institution in case of known liver metastases
  - Alanine aminotransferase (ALT) >3.5 × ULN for the institution or ALT >5 × ULN for the institution in case of known liver metastases
  - Total bilirubin >1.5 × ULN for the institution
  - Prothrombin time as assessed by International Normalized Ratio (INR) >1.5 × ULN for the institution*

	○ Partial thromboplastin time (PTT) >1.5 × ULN for the institution* *Unless on a stable dose of anticoagulant therapy for a prior thrombotic event • Any of the following within 2 weeks prior to C1/D1: ○ Any serious or uncontrolled infection ○ Any infection requiring parenteral antibiotics ○ Unexplained fever >38.0 °C **Additional main exclusion criteria applicable to Part 2 patients ONLY:** • <u>Basket Cohort ONLY</u>: ○ Prior therapy with MET-inhibiting agents Note: Exceptions will be a subset of approximately 6 patients entered to the Basket Cohort after having received prior therapy with a MET-targeting TKI. ○ Prior therapy with antibody to hepatocyte growth factor (HGF) • <u>Basket Cohort and NSCLC *MET*-Amplified Cohort ONLY</u>: Tumor status demonstrating *MET*-polysomy in the absence of *MET*-amplification, as specified Note: Patients in the NSCLC *MET*^{Ex14Del} Cohort with polysomy are eligible • Radiotherapy against target lesions within 4 weeks prior to C1/D1, unless there is documented progression of the lesion following the radiotherapy
Investigational Medicinal Product, Dose(s) and Treatment Schedule	The Investigational Medicinal Product (IMP) is Sym015. Sym015 is a recombinant antibody mixture containing 2 humanized immunoglobulin G1 (IgG1) monoclonal antibodies (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 a 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. Sym015 will be administered on a Q2W schedule by IV infusion. • Q2W dosing: Day 1 and Day 15 of each 28-day cycle (± 2 days) Sym015 will be administered over a 1.5-hour (+10 minutes) period for doses ≥18 mg/kg and over a 1-hour (+10 minutes) period for doses <18 mg/kg, following delivery of premedication prior to each infusion. In Part 2, if the patient is without evidence of infusion related reactions (IRRs) after Cycle 1, the Investigator may opt to withdraw premedication on a patient-by-patient basis with subsequent dosing. **Part 1/Dose-Escalation** During the dose-escalation part of the trial, the following dose levels of Sym015 administered Q2W will potentially be evaluated in a standard 3+3 dose-escalation design: • Dose Level 1: 6 mg/kg • Dose Level 2: 12 mg/kg • Dose Level 3: 18 mg/kg

	• Dose Level 4: 24 mg/kg A substitute or additional dose level, within the dose levels listed above, could potentially be evaluated. Enrollment will be staggered between the first and second patient in each new higher dose level tested. The first patient must have completed and tolerated the first dose of Sym015, including follow-up until Day 8 of Cycle 1 (C1/D8), in order to allow for review of clinical and laboratory assessments. Thereafter patients within a cohort may be added concurrently. **Part 2** Once the Q2W RP2D has been established during dose-escalation, the enrollment into Part 2 will commence. 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 of 18 mg/kg infused over 1.5 hours on C1/D1, followed by Q2W maintenance doses of 12 mg/kg 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 24 mg/kg.
Trial Assessments	All assessments will be repeated throughout the trial at protocol-specified intervals, unless otherwise stated. **Safety Assessments** • Medication/Procedure survey • (Serious) Adverse Event ([S]AE) survey • DLT evaluation (Part 1, dose-escalation only) during Cycle 1 with a final assessment 14 (±2) days after the last dose of Cycle 1 or prior to dosing on Cycle 2/Day 1 (C2/D1) • Vital signs and body weight • ECOG PS • Physical examination • Electrocardiogram (ECG) at screening, EOT and as clinically indicated during trial participation • Transthoracic echocardiogram (ECHO) or multi-gated acquisition (MUGA) scan at screening and in the event of cardiac symptoms and as otherwise clinically indicated during trial participation • Safety blood samples • Urinalysis • Pregnancy test at screening, EOT, and if clinically indicated during trial participation **Disease Assessments** • Disease status evaluation by CT or MRI at screening, at the EOC2 and every second cycle thereafter. Further potential timepoints are in the event of suspected PD, in the event of CR/PR and at EOT/1M FUP • Tumor marker evaluation as indicated by tumor type, if applicable • Archival tumor tissue for *MET* and *KRAS* assessment (Part 1 and Part 2 Basket Cohort):

- For patients in Part 1, local eligibility assessment for *KRAS* mutational status will be done using archival tissue, whenever possible. If archival tissue is not available, a tumor biopsy will be performed for eligibility assessment. Assessment of *MET*-amplification status is not required for patients in Part 1, but tissue should be assessed if available
- For patients in Part 2, local eligibility assessment for *KRAS* mutational status may be done using archival tumor tissue. If archival tissue is not available, tissue from the tumor biopsy performed during screening will be used.
  - It is preferred that the 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.

    Note: During Part 2 ONLY, peripheral blood collection for *KRAS*-mutation assessment and for *MET*-amplification assessment in ctDNA is allowed as a local pre-screening methodology by Guardant360 analysis. Other liquid biopsy methodologies, except if used to detect $MET^{Ex14Del}$, will only be allowed if previously approved by the Sponsor. Subsequent required tumor tissue evaluation to confirm *MET*-amplification must meet the protocol-specified inclusion criteria.
  - NSCLC $MET^{Ex14Del}$ Cohort *(pre-protocol v8.0)*: Eligibility assessment for $MET^{Ex14Del}$ status will be done according to local institutional standards. Assessment in ctDNA by Guardant360 technology or equivalent is allowed. Subsequent confirmation in tumor tissue is preferred but not required, however, archival tissue to be submitted for central testing, if available (applies only to patients with $MET^{Ex14Del}$ tumors entered prior to suspension of the Basket Cohort and establishment of NSCLC $MET^{Ex14Del}$ Cohort).

- Tumor biopsy for *MET* status and biomarker analysis (Part 2 NSCLC *MET*-Amplified Cohort and NSCLC $MET^{Ex14Del}$ Cohort):
  - Screening (Mandatory)
    - NSCLC *MET*-Amplified Cohort: Required; tissue from a newly performed pre-dosing tumor biopsy must be submitted for central confirmation of *MET*-amplification

      (Patients may be entered and treated based on local assessment of a recent tumor biopsy [if available and performed outside of the screening process as part of the site's usual practice] provided no intervening antineoplastic therapy has been administered; otherwise tissue from a newly performed pre-dosing biopsy must be obtained and submitted)
    - NSCLC $MET^{Ex14Del}$ Cohort: Required; tissue from a recent or newly performed pre-dosing tumor biopsy must be submitted for central assessment of $MET^{Ex14Del}$

      (Patients may be entered and treated based on local institutional standards; alternatively, assessment in ctDNA by Guardant360 technology or equivalent is allowed; a recent [as defined above] or newly performed pre-dosing biopsy must still be submitted)
  - Post-Dosing (Optional)

	EOC2 (i.e., coinciding with time of first response assessment) or upon PD, whichever occurs first. **Additional Assessments** • PK sampling with extended PK-profiling after the first infusion • Anti-drug antibody (ADA) testing • Part 1 only: Skin biopsy for biomarker analysis at screening, at the EOC2 or upon PD, whichever comes first • Blood sample for genomic/biomarker analyses at screening, at the EOC2 or upon PD, whichever comes first, and at EOT
Statistical Methods and Sample Size Calculation	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. All DLT events will be listed by dose cohort and patient. A summary table of DLTs by System Organ Class (SOC) and Preferred Term will be presented for each dose cohort, if applicable. The summaries will include number of DLTs and number and percentages of patients experiencing a DLT. The MTD is defined as the highest dose with a maximum of 1 out of 6 patients experiencing a DLT. The MTD may or may not be found within the dose levels tested. Based on an overall evaluation of the dose-escalation part, the Q2W RP2D and highest safe dose tested will be selected. 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 approximately 25 patients with 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 a total of approximately 51-57 patients in Part 2. The expected (target) range of OR in any of the three cohorts is in the range of 20%-50%, depending on histology, previous therapies, and other prognostic factors defining the enrolled patient population. Number and percentages of patients with documented OR will be presented including corresponding 90% exact Confidence Intervals (CI).

2. LIST OF ABBREVIATIONS AND EXPANDED TERMS

1M FUP	1-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
BOR	Best Overall Response
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
CNS	Central Nervous System
CR	Complete Response
CRF	Case Report Form
CT	Computed Tomography
ctDNA	Circulating Tumor Deoxyribonucleic Acid
CTCAE v4.03	Common Terminology Criteria for Adverse Events (Version 4.03)
CTR	Clinical Trial Report
DLT	Dose-Limiting Toxicity
DMP	Data Management Plan
DR	Duration of Response
DSUR	Development Safety Update Report
EC	Ethics Committee
ECG	Electrocardiogram
ECHO	Echocardiogram
ECOG	Eastern Cooperative Oncology Group

EDC	Electronic Data Capture
EEA	European Economic Area
EGFR	Epidermal Growth Factor Receptor
EOC	End of Cycle
EOI	End of Infusion
EOS	End of Study
EOT	End of Treatment
FAS	Full Analysis Set
FISH	Fluorescence *In Situ* Hybridization
FUP	Follow-up
G:CN	Gene Copy Number to Control Probe Ratio
GCP	Good Clinical Practice
GDPR	General Data Protection Regulation
GTP	Gamma-Glutamyl Transpeptidase
hCG	Human Chorionic Gonadotropin
HGF	Hepatocyte Growth Factor
HIV	Human Immunodeficiency Virus
HRT	Hormone Replacement Therapy
ICH	International Council for Harmonisation of Technical Requirements for Pharmaceuticals for Human Use
ICMJE	International Committee of Medical Journal Editors
IgG1	Immunoglobulin G1
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	*KRAS* proto-oncogene
mAb	Monoclonal Antibody
MedDRA	Medical Dictionary for Regulatory Activities
MET	MET proto-oncogene tyrosine kinase, hepatocyte growth factor receptor

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
NE	Not Evaluable
NGS	Next-Generation Sequencing
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
OS	Overall Survival
PD	Progressive Disease
PDF	Portable Document Format
PDX	Patient-Derived Xenograft
PFS	Progression-free Survival
PK	Pharmacokinetic(s)
PO	Orally, by mouth
PR	Partial Response
PS	Performance Status
PSA	Prostate-Specific Antigen
PTT	Partial Thromboplastin Time
qPCR	Quantitative Polymerase Chain Reaction
Q2W	Every Second Week
RECIST v1.1	Response Evaluation Criteria in Solid Tumors (Version 1.1)
RP2D	Recommended Phase 2 Dose
RTK	Receptor Tyrosine Kinase
TKI	Tyrosine Kinase Inhibitor
SAE	Serious Adverse Event
SD	Stable Disease
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 Reaction
TEAE	Treatment Emergent Adverse Event
TTP	Time to Progression
ULN	Upper Limit of Normal
USA	United States
WHO	World Health Organization
WT	Wild-Type

PHARMACOKINETIC TERMS

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
CL	Clearance
C_{max}	Maximum Concentration
C_{trough}	Trough Concentration
C_z	Last Quantifiable Concentration
$T_{½}$	Elimination Half-Life
T_{max}	Time of Maximum Concentration
V_z	Volume of Distribution
λ_z	Terminal Rate Constant

3. BACKGROUND AND RATIONALE

3.1 Disease and Treatment

3.1.1 Solid Tumor Malignancies

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, only surpassed by heart disease. In 2012, 14.1 million people were diagnosed with cancer worldwide. An estimated 8.2 million people died from the disease. The World Health Organization (WHO) projected that by 2035, these figures could increase to 24 million new cases and 14.6 million cancer deaths worldwide. 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 (31).

3.1.2 *MET*-Amplified Solid Tumor Malignancies

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 (2).

Dysregulation of MET or HGF activity may occur through overexpression, gene-amplification, mutation, or alternative splicing of MET, or through HGF ligand-induced autocrine/paracrine loop signaling. Such dysregulation 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 (3,4).

Depending on the methodology used for detection, varying frequencies of *MET* amplification have been reported in solid tumor malignancies over the past few years. Fluorescence *in situ* hybridization (FISH) is currently considered the gold standard for detection of *MET*-amplification, as this methodology makes it possible to distinguish between polysomy and true gene-amplification (3). In accordance with the American Society of Clinical Oncology (ASCO) and the College of American Pathologists (CAP) guidelines for testing of HER2 amplification (5), *MET*-amplification may be defined as positive with a MET/CEP7 ratio (CEP7 being the centromeric region of chromosome 7) of >2.2 (occasionally 2.0), equivocal with a ratio between 1.8 and 2.2, and negative with a ratio of <1.8. Polysomy tends to yield a ratio in the equivocal range.

In a recent study, *MET*-amplification (MET/CEP7 ratio >2 by FISH) was detected in 29 out of 1,115 (2.6%) patients with advanced solid tumor malignancies (6). Tumor types where *MET*-amplification was detected included adrenocortical, renal cell, gastro-esophageal, breast, ovarian, colorectal, biliary, bladder, salivary gland and lung carcinomas, as well as malignant melanoma. This study also reported *MET*-amplification frequencies above 10% for certain tumors, albeit based on a limited number of patients. Based on FISH analysis in larger cohorts of patients, *MET*-amplification has been shown to occur in 3%-4% of NSCLC (7,8,9,10) and in 4%-6% of gastric cancers (11,12,13). A number of studies have also demonstrated a correlation between MET-expression by immunohistochemistry (IHC) and *MET*-amplification by FISH (10,11).

Mutations leading to skipping of *MET* exon 14 ($MET^{Ex14Del}$) result in the deletion of the juxtamembrane domain of MET, which stabilizes and accumulates receptor on the cell surface and leads to enhanced signaling through the MET receptor pathway (13). *MET* alterations that result in exon 14 skipping are found in 3%-4% of lung adenocarcinomas, both in the presence and absence of *MET*-amplification and studies have demonstrated clinical benefit of targeting patients with tumors harboring $MET^{Ex14Del}$ (14-17). Over 100 mutations in *MET*-mutated cancers resulting in exon 14 skipping have been described (15). *KRAS* proto-oncogene (*KRAS*) mutation appears to be a cause of resistance to MET inhibition both in preclinical models (19) and in the clinic (20). According to the single study published to date that deals with the prevalence of *KRAS* mutation in *MET*-amplified tumors, 25% (4/16) of *MET*-amplified lung adenocarcinomas were found to harbor *KRAS* mutations, and alterations of both *MET* and *KRAS* were found in 0.8% (4/519) of treatment-naïve lung adenocarcinomas (10). Because these two molecular

alterations are rare in NSCLC patients, testing of *KRAS* status in clinical trials involving anti-MET therapy may not be warranted (10,19).

NSCLC patients with either *MET*-amplification or $MET^{Ex14Del}$ have been documented to have a poor prognosis (32). *MET*-amplification was observed in 0.7% of all patients with NSCLC and *MET* mutations were observed in 2.6% of patients in this population.

3.1.3 Current Treatment of *MET*-Amplified Solid Tumor Malignancies

There are currently no approved therapeutics for targeted treatment of *MET*-amplified solid tumor malignancies. However, multiple compounds targeting the MET/HGF pathway are being evaluated in the clinic. These include both small-molecule tyrosine-kinase inhibitors, such as crizotinib, cabozantinib, tivantinib, tepotinib, and capmatinib as well as single monoclonal antibodies (mAbs). The small-molecule inhibitors are generally promiscuous in their target specificity and may have activity on additional RTKs besides MET. The activity of MET inhibitors in patients with NSCLC has recently been reviewed (33), and more recent data are cited below with respect to additional inhibitors.

Crizotinib is an inhibitor of MET, ALK, and ROS1. Crizotinib has been approved for treatment of advanced NSCLC harboring ALK translocations and has shown promising results in an ongoing Phase 1 clinical trial in *MET*-amplified NSCLC patients (21). The degree of *MET*-amplification, determined by FISH, correlated closely with the observed response rate; there were no responses in patients with tumors classed as low-level amplified, and response rates of 20% and 50% were observed in tumors classed as having medium or high levels of *MET*-amplification, respectively.

Tepotinib is another MET tyrosine kinase inhibitor (TKI) that has been studied in Phase 1 and Phase 2 clinical studies. A recent study was reported showing evidence of antitumor activity in patients with $MET^{Ex14Del}$. The preliminary data documented that 60% of patients treated with tepotinib in this study had confirmed partial responses (PR) (34).

Capmatinib (INC280), a MET TKI, is also in Phase 2 studies enrolling NSCLC patients with $MET^{Ex14Del}$ as well as in combination with gefitinib in patients with epidermal growth factor receptor (*EGFR)*-mutated *MET* dysregulated NSCLC. An overall response rate of 72% was observed in treatment-naïve patients compared to a 39% objective response rate in previously treated patients with advanced $MET^{Ex14Del}$-positive NSCLC (35).

AMG 337 is an investigational selective MET inhibitor that has shown promising clinical activity. An objective response (OR) was observed in 8 out of 13 patients with *MET*-amplified gastroesophageal junction, gastric, or esophageal cancer (22).

LY2875358 (emibetuzumab) is a humanized IgG4 anti-MET mAb that is reported to block ligand binding and induce target internalization. LY2875358 has demonstrated preliminary evidence of antitumor activity (durable PR in 2 of 13 patients) in combination with erlotinib in patients with tumors positive for MET-expression and is currently being evaluated in Phase 2 trials (23).

ABT-700 is a humanized immunoglobulin G1 (IgG1) mAb with an engineered hinge region that inhibits MET receptor dimerization and induces receptor internalization and antibody-dependent cellular cytotoxicity (ADCC) in tumor cell lines *in vitro*. ABT-700 has demonstrated potent activity as a single agent in patients with *MET*-amplified tumors (tumor regression in 5/8 patients) (24).

ARGX-111 is a third mAb that has recently entered clinical trials. ARGX-111 is a human IgG1 mAb, which has been glyco-engineered to enhance ADCC activity. In the Phase 1 dose-escalation trial, the only patient with a *MET*-amplified tumor maintained stable disease during 6 months of treatment (25).

3.2 Investigational Medicinal Product

3.2.1 Sym015

The investigational medicinal product (IMP) tested in this trial is Sym015.

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.

Sym015 is a clear to opalescent, colorless to slightly yellow liquid to be administered as an intravenous (IV) infusion through a peripheral line or indwelling catheter.

3.2.2 Mechanism of Action

The two antibodies of Sym015 bind to non-overlapping epitopes on the SEMA-α domain of MET. This allows the antibodies to bind simultaneously to the receptor and effectively induce

receptor internalization and degradation. Through this mechanism, Sym015 effectively inhibits cell-proliferation and tumor growth in models where MET is constitutively activated. Moreover, Sym015 blocks HGF-binding to the receptor and is thus also capable of inhibiting HGF-induced MET phosphorylation and cell-proliferation. In addition, Sym015 induces effector functions, including ADCC, which may contribute to the activity observed *in vivo*.

3.2.3 Summary of Non-Clinical Findings

Sym015 demonstrates potent antitumor activity in a number of MET-dependent cell line and patient-derived xenograft (PDX) tumor models, including esophagogastric and NSCLC models. Response to Sym015 was observed in models with *MET*-amplification, $MET^{Ex14Del}$, and autocrine HGF-expression. Sym015 also retains full efficacy in *MET*-amplified models in human HGF transgenic mice. Sym015 is in many cases superior to a LY2875358 (emibetuzumab) analogue and is also active in tumor models that escape treatment with this antibody. Based on the preclinical models, *KRAS* mutation appears to predict resistance to Sym015 treatment (25,26).

In vivo safety and pharmacokinetics (PK) of Sym015 were evaluated in non-human primates. MET is evolutionarily conserved between cynomolgus monkeys and humans and Sym015 recognizes both human and cynomolgus MET with the same, high affinity. Thus, the cynomolgus monkey is considered a pharmacologically relevant model in which to study toxicity and PK.

In the pivotal repeat-dose toxicity study, the toxicity of Sym015 was determined following weekly IV infusions (30 minutes infusion time) at 15 mg/kg, 50 mg/kg, or 100 mg/kg to cynomolgus monkeys for 4 weeks followed by a 6-week treatment-free period in the high dose group.

No unscheduled deaths occurred during the course of the study. Sym015 did not exert effects on cardiovascular functions and was overall well tolerated in the monkeys. However, soft, liquid, or loose feces were observed in treated animals, with a higher incidence in high dose males. At the end of the recovery period, there was no evidence of delayed onset toxicity in previously treated animals.

No *in vivo* agonistic activity of Sym015 was observed as judged by Ki67 expression (proliferation marker) in liver, kidney, duodenum, and heart at study termination. Toxicokinetic profiles showed that all treated animals were exposed to Sym015 throughout the entire duration

of the study. Target engagement, documented by reduced MET expression in tissues, was observed for all dose levels tested.

In the initial elimination phase, the serum half-life ($T_{½}$) of Sym015 after a single dose of 15 mg/kg ranged from 8-23 days, while in the terminal elimination phase the $T_{½}$ ranged from 5-8 days. Upon repeat, once-weekly dosing of Sym015 at 15 mg/kg, 50 mg/kg, or 100 mg/kg produced a 2-fold accumulation of Sym015 over a period of four weeks.

In conclusion, the 100 mg/kg dose level is considered the *no observed adverse effect level* (NOAEL) of Sym015 in monkeys.

For further information, refer to the Investigator's Brochure.

3.2.4 Summary of Clinical Findings

3.2.4.1 Protocol Sym015-01

This is the first clinical trial to study Sym015. As of Amendment 5, a total of 12 patients were enrolled in the completed Part 1 of this trial: 3 patients at each of 4 dose levels (6 mg/kg, 12 mg/kg, 18 mg/kg, and 24 mg/kg, dosed every second week [Q2W]). All 4 dose levels were considered well tolerated, no DLTs or trial drug-associated serious adverse events (SAEs) were reported. A total of 2 of 3 patients entered to the 18 mg/kg cohort experienced infusion-related reactions (IRRs) with the first dose of trial drug. Reactions were characterized in one patient by nausea, a "cotton-mouth" sensation, and wheezing, and characterized in the second patient by cough, shortness of breath, and a transient oxygen saturation decrease to 87% that did not require delivery of supplemental oxygen. In each case, the infusion was interrupted for approximately 30 minutes while the patient was treated with a glucocorticoid and an antihistamine; upon resolution of symptoms, the infusion was restarted at a slower rate and completed without further incident. As a result of these two events, the duration of Sym015 infusion was extended from 1 hour to 2 hours for the affected patients, and the duration of Sym015 infusion was extended per protocol from 1 hour to 1.5 hours for subsequent patients entered at this dose and higher doses. No additional IRRs were reported with the longer duration of infusion in the remaining patients treated during Part 1 of the trial. While data in this ongoing clinical trial have not been fully monitored, other observed trial drug-associated adverse events (AEs) noted have included fatigue in 2 patients, and single episodes of nausea, dyspepsia, vomiting, diarrhea, peripheral edema, weight decrease, and hypokalemia; all AEs were Grade 1 or Grade 2 in severity. Part 2 of the study is open to accrual.

As of September 2018, a total of 21 *MET*-amplified patients and 2 *MET*^{Ex14Del} patients have been enrolled in the ongoing Part 2 portion of this trial to receive Sym015 at a loading dose of 18 mg/kg delivered over 1.5 hours, followed by Q2W maintenance doses of 12 mg/kg delivered over 1 hour. In a single patient, the SAEs of Grade 3 colitis which resulted in Grade 3 septic shock (both possibly-related) have been reported; these 2 events occurred in a patient with metastatic gastric carcinoma and a history of total gastrectomy with esophagojejunostomy whose diarrhea present at baseline worsened after administration of 3 doses of Sym015. In another patient, the SAEs of Grade 3 anasarca and Grade 3 hypoalbuminemia (both possibly related) have been reported. Other study drug-related AEs have been limited to Grade 2 fatigue and mouth sores, and Grade 1 asthenia, anorexia, gastric pain, abdominal cramping, abdominal gas, nausea, diarrhea, constipation, xerosis, pruritus, and voice change. In addition to the Grade 3 hypoalbuminemia noted, other laboratory abnormalities reported as study drug-related AEs have been Grade 1 in severity and have included: anemia; prolongations in prothrombin time and international normalized ratio (INR); and elevations in aspartate aminotransferase (AST), alanine aminotransferase (ALT), gamma-glutamyl transpeptidase (GTP), and blood bilirubin. Accrual to the Part 2 portion of the trial continues.

Note: Effective with protocol version 8.0 (December 2018), accrual to the Part 2 Basket Cohort comprised of patients with *MET*-amplified solid tumor malignancies is suspended; accrual will continue to cohorts of patients with *MET*-amplified NSCLC or *MET*^{Ex14Del} NSCLC.

3.2.4.2 Other Monoclonal Antibodies Targeting MET

Based on available literature/reports, mAbs targeting MET appear to be generally well tolerated. No dose-limiting toxicities (DLTs) or SAEs were observed in the Phase 1 trials with LY2875358 or ABT-700. The most frequent treatment-related AEs were nausea, vomiting, and diarrhea for LY2875358 and constipation, fatigue and decreased appetite for ABT-700 (23,24). Two DLTs of infusion-related reactions (IRRs) have been reported with the glyco-engineered ARGX-111. IRRs were the overall most common adverse event with this drug (likely a class effect of glyco-engineered antibodies), followed by fatigue and nausea (25). Based on nonclinical results, Sym015 appears to have a safety profile similar to that of LY2875358 and ABT-700.

3.3 Trial Rationale

As outlined in the sections above, recent results suggest that *MET*-amplification and *MET*^{Ex14Del} identify small but clinically important subgroups of patients who are likely to respond to MET targeted therapies. The potent tumor inhibitory activity, observed in preclinical studies in models with *MET*-amplification and/or *MET*^{Ex14Del}, suggests that Sym015 may provide a clinically

relevant effect in these patient populations. Based on the nonclinical pharmacology and toxicity testing, Sym015 is expected to continue to be well tolerated and the benefit-risk ratio for patients enrolled is considered to be favorable.

3.4 Dose Rationale

3.4.1 Rationale for Starting Dose

The starting dose of 6 mg/kg Sym015 has been selected based on demonstrated safety of Sym015 in nonclinical studies in cynomolgus monkeys (refer to Section 3.2.3). In these studies, dose levels that are multiples (2.5- to 17-fold) of the anticipated clinical starting dose of 6 mg/kg were tested to provide a safety margin. All dose levels resulted in high levels of exposure to Sym015. The NOAEL was determined as 100 mg/kg in cynomolgus monkeys. In addition, the results of nonclinical pharmacology, pharmacodynamic, PK, and toxicology studies provide guidance with respect to potential target serum levels of Sym015 to down-regulate MET in tissues and that correlate with efficacy in animal models.

The dosing schedule to be explored in this clinical trial is based on nonclinical data documenting the concentrations of Sym015 required for downregulation of MET, inhibition of cancer cell lines *in vitro*, and *in vivo* activity in murine models. PK data (long terminal $T_{½}$ and accumulation with weekly dosing) support the selection of the dosing schedule, dosing every second week (Q2W), to be evaluated in this trial.

IV dosing is being pursued to maximize exposure to Sym015 while minimizing the potential for adverse effects and immunogenicity. Based on the anticipated doses required, neither subcutaneous nor intramuscular dosing have been considered for initial evaluation of Sym015.

3.4.2 Rationale for Recommended Phase 2 Dose

As of Amendment 4, following review of available safety (refer to Section 3.2.4.1) and PK data, the decision has been made to choose the following as the recommended Phase 2 dose (RP2D) on a Q2W schedule of Sym015 (referenced as the Q2W RP2D):

- Loading dose of 18 mg/kg infused over 1.5 hours on Cycle 1/Day 1 (C1/D1)
- Followed by Q2W maintenance doses of 12 mg/kg infused over 1 hour beginning on Cycle 1/Day 15 (C1/D15)

The rational for this choice is based upon preliminary PK data from the initial 6 mg/kg Q2W (N=3, 2-3 cycles) and 12 mg/kg Q2W (N=3, up to Cycle 2/Day 1) cohorts treated in the dose-escalation phase of this trial. These data were used to establish a population PK model.

The summary PK parameters for these data, based on non-compartmental analysis, are listed in Table 1.

Table 1 Preliminary Sym015 Geometric Mean PK Parameters

Dose Q2W	N	$AUC_{0\text{-}336h}$ 1st dose (h x µg/mL)	C_{max} 1st dose (µg/mL)	C_{trough} 2nd dose (µg/mL)	C_{max} 3rd dose (µg/mL)	$t_{½}$ 1st dose (h)
6 mg/kg	3	19400	146	35.9	196	158
12 mg/kg	3	40000	294	119	396	213 (n=1)

Abbreviations: AUC, area under the concentration-time curve in a dosing interval; C_{max}, maximum concentration; C_{trough}, trough concentration; h, hour; N, number of patients; Q2W, dosing every second week; $t_{½}$, elimination half-life

The model was used to simulate average and 90% confidence intervals for Sym015 PK profiles for the 18+12 mg/kg Q2W regimen, and demonstrated that pre-dose serum concentrations, C_{trough}, are likely to be above 100 µg/mL for the vast majority of patients for all dose administrations. The serum concentration of 100 µg/mL has been defined as an approximate threshold for clinical efficacy. This has been deduced from the 750 mg Q2W dose regimen of another anti-MET monoclonal antibody, emibetuzumab, which has shown signs of efficacy in patients with *MET*-amplified tumors (23,28). It is assumed that similar serum concentrations of Sym015 and emibetuzumab will result in similar clinical efficacy because similar potencies between the two compounds have been observed in preclinical *in vitro* and *in vivo* studies (refer to Investigator's Brochure). *In vivo* studies also support that efficacy can be expected at concentrations above 100 µg/mL for both compounds.

3.5 Overall Benefits/Risk

It is not possible to quantify the potential benefit to individual patients entering this Phase 1 trial. Definite, but sometimes limited, antitumor activity has been reported in many Phase 1 trials, including other trials of MET-targeted agents.

In this trial there will be an ongoing assessment of the risks with periodic evaluation of safety data. The trial will be discontinued in the event of any new finding indicating a risk that would render continuation of the trial unjustifiable.

In order to mitigate potential risks, the trial is designed to detect DLTs, if any, and to define a maximum tolerated dose (MTD), if this is observed in the range of doses planned for the trial.

Enrollment will be staggered between the first and second patient in each new higher dose level tested in order to ensure safety, before allowing concurrent enrollment of further patients at the given dose level. If the dose administered in a cohort is safe and well-tolerated, dose-escalation may proceed, and enrollment of subsequent cohorts may occur in order to establish a Q2W RP2D and to define an MTD or highest safe dose. The potential to slow infusions, interrupt dosing, decrease the dose administered, and discontinue administration of Sym015 in the event of specific AEs is outlined. In addition, steps to prevent IRRs, and measures to intervene in the event of their occurrence are specified.

4. TRIAL OBJECTIVES

4.1 Objectives of Part 1, Dose-Escalation

4.1.1 Primary Objective

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

4.1.2 Secondary Objectives

1. To determine a Q2W 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

4.2 Objectives of Part 2

4.2.1 Primary Objective

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

1. Basket Cohort: *MET*-amplified, *KRAS* WT solid tumor malignancies without available therapeutic options; patients may not have received prior therapy with a MET-targeting TKI
2. NSCLC *MET*-Amplified Cohort: *MET*-amplified advanced NSCLC without available therapeutic options; patients may have received prior therapy with MET-targeting and/or EGFR-targeting agents
3. NSCLC $MET^{Ex14Del}$ Cohort: $MET^{Ex14Del}$ advanced NSCLC without available therapeutic options; patients may have received prior therapy with MET-targeting and/or EGFR-targeting agents

4.2.2 Secondary Objectives

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
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

5. TRIAL DESIGN

5.1 Overall Design and Plan

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

- Part 1 is a Phase 1a dose-escalation in patients with *KRAS* WT advanced solid tumor malignancies without available therapeutic options.
- Part 2 is a Phase 2a dose-expansion in which dosing will be at the RP2D on an every second week (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.
      Note: Effective with protocol version 8.0 (December 2018), accrual to the Basket Cohort is suspended.
    - 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.

    *A basket cohort is designed to evaluate the potential antitumor effects of a targeted therapy by enriching for patients with a defined genetic alteration (e.g., mutations in or overexpression of a specific gene(s)) regardless of the histotype of the enrolled patients' tumors.

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 24 mg/kg 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: 6 mg/kg

- Dose Level 2: 12 mg/kg
- Dose Level 3: 18 mg/kg
- Dose Level 4: 24 mg/kg

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

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

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 of 18 mg/kg infused over 1.5 hours on C1/D1, followed by Q2W maintenance doses of 12 mg/kg 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 24 mg/kg.

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

- Basket Cohort: A basket cohort of *KRAS* WT, advanced solid tumor malignancy patients with *MET*-amplification will be evaluated. Patients must be MET-targeting TKI-naïve; an exception will be a subset of approximately 6 patients entered who have received prior therapy with a MET-targeting TKI.

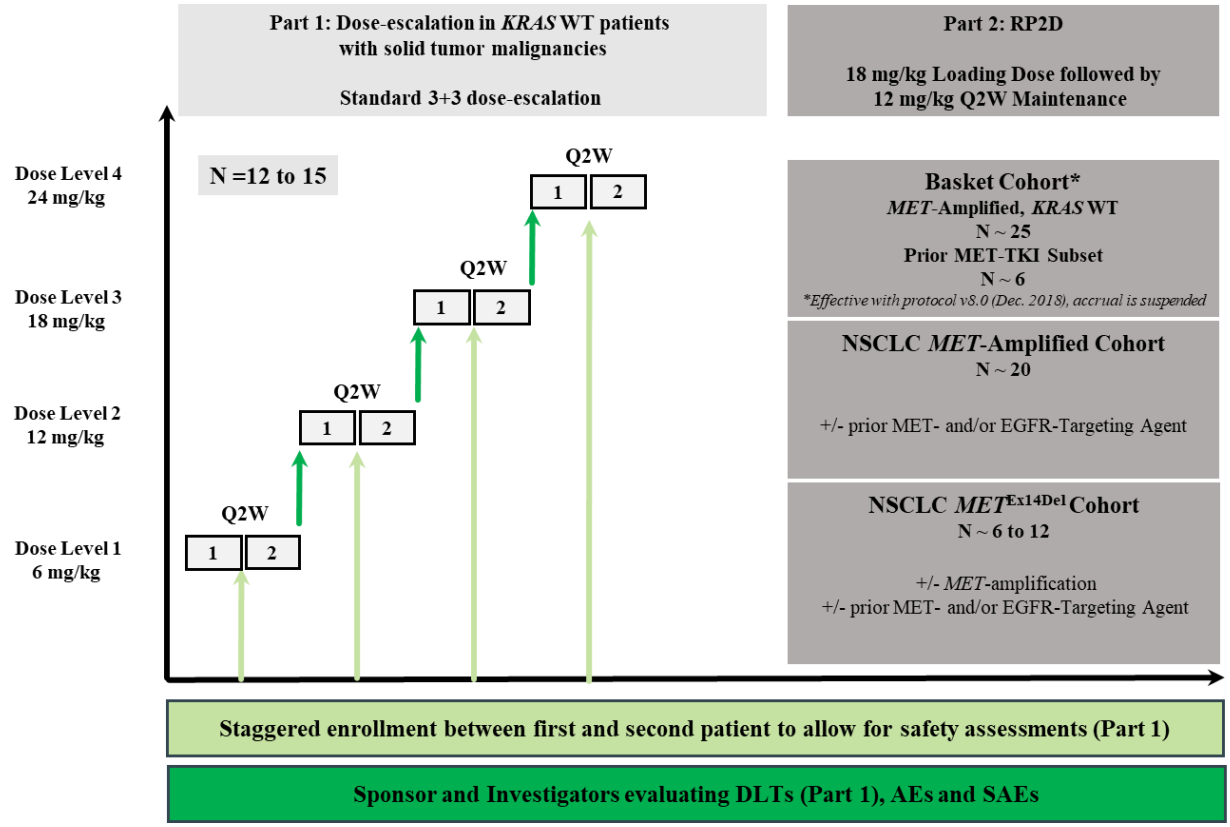
  Note: Effective with protocol version 8.0 (December 2018), accrual to the Basket Cohort is suspended.

- NSCLC *MET*-Amplified Cohort: A cohort of advanced NSCLC patients with *MET*-amplification will be evaluated. Patients may have received prior therapy with MET-targeting and/or EGFR-targeting agents.

- NSCLC $MET^{Ex14Del}$ Cohort: A cohort of advanced NSCLC patients with $MET^{Ex14Del}$ will be evaluated. Tumors need not be *MET*-amplified, and patients may have received prior therapy with MET-targeting and/or EGFR-targeting agents.

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*^{Ex14Del}, *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, hereafter called "trial sites", expected to participate, will be approximately 2 to 3 in Part 1 and 15 to 27 in Part 2.

5.2 Discussion of Trial Design

5.2.1 Rationale for Trial Design

Part 1 of this trial utilizes a standard dose-cohort escalation with groups of a minimum of three patients evaluated for safety and tolerability of Sym015 in each cohort. In the event of a DLT, a cohort will be expanded to six patients. If tolerability is demonstrated (0/3 DLT, 1/6 DLT) in any cohort, escalation to the next dose level will be permitted. This part of the trial is designed to select a safe and well-tolerated dose of Sym015 on a Q2W schedule. Part 2 of this trial is

designed to evaluate the antitumor activity of Sym015 administered at the selected RP2D on a Q2W schedule.

The choice of a basket cohort (i.e., patients with *MET*-amplified, *KRAS* WT, advanced solid tumor malignancies of any tissue origin) for Part 2 is expected to allow for effective recruitment of patients with this relatively rare molecular alteration within a reasonable period of time. Emerging literature allowed for the identification of specific tumor types that are more likely to respond to Sym015 treatment (e.g., NSCLC).

Note: Effective with protocol version 8.0 (December 2018), accrual to the Basket Cohort is suspended.

5.2.2 Rationale for Trial Population

In Part 1, patients with *KRAS* WT advanced solid tumor malignancies without other treatment options will be entered in order to evaluate the safety and tolerability of Sym015.

In Part 2, patients with *MET*-amplified, *KRAS* WT, advanced solid tumor malignancies of any tissue origin will be entered to evaluate the antitumor activity of Sym015 in the Basket Cohort. In addition, a cohort of NSCLC patients with *MET*-amplification and a cohort of NSCLC patients with $MET^{Ex14Del}$ will be entered to evaluate the antitumor activity of Sym015 in these populations.

Nonclinical studies have documented that the activity of Sym015 is greater in tumors with *MET*-amplification and/or $MET^{Ex14Del}$, suggesting that Sym015 may provide a clinically relevant effect in these patient populations. Similar findings have been observed in preliminary studies in patients with *MET*-amplified tumors with other anti-MET mAbs in early clinical trials.

5.3 Schedule of Events

The overall trial plan is introduced in Table 2 and further defined in the following sections.

Table 2 Overall Trial Plan

Screening Period	
Screening	Within 14 days prior to the first dose of Sym015
Treatment Period	
Treatment Allocation	The allocated dose and dosing schedule of Sym015 will depend upon cohort assignment and will be confirmed in writing by the Sponsor or designee on the Screening and Allocation Form.
Sym015	Sym015 will be initiated on C1/D1 and will be administered by IV infusion in cycles of treatment: • Q2W dosing o Day 1 and Day 15 of each 28-day cycle (± 2 days) Sym015 will be administered following delivery of premedication prior to each infusion. In Part 2, if the 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.
Discontinuation of Sym015	Treatment will continue until unacceptable toxicity or other conditions preventing further treatment, PD, termination of the trial, or patient's decision to withdraw.
End of Treatment	
End of Treatment Visit	Within 10 days following the decision to discontinue Sym015, an EOT Visit must be performed.
Follow-up	
1-Month Follow-up Visit	Follow-up continues until 1 month (30 + 7 days) after the last dose of Sym015. At that time, a 1M FUP Visit must be performed.
Continued follow-up for response and/or for OS	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. Occurrence of one of these events constitutes the end of study (EOS) for the patient. The continued follow-up does not require an in-person visit at the trial site, but may be obtained by collection of data/documentation.

Abbreviations (in alphabetical order): C1/D1, Cycle 1/Day 1; CR, complete response; EOS, End of Study; EOT, End of Treatment Visit; IRR, infusion-related reaction; 1M FUP, 1-Month Follow-up Visit; OS, overall survival; PD, progressive disease, PR, partial response; Q2W, every second week; SD, stable disease

5.3.1 Prescreening for *MET*-amplification and *MET*^{Ex14Del} Status

The trial site may choose to prescreen patients utilizing genomic analysis (e.g., Guardant360 or other similar liquid biopsy methodology) or tumor tissue (archival, or recently obtained if acquired outside of the screening process as part of the site's usual practice) to assess *MET*-amplification status and *MET*^{Ex14Del} status before entering patients into screening for the treatment portion of the trial. In this case, the site will use a separate pre-screening informed consent form.

Peripheral blood collection for assessment in circulating tumor deoxyribonucleic acid (ctDNA) (also referred to as "liquid biopsy") may be used as a local pre-screening methodology by Guardant360 analysis (http://guardanthealth.com). Other liquid biopsy methodologies, if used to detect *MET*^{Ex14Del}, are acceptable alternatives.

All patients giving informed consent for prescreening will receive a unique prescreening number. This number is composed of the prefix "PS", followed by a three-digit number, allocated sequentially starting from 001, i.e.. PS001, PS002, PS003, etc. The trial site must maintain a prescreening log detailing the results for prescreened patients. This log will list the patient's prescreening number, and if the patient continues into full screening, the patient's unique patient number as defined in the following section.

5.3.2 Screening

When the trial site identifies a patient suitable for screening, the Sponsor or designee should be contacted to ensure that a cohort is open for inclusion (applies to Part 1 only). With this assurance, the patient may be approached for informed consent. Screening activities may begin only once written informed consent has been obtained.

All patients giving informed consent to participate in the trial will receive a unique patient number. This number will identify the patient throughout the trial and will be composed of: a five-digit prefix, which identifies the country and site; a three-digit number, allocated sequentially starting from 001 for the first patient screened at the site, 002 for the second patient screened, etc.

The trial site staff must complete a Screening and Allocation Form, stating the allocated patient number along with the planned dates of screening and the day of first scheduled Sym015 administration (C1/D1). The planned date of C1/D1 will be agreed upon in collaboration with Sponsor or designee for the dose-escalation cohorts in order to ensure adequate time between dosing of the first patient and dosing of subsequent patients within each cohort (applies to Part 1 only). The completed Screening and Allocation Form will then be sent to the Sponsor or designee prior to or on the day of Screening.

Once eligibility has been confirmed in accordance with the inclusion and exclusion criteria, the Screening and Allocation Form will be fully completed and signed by the Investigator and resent to the Sponsor or designee. Sponsor or designee will approve each patient for start of treatment. A copy of the fully executed Screening and Allocation Form will be returned to the trial site for archiving. This form documents the allocated dose and dosing schedule of Sym015.

- Part 1: Patients in Part 1 with known *MET*-amplification who consent to optional biopsies will have a biopsy performed for biomarker analysis (archival tissue or tissue from a biopsy performed during screening as part of eligibility assessment may be submitted)
- Basket Cohort: All patients in the Part 2 Basket Cohort will have a tumor biopsy performed for biomarker analysis (tissue from a biopsy performed during screening as part of eligibility assessment is preferred, however archival tissue may be submitted at the Investigator's discretion).
- NSCLC *MET*-Amplified Cohort: All patients in the Part 2 NSCLC *MET*-Amplified Cohort will have a tumor biopsy performed and submitted for central confirmation of *MET*-amplification status, and for biomarker analysis.

  Note: Peripheral blood for ctDNA analysis by Guardant 360 will be obtained for assessment of *MET*-amplification status. If central confirmation of *MET*-amplification status cannot be assessed in tumor due to assay failure/technical error, the Sponsor may decide to enroll based on *MET*-amplification detected by Guardant360 on a case per case basis. As data are acquired on concordance between findings in tumor tissue versus ctDNA, the Sponsor may decide to transition to screening for *MET*-amplification using Guardant360 analysis only (e.g., 2+ or 3+ amplification score) without requiring confirmation in a recent or newly performed tumor biopsy.
- NSCLC $MET^{Ex14Del}$ Cohort: All patients in the Part 2 NSCLC $MET^{Ex14Del}$ Cohort will have a tumor biopsy performed and submitted for central assessment of $MET^{Ex14Del}$ status, and for biomarker analysis.
- All patients in Part 1 will have a skin biopsy performed for biomarker analysis
- All patients in Part 1 and Part 2 will have a blood sample taken for biomarker analysis

All safety screening activities must be performed within 14 days prior to C1/D1, unless otherwise specified. Individual safety screening assessments may be repeated prior to C1/D1, if justified and documented by the Investigator.

5.3.3 Screening Failures

A patient found not eligible after giving informed consent to the trial is considered a screening failure. The Screening and Allocation Form must be completed and sent to the Sponsor or designee to confirm the outcome of the screening process.

Re-screening of a patient will be allowed, if justified and documented by the Investigator.

5.3.4 Treatment

On the day of the first scheduled Sym015 infusion (C1/D1) and prior to the start of infusion (SOI), the Investigator must assess whether any changes have occurred in the clinical state of the patient, which would exclude the patient from the trial.

Sym015 will be administered on a Q2W schedule by IV infusion:

- Q2W dosing: Day 1 and Day 15 of each 28-day cycle (± 2 days)

There will be no intra-patient dose-escalation.

For all patients, the dose to be administered and the dosing schedule will be documented on the Screening and Allocation Form.

In the event of toxicity due to Sym015, dosing may be delayed, and/or the dose may be reduced, as described in Section 7.1.4.

Treatment will continue until unacceptable toxicity or other conditions preventing further treatment, progressive disease (PD), termination of the trial, or patient's decision to withdraw.

5.3.5 End of Treatment and Follow-up Visits

An End of Treatment (EOT) Visit will be performed for all patients within 10 days following the decision to discontinue treatment.

The patient will return for a 1-Month Follow-up Visit (1M FUP) 30 (+7) days after the last dose of Sym015.

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. Response assessment follow-up is required in the event of an ongoing stable disease (SD) or objective response (OR, defined as PR or complete response [CR]), as per the Response Evaluation Criteria in Solid Tumors (Version 1.1) (RECIST v1.1) (29) 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. Occurrence of one of these events constitutes the EOS for the patient. This continued follow-up does not require an in-person visit at the trial site, but may be obtained by collection of data/documentation.

5.3.6 Flow Chart – Schedule of Assessments

Schedules of assessments are provided in the trial flow charts in Table 3 (Part 1 and Part 2 Basket Cohort) and Table 4 (Part 2 NSCLC Cohorts).

All efforts should be made to perform assessments as close as possible to the scheduled time points. Visit windows are included in the flow chart.

The projection of visit days within each cycle must be made from Day 1 of the respective cycle. Furthermore, each new cycle must be initiated as soon as possible after completion of the previous cycle in order to achieve the Q2W dosing schedule.

Table 3 Flow Chart: 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[2]**
Day within Cycle Visit Window (± days)	D-14 to D-1	D1	D3	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[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
DLT Evaluation[4] **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[5]	X	X[5]					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[5,8]	X	X[5]	X	X	X	X	X	X		X	X	X	X
Urinalysis[5,8]	X	X[5]			X		X			X		X	X
Pregnancy Test	X											X	
Disease Assessments													
Disease Status Evaluation by CT/ MRI[9]	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[13]								C2 only[13]				
Additional Assessments													
PK Samples[14]		X	X	X	X		X	X		X	X	X	X
ADA Sample[15]		X					C2 only[15]			X		X	X
Skin Biopsy[16] **Part 1/Dose-Escalation only**	X								C2 only[16]				
Biomarker Blood Sample[17]	X								C2 only[17]			X	
Trial Treatment													
Sym015 Premedication[18]		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 C2/D1.
5) Does not need to be performed prior to C1/D1 if performed during screening ≤ 7 days from C1/D1.
6) In addition to the scheduled timepoints, an ECG should be performed if clinically indicated.
7) In addition to the scheduled timepoint, 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 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 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 >3 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 maker 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 *MET*ex14 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 C1/D1. 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.

Table 4 Flow Chart: Schedule of Assessments (Part 2 NSCLC Cohorts)

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[4]	X	X[4]					X			X		X	X
ECG[5]	X											X	
ECHO or MUGA scan[6]	X												
Safety blood samples[4,7]	X	X[4]	X	X	X	X	X	X		X	X	X	X
Urinalysis[4,7]	X	X[4]			X		X			X		X	X
Pregnancy Test	X											X	
Disease Assessments													
Disease Status Evaluation by CT/MRI[8]	X								X			X	X
Tumor Biopsy[9]	X								EOC2 only *optional*				
Additional Assessments													
PK Samples[10]		X	X	X	X		X	X		X	X	X	X
ADA Sample		X					C2 only			X		X	X
Genomic/Biomarker Blood Sample[11]	X								EOC2 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/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 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) 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 >3 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.

5.4 Recruitment Period

Part 1 of the trial is expected to begin Q1 2016.

Patients will be sequentially enrolled to dose-escalation cohorts until completion of Dose Level 4 or establishment of an MTD, whichever comes first, expected by Q1 2017.

Enrollment to Part 2 of the trial will commence upon establishment of the Q2W RP2D. Enrollment is expected to complete by Q4 2019.

5.5 Number of Patients

In total, approximately 63-72 patients will be included in this trial.

It is estimated that approximately 12-15 patients will be enrolled to receive increasing doses of Sym015 during Part 1. The exact number of patients will depend upon the observed tolerability of Sym015 and the potential for adding additional patients to a cohort to assure a sufficient number of evaluable patients per cohort. For details, refer to Section 7.1.3.2.

It is estimated that approximately 51-57 patients will be enrolled to receive Sym015 at the RP2D on a Q2W schedule during Part 2. Three cohorts will be included:

- Basket Cohort: Approximately 25 patients with *KRAS* WT, advanced solid tumor malignancies with documented *MET*-amplification will be enrolled and treated. A subset of approximately 6 patients will have received prior therapy with a MET-targeting TKI.

  Note: Effective with protocol version 8.0 (December 2018), accrual to the Basket Cohort is suspended.

  NSCLC *MET*-Amplified patients entered to the Basket Cohort will be counted toward the NSCLC *MET*-Amplified Cohort; NSCLC $MET^{Ex14Del}$ patients entered to the Basket Cohort will be counted toward the NSCLC $MET^{Ex14Del}$ Cohort; patients with both will be counted as *MET*-Amplified.

- NSCLC *MET*-Amplified Cohort: approximately 20 patients with advanced NSCLC with documented *MET*-amplification will be enrolled and treated. Patients may have received prior therapy with MET-targeting agents and/or EGFR-targeting agents.

- NSCLC $MET^{Ex14Del}$ Cohort: approximately 6-12 patients with advanced NSCLC with documented $MET^{Ex14Del}$ will be enrolled and treated. Tumors need not be *MET*-amplified, and patients may have received prior therapy with MET-targeting and/or EGFR-targeting agents.

  Note: NSCLC patients with tumors identified as both *MET*-Amplified and $MET^{Ex14Del}$ will be enrolled to the *MET*-Amplified cohort.

For details regarding the sample size considerations, refer to Section 10.1.

5.6 End of Trial

The end of trial will be reached at the latest 1 month (30 +7 days) after the last patient has been withdrawn from Sym015.

6. PATIENT SELECTION AND WITHDRAWAL

Questions regarding patient eligibility must be addressed and resolved by the Investigator in consultation with the Sponsor or designee prior to enrollment.

6.1 Inclusion Criteria

For inclusion in the trial, all of the following criteria must be fulfilled:

1. Written informed consent given before any trial-specific procedure is initiated
2. Male or female, at least 18 years of age at the time of informed consent
3. Eastern Cooperative Oncology Group (ECOG) performance status (PS) of 0 or 1
4. Life expectancy >3 months assessed during Screening
5. Documented (histologically- or cytologically-proven) solid tumor malignancy that is locally advanced or metastatic, and that is refractory to standard therapy or for which no standard therapy is available or accessible (i.e., patients must have recurrent and/or progressive disease and be without available therapeutic options)
6. Part 1 ONLY: Tumor documented to be *KRAS* WT by local assessment according to institutional standards. If *KRAS* WT is not previously documented and if archival tissue is not available for pretrial assessment, patient must be willing to undergo a tumor biopsy to confirm eligibility
7. Part 2 ONLY:
   a. Measurable disease according to the RECIST v1.1 that has been confirmed by computed tomography (CT) or magnetic resonance imaging (MRI) within 4 weeks prior to C1/D1

      Note: Measurable disease is defined as 1 or more target lesions assessed by CT or MRI. A tumor lesion situated in a previously irradiated area is considered measurable only if subsequent PD has been documented in the lesion

   b. Basket Cohort ONLY:

      - Tumor documented to be *KRAS* WT by local assessment according to institutional standards. If *KRAS* WT is not previously documented and if archival tissue is not available for pretrial assessment, patient must be willing to undergo a tumor biopsy to confirm eligibility.

        Note: Peripheral blood collection for *KRAS*-mutation assessment in ctDNA will be allowed as a local pre-screening methodology by Guardant360* analysis. Other liquid biopsy methodologies, if used to detect $MET^{Ex14Del}$, are acceptable alternatives.

        *<http://guardanthealth.com>

      - Confirmed *MET*-amplification by local assessment; i.e., *MET* gene copy number to control probe ratio [G:CN] >2.2 scored in 50 tumor nuclei by FISH, chromogenic *in situ* hybridization (CISH), silver *in situ* hybridization (SISH) or

similar (5), or a copy number >5 by next-generation sequencing (NGS) or quantitative polymerase chain reaction (qPCR)

Note: Peripheral blood collection for MET-amplification assessment in ctDNA will be allowed as a local pre-screening methodology provided results are 3+ by Guardant360* analysis (or equivalent to 3+ by Guardant360 if an alternative Sponsor-approved methodology is used), and provided subsequent required confirmatory tumor tissue evaluation results meet the above inclusion criterion.

*<http://guardanthealth.com>

- No prior therapy with MET-targeting agents

  Note: An exception will be a subset of approximately 6 patients entered to the Basket Cohort after having received prior therapy with a MET-targeting TKI.

- Willingness to undergo a pre- and post-dosing biopsy (maximum of 2 biopsies) from primary or metastatic tumor site(s) considered safely accessible for biopsy

c. NSCLC *MET*-Amplified Cohort ONLY:

- Documented NSCLC meeting disease criteria as defined above
- Documented *MET*-amplification by either:
  - Local assessment in a recent* tumor biopsy; i.e., G:CN ≥3.0 scored in 50 tumor nuclei by FISH, CISH, SISH or similar assay, or a copy number >5 by NGS or qPCR (subsequent central confirmation required, however patient may be enrolled and treated based on local assessment, before central confirmation results have been obtained)

    *Tissue for local assessment may be from a recent tumor biopsy, defined as one performed since last documented disease progression as part of the site's usual practice, and where no intervening antineoplastic therapy has been administered; otherwise tissue from a newly performed biopsy must be obtained and submitted.

  - Central confirmation** in a newly performed pre-dosing tumor biopsy; i.e., G:CN ≥3.0 scored in 50 tumor nuclei by FISH

    **If central confirmation of *MET*-amplification status cannot be assessed in tumor due to assay failure/technical error, the Sponsor may decide to enroll based on *MET*-amplification detected by Guardant360 on a case per case basis (see Note below regarding Guardant360 analysis).

- May have received prior therapy with MET-targeting and/or EGFR-targeting agents (antibodies or TKIs)

- Willingness to undergo a pre-dosing biopsy (mandatory unless a recent* tumor biopsy as defined above is available), and potentially a biopsy at the End of Cycle 2 (EOC2) (optional), from a primary or metastatic tumor site considered safely accessible for biopsy

Note: Peripheral blood for ctDNA analysis by Guardant 360 will be obtained for assessment of *MET*-amplification status. As data are acquired on concordance between findings in tumor tissue versus ctDNA, the Sponsor may decide to transition to screening for *MET*-amplification using Guardant360 analysis only (e.g., 2+ or 3+ amplification score) without requiring confirmation in a recent or newly performed tumor biopsy.

d. NSCLC *MET*^{Ex14Del} Cohort ONLY:

- Documented NSCLC meeting disease criteria as defined above
- Documented MET^{Ex14Del} (tumors need not be *MET*-amplified)

  Note: *MET*^{Ex14Del} status to be documented according to local institutional standards. Assessment in ctDNA by Guardant360 technology or equivalent is allowed. Tissue from a recent* or newly performed pre-dosing tumor biopsy must be submitted for central assessment.

  *Recent tumor biopsy, defined as one performed since last documented disease progression as part of the site's usual practice, and where no intervening antineoplastic therapy has been administered; otherwise tissue from a newly performed biopsy must be obtained and submitted.

- May have received prior therapy with MET-targeting and/or EGFR-targeting agents (antibodies or TKIs)

- Willingness to undergo a pre-dosing biopsy (mandatory unless a recent* tumor biopsy as defined above is available), and potentially a biopsy at the EOC2 (optional), from a primary or metastatic tumor site considered safely accessible for biopsy

  Note: Peripheral blood for ctDNA analysis by Guardant 360 will be obtained for assessment of *MET*^{EX14Del} status.

8. If female and of childbearing potential, a negative pregnancy test
9. Male or female, either not of childbearing potential or agreeing to use a medically effective method of contraception as per institutional standards during the trial and for 4 months after the last dose of trial drug

6.2 Exclusion Criteria

Patients meeting any of the following criteria will not be permitted to enter the trial:

1. Any antineoplastic agent for the primary malignancy (standard or investigational) without delayed toxicity within 4 weeks or 5 plasma half-lives, whichever is shortest, prior to C1/D1 except:
   - Nitrosoureas and mitomycin C within 6 weeks prior to C1/D1
2. Part 2 ONLY:
   a. Basket Cohort:
      - Prior therapy with MET-inhibiting agents

Note: Exceptions will be a subset of approximately 6 patients entered to the Basket Cohort after having received prior therapy with a MET-targeting TKI

- Prior therapy with antibody to HGF

b. Basket Cohort and NSCLC *MET*-Amplified Cohort: Tumor status demonstrating *MET*-polysomy in the absence of *MET*-amplification, as specified

Note: Patients in the NSCLC *MET*^{Ex14Del} Cohort with polysomy are eligible.

c. Radiotherapy against target lesions within 4 weeks prior to C1/D1, unless there is documented progression of the lesion following the radiotherapy

Note: Radiotherapy for pain control against non-target lesions is allowed, as long as it does not influence bone marrow function

3. Immunosuppressive or systemic hormonal therapy (> 10 mg daily prednisone equivalent) within 2 weeks prior to C1/D1 (for exceptions, see Section 7.5.2)
4. Use of hematopoietic growth factors within 2 weeks prior to C1/D1
5. Active second malignancy or history of another malignancy within the last 3 years, with the exception of:
   a. Treated, non-melanoma skin cancers
   b. Treated carcinoma *in situ* of the breast or cervix
   c. Controlled, superficial carcinoma of the urinary bladder
   d. T1a or b carcinoma of the prostate treated according to local standard of care, with prostate-specific antigen (PSA) within normal limits for the institution
6. Central nervous system (CNS) malignancy including:
   a. Primary malignancies of the CNS
   b. Known, untreated CNS or leptomeningeal metastases, or spinal cord compression; patients with any of these not controlled by prior surgery or radiotherapy, or symptoms suggesting CNS metastatic involvement for which treatment is required

   Note: Patients with treated CNS metastases will be eligible if they are asymptomatic, do not require corticosteroids or anticonvulsants, and have confirmation of at least stable brain disease status as assessed by 2 imaging studies performed ≥ 4 weeks apart with the most recent performed within 4 weeks prior to first trial drug administration

   Patients with newly identified CNS metastases during study treatment will be considered to have PD and will be discontinued from treatment
7. Inadequate recovery from an acute toxicity associated with any prior antineoplastic therapy

Note: With the exception of persistent Grade 2 alopecia and/or peripheral neuropathy, patients must have recovered (to Grade ≤ 1) from acute toxicity by C1/D1

8. Major surgical procedure within 4 weeks prior to C1/D1 or inadequate recovery from any prior surgical procedure
9. Non-healing wounds on any part of the body
10. Active thrombosis, or a history of deep vein thrombosis or pulmonary embolism, within 1 month prior to C1/D1, unless adequately treated and stable
11. Active uncontrolled bleeding or a known bleeding diathesis
12. Significant cardiovascular disease or condition, including:
    a. Congestive heart failure currently requiring therapy
    b. Class III or IV cardiovascular disease according to the New York Heart Association's (NYHA) functional criteria (30)
    c. Need for antiarrhythmic medical therapy for a ventricular arrhythmia
    d. Severe conduction disturbance (e.g., 3rd degree heart block)
    e. Unstable angina pectoris (last episode at least 6 months prior to C1/D1)
    f. Uncontrolled hypertension (per the Investigator's discretion)
    g. Myocardial infarction within 6 months prior to C1/D1
13. Abnormal hematologic, renal or hepatic function as defined by the following criteria:
    a. Absolute neutrophil count (ANC) <1.5 $\times 10^9$/L (1500/mm^3)
    b. Hemoglobin ≤9 g/dL
    c. Platelet count <75 $\times 10^9$/L (75,000/mm^3)
    d. Serum creatinine >1.5 × upper limit of normal (ULN) for the institution
    e. Aspartate aminotransferase (AST) >3.5 × ULN for the institution or AST >5 × ULN for the institution in case of known liver metastases
    f. Alanine aminotransferase (ALT) >3.5 × ULN for the institution or ALT >5 × ULN for the institution in case of known liver metastases
    g. Total bilirubin >1.5 × ULN for the institution
    h. Prothrombin time as assessed by International Normalized Ratio (INR) >1.5 × ULN for the institution*
    i. Partial thromboplastin time (PTT) >1.5 × ULN for the institution*

    * unless the patient is on a stable dose of anticoagulant therapy for a prior thrombotic event
14. Any of the following within 2 weeks prior to C1/D1:

a. Any serious or uncontrolled infection

b. Any infection requiring parenteral antibiotics

c. Unexplained fever >38.0 °C

15. Known or suspected hypersensitivity to any of the excipients of the Sym015 drug product
16. Any other life-threatening illness, significant organ system dysfunction, or clinically significant laboratory abnormality, which in the opinion of the Investigator, would either compromise the patient's safety or interfere with the evaluation of the safety of the trial drug
17. Any kind of disorder that compromises the ability of the patient to give written informed consent and/or to comply with trial procedures or is unwilling or unable to comply with trial requirements at the discretion of the Investigator
18. Breast feeding, or plans by the patient (or the patient's partner) to become pregnant during treatment or within 4 months after the end of treatment

6.3 Withdrawal

The visit schedule for the treatment period will apply until Sym015 has been discontinued. Once this has occurred, an EOT Visit will be performed within 10 days following the decision to discontinue Sym015.

After EOT, the patient will continue to be followed for safety until 1 month (30 +7 days) after the last dose of Sym015, when the 1M FUP Visit must be completed.

6.3.1 Withdrawal from Treatment with Sym015

The patient must be withdrawn from treatment with Sym015 in the event of any of the following:

- A DLT considered by the Investigator to require treatment discontinuation. Refer to Section 9.5 for DLT definition (dose-escalation cohorts only)
- Occurrence of an AE considered by the Investigator to require treatment discontinuation
- Basket Cohort ONLY: Results from archival tumor tissue or a tumor biopsy submitted to confirm *MET*-amplification status that do not meet study eligibility criteria.

  Note: Such patients may remain on study if there is evidence of an OR, SD, or other clinical benefit, but will not be included in the Evaluable for Response Population.
- PD, verified by CT/MRI according to RECIST v1.1
- Treatment failure not meeting the criteria for PD, but considered by the Investigator to require treatment discontinuation
- Requirement for a significant surgical procedure

Note: Patients requiring a minor surgical procedure (e.g., port placement, skin abscess drainage) may continue at the Investigator's discretion following discussion with the Sponsor or designee. A brief interruption in therapy may be considered

- An intercurrent illness which, in the opinion of the Investigator, would prevent completion of trial-related evaluations
- Use of prohibited concomitant medication, as defined in Section 7.5.2
- Pregnancy
- Significant deviation from the eligibility criteria may require discontinuation after discussion with the Sponsor
- Noncompliance with trial procedures may require discontinuation after discussion with the Sponsor
- Patient withdrawal of consent and election to discontinue treatment. (Patients may leave the trial at any time for any reason if they wish to do so, without any consequences)
- Termination of the trial by the Sponsor
- Patients who meet Hy's Law criteria that cannot be explained by factors not related to Sym015.

  Note: Patients meeting all three of the following are considered to have met Hy's Law criteria:

  - The drug causes hepatocellular injury, generally shown by a higher incidence of 3-fold or greater elevations above ULN of ALT or AST
  - Among trial subjects showing such aminotransferase elevations, often much greater than 3xULN, one or more show elevation of serum total bilirubin to ≥2xULN, without initial findings of cholestasis (elevated serum alkaline phosphatase [ALP]).
  - No other reason can be found to explain the combination of increased aminotransferase and serum total bilirubin, such as viral hepatitis A, B, or C; preexisting or acute liver disease; or another drug capable of causing the observed injury.

6.3.2 Withdrawal from Trial

The patient must be withdrawn from trial in the event of any of the following:

- The patient withdraws consent to participate
- The Investigator judges it necessary due to medical reasons

The EOT and the 1M FUP visits should be performed to the extent possible and the Investigator should ensure any SAE is followed as described in Section 9.3.

After the 1M FUP Visit, the Investigator will make every effort to obtain follow-up information on response assessment and/or OS every 2 months. Response assessment follow-up is required in

the event of an ongoing SD, PR or CR, as per RECIST v1.1 at the 1M FUP Visit, until PD or another therapeutic intervention is initiated. Survival follow-up is required until death, withdrawal of consent, or termination 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.

6.4 Replacement of Patients

6.4.1 Part 1, Dose-Escalation

Patients who do not complete Cycle 1 as defined in Section 9.5.2, for reasons other than drug toxicity, will be replaced.

Data from these patients will be included in the safety analysis, but will not contribute to the determination of the Q2W RP2D.

6.4.2 Part 2

Basket Cohort ONLY: Patients enrolled to the study based on local *MET*-amplification assessments conducted in ctDNA, but with subsequent confirmatory tumor tissue evaluation results not meeting the protocol-specified inclusion criteria, will be replaced (patients may remain on study if there is evidence of an OR, SD, or other clinical benefit, but will not be included in the Evaluable for Response Population).

7. TREATMENT

7.1 Investigational Medicinal Product/Sym015

The IMP in this trial is Sym015.

Sym015 is a [redacted]

Table 5 Description of Investigational Medicinal Product/Sym015

Ingredients	Quantity per mL	Function
[redacted]		

Abbreviations (in alphabetical order): q.s., quantum sufficiat (as much as suffices); 6N, normality of 6

1) Acid added for pH adjustment – amount vary from batch to batch

7.1.1 Packaging and Labeling of Sym015

Sym015 will be provided as [redacted] Type 1.

Labeling will be in accordance with applicable local regulatory requirements.

7.1.2 Handling, Storage and Preparation of Sym015

All handling, storage, and preparation of IMP should take place at the trial site pharmacy. The Investigator is responsible for informing the pharmacy of the dose of Sym015 to be administered to a given patient, taking into account the patient's body weight.

Sym015 will be [redacted] bag prior to administration. The infusion must be completed within 24 hours after preparation of the infusion bag.

A detailed pharmacy guide, specifying handling, storage, and preparation of Sym015, will be provided to the trial sites.

7.1.3 Administration of Sym015

7.1.3.1 Treatment Schedule

All patients will be administered IV infusions of Sym015, dosed according to body weight, through a peripheral line or indwelling catheter, and with the use of an infusion pump and an inline filter. Sym015 will be administered Q2W (Day 1 and Day 15 of each 28-day cycle [±2 days]).

For all Sym015 infusions, a complete dosing history will be recorded, i.e.,:

- Total dose and volume administered
- Start and stop time of infusion
- Infusion interruption or termination and reason for such actions

7.1.3.2 Part 1, Dose-Escalation

During the dose-escalation part of the trial, the following dose levels of Sym015 administered Q2W will potentially be evaluated in a standard 3+3 dose-escalation design:

- Dose Level 1: 6 mg/kg
- Dose Level 2: 12 mg/kg
- Dose Level 3: 18 mg/kg
- Dose Level 4: 24 mg/kg

A substitute or additional dose level, within the dose levels listed above, could potentially be evaluated. Any decision to add or replace a dose to be tested will be guided by PK data and/or data on target occupancy in skin biopsy samples. This substitute or additional dose level would be chosen between the currently listed dose levels, and a dose higher than 24 mg/kg will not be evaluated without a formal amendment to this protocol.

Cohorts will be filled sequentially until establishment of the highest safe dose. Patients will be allocated to the next available treatment slot within the current or next cohort, as appropriate and depending on the ongoing observation of DLTs and other safety parameters.

Enrollment will be staggered between the first and second patient in each new higher dose level tested. The first patient must have completed and tolerated the first dose of Sym015, including follow-up until Day 8 of Cycle 1 (C1/D8), in order to allow for review of clinical and laboratory assessments. Thereafter patients within a cohort may be added concurrently.

There is potential for entry of additional patients in the dose-escalation portion of the trial to assure a sufficient number of evaluable patients per cohort by entering an additional patient to a cohort (e.g., increase a 3 patient cohort to 4 patients, or a 6 patient cohort to 7 patients).

Note: Should this action be taken, cohort tolerability assessment and subsequent dose-escalation will occur when the minimum number of patients required to evaluate tolerability have completed Cycle 1. However, if any additional patient experiences an event that would, per protocol, result in either cohort expansion or the halting of dose-escalation, protocol rules as outlined herein will be followed.

Progression from a current dose level to the next will only proceed following evaluation of tolerability of the current dose level. Thus, dosing of the first patient at Dose Level 2 will commence only once all patients to be treated at Dose Level 1 have completed Cycle 1, and Dose Level 1 has been found to be tolerable. Similarly, dosing in Dose Level 3 will only commence once all patients to be treated at Dose Level 2 have completed Cycle 1, and Dose Level 2 has been found to be tolerable. The dose-escalation decision points are listed below:

- If no DLTs are encountered in any of the first 3 patients completing Cycle 1 within a dose level, dose-escalation may continue to the next level
- If 1 of 3 patients within a dose level experiences a DLT, 3 more patients will be enrolled at the same dose level. If no DLTs are encountered in the 3 additional patients, dose-escalation may continue to the next level
- If ≥ 2 patients within a dose level (of up to 6 patients) experience a DLT, then that dose will be considered to have exceeded the MTD and the dose level just below this dose level will be considered to be the MTD
- If no DLTs are encountered in any of the first 3 patients at Dose Level 4, 24 mg/kg will be considered the highest safe dose tested

The SMC will review safety data throughout the trial. During Part 1, the SMC will make decisions regarding the advisability of: continuing accrual to a particular dose cohort; dose-escalation and accrual of patients to a higher dose cohort; and the dose(s) to be used in Part 2 (i.e., Q2W RP2D to be evaluated).

Each patient enrolled will receive Sym015 at the allocated dose until treatment withdrawal, unless dose-reduction is necessary as specified in Section 7.1.4. There will be no intra-patient dose-escalation.

7.1.3.3 Part 2

During Part 2 of this trial, patients will receive the RP2D of Sym015 on a Q2W dosing schedule.

The SMC will continue to review safety data and assess the tolerability of Sym015 during Part 2 of the trial.

7.1.3.4 Duration of Infusion for Administration of Sym015

Sym015 will be administered over a 1.5-hour (+10 minutes) period for doses ≥18 mg/kg, and over a 1 hour (+10 minutes) period for doses <18 mg/kg, following delivery of premedication as specified in section 7.2.1.

Note: Effective with protocol version 5.0 (November 2016), the duration of infusion has been extended to 1.5 hours for all patients receiving doses ≥18 mg/kg due to the occurrence of Grade 2 IRRs in 2 of 3 patients treated in the 18 mg/kg cohort during Part 1 (This action was implemented 13Sep2016).

Administration should be at a constant rate using a programmable volumetric infusion pump in order to assure accuracy of delivery. The times of infusion initiation and completion must be recorded.

The duration of Sym015-infusion will be prolonged for all subsequent patients entered to the trial in the following situations:

- In the event of a Grade 2 IRR in ≥ two thirds of the patients entered to a cohort, the duration of infusion for subsequent patients entered at that dose and higher doses will be extended from 1 hour (+10 minutes) to 1.5 hours (+10 minutes) (or longer, if indicated)

  Note: This action was implemented 13Sep2016 and applies to doses ≥18 mg/kg.

- In the event of a Grade 3 or greater IRR in any patient within a cohort, the duration of infusion for subsequent patients entered at that dose and higher doses will be extended from 1 hour (+10 minutes) to 1.5 hours (+10 minutes) (or longer, if indicated). Such a case will also be considered to have met the protocol criteria for a DLT, thus requiring expansion of the cohort

These same criteria will be applied in the event IRRs occur on the extended 1.5 hours infusion schedule. In such a case, the duration of infusion for subsequent patients entered at that dose and higher doses will be extended to 2 hours (or longer, if indicated).
Recommendations for management of an IRR in individual patients can be found in Section 7.1.3.7.

7.1.3.5 Patient Monitoring During and After Infusion of Sym015

Patients will be treated on an outpatient basis.

Sym015 infusions must be administered under the close supervision of an experienced physician in an environment where full resuscitation facilities are immediately available.

Patients will be carefully observed for a minimum of 2 hours following completion of the first administration of Sym015 and a minimum of 1 hour following completion of subsequent administrations. At the end of each infusion, the IV line must remain in place for at least 1 hour to allow administration of IV drugs, if necessary.

7.1.3.6 Infusion-Related Reactions to Sym015

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.

7.1.3.7 Handling of Infusion-Related Reactions to Sym015

The risk of an IRR is highest for the first administration of a mAb and diminishes with subsequent infusions.

If an IRR occurs, it should be classified according to the Common Terminology Criteria for Adverse Events (Version 4.03) (CTCAE v4.03). Recommended management guidelines are shown in Table 6. In all cases, the Investigator should use best clinical judgment in managing such reactions.

Table 6 Infusion-Related Reactions Management Guidelines

CTCAE Grade	Management/Treatment
Grade 1 Mild transient reaction; infusion interruption not indicated; intervention not indicated	• Continue infusion; consider slowing to 50% of the prior rate • Monitor closely • If infusion is extended, administer subsequent infusions during Cycle 1 at the prolonged rate • Thereafter, if vital signs remain stable and symptoms do not recur, at the discretion of the Investigator an attempt may be made to slowly increase the rate of infusion. Final infusion duration should not be briefer than the initial rate attempted in the patient
Grade 2 Therapy or infusion interruption indicated but responds promptly to symptomatic treatment (e.g., antihistamines, NSAIDs, narcotics, IV fluids); prophylactic medications indicated for ≤ 24 h	• Interrupt infusion for a minimum of 30 minutes • Administer symptomatic treatment (e.g., antihistamines, NSAIDs, etc.) and appropriate supportive care (e.g., bronchodilator, oxygen, etc.), as indicated • When symptoms have resolved or decreased to Grade 1, restart infusion at 50% of the prior rate • Monitor closely • If symptoms recur, stop the infusion, institute remedial therapy, monitor closely and evaluate whether the patient can continue the trial • Administer subsequent infusions during Cycle 1 at the prolonged rate • Thereafter, if vital signs remain stable and symptoms do not recur, at the discretion of the Investigator an attempt may be made to slowly increase the rate of infusion. Final infusion duration should not be briefer than the initial rate attempted in the patient
Grade 3 Prolonged (e.g., not rapidly responsive to symptomatic medication and/or brief interruption of infusion); recurrence of symptoms following initial improvement; hospitalization indicated for clinical sequelae	• Discontinue the infusion • Administer symptomatic treatment (e.g., antihistamines, NSAIDs, glucocorticoid etc.) and appropriate supportive care (e.g., bronchodilator, oxygen, IV fluid etc.), as indicated • Do not resume infusion • Patient will either be discontinued from further treatment or receive subsequent treatments at a reduced dose; if treatment is continued administer subsequent infusions during Cycle 1 at 50% of the prior rate • Thereafter, if vital signs remain stable and symptoms do not recur, at the discretion of the Investigator an attempt may be made to slowly increase the rate of infusion. Final infusion duration should not be briefer than the initial rate attempted in the patient.
Grade 4 Life-threatening consequences; urgent intervention indicated	• Discontinue infusion • Administer necessary life-support measures, as indicated • Discontinue from further treatment

Abbreviations (in alphabetical order): CTCAE, Common Terminology Criteria for Adverse Events v4.03; h, hours; IRR, infusion-related reaction; IV, intravenous; NSAID, nonsteroidal anti-inflammatory drug

7.1.4 Dose-Adjustment and Delays of Sym015

The dose of Sym015 in mg/kg assigned to the individual patient will be confirmed by the Sponsor or designee prior to C1/D1 on the Screening and Allocation Form.

Based on the body weight of the patient, the site will calculate the nominal dose of Sym015 to be administered in mg.

Weight changes (> ±10%) for a patient during trial will require recalculation of the dose. Refer to Section 7.1.4.1.

Furthermore, dose-delays of Sym015 and intra-patient dose-reduction(s) may also be required upon occurrence of specific toxicities. Refer to Section 7.1.4.2.

7.1.4.1 Dose-Adjustment for Body Weight

Sym015 is dosed in mg/kg and the dose to be administered will be calculated based on the actual body weight of the patient. The dose calculated may be used for subsequent infusions, unless body weight changes of ≥ ± 10%, in which case the dose should be adjusted according to the change in body weight. Recalculation for lower weight changes is allowed.

7.1.4.2 Dose-Delays for Sym015-Related or Disease-Related Toxicities

Clinical judgment will be used when determining whether it is advisable to continue a patient on to the next dosing. In order to dose a patient, the following criteria must be met:

- ANC >1.0 $\times 10^9$/L (1000/mm^3)
- Platelet count >60 $\times 10^9$/L (60,000/mm^3)
- Any ongoing AEs should NOT meet the criteria for DLT, during the DLT observation period
- Any ongoing AEs, assessed as possibly, probably, or related to Sym015, should have either ameliorated to ≤ Grade 1 severity, returned to baseline status, or resolved with the exception of Grade 2 clinical events that are being adequately controlled with best supportive care (e.g., nausea, vomiting, diarrhea, fatigue) and asymptomatic laboratory abnormalities that are considered clinically insignificant or that are resolving with medical therapy

Should any one of the criteria above not be met, dosing of Sym015 must be delayed until the patient meets the above criteria. All per protocol assessments must be done.

7.1.4.3 Dose-Reduction for Sym015-Related Toxicities

Patients experiencing any of the following toxicities, assessed as possibly, probably, or related to Sym015, will have their dose reduced in accordance with the reduction schedule outlined in Table 7.

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 without requiring hospitalization
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 mm^3, duration >5 days)
4. Thrombocytopenia that is:
   a. Grade 3 with clinically significant hemorrhage
   b. Grade 4 (platelets <25,000 per mm^3)
5. AST/ALT elevation > 3×ULN with bilirubin elevation >2×ULN that cannot be explained by factors not related to study drug

Table 7 Sym015 Dose-Reduction Schedule

Allocated Dose	First Reduction	Second Reduction	Subsequent Reductions
6 mg/kg	3 mg/kg	1.5 mg/kg	Reduce by 50%
12 mg/kg	6 mg/kg	3 mg/kg	Reduce by 50%
18 mg/kg	12 mg/kg	6 mg/kg	Reduce by 50%
24 mg/kg	18 mg/kg	12 mg/kg	Reduce to 6 mg/kg, then by 50%

Note: In the event that an intermediate dose is explored in this study, dose-reductions in such cases will be to the next lower established tolerated dose level(s). If further dose-reductions are indicated, proceed as outlined above.

7.2 Other Drugs to be Used in the Trial

7.2.1 Premedication for Sym015 Infusions

There is an inherent risk for IRRs with the administration of mAbs. A premedication schedule will therefore be 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.

All patients must be premedicated as described with standard therapies that include a glucocorticoid and an H1 antagonist. Where indicated, consideration may be given to including an H2 antagonist and/or acetaminophen. The recommended premedication doses are as follows:

- Glucocorticoid therapy equivalent to 80-100 mg IV methylprednisolone, approx. 0.5 to 2 hours prior to the start of Sym015 infusion
- Antihistamine (H1 antagonist) equivalent to 25-50 mg IV diphenhydramine, approx. 0.5 hours prior to the start of Sym015 infusion
- Antihistamine (H2) antagonist (optional) such as 50 mg IV ranitidine or 30 mg famotidine, approx. 0.5 hours prior to the start of Sym015 infusion
- Acetaminophen (optional) such as 1000 mg IV or PO (orally), approx. 0.5 hours prior to the start of Sym015 infusion

In Part 2, 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 in order to determine whether such continued therapy is necessary in that patient. Where practical, it is recommended that withdrawal of premedication be done in a gradual fashion.

For those patients who experienced symptoms suggestive of an IRR after Cycle 1, consideration should be given to continuing premedication for at minimum 1 to 2 additional doses before any future attempt to withdraw.

7.2.2 Prophylactic and Therapeutic Treatment

7.2.2.1 Mandatory Prophylactic Treatment

Mandatory prophylactic treatment will be implemented for all patients treated in this trial should an increased incidence begin to occur of mild-to-moderate Sym015-related reactions that are amenable to prophylaxis with standard agents. Such actions will occur following discussions within the SMC.

7.3 Blinding

Not applicable as this is an open-label trial.

7.4 Drug Accountability and Compliance Check

The Investigator is responsible for ensuring accountability for the IMP, including maintenance of IMP accountability records.

IMP accountability records will include a full inventory of the IMP including:

- Confirmation of IMP delivery to the trial site
- Record of each dose dispensed
- The return of unused IMP to the Sponsor or designee
- Record of any on-site destruction of unused IMP, as agreed with the Sponsor or designee

Records will specify dates, quantities, batch numbers, use-by dates and patient numbers, as applicable.

The Investigator, or designee, should maintain records that adequately document:

- That the patients were provided the doses specified by the protocol, and
- That all IMP provided by the Sponsor was fully reconciled

7.5 Concomitant Medication/Therapy

7.5.1 Allowed Medication/Therapy and Procedures During the Trial

Patients may receive their current concomitant medication and any medication considered necessary for the welfare of the patient during trial, except if listed in Section 7.5.2.

Furthermore, the following are permitted during the trial:

- Premedication with standard therapies prior to Sym015 administration to reduce the risk of IRRs
- Prophylaxis and treatment of Sym015-related toxicities
- Radiotherapy for pain control against non-target lesions, as long as it does not influence bone marrow function
- Bisphosphonates and denosumab: Bisphosphonates and denosumab for bone metastases and other skeletal conditions provided the patient is on a stable dose for at least 2 months prior to study start and remains on the stable dose while receiving study treatment

7.5.2 Prohibited Medication/Therapy and Procedures During the Trial

The following medications and procedures are not allowed from C1/D1, or as specified in the inclusion/exclusion criteria, until the EOT Visit:

- Anti-cancer treatment, including cytotoxic or cytostatic agents, hormonal therapy (except as physiologic hormone replacement)

- Basket Cohort ONLY: MET-targeting therapies, except in subset of approximately 6 patients
- Radiotherapy against target lesion(s) (Part 2 only)
- Systemic immunosuppressive or systemic hormonal therapy with the exception of the following allowed therapies:
    - Hormonal therapy (e.g., Megace) for appetite stimulation
    - Nasal, ophthalmic, inhaled, and topical glucocorticoid preparations
    - Oral replacement glucocorticoid therapy for adrenal insufficiency
    - Low-dose maintenance steroid therapy for other conditions (excluding steroid tapers for brain edema/metastases/radiation)
    - Steroid therapy as prophylaxis for contrast reactions
    - Stable hormonal therapy for ovarian suppression for non-malignant conditions, hormonal contraceptive therapy, or post-menopausal HRT*
    - GnRH analogs in patients with prostate cancer
    - Intra-articular steroid injections
    - Higher dose steroid therapy for treatment of an acute intercurrent illness in patients with stable disease or an ongoing response. In such situations, protocol therapy treatment should be interrupted.

    *Prior or concomitant therapies are permitted; however, patients must have been on a stable dose for at least 6 months prior to study start, and if continuing must remain on the stable dose while receiving study treatment (i.e., such treatment will not be considered as systemic hormonal therapy for the purpose of study eligibility).
- Prophylactic use of hematopoietic growth factors during Cycle 1
- Major surgery that would preclude the patient from complying with the requirements of the protocol

If any one of the above listed medications/procedures becomes necessary during the trial, the patient must be withdrawn from Sym015 and the EOT Visit should be performed. The 1M FUP Visit should then be performed, no less than 1 month (30 +7 days) after the last dose of Sym015.

7.6 Medical Care of Patients after End of Trial Participation

After completing treatment in this trial, patients will be offered standard of care treatment in accordance with generally accepted medical practice and depending on the patient's individual medical need. Patients will continue to be followed for survival.

8. TRIAL ASSESSMENTS

All trial assessments are considered mandatory for all patients included in the trial, unless otherwise stated. All assessments are to be performed on or about the indicated visit day, i.e., ±2 days, unless otherwise stated. A slightly longer allowance for routine assessments is permissible in the event of scheduling difficulties associated with weekends, holidays, etc.

8.1 Baseline Characteristics / Eligibility Assessments

8.1.1 Signing of Informed Consent

Prior to any protocol-related procedure, unless such testing was performed previously as part of the routine clinical management of the patient.

- Screening

  Note: Informed consent may be obtained outside the 14-day screening period prior to C1/D1

8.1.2 Demographics

To include date of birth, sex, race and ethnicity (as allowed by country)

- Screening

8.1.3 Medical History

To include prior and ongoing medical illnesses and conditions and prior surgical procedures not related to the primary diagnosis.

- Screening
- C1/D1 (prior to dosing)

8.1.4 Tumor Characteristics and Extent of Disease

To include diagnosis and date of initial diagnosis, staging at time of initial diagnosis and at screening, tumor histology, current location of metastases, and date of most recent disease progression, and mutation status.

- Screening

8.1.5 Prior Cancer Treatments

To include prior surgical procedures for the primary diagnosis, as well as prior radiotherapy, chemotherapy and/or biological targeted therapy, investigational treatment, and/or procedures. Include dates of treatments, numbers of cycles, and best response to such treatments.

- Screening
- C1/D1 (prior to dosing)

8.2 Safety Assessments

To be performed within 14 days of C1/D1, unless otherwise specified.

8.2.1 Medication/Procedure Survey

To include all medications taken other than Sym015 and all procedures performed during trial. For medications: Include 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: Include date and reason for procedure.

- Starting from the date of Screening
- Until the date of the 1M FUP

8.2.2 Adverse Events Survey

For details about (S)AEs and (S)AE reporting, refer to Section 9.

- Starting from signing of informed consent for participation in the trial
- Until the date of the 1M FUP

  Note: Patients who sign informed consent and are subsequently deemed to be screening failures will be followed for the occurrence of SAEs/AEs until it is determined that they will not be participating in the trial

8.2.3 Dose-Limiting Toxicities Evaluation (Part 1 Only)

For details about AEs meeting DLT criteria, refer to Section 9.5.

- Starting from the first dose of trial drug (C1/D1)
- Reported during Cycle 1 with a final assessment 14 (±2) days after the last dose of Cycle 1 or prior to dosing on C2/D1

8.2.4 Vital Signs and Body Weight

To include temperature, heart rate, blood pressure, and body weight

- Screening
- Prior to each dosing
- EOT
- 1M FUP

- As clinically indicated

8.2.5 Performance Status

To be assessed by ECOG PS score.

- Screening
- 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
- EOT
- 1M FUP
- As clinically indicated

8.2.6 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.

- Screening
- 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
- EOT
- 1M FUP
- As clinically indicated

8.2.7 Electrocardiogram

To include standard 12-lead electrocardiogram (ECG). The Investigator, or qualified designee, should document the evaluation of the ECG, including specification of any abnormality as clinically significant or not clinically significant.

- Screening
- EOT
- As clinically indicated

8.2.8 Echocardiogram or Multi-Gated Acquisition Scan

Patients will be scheduled for a transthoracic echocardiogram (ECHO) at baseline to exclude enrollment of patients with insufficient heart function; alternatively, a radionuclide angiography (Multi-Gated Acquisition [MUGA] scan) of the heart may be performed.

- Screening
- In the event of cardiac symptoms (e.g., shortness of breath, edema) an ECHO or MUGA is to be scheduled as soon as possible
- As otherwise clinically indicated

8.2.9 Laboratory Assessments and Pregnancy Test

All routine laboratory analyses will be performed at a laboratory facility local to the trial site. Results must be available and assessed prior to each dosing of Sym015.

Sponsor or designee must be provided with a list of trial site laboratory normal ranges for all required parameters prior to screening of the first patient at the site. Likewise, any change in laboratory normal ranges during the trial should be forwarded to the Sponsor or designee promptly during the trial.

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

Table 8 Schedule of Safety Blood and Urine Samples

Sample Analysis	Screening	Cycle 1				Cycles Thereafter		EOT	IM 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

8.2.9.1 Hematology Panel

To include complete blood count with differential, ANC, and platelet count.

- Screening
- Cycle 1
  - Weekly (prior to Sym015 administration on days of dosing)
    - Does not need to be performed prior to C1/D1 if performed during screening ≤7 days from C1/D1
  - Day 3
- Each cycle thereafter
  - Prior to each dosing
- EOT
- 1M FUP
- As clinically indicated

In the event of hematologic toxicity, the evaluation frequency should be increased to include additional evaluations between scheduled assessments, as clinically indicated.

8.2.9.2 Biochemistry Panel

To include 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 (fasting not required). Clinically significant electrolyte abnormalities should be corrected prior to dosing.

- Screening
- Cycle 1
  - Weekly (prior to Sym015 administration on days of dosing)
    - Does not need to be performed prior to C1/D1 if performed during screening ≤7 days from C1/D1
  - Day 3
- Each cycle thereafter
  - Prior to each dosing
- EOT

- 1M FUP
- As clinically indicated

In the event of significant biochemistry abnormalities, the evaluation frequency should be increased to include additional evaluations between the scheduled assessments, as clinically indicated. In the event of creatine kinase abnormalities, isoenzyme analysis should be performed.

8.2.9.3 Coagulation Panel

To include prothrombin time, PTT and INR.

- Screening
- Cycle 1
    - Weekly (prior to Sym015 administration on days of dosing)
        - Does not need to be performed prior to C1/D1 if performed during screening ≤7 days from C1/D1
    - Day 3
- Each cycle thereafter
    - Prior to each dosing
- EOT
- 1M FUP
- As clinically indicated

8.2.9.4 Urinalysis

Multi-parameter chemical test strips are acceptable and should include assessment of: specific gravity, pH, protein, glucose, ketones, occult blood, leukocyte esterase, nitrite, bilirubin, and urobilinogen.

- Screening
- Cycle 1
    - Prior to each dosing
        - Does not need to be performed prior to C1/D1 if performed during screening ≤7 days from C1/D1
    - Day 1 of each cycle thereafter (prior to dosing)

- EOT
- 1M FUP
- As clinically indicated

8.2.9.5 Pregnancy Test

Serum human Chorionic Gonadotropin (β-hCG) at screening, urine β-hCG thereafter, in women of childbearing potential.

- Screening
- EOT
- As clinically indicated

Women are considered of childbearing potential unless they have been hysterectomized, have undergone tubal ligation or have been postmenopausal for at least one year.

8.3 Disease Assessments

8.3.1 Disease Status Evaluation by CT or MRI

The anti-tumor activity of Sym015 will be assessed by the Investigator, or qualified designee, according to RECIST v1.1 (29). Refer to Appendix 1.

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. Use of contrast is preferred but is at the discretion of the Investigator, as medically indicated.

- 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.

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.

Imaging data (imaging studies and derived assessments) will be stored by the sites and will be available upon request for potential review by the Sponsor or an independent radiology reviewer. For Part 2 only: In addition, imaging studies will be sent to an imaging facility for storage in order to ensure central availability and readiness for read at a future time upon Sponsor or Health Authority request.

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]).

8.3.2 Tumor Marker Evaluation (Part 1 and Part 2 Basket Cohort)

To include tumor markers that are part of the trial site standard practices as indicated by tumor type, if applicable.

It is recommended that tumor markers are evaluated at timepoints coinciding with the CT/MRI imaging studies as listed in Section 8.3.1.

8.3.3 Archival Tumor Tissue for *MET* and *KRAS* Assessment (Part 1 and Part 2 Basket Cohort)

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. May be performed as part of prescreening outside the 14-day screening period, provided separate informed consent has been obtained.

- Screening

- Part 1: Eligibility assessment for *KRAS* mutational status will be done using archival tumor tissue, whenever possible. If archival tissue is not available, tissue from a tumor biopsy performed during screening will be used.

  Assessment of *MET*-amplification status is not required, but tissue should be assessed if feasible.

- Part 2:

  Eligibility assessment for *KRAS* mutational status may be done using archival tumor tissue. If archival tissue is not available, tissue from the tumor biopsy performed during screening will be used. Refer to Section 8.3.4.

  It is preferred that the eligibility assessment for *MET*-amplification be done using tissue from a tumor biopsy performed during screening, however archival tumor tissue may be used at the investigator's discretion.

  Note: If a new biopsy is performed for *MET*-amplification testing, tissue from this biopsy may be used for *KRAS* mutation testing as well.

  During Part 2 ONLY, peripheral blood collection for *KRAS*-mutation assessment and for *MET*-amplification assessment in ctDNA is allowed as a local pre-screening methodology by Guardant360 analysis. Other liquid biopsy methodologies, except if used to detect $MET^{Ex14Del}$, will only be allowed if previously approved by the Sponsor. Subsequent required tumor tissue evaluation to confirm *MET*-amplification must meet the protocol-specified inclusion criteria.

  NSCLC $MET^{Ex14Del}$ Cohort *(pre-protocol v8.0)*: Eligibility assessment for $MET^{Ex14Del}$ status will be done according to local institutional standards. Assessment in ctDNA by Guardant360 technology or equivalent is allowed. Subsequent confirmation in tumor tissue is preferred but not required, however, archival tissue to be submitted, if available (applies only to patients with $MET^{Ex14Del}$ tumors entered prior to suspension of the Basket Cohort and establishment of NSCLC $MET^{Ex14Del}$ Cohort).

8.3.4 Tumor Biopsy for Eligibility Assessment and Biomarker Analysis (Part 1 and Part 2 Basket Cohort)

To be assessed locally for eligibility:

- Screening; Part 1 and Part 2, if applicable as per Section 8.3.3 (i.e., Basket Cohort)

  Note: It will be permissible to perform this procedure outside the 14-day screening period, provided informed consent for the trial has been obtained

To be assessed centrally for biomarker analysis:

- Screening
  - Part 1: Optional; only applicable for patients with known *MET*-amplification who consent to this optional procedure; to be performed after confirmation of eligibility
  - Part 2:

Basket Cohort: Required, if archival tissue is unavailable or insufficient for central analysis; to be performed after confirmation of eligibility

Note: 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 as specified in the laboratory manual. It must be ensured that the archival tissue can be made available to the central laboratory prior to deciding to omit the tumor biopsy procedure at time of screening

NSCLC *MET*^{Ex14Del} Cohort: Optional

- Post-dosing

  If feasible, it is preferred that the second biopsy is taken from the same tumor site from which the first biopsy was taken.

  - Part 1: Optional; only applicable for patients with known *MET*-amplification who consent specifically to this optional procedure; to be performed as specified below for Part 2 patients
  - Part 2:

    Basket Cohort: Required; EOC2 (i.e., coinciding with time of first response assessment) or upon PD, whichever occurs first

    Note: 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

    NSCLC *MET*^{Ex14Del} Cohort: Optional, at the timepoint specified above

8.3.5 Tumor Biopsy for *MET* Status and Biomarker Analysis (Part 2 NSCLC *MET*-Amplified Cohort and NSCLC *MET*^{Ex14Del} Cohort)

To be assessed centrally:

- Screening (Mandatory)

  Note: It will be permissible to perform this procedure outside the 14-day screening period, provided informed consent for the trial has been obtained

  - NSCLC *MET*-Amplified Cohort: Required; tissue from a newly performed pre-dosing tumor biopsy must be submitted for central confirmation of *MET*-amplification

    (Patients may be entered and treated based on local assessment of a recent tumor biopsy [if available and performed outside of the screening process as part of the site's usual practice] provided no intervening antineoplastic therapy has been administered; otherwise tissue from a newly performed biopsy must be obtained and submitted)
  - NSCLC *MET*^{Ex14Del} Cohort: Required; tissue from a recent or newly performed pre-dosing tumor biopsy must be submitted for central assessment of *MET*^{Ex14Del}

(Patients may be entered and treated based on local institutional standards; alternatively, assessment in ctDNA by Guardant360 technology or equivalent is allowed; a recent [as defined above] or newly performed pre-dosing biopsy must still be submitted)

- Post-dosing (Optional)

  EOC2 (i.e., coinciding with time of first response assessment) or upon PD, whichever occurs first

  Note: 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

To include a tumor biopsy performed by a core biopsy of a locally recurrent or metastatic lesion. This procedure will take place prior to the first Sym015 administration. The tumor biopsy must be performed with minimal morbidity to the patient by a percutaneous core needle biopsy either with or without the aid of an imaging modality chosen at the discretion of the physician performing the biopsy.

Biopsy specimens will be obtained using standard sterile surgical techniques and formalin-fixed, paraffin-embedded according to standard laboratory techniques. All tumor tissue samples should be reviewed by a pathologist to confirm the presence of tumor cells before the tissue sample (blocks or slides) is sent to the central laboratory for analysis. A detailed laboratory manual specifying sample collection, handling, storage, and shipment will be provided to the trial sites.

Analysis of tumor biopsies 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.

All analyses will be related to and used only in connection with the data collected in the present trial and future development of Sym015, and the identity of the patient will remain confidential. The analyses will not have any medical consequences for the patient or their relatives.

Tumor biopsy samples will be stored for up to 15 years after completion of the trial, where after all samples will be destroyed.

8.4 Pharmacokinetic Assessments

PK samples will be taken according to the schedules shown in Table 9.

Analysis of PK will be performed at a central laboratory. A detailed laboratory manual specifying sample collection, handling, storage, and shipment will be provided to the trial sites.

In the event that a collected serum sample is inadequate or insufficient for PK analysis, the analysis of PK can be done using an anti-drug antibody (ADA) serum sample from the same time point, if available.

Note: Comprehensive collection of clinical samples is critical to the conduct of this study. In situations where collection of EOI + 8h samples is logistically difficult due to clinic staff availability, the observation period may be shortened and an "end of day" sample may be obtained at the latest practical time. Such an option (if to be routinely employed) is available only after previous discussion with and approval by the Sponsor.

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; 1M FUP, 1-Month Follow-up Visit; SOI, Start of Infusion

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

8.5 Anti-Drug Antibody Testing

To assess formation of ADA. 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 central laboratory. A detailed laboratory manual specifying sample collection, handling, storage, and shipment will be provided to the trial sites. In the event that a collected serum sample is inadequate or insufficient for ADA analysis, the analysis of ADA can be done using a PK serum sample from the same time point, if available.

- C1/D1
- C2/D1 (Part 2 only)
- Day 1 of to every second cycle thereafter, i.e., Cycle 3, 5, 7 etc. (prior to dosing)
- EOT
- 1M FUP

8.6 Skin Biopsy (Part 1 only)

To be performed only after eligibility has been confirmed

Analysis of skin biopsy samples will be performed at a central laboratory. Biopsy specimens will be obtained using standard techniques and formalin-fixed, paraffin-embedded according to standard laboratory techniques. A detailed laboratory manual specifying sample collection, handling, storage, and shipment will be provided to trial sites.

Skin biopsies are requested from a rash-free area.

- Screening, after confirmation of eligibility
- EOC2 (i.e., coinciding with time of first response assessment) or upon PD, whichever occurs first

  Note: 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

8.7 Blood Sample for Genomic and Biomarker Analyses

To include assessment of *MET*-amplification and *MET*^{Ex14Del} status; analysis of all samples taken will be performed at a central laboratory. A detailed laboratory manual specifying sample collection, handling, storage, and shipment will be provided to the trial sites.

- Screening (it will be permissible to perform this procedure outside the 14-day screening period, provided informed consent for the trial has been obtained)
- EOC2 (coinciding with time of first response assessment or upon PD, whichever occurs first)

  Note: 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

- EOT (if after EOC2; need not repeat if patient is discontinuing at the EOC2 or if a sample was obtained upon PD)

Note: 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.

The purpose of the pharmacodynamic biomarker assessments is to develop an approach for the identification and validation of genes or proteins that may predict which patients are likely to respond to Sym015, and that may change with the possible development of acquired resistance to Sym015. Potential biomarkers of interest include genes, gene transcripts and proteins of the RTKs and molecules of the MET signaling 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.

All analyses will be related to and used only in connection with the data collected in the present trial and future development of Sym015, and the identity of the patient will remain confidential. The analyses will not have any medical consequences for the patient or their relatives.

Biomarker samples will be stored for up to 15 years after completion of the trial, where after all samples will be destroyed.

8.8 Handling of Biological Samples

All biological samples to be analyzed locally will be collected and handled according to institutional practices.

All biological samples to be analyzed centrally will be collected and handled according to a detailed laboratory manual.

Retention time for biologic specimens will be specified in the laboratory manual.

8.9 Follow-up Assessments

Assessments at the 1M FUP Visit include disease status and subsequent cancer therapy.

After the 1M FUP Visit, the Investigator will make every effort to obtain follow-up information on response assessment and/or OS every 2 months. Response assessment follow-up is required in the event of an ongoing SD, PR or CR, as per RECIST v1.1 at the 1M FUP Visit, until PD or another therapeutic intervention is initiated. Survival follow-up is required until death, withdrawal of consent, or termination 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.

8.10 Appropriateness of Measurements

Standardized methods for assessments of efficacy and safety variables will be used.

9. ADVERSE EVENTS

9.1 Definitions of Adverse Events

9.1.1 Adverse Event

An AE is any untoward medical occurrence in a patient or a clinical investigation subject 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 as: Related to IMP, Possibly Related to IMP, Probably Related to IMP, Unlikely Related to IMP, or Not Related to IMP. In addition, any AE, regardless of causality, that also meets the seriousness criteria, will be reported on an SAE form.

9.1.2 Events Not to be Considered as Adverse Events

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

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).

Note: PD may be reported as an AE in the case of patient death, with death being the outcome of the event.

An abnormal laboratory value or an abnormality in physiological testing (such as ECGs) need not be reported as an AE unless one of the following applies:

- The Investigator considers the abnormality clinically significant
- The event meets the definition of an SAE
- The event requires an intervention
- The event results in an action taken with Sym015 (dose-reduction and/or withdrawal)

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

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

9.1.3 Adverse Events of Medical Interest

Not applicable.

9.1.4 Serious Adverse Events

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

- Results in death

  Note: In the case of deaths, the event(s) leading to the death should be recorded and reported as SAE(s) with the outcome "Fatal". The death itself will not be reported as an event (SAE), unless the cause of the death is unknown (e.g., in case of unexplained or sudden death)

- Is life-threatening

  Note: The term "life-threatening" in this definition refers to an event in which the 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

  Note: Medical and scientific judgment must be exercised in deciding whether an AE is believed to be "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

9.1.5 Events that Do Not Meet the Definition of Serious Adverse Events

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

Note: PD may be reported as an SAE in the case of patient death, with death being the outcome of the event.

Elective surgery or other scheduled hospitalization periods that were planned before the patient was included in this trial are not to be recorded as SAEs, unless an outcome is considered serious.

Hospitalization for observation or convenience following the Sym015 infusions without an SAE occurring should not be recorded as an SAE, e.g., if a patient is hospitalized merely for

observation, or if a patient finalizes the infusion at a time of day requiring a convenience overnight stay in the hospital.

If procedures to support the treatment regimens require hospitalization, they should not be recorded as SAEs. However, in cases where a procedure results in complications requiring/prolonging hospitalization, this must be recorded and reported as an SAE.

9.2 Adverse Event Recording and Reporting Instructions

9.2.1 Adverse Event Recording Period

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.

Note: Patients who sign informed consent and are subsequently deemed to be screening failures will be followed for the occurrence of SAEs/AEs until it is determined that they will not be participating in the trial.

The Investigator must record all directly observed AEs and all AEs spontaneously reported by the patient. A general, open-ended type of question should be used to elicit a response from the patient, such as, “How have you been feeling?” or “Have you had any health problems since your last visit?”.

All AEs that occur in patients during the AE recording period must be recorded/entered on the AE section of the Case Report Form (CRF), whether or not the event is assessed as related to Sym015. If the AE is serious, the SAE report forms must also be completed and submitted. Refer to Section 9.3.

9.2.2 Diagnosis

A diagnosis should be recorded if possible. If no diagnosis is available, signs and symptoms should be recorded instead.

9.2.3 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.

Generally, an AE of CTCAE Grade 4 or 5 qualifies for SAE reporting to the Sponsor or designee. However, a laboratory abnormality of CTCAE Grade 4 does not need to be reported as an SAE, unless it meets one of the seriousness criteria in Section 9.1.4.

9.2.4 Relationship to Investigational Medicinal Product/Sym015

The Investigator must assess causal relationship to the IMP, Sym015. Relatedness has to be assessed and recorded within the initial report (CRF and SAE report form).

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

9.2.5 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.

9.2.6 Follow-up of Adverse Events

All AEs should be followed until they are resolved or until the 1M FUP Visit, whichever comes first.

Note: Patients who sign informed consent and are subsequently deemed to be screening failures will be followed for the occurrence of SAEs/AEs until it is determined that they will not be participating in the trial.

9.3 Serious Adverse Event Recording and Reporting

All SAEs occurring at any time from signing of informed consent for participation in the trial and until the 1M FUP Visit must be recorded on the SAE Report Form and recorded as an SAE in the CRF.

Note: Patients who sign informed consent and are subsequently deemed to be screening failures will be followed for the occurrence of SAEs/AEs until it is determined that they will not be participating in the trial.

In case of an SAE, the Investigator must, within 24 hours of first awareness of the event, report the SAE to the Sponsor (or designee) by fax or e-mail. Fax number(s) and e-mail address(es) will be stated on the SAE Report Form and the SAE Report Form Completion Instructions. SAE follow-up information must also be reported to the Sponsor (or designee) within 24 hours of awareness.

SAEs still ongoing after the 1M FUP Visit should be followed on a regular basis according to the Investigator's clinical judgment, until the event resolves or until the Investigator assesses it as chronic or stable. The Sponsor (or designee) will pursue sufficient information and will return to the trial sites for such information as deemed required.

If the Investigator becomes aware of an SAE that occurred after the 1M FUP Visit and finds it to be related to the IMP (possibly-, probably-, or related to the IMP) or trial conduct, it must be recorded and reported to the Sponsor (or designee) as an SAE. These SAEs considered related to the IMP and occurring after the 1M FUP Visit will not be reported in the CRF but only on an SAE Report Form for recording in the Safety Database.

The Investigator should be aware of local reporting regulations to the Institutional Review Board (IRB)/Ethics Committee (EC). The Sponsor (or designee) will either supply the Investigator with the reports, which should be forwarded to the IRB/EC, or report directly to the IRB/EC depending on local regulations.

9.4 Safety Reporting to Health Authorities, Institutional Review Boards/Ethics Committees, and Investigators

Reportability of an SAE as a "suspected unexpected serious adverse reaction" (SUSAR) will be determined solely by the Sponsor, based on seriousness, causality and expectedness. In addition to SUSARs, the Sponsor or designee is responsible for reporting all relevant safety information regarding SUSARs, or other safety developments, to appropriate Health Authorities and central

IRBs/ECs, as well as participating Investigators. Requirements for reporting SUSARs to local IRBs/ECs will be handled via the Investigator. The timeline for notification of SUSARs is within 7 calendar days for fatal/life-threatening events and within 15 calendar days for all other SUSARs.

Additionally, the annual Development Safety Update Report (DSUR) will be 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 will handled as per local regulations and/or requests.

9.5 Dose-Limiting Toxicities (Part 1 Only)

9.5.1 Definition of Dose-Limiting Toxicities

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 mm^3, duration >5 days)
4. Thrombocytopenia that is:
    a. Grade 3 with clinically significant hemorrhage
    b. Grade 4 (platelets < 25,000 per mm^3)
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

9.5.2 Observation Period for Dose-Limiting Toxicities

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.

9.5.3 Reporting of Dose-Limiting Toxicities

All presumed DLTs must be reported to the Sponsor or designee within 24 hours after the Investigator or designee have become aware of the event. In addition, DLTs fulfilling the SAE criteria must be reported in an expedited manner according to the procedure for SAEs, as outlined in Section 9.3.

9.6 Reporting of Infusion-Related Reactions

The definition of an IRR is included in Section 7.1.3.6.

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").

To facilitate ongoing safety review throughout the course of this trial, the occurrence of ≥ Grade 2 IRRs must be reported to the Sponsor or designee within 24 hours of occurrence.

IRRs fulfilling the SAE criteria must be reported in an expedited manner according to the procedure for SAEs, as outlined in Section 9.3.

9.7 Pregnancy

If any trial patient becomes pregnant during the course of the trial, the patient must be discontinued from Sym015 immediately and the pregnancy must be reported to the Sponsor or designee according to the same timelines as an SAE. While pregnancy is not considered an AE, all pregnancies are tracked as SAEs within the safety database in order to follow-up on exposure to the fetus/infant.

Pregnancies reported in female partners of male trial patients must also be included in the database; therefore, a pregnant partner must provide informed consent before information can be collected.

All pregnancies must be followed up every third month to determine outcome (including premature termination) and status of mother and child. Pregnancy complications and elective terminations for medical reasons must be reported as AEs or SAEs as appropriate (trial patients only). Elective terminations for non-medical reasons should not be reported as AEs. Spontaneous abortion must be reported as an SAE.

Any SAE occurring in association with a pregnancy brought to the Investigator's attention after the patient has completed the trial and considered by the Investigator as possibly related to the IMP (possibly, probably, or related to Sym015), must be promptly reported to the Sponsor or designee.

All pregnancy information including follow-up information must be reported in a designated pregnancy form provided by the Sponsor or designee.

10. STATISTICS

10.1 Statistical Considerations and Analysis Plan

No formal hypothesis testing is planned. Descriptive statistics will be used to summarize the safety, tolerability, pharmacokinetics, and clinical activity of Sym015 in all patient cohorts.

Data will be described and summarized as warranted by sample sizes. Listings will be used in place of tables in the event of small sample sizes. Dose-escalation assessment will be based on the DLT-evaluable population, defined as patients who complete the DLT assessment window. All other analyses will be based on the safety-evaluable population, defined as all patients who receive any amount of the study drug.

Continuous variables will be summarized with the use of means, standard deviations, medians, and ranges; categorical variables will be summarized using counts and percentages. All summaries will be presented separately by cohort, in both Part 1 and Part 2 of the study.

All details of the data analyses will be described in the Statistical Analysis Plan.

10.2 Sample Size Determination

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. Refer to Section 7.1.3.1 for a description of planned dose levels and decision points for dose-escalation. 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 (Table 10).

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.

Table 10 90% Confidence Intervals for Observed Response Rates for N=20 and N=25

	Method	Responses	N	Mean	Lower	Upper
1	exact	1	20	0.05	0.002561379	0.2161062
2	exact	2	20	0.10	0.018065203	0.2826185
3	exact	3	20	0.15	0.042169408	0.3436638
4	exact	4	20	0.20	0.071353884	0.4010281
5	exact	5	20	0.25	0.104080836	0.4555824
6	exact	6	20	0.30	0.139553749	0.5078184
7	exact	7	20	0.35	0.177310918	0.5580345
8	exact	8	20	0.40	0.217068589	0.6064151
9	exact	9	20	0.45	0.258650610	0.6530686
10	exact	10	20	0.50	0.301953911	0.6980461
11	exact	11	20	0.55	0.346931398	0.7413494
12	exact	12	20	0.60	0.393584887	0.7829314
1	exact	1	25	0.04	0.002049628	0.1761207
2	exact	2	25	0.08	0.014403198	0.2310399
3	exact	3	25	0.12	0.033519595	0.2817225
4	exact	4	25	0.16	0.056562559	0.3296083
5	exact	5	25	0.20	0.082290900	0.3754051
6	exact	6	25	0.24	0.110056200	0.4195200
7	exact	7	25	0.28	0.139475307	0.4622089
8	exact	8	25	0.32	0.170303654	0.5036416
9	exact	9	25	0.36	0.202377780	0.5439332
10	exact	10	25	0.40	0.235586130	0.5831620
11	exact	11	25	0.44	0.269853059	0.6213784
12	exact	12	25	0.48	0.305129680	0.6586113
13	exact	13	25	0.52	0.341388663	0.6948703
14	exact	14	25	0.56	0.378621563	0.7301469
15	exact	15	25	0.60	0.416838037	0.7644139
16	exact	16	25	0.64	0.456066786	0.7976222
17	exact	17	25	0.68	0.496358438	0.8296963
18	exact	18	25	0.72	0.537791078	0.8605247
19	exact	19	25	0.76	0.580479993	0.8899438
20	exact	20	25	0.80	0.624594865	0.9177091

10.3 Analysis Population

Analysis sets will be 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.

10.4 Primary Endpoint and Analysis

10.4.1 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.

All DLT events will be listed by dose cohort and patient. A summary table of DLTs by System Organ Class (SOC) and Preferred Term will be presented for each dose cohort, if applicable. The summaries will include number of DLTs, and number and percentages of patients experiencing a DLT. The definition of a DLT is included in Section 9.5.1.

The MTD is defined as the highest dose with a maximum of 1 out of 6 patients experiencing a DLT. The MTD may or may not be found within the dose levels tested. Based on an overall evaluation of the dose-escalation part, the Q2W RP2D and highest safe dose tested will be selected. The Q2W RP2D might not necessarily be the MTD or the highest administered dose.

10.4.2 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.

Number and percentages of patients with documented OR will be presented including corresponding 90% exact Confidence Intervals (CI), separately for each cohort.

10.5 Secondary Endpoint and Analysis

All statistical analyses of the secondary endpoints for both phases will be performed after completion of Part 2 of the trial.

10.5.1 Efficacy Endpoints and Analyses

All statistical analyses of the secondary endpoints will be presented using the FAS.

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
    - Time to disease progression (TTP) as determined based on radiological evidence
    - Progression-free survival (PFS)
    - Overall survival (OS)

Best overall response (BOR) by RECIST v1.1 will be summarized by trial part and dose cohort by means of counts and percentages for the categories CR, PR, SD, PD and NE. In addition, the number and percentages of patients with SD for more than 4 months will be presented.

Number and percentages of patients with documented OR in the dose-escalation part will be presented including corresponding 90% exact CI. All documented ORs (Part 1 and Part 2) will be listed including duration (in days) of OR, measured from time of first PR or CR to PD.

Time to disease progression (TTP), PFS, and OS will be summarized using the product-limit method and Kaplan-Meier plots. The median TTP, PFS, and OS, including 90% CI, will be calculated.

10.5.2 Other Efficacy Assessments

Tumor markers will be listed and summarized descriptively, as appropriate.

10.5.3 Safety Endpoints and Analyses

The safety endpoints are presented below. These endpoints will all be presented for the FAS by trial part. Safety data will be summarized using descriptive statistics and frequency distributions as appropriate.

In Part 1 and Part 2 of the trial, the following safety endpoints will be assessed:

- Nature, incidence and severity of AEs measured from baseline to end of trial participation
- AEs leading to dose-reductions, dose delays and permanent treatment cessation
- Changes in safety laboratory values from baseline to end of trial participation
- Changes in vital signs and physical examinations from baseline to end of trial participation
- Occurrence of ADAs to Sym015 measured in serum at selected timepoints from baseline to end of trial participation

10.5.3.1 Adverse Events

The AEs will be coded using Medical Dictionary for Regulatory Activities (MedDRA) current version. AEs will be regarded as treatment emergent AEs (TEAEs) if they occur after first treatment. Non-treatment emergent AEs (non-TEAEs) are defined as AEs collected before dosing. TEAEs will be presented by SOC and Preferred Term unless stated otherwise. The frequencies of TEAEs will be presented including number and percentages of patients having experienced an event and the total number of events.

AEs including SAEs are reported from signing of the informed consent for participation in the trial and until the end of trial participation. SAEs reported outside the required reporting window are only entered into the safety database and will be described separately in the report.

Note: Patients who sign informed consent and are subsequently deemed to be screening failures will be followed for the occurrence of SAEs/AEs until it is determined that they will not be participating in the trial.

All AEs will be listed. The TEAEs will be presented using summary tables by trial phase including:

- AEs, in total and sorted by frequency
- AEs by relationship
- AEs by CTCAE Grade and maximum CTCAE Grade

- SAEs, in total, and by relationship
- AEs leading to withdrawal from treatment
- AEs leading to trial drug-interruption or dose-reduction
- Fatal AEs

10.5.3.2 Clinical Laboratory Values

Biochemistry, hematology, and coagulation parameters will be presented using box plots by visits and by cohort and trial part. In addition, individual patient biochemistry, hematology, and coagulation parameters during the trial will be presented graphically using longitudinal plots. Urinalysis parameters will be summarized using descriptive statistics.

Laboratory values outside normal range will be flagged, and all laboratory values will be listed including CTCAE grading of abnormal values.

10.5.3.3 Other Safety Assessments

Change in vital signs from baseline to end of trial participation will be summarized by visit, cohort, and trial part. Normal and abnormal findings in physical examination and ECG measurements will be presented in shift tables by visit, cohort, and trial part.

ECOG PS, body weight, and ADA results will be listed.

10.5.4 Pharmacokinetic Endpoints and Analyses

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

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
$T_{½}$	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)

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.

Individual curves of serum concentration versus time after the first dosing of Sym015 will be presented on log- and linear scale for all patients in the FAS. Furthermore, trough serum concentrations for the period from first dose to end of treatment will be presented on linear scale individual plots. In addition, mean concentration time curves will be presented on linear scale using nominal time point by cohort and trial part. All PK endpoints will be listed and summarized by cohort and trial part.

10.5.5 Additional Endpoints and Analyses

The following additional endpoints will be assessed in Part 1 and Part 2 of the trial:

- Part 1 only: MET-receptor down-regulation measured by percentage and nominal change in target expression from baseline to EOC2 or PD (whichever comes first) in skin biopsy samples
- Biomarkers relevant to Sym015 activity
- Tumor genetics, drug target genes, and other biomarker genes that are known to be involved in the development and progression of *MET*-amplified solid tumor malignancies

The additional endpoints, outlined above may include genes 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.

Percentage and nominal change in target expression from baseline to EOC2 or PD (whichever comes first) in skin biopsy samples will be presented. Descriptive statistics will be used, including scatter plots of values at EOC2 versus baseline.

Potential biomarkers include genes, gene transcripts, and proteins of RTKs and molecules of the MET signaling pathway. All biomarkers will be listed and descriptively summarized.

Exploratory analyses using the biomarkers might be performed.

10.6 Interim Analysis

No interim analysis is planned.

10.7 Deviations from the Statistical Plan

Any deviation(s) from the original analysis plan will be described in a protocol amendment and/or in a statistical analysis plan and/or in the final CTR, as appropriate.

11. ETHICS

11.1 Institutional Review Board/Ethics Committee

An IRB/EC will review the protocol and any amendments and advertisements used for recruitment, as well as the informed consent documents, their updates (if any), and any other written materials given to the patients. The CTR will include a list of all IRBs/ECs to which the protocol has been submitted and the name of the committee chair.

11.2 Patient Information and Informed Consent

The Investigator or his/her designee must obtain written informed consent from each patient before any trial related procedures are performed. Each patient must receive full patient information before giving consent. The patient information must contain full and adequate verbal and written information regarding the objective and procedures of the trial and the possible risks involved.

Before signing the informed consent form the patient must be given sufficient time to consider his/her possible participation. Each patient must also be informed about his/her right to withdraw from the trial at any time.

Each patient must sign the informed consent form; the patient receives a copy of the signed form and the original is retained in the Investigator Site File (ISF). The informed consent form must be signed and dated both by the patient and by the Investigator or designee providing the information to the patient.

12. SAFETY SURVEILLANCE SET-UP

12.1 Safety Review

An SMC will be established. This committee will include Investigator(s), Medical Monitor(s), Drug Safety Physician, and Sponsor's medical representatives. The SMC will review clinical and laboratory safety data regularly throughout the trial and make decisions regarding the advisability of continuing accrual to a particular dose cohort, and/or escalating the dose and allowing accrual to a higher dose cohort. In order to do so, the Investigator must ensure to report safety data to the Sponsor or designee in a timely manner. This includes, but is not limited to:

- SAEs must be reported within 24 hours of awareness (SAE report form)
- DLTs must be reported within 24 hours of occurrence
- IRRs of ≥ Grade 2 must be reported within 24 hours of occurrence
- All AEs will be reported in the CRF in a timely manner
- Dose-modifications (i.e., dose-reduction, temporary interruptions regardless of cause) will be reported in the CRF in a timely manner
- Local laboratory data will be reported in the CRF in a timely manner

Availability of these data will enable the Sponsor to act promptly in response to safety signals and to ensure Health Authorities, as well as Investigators, who may be participating in other Sym015 clinical trials, are informed of events occurring during this trial.

Safety teleconferences will be held between the Investigational Site(s) and the Sponsor and/or designee. Patients will be carefully evaluated for evidence of all AEs, including potential cumulative and/or delayed toxicities throughout the duration of their time in the trial.

- Part 1: It is intended that safety teleconferences will be held biweekly; however, frequency may fluctuate based on accrual and trial activity, as indicated
- Part 2: It is intended that safety teleconferences will be conducted after enrollment of approximately 15 and 30 patients. If safety concerns emerge, more frequent meetings will be held on an ad hoc basis.

12.2 Other Safety Surveillance Activities

A Medical Monitor is assigned to review and evaluate relevant clinical/safety information concerning the clinical trial. The responsibilities of the Medical Monitor include, but are not limited to:

- Evaluation of coding and trending of AEs in conjunction with the Drug Safety physician
- Performing surveillance on potential safety signals in conjunction with the Drug Safety physician
- Evaluating abnormal laboratory values
- Providing medical support to the Sponsor in answering questions related to the trial protocol
- Updating the SMC on trial status at scheduled meetings

A Drug Safety physician is assigned to review, assess, and approve all SAE cases and associated reports. This physician will also perform the following:

- Assess for safety signals and trends in conjunction with the Medical Monitor
- Assist with questions regarding medical coding of SAEs
- Discussing with the Sponsor Chief Medical Officer, any cases which may present a concern with regard to a signal or safety issue.

13. MONITORING AND QUALITY ASSURANCE

13.1 Compliance with Good Clinical Practice

The responsibilities of the Sponsor, the Monitor, and the Investigator are defined in ICH GCP E6(R2), and applicable regulatory requirements in the country where the trial takes place. The Investigator is responsible for adhering to the ICH GCP responsibilities of the Investigators, and for dispensing IMP only in accordance with this protocol or a signed amendment, and for its storage and safe handling throughout the trial.

13.2 Source Documents

Each trial site will permit authorized representatives of the Sponsor and relevant authorities direct access to (and when required by applicable law, to copy) clinical records for the purposes of quality assurance reviews, audits, and evaluation of the trial safety and progress.

Source data are all information, original records of clinical findings, observations, or other activities in a clinical trial necessary for the reconstruction and evaluation of the trial. Examples of these original documents and data records include, but are not limited to: Hospital records, clinical and office charts, laboratory notes, memoranda, patients' written diaries or evaluation checklists, pharmacy dispensing records, recorded data from automated instruments, copies or transcriptions certified after verification as being accurate and complete, microfiches, photographic negatives, microfilm or magnetic media, x-rays, and patient files and records kept at the pharmacy, at the laboratories, and medico-technical departments involved in the clinical trial.

The Investigator must maintain source documentations for each patient in the trial and all information in the CRF must be traceable to these source documents in the patient's file. Data not requiring a separate written record, i.e., data, which may be recorded directly in the CRF, will be defined before trial start.

13.3 Monitoring

Monitoring visits to the trial sites will be made periodically during the trial to ensure that all aspects of the protocol are followed. The Investigator must give the Sponsor and/or their representatives direct access to all relevant source documents to confirm consistency with the CRF entries. Source Data Verification will be conducted according to Sponsor or designee Standard Operating Procedures (SOPs) and requirements will be specified in a trial specific monitoring plan.

It is important that the Investigator and their relevant personnel are available during monitoring visits and possible audits and that sufficient time is devoted to the process.

14. DATA HANDLING AND RECORD KEEPING

Study data collection, processing, transfer, and reporting, as well as handling of study personnel information, will be done in compliance with ICH E6(R2) GCP and all applicable data protection regulations, including Regulation (EU) 2016/679 of the European Parliament and of the Council of 27 April 2016 on the protection of natural persons with regard to the processing of personal data and on the free movement of such data (General Data Protection Regulation; GDPR).

14.1 Data Protection

The Investigator, Sponsor, and Sponsor designee(s) will ensure that the confidentiality of the patients' data is preserved. Each participating site will maintain appropriate medical and research records for this trial, in compliance with ICH GCP E6(R2) and regulatory and institutional requirements for the protection of confidentiality of patients.

14.2 Data Transactions and Access

The trial data and any other documents transferred to the Sponsor or designee will not contain patient names or other confidential personal data, but patients will be identified using the assigned trial specific patient numbers.

When data are transferred to the Sponsor or designee, access will be limited to relevant persons.

Documents that are not for collection by the Sponsor, e.g., patient identification list and the signed informed consent forms, will be maintained by the Investigator in confidence.

14.3 Data Processing

A Data Management Plan (DMP) will be prepared for this trial. The Sponsor (or designee) will be responsible for data processing in accordance with applicable Data Management SOPs and the trial DMP.

Once recorded within the electronic CRF, study data will pass through a set of preprogrammed data validation checks designed to identify inconsistencies and other data errors, and will undergo an additional study-specific data review process. Data issues will be queried via the electronic data capture (EDC) system and query resolutions will be documented.

Entry and processing of data other than those directly recorded on electronic CRFs by trial sites (e.g., imports of laboratory results) will follow vendors' SOPs. Transfer of such data from vendors to Sponsor (or designee) will be handled according to vendors' data transfer SOPs and the Sponsor data transfer requirements with full compliance to applicable regulations.

Database Lock will occur upon reaching the predefined data cut-off for primary analysis and completion of Sponsor's (or designee's) quality control and quality assurance procedures.

Portable Document Format (PDF) files of the electronic CRFs will be provided to the Investigator upon removal of access to the electronic CRFs.

14.4 Clinical Trial Report

Following study completion, a final integrated clinical/statistical CTR will be prepared.

14.5 Compliance with the General Data Protection Regulation

The applicable EU data protection legislation requires that parties enter into a written contract if one party (data processor) processes personal data on behalf of the other party (data controller). This written contract must regulate the subject-matter and duration of the processing, the nature and purpose of the processing, the types of personal data and categories of data subjects, as well as the obligations and rights of the data controller. Accordingly, the parties must enter into a data processing agreement. To the extent the processing of personal data involves transfers of personal data to third countries (e.g., jurisdictions outside of the European Economic Area [EEA]), the parties will enter into the European Commission's standard contractual clauses between the data controller, the data processor, and all sub-processors, if any. The European Commission's standard contractual clauses ensure an adequate level of protection in relation to transfers of personal data to third countries.

14.6 Retention of Trial Documents at Site

The Investigator at each trial site must make arrangements to store the essential trial documents (including the ISF) after the end of the trial according to ICH GCP E6(R2) and local requirements. In addition, the Investigator is responsible for archiving all relevant source documents so that the trial data can be compared against source data after completion of the trial (e.g., in case of inspection from relevant authorities). The Investigator is required to ensure the continued storage of the documents, even if the Investigator should leave the clinic/practice or retire before the end of the required storage period.

15. REGISTRATION AND COMMUNICATION OF RESULTS

15.1 Use of Information

All unpublished information relating to this trial and the IMP is considered confidential by the Sponsor and shall remain the sole property of the Sponsor. The Investigator must accept that the Sponsor may use information from this trial in connection with the development of the IMP, and therefore, may disclose it as required to Investigators, government licensing authorities, Health Authorities of other governments, stock exchange market, and commercial partners.

15.2 Registration and Publication

The trial will be registered in one or more public trial registries (e.g., ClinicalTrials.gov). The trial results will be posted in the same clinical trial registries as the initial registration in accordance with the latest International Committee of Medical Journal Editors (ICMJE) recommendations (URL: www.icmje.org).

The Sponsor acknowledges the Investigators' rights to publish the full results of the trial, regardless of the outcome, in accordance with the latest ICMJE recommendations.

The Coordinating Investigator and the Sponsor will decide on the publication strategy. The Coordinating Investigator has the right to publish and present the results and methods as first or last author of multicenter publications. Co-authorship will be decided by the Sponsor and the Coordinating Investigator and will be limited to a number of persons who have contributed substantially to the trial. The Sponsor will have representation in the list of authors.

Publication is subject to the following conditions:

- No publication before the completion of the trial at all participating trial sites without preceding written approval from the Sponsor
- Publications shall not disclose any Sponsor confidential information and property (not including the trial results)
- The Sponsor reserves the right to review results communications prior to public release and can embargo communications regarding trial results for a period that is less than or equal to 60 days. The Sponsor cannot require changes to the communication and cannot extend the embargo.

16. INSURANCE AND LIABILITY

The Sponsor will obtain Human Clinical Trials Insurance for its legal liability in accordance with laws and regulations, and with limits customary or required by law in the territory in question.

17. CHANGES TO THE FINAL CLINICAL TRIAL PROTOCOL

Changes to the protocol will not be implemented without agreement from the Sponsor and prior review and written approval from the appropriate Health Authority (as indicated) and the IRB/EC, except where necessary to eliminate an immediate hazard to the patients. No protocol waivers will be allowed.

Protocol changes to eliminate an apparent hazard to trial patients may be implemented by the Investigator immediately. The Investigator must then, without delay, inform the local IRB/EC, and the Sponsor (or designee) will immediately notify local governing Health Authorities.

18. PREMATURE TERMINATION OF THE TRIAL OR A TRIAL SITE

18.1 Premature Termination of the Trial

If the Sponsor, the Coordinating Investigator, or the SMC discovers conditions arising during the trial, which indicates that the trial should be halted, the trial can be terminated after appropriate consultation between the Sponsor, the SMC, and the Coordinating Investigator. The Health Authority and IRB/EC will be notified in writing. The reason will be stated.

Conditions that may warrant termination of the trial include, but are not limited to the following:

- The discovery of an unexpected and significant or unacceptable risk to the patients enrolled in the trial
- The discovery of lack of efficacy
- Failure of the Investigators to enter patients at an acceptable rate in the trial as a whole
- A decision on the part of the Sponsor to suspend or discontinue development of the IMP

18.2 Premature Termination of a Trial Site

The Sponsor can also decide to terminate single trial sites prematurely. Conditions that may warrant termination include, but are not limited to the following:

- Insufficient adherence to protocol requirements
- Failure to enter patients at an acceptable rate

19. REFERENCES

1. WHO World Cancer Report 2014. Edited by Bernard W. Stewart and Christopher P. Wild.

2. Petrini I: Biology of MET: a double life between normal tissue repair and tumor progression. Ann Transl Med. 2015 Apr;3(6):82.

3. Kawakami H, Okamoto I, Okamoto W, et al: Targeting *MET* Amplification as a New Oncogenic Driver. Cancers (Basel). 2014 Jul 22;6(3):1540-52.

4. Sacco JJ, Clague MJ: Dysregulation of the Met pathway in non-small cell lung cancer: implications for drug targeting and resistance. Transl Lung Cancer Res. 2015 Jun;4(3):242-52.

5. Wolff AC, Hammond ME, Hicks DG: Recommendations for Human Epidermal Growth Factor Receptor 2 Testing in Breast Cancer: American Society of Clinical Oncology/College of American Pathologists Clinical Practice Guideline Update. J Clin Oncol. 2013 Nov 1;31(31):3997-4013.

6. Jardim DL, Tang C, Gagliato Dde M, et al: Analysis of 1,115 patients tested for MET amplification and therapy response in the MD Anderson Phase I Clinic. Clin Cancer Res 2014 Dec 15;20(24):6336-45.

7. Cappuzzo F, Marchetti A, Skokan M, et al: Increased *MET* Gene Copy Number Negatively Affects Survival of Surgically Resected Non-Small-Cell Lung Cancer Patients. J Clin Oncol. 2009 Apr 1;27(10):1667-74.

8. Go H, Jeon YK, Park HJ, et al: High *MET* Gene Copy Number Leads to Shorter Survival in Patients with Non-small Cell Lung Cancer. J Thorac Oncol. 2010 Mar;5(3):305-13.

9. Okamoto I, Sakai K, Morita S, et al: Multiplex genomic profiling of non–small cell lung cancers from the LETS phase III trial of first-line S-1/carboplatin versus paclitaxel/carboplatin: results of a West Japan Oncology Group study. Oncotarget. 2014 Apr 30;5(8):2293-304.

10. Schildhaus HU, Schultheis AM, Rüschoff J, et al: MET Amplification Status in Therapy-Naïve Adeno- and Squamous Cell Carcinomas of the Lung. Clin Cancer Res. 2015 Feb 15;21(4):907-15.

11. Gavine PR, Ren Y, Han L, et al: Volitinib, a potent and highly selective c-Met inhibitor, effectively blocks c-Met signaling and growth in *c-MET* amplified gastric cancer patient-derived tumor xenograft models. Mol Oncol. 2015 Jan;9(1):323-33.

12. Catenacci DVT, Tang R, Oliner KS, et al: MET as a prognostic biomarker of survival in a large cohort of patients with gastroesophageal cancer (GEC). J Clin Oncol 33, 2015 (suppl; abstr 4034).

13. Kong-Beltran M, Seshagiri S, Zha J, et al. Somatic mutations lead to an oncogenic deletion of *MET* in lung cancer. Cancer Res. 2006 Jan 1;66(1):283-9.

14. Awad MM, Oxnard GR, Jackman DM, et al. *MET* Exon 14 Mutations in non-small-cell lung cancer are associated with advanced age and stage-dependent *MET* genomic amplification and c-Met overexpression. J Clin Oncol. 2016 Mar 1;34(7):721-30.

15. Frampton, GM, Ali SM, Rosenzweig M, et al. Activation of MET via diverse exon 14 splicing alterations occurs in multiple tumor types and confers clinical sensitivity to MET inhibitors. Cancer Discov. 2015 Aug;5(8):850-9.

16. Paik PK, Drilon A, Fan PD, et al. Response to MET inhibitors in patients with stage IV lung adenocarcinomas harboring *MET* mutations causing exon 14 skipping. Cancer Discov. 2015 Aug;5(8):842-9.

17. Seo JS, Ju YS, Lee WC, et al. The transcriptional landscape and mutational profile of lung adenocarcinoma. Genome Res. 2012 Nov;22(11):2109-19.

18. Xu R, Qiu M, Zhou Y, et al: Evaluation of tumor MET protein expression, *MET* gene amplification, and HER2 expression in Chinese patients with advanced gastric or gastroesophageal junction (G/GEJ) cancer. J Clin Oncol 33, 2015 (suppl; abstr 4048).

19. Leiser D, Medová M, Mikami K, et al: KRAS and HRAS mutations confer resistance to MET targeting in preclinical models of MET-expressing tumor cells. Mol Oncol. 2015 Aug;9(7):1434-46.

20. Kwak EL, Ahronian LG, Sirabegna G, et al: Molecular Heterogeneity and Receptor Coamplification Drive Resistance to Targeted Therapy in *MET*-Amplified Esophagogastric Cancer. Cancer Discov. 2015 Oct 2.

21. Camidge DR, Ou SH, Shapiro G, et al: Efficacy and safety of crizotinib in patients with advanced *c-MET*-amplified non-small cell lung cancer (NSCLC). J Clin Oncol 32:5s, 2014 (suppl; abstr 8001).

22. Kwak EL, LoRusso P, Hamid O, et al: Clinical activity of AMG 337, an oral MET kinase inhibitor, in adult patients (pts) with MET-amplified gastroesophageal junction (GEJ), gastric (G), or esophageal (E) cancer. J Clin Oncol 33, 2015 (suppl 3; abstr 1).

23. Goldman JW, Rosen LS, Algazi AP, et al: First-in-human dose escalation study of LY2875358 (LY), a bivalent MET antibody, as monotherapy and in combination with erlotinib (E) in patients with advanced cancer. J Clin Oncol 31, 2013 (suppl; abstr 8093).

24. Strickler JH, LoRusso P, Yen C, et al: Phase 1, open-label, dose-escalation, and expansion study of ABT-700, an anti-C-met antibody, in patients (pts) with advanced solid tumors. J Clin Oncol 32:5s, 2014 (suppl; abstr 2507).

25. Mol Cancer Ther. 2017 Aug 11. pii: molcanther.0374.2017. doi: 10.1158/1535-7163.MCT-17-0374. [Epub ahead of print] <https://www.ncbi.nlm.nih.gov/pubmed/28802255>

26. Poulsen TT, Grandal MM, Skartved NJØ, et al: Sym015: A highly efficacious antibody mixture against MET-amplified tumors. Clin Cancer Res. 2017 Oct 1;23(19):5923-5935.

27. Aftimos PG, Barthelemy P, Rolfo CD, et al: A phase I, first-in-human study of argx-111, a monoclonal antibody targeting c-met in patients with solid tumors. J Clin Oncol 33, 2015 (suppl; abstr 2580).

28. Camidge DR, Moran T, Demedts I, et al: A randomized, open-label, phase 2 study of emibetuzumab plus erlotinib (LY+E) and emibetuzumab monotherapy (LY) in patients with acquired resistance to erlotinib and MET diagnostic positive (MET Dx+) metastatic NSCLC. J Clin Oncol 34, 2016 (suppl; abstr 9070).

29. 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.

30. American Heart Association. Classification of Functional Capacity and Objective Assessment. Available at: http://my.americanheart.org/professional/StatementsGuidelines/ByPublicationDate/PreviousYears/Classification-of-Functional-Capacity-and-Objective-Assessment_UCM_423811_Article.jsp

31. Dela Cruz CS, Tanoue LT, and Matthay RA. Lung cancer: Epidemiology, etiology, and prevention. Clin Chest Med 2011; 32(4):doi:10.1016/j.ccm.2011.09.001.

32. Tong JH, Yeung SF, Chan AWH, et al. *MET* amplification and exon 14 splice site mutation define unique molecular subgroups of non-small cell lung carcinoma with poor prognosis. Clinical Cancer Research 2016; 22(12):3048-3056.

33. Ye S, Li, J, Hao K, et al. The efficacy and risk profile of c-Met inhibitors in non-small cell lung cancer: a meta-analysis. Scientific Reports 2016; 6:35770: doi:10.1038/srep35770.

34. Felip E, Horn L, Patel JD, et al. Tepotinib in patients with advanced non-small cell lung cancer (NSCLC) harboring *MET* exon 14-skipping mutations: Phase II trial. J Clin Oncol 2018; 36 (suppl; abstr 9016).

35. Wolf J, Seto T, Han J-Y, et al. Results of the GEOMETRYmono-1 phase II study for evaluation of the MET inhibitor capmatinib (INC280) in patients (pts) with METex14 mutated advanced non-small cell lung cancer (NSCLC). Annals of Oncology 2018, 29(8), https://doi.org/10.1093/annonc/mdy424.090.

20. APPENDICES

Appendix 1: Summary of Response Evaluation Criteria in Solid Tumors (RECIST v1.1)

For details, see Eisenhauer EA, Therasse P, Bogaerts J, et al (2009). New response evaluation criteria in solid tumours: Revised RECIST guideline (version 1.1). Eur J Cancer 45:228-247 (29)

Definitions

At baseline, tumor lesions/lymph nodes will be categorized as measurable or non-measurable as follows:

Measurable:

Tumor lesions: Must be accurately measured in at least one dimension (longest diameter in the plane of measurement is to be recorded) with a minimum size of:

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

Malignant lymph nodes: To be considered pathologically enlarged and measurable, a lymph node must be ≥ 15 mm in short axis when assessed by CT scan (CT scan slice thickness recommended to be no greater than 5 mm). At baseline and in follow-up, only the short axis will be measured and followed. See also notes below on "Baseline documentation of target and non-target lesions" for information on lymph node measurement.

Non-measurable:

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

Special considerations regarding lesion measurability:

Bone lesions, cystic lesions, and lesions previously treated with local therapy require particular comment:

Bone lesions

- Bone scan, PET scan, or plain films are not considered adequate imaging techniques to measure bone lesions. However, these techniques can be used to confirm the presence or disappearance of bone lesions
- Lytic bone lesions or mixed lytic-blastic lesions, with identifiable soft tissue components, that can be evaluated by cross sectional imaging techniques such as CT or MRI can be considered as measurable lesions if the soft tissue component meets the definition of measurability described above
- Blastic bone lesions are non-measurable

Cystic lesions

- Lesions that meet the criteria for radiographically defined simple cysts should not be considered as malignant lesions (neither measurable nor non-measurable) since they are, by definition, simple cysts
- "Cystic lesions" thought to represent cystic metastases can be considered as measurable lesions, if they meet the definition of measurability described above. However, if non-cystic lesions are present in the same patient, these are preferred for selection as target lesions

Lesions with prior local treatment

- Tumor lesions situated in a previously irradiated area, or other loco-regional therapy area, are usually not considered measurable unless there has been demonstrated progression in the lesion. Study protocols should detail the conditions under which such lesions would be considered measurable

Methods of measurement

Measurement of lesions

All measurements should be recorded in metric notation, using calipers if clinically assessed. All baseline evaluations should be performed as close as possible to the treatment start and never more than 4 weeks before the beginning of the treatment.

Method of assessment

The same method of assessment and the same technique should be used to characterize each identified and reported lesion at baseline and during follow-up. Imaging based evaluation should always be done rather than clinical examination unless the lesion(s) being followed cannot be imaged but are assessable by clinical exam.

- Clinical lesions: Clinical lesions will only be considered measurable when they are superficial and ≥10 mm diameter as assessed using calipers (e.g., skin nodules). For the case of skin lesions, documentation by color photography including a ruler to estimate the size of the lesion is suggested. As noted above, when lesions can be evaluated by both clinical exam and imaging, imaging evaluation should be undertaken since it is more objective and may also be reviewed at the end of the study

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

- CT, MRI: CT is the best currently available and reproducible method to measure lesions selected for response assessment. This guideline has defined measurability of lesions on CT scan based on the assumption that CT slice thickness is 5 mm or less. When CT scans have slice thickness greater than 5 mm, the minimum size for a measurable lesion should be twice the slice thickness. MRI is also acceptable in certain situations (e.g., for body scans)

- Ultrasound: Ultrasound is not useful in assessment of lesion size and should not be used as a method of measurement

- Endoscopy, laparoscopy: The utilization of these techniques for objective tumor evaluation is not advised. However, they can be useful to confirm complete pathological response when biopsies are obtained or to determine relapse in trials where recurrence following CR or surgical resection is an endpoint

- Tumor markers: Tumor markers alone cannot be used to assess objective tumor response

- Cytology, histology: These techniques can be used to differentiate between PR and CR in rare cases if required by protocol (for example, residual lesions in tumor types such as germ cell tumors, where known residual benign tumors can remain). When effusions are known to be a potential adverse effect of treatment (e.g., with certain taxane compounds or angiogenesis inhibitors), the cytological confirmation of the neoplastic origin of any effusion that appears or worsens during treatment can be considered if the measurable tumor has met criteria for response or SD in order to differentiate between response (or SD) and progressive disease

Tumor response evaluation

To assess objective response or future progression, it is necessary to estimate the overall tumor burden at baseline and use this as a comparator for subsequent measurements. Only patients with

measurable disease at baseline should be included in protocols where objective tumor response is the primary endpoint. Measurable disease is defined by the presence of at least one measurable lesion. Response criteria are listed in Table 12 and Table 13.

Table 12 Response Criteria for Evaluation of Target Lesions

	Evaluation of Target Lesions
Complete Response (CR)	Disappearance of all target lesions. Any pathological lymph nodes (whether target or non-target) must have reduction in short axis to <10 mm
Partial Response (PR)	At least a 30% decrease in the sum of diameters of target lesions, taking as reference the baseline sum diameters
Progressive Disease (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 diameters while on study

Table 13 Response Criteria for Evaluation of Non-Target Lesions

	Evaluation of Target Lesions
Complete Response (CR)	Disappearance of all non-target lesions and normalization of tumor marker level. All lymph nodes must be non-pathological in size (<10 mm short axis)
Progressive Disease (PD)	Unequivocal progression of existing non-target lesions. (Note: the appearance of one or more new lesions is also considered progression)
Non-CR/Non-PD	Persistence of one or more non-target lesion(s) and/or maintenance of tumor marker level above the normal limits

Evaluation of Best Overall Response

It is assumed that at each protocol specified time point, a response assessment occurs. Table 14 provides a summary of the overall response status calculation at each time point for patients who have measurable disease at baseline.

Table 14 Overall Response Status for Patients with Baseline Measurable 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

Abbreviation: CR, complete response; NE, non-evaluable; PD, progressive disease; PR, partial response; SD, stable disease

The best overall response is determined once all the data for the patient is known.

Best response determination in trials where confirmation of CR or PR is NOT required:

Best response in these trials is defined as the best response across all time points (for example, a patient who has SD at first assessment, PR at second assessment, and PD on last assessment has a best overall response of PR). When SD is believed to be best response, it must also meet the protocol specified minimum time from baseline. 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.

Best response determination in trials where confirmation of CR or PR 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 (generally 4 weeks later). In this circumstance, the best overall response can be interpreted as shown in Table 15.

Table 15 Best Overall Response when Confirmation of CR and PR Required

Overall Response First Time Point	Overall Response Subsequent Time Point	Best Overall Response
CR	CR	CR
CR	PR	SD, PD or PR[1]
CR	SD	SD provided minimum criteria for SD duration met, otherwise PD
CR	PD	SD provided minimum criteria for SD duration met, otherwise PD
CR	NE	SD provided minimum criteria for SD duration met, otherwise NE
PR	CR	PR
PR	PR	PR
PR	SD	SD
PR	PD	SD provided minimum criteria for SD duration met, otherwise PD
PR	NE	SD provided minimum criteria for SD duration met, otherwise NE
NE	NE	NE

Abbreviation: CR, complete response; NE, non-evaluable; PD, progressive disease; PR, partial response; SD, stable disease

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

21. SUMMARY OF CHANGES

21.1 Protocol Amendment 1 dated 17-Feb-2016

1. Modified Part 1 of the trial to make premedication mandatory prior to each dose of Sym015. Modified Part 2 of the trial to make premedication mandatory prior to each dose of Sym015 during Cycle 1
2. Modified the definition of dose-limiting toxicities
3. Modified protocol to discontinue therapy for all patients who meet Hy's Law criteria that cannot be explained by factors not related to Sym015
4. Included additional criteria for dose reduction due to toxicity
5. Allowed GnRH analogs in patients with prostate cancer

Refer to Table 16 for the changes in Protocol Amendment 1.

Table 16 Protocol Amendment 1

SECTION	ORIGINAL TEXT	NEW TEXT
1. Synopsis: Investigational Medicinal Product, Dose(s) and Treatment Schedule	Sym015 will be administered over a 1-hour (+10 minutes) period following delivery of premedication prior to the first infusion. If the patient is without evidence of infusion related reactions (IRRs) after the first dose of Sym015, the Investigator may opt to withdraw premedications with subsequent dosing.	For Part 1 of the trial, Sym015 will be administered over a 1-hour (+10 minutes) period, following delivery of premedication prior to each infusion. For Part 2 of the trial, Sym015 will be administered over a 1-hour (+10 minutes) period, following delivery of premedication prior to each infusion during Cycle 1. In Part 2, if the patient is without evidence of infusion related reactions (IRRs) after Cycle 1, the Investigator may opt to withdraw premedication on a patient-by-patient basis with subsequent dosing.
6.2 Exclusion Criteria	*Not applicable*	f. GnRH analogs in patients with prostate cancer
6.3.1 Withdrawal from Treatment with Sym015	*Not applicable*	Patients who meet Hy's Law criteria that cannot be explained by factors not related to Sym015…
7.1.4.3 Dose-Reduction for Sym015-Related Toxicities	1. Grade 3 non-hematologic toxicity regardless of duration, with the exceptions of: b. Grade 3 asymptomatic electrolyte abnormalities… 3. Neutropenia that is: a. Grade 3 or 4, associated with fever (ANC <1000 per mm^3; temperature >38.5ºC), and requiring antibiotic therapy b. Grade 4 and sustained (i.e. ANC <500 per mm^3, duration >5 days) 4. Thrombocytopenia that is Grade 4 (platelets <25,000 per mm^3)	1. Grade 3 non-hematologic toxicity regardless of duration, with the exceptions of: b. Grade 3 asymptomatic electrolyte abnormalities… without requiring hospitalization 3. Neutropenia that is: a. Grade 3-4 febrile neutropenia b. Grade 4 and sustained (i.e. ANC <500 per mm^3, duration >5 days) 4. Thrombocytopenia that is: a. Grade 3 with clinically significant hemorrhage b. Grade 4 (platelets <25,000 per mm^3)
7.2.1 Pre-Medication for Sym015 Infusions	Prior to the first infusion of Sym015, all patients will receive… If a patient is without evidence of IRRs after the first dose of Sym015, the Investigator may opt to withdraw premedications with subsequent dosing in order to determine whether such continued therapy is necessary in that patient. Where practical, it is recommended that withdrawal of premedication be	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. All patients will receive the following premedication… In Part 2, if a patient is without evidence of IRRs after

Table 16 Protocol Amendment 1		
SECTION	**ORIGINAL TEXT**	**NEW TEXT**
	done in a gradual fashion. For those patients who have previously experienced an IRR, consideration should be given to continuing premedications for at minimum 1 to 2 additional doses.	Cycle 1, the Investigator may opt to withdraw premedication on a patient-by-patient basis with subsequent dosing in order to determine whether such continued therapy is necessary in that patient. Where practical, it is recommended that withdrawal of premedication be done in a gradual fashion. For those patients who experienced symptoms suggestive of an IRR after Cycle 1, consideration should be given to continuing premedication for at minimum 1 to 2 additional doses before any future attempt to withdraw.
7.5.2 Prohibited Medication/ Therapy and Procedures During the Trial	*Not applicable*	o GnRH analogs in patients with prostate cancer
9.5.1 Definition of Dose-Limiting Toxicities	A DLT is defined as any of the following… 3. Neutropenia that is: a. Grade 3 or 4, associated with fever (ANC <1000 per mm^3; temperature >38.5ºC), and requiring antibiotic therapy b. Grade 4 and sustained (i.e. ANC <500 per mm^3, duration >5 days) 4. Thrombocytopenia that is Grade 4 (platelets <25,000 per mm^3)	A DLT is defined as any of the following... 3. Neutropenia that is: a. Grade 3-4 febrile neutropenia b. Grade 4 and sustained (i.e. ANC <500 per mm^3, duration >5 days) 4. Thrombocytopenia that is: a. Grade 3 with clinically significant hemorrhage b. Grade 4 (platelets <25,000 per mm^3) 5. AST/ALT elevation > 3xULN with bilirubin elevation > 2xULN that cannot be explained by factors not related to study drug

21.2 Protocol Amendment 2 dated 22-Feb-2016

1. Modified Part 1 of the trial to make *KRAS* mutation testing mandatory to include only patients with *KRAS* WT solid tumor malignancies

Refer to Table 17 for the changes in Protocol Amendment 2.

Table 17 Protocol Amendment 2		
SECTION	**ORIGINAL TEXT**	**NEW TEXT**
1. Synopsis: Phase and Overall Trial Design	Part 1 is a Phase 1a dose-escalation in patients with advanced solid tumor malignancies…	Part 1 is a Phase 1a dose-escalation in patients with Kirsten Rat Sarcoma (*KRAS*) wild-type (WT) advanced solid tumor malignancies…
1. Synopsis: Objectives	Primary objective of Part 1, Dose-Escalation: To assess… with advanced solid tumor malignancies…	Primary objective of Part 1, Dose-Escalation: To assess… with *KRAS* WT advanced solid tumor malignancies…
1. Synopsis: Overall Trial Design	During Part 1 of the trial, patients with advanced solid tumor malignancies…	During Part 1 of the trial, patients with *KRAS* WT advanced solid tumor malignancies…
1. Synopsis: Main Inclusion and Exclusion Criteria	*Not applicable*	**Main inclusion criteria all patients, Part 1 and Part 2:…** • Tumor documented to be *KRAS* WT by local assessment (i.e. the tumor must express the

Table 17 Protocol Amendment 2		
SECTION	**ORIGINAL TEXT**	**NEW TEXT**
		KRAS WT, exon 2, 3 and 4)
	Additional main inclusion criteria applicable to Part 2, Basket Cohort patients <u>ONLY</u>:… • Tumor documented to be without *KRAS* gene mutation by local assessment (i.e. the tumor must express the *KRAS* WT, exon 2, 3 and 4)	**Additional main inclusion criteria applicable to Part 2, Basket Cohort patients <u>ONLY</u>:…** *Removed indicated text under this heading*
	Additional main exclusion criteria applicable to Part 1, Dose-escalation cohort patients <u>ONLY</u>: • Patients with known *KRAS* gene mutation	*Removed heading and text*
1. Synopsis: Trial Assessments	**Disease Assessments** • Archival tumor tissue for *MET* and *KRAS* assessment: Not required for patients in Part 1, but tissue should be assessed if available...	**Disease Assessments** • Archival tumor tissue for *MET* and *KRAS* assessment: For patients in Part 1, local eligibility assessment for *KRAS* mutational status will be done. Assessment of *MET*-amplification status is not required for patients in Part 1, but tissue should be assessed if available...
4.1.1 Primary Objective	To assess… with advanced solid tumor malignancies…	To assess… with *KRAS* wild-type (WT) advanced solid tumor malignancies…
5.1 Overall Design and Plan	Part 1 is a Phase 1a dose-escalation in patients with advanced solid tumor malignancies… During Part 1, dose-escalation, cohorts of patients with advanced solid tumor malignancies…	Part 1 is a Phase 1a dose-escalation in patients with *KRAS* WT advanced solid tumor malignancies… During Part 1, dose-escalation, cohorts of patients with *KRAS* WT advanced solid tumor malignancies…
5.2.2 Rationale for Trial Population	In Part 1, patients with advanced solid tumor malignancies…	In Part 1, patients with *KRAS* WT advanced solid tumor malignancies…
6.1 Inclusion Criteria	6. <u>Part 2, Basket Cohort ONLY</u>:… c. Tumor documented to be without *KRAS* gene mutation by local assessment (i.e. the tumor must express the *KRAS* WT, exon 2, 3 and 4)	6. Tumor documented to be *KRAS* WT by local assessment (i.e. the tumor must express the KRAS WT, exon 2, 3 and 4) 7. <u>Part 2, Basket Cohort ONLY</u>:… *<u>Removed indicated text under this heading</u>*
6.2 Exclusion Criteria	2. <u>Part 1, dose-escalation cohorts ONLY</u>: Patients with known *KRAS* gene mutation	*Removed*
8.3.3 Archival Tumor Tissue for *MET* and *KRAS* Assessment	• Screening o Part 1: Not required; to be assessed if available	• Screening o Part 1: Local eligibility assessment for *KRAS* mutational status will be done. Assessment of *MET*-amplification status is not required for patients in Part 1, but tissue should be assessed if available.

21.3 Protocol Amendment 3 dated 02-May-2016

1. Modified inclusion criteria No. 6 to require *KRAS* mutation testing according to institutional standards in order to utilize the various testing platforms that are available at the participating trial sites
2. Modified Part 1 of the trial to include a tumor biopsy during screening for assessment of *KRAS* mutational status, if necessary for eligibility assessment
3. Modified Part 2 of the trial to include an ADA sample timepoint at C2/D1
4. Clarified that AEs/SAEs are reported from signing of informed consent for participation in the trial. Furthermore, clarified that patients who sign informed consent and are

subsequently deemed to be screening failures will be followed for AEs/SAEs until it is determined that they will not be participating in the trial

5. Clarified reporting requirements for safety data to Sponsor or designee
6. Clarified that the sample size considerations are based on a 2-stage design, not a 2-stage Minmax design

Refer to Table 18 for the changes in Protocol Amendment 3.

Table 18 Protocol Amendment 3

SECTION	ORIGINAL TEXT	NEW TEXT
1. Synopsis: Main Inclusion and Exclusion Criteria 6.1 Inclusion Criteria No. 6	Tumor documented to be *KRAS* WT by local assessment (i.e. the tumor must express the *KRAS* WT, exon 2, 3 and 4)	Tumor documented to be *KRAS* WT by local assessment according to institutional standards. If *KRAS* WT is not previously documented and if archival tissue is not available for pretrial assessment, patient must be willing to undergo a tumor biopsy to confirm eligibility
1. Synopsis: Trial Assessments	**Safety Assessments** DLT evaluation (Part 1, dose-escalation only) during Cycle 1 with a final assessment on scheduled first day of Cycle 2, prior to dosing **Disease Assessments** For patients in Part 1, local eligibility assessment for *KRAS* mutational status will be done. Tumor biopsy (optional for patients in Part 1 with known *MET*-amplification; required for patients in Part 2): **Additional Assessments** Skin biopsy	**Safety Assessments** DLT evaluation (Part 1, dose-escalation only) during Cycle 1 with a final assessment 14 (±2) days (Q2W dosing) or 21 (±2) days (Q3W dosing) after the last dose of Cycle 1 or prior to dosing on Cycle 2/Day 1 (C2/D1) **Disease Assessments** For patients in Part 1, local eligibility assessment for *KRAS* mutational status will be done using archival tissue whenever possible. If archival tissue is not available, a tumor biopsy will be performed for eligibility assessment. Tumor biopsy to be assessed locally as part of eligibility assessment for Part 1 and Part 2 patients, if applicable. In addition, to be assessed centrally for biomarker analysis (optional for patients in Part 1 with known *MET*-amplification; required for patients in Part 2): **Additional Assessments** Skin biopsy for biomarker analysis
1. Synopsis: Statistical Methods and Sample Size Calculation 10.1 Sample Size Determination	Sample size considerations are based on a 2-stage MinMax design, testing a null hypothesis…	Sample size considerations are based on a 2-stage design, testing a null hypothesis…
5.3.1 Screening	Furthermore, once eligibility is confirmed: • All patients in Part 1 and 2 will have a blood sample taken for exploratory biomarker analysis • All patients in Part 1 and 2 will have a skin biopsy performed • Patients in Part 1 with known *MET*-amplification who consent to optional biopsies will have a biopsy performed, unless it is confirmed that suitable archival tissue is available for central analysis	Furthermore, once eligibility is confirmed: • Patients in Part 1 with known *MET*-amplification who consent to optional biopsies will have a biopsy performed for biomarker analysis (archival tissue or tissue from a biopsy performed during screening as part of eligibility assessment may be submitted) • All patients in Part 2 will have a tumor biopsy performed for biomarker analysis (archival tissue or tissue from a biopsy performed during screening as part of eligibility assessment may

Table 18 Protocol Amendment 3		
SECTION	**ORIGINAL TEXT**	**NEW TEXT**
	• All patients in Part 2 will have a tumor biopsy performed, unless it is confirmed that suitable archival tissue is available for central analysis Note: The tumor biopsy at screening may be assessed locally as part of eligibility assessment in Part 2 patients for whom *MET*-amplification and *KRAS* mutational status have not previously been assessed and no archival tissue is available	be submitted) • All patients in Part 1 and 2 will have a skin biopsy performed for biomarker analysis • All patients in Part 1 and 2 will have a blood sample taken for biomarker analysis
8.1.1 Signing of Informed Consent	*Not applicable*	Note: Informed consent may be obtained outside the 14-day screening period prior to C1/D1
8.2.2 Adverse Events Survey	Starting from signing of informed consent	Starting from signing of informed consent for participation in the trial
8.2.2 Adverse Events Survey 9.2.1 Adverse Event Recording Period 9.2.6 Follow-up of Adverse Events 9.3 Serious Adverse Event Recording and Reporting 10.4.3.1 Adverse Events	*Not applicable*	Note: Patients who sign informed consent and are subsequently deemed to be screening failures will be followed for the occurrence of SAEs/AEs until it is determined that they will not be participating in the trial.
8.2.3 Dose-Limiting Toxicities Evaluation (Part 1 Only)	Reported during Cycle 1 with final assessment on scheduled Day 1 of Cycle 2 (C2/D1)	Reported during Cycle 1 with a final assessment 14 (±2) days (Q2W dosing) or 21 (±2) days (Q3W dosing) after the last dose of Cycle 1 or prior to dosing on C2/D1
8.3.3 Archival Tumor Tissue for *MET* and *KRAS* Assessment	To be assessed locally, if tissue is available… • Screening o Part 1: Local eligibility assessment for *KRAS* mutational status will be done. Assessment of *MET*-amplification status is not required for patients in Part 1… o Part 2: Local eligibility assessment…	To be assessed locally… • Screening o Part 1: Eligibility assessment for *KRAS* mutational status will be done using archival tumor tissue, whenever possible. If archival tissue is not available, tissue from a tumor biopsy performed during screening will be used. Assessment of *MET*-amplification status is not required… o Part 2: Eligibility assessment…
8.3.4 Tumor Biopsy for Eligibility Assessment and Biomarker Analysis	To be assessed centrally. In addition; to be assessed locally as part of eligibility assessment for Part 2 patients, if applicable as per Section 8.3.3. Archival tissue may be accepted for central analysis if suitable as specified in the laboratory manual. It must be ensured that the archival tissue can be made available to the central laboratory prior to deciding to omit the tumor biopsy procedure at time of screening.	To be assessed locally for eligibility: • Screening; Part 1 and Part 2, if applicable as per Section 8.3.3 Note: It will be permissible to perform this procedure outside the 14-day screening period, provided informed consent has been obtained To be assessed centrally for biomarker analysis: • Screening

Table 18 Protocol Amendment 3		
SECTION	**ORIGINAL TEXT**	**NEW TEXT**
	• Screening o Part 1:… o Part 2:…	o Part 1:… o Part 2:… Note: Archival tissue may be accepted for central analysis if suitable as specified in the laboratory manual…
8.5 Anti-Drug Antibody Testing	*Not applicable*	*Added additional timepoint:* • C2/D1 (Part 2 only)
9.2.1 Adverse Event Recording Period	All AEs will be recorded from signing of informed consent.	All AEs will be recorded from signing of informed consent for participation in the trial.
9.3 Serious Adverse Event Recording and Reporting	All SAEs occurring at any time from signing of informed consent and until the 1M FUP Visit, must be recorded…	All SAEs occurring at any time from signing of informed consent for participation in the trial and until the 1M FUP Visit must be recorded…
9.5.2 Observation Period for Dose-Limiting Toxicities	The observation period for DLTs is defined as Cycle 1, i.e. the initial 28-day (± 2 days) period of Q2W dosing or 42-day (± 2 days) period of Q3W dosing, starting from C1/D1.	The observation period for DLTs is defined as Cycle 1 with a final assessment 14 (±2) days (Q2W dosing) or 21 (±2) days (Q3W dosing) after the last dose of Cycle 1 or prior to dosing on C2/D1.
9.5.3 Reporting of Dose-Limiting Toxicities	All presumed DLTs must be reported in the eCRF within 24 hours…	All presumed DLTs must be reported to the Sponsor or designee within 24 hours…
9.6 Reporting of Infusion-Related Reactions	To facilitate ongoing safety review… in the eCRF within 24 hours of occurrence.	To facilitate ongoing safety review… to the Sponsor or designee within 24 hours of occurrence.
10.4.3.1 Adverse Events	AEs including SAEs are reported from signing of the informed consent and until the end of trial participation	AEs including SAEs are reported from signing of the informed consent for participation in the trial and until the end of trial participation.
12.1 Safety Review	In order to do so, the Investigator must ensure the data in the eCRF is up to date at all times. This includes, but is not limited to: • SAEs must be reported within 24 hours of awareness (SAE report form and eCRF) • DLTs must be reported in the eCRF within 24 hours of occurrence • Grade 2 IRRs must be reported in the eCRF within 24 hours of occurrence… …Such Safety Team teleconferences may fluctuate in frequency based on accrual and trial activity, as indicated…	In order to do so, the Investigator must ensure to report safety data to the Sponsor or designee in a timely manner. This includes, but is not limited to: • SAEs must be reported within 24 hours of awareness (SAE report form) • DLTs must be reported within 24 hours of occurrence • IRRs of ≥ Grade 2 must be reported within 24 hours of occurrence… …Such safety teleconferences may fluctuate in frequency based on accrual and trial activity, as indicated…

21.4 Protocol Amendment 4 dated 04-Nov-2016

1. Modified the overall trial design by moving the Q3W cohort from Part 1 to Part 2 to ensure patients with *MET*-amplification are treated in this cohort and thereby introducing a Q2W Basket Cohort as well as a Q3W Basket Cohort in Part 2
2. Updated trial objectives, trial endpoints and patient numbers according to the change in overall trial design
3. Allowed 6-12 patients to be included in the Q3W Basket Cohort
4. Confirmed the selection of the Q2W RP2D as 18 mg/kg loading dose infused over 1.5 hours on C1/D1 followed by Q2W maintenance doses of 12 mg/kg infused over 1 hour beginning on C1/D15
5. Modified select inclusion criteria

6. Modified and/or deleted select exclusion criteria
7. Clarified that a trial site may choose to prescreen patients utilizing archival tumor tissue to confirm *MET*-amplification status and/or *KRAS* mutational status before entering patients into screening for the treatment portion of the trial
8. Modified the Sym015 infusion time to 1.5 hour (+10 minutes) for doses ≥18 mg/kg
9. Clarified preference for the eligibility assessment for *MET*-amplification be done using tissue from a tumor biopsy performed during screening and that this biopsy be submitted to the central laboratory
10. Removed skin biopsies from Part 2 of the trial
11. Updated dose-delay criteria #4
12. Clarified one of the dose-limiting toxicities (#2)
13. Updated dose-reduction criteria #2 and #5 to be in accordance with dose-limiting toxicity criteria
14. Included overall survival status in the continued follow-up after the 1M FUP Visit and adjusted the follow-up schedule to be every 2 months
15. Updated events not to be considered as AEs to include PD, unless the nature of the PD is different than expected
16. Updated timelines for reporting of SAE Follow-up information
17. Updated sample size determination to be based on a Simon's Optimal 2-stage design. Futility will be performed when 20 patients evaluable for OR have been included in the Q2W Basket Cohort
18. Made updates and clarifications to the secondary endpoints and PK endpoints

Refer to Table 19 for the changes in Protocol Amendment 4.

Table 19 Protocol Amendment 4

SECTION	ORIGINAL TEXT	NEW TEXT
1. Synopsis: Phase and Overall Trial Design	Part 2 is a Phase 2a dose-expansion, in which the recommended phase 2 dose (RP2D) and regimen will be explored in a Basket Cohort of patients with *MET*-amplified, *KRAS* WT solid tumor malignancies without available therapeutic options…	Part 2 is a Phase 2a dose-expansion in patients with *MET*-amplified, *KRAS* WT solid tumor malignancies without therapeutic options. Two cohorts will be included: o Q2W Basket Cohort: A cohort of approximately 45 patients… o Q3W Basket Cohort: A cohort of 6-12 patients…
1. Synopsis: Trial Site and Countries	Part 2, Basket Cohort: 15 to 20 investigational trial sites…	Part 2: 15 to 20 investigational trial sites… Enrollment to the Q3W Basket Cohort is expected to take place at select sites only.
1. Synopsis: Planned Trial Period	Patients will be enrolled in dose-escalation cohorts until establishment of a RP2D and regimen, expected by Q2 2017. Enrollment to the Basket Cohort in Part 2 of the trial will commence once the RP2D and regimen has been established. Enrollment is expected completed by Q3 2018. The end of trial will be reached... Patients with stable disease (SD) or an ongoing objective response…at that time will continue to be followed to assess duration of disease stabilization or response.	Patients will be enrolled in dose-escalation cohorts until establishment of a maximum tolerated dose (MTD) or until 24 mg/kg has been evaluated, whichever comes first, expected by Q1 2017. Enrollment to Part 2 of the trial will commence upon establishment of the Q2W RP2D. Enrollment is expected to complete by Q3 2018. The end of trial will be reached… Patients will continue to be followed to assess duration of disease stabilization, response, and overall survival (OS).
1. Synopsis: Objectives	Primary objective of Part 1, Dose-Escalation: To assess the safety and tolerability… to patients…	Primary objective of Part 1, Dose-Escalation: To assess the safety and tolerability… on a Q2W schedule to patients…

Table 19 Protocol Amendment 4		
SECTION	**ORIGINAL TEXT**	**NEW TEXT**
4.1.1 Primary Objective 4.2.1 Primary Objective	Primary objective of Part 2, Basket Cohort: To evaluate the antitumor activity of Sym015 when administered at the RP2D and regimen….	Primary objective of Part 2: To evaluate the antitumor activity of Sym015 when administered at the Q2W RP2D…
1. Synopsis: Endpoints	Primary Endpoint of Part 1, Dose-Escalation: The occurrence of dose-limiting toxicities (DLT) measured during Cycle 1 of Sym015 administration on an every second week (Q2W, 28 days equals 1 cycle) or every third week (Q3W, 42 days equals 1 cycle) dosing schedule. Primary Endpoint of Part 2, Basket Cohort: Documented OR (defined as PR or CR)…	Primary Endpoint of Part 1, Dose-Escalation: The occurrence of dose-limiting toxicities (DLT) measured during Cycle 1 of Sym015 administration on a Q2W (28 days equals 1 cycle) dosing schedule. Primary Endpoint of Part 2: Documented objective response (OR) (defined as partial response [PR] or complete response [CR]) in the Q2W Basket Cohort…
1. Synopsis: Overall Trial Design	During Part 1 of the trial, patients… will receive increasing doses of Sym015 until establishment of a RP2D and regimen to be used in Part 2… Patients will be assigned to the next available open treatment cohort until establishment of the RP2D and regimen…The highest dose level tested and evaluated to be safe will be explored… The second-highest dose level tested will be expanded…	During Part 1 of the trial, patients… will receive increasing doses of Sym015 on a Q2W schedule until establishment of the MTD or until 24 mg/kg has been evaluated…
	The SMC will review clinical and laboratory safety data regularly throughout the trial and will select the RP2D and regimen to be used in Part 2…	The SMC will review clinical and laboratory safety data regularly throughout the trial. The SMC will select the Q2W RP2D and the highest safe dose for the Q3W regimen to be used in Part 2…
	During Part 2, the RP2D and regimen will be evaluated in a Basket Cohort of patients with *MET*-amplified, *KRAS* WT advanced solid tumor malignancies.	During Part 2, basket cohorts of patients with *MET*-amplified, *KRAS* WT advanced solid tumor malignancies will be evaluated: Q2W Basket Cohort administering the Q2W RP2D on a Q2W dosing schedule and Q3W Basket Cohort administering the highest safe dose tested in Part 1 on a Q3W dosing schedule.
1. Synopsis: Trial Periods 6.3.2 Withdrawal from Trial 8.9 Follow-up Assessments	In the event of an ongoing SD or OR as per RECIST v1.1 at the 1M FUP Visit, the Investigator will make every effort to obtain follow-up information on response assessments every 3 months during the first year and every 6 months thereafter, until disease progression or another therapeutic intervention is initiated.	After the 1M FUP Visit, the Investigator will make every effort to obtain follow-up information on response assessment and/or OS, every 2 months. Response assessment follow-up is required in the event of an ongoing stable disease (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, or termination of the trial.
1. Synopsis: Number of Patients	It is planned to enroll approximately 70 patients… Approximately 21-25 patients… during Part 1. Approximately 45 patients… during Part 2.	It is planned to enroll approximately 63-72 patients… Approximately 12-15 patients… during Part 1. Approximately 51-57 patients… during Part 2.
1. Synopsis: Main Inclusion and Exclusion Criteria 6.1 Inclusion Criteria	**Additional main inclusion criteria applicable to Part 2, Basket Cohort patients <u>ONLY</u>:** • Confirmed *MET*-amplification by local assessment; i.e… • Willingness to undergo… (total of 2 biopsies)…	**Additional main inclusion criteria applicable to Part 2 patients <u>ONLY</u>:** • Confirmed *MET*-amplification by local assessment; i.e… silver *in situ* hybridization (SISH)… • Willingness to undergo… (maximum of 2 biopsies)…
1. Synopsis: Main Inclusion and Exclusion Criteria	**Main exclusion criteria all patients, Part 1 and Part 2:** • Known central nervous system (CNS) or leptomeningeal metastases not controlled by prior surgery or radiotherapy, or symptoms	**Main exclusion criteria all patients, Part 1 and Part 2:** • Central nervous system (CNS) malignancy including primary malignancies of the CNS and/or known CNS or leptomeningeal… • Abnormal hematologic, renal or hepatic function

Table 19 Protocol Amendment 4		
SECTION	**ORIGINAL TEXT**	**NEW TEXT**
6.2 Exclusion Criteria	suggesting CNS involvement for which treatment is required • Abnormal hematologic, renal or hepatic function as defined by the following criteria: o Prothrombin time… institution o Partial thromboplastin time (PTT)… institution • Known history of human immunodeficiency virus (HIV) infection • Known active hepatitis B or C virus infection	as defined by the following criteria: o Prothrombin time… institution* o Partial thromboplastin time (PTT)… institution* *Unless on a stable dose of anticoagulant therapy for a prior thrombotic event *Removed known history of HIV infection* *Removed known active hepatitis B or C virus infection*
	Additional main exclusion criteria applicable to Part 2, Basket Cohort patients <u>ONLY</u>: Radiotherapy against target lesions within 4 weeks prior to C1/D1	**Additional main exclusion criteria applicable to Part 2 patients <u>ONLY</u>:** • Prior therapy with antibody to hepatocyte growth factor (HGF) • Radiotherapy against…unless there is documented progression of the lesion following the radiotherapy
1. Synopsis: Investigational Medicinal Product, Dose(s) and Treatment Schedule	Note: Q3W dosing is implemented after highest… For Part 1 of the trial, Sym015 will be administered over a 1-hour (+10 minutes) period, following delivery of premedication prior to each infusion. For Part 2 of the trial, Sym015 will be administered over a 1-hour (+10 minutes) period, following delivery of premedication prior to each infusion during Cycle 1.	Note: Q3W dosing is implemented in Part 2 after highest… Sym015 will be administered over a 1.5-hour (+10 minutes) period for doses ≥18 mg/kg and over a 1 hour (+10 minutes) period for doses <18 mg/kg, following delivery of premedication prior to each infusion.
	Part 1/Dose-Escalation During the dose-escalation part of the trial, the following dose levels… Dosing will be on a Q2W schedule for all cohorts until completion of Dose Level 4 or establishment of an MTD, whichever comes first. At this point, a Q3W schedule will be evaluated…	**Part 1/Dose-Escalation** During the dose-escalation part of the trial, the following dose levels of Sym015 administered Q2W…
	Part 2/Basket Cohort Once the RP2D and regimen has been established during dose-escalation, the enrollment into the Basket Cohort will commence. All patients enrolled to the Basket Cohort will be treated with the established RP2D on the selected dosing schedule of Sym015 (Q2W or Q3W).	**Part 2** Once the Q2W RP2D has been established during dose-escalation, the enrollment into the Q2W Basket Cohort will commence. <u>Note:</u> Effective with clinical trial protocol (CTP) version 5.0 (November 2016), following review… Once the highest safe dose tested in Part 1 has been determined, all patients in the Q3W Basket Cohort will be treated at that dose level on a Q3W dosing schedule.
1. Synopsis: Trial Assessments	**Safety Assessments** • Medication survey • DLT evaluation (Part 1, dose-escalation only) during Cycle 1 with a final assessment 14 (±2) days (Q2W dosing) or 21 (±2) days (Q3W dosing)…	**Safety Assessments** • Medication/Procedure survey • DLT evaluation (Part 1, dose-escalation only) during Cycle 1 with a final assessment 14 (±2) days…
1. Synopsis: Trial Assessments	**Disease Assessments** Archival tumor tissue for *MET* and *KRAS* assessment:	**Disease Assessments** Archival tumor tissue for *MET* and *KRAS* assessment:

Table 19 Protocol Amendment 4		
SECTION	**ORIGINAL TEXT**	**NEW TEXT**
8.3.4 Tumor Biopsy for Eligibility Assessment and Biomarker Analysis	○ For patients in Part 2, local eligibility assessment for *MET*-amplification and *KRAS* mutational status will be done using archival tumor tissue whenever possible… Tumor biopsy to be assessed locally as part of eligibility assessment for Part 1 and Part 2 patients… ○ Q2W dosing… Archival tissue may be acceptable at screening, if suitable for central analysis ○ Q3W dosing… Archival tissue may be acceptable at screening, if suitable for central analysis	○ For patients in Part 2, local eligibility assessment for *KRAS* mutational status may be done using archival tumor tissue… It is preferred that the eligibility assessment for *MET*-amplification will be done using tissue from a tumor biopsy performed during screening… Tumor biopsy to be assessed locally as part of eligibility assessment for Part 1 and Part 2 patients… ○ Q2W dosing: At screening and at the end… ○ Q3W Basket Cohort: At screening and at the end… Tissue from a tumor biopsy performed during screening is preferred, however archival tissue may be submitted for central analysis…
1. Synopsis: Trial Assessments	**Additional Assessments** Skin biopsy for biomarker analysis: ○ Q2W dosing: At screening, at the end… ○ Q3W dosing: At screening and at the end…	**Additional Assessments** Part 1 only: Skin biopsy for biomarker analysis at screening, at the end of Cycle 2 or upon PD, whichever comes first
1. Synopsis: Statistical Methods and Sample Size Calculation 10.1 Sample Size Determination 10.3.1 Part 1, Dose-Escalation 10.3.2 Part 2 10.5 Interim Analysis	Based on a 3 + 3 design and inclusion of a Q3W cohort, it is planned to enroll between 21 and 25 patients during dose-escalation. Based on an overall evaluation of the dose-escalation part, the RP2D and regimen to be used in Part 2 will be selected. In Part 2 of the trial, the primary endpoint is documented OR, assessed by RECIST v1.1 at any time during trial participation by Investigator assessment. It is planned to include… Sample size considerations are based on a 2-stage design, testing a null hypothesis (poor response) of 10% OR versus an alternative hypothesis (promising response) of 25% OR at an approximate 5% 1-sided significance level and 80% power…	Based on a 3+3 design, it is planned to enroll between 12 and 15 patients during dose-escalation. Based on an overall evaluation of the dose-escalation part, the Q2W RP2D and highest safe dose tested will be selected. In Part 2 of the trial, the primary endpoint is documented OR in the Q2W Basket Cohort, assessed by RECIST v1.1 at any time during trial participation by Investigator assessment. It is planned to include… in this cohort. Sample size considerations are based on Simon's Optimal 2-stage design, testing a null hypothesis (poor response) of 11% OR versus an alternative hypothesis (promising response) of 25% OR at an approximate 10% 1-sided significance level and 85% power… For the Q3W Basket Cohort, assuming the response rate is at least 20%, there is a 74-93% probability of observing 1 or more responses in 6-12 patients.
3.2.4.1 Protocol Sym015-01	This is the first clinical trial to study Sym015.	*Addition of new section heading* This is the first clinical trial to study Sym015. As of 19 October 2016, a total of 9 patients have been enrolled in this trial…
3.2.4.2 Other Monoclonal Antibodies Targeting MET	*Section heading did not previously exist* Based on available literature/reports…	*Addition of new section heading only* Based on available literature/reports…
3.4.1 Rationale for Starting Dose	*Section heading did not previously exist* The starting dose of Sym015…	*Addition of new section heading* The starting dose of 6 mg/kg Sym015…
3.4.2 Rationale for Recommended Phase 2 Dose	*Section did not previously exist*	As of 19 October 2016, following review of available safety… *Addition of new Table 1: Preliminary Sym015 Geometric Mean PK Parameters*
3.5 Overall Benefits/Risk	If the dose administered in a cohort is safe… to establish a recommended phase 2 dose (RP2D) and regimen.	If the dose administered in a cohort is safe… to establish a Q2W RP2D and to define an MTD or highest safe dose.

Table 19 Protocol Amendment 4		
SECTION	**ORIGINAL TEXT**	**NEW TEXT**
4.1.2 Secondary Objectives	1. To determine a RP2D and regimen of Sym015	1. To determine a Q2W RP2D of Sym015
4.2.2 Secondary Objectives	1. To further evaluate the safety… 2. To further evaluate the PK… 3. To further evaluate target-engagement in skin biopsy tissue 4. To further evaluate the immunogenicity… 5. To further evaluate potential pharmacodynamic…	1. To further evaluate the safety… when administered at the Q2W RP2D 2. To further evaluate the PK… when administered at the Q2W RP2D 3. To further evaluate the immunogenicity… when administered at the Q2W RP2D 4. To further evaluate potential pharmacodynamic… when administered at the Q2W RP2D 5. To make a preliminary evaluation of the antitumor activity of Sym015, and to evaluate…
5.1 Overall Design and Plan	Part 2 is a Phase 2a dose-expansion, in which the RP2D and regimen will be explored in a Basket Cohort of patients with *MET*-amplified, *KRAS* WT solid tumor malignancies without available therapeutic options. During Part 1… doses of Sym015 until establishment of a RP2D and regimen to be used in Part 2.	Part 2 is a Phase 2a dose-expansion in patients with *MET*-amplified, *KRAS* WT solid tumor malignancies without therapeutic options. Two cohorts will be included: o A Basket Cohort of approximately 45 patients… o A Basket Cohort of 6-12 patients… During Part 1… doses of Sym015 on a Q2W schedule until establishment of the MTD or until 24 mg/kg has been evaluated.
	Dosing will be on a Q2W schedule for all cohorts until completion of Dose Level 4 or establishment of an MTD, whichever comes first. At this point, a Q3W schedule will be evaluated in 6 patients at the highest safe dose tested. Furthermore, the dose level below the highest safe dose will be expanded to 6 patients on a Q2W schedule, if this has not already been done.	*Removed*
	The SMC will… select the RP2D and regimen to be used in Part 2 based on safety data, as well as available PK and target engagement results in skin tissue biopsies.	The SMC will… select the Q2W RP2D and the highest safe dose for the Q3W regimen to be used in Part 2 based on safety data and available PK results. Note: Effective with CTP 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…
	During Part 2, the RP2D and regimen will be evaluated in a Basket Cohort of patients with *MET*-amplified, *KRAS* WT, advanced solid tumor malignancies.	During Part 2, basket cohorts of patients with *MET*-amplified, *KRAS* WT, advanced solid tumor malignancies will be evaluated: Q2W Basket Cohort administering the Q2W RP2D on a Q2W schedule and Q3W Basket Cohort administering the highest safe dose tested in Part 1 on a Q3W schedule. Enrollment to the Q3W Basket Cohort is expected to take place at select trial sites only.
5.2.1 Rationale for Trial Design	The trial is designed to select a safe and well-tolerated dose of Sym015 on a Q2W basis (3 to 6 patients to be treated at the highest safe dose and 6 patients to be treated at the next lower dose) and also to explore the safety of a Q3W dosing schedule at the highest safe dose (6 patients). Part 2 of this trial is designed…	This part of the trial is designed to select a safe and well-tolerated dose of Sym015 on a Q2W schedule. Part 2 of this trial is designed…
5.3.1 Prescreening for *MET*-	*Section did not previously exist*	The trial site may choose to prescreen patients utilizing archival tumor tissue to confirm *MET*-amplification status and/or *KRAS* mutational status before entering patients into

Table 19 Protocol Amendment 4		
SECTION	**ORIGINAL TEXT**	**NEW TEXT**
amplification and *KRAS* Mutational Status		screening for the treatment portion of the trial. In this case, the site will use a separate pre-screening informed consent form…
5.3.2 Screening	This number is composed… Furthermore, once eligibility is confirmed: • All patients in Part 2 will have a tumor biopsy performed for biomarker analysis (archival tissue or tissue from a biopsy performed during screening as part of eligibility assessment may be submitted) • All patients in Part 1 and 2 will have a skin biopsy performed for biomarker analysis	This number will identify the patient throughout the trial and will be composed… Furthermore, once eligibility is confirmed: • All patients in Part 2 will have a tumor biopsy performed for biomarker analysis (tissue from a biopsy performed during screening as part of eligibility assessment is preferred…, however archival tissue may be submitted at the Investigator's discretion) • All patients in Part 1 will have a skin biopsy…
5.3.4 Treatment	*Heading previously 5.3.3* Patients in Part 1 will receive infusions of Sym015 Q2W at the specified dose level until… During Part 2, all patients will receive the RP2D of Sym015…	*Removed* *Removed*
5.3.5 End of Treatment and Follow-up Visits	*Heading previously 5.3.4* In the event of an ongoing stable disease (SD) or objective response (OR, defined as partial response [PR] or complete response [CR])…	After the 1M FUP Visit, the Investigator will make every effort to obtain follow-up information on response assessment and/or overall survival (OS) every 2 months. Response assessment follow-up is required… Survival follow-up is required until…
5.4 Recruitment Period	Patients will be sequentially enrolled to dose-escalation cohorts until establishment of a RP2D and regimen, expected by Q2 2017. Enrollment to the Basket Cohort in Part 2 of the trial will commence once the RP2D and regimen have been established. Enrollment is expected completed by Q3 2018.	Patients will be sequentially enrolled to dose-escalation cohorts until completion of Dose Level 4 or establishment of an MTD, whichever comes first, expected by Q1 2017. Enrollment to Part 2 of the trial will commence upon establishment of the Q2W RP2D. Enrollment is expected to complete by Q3 2018.
5.5 Number of Patients	In total, approximately 70 patients will be included in this trial. It is estimated that approximately 21-25 patients… Sym015 and occurrence of discontinuation of patients during the DLT observation period for reasons other than toxicity. It is planned to enroll and treat approximately 45 patients with documented and confirmed MET-amplified and KRAS WT advanced solid tumor malignancies during Part 2.	In total, approximately 63-72 patients will be included in this trial. It is estimated that approximately 12-15 patients… Sym015 and the potential for adding additional patients to a cohort to assure a sufficient number of evaluable patients per cohort… During Part 2, it is planned to enroll and treat approximately 45 patients in the Q2W Basket Cohort and 6-12 patients in the Q3W Basket Cohort…
5.6 End of Trial	Patients with SD or an ongoing OR at that time will continue to be followed to assess duration of disease stabilization or response.	Patients will continue to be followed to assess duration of disease stabilization, response and/or overall survival.
7.1.3.2 Part 1, Dose-Escalation	Dosing will be on a Q2W schedule for all cohorts until completion of Dose Level 4 or establishment of an MTD, whichever comes first. At this point, a Q3W schedule…	*Removed*
	Not applicable	There is potential for entry of additional patients in the dose-escalation portion of the trial to assure a sufficient number of evaluable patients per cohort…

Table 19 Protocol Amendment 4		
SECTION	**ORIGINAL TEXT**	**NEW TEXT**
		Note: Should this action be taken, cohort tolerability assessment and subsequent dose-escalation…
	If the MTD is declared, 6 patients will be included on a Q3W dosing schedule at the MTD…	*Removed*
	If no DLTs are encountered in any of the first 3 patients at Dose Level 4, 6 patients will be included on a Q3W dosing schedule…	If no DLTs are encountered in any of the first 3 patients at Dose Level 4, 24 mg/kg will be considered the highest safe dose tested
	The SMC will review safety data and make decisions regarding the advisability of; continuing accrual to a particular dose cohort; dose-escalation and accrual of patients to a higher dose cohort; and the RP2D and regimen to be used in Part 2, the Basket Cohort.	The SMC will review safety data throughout the trial. During Part 1, the SMC will make decisions regarding the advisability of: continuing accrual to a particular dose cohort; dose-escalation and accrual of patients to a higher dose cohort; and the doses to be used in Part 2…
7.1.3.3 Part 2	During Part 2 of this trial, all patients will receive the RP2D of Sym015 on the chosen dosing schedule (Q2W or Q3W).	During Part 2 of this trial, patients included in the Q2W Basket Cohort will receive the Q2W RP2D of Sym015 on a Q2W dosing schedule. Patients included in the Q3W Basket Cohort… The SMC will continue to review safety data and assess the tolerability of Sym015 during Part 2 of the trial.
7.1.3.4 Duration of Infusion for Administration of Sym015	Sym015 will be administered over a 1-hour (+10 minutes) period following delivery of premedication… In the event of a Grade 2 IRR… entered to the trial will be extended to 1.5 hours (+10 minutes) (or longer, if indicated) In the event of a Grade 3 or greater IRR… entered to the trial will be extended to 1.5 hours (+10 minutes) (or longer, if indicated)… These same criteria will be applied in the event IRRs occur on the extended 1.5 hours infusion schedule. In such a case, the duration of infusion for subsequent patients entered to the trial will be extended to 2 hours (or longer, if indicated).	Sym015 will be administered over a 1.5-hour (+10 minutes) period for doses $\geq$ 18 mg/kg, and over a 1 hour (+10 minutes) period for doses <18 mg/kg, following… Note: Effective with CTP version 5.0 (November 2016), the duration of infusion has been extended to 1.5 hours… In the event of a Grade 2 IRR... entered at that dose and higher doses will be extended from 1 hour (+10 minutes) to 1.5 hours (+10 minutes) (or longer, if indicated) Note: This action was implemented 13Sep2016 and applies to doses $\geq$ 18 mg/kg. In the event of a Grade 3 or greater IRR… entered at that dose and higher doses will be extended from 1 hour (+10 minutes) to 1.5 hours (+10 minutes) (or longer, if indicated)…. These same criteria will be applied in the event IRRs occur on the extended 1.5 hours infusion schedule. In such a case, the duration of infusion for subsequent patients entered at that dose and higher doses will be extended to 2 hours (or longer, if indicated).
7.1.4.2 Dose-Delays for Sym015-Related or Disease-Related Toxicities	4. Any ongoing AEs, assessed as possibly, probably, or related to Sym015, should have either ameliorated to $\leq$ Grade 1 severity, returned to baseline status, or resolved with the exception of laboratory abnormalities that are considered clinically insignificant	4. Any ongoing AEs, assessed as possibly, probably, or related to Sym015… with the exception of Grade 2 clinical events that are being adequately controlled with best supportive care (e.g. nausea, vomiting, diarrhea, fatigue) and asymptomatic laboratory abnormalities that are considered clinically insignificant or that are resolving with medical therapy
7.1.4.3 Dose-Reduction for Sym015-Related Toxicities	2. Any Grade 4 non-hematologic toxicity	2. Any Grade 4 non-hematologic toxicity, with the exception of: b. Grade 4 asymptomatic electrolyte abnormalities lasting $\leq$ 3 days that are not considered clinically

Table 19 Protocol Amendment 4		
SECTION	**ORIGINAL TEXT**	**NEW TEXT**
9.5.1 Definition of Dose-Limiting Toxicities		relevant by the Investigator and that resolve with medical therapy 5. AST/ALT elevation > 3×ULN with bilirubin elevation >2×ULN that cannot be explained by factors not related to study drug
7.6 Medical Care of Patients after End of Trial Participation	After completing participation…	After completing treatment… Patients will continue to be followed for survival.
8.2.1 Medication/ Procedure Survey	To include all medications and/or treatments taken…	To include all medications taken other than Sym015 and all procedures performed during trial. For medications… For procedures: Include date and reason for procedure.
8.2.6 Physical Examination	To include evaluation of: General appearance, skin, head…	*Removed breasts, lungs, pulses*
8.3.3 Archival Tumor Tissue for *MET* and *KRAS* Assessment	*Not applicable*	May be performed as part of prescreening outside the 14-day screening period, provided separate informed consent has been obtained.
	Part 2: Eligibility assessment for *MET*-amplification and *KRAS* mutational status will be done using archival tumor tissue, <u>whenever</u> possible. If archival tissue is not available, tissue from the tumor biopsy performed during screening will be used.	Part 2: Eligibility assessment for KRAS mutational status may be done using archival tumor tissue. If archival tissue is not available… It is preferred that the eligibility assessment for *MET*-amplification will be done using… Note: If a new biopsy is performed for *MET*-amplification testing, tissue from this biopsy…
8.6 Skin Biopsy (Part 1 only)	Skin biopsies are requested from a rash-free area. • Screening, after confirmation of eligibility • For Q2W dosing schedule only: End of Cycle 2 (i.e. coinciding with time of first response assessment) or upon PD, whichever occurs first • For Q3W dosing schedule only: At the end of the follow-up…	Skin biopsies are requested from a rash-free area. • Screening, after confirmation of eligibility • End of Cycle 2 (i.e. coinciding with time of first response assessment) or upon PD, whichever occurs first
9.1.1 Adverse Event	PD will be captured as an AE. Events associated with the actual PD will also be captured, as determined by the Investigator. Additionally, AEs occurring simultaneously with PD, but which may not be related to the actual PD, will also be captured.	*Removed*
9.1.2 Events Not to be Considered as Adverse Events 9.1.5 Events that Do Not Meet the Definition of Serious Adverse Events	*Not applicable*	PD will not be captured as an AE/SAE unless the nature of the PD is different than expected (i.e. other diagnosis and/or signs/symptoms that are not typical of PD). PD may be reported as an AE/SAE in the case of patient death, with death being the outcome of the event. An abnormal laboratory value or an abnormality in physiological testing (such as ECGs) need not be reported as an AE unless one of the following applies: • The Investigator considers the abnormality clinically significant • The event meets the definition of an SAE • The event requires an intervention • The event results in an action taken with Sym015 (dose-reduction and/or withdrawal)

Table 19 Protocol Amendment 4		
SECTION	**ORIGINAL TEXT**	**NEW TEXT**
9.5.1 Definition of Dose-Limiting Toxicities	2. Any Grade 4 non-hematologic toxicity	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
10.4.1 Efficacy Endpoints and Analyses	The following anti-tumor response endpoints will be measured in Part 1, Dose-Escalation… • The following anti-tumor response endpoints will be measured in Part 2, Basket Cohort: o Changes in sum of diameters of target lesions from baseline to end of trial participation o SD for >4 months from baseline o Time to documented PD, death, patient withdrawal or end of trial participation, whichever comes first Number and percentages of patients with documented OR in the dose-escalation part will be presented including corresponding 95% exact CI. All documented ORs (Part 1 and 2) will be listed including duration (in days) of OR, measured from time of first PR or CR to PD. Duration of SD is calculated from baseline until first measurement of PD… Time to documented PD, death, patient withdrawal or end of trial participation, whichever comes first, will be presented in a Kaplan-Meier plot. The median progression free survival time, including 95% CI, will be derived.	The following anti-tumor response endpoints will be measured in Part 1 and in the Q3W Basket Cohort… • Additionally, the following anti-tumor response endpoints will be measured in both Part 1 and 2: o Duration of response (DR) o Best overall response (BOR) o SD for >4 months o Time to disease progression (TTP) as determined based on radiological evidence o Progression-free survival (PFS) o Overall survival (OS) In addition, the number and percentages of patients with SD for more than 4 months will be presented… TTP, PFS, and OS will be summarized using the product-limit method and Kaplan-Meier plots. The median TTP, PFS, and OS, including 95% CI, will be calculated.
12.1 Safety Review	Biweekly safety teleconferences will be held between the Investigational Site(s) and the Sponsor and/or designee. Such safety teleconferences may fluctuate in frequency based on accrual and trial activity, as indicated. Patients will be carefully evaluated…	Safety teleconferences will be held between the Investigational Site(s) and the Sponsor and/or designee. Patients will be carefully evaluated… • Part 1: It is intended that safety teleconferences will be held biweekly; however frequency may fluctuate based on accrual and trial activity, as indicated • Part 2: It is intended that safety teleconferences will be conducted after enrollment of approximately 15 and 30 patients. If safety concerns emerge, more frequent meetings will be held on an ad hoc basis.

21.5 Protocol Amendment 5 dated 11-May-2017

1. Modified inclusion criterion 5 to clarify that patients must have recurrent and/or progressive disease and be without other therapeutic options
2. Revised inclusion criterion 7 to allow local assessment of *KRAS*-mutation and MET-amplification based on a peripheral blood sample (liquid biopsy)

3. Modified inclusion and exclusion criteria to allow a subset of patients pretreated with a MET-targeting TKI
4. Specified that patients included based on MET-amplification from a liquid biopsy will be withdrawn if subsequent analysis of a tumor biopsy does not meet eligibility criteria, and the patients do not have clinical benefit from therapy. Such patients will be replaced
5. Added the option for investigators to include an H2 antagonist and/or acetaminophen premedication, where indicated
6. Modified prohibited medication section to allow steroid therapy as prophylaxis for contrast reactions
7. Included other minor updates and clarifications

Refer to Table 20 for the changes in Protocol Amendment 5.

Table 20 Protocol Amendment 5

SECTION	ORIGINAL TEXT	NEW TEXT
1. Synopsis: Phase and Overall Trial Design 5.1 Overall Design and Plan	Part 2 is a Phase 2a dose-expansion in patients with *MET*-amplified, *KRAS* WT solid tumor malignancies without therapeutic options. Two cohorts will be included: • Q2W Basket Cohort: A cohort of approximately 45 patients, in which dosing will be…	Part 2 is a Phase 2a dose-expansion in patients with *MET*-amplified, *KRAS* WT solid tumor malignancies without therapeutic options. With the exception of a subset of patients entered to the Q2W Basket Cohort, patients must not have received prior therapy with MET-inhibiting agents. Two cohorts will be included: • Q2W Basket Cohort: A cohort of approximately 45 patients, in which dosing will be… Included in this group will be a subset of approximately 6 patients who have received prior therapy with a MET-targeting tyrosine kinase inhibitor (TKI).
1. Synopsis: Main Inclusion and Exclusion Criteria 6.1 Inclusion Criteria	Documented (histologically- or cytologically-proven) solid tumor malignancy…	Documented (histologically- or cytologically-proven) solid tumor malignancy… (i.e. patients must have recurrent and/or progressive disease and be without other therapeutic options)
	Not applicable	**Additional main inclusion criteria applicable to Part 2 patients <u>ONLY</u>:** • Tumor documented to be *KRAS* WT by local assessment according to institutional standards. Note: Peripheral blood collection for *KRAS*-mutation assessment in circulating tumor deoxyribonucleic acid (ctDNA)…
	Additional main inclusion criteria applicable to Part 2 patients <u>ONLY</u>: • Confirmed *MET*-amplification by local assessment; i.e. gene [G]-to-copy number [CN] control probe ratio…	**Additional main inclusion criteria applicable to Part 2 patients <u>ONLY</u>:** • Confirmed *MET*-amplification by local assessment; i.e. gene [G]-to-copy number [CN] control probe ratio… Note: Peripheral blood collection for MET-amplification assessment in ctDNA will be allowed…
	Not applicable	**Additional main inclusion criteria applicable to Part 2 patients <u>ONLY</u>:** • No prior therapy with MET-targeting agents Note: An exception will be a subset of approximately 6 patients entered to the Q2W Basket Cohort after having received prior therapy with a MET-targeting TKI.
1. Synopsis: Main Inclusion and Exclusion Criteria	**Additional main exclusion criteria applicable to Part 2 patients <u>ONLY</u>:** • Prior therapy with MET-inhibiting agents	**Additional main exclusion criteria applicable to Part 2 patients <u>ONLY</u>:** • Prior therapy with MET-inhibiting agents Note: An exception will be a subset of approximately 6

Table 20 Protocol Amendment 5		
SECTION	**ORIGINAL TEXT**	**NEW TEXT**
6.2 Exclusion Criteria		patients entered to the Q2W Basket Cohort after having received prior therapy with a MET-targeting TKI.
	6. Central nervous system (CNS) malignancy including: Note: Patients with treated CNS metastases… performed at least 4 weeks prior to first trial drug administration	6. Central nervous system (CNS) malignancy including: Note: Patients with treated CNS metastases… performed ≥ 4 weeks apart with the most recent performed within 4 weeks prior to first trial drug administration
	7. Inadequate recovery from an acute toxicity… Note: With the exception of alopecia, patients must have recovered…	7. Inadequate recovery from an acute toxicity… Note: With the exception of persistent Grade 2 alopecia and/or peripheral neuropathy, patients must have recovered…
1. Synopsis: Trial Assessments	**Disease Assessments** • Archival tumor tissue for *MET* and *KRAS* assessment: o For patients in Part 2… It is preferred that the eligibility assessment for *MET*-amplification will be done using tissue…	**Disease Assessments** • Archival tumor tissue for *MET* and *KRAS* assessment: o For patients in Part 2… It is preferred that the eligibility assessment for *MET*-amplification will be done using tissue… Note: During Part 2 ONLY, peripheral blood collection for *KRAS*-mutation assessment and for MET-amplification assessment in ctDNA is allowed…
3.2.4.1 Protocol Sym015-01	As of 19 October 2016, a total of 9 patients have been enrolled in this trial: 3 patients at each of 3 dose levels (6, 12, and 18 mg/kg, dosed every second week [Q2W]). All 3 dose levels have been considered well tolerated, no DLTs or trial drug-associated serious adverse events (SAEs) have been reported to date…	As of Amendment 5, a total of 12 patients were enrolled in the completed Part 1 of this trial: 3 patients at each of 4 dose levels (6, 12, 18, and 24 mg/kg, dosed every second week [Q2W]). All 4 dose levels were considered well tolerated, no DLTs or trial drug-associated serious adverse events (SAEs) were reported….
3.4.2 Rationale for Recommended Phase 2 Dose	As of 19 October 2016…	As of Amendment 4…
4.2.2 Secondary Objectives	*Not applicable*	5. To make a preliminary evaluation of the antitumor activity of Sym015, and to evaluate all of the above secondary objectives, in a subset of approximately 6 patients administered Sym015 at the Q2W RP2D after having received prior therapy with a MET-targeting tyrosine kinase inhibitor (TKI)
5.3.1 Prescreening for *MET*-amplification and *KRAS* Mutational Status	*Not applicable*	*Part 2 ONLY: Peripheral blood collection for MET-amplification assessment and for *KRAS*-mutation assessment in circulating tumor deoxyribonucleic acid (ctDNA) (also referred to as "liquid biopsy") will be allowed…
5.3.2 Screening	The trial site staff must complete a Screening and Allocation Form, stating the allocated patient number…	The trial site staff must complete a Screening and Allocation Form, stating the allocated patient number… and whether the patient has received prior therapy with MET-inhibiting agents.
6.3.1 Withdrawal from Treatment with Sym015	*Not applicable*	Results from archival tumor tissue or a tumor biopsy submitted to confirm MET-amplification status that do not meet study eligibility criteria. Note: Such patients may remain on study if there is evidence of an OR, SD, or other clinical benefit, but will not be included in the Evaluable for Response Population.
6.4.2 Part 2	It is not planned to replace any patients in Part 2 of the trial.	Patients enrolled to the study based on local MET-amplification assessments conducted in ctDNA, but with subsequent confirmatory tumor tissue evaluation…

Table 20 Protocol Amendment 5		
SECTION	**ORIGINAL TEXT**	**NEW TEXT**
7.2.1 Premedication for Sym015 Infusions	All patients will receive the following premedication	All patients must be premedicated as described with standard therapies that include a glucocorticoid and an H1 antagonist. Where indicated, consideration may be given to including an H2 antagonist and/or acetaminophen... • Antihistamine (H2) antagonist (optional) such as 50 mg IV ranitidine or 30 mg famotidine, approx. 0.5 hours prior to the start of Sym015 infusion • Acetaminophen (optional) such as 1000 mg IV or PO (orally), approx. 0.5 hours prior to the start of Sym015 infusion
7.5.2 Prohibited Medication/ Therapy and Procedures During the Trial	*Not applicable*	Steroid therapy as prophylaxis for contrast reactions
8.3.3 Archival Tumor Tissue for *MET* and *KRAS* Assessment	*Not applicable*	During Part 2 ONLY, peripheral blood collection for *KRAS*-mutation assessment and for MET-amplification assessment in ctDNA is allowed as a local pre-screening methodology by Guardant360 analysis…
8.4 Pharmacokinetic Assessments	*Not applicable*	Note: Comprehensive collection of clinical samples is critical to the conduct of this study. In situations where collection of EOI + 8h samples is logistically difficult…
8.7 Biomarker Blood Sample	Aliquots of plasma samples will be stored…	Biomarker samples will be stored…

21.6 Protocol Amendment 6 dated 20-Nov-2017

1. Modified the overall trial design by removing Q3W dosing with Sym015, which will not be evaluated, and added a separate cohort of *KRAS* WT, advanced NSCLC patients with *METex*14 mutation.
2. Updated secondary trial objectives according to the change in overall trial design.
3. Updated the summary of clinical findings based on the 7 *MET*-amplified patients that have been enrolled in the ongoing Part 2 Basket Cohort at the time of the amendment.
4. Modified inclusion and exclusion criteria to allow enrollment of patients with NSCLC and other malignancies with *METex*14 mutation, and who have been pre-treated with MET-targeting TKI.
5. Modified exclusion criteria to specify time required between prior antineoplastic agent and C1/D1, and prior immunosuppressive or systemic hormonal therapy.
6. Modified prohibited medication to specify when the use of steroid therapy is considered not allowed.
7. Specified the order of collection of tumor biopsy and biomarker blood sample if collected at the same timepoint.
8. Included other minor updates and clarifications.

Refer to Table 21 for the changes in Protocol Amendment 6.

Table 21 Protocol Amendment 6		
SECTION	**ORIGINAL TEXT**	**NEW TEXT**
1. Synopsis: Trial Phases	• Part 1 is a Phase 1a dose-escalation in patients with Kirsten Rat Sarcoma (*KRAS*)… • Part 2 is a Phase 2a dose-expansion in patients with *MET*-amplified, *KRAS* WT solid tumor malignancies without therapeutic options. With the exception of a subset of patients entered to the Q2W Basket Cohort, patients must not have received prior therapy with MET-inhibiting agents. Two cohorts will be included: o Q2W Basket Cohort: A cohort of approximately 45 patients, in which dosing will be at the recommended phase 2 dose (RP2D) on an every second week (Q2W) schedule, in the following referred to as the Q2W RP2D… o Q3W Basket Cohort: A cohort of 6-12 patients, in which the highest safe dose tested in Part 1 will be evaluated on an every third week (Q3W) schedule A basket trial is designed…	• Part 1 is a Phase 1a dose-escalation in patients with *KRAS* proto-oncogene (*KRAS*)… • Part 2 is a Phase 2a dose-expansion in which dosing will be at the recommended phase 2 dose (RP2D) on an every second week (Q2W) schedule. Two cohorts will be included: o Basket* Cohort: A cohort of approximately 45 patients with *KRAS* WT advanced solid tumor malignancies with *MET*-amplification, and without therapeutic options… o NSCLC Cohort: A cohort of 6-12 patients with *KRAS* WT non-small cell lung carcinoma (NSCLC) with *MET* exon 14 skipping mutation (*METex14*), and without therapeutic options. Patients need not be *MET*-amplified and may have received prior therapy with a MET-targeting TKI. Note: Patients with malignancies other than NSCLC may be considered for entry to this cohort following discussion with the Sponsor's Medical Monitor(s). *A basket cohort is designed…
1. Synopsis: Trial Sites and Countries	Part 2: 15 to 20 investigational trial sites, located within the USA, Asia Pacific, and Europe. Enrollment to the Q3W Basket Cohort is expected to take place at select sites only.	Part 2: 15 to 25 investigational trial sites, located within the USA, Asia Pacific, and Europe.
1. Synopsis: Planned Trial Period	Enrollment to Part 2… Enrollment is expected to complete by Q3 2018.	Enrollment to Part 2… Enrollment is expected to complete by Q2 2019.
1. Synopsis: Overall Trial Design	The SMC will select the Q2W RP2D and the highest safe dose for the Q3W regimen to be used in Part 2… During Part 2, basket cohorts of patients with *MET*-amplified, *KRAS* WT advanced solid tumor malignancies will be evaluated: Q2W Basket Cohort administering the Q2W RP2D on a Q2W dosing schedule and Q3W Basket Cohort administering the highest safe dose tested in Part 1 on a Q3W dosing schedule.	The SMC will select the Q2W RP2D to be used in Part 2… During Part 2, two cohorts will receive Sym015 at the RP2D on a Q2W dosing schedule: • Basket Cohort: A basket cohort of *KRAS* WT, advanced solid tumor malignancy patients with *MET*-amplification will be evaluated. Patients must be MET-targeting TKI-naïve; an exception will be a subset of approximately 6 patients entered who have received prior therapy with a MET-targeting TKI. • NSCLC Cohort: A cohort of *KRAS* WT, advanced NSCLC patients with *METex14* mutation will be evaluated. Patients need not be *MET*-amplified and may have received prior therapy with a MET-targeting TKI.
1. Synopsis: Trial Periods	Treatment Period: Patients in the trial will receive IV infusions of Sym015 on a Q2W or Q3W schedule…	Treatment Period: Patients in the trial will receive IV infusions of Sym015 on a Q2W schedule…

Table 21 Protocol Amendment 6		
SECTION	**ORIGINAL TEXT**	**NEW TEXT**
	End of Treatment/Follow-up: …This One-Month Follow-up (1M FUP) visit will constitute the end of trial participation for the patient. After the 1M FUP Visit, the Investigator will make every effort to obtain follow-up information on response assessment and/or OS, every 2 months… Survival follow-up is required until death, withdrawal of consent, or termination of the trial.	End of Treatment/Follow-up: …*Removed* After the 1-Month Follow-up (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… 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 end of trial for the patient.
1. Synopsis: Number of Patients	Approximately 51-57 patients with documented and confirmed *MET*-amplified and *KRAS* WT advanced solid tumor malignancies will be enrolled and treated during Part 2.	Approximately 51-57 patients will receive Sym015 at the RP2D on a Q2W schedule during Part 2. Two cohorts will be included: • Approximately 45 patients with *KRAS* WT, advanced solid tumor malignancies with documented and confirmed *MET*-amplification will be enrolled and treated. A subset of approximately 6 patients will have received prior therapy with a MET-targeting TKI. • 6-12 patients with *KRAS* WT, advanced NSCLC with documented *METex14* mutation will be enrolled and treated. Patients need not be *MET*-amplified and may have received prior therapy with a MET-targeting TKI.
1. Synopsis: Main Inclusion and Exclusion Criteria	**Additional main inclusion criteria applicable to Part 2 patients <u>ONLY</u>:** • Tumor documented to be *KRAS* WT… Note: …Other liquid biopsy methodologies will only be allowed if previously approved by the Sponsor. • Confirmed MET-amplification by local assessment… • No prior therapy with MET-targeting agents Note: An exception will be a subset of approximately 6 patients entered to the Q2W Basket Cohort… **Main exclusion criteria all patients, Part 1 and Part 2:** • Any antineoplastic agent (standard or	**Additional main inclusion criteria applicable to Part 2 patients <u>ONLY</u>:** • Tumor documented to be *KRAS* WT… Note: …Other liquid biopsy methodologies, except if used to detect *METex14* mutation, will only be allowed if previously approved by the Sponsor. • Basket Cohort ONLY: o Confirmed MET-amplification by local assessment… o No prior therapy with MET-targeting agents Note: An exception will be a subset of approximately 6 patients entered to the Basket Cohort… • NSCLC Cohort ONLY: o Documented *METex14* mutations* (patients need not be *MET*-amplified and may have received prior therapy with a MET-targeting TKI) Note: Patients with malignancies other than NSCLC may be considered for entry to this cohort following discussion with the Sponsor's Medical Monitor(s). *METex14* mutation status to be documented according to local institutional standards. Assessment in ctDNA by Guardant360 technology or equivalent is allowed. Subsequent confirmation in tumor tissue is preferred but not required. **Main exclusion criteria all patients, Part 1 and Part 2:** • Any antineoplastic agent for the primary malignancy (standard or investigational) without

Table 21 Protocol Amendment 6		
SECTION	**ORIGINAL TEXT**	**NEW TEXT**
	investigational) within 4 weeks prior to C1/D1 • Central nervous system (CNS) malignancy including primary malignancies of the CNS and/or known CNS or leptomeningeal metastases not controlled by prior surgery… **Additional main exclusion criteria applicable to Part 2 patients <u>ONLY</u>:** • Prior therapy with MET-inhibiting agents Note: An exception will be a subset of approximately 6 patients entered to the Q2W Basket Cohort… • Tumor status demonstrating MET-polysomy	delayed toxicity within 4 weeks or 5 plasma half-lives, whichever is shortest, prior to C1/D1, except: o Nitrosoureas and mitomycin C within 6 weeks prior to C1/D1 • Central nervous system (CNS) malignancy including primary malignancies of the CNS and/or known, untreated CNS or leptomeningeal metastases, or spinal cord compression; patients with any of these not controlled by prior surgery… **Additional main exclusion criteria applicable to Part 2 patients <u>ONLY</u>:** • Prior therapy with MET-inhibiting agents Note: Exceptions will be a subset of approximately 6 patients entered to the Basket Cohort…, and patients entered to the NSCLC Cohort who may have received prior therapy with a MET-targeting TKI. • Basket Cohort ONLY: Tumor status demonstrating *MET*-polysomy in the absence of *MET*-amplification, as specified Note: Patients in the NSCLC Cohort with polysomy are eligible
1. Synopsis: Investigational Medicinal Product, Dose(s) and Treatment Schedule	Sym015 will be administered on a Q2W or Q3W schedule by IV infusion. • Q2W dosing: Day 1 and Day 15 of each 28-day cycle (± 2 days) • Q3W dosing: Day 1 and Day 22 of each 42-day cycle (± 2 days) Note: Q3W dosing is implemented in Part 2 after highest safe dose is identified on Q2W schedule **Part 2** Once the Q2W RP2D has been established during dose-escalation, the enrollment into the Q2W Basket Cohort will commence… Once the highest safe dose tested in Part 1 has been determined, all patients in the Q3W Basket Cohort will be treated at that dose level on a Q3W dosing schedule.	Sym015 will be administered on a Q2W schedule by IV infusion. • Q2W dosing: Day 1 and Day 15 of each 28-day cycle (± 2 days) **Part 2** Once the Q2W RP2D has been established during dose-escalation, the enrollment into the Basket Cohort and NSCLC Cohort will commence. *Removed*
1. Synopsis: Trial Assessments	**Disease Assessments** • Q2W dosing schedule: Disease status evaluation… • Q3W Basket Cohort only: Disease status evaluation by CT or MRI at screening and at the end of the follow-up period following every third dose. Further potential timepoints are in the event of suspected PD, in the event of CR/PR and at EOT/1M FU • Archival tumor tissue for *MET* and *KRAS* assessment: o For patients in Part 2… It is preferred…	**Disease Assessments** • Disease status evaluation… *Removed* • Archival tumor tissue for *MET* and *KRAS* assessment: o For patients in Part 2… ▪ Basket Cohort: It is preferred… Note: …Other liquid biopsy methodologies,

Table 21 Protocol Amendment 6		
SECTION	**ORIGINAL TEXT**	**NEW TEXT**
	Note: …Other liquid biopsy methodologies will only be allowed if previously approved by the Sponsor. • Tumor biopsy to be assessed locally as part of eligibility assessment for Part 1 and Part 2 patients, if applicable. In addition, to be assessed centrally for biomarker analysis (optional for patients in Part 1 with known *MET*-amplification; required for patients in Part 2): o Q2W dosing: At screening and at the end of Cycle 2 or upon PD, whichever comes first. o Q3W Basket Cohort: At screening and at the end of the follow-up period following the third dose or upon PD, whichever comes first. 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 as specified in the laboratory manual. **Additional Assessments** • Biomarker blood sample: o Q2W dosing: At screening, at the end of Cycle 2 or upon PD, whichever comes first, and at EOT o Q3W Basket Cohort: At screening, at the end of the follow-up period following the third dose or upon PD, whichever comes first, and at EOT	except if used to detect *METex14* mutation, will only be allowed if previously approved by the Sponsor. ▪ NSCLC Cohort: Eligibility assessment for *METex14* mutation status will be done according to local institutional standards. Assessment in ctDNA by Guardant360 technology or equivalent is allowed. Subsequent confirmation in tumor tissue is preferred but not required, however, archival tissue to be submitted for central testing, if available. • Tumor biopsy for eligibility assessment and biomarker analysis: o To be assessed locally for eligibility assessment for Part 1 and Part 2 patients if not already assessed in archival tumor tissue and if applicable (i.e. Basket Cohort only) o To be assessed centrally for biomarker analysis ▪ Part 1, optional for patients with known *MET*-amplification ▪ Part 2: • Basket Cohort: Required at screening if archival tissue is unavailable or insufficient, and at the end of Cycle 2 or upon PD, whichever comes first. At screening, tissue from a tumor biopsy is preferred, however archival tissue may be submitted for central analysis at the Investigator's discretion, provided the archival tissue is suitable as specified in the laboratory manual. • NSCLC Cohort: Optional, at the timepoints specified **Additional Assessments** • Biomarker blood sample: At screening, at the end of Cycle 2 or upon PD, whichever comes first, and at EOT *Removed*
1. Synopsis: Statistical Methods and Sample Size Calculation	In Part 2 of the trial, the primary endpoint is documented OR in the Q2W Basket Cohort… For the Q3W Basket Cohort, assuming the response…	In Part 2 of the trial, the primary endpoint is documented OR in the Basket Cohort… For the NSCLC Cohort, assuming the response…
3.1.2 *MET*-amplified Solid Tumor	*Not applicable*	Mutations leading to skipping of *MET* exon 14 (*METex14*) result in the deletion of the juxtamembrane domain of MET, which stabilizes and accumulates

Table 21 Protocol Amendment 6		
SECTION	**ORIGINAL TEXT**	**NEW TEXT**
Malignancies		receptor on the cell surface and leads to enhanced signaling through the MET receptor pathway. *MET* alterations that result in exon 14 skipping are found in 3-4% of lung adenocarcinomas, both in the presence and absence of *MET*-amplification and studies have demonstrated clinical benefit of targeting patients with tumors harboring *METex14* mutations. Over 100 mutations in *MET*-mutated cancers resulting in exon 14 skipping have been described.
3.2.3 Summary of Non-Clinical Findings	Responsive models include *MET*-amplified, *MET*-exon 14 deleted, and autocrine HGF-expressing tumors.	Response to Sym015 was observed in models with *MET*-amplification, *METex14* mutations, and autocrine HGF-expression.
3.2.4.1 Protocol Sym015-01	While data in this ongoing clinical trial have not been fully monitored…	While data in this ongoing clinical trial have not been fully monitored… all AEs were Grade 1 or Grade 2 in severity. As of Amendment 6, a total of 7 *MET*-amplified patients have been enrolled in the ongoing Part 2 Basket Cohort of this trial…
3.3 Trial Rationale	As outlined in the sections above, recent results suggest that *MET*-amplification identifies a small but clinically important subgroup of patients who are likely to respond to MET targeted therapies. The potent tumor inhibitory activity, observed in preclinical studies in *MET*-amplified models, suggests that Sym015 may provide a clinically relevant effect in this patient population. Based on the nonclinical pharmacology and toxicity testing, Sym015 is expected to be well tolerated and the benefit-risk ratio for patients enrolled is considered to be favorable.	As outlined in the sections above, recent results suggest that *MET*-amplification and *METex14* mutations identify small but clinically important subgroups of patients who are likely to respond to MET targeted therapies. The potent tumor inhibitory activity, observed in preclinical studies in models with *MET*-amplification and/or *METex14* mutations, suggests that Sym015 may provide a clinically relevant effect in these patient populations. Based on the nonclinical pharmacology and toxicity testing, Sym015 is expected to continue to be well tolerated and the benefit-risk ratio for patients enrolled is considered to be favorable.
3.4.1 Rationale for Starting Dose	The dosing schedules to be explored in this clinical trial are based on... PK data (long terminal T½ and accumulation with weekly dosing) support the selection of the dosing schedules, dosing every second week (Q2W) and dosing every third week (Q3W), to be evaluated in this trial.	The dosing schedule to be explored in this clinical trial is based on... PK data (long terminal T½ and accumulation with weekly dosing) support the selection of the dosing schedule, dosing every second week (Q2W), to be evaluated in this trial.
4.2.2 Secondary Objectives	6. To make a preliminary evaluation of the antitumor activity of Sym015, and to evaluate all of the above secondary objectives, in a cohort of patients administered Sym015 on a Q3W dosing schedule at the highest safe dose tested in Part 1	6. To make a preliminary evaluation of the antitumor activity of Sym015, and to evaluate all the above secondary objectives, in a subset of approximately 6-12 *KRAS* WT NSCLC patients with *METex14* mutations administered Sym015 at the Q2W RP2D. Patients need not be *MET*-amplified and may have received prior therapy with a MET-targeting TKI. Note: Patients with malignancies other than NSCLC may be considered for entry to this cohort following discussion with the Sponsor's Medical Monitor(s).
5.1 Overall Design Plan	• Part 2 is a Phase 2a dose-expansion in patients with *MET*-amplified, *KRAS* WT solid tumor malignancies without therapeutic options. With the exception of a subset of patients entered to the Q2W Basket Cohort, patients must not have received prior therapy with MET-inhibiting agents. Two cohorts will be	• Part 2 is a Phase 2a dose-expansion in which dosing will be at the recommended phase 2 dose (RP2D) on an every second week (Q2W) schedule, in the following referred to as the Q2W RP2D. Two cohorts will be included:

Table 21 Protocol Amendment 6		
SECTION	**ORIGINAL TEXT**	**NEW TEXT**
	included: ○ A Basket Cohort of approximately 45 patients, in which dosing will be at the Q2W RP2D (Q2W Basket Cohort). Included in this group will be a subset of approximately 6 patients who have received prior therapy with a MET-targeting TKI. ○ A Basket Cohort of 6-12 patients, in which the highest safe dose tested in Part 1 will be evaluated on a Q3W schedule (Q3W Basket Cohort) A basket trial is designed… The SMC will select the Q2W RP2D and the highest safe dose for the Q3W regimen to be used in Part 2… During Part 2, basket cohorts of patients with *MET*-amplified, *KRAS* WT, advanced solid tumor malignancies will be evaluated: Q2W Basket Cohort administering the Q2W RP2D on a Q2W schedule and Q3W Basket Cohort administering the highest safe dose tested in Part 1 on a Q3W schedule. The number of investigational trial sites…15 to 20 in Part 2. Enrollment to the Q3W Basket Cohort is expected to take place at select trial sites only.	○ Basket* Cohort: A cohort of approximately 45 patients with *KRAS* WT advanced solid tumor malignancies with *MET*-amplification, and without 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 Cohort: A cohort of 6-12 patients with *KRAS* WT NSCLC with *METex14* mutation, and without therapeutic options. Patients need not be *MET*-amplified and may have received prior therapy with a MET-targeting TKI. *A basket cohort is designed… The SMC will select the Q2W RP2D to be used in Part 2… During Part 2, two cohorts will receive Sym015 at the RP2D on a Q2W dosing schedule: • Basket Cohort: A basket cohort of *KRAS* WT, advanced solid tumor malignancy patients with *MET*-amplification will be evaluated. Patients must be MET-targeting TKI-naïve; an exception will be a subset of approximately 6 patients entered who have received prior therapy with a MET-targeting TKI. • NSCLC Cohort: A cohort of *KRAS* WT advanced NSCLC patients with *METex14* mutation will be evaluated. Patients need not be *MET*-amplified and may have received prior therapy with a MET-targeting TKI. The number of investigational trial sites…15 to 25 in Part 2.
5.2.1 Rationale for Trial Design	Part 2 of this trial is designed: to evaluate the antitumor activity of Sym015 administered at the selected Q2W RP2D on a Q2W schedule and to further explore safety, tolerability and preliminary antitumor effect of the highest safe dose tested in Part 1 on a Q3W schedule. The choice of basket cohorts…	Part 2 of this trial is designed to evaluate the antitumor activity of Sym015 administered at the selected Q2W RP2D on a Q2W schedule. The choice of a basket cohort…
5.2.2 Rationale for Trial Population	Nonclinical studies have documented that the activity of Sym015 is greater in *MET*-amplified tumors, and similar findings have been observed in preliminary studies of other anti-MET mAbs in early clinical trials.	In addition, a cohort of *KRAS* WT NSCLC patients with *METex14* mutation will be entered to evaluate the antitumor activity of Sym015. Nonclinical studies have documented that the activity of Sym015 is greater in tumors with *MET*-amplification and/or *METex14* mutation, suggesting that Sym015 may provide a clinically relevant effect in these patient populations. Similar findings have been observed in preliminary studies in patients with *MET*-amplified tumors of other anti-MET mAbs in early clinical trials.

Table 21 Protocol Amendment 6		
SECTION	**ORIGINAL TEXT**	**NEW TEXT**
5.3.1 Prescreening for *MET*-amplification, *METex14*, and *KRAS* Mutational Status	The trial site may choose to prescreen patients utilizing archival tumor tissue to confirm *MET*-amplification status* and/or *KRAS* mutational status*... *Part 2 ONLY: Peripheral blood collection for *MET*-amplification assessment and for *KRAS*-mutation assessment… Other liquid biopsy methodologies will only be allowed if previously approved by the Sponsor…	The trial site may choose to prescreen patients utilizing archival tumor tissue to confirm *MET*-amplification status*, *METex14* mutation status*, and/or *KRAS* mutational status*... *Part 2 ONLY: Peripheral blood collection for *MET*-amplification assessment, *METex14* assessment, and *KRAS*-mutation assessment… Other liquid biopsy methodologies, except if used to detect *METex14* mutation, will only be allowed if previously approved by the Sponsor…
5.3.2 Screening	Furthermore, once eligibility is confirmed: • All patients in Part 2 will have a tumor biopsy performed…	Furthermore, once eligibility is confirmed: • All patients in the Part 2 Basket Cohort will have a tumor biopsy performed… • For patients in the Part 2 NSCLC Cohort, biopsy for biomarker analysis is optional; archival tissue to be submitted, if available
5.3.4 Treatment	Sym015 will be administered on a Q2W or Q3W schedule by IV infusion: • Q2W dosing: Day 1 and Day 15 of each 28-day cycle (± 2 days) • Q3W dosing: Day 1 and Day 22 of each 42-day cycle (± 2 days) (Q3W Basket Cohort only)	Sym015 will be administered on a Q2W schedule by IV infusion: • Q2W dosing: Day 1 and Day 15 of each 28-day cycle (± 2 days)
5.3.5 End of Treatment and Follow-up Visits	After the 1M FUP Visit, the Investigator will make every effort… every 2 months… Survival follow-up is required until death, withdrawal of consent, or termination of the trial…	After the 1M FUP Visit, the Investigator will make every effort… 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…
5.3.6 Flow Chart – Schedule of Assessments	Schedules of assessments are provided in the trial flow charts in Table 3 (Q2W dosing) and Table 4 (Q3W dosing, Q3W Basket Cohort only), respectively. Furthermore, each new cycle must be initiated as soon as possible after completion of the previous cycle in order to achieve the Q2W/Q3W dosing schedule as applicable for the individual patient.	Schedules of assessments are provided in the trial flow chart in Table 3 (Q2W dosing). Furthermore, each new cycle must be initiated as soon as possible after completion of the previous cycle in order to achieve the Q2W dosing schedule.
5.5 Number of Patients	During Part 2, it is planned to enroll and treat approximately 45 patients in the Q2W Basket Cohort and 6-12 patients in the Q3W Basket Cohort; i.e. a total of 51-57 patients with documented and confirmed *MET*-amplified and *KRAS* WT advanced solid tumor malignancies.	It is estimated that approximately 51-57 patients will be enrolled to receive Sym015 at the RP2D on a Q2W schedule during Part 2. Two cohorts will be included: • Basket Cohort: Approximately 45 patients with *KRAS* WT, advanced solid tumor malignancies with documented and confirmed *MET*-amplification will be enrolled and treated. A subset of 6 patients will have received prior therapy with a MET-targeting TKI. • NSCLC Cohort: 6-12 patients with *KRAS* WT, advanced NSCLC with documented *METex14* mutation will be enrolled and treated. Patients need not be *MET*-amplified and may have received prior therapy with a MET-targeting TKI.
5.6 End of Trial	The end of trial will be reached at the latest 1 month	The end of trial will be reached at the latest 1 month

Table 21 Protocol Amendment 6		
SECTION	**ORIGINAL TEXT**	**NEW TEXT**
	(30 +7 days) after the last patient has been withdrawn from Sym015. Patients will continue to be followed to assess duration of disease stabilization, response and/or overall survival.	(30 +7 days) after the last patient has been withdrawn from Sym015.
6.1 Inclusion Criteria	Part 2 ONLY: b. Tumor documented to be *KRAS* WT… Note: …Other liquid biopsy methodologies will only be allowed if previously approved by the Sponsor. c. Confirmed *MET*-amplification by local… d. No prior therapy with MET-targeting agents Note: An exception will be a subset of approximately 6 patients entered to the Q2W Basket Cohort…	Part 2 ONLY: b. Tumor documented to be *KRAS* WT… Note: …Other liquid biopsy methodologies, except if used to detect *METex14* mutation, will only be allowed if previously approved by the Sponsor. c. Basket Cohort ONLY: • Confirmed *MET*-amplification by local… • No prior therapy with MET-targeting agents Note: An exception will be a subset of approximately 6 patients entered to the Basket Cohort… d. NSCLC Cohort ONLY: • Documented *METex14* mutations (patients need not be *MET*-amplified and may have received prior therapy with a MET-targeting TKI) Note: Patients with malignancies other than NSCLC and with documented *METex14* mutation may be considered for entry to this cohort following discussion with the Sponsor's Medical Monitor(s). Note: *METex14* mutation status to be documented according to local institutional standards. Assessment in ctDNA by Guardant360 technology or equivalent is allowed. Subsequent confirmation in tumor tissue is preferred but not required.
6.2 Exclusion Criteria	1. Any antineoplastic agent (standard or investigational) within 4 weeks prior to C1/D1 2. Part 2 ONLY: a. Prior therapy with MET-inhibiting agents Note: An exception will be a subset of approximately 6 patients entered to the Q2W Basket Cohort after having received prior therapy with a MET-targeting TKI. c. Tumor status demonstrating *MET*-polysomy 3. Immunosuppressive or systemic hormonal therapy within 2 weeks prior to C1/D1 with the exception of the following allowed therapies: e. Hormonal contraceptive therapy f. GnRH analogs in patients with prostate cancer	1. Any antineoplastic agent for the primary malignancy (standard or investigational) without delayed toxicity within 4 weeks or 5 plasma half-lives, whichever is shortest, prior to C1/D1 except: • Nitrosoureas and mitomycin C within 6 weeks prior to C1/D1 2. Part 2 ONLY: a. Prior therapy with MET-inhibiting agents Note: Exceptions will be a subset of approximately 6 patients entered to the Basket Cohort after having received prior therapy with a MET-targeting TKI, and patients entered to the NSCLC Cohort who may have received prior therapy with a MET-targeting TKI. c. Basket Cohort ONLY: Tumor status demonstrating *MET*-polysomy in the absence of *MET*-amplification, as specified Note: Patients in the NSCLC Cohort with polysomy are eligible 3. Immunosuppressive or systemic hormonal therapy (> 10 mg daily prednisone equivalent) within 2 weeks prior to C1/D1 with the exception of the following allowed therapies: e. Steroid therapy for contrast reaction prophylaxis f. Stable hormonal therapy for ovarian suppression

Table 21 Protocol Amendment 6		
SECTION	**ORIGINAL TEXT**	**NEW TEXT**
		for non-malignant conditions, hormonal contraceptive therapy, or post-menopausal hormone replacement therapy (HRT)* g. GnRH analogs in patients with prostate cancer h. Intra-articular steroid injections i. Higher dose steroid therapy for treatment of an acute intercurrent illness in patients with stable disease or an ongoing response. In such situations, protocol therapy treatment should be interrupted. *Prior or concomitant therapies are permitted; however, patients must have been on a stable dose for at least 6 months prior to study start, and if continuing must remain on the stable dose while receiving study treatment (i.e. such treatment will not be considered as systemic hormonal therapy for the purpose of study eligibility).
	6. Central nervous system (CNS) malignancy including: b. Known CNS or leptomeningeal metastases not controlled by prior surgery… Note: Patients with treated CNS metastases…	6. Central nervous system (CNS) malignancy including: b. Known, untreated CNS or leptomeningeal metastases, or spinal cord compression; patients with any of these not controlled by prior surgery… Note: Patients with treated CNS metastases… Patients with newly identified CNS metastases during study treatment will be considered to have PD and will be discontinued from treatment
6.3.1 Withdrawal from Treatment with Sym015	• Results from archival tumor tissue or a tumor biopsy submitted to confirm *MET*-amplification status that do not meet study eligibility criteria.	• Basket Cohort ONLY: Results from archival tumor tissue or a tumor biopsy submitted to confirm *MET*-amplification status that do not meet study eligibility criteria.
6.4.2 Part 2	Patients enrolled to the study…	Basket Cohort ONLY: Patients enrolled to the study…
7.1.3.1 Treatment Schedule	Sym015 will be administered Q2W (Day 1 and Day 15 of each 28-day cycle [±2 days]) or Q3W (Day 1 and Day 22 of each 42-day cycle [±2 days]).	Sym015 will be administered Q2W (Day 1 and Day 15 of each 28-day cycle [±2 days]).
7.1.3.2 Part 1, Dose-Escalation	The SMC will review safety data… and the doses to be used in Part 2 (i.e. Q2W RP2D to be evaluated in the Q2W Basket Cohort and the highest safe dose in Part 1 to be evaluated in the Q3W Basket Cohort).	The SMC will review safety data… and the dose(s) to be used in Part 2 (i.e. Q2W RP2D to be evaluated).
7.1.3.3 Part 2	During Part 2 of this trial, patients included in the Q2W Basket Cohort will receive the Q2W RP2D of Sym015 on a Q2W dosing schedule. Patients included in the Q3W Basket Cohort will receive the highest safe dose tested in Part 1 on a Q3W dosing schedule.	During Part 2 of this trial, patients will receive the RP2D of Sym015 on a Q2W dosing schedule.
7.1.4 Dose-Adjustment and Delays of Sym015	The dose of Sym015 in mg/kg and the dosing schedule, Q2W or Q3W, assigned to the individual patient, will be confirmed by the Sponsor…	The dose of Sym015 in mg/kg assigned to the individual patient will be confirmed by the Sponsor…
7.5.2 Prohibited Medication/ Therapy and	• Systemic immunosuppressive or systemic hormonal therapy with the exception of the following allowed	• Systemic immunosuppressive or systemic hormonal therapy with the exception of the following allowed

Table 21 Protocol Amendment 6		
SECTION	**ORIGINAL TEXT**	**NEW TEXT**
Procedures During the Trial	therapies: o Hormonal contraceptive therapy	therapies: o Stable hormonal therapy for ovarian suppression for non-malignant conditions, hormonal contraceptive therapy, or post-menopausal HRT* o Intra-articular steroid injections o Higher dose steroid therapy for treatment of an acute intercurrent illness in patients with stable disease or an ongoing response. In such situations, protocol therapy treatment should be interrupted. *Prior or concomitant therapies are permitted; however, patients must have been on a stable dose for at least 6 months prior to study start, and if continuing must remain on the stable dose while receiving study treatment (i.e. such treatment will not be considered as systemic hormonal therapy for the purpose of study eligibility).
8.3.1 Disease Status Evaluation by CT or MRI	• For Q2W dosing schedule only: o End of Cycle 2 and end of every second cycle thereafter, i.e. end of Cycle 4, 6, 8, etc. Note: May be performed at any time during the week prior to Day 1 of the next cycle • For Q3W Basket Cohort only: o At the end of the follow-up period following every third dose, i.e. end of the follow-up period following C2/D1, C3/D22, C5/D1 etc. Note: May be performed at any time during the week prior to the next scheduled dose	• End of Cycle 2 and end of every second cycle thereafter, i.e. end of Cycle 4, 6, 8, etc. Note: May be performed at any time during the week prior to Day 1 of the next cycle *Removed*
8.3.3 Archival Tumor Tissue for *MET* and *KRAS* Assessment	• Screening o Part 2… It is preferred that the eligibility assessment for *MET*-amplification will be done using… During Part 2 ONLY… Other liquid biopsy methodologies will only be allowed if previously approved by the Sponsor…	• Screening o Part 2… Basket Cohort: It is preferred that the eligibility assessment for *MET*-amplification be done using… During Part 2 ONLY… Other liquid biopsy methodologies, except if used to detect *METex14* mutation, will only be allowed if previously approved by the Sponsor… NSCLC Cohort: Eligibility assessment for *METex14* mutation status will be done according to local institutional standards. Assessment in ctDNA by Guardant360 technology or equivalent is allowed. Subsequent confirmation in tumor tissue is preferred but not required, however, archival tissue to be submitted, if available.
8.3.4 Tumor Biopsy for Eligibility	• Screening o Part 2: Required, if archival tissue…	• Screening o Part 2: Basket Cohort: Required, if archival tissue…

Table 21 Protocol Amendment 6		
SECTION	**ORIGINAL TEXT**	**NEW TEXT**
Assessment and Biomarker Analysis	• Post-dosing ○ Part 2: Required ▪ For Q2W dosing schedule only: End of Cycle 2… ▪ For Q3W Basket Cohort only: At the end of the follow-up period following the third dose (i.e. coinciding with time of first response assessment) or upon PD, whichever occurs first Note: May be performed at any time during the week prior to the next scheduled dose	NSCLC Cohort: Optional • Post-dosing ○ Part 2: Basket Cohort: Required; End of Cycle 2… NSCLC Cohort: Optional, at the timepoint specified above
8.7 Biomarker Blood Sample	• Screening, after confirmation of eligibility • For Q2W dosing schedule only: End of Cycle 2… • For Q3W Basket Cohort only: At the end of the follow-up period following the third dose (coinciding with time of first response assessment) or upon PD, whichever occurs first Note: May be performed at any time during the week prior to the next scheduled dose • EOT	• Screening, after confirmation of eligibility • End of Cycle 2… *Removed* • EOT Note: 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.
10.1 Sample Size Determination	In Part 2 of the trial, the primary endpoint is documented OR in the Q2W Basket Cohort… For the Q3W Basket Cohort, assuming the response…	In Part 2 of the trial, the primary endpoint is documented OR in the Basket Cohort… For the NSCLC Cohort, assuming the response…
10.3.2 Part 2	This will be assessed by the primary endpoint for Part 2, documented OR in the Q2W Basket Cohort…	This will be assessed by the primary endpoint for Part 2, documented OR in the Basket Cohort…
10.4.1 Efficacy Endpoints and Analyses	The following anti-tumor response endpoints will be measured in Part 1 and in the Q3W Basket Cohort…	The following anti-tumor response endpoints will be measured in Part 1…
10.4.5 Additional Endpoints and Analyses	• Part 1 only: MET-receptor down-regulation measured by percentage and nominal change in target expression from baseline to end of Cycle 2/end of follow-up period following the third dose (Q2W/Q3W) or PD (whichever comes first) in skin biopsy samples	• Part 1 only: MET-receptor down-regulation measured by percentage and nominal change in target expression from baseline to end of Cycle 2 or PD (whichever comes first) in skin biopsy samples
10.5 Interim Analysis	In Part 2 an assessment of futility will be performed… in the Q2W Basket Cohort.	In Part 2 an assessment of futility will be performed… in the Basket Cohort.

21.7 Protocol Amendment 7 dated 07-Dec-2018

1. Effective with this protocol amendment, accrual to the Basket Cohort is suspended. Emerging literature allowed for the identification of specific tumor types that are more likely to respond to Sym015 treatment (e.g., NSCLC). With this change, a new cohort of NSCLC *MET*-amplified patients has been added to Part 2 of the trial design, for a total of three cohorts.
2. With the suspension of the Basket Cohort, NSCLC *MET*-amplified patients entered to the Basket Cohort will be counted toward the NSCLC *MET*-Amplified Cohort; NSCLC $MET^{Ex14Del}$ patients entered to the Basket Cohort will be counted toward the NSCLC $MET^{Ex14Del}$ Cohort; patients with both will be counted as *MET*-Amplified.
3. Updated clinical experience information have been added to the scientific background.
4. According to the ASCO/CAP guidelines for testing of HER2 amplification, *MET*-amplification may be defined as positive with a MET/CEP7 ratio of >2.2 (occasionally 2.0). Symphogen has opted to change the cutoff to $\geq$ 3.0 based on emerging data that suggest higher degrees of *MET*-amplification are associated with higher degree of response.
5. Specified that concomitant therapy with bisphosphonates and denosumab are allowed during the dosing portion of the trial.
6. Clarified that after the Screening assessments, targeted physical examination may be performed as indicated.
7. The number of pharmacokinetic timepoints have been reduced for patients entered to the NSCLC cohorts.
8. The mandatory post-dosing tumor biopsy scheduled to be performed at the EOC2 or upon disease progression is now optional.
9. Clarified that all analyses will be related to and used only in connection with the data collected in the present trial as well as future development of Sym015.
10. Clarified that 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.
11. Clarified that initial SAE and follow-up SAE information are to be submitted within 24 hours of awareness.
12. Due to the new cohort sample sizes, an initially planned interim analysis becomes obsolete and will no longer be performed.
13. Guidelines pertaining to the General Data Protection Regulation have been added.
14. Formatting adjustments, typographical corrections, outline modifications, and wording/abbreviation changes are included.
15. The synopsis, figure, tables, and references have been updated based on changes described, where applicable.

Refer to Table 22 for the changes in Protocol Amendment 7.

Table 22 Protocol Amendment 7		
SECTION	**ORIGINAL TEXT**	**NEW TEXT**
3.1.1 Solid Tumor Malignancies	*Not applicable*	Non-small cell lung cancer (NSCLC) is the leading cause of death due to malignancy globally.
3.1.2 *MET*-Amplified Solid Tumor Malignancies	Mutations leading to skipping of MET exon 14 (*METex14*) result in the deletion of the juxtamembrane domain of MET,… Although this molecular alteration is rare, testing of *KRAS* status in clinical trials involving anti-MET therapy may be warranted to avoid treating patients that may not experience clinical benefit from these agents (10,19).	Mutations leading to skipping of MET exon 14 (*MET*^{Ex14Del}) result in the deletion of the juxtamembrane domain of MET,… Because these two molecular alterations are rare in NSCLC patients, testing of *KRAS* status in clinical trials involving anti-MET therapy may not be warranted (10,19). NSCLC patients with either *MET*-amplification or *MET*^{Ex14Del} have been documented to have a poor prognosis (32). *MET*-amplification was observed in 0.7% of all patients with NSCLC and *MET* mutations were observed in 2.6% of patients in this population.
3.1.3 Current Treatment of *MET*-Amplified Solid Tumor Malignancies	These include both small-molecule tyrosine-kinase inhibitors, such as crizotinib, cabozantinib and tivantinib, as well as monoclonal antibodies (mAbs). The small-molecule inhibitors are generally promiscuous in their target specificity and thus have activity on additional RTKs besides MET.	These include both small-molecule tyrosine-kinase inhibitors, such as crizotinib, cabozantinib, tivantinib, tepotinib, and capmatinib as well as single monoclonal antibodies (mAbs). The small-molecule inhibitors are generally promiscuous in their target specificity and may have activity on additional RTKs besides MET. The activity of MET inhibitors in patients with NSCLC has recently been reviewed (33), and more recent data are cited below with respect to additional inhibitors.
	Not applicable	Tepotinib is another MET tyrosine kinase inhibitor (TKI) that has been studied in Phase 1 and Phase 2 clinical studies…. (34). Capmatinib (INC280), a MET TKI, is also in Phase 2 studies enrolling NSCLC patients with *MET*^{Ex14Del} as well as in combination with gefitinib in patients with epidermal growth factor receptor (*EGFR*)-mutated MET dysregulated NSCLC... (35).
3.2.4.1 Protocol Sym015-01	As of Amendment 6, a total of 7 *MET*-amplified patients have been enrolled in the ongoing Part 2 Basket Cohort of this trial to receive Sym015 at a loading dose of 18 mg/kg delivered over 1.5 hours, followed by Q2W maintenance doses of 12 mg/kg delivered over 1 hour… Other study drug-related AEs have been limited to fatigue (Grade 2) and prolonged prothrombin time (Grade 1). Accrual to this portion of the trial continues.	As of September 2018, a total of 21 *MET*-amplified patients and 2 *MET*^{Ex14Del} patients have been enrolled in the ongoing Part 2 portion of this trial to receive Sym015 at a loading dose of 18 mg/kg delivered over 1.5 hours, followed by Q2W maintenance doses of 12 mg/kg delivered over 1 hour… In another patient, the SAEs of Grade 3 anasarca and Grade 3 hypoalbuminemia (both possibly related) have been reported. Other study drug-related AEs have been limited to Grade 2 fatigue and mouth sores, and Grade 1 asthenia, anorexia, gastric pain, abdominal cramping, abdominal gas, nausea, diarrhea, constipation, xerosis, pruritus, and voice change… Accrual to the Part 2 portion of the trial continues. Note: Effective with protocol version 8.0 (December 2018), accrual to the Part 2 Basket Cohort comprised of patients with *MET*-amplified solid tumor malignancies is suspended; accrual will continue to cohorts of patients with *MET*-amplified NSCLC or *MET*^{Ex14Del} NSCLC.

Table 22 Protocol Amendment 7		
SECTION	**ORIGINAL TEXT**	**NEW TEXT**
4.2.1 Primary Objective	To evaluate the antitumor activity of Sym015 when administered at the Q2W RP2D to patients with *MET*-amplified, *KRAS* WT solid tumor malignancies without available therapeutic options.	To evaluate the antitumor activity of Sym015 when administered at the Q2W RP2D to patients in the following cohorts: 1. Basket Cohort: *MET*-amplified, *KRAS* WT solid tumor malignancies without available therapeutic options; patients may not have received prior therapy with a MET-targeting TKI 2. NSCLC *MET*-Amplified Cohort: *MET*-amplified advanced NSCLC without available therapeutic options; patients may have received prior therapy with MET-targeting and/or EGFR-targeting agents 3. NSCLC $MET^{Ex14Del}$ Cohort: $MET^{Ex14Del}$ NSCLC without available therapeutic options; patients may have received prior therapy with MET-targeting and/or EGFR-targeting agents
4.2.2 Secondary Objectives	5. To make a preliminary evaluation of the antitumor activity of Sym015, and to evaluate all of the above secondary objectives, in a subset of approximately 6 patients administered Sym015 at the Q2W RP2D after having received prior therapy with a MET-targeting tyrosine kinase inhibitor (TKI)	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
	6. To make a preliminary evaluation of the antitumor activity of Sym015, and to evaluate all the above secondary objectives, in a subset of approximately 6-12 *KRAS* WT NSCLC patients with *METex14* mutations administered Sym015 at the Q2W RP2D. Patients need not be *MET*-amplified and may have received prior therapy with a MET-targeting TKI. Note: Patients with malignancies other than NSCLC may be considered for entry to this cohort following discussion with the Sponsor's Medical Monitor(s).	*Text removed*
5.1 Overall Design and Plan	• Part 2 is a Phase 2a dose-expansion in which dosing will be at the recommended phase 2 dose (RP2D) on an every second week (Q2W) schedule, in the following referred to as the Q2W RP2D. Two cohorts will be included: ○ Basket* Cohort: A cohort of approximately 45 patients with *KRAS* WT advanced solid tumor malignancies with *MET*-amplification, and without 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 Cohort: A cohort of 6-12 patients with *KRAS* WT NSCLC with *METex14* mutation, and without therapeutic options. Patients need not be *MET*-amplified and may have received prior therapy with a MET-targeting TKI.	• Part 2 is a Phase 2a dose-expansion in which dosing will be at the RP2D on an every second week (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. Note: Effective with protocol version 8.0 (December 2018), accrual to the Basket Cohort is suspended. ○ 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*-

Table 22 Protocol Amendment 7		
SECTION	**ORIGINAL TEXT**	**NEW TEXT**
		amplified, and patients may have received prior therapy with MET-targeting and/or EGFR-targeting agents.
5.1 Overall Design and Plan (continued)	During Part 2, two cohorts will receive Sym015 at the RP2D on a Q2W dosing schedule: • Basket Cohort: A basket cohort of *KRAS* WT, advanced solid tumor malignancy patients with *MET*-amplification will be evaluated. Patients must be MET-targeting TKI-naïve; an exception will be a subset of approximately 6 patients entered who have received prior therapy with a MET-targeting TKI. • NSCLC Cohort: A cohort of *KRAS* WT advanced NSCLC patients with *METex14* mutation will be evaluated. Patients need not be *MET*-amplified and may have received prior therapy with a MET-targeting TKI.	During Part 2, three cohorts will receive Sym015 at the RP2D on a Q2W dosing schedule: • Basket Cohort: A basket cohort of *KRAS* WT, advanced solid tumor malignancy patients with *MET*-amplification will be evaluated. Patients must be MET-targeting TKI-naïve; an exception will be a subset of approximately 6 patients entered who have received prior therapy with a MET-targeting TKI. Note: Effective with protocol version 8.0 (December 2018), accrual to the Basket Cohort is suspended. • NSCLC *MET*-Amplified Cohort: A cohort of advanced NSCLC patients with *MET*-amplification will be evaluated. Patients may have received prior therapy with MET-targeting and/or EGFR-targeting agents. • NSCLC $MET^{Ex14Del}$ Cohort: A cohort of advanced NSCLC patients with $MET^{Ex14Del}$ will be evaluated. Tumors need not be *MET*-amplified, and patients may have received prior therapy with MET-targeting and/or EGFR-targeting agents.
	The number of investigational trial sites…15 to 25 in Part 2.	The number of investigational trial sites…15 to 27 in Part 2.
5.2.1 Rationale for Trial Design	Additionally, this trial design may also allow for the identification of specific tumor types that are more likely to respond to Sym015 treatment.	Emerging literature allowed for the identification of specific tumor types that are more likely to respond to Sym015 treatment (e.g., NSCLC). Note: Effective with protocol version 8.0 (December 2018), accrual to the Basket Cohort is suspended.
5.2.2 Rationale for Trial Population	In Part 2, patients with *MET*-amplified, *KRAS* WT, advanced solid tumor malignancies of any tissue origin will be entered to evaluate the antitumor activity of Sym015. In addition, a cohort of *KRAS* WT NSCLC patients with *MET*ex14 mutation will be entered to evaluate the antitumor activity of Sym015. Nonclinical studies have documented that the activity of Sym015 is greater in tumors with *MET*-amplification and/or *MET*ex14 mutation, suggesting that Sym015 may provide a clinically relevant effect in these patient populations. Similar findings have been observed in preliminary studies in patients with *MET*-amplified tumors of other anti-MET mAbs in early clinical trials.	In Part 2, patients with *MET*-amplified, *KRAS* WT, advanced solid tumor malignancies of any tissue origin will be entered to evaluate the antitumor activity of Sym015 in the Basket Cohort. In addition, a cohort of NSCLC patients with *MET*-amplification and a cohort of NSCLC patients with $MET^{Ex14Del}$ will be entered to evaluate the antitumor activity of Sym015 in these populations. Nonclinical studies have documented that the activity of Sym015 is greater in tumors with *MET*-amplification and/or $MET^{Ex14Del}$, suggesting that Sym015 may provide a clinically relevant effect in these patient populations. Similar findings have been observed in preliminary studies in patients with *MET*-amplified tumors with other anti-MET mAbs in early clinical trials.

Table 22 Protocol Amendment 7		
SECTION	**ORIGINAL TEXT**	**NEW TEXT**
5.3.1 Prescreening for *MET*-amplification and *MET*^{Ex14Del} Status	5.3.1 Prescreening for *MET*-amplification, *METex14*, and *KRAS* Mutational Status The trial site may choose to prescreen patients utilizing archival tumor tissue to confirm *MET*-amplification status*, *METex14* mutation status*, and/or *KRAS* mutational status*... *Part 2 ONLY: Peripheral blood collection for *MET*-amplification assessment, *METex14* assessment, and *KRAS*-mutation assessment… Other liquid biopsy methodologies, except if used to detect *METex14* mutation, will only be allowed if previously approved by the Sponsor…	5.3.1 Prescreening for *MET*-amplification and *MET*^{Ex14Del} Status The trial site may choose to prescreen patients utilizing genomic analysis (e.g., Guardant360 or other similar liquid biopsy methodology) or tumor tissue (archival, or recently obtained if acquired outside of the screening process as part of the site's usual practice) to assess *MET*-amplification status and *MET*^{Ex14Del} status… Peripheral blood collection for assessment in circulating tumor deoxyribonucleic acid (ctDNA) (also referred to as "liquid biopsy") may be used as a local pre-screening methodology by Guardant360 analysis (http://guardanthealth.com/guardant360/). Other liquid biopsy methodologies, if used to detect *MET*^{Ex14Del}, are acceptable alternatives.
5.3.2 Screening	When the trial site identifies a patient suitable for screening, the Sponsor or designee should be contacted to ensure that a cohort is open for inclusion. Once confirmed, the patient may be approached for informed consent.	When the trial site identifies a patient suitable for screening, the Sponsor or designee should be contacted to ensure that a cohort is open for inclusion (applies to Part 1 only). With this assurance, the patient may be approached for informed consent.
	The trial site staff must complete a Screening and Allocation Form, stating the allocated patient number along with the planned dates of screening and the day of first scheduled Sym015 administration (C1/D1), and whether the patient has received prior therapy with MET-inhibiting agents. The planned date of C1/D1 will be agreed upon in collaboration with Sponsor or designee for the dose-escalation cohorts in order to ensure adequate time between dosing of the first patient and dosing of subsequent patients within each cohort.	The trial site staff must complete a Screening and Allocation Form, stating the allocated patient number along with the planned dates of screening and the day of first scheduled Sym015 administration (C1/D1). The planned date of C1/D1 will be agreed upon in collaboration with Sponsor or designee for the dose-escalation cohorts in order to ensure adequate time between dosing of the first patient and dosing of subsequent patients within each cohort (applies to Part 1 only).
	Furthermore, once eligibility is confirmed: • Patients in Part 1… • All patients in the Part 2 Basket Cohort… • For patients in the Part 2 NSCLC Cohort, biopsy for biomarker analysis is optional; archival tissue to be submitted, if available	• Part 1: Patients in Part 1… • Basket Cohort: All patients in the Part 2 Basket Cohort… • NSCLC *MET*-Amplified Cohort: All patients in the Part 2 NSCLC *MET*-Amplified Cohort will have a tumor biopsy performed and submitted for central confirmation of *MET*-amplification status, and for biomarker analysis. Note: Peripheral blood for ctDNA analysis by Guardant 360 will be obtained for assessment of *MET*-amplification status. If central confirmation of *MET*-amplification status cannot be assessed in tumor due to assay failure/technical error, the Sponsor may decide to enroll based on *MET*-amplification detected by Guardant360 on a case per case basis. As data are acquired on concordance between findings in tumor tissue versus ctDNA, the Sponsor may decide to transition to screening for *MET*-amplification using Guardant360 analysis only (e.g., 2+ or 3+ amplification score) without requiring confirmation in a recent or newly performed tumor biopsy.
	Not applicable	• NSCLC *MET*^{Ex14Del} Cohort: All patients in the Part 2 NSCLC *MET*^{Ex14Del} Cohort will have a tumor biopsy performed and submitted for central assessment of *MET*^{Ex14Del} status, and for biomarker analysis.
5.3.6 Flow Chart – Schedule of Assessments	Schedules of assessments are provided in the trial flow chart in Table 3 (Q2W dosing).	Schedules of assessments are provided in the trial flow charts in Table 3 (Part 1 and Part 2 Basket Cohort) and Table 4 (Part 2 NSCLC Cohorts).

Table 22 Protocol Amendment 7		
SECTION	**ORIGINAL TEXT**	**NEW TEXT**
5.4 Recruitment Period	Enrollment is expected to complete by Q3 2018.	Enrollment is expected to complete by Q4 2019.
5.5 Number of Patients	It is estimated that approximately 51-57 patients will be enrolled to receive Sym015 at the RP2D on a Q2W schedule during Part 2. Two cohorts will be included: • Basket Cohort: Approximately 45 patients with *KRAS* WT, advanced solid tumor malignancies with documented and confirmed *MET*-amplification will be enrolled and treated. A subset of 6 patients will have received prior therapy with a MET-targeting TKI.	It is estimated that approximately 51-57 patients will be enrolled to receive Sym015 at the RP2D on a Q2W schedule during Part 2. Three cohorts will be included: • Basket Cohort: Approximately 25 patients with *KRAS* WT, advanced solid tumor malignancies with documented *MET*-amplification will be enrolled and treated. A subset of approximately 6 patients will have received prior therapy with a MET-targeting TKI. Note: Effective with protocol version 8.0 (December 2018), accrual to the Basket Cohort is suspended. NSCLC *MET*-Amplified patients entered to the Basket Cohort will be counted toward the NSCLC *MET*-Amplified Cohort; NSCLC $MET^{Ex14Del}$ patients entered to the Basket Cohort will be counted toward the NSCLC $MET^{Ex14Del}$ Cohort; patients with both will be counted as *MET*-Amplified.
	• NSCLC Cohort: 6-12 patients with *KRAS* WT, advanced NSCLC with documented *METex14* mutation will be enrolled and treated. Patients need not be *MET*-amplified and may have received prior therapy with a MET-targeting TKI.	• NSCLC *MET*-Amplified Cohort: approximately 20 patients with advanced NSCLC with documented *MET*-amplification will be enrolled and treated. Patients may have received prior therapy with MET-targeting agents and/or EGFR-targeting agents.
	Not applicable	• NSCLC $MET^{Ex14Del}$ Cohort: approximately 6-12 patients with advanced NSCLC with documented $MET^{Ex14Del}$ will be enrolled and treated. Tumors need not be *MET*-amplified, and patients may have received prior therapy with MET-targeting and/or EGFR-targeting agents. Note: NSCLC patients with tumors identified as both *MET*-Amplified and $MET^{Ex14Del}$ will be enrolled to the *MET*-Amplified cohort.
6.1 Inclusion Criteria	Part 2 ONLY: b. Tumor documented to be KRAS WT by local assessment according to institutional standards. Note: Peripheral blood collection for *KRAS*-mutation assessment in ctDNA will be allowed as a local pre-screening methodology by Guardant360* analysis. Other liquid biopsy methodologies, except if used to detect *MET*ex14 mutation, will only be allowed if previously approved by the Sponsor. c. Basket Cohort ONLY: • Confirmed *MET*-amplification by local… • No prior therapy with MET-targeting agents… • Willingness to undergo a pre- and post-dosing biopsy…	Part 2 ONLY: b. Basket Cohort ONLY: • Tumor documented to be *KRAS* WT by local assessment according to institutional standards. If *KRAS* WT is not previously documented and if archival tissue is not available for pretrial assessment, patient must be willing to undergo a tumor biopsy to confirm eligibility. Note: Peripheral blood collection for *KRAS*-mutation assessment in ctDNA will be allowed as a local pre-screening methodology by Guardant360* analysis. Other liquid biopsy methodologies, if used to detect $MET^{Ex14Del}$, are acceptable alternatives. • Confirmed *MET*-amplification by local… • No prior therapy with MET-targeting agents… • Willingness to undergo a pre- and post-dosing biopsy…

Table 22 Protocol Amendment 7		
SECTION	**ORIGINAL TEXT**	**NEW TEXT**
6.1 Inclusion Criteria (continued)	d. NSCLC Cohort ONLY: • Documented *METex14* mutations (patients need not be *MET*-amplified and may have received prior therapy with a MET-targeting TKI) Note: Patients with malignancies other than NSCLC and with documented *METex14* mutation may be considered for entry to this cohort following discussion with the Sponsor's Medical Monitor(s). Note: *METex14* mutation status to be documented according to local institutional standards. Assessment in ctDNA by Guardant360 technology or equivalent is allowed. Subsequent confirmation in tumor tissue is preferred but not required.	c. NSCLC *MET*-Amplified Cohort ONLY: • Documented NSCLC meeting disease criteria as defined above • Documented *MET*-amplification by either: o Local assessment in a recent* tumor biopsy; i.e., G:CN ≥3.0 scored in 50 tumor nuclei by FISH, CISH, SISH or similar assay, or a copy number >5 by NGS or qPCR (subsequent central confirmation required, however patient may be enrolled and treated based on local assessment, before central confirmation results have been obtained) *Tissue for local assessment may be from a recent tumor biopsy, defined as one performed since last documented disease progression as part of the site's usual practice, and where no intervening antineoplastic therapy has been administered; otherwise tissue from a newly performed biopsy must be obtained and submitted. o Central confirmation** in a newly performed pre-dosing tumor biopsy; i.e., G:CN ≥3.0 scored in 50 tumor nuclei by FISH o **If central confirmation of *MET*-amplification status cannot be assessed in tumor due to assay failure/technical error, the Sponsor may decide to enroll based on *MET*-amplification detected by Guardant360 on a case per case basis (see Note below regarding Guardant360 analysis). • May have received prior therapy with MET-targeting and/or EGFR-targeting agents (antibodies or TKIs) • Willingness to undergo a pre-dosing biopsy (mandatory unless a recent* tumor biopsy as defined above is available), and potentially a biopsy at the End of Cycle 2 (EOC2) (optional), from a primary or metastatic tumor site considered safely accessible for biopsy Note: Peripheral blood for ctDNA analysis by Guardant 360 will be obtained for assessment of *MET*-amplification status. As data are acquired on concordance between findings in tumor tissue versus ctDNA, the Sponsor may decide to transition to screening for *MET*-amplification using Guardant360 analysis only (e.g., 2+ or 3+ amplification score) without requiring confirmation in a recent or newly performed tumor biopsy.
6.1 Inclusion Criteria (continued)	*Not applicable*	d. NSCLC $MET^{Ex14Del}$ Cohort ONLY: • Documented NSCLC meeting disease criteria as defined above • Documented $MET^{Ex14Del}$ (tumors need not be MET-amplified)

Table 22 Protocol Amendment 7		
SECTION	**ORIGINAL TEXT**	**NEW TEXT**
		• Note: *MET*^{Ex14Del} status to be documented according to local institutional standards. Assessment in ctDNA by Guardant360 technology or equivalent is allowed. Tissue from a recent* or newly performed pre-dosing tumor biopsy must be submitted for central assessment. *Recent tumor biopsy, defined as one performed since last documented disease progression as part of the site's usual practice, and where no intervening antineoplastic therapy has been administered; otherwise tissue from a newly performed biopsy must be obtained and submitted. • May have received prior therapy with MET-targeting and/or EGFR-targeting agents (antibodies or TKIs) • Willingness to undergo a pre-dosing biopsy (mandatory unless a recent* tumor biopsy as defined above is available), and potentially a biopsy at the EOC2 (optional), from a primary or metastatic tumor site considered safely accessible for biopsy Note: Peripheral blood for ctDNA analysis by Guardant 360 will be obtained for assessment of METEX14Del status.
6.2 Exclusion Criteria	2. <u>Part 2 ONLY</u>: a. Prior therapy with MET-inhibiting agents Note: Exceptions will be a subset of approximately 6 patients entered to the Basket Cohort after having received prior therapy with a MET-targeting TKI, and patients entered to the NSCLC Cohort who may have received prior therapy with a MET-targeting TKI. b. Prior therapy with antibody to HGF c. <u>Basket Cohort ONLY</u>: Tumor status demonstrating *MET*-polysomy in the absence of *MET*-amplification, as specified Note: Patients in the NSCLC Cohort with polysomy are eligible d. Radiotherapy against target lesions within 4 weeks prior to C1/D1, unless there is documented progression of the lesion following the radiotherapy Note: Radiotherapy for pain control against non-target lesions is allowed, as long as it does not influence bone marrow function	2. <u>Part 2 ONLY</u>: a. <u>Basket Cohort</u>: • Prior therapy with MET-inhibiting agents Note: Exceptions will be a subset of approximately 6 patients entered to the Basket Cohort after having received prior therapy with a MET-targeting TKI • Prior therapy with antibody to HGF b. <u>Basket Cohort and NSCLC *MET*-Amplified Cohort</u>: Tumor status demonstrating *MET*-polysomy in the absence of *MET*-amplification, as specified Note: Patients in the NSCLC *MET*^{Ex14Del} Cohort with polysomy are eligible. c. Radiotherapy against target lesions within 4 weeks prior to C1/D1, unless there is documented progression of the lesion following the radiotherapy Note: Radiotherapy for pain control against non-target lesions is allowed, as long as it does not influence bone marrow function
	3. Immunosuppressive or systemic hormonal therapy (> 10 mg daily prednisone equivalent) within 2 weeks prior to C1/D1 with the exception of the following allowed therapies: a. Hormonal therapy… b. Nasal, ophthalmic, inhaled… c. Oral replacement glucocorticoid… d. Low-dose maintenance steroid therapy…	3. Immunosuppressive or systemic hormonal therapy (> 10 mg daily prednisone equivalent) within 2 weeks prior to C1/D1 (for exceptions, see Section 7.5.2)

Table 22 Protocol Amendment 7		
SECTION	**ORIGINAL TEXT**	**NEW TEXT**
7.5.1 Allowed Medication/ Therapy and Procedures During the Trial	*Not applicable*	Bisphosphonates and denosumab: Bisphosphonates and denosumab for bone metastases and other skeletal conditions provided the patient is on a stable dose for at least 2 months prior to study start and remains on the stable dose while receiving study treatment
7.5.2 Prohibited Medication/ Therapy and Procedures During the Trial	*Not applicable*	Basket Cohort ONLY: MET-targeting therapies, except in subset of approximately 6 patients
8.1.2 Demographics	To include date of birth, sex, race and ethnicity.	To include date of birth, sex, race and ethnicity (as allowed by country)
8.2.6 Physical Examination	To include evaluation of the following: General appearance, skin, head, ears, eyes, nose, throat, neck/thyroid, chest, cardiovascular system, abdomen, musculoskeletal system, lymph nodes, neurologic status, and mental status. At Screening, include height (without shoes, rounded to nearest centimeter).	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.
8.3.3 Archival Tumor Tissue for *MET* and *KRAS* Assessment (Part 1 and Part 2 Basket Cohort)	8.3.3 Archival Tumor Tissue for *MET* and *KRAS* Assessment o Part 2: Eligibility assessment for *KRAS* mutational status… Basket Cohort: It is preferred that the eligibility assessment for *MET*-amplification be done… NSCLC Cohort: Eligibility assessment for *METex14* mutation status…	8.3.3 Archival Tumor Tissue for *MET* and *KRAS* Assessment (Part 1 and Part 2 Basket Cohort) o Part 2: Eligibility assessment for KRAS mutational status… It is preferred that the eligibility assessment for *MET*-amplification be done… NSCLC *MET*^{Ex14Del} Cohort (*pre-protocol v8.0*): Eligibility assessment for *MET*^{Ex14Del} status… (applies only to patients with *MET*^{Ex14Del} tumors entered prior to suspension of the Basket Cohort and establishment of NSCLC *MET*^{Ex14Del} Cohort).
8.3.5 Tumor Biopsy for *MET* Status and Biomarker Analysis (Part 2 NSCLC *MET*-Amplified Cohort and NSCLC *MET*^{Ex14Del} Cohort)	*Not applicable*	To be assessed centrally: • Screening (Mandatory) Note: It will be permissible to perform this procedure outside the 14-day screening period, provided informed consent for the trial has been obtained o NSCLC *MET*-Amplified Cohort: Required; tissue from a newly performed pre-dosing tumor biopsy must be submitted for central confirmation of *MET*-amplification (Patients may be entered and treated based on local assessment of a recent tumor biopsy [if available and performed outside of the screening process as part of the site's usual practice] provided no intervening antineoplastic therapy has been administered; otherwise tissue from a newly performed biopsy must be obtained and submitted) o NSCLC *MET*^{Ex14Del} Cohort: Required; tissue from a recent or newly performed pre-dosing tumor biopsy must be submitted for central assessment of *MET*^{Ex14Del}

Table 22 Protocol Amendment 7		
SECTION	**ORIGINAL TEXT**	**NEW TEXT**
		(Patients may be entered and treated based on local institutional standards; alternatively, assessment in ctDNA by Guardant360 technology or equivalent is allowed; a recent [as defined above] or newly performed pre-dosing biopsy must still be submitted) • Post-dosing (Optional) EOC2 (i.e., coinciding with time of first response assessment) or upon PD, whichever occurs first Note: 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
8.7 Blood Sample for Genomic and Biomarker Analyses	8.7 Biomarker Blood Sample To be performed only after eligibility has been confirmed. Analysis of all samples taken for pharmacodynamic assessments will be performed at a central laboratory. A detailed laboratory manual specifying sample collection, handling, storage, and shipment will be provided to the trial sites. • Screening, after confirmation of eligibility • End of Cycle 2 (coinciding with time of first response assessment) or upon PD, whichever occurs first Note: End of cycle assessments may be performed at any time during the week prior to Day 1 of the next cycle • EOT	8.7 Blood Sample for Genomic and Biomarker Analyses To include assessment of *MET*-amplification and *MET*^{Ex14Del} status; analysis of all samples taken will be performed at a central laboratory. A detailed laboratory manual specifying sample collection, handling, storage, and shipment will be provided to the trial sites. • Screening (it will be permissible to perform this procedure outside the 14-day screening period, provided informed consent for the trial has been obtained) • EOC2 (coinciding with time of first response assessment or upon PD, whichever occurs first) • Note: 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 • EOT (if after EOC2; need not repeat if patient is discontinuing at the EOC2 or if a sample was obtained upon PD)
9.3 Serious Adverse Event Recording and Reporting	In case of an SAE, the Investigator must, within 24 hours of first awareness of the event, report the SAE to the Sponsor or designee by fax or e-mail. Fax number(s) and e-mail address will be stated in the SAE report form and the SAE report form instructions.	In case of an SAE, the Investigator must, within 24 hours of first awareness of the event, report the SAE to the Sponsor (or designee) by fax or e-mail. Fax number(s) and e-mail address(es) will be stated on the SAE Report Form and the SAE Report Form Completion Instructions. SAE follow-up information must also be reported to the Sponsor (or designee) within 24 hours of awareness.
10.1 Statistical Considerations and Analysis Plan	*Not applicable*	No formal hypothesis testing is planned. Descriptive statistics will be used to summarize the safety, tolerability, pharmacokinetics, and clinical activity of Sym015 in all patient cohorts. Data will be described and summarized as warranted by sample sizes. Listings will be used in place of tables in the event of small sample sizes. Dose-escalation assessment will be based on the DLT-evaluable population, defined as patients who complete the DLT assessment window. All other analyses will be based on the safety-evaluable population, defined as all patients who receive any amount of the study drug. Continuous variables will be summarized with the use

Table 22 Protocol Amendment 7		
SECTION	**ORIGINAL TEXT**	**NEW TEXT**
		of means, standard deviations, medians, and ranges; categorical variables will be summarized using counts and percentages. All summaries will be presented separately by cohort, in both Part 1 and Part 2 of the study. All details of the data analyses will be described in the Statistical Analysis Plan.
10.2 Sample Size Determination	In Part 2 of the trial, the primary endpoint is documented OR in the Basket Cohort, assessed by RECIST v1.1, at any time during trial participation by Investigator assessment. It is planned to include 45 patients with various advanced solid tumor malignancies, documented and confirmed as MET-amplified and KRAS WT in this cohort. It is expected to see a meaningful number of patients with OR, based on preclinical data as well as data from other MET-targeting mAbs presently in clinical development. The expected range of OR is in the range of 25-50%, depending on histology, previous therapies and other prognostic factors defining the enrolled patient population. Sample size considerations are based on a Simon's Optimal 2-stage design (31), testing a null hypothesis (poor response) of 11% OR versus an alternative hypothesis (promising response) of 25% OR at an approximate 10% 1-sided significance level and 85% power. In Stage 1 (futility assessment) enrollment will include 20 evaluable patients for OR assessment and accrual will continue to Stage 2, if at least 3 of 20 (15%) patients respond (PR or CR). The probability of early stopping assuming poor response is about 62%. In stage 2, if the futility boundary is exceeded, an additional 25 patients evaluable for OR assessment will be enrolled for a total of 45 patients. Further development will be considered warranted if at least 8 of 45 (18%) patients respond. For the NSCLC Cohort, assuming the response rate is at least 20%, there is a 74 93% probability of observing 1 or more responses in 6-12 patients.	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 (Table 10). 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.
10.4.2 Part 2	The primary objective of Part 2 is to evaluate the antitumor activity of Sym015 when administered at the Q2W RP2D. This will be assessed by the primary endpoint for Part 2, documented OR in the Basket Cohort, 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. Number and percentages of patients with documented OR will be presented including corresponding 95% exact Confidence Intervals (CI).	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. Number and percentages of patients with documented OR will be presented including corresponding 90% exact Confidence Intervals (CI), separately for each cohort.
10.5.1 Efficacy Endpoints and Analyses	Number and percentages of patients with documented OR in the dose-escalation part will be presented including corresponding 95% exact CI. All documented ORs (Part 1 and 2) will be listed including duration (in days) of OR, measured from time of first PR or CR to PD. Time to disease progression (TTP), PFS, and OS will	Number and percentages of patients with documented OR in the dose-escalation part will be presented including corresponding 90% exact CI. All documented ORs (Part 1 and Part 2) will be listed including duration (in days) of OR, measured from time of first PR or CR to PD. Time to disease progression (TTP), PFS, and OS will

Table 22 Protocol Amendment 7		
SECTION	**ORIGINAL TEXT**	**NEW TEXT**
	be summarized using the product-limit method and Kaplan-Meier plots. The median TTP, PFS, and OS, including 95% CI, will be calculated.	be summarized using the product-limit method and Kaplan-Meier plots. The median TTP, PFS, and OS, including 90% CI, will be calculated.
10.6 Interim Analysis	All relevant safety and toxicity data will be reviewed on an ongoing base throughout the trial. Refer to Section 12. During Part 1, clinical and laboratory safety data will be assessed when the first patient in a 3-patient cohort has completed the first dose of Sym015, when 3 patients have completed Cycle 1, and if the cohort is expanded, when 6 patients have completed Cycle 1. Based on an overall evaluation of Part 1 of the trial, the Q2W RP2D and highest safe dose tested will be determined. In Part 2 an assessment of futility will be performed when 20 patients evaluable for OR have been included in the Basket Cohort. The trial will be stopped for futility if less than 3 of the evaluable patients have documented OR.	No interim analysis is planned.
14. Data Handling and Record Keeping	Data will be handled according to good data management practices and comply with Federal regulations including, but not limited to, 21 CFR Part 11 and ICH GCP E6(R2).	Study data collection, processing, transfer, and reporting, as well as handling of study personnel information, will be done in compliance with ICH E6(R2) GCP and all applicable data protection regulations, including Regulation (EU) 2016/679 of the European Parliament and of the Council of 27 April 2016 on the protection of natural persons with regard to the processing of personal data and on the free movement of such data (General Data Protection Regulation; GDPR).
14.3 Case Report Form	The Investigator or designee will be responsible for entering trial data in the CRF provided. It is the responsibility of the Investigator to ensure the accuracy of the data entered in the CRF. All collected data will be entered into a validated database.	*Text removed; section replaced (see below)*
14.3 Data Processing	The process of entering or uploading of data from trial sites will assure the accuracy of data entry into the database and include a validation at data entry time (real time validation). Entry or electronic transfer of other data than those directly from trial sites (e.g. imports of laboratory results) will follow the Sponsor requirements for data flow and transfer. The Sponsor or designee will be responsible for data processing in accordance with the applicable data management SOPs. A Data Management Plan will be generated for this trial. Database lock will occur once quality control procedure, and quality assurance procedures (if applicable) have been completed. The PDF files of the CRFs will be provided to the Investigator before access to the CRF is revoked.	A Data Management Plan (DMP) will be prepared for this trial. The Sponsor (or designee) will be responsible for data processing in accordance with applicable Data Management SOPs and the trial DMP. Once recorded within the electronic CRF, study data will pass through a set of preprogrammed data validation checks designed to identify inconsistencies and other data errors, and will undergo an additional study-specific data review process. Data issues will be queried via the electronic data capture (EDC) system and query resolutions will be documented. Entry and processing of data other than those directly recorded on electronic CRFs by trial sites (e.g., imports of laboratory results) will follow vendors' SOPs. Transfer of such data from vendors to Sponsor (or designee) will be handled according to vendors' data transfer SOPs and the Sponsor data transfer requirements with full compliance to applicable regulations. Database Lock will occur upon reaching the predefined

Table 22 Protocol Amendment 7		
SECTION	**ORIGINAL TEXT**	**NEW TEXT**
		data cut-off for primary analysis and completion of Sponsor's (or designee's) quality control and quality assurance procedures. Portable Document Format (PDF) files of the electronic CRFs will be provided to the Investigator upon removal of access to the electronic CRFs.
14.4 Clinical Trial Report	*Not applicable*	Following study completion, a final integrated clinical/statistical CTR will be prepared.
14.5 Compliance with the General Data Protection Regulation	*Not applicable*	The applicable EU data protection legislation requires that parties enter into a written contract if one party (data processor) processes personal data on behalf of the other party (data controller). This written contract must regulate the subject-matter and duration of the processing, the nature and purpose of the processing, the types of personal data and categories of data subjects, as well as the obligations and rights of the data controller…
17 Changes to the Final Clinical Trial Protocol	Changes to the CTP will not be implemented without agreement from the Sponsor and prior review and written approval from the HA and IRB/EC, except where necessary to eliminate an immediate hazard to the patient. No protocol waivers will be allowed.	Changes to the protocol will not be implemented without agreement from the Sponsor and prior review and written approval from the appropriate Health Authority (as indicated) and the IRB/EC, except where necessary to eliminate an immediate hazard to the patients. No protocol waivers will be allowed. Protocol changes to eliminate an apparent hazard to trial patients may be implemented by the Investigator immediately. The Investigator must then, without delay, inform the local IRB/EC, and the Sponsor (or designee) will immediately notify local governing Health Authorities.

Signature Page for VV-CLIN-000572 v1.0

Approval	[redacted] Medical 11-Dec-2018 07:02:56 GMT+0000
Approval	[redacted] Clinical 11-Dec-2018 09:44:32 GMT+0000
Approval	[redacted] Regulatory 11-Dec-2018 16:32:49 GMT+0000
Approval	[redacted] Clinical 11-Dec-2018 16:40:25 GMT+0000

Signature Page for VV-CLIN-000572 v1.0