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Protocol for Study M22-137

Non-Small Cell Lung Cancer: Telisotuzumab Vedotin (ABBV-399) Phase 2 Study

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FULL TITLE: Phase 2, Open-Label Study in Subjects with Previously Untreated *MET* Amplified Locally Advanced/Metastatic Non-Squamous Non-Small Cell Lung Cancer (NSCLC)

Incorporating Versions 1.0, 2.0, 2.1 (China Only), 2.2 (Japan Only), 2.3 (EU Only), and 3.0

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1 SYNOPSIS

Title: Phase 2, Open-Label Study in Subjects with Previously Untreated *MET* Amplified Locally Advanced/Metastatic Non-Squamous Non-Small Cell Lung Cancer (NSCLC)	
Background and Rationale:	Telisotuzumab vedotin (ABBV-399) is an anti-c-Met antibody drug conjugate (ADC) for the treatment of c-Met-overexpressing solid tumors. The pharmacology, toxicology, and pharmacokinetic profiles of telisotuzumab vedotin were characterized to support initiation of a Phase 2 clinical trial in previously untreated subjects with *MET* amplified non-squamous, non-small cell lung cancer (NSCLC). The non-clinical and clinical data together are considered an acceptable rationale for the treatment of previously untreated subjects with *MET* amplified non-squamous NSCLC with telisotuzumab vedotin in the context of a clinical trial.
Objective(s) and Endpoint(s):	**Objectives** The primary objective is to determine: • Objective response rate (ORR) of telisotuzumab vedotin in previously untreated subjects with *MET* amplified non-squamous NSCLC. The secondary objectives are to determine: • Duration of response (DoR); • Disease control rate (DCR); • Progression-free survival (PFS); • Overall Survival (OS); • Time to deterioration in cough or pain or dyspnea as measured by the cough, pain, and dyspnea items of the European Organization for Research and Treatment of Cancer Quality of Life Questionnaire Lung Cancer Module 13 (EORTC QLQ-LC13); • Time to deterioration of physical functioning as measured by the physical functioning domain of the EORTC-QLQ-Core 30 (EORTC QLQ-C30); • Change from baseline in quality of life as measured by the global health status/quality of life domain of the EORTC QLQ-C30; • Safety and tolerability. The additional objectives are: • Correlative studies comparing c-Met status (nucleic acid and protein) in tumor and plasma circulating tumor deoxyribonucleic acid (ctDNA) with PFS, ORR and DoR; • Correlative studies to identify predictive biomarkers that associate with PFS, ORR, DoR; • Explore the relationship between pharmacokinetic (PK) and pharmacodynamic (PDx), safety, and efficacy endpoints; • Assess the following patient reported outcomes (PROs): • EuroQoL 5 Dimension 5 Level (EQ-5D-5L);

	• Patient-Reported Outcome Common Terminology Criteria for Adverse Events (PRO-CTCAE) data will be presented using descriptive statistics; • Remaining scales and subscales of the EORTC QLQ-C30; • Remaining items of the EORTC QLQ-LC13; • Patient Global Impression of Change (PGIC) and Patient Global Impression of Severity (PGIS). **Endpoints** Primary Endpoint: • Objective response rate (ORR) assessed by an independent central review (ICR). ORR will be defined as the proportion of subjects with a confirmed complete response (CR) or confirmed partial response (PR) based on Response Evaluation Criteria in Solid Tumors (RECIST), version 1.1. Secondary Endpoints: • Duration of Response (DoR): DoR will be defined for confirmed responders by ICR as the time from the initial response (CR or PR) to the first occurrence of radiographic progression per RECIST v1.1, or death from any cause. • Disease control rate (DCR): Disease control rate will be defined as the percentage of subjects with best overall response of confirmed CR or confirmed PR, or stable disease (SD) for at least 12 weeks following first dose of study drug, based on RECIST, version 1.1. • Progression Free Survival (PFS) per ICR: PFS will be defined as the time from the subject's first dose of study drug to the first occurrence of radiographic progression based on RECIST, version 1.1 or death from any cause. Subjects with no PFS event will be censored at the last evaluable radiographic assessment per ICR. Subjects with no event and no evaluable post-baseline assessment will be censored at subject's first dose of study drug. • Overall Survival (OS): OS will be defined as the time from subject's first dose of study drug to the event of death from any cause. Subjects with no documented death will be censored at the last known alive date. • Time to deterioration in cough or pain or dyspnea as measured respectively by the cough, pain, and dyspnea items of the European Organization Lung Cancer Module 13 (EORTC QLQ-LC13). Time to first deterioration will be defined as the time from baseline until a first ≥ 10-point change or a confirmed clinically meaningful deterioration in a symptom score or an initial ≥ 10-point change or a confirmed clinically meaningful deterioration followed by death. • Time to deterioration of physical functioning as measured by the physical functioning domain of the EORTC-QLQ-Core 30 (EORTC QLQ-C30). Time to first deterioration will be defined as the time from baseline until a first ≥ 10-point change or a

	confirmed clinically meaningful deterioration in a symptom score occurs. • Change from baseline in quality of life as measured by the global health status/quality of life domain of the EORTC QLQ-C30. <u>Additional Efficacy Endpoints:</u> • Change from baseline in the EuroQoL 5 Dimension 5 Level (EQ-5D-5L) including the Visual Analog Scale (VAS). • Patient-Reported Outcome Common Terminology Criteria for Adverse Events (PRO-CTCAE) data. • Change from baseline in cough or pain or dyspnea as measured respectively by the cough, pain, and dyspnea items of the EORTC QLQ-LC13. • Change from baseline in remaining scales and sub-scales of the EORTC QLQ-C30. • Change from baseline in items of the EORTC QLQ-LC13. • Change from baseline in Patient Global Impression of Change (PGIC) and Patient Global Impression of Severity (PGIS) scores. <u>Safety Endpoints:</u> Safety and tolerability will be assessed by evaluating AEs, physical examinations, and changes in laboratory data and vital signs, as well as drug discontinuation or dosing modification due to adverse events (AEs). <u>Pharmacokinetic Endpoints:</u> Blood samples for assay of telisotuzumab vedotin conjugate in serum and free cytotoxin monomethyl auristatin E (MMAE) toxin levels in plasma, will be collected at specific time-points, will be tabulated and summarized, and may be used for additional exploratory analyses as deemed appropriate. Serum samples for assay of telisotuzumab vedotin anti-drug antibodies and neutralizing anti-drug antibodies (ADA/nADA) will also be collected at specified time-points. <u>Biomarker Research:</u> Known and/or novel disease-related or drug-related biomarkers will be evaluated in circulation or in tumor tissue. Types of biomarkers may include nucleic acids, proteins, lipids, and/or metabolites, either free or in association with particular cell types. The analyses may include but are not limited to c-Met protein/gene expression, genomic alterations in *MET* (exon 14 skipping, somatic mutations), gene alterations in NSCLC (*KRAS*, *RET*, *p53* mutations, etc.), immune cell infiltrates, or biomarkers related to NSCLC. Correlative studies of the association of biomarkers with clinical responses may be carried out. Biospecimens (plasma and tumor tissue) will be collected to support the biomarker research objectives of the study. Subjects will have *MET* amplification in tissue determined by the Sponsor-designated central laboratory or in plasma and/or tissue by a Sponsor-approved assay. For all enrolled subjects, tumor material and

	plasma are requested to allow central assay evaluation. The tumor material will also be used for other biomarker analysis. Plasma will be collected at various time points in all parts of the study. An optional tumor biopsy at the time of disease progression should be collected to understand the mechanism of resistance.
Investigator(s):	Multicenter
Study Site(s):	Up to 110 sites in approximately 15 countries.
Study Population and Number of Subjects to be Enrolled:	A total of approximately 70 efficacy evaluable subjects with previously untreated *MET* amplified locally advanced/metastatic non-squamous NSCLC will be enrolled in the trial.
Investigational Plan:	This is a Phase 2, single arm, open-label, global study to determine the ORR of telisotuzumab vedotin in previously untreated subjects with *MET* amplified locally advanced/metastatic non-squamous NSCLC. The study will enroll approximately 70 efficacy evaluable subjects and has two interim analyses planned after approximately 20 and 50 efficacy evaluable subjects have had the chance to be followed for at least 6 months. Efficacy and safety of telisotuzumab vedotin will be evaluated. Subjects will receive telisotuzumab vedotin until meeting study drug discontinuation criteria.
Key Eligibility Criteria:	• Subjects must have completed an informed consent. • Subject must be an adult, at least 18 years old. • Subject must have *MET* amplification in tumor tissue as determined by the Sponsor-designated central laboratory *MET* FISH Assay or in plasma and/or tissue by a Sponsor-approved assay. • Subject must have histologically documented non-squamous adenocarcinoma NSCLC that is locally advanced or metastatic. • Subjects with alterations in *EGFR*, *ALK*, *ROS1*, or *BRAF* that predict sensitivity to available targeted therapy are not eligible. Subjects with other alterations that are candidates for available targeted therapy are not eligible. • Subject must have measurable disease per RECIST version 1.1. • Subject must have an Eastern Cooperative Oncology Group (ECOG) Performance Status of 0 or 1. • Subject must have no prior systemic therapy for locally advanced/metastatic NSCLC. Limited treatment with no more than 1 cycle of chemotherapy is allowed prior to receiving the first dose of study drug provided there is no evidence of progression. Subject may have received prior adjuvant/neoadjuvant systemic chemotherapy and/or radiation and/or immunotherapy provided that the subject has not progressed on or within 6 months of completing the regimen and it was completed ≥ 6 months before subject's first dose of study drug. • Subject must not have received prior c-Met-targeted antibodies.

	• Subject must not have NSCLC that is eligible for treatment with curative intent.
	• Subjects with metastases to the central nervous system (CNS) are eligible only after definitive therapy (such as surgery or radiotherapy) is provided and:
	  • There is no evidence of progression of CNS metastases at least 2 weeks after definitive therapy.
	  • They are asymptomatic and off or on a stable or reducing dose of systemic steroids and/or anticonvulsants for at least 2 weeks prior to first dose of telisotuzumab vedotin.
	• Subjects must not have a history of other malignancies except:
	  • Malignancy treated with curative intent and with no known active disease present for ≥ 2 years before the first dose of study drug and felt to be at low risk for recurrence by investigator.
	  • Adequately treated non-melanoma skin cancer or lentigo maligna without evidence of disease.
	  • Adequately treated carcinoma in situ without current evidence of disease.
	• Subject must not have a history of idiopathic pulmonary fibrosis, organizing pneumonia (e.g., bronchiolitis obliterans), drug-induced pneumonitis, or idiopathic pneumonitis, or evidence of active pneumonitis on screening chest computed tomography (CT) scan.
	• History of radiation pneumonitis in the radiation field (fibrosis) is permitted.
	• Subject must not have unresolved adverse events (AEs) ≥ Grade 2 from prior anticancer therapy, except for alopecia or anemia.
	• Subject must not have had major surgery within 21 days prior to the first dose of telisotuzumab vedotin.
	• Subject must not have clinically significant condition(s) including but not limited to the following:
	  • Clinically significant vascular disease, including:
	  Myocardial infarction within 1 year or stroke within 6 months prior to first dose of study drug, or unstable or uncontrolled disease/condition related to or affecting cardiac function (e.g., unstable angina, congestive heart failure, New York Heart Association Class III – IV), cardiac arrhythmia (CTCAE Version 5 Grade 2 or higher), or clinically significant electrocardiogram (ECG) abnormalities.
	  • Clinically significant liver disease, including hepatitis, current alcohol abuse, or cirrhosis.
	  • Grade ≥ 2 edema or lymphedema.
	  • Grade ≥ 2 ascites or pleural effusion.
	  • Grade ≥ 2 neuropathy.
	  • Active uncontrolled bacterial or viral infection.

Study Drug and Duration of Treatment:	Enrolled subjects will receive telisotuzumab vedotin at 1.9 mg/kg every 2 weeks IV. Subjects will receive treatment until meeting study drug discontinuation criteria.
Date of Protocol Synopsis:	07 March 2023

2 INTRODUCTION

2.1 Background and Rationale

Why Is This Study Being Conducted?

The c-Met receptor tyrosine kinase (TK) is the cell surface receptor for hepatocyte growth factor (HGF) encoded for by the *MET* proto-oncogene.[1] The c-Met/HGF axis is aberrantly activated in multiple cancers through *MET* genomic amplification, exon 14 skipping, transcription, and ligand-dependent mechanisms, thereby contributing to tumor progression, angiogenesis, invasive growth, metastasis, and resistance to therapies.[1] Reported prevalence of *MET* amplification in NSCLC is dependent upon the assay and cut-off used. Based on the *MET/CEP7* ratio, reported prevalence of low (≥1.8 to ≤2.2), intermediate (>2.2 to <5), and high (≥5) amplification is 3.6%, 3.0%, and 0.8%, respectively.[2] About 90% of *MET* amplified tumors display c-Met protein overexpression by IHC.[3] The development of c-Met/HGF axis inhibitors, both antibodies and small molecules, has been an active area of cancer research and several of these inhibitors have been clinically validated in Phase 2 trials in patients with NSCLC tumors harboring *MET* exon 14 skipping mutations. Single arms trials have also shown preliminary activity of small molecule inhibitors of the c-Met/HGF axis in patients with *MET* amplified non-small cell lung cancer (NSCLC).[4,5]

Treatment options for patients with tumors harboring *MET* amplification are extremely limited, with no approved therapeutics. For patients whose tumors harbor actionable alterations for which targeted therapy is approved in the frontline, treatment with targeted agents would be indicated. For patients without targetable genetic alteration, first line treatment typically includes an immune checkpoint inhibitor with or without platinum-based chemotherapy.

Telisotuzumab vedotin (ABBV-399) is an antibody-drug conjugate (ADC) comprised of the antibody ABT-700 (telisotuzumab) conjugated to the microtubule inhibitor and cytotoxin monomethylauristatin E (MMAE) via a cleavable valine-citrulline (vc) linker. ABT-700 is a "humanized" recombinant $IgG_1\kappa$ that targets a unique epitope of c-Met resulting in blockade of both HGF-dependent and HGF-independent c-Met signaling.[6]

Nonclinical data demonstrates that telisotuzumab vedotin is potently cytotoxic against human tumor cells lines that over-express c-Met in both amplified and non-amplified *MET* genetic settings.[7]

In the c-Met overexpressing EGFR WT NSQ NSCLC cohort of 52 efficacy evaluable subjects from Study M14-239, an ORR of 36.5% has been observed.[8] An exploratory analysis of 10 subjects (from a subsequent interim analysis) with *MET* amplification demonstrated encouraging preliminary efficacy with an ORR of 80% (8/10 subjects) (AbbVie data on file). The overall safety profile of telisotuzumab vedotin in Study M14-239 is consistent with that previously observed and as reported in IB edition 8.

Given the encouraging preliminary efficacy and the acceptable safety profile in c-Met overexpressing NSQ NSCLC in both amplified and non-amplified *MET* genetic settings, the benefit:risk of telisotuzumab vedotin monotherapy in patients with non-squamous NSCLC is positive and warrants continued investigation.

The main purpose of the study is to determine the objective response rate (ORR) of telisotuzumab vedotin in previously untreated subjects with *MET* amplified non-squamous NSCLC.

The clinical hypothesis is the objective response rate (ORR) of telisotuzumab vedotin in previously untreated subjects with *MET* amplified non-squamous NSCLC is greater than 40%.

2.2 Benefits and Risks to Subjects

This is the second study in the Phase 2 program for telisotuzumab vedotin. Telisotuzumab vedotin is an ADC that exhibits robust preclinical efficacy in a broad range of tumor types. The pharmacology, toxicology, and pharmacokinetic profiles of telisotuzumab vedotin were characterized to support initiation of a Phase 1 clinical trial in subjects with advanced solid tumors. The ongoing Phase 2 study (M14-239) in previously treated c-MET overexpressing NSCLC has encouraging activity and acceptable safety with the safety data from the most recent interim analysis (#4) demonstrating a safety profile that is consistent with the previous interim analysis. Of note, the safety profile in the 10 MET amplified subjects was consistent with the safety dataset in the M14-239 study (AbbVie, data on file). In totality, the clinical data demonstrate an acceptable benefit and risk to support initiation of a Phase 2 clinical trial in previously untreated subjects with *MET* amplified non-squamous NSCLC.

Further details, including safety data, are provided in the current Telisotuzumab Vedotin Investigator's Brochure.

Considering the coronavirus – 2019 (COVID-19) pandemic, the benefit/risk to subjects participating in this study has been re-evaluated. As subjects with NSCLC are considered to be immunocompromised, and therefore more susceptible to bacterial or viral infection, subjects receiving telisotuzumab vedotin may be at an increased risk for COVID-19 or experience serious illness if infected. Management of these adverse events (AEs) will be made on a case-by-case basis with consideration of benefit/risk. However, based on the population and disease being studied and the anticipation that COVID-19 related risks are not expected to differ substantially between study subjects and the broader population of subjects receiving treatment for MET amplified NSCLC, no change to the benefit/risk balance for subjects in this study is expected.

3 OBJECTIVES AND ENDPOINTS

3.1 Objectives, Hypotheses, and Estimands

The study is designed to determine the ORR of telisotuzumab vedotin in previously untreated subjects with *MET* amplified non-squamous NSCLC.

The clinical hypothesis is that telisotuzumab vedotin in previously untreated subjects with *MET* amplified non-squamous NSCLC will be safe, tolerable, and will demonstrate a clinically meaningful benefit of ORR greater than 40%[1].

The estimand corresponding to the above efficacy objective is complete response (CR) or partial response (PR) for previously untreated *MET* amplified non-squamous NSCLC subjects receiving telisotuzumab vedotin at 1.9 mg/kg every 2 weeks IV, regardless of premature discontinuation of study drug. All available disease assessment prior to or on the date of initiation of new anti-cancer therapy will be used for the analysis of ORR. The proportion of subjects with best confirmed overall response (i.e., CR or PR) defined by RECIST v1.1 as assessed by ICR will be derived and summarized in this single arm study.

3.2 Primary Endpoint

The primary endpoint is the ORR assessed by an independent central review (ICR) according to RECIST, version 1.1.

Objective response rate will be defined as the proportion of subjects with a confirmed complete response (CR) or confirmed partial response (PR) based on Response Evaluation Criteria in Solid Tumors (RECIST), version 1.1.

3.3 Secondary Endpoints

Key Secondary Endpoint

1. Duration of Response (DoR): Duration of Response will be defined for confirmed responders by ICR as the time from the initial response (CR or PR) to the first occurrence of radiographic progression per RECIST v1.1, or death from any cause.

Other Secondary Endpoints

1. Disease control rate (DCR): Disease control rate will be defined as the percentage of subjects with best overall response of confirmed CR or confirmed PR, or stable disease (SD) for at least 12 weeks following first dose of study drug, based on RECIST, version 1.1.
2. Progression Free Survival (PFS) per ICR: Progression Free Survival will be defined as the time from the subject's first dose of study drug to the first occurrence of radiographic progression based on RECIST, version 1.1 or death from any cause. Subjects with no PFS event will be censored at the last evaluable radiographic assessment per ICR. Subjects with no event and no evaluable post-baseline assessment will be censored at subject's first dose of study drug.

[1] This study follows a combined trial approach, in which the safety and efficacy of the investigational therapy(ies) and the clinical performance of the investigational in vitro diagnostic (IVD) will be evaluated. As part of this combined approach, the efficacy analyses from M22-137 will also provide the basis to evaluate the clinical performance of NeoGenomics *MET* FISH Assay as an IVD device for the identification of previously untreated *MET* amplified, non-squamous non-small cell lung cancer who may benefit from telisotuzumab vedotin.

3. Overall Survival (OS): Overall Survival will be defined as the time from subject's first dose of study drug to the event of death from any cause. Subjects with no documented death will be censored at the last known alive date.
4. Time to deterioration in cough or pain or dyspnea as measured respectively by the cough, pain, and dyspnea items of the European Organization for Research and Treatment of Cancer Quality of Life Questionnaire Lung Cancer Module 13 (EORTC QLQ-LC13). *Time to first deterioration will be defined as the time from baseline until a first ≥ 10-point change or a confirmed clinically meaningful deterioration in a symptom score or an initial ≥ 10-point change or a confirmed clinically meaningful deterioration followed by death.*[9]
5. Time to deterioration of physical functioning as measured by the physical functioning domain of the EORTC-QLQ-Core 30 (EORTC QLQ-C30). *Time to first deterioration will be defined as the time from baseline until a first ≥ 10-point change or a confirmed clinically meaningful deterioration in a symptom score occurs.*
6. Change from baseline in quality of life as measured by the global health status/quality of life domain of the EORTC QLQ-C30.

3.4 Additional Efficacy Endpoints

1. Change from baseline in the EuroQoL 5 Dimension 5 Level (EQ-5D-5L) including the Visual Analog Scale (VAS).
2. Patient-Reported Outcome Common Terminology Criteria for Adverse Events (PRO-CTCAE) data.
3. Change from baseline in cough or pain, or dyspnea as measured respectively by the cough, pain, and dyspnea items of the EORTC QLQ-LC13.
4. Change from baseline in remaining scales and sub-scales of the EORTC QLQ-C30.
5. Change from baseline in items of the EORTC QLQ-LC13.
6. Change from baseline in Patient Global Impression of Change (PGIC) and Patient Global Impression of Severity (PGIS) scores.

3.5 Safety Endpoints

Safety and tolerability will be assessed by evaluating AEs, physical examinations, and changes in laboratory data and vital signs, as well as drug discontinuation or dosing modification due to AEs, for the entire study duration.

3.6 Pharmacokinetic Endpoints

Pharmacokinetic samples will be obtained at the visits indicated in the activity schedule (Appendix E) and at the time points specified in the Operations Manual, (Appendix I) Section 2.1 and Section 3.6. Blood samples for assay of telisotuzumab vedotin conjugate in serum and free cytotoxin monomethyl auristatin E (MMAE) toxin levels in plasma, will be collected at specific time-points, will be tabulated and

summarized, and may be used for additional exploratory analyses as deemed appropriate. Serum samples for assay of telisotuzumab vedotin anti-drug antibodies and neutralizing anti-drug antibodies (ADA/nADA) will also be collected at specified time-points.

3.7 Biomarker Research

Known and/or novel disease-related or drug-related biomarkers will be evaluated in circulation or in tumor tissue. Types of biomarkers may include nucleic acids, proteins, lipids, and/or metabolites, either free or in association with particular cell types. The analyses may include but are not limited to c-Met protein/gene expression, genomic alterations in *MET* (exon 14 skipping, somatic mutations), gene alterations in NSCLC (*KRAS*, *RET*, *p53* mutations, etc.), immune cell infiltrates, or biomarkers related to NSCLC. Correlative studies of the association of biomarkers with clinical responses may be carried out.

Biospecimens (plasma and tumor tissue) will be collected to support the biomarker research objectives of the study.

Subjects will have *MET* amplification in tissue determined by the Sponsor-designated central laboratory or in plasma and/or tissue by a Sponsor-approved assay. For all enrolled subjects, tumor material and plasma are requested to allow central assay evaluation. The tumor material will also be used for other biomarker analysis.

Plasma will be collected at various time points in all parts of the study.

An optional tumor biopsy at the time of disease progression should be collected to understand the mechanism of resistance.

All biomarker samples should be labeled and shipped as outlined in the study-specific laboratory manual. AbbVie (or people or companies working with AbbVie) will store the samples and data in a secure storage space with adequate measures to protect confidentiality. The samples may be retained for 20 years.

Further details regarding the biomarker research rationale and collection time points are provided in Appendix E and the Operations Manual, (Appendix I) Section 2.1 and Section 3.7.

4 INVESTIGATIONAL PLAN

4.1 Overall Study Design and Plan

This is a Phase 2, open-label, single arm study in subjects with previously untreated *MET* amplified locally advanced/metastatic non-squamous NSCLC. A total of approximately 70 efficacy evaluable (defined in Section 7.2) subjects will be enrolled in the trial, with two interim analyses planned after approximately 20 and 50 efficacy evaluable subjects have had the chance to be followed for at least 6 months.

Pre-Screening

Subjects can be eligible for the study with documentation of local test results of tumor *MET* amplification reviewed and approved by Sponsor. Subjects without local documentation of *MET* amplification will be pre-screened prospectively for tumor *MET* amplification at a Sponsor designated central laboratory using the *MET* FISH Assay to determine eligibility, following signature of informed consent. The *MET* FISH assay is an investigational device (Investigational Use Only) intended to be used as a clinical trial assay to assess for *MET* gene amplification in formalin-fixed paraffin embedded (FFPE) specimens from clinical trial subjects with a confirmed diagnosis of NSCLC. Subjects with a MET/CEP7 ratio of ≥ 1.8 are eligible for enrollment.

Screening

All screening procedures must be performed within 28 days prior to the first dose. Following signature of informed consent, a subject may then proceed to screening procedures including collection of appropriate biospecimens.

The schematic of the study is shown in Figure 1. Further details regarding study procedures are located in the Operations Manual (Appendix I). Once all screening procedures are complete and eligibility is confirmed, subjects will be enrolled and proceed to the treatment period.

Treatment Period

Enrolled subjects will receive telisotuzumab vedotin at 1.9 mg/kg every 2 weeks IV. Subjects will receive treatment until meeting study drug discontinuation criteria.

Tumor Assessment and Follow-up Period

Tumor assessments (contrast CT or MRI) will be performed at baseline and approximately every 6 weeks for the first year, every 8 weeks for the second year, and every 12 weeks for the third year and beyond. Subjects who discontinue study drug for any reason other than progressive disease demonstrated by imaging will be followed until progressive disease is documented by imaging or until withdrawal of consent. Whenever possible, the same imaging technique should be used throughout the study for all lesions identified at baseline. Tumor assessments should continue until progressive disease per independent central review.

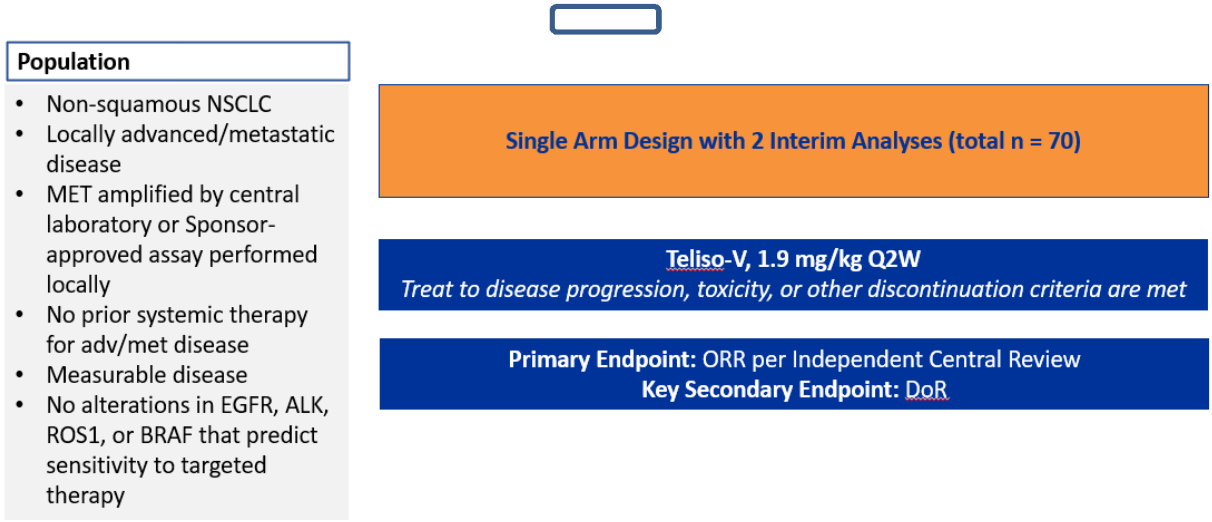
All subjects will be followed for survival. Follow-up will continue until the endpoint of death via subject contact, phone call or medical chart review as appropriate.

The overall study enrollment is projected to be approximately 2.5 years.

See Section 5 for information regarding eligibility criteria.

There will be 2 interim analyses. The first interim analysis (IA1) for efficacy will take place after approximately 20 efficacy evaluable subjects have enrolled and have had the chance to be followed for at least 6 months. A second interim analysis (IA2) for efficacy will take place after approximately 50 efficacy evaluable subjects have enrolled and have had the chance to be followed for at least 6 months. Additional details will be provided in the statistical analysis plan (SAP).

Figure 1. Overall Study Schematic



DoR = duration of response; NSCLC = non-small cell lung cancer; ORR = objective response rate; Q2W = Every 2 weeks

4.2 Discussion of Study Design

Choice of Control Group

This study contains no control group.

Appropriateness of Measurements

Standard statistical, clinical, and laboratory procedures will be utilized in this study. All efficacy and safety-related measurements in this study are standard for assessing disease activity in subjects with *MET* amplified non-squamous NSCLC. All clinical and laboratory procedures in this study are standard and generally accepted.

Suitability of Subject Population

In the c-Met overexpressing 2L/3L EGFR WT NSQ NSCLC cohort of 52 efficacy evaluable subjects from Study M14-239, an ORR of 36.5% has been observed.[8] An exploratory analysis of 10 subjects (from a subsequent interim analysis) with *MET* amplification demonstrated encouraging preliminary efficacy with an ORR of 80% (8/10 subjects) (AbbVie data on file). The overall safety profile of telisotuzumab vedotin in Study M14-239 is consistent with that previously observed and as reported in IB Edition 8.

Given the encouraging preliminary efficacy and the acceptable safety profile in c-Met overexpressing NSQ NSCLC in both amplified and non-amplified *MET* genetic settings, the benefit:risk of telisotuzumab vedotin monotherapy in patients with non-squamous NSCLC is positive and warrants continued investigation.

Selection of Doses in the Study

The clinical dosing regimen for telisotuzumab vedotin is 1.9 mg/kg administered every 2 weeks (Q2W) as an intravenous (IV) infusion. While additional data is being collected on the telisotuzumab vedotin monotherapy dose of 1.6 mg/kg Q2W in the ongoing Phase 1 Study M14-237 and in Phase 2 Study M14-239, the telisotuzumab vedotin monotherapy recommended Phase 2 dose (RP2D) of 1.9 mg/kg dose and the Q2W regimen was selected based on clinical safety, efficacy, exposure-response analyses for efficacy and safety, and dose-intensity assessments. The Q2W dosing schedule has been compared to 2.7 mg/kg administered every 3 weeks (Q3W) from the Phase 1 Study M14-237. Observed clinical efficacy data from the Phase 1 Study M14-237 indicated therapeutic benefit in subjects who received more frequent (Q2W) dosing of telisotuzumab vedotin (i.e., favorable ORR, median PFS, disease control rate and allowed patients to remain on treatment with telisotuzumab vedotin longer) compared to the Q3W regimen, with a manageable safety profile. While the average weekly dose is similar between these two regimens, exposure-response analyses for efficacy (ORR and disease control rate [DCR]) and safety (Grade 2+ neuropathy) suggest potential for improved efficacy (ORR) with Q2W dosing regimen, although accompanied with higher rates of Grade 2+ peripheral neuropathy compared to the Q3W regimen.

Therefore, the 1.9 mg/kg Q2W dosing schedule was selected as the recommended Phase 2 dose and has been evaluated in the Phase 2 Study M14-239 of telisotuzumab vedotin in subjects with previously treated locally/advanced metastatic NSCLC. Interim data from the Phase 2 Study M14-239 support the activity and manageable safety profile of telisotuzumab vedotin at this dose and schedule, as well as exposure-response analyses from the ongoing Phase 2 Study M14-239 demonstrate the 1.9 mg/kg Q2W dose provides a balance between safety and efficacy for telisotuzumab vedotin in NSCLC.

5 STUDY ACTIVITIES

5.1 Eligibility Criteria

Subjects must meet all of the following criteria in order to be included in the study. Anything other than a positive response to the questions below will result in exclusion from study participation.

Consent

- 1. Subjects or their legally authorized representative must voluntarily **sign and date an informed consent**, approved by an Independent Ethics Committee (IEC)/Institutional Review Board (IRB), prior to the initiation of any screening or study-specific procedures. Where confirmed as a local requirement, the subject (not a representative) must provide the written consent.

Demographic and Laboratory Assessments

- 2. Subject must be at least 18 years old.

- 3. Subjects must have *MET* amplification in tumor tissue as determined by the Sponsor-designated central laboratory *MET* FISH Assay or in plasma and/or tissue by a Sponsor-approved assay. The *MET* FISH assay shall have MET/CEP7 ratio ≥ 1.8 and is based on the average across a minimum of 50 tumor cells. For enrolled subjects, sufficient tumor material and plasma are requested to allow central assay evaluation and biomarker testing. Where confirmed as a local requirement, the central assay can only be utilized after IVDR certification is obtained.
- 4. Subject has adequate bone marrow, renal, and hepatic function as follows:
  - Bone marrow: Absolute neutrophil count (ANC) > 1,000/mm^3, platelets ≥ 100,000/mm^3, hemoglobin ≥ 9.0 g/dL.
  - Renal function: Creatinine clearance (CrCl) ≥ 30 mL/min measured by 24-hour urine or estimated by the Cockcroft Gault formula:

$$\text{CrCl (mL/min)} = \frac{(140 - \text{age in years}) \times (\text{weight in kg})}{72 \times \text{serum creatinine (mg/dL)}} \quad (\times 0.85 \text{ if female})$$

  - Hepatic function: Bilirubin ≤ 1.5 × ULN, aspartate aminotransferase (AST) and alanine aminotransferase (ALT) ≤ 3.0 × ULN, and albumin ≥ 3.0 g/dL.
  - Hepatic function for subjects with liver metastases: Bilirubin ≤ 1.5 × ULN, AST and ALT ≤ 5.0 × ULN, and albumin ≥ 3.0 g/dL.
- 5. Subject is willing and able to comply with procedures required in this protocol.

Disease/Condition Activity

- 6. Subject must have histologically documented non-squamous adenocarcinoma NSCLC that is locally advanced or metastatic according to accepted guidelines (e.g., NCCN, IASLC edition 8).[10]
- 7. Subjects with alterations in *EGFR*, *ALK*, *ROS1*, or *BRAF* that predict sensitivity to available targeted therapy are not eligible. Subjects with other alterations that are candidates for available targeted therapy are not eligible.
- 8. Subject must have measurable disease per RECIST version 1.1.
- 9. Subject must have an Eastern Cooperative Oncology Group (ECOG) Performance Status of 0 or 1.

Subject History

- 10. Subjects must have no prior systemic therapy for locally advanced/metastatic NSCLC. Limited treatment with no more than 1 cycle of chemotherapy is allowed prior to receiving the first dose of study drug provided there is no evidence of progression. Subjects may have received prior adjuvant/neoadjuvant systemic chemotherapy and/or radiation and/or immunotherapy provided that the subject has not progressed on or within 6 months of completing the regimen and it was completed ≥ 6 months before subject's first dose of study drug.
- 11. Subject must not have received prior c-Met-targeted antibodies.

- 12. Subject must not have NSCLC that is eligible for treatment with curative intent.
- 13. Subjects with metastases to the central nervous system (CNS) are eligible only after definitive therapy (such as surgery or radiotherapy) is provided and:
  - There is no evidence of progression of CNS metastases at least 2 weeks after definitive therapy.
  - They are asymptomatic and off or on a stable or reducing dose of systemic steroids and/or anticonvulsants for at least 2 weeks prior to first dose of telisotuzumab vedotin.
- 14. Subjects must not have a history of other malignancies except:
  - Malignancy treated with curative intent and with no known active disease present for ≥ 2 years before the first dose of study drug and felt to be at low risk for recurrence by investigator.
  - Adequately treated non-melanoma skin cancer or lentigo maligna without evidence of disease.
  - Adequately treated carcinoma in situ without current evidence of disease.
- 15. Subject must not have a history of idiopathic pulmonary fibrosis, organizing pneumonia (e.g., bronchiolitis obliterans), drug-induced pneumonitis, or idiopathic pneumonitis, or evidence of active pneumonitis on screening chest CT scan.
- 16. History of radiation pneumonitis in the radiation field (fibrosis) is permitted.
- 17. Subject must not have unresolved AEs ≥ Grade 2 from prior anticancer therapy, except for alopecia or anemia.
- 18. Subject must not have had major surgery within 21 days prior to the first dose of telisotuzumab vedotin.
- 19. Subjects must not have the following:
  - Known human immunodeficiency virus (HIV) infection. Note: HIV testing is not required for eligibility for this protocol unless mandated by local regulatory authority or ethics committee/institutional review board.
  - Active hepatitis B virus (HBV) infection, defined by HBV DNA ≥ 500 IU/mL or hepatitis B surface antigen (HbsAG) positivity associated with HBV DNA ≥ 500 IU/mL . In subjects with known HBV infection, the presence of active infection must be tested locally. If HBV status is unknown, it must be tested locally at screening if required by local regulatory authority or ethics committee/institutional review board.
  - Active hepatitis C virus (HCV) infection, defined by HCV RNA positivity. Subjects cured of HCV infection may be included in the study. In subjects with known HCV infection, the presence of active infection must be tested locally. If HCV status is unknown, it must be tested locally at screening if required by local regulatory authority or ethics committee/institutional review board.
  - Uncontrolled autoimmune disease.
- 20. Subject must not have clinically significant condition(s) including but not limited to the following:

- Clinically significant vascular disease, including:
  - Myocardial infarction within 1 year or stroke within 6 months prior to first dose of study drug, or unstable or uncontrolled disease/condition related to or affecting cardiac function (e.g., unstable angina, congestive heart failure, New York Heart Association Class III-IV), cardiac arrhythmia (CTCAE Version 5 Grade 2 or higher), or clinically significant electrocardiogram (ECG) abnormalities.
- Clinically significant liver disease, including hepatitis, current alcohol abuse, or cirrhosis.
- Grade ≥ 2 edema or lymphedema.
- Grade ≥ 2 ascites or pleural effusion.
- Grade ≥ 2 neuropathy.
- Active uncontrolled bacterial or viral infection.

✔ 21. Subject must not have psychiatric illness/social situation that would limit compliance with the study.

✔ 22. Subject must not have a history of major immunologic reaction to any immunoglobulin G (IgG)-containing agent.

✔ 23. Subject must not have any medical condition which in the opinion of the Investigator or Medical Monitor places the subject at an unacceptably high risk for toxicities.

✔ 24. No known active severe acute respiratory syndrome coronavirus 2 (SARS-CoV-2) infection. If a subject has signs/symptoms suggestive of SARS-CoV-2 infection, the subject must have a negative molecular (e.g., polymerase chain reaction [PCR]) test result or 2 negative antigen test results at least 24 hours apart. Note: SARS-CoV-2 diagnostic tests should be applied following local requirements/recommendations. Subject must not have had any serious SARS-CoV-2 infection that required mechanical ventilation/endotracheal intubation or extracorporeal membrane oxygenation (ECMO) support in the past 6 months, or long-term complications from SARS-CoV-2 infection that are not resolved at the time of prescreening.

✔ 25. Subjects who do not meet SARS-CoV-2 infection eligibility criteria must be screen failed and may only rescreen after they meet the following SARS-CoV-2 infection viral clearance criteria:

- At least 10 days since first PCR test result have passed in asymptomatic patients or 10 days since recovery, defined as resolution of fever without use of antipyretics and improvement in symptoms.

Contraception

✔ 26. For all females of child-bearing potential; a **negative serum pregnancy test** at the Screening Visit and a negative urine pregnancy test at baseline prior to the first dose of study drug. If subsequent investigation indicates that a patient with a positive serum pregnancy test is not pregnant, subject may be eligible per the discretion of the investigator after consultation with the AbbVie medical monitor.

✔ 27. Female subjects of childbearing potential must practice at least 1 protocol-specified **method of birth control**, that is effective from Study Day 1 through at least 7 months after the last dose of study drug.

- 28. Females who are not **pregnant, breastfeeding, or donating oocytes, or considering becoming pregnant** during the study and for at least 7 months after the last dose of study drug.
- 29. Males who are **sexually active with female partner(s) of childbearing potential**, must agree, from Study Day 1 through at least 4 months after the last dose of study drug, to practice the protocol-specified contraception.
- 30. Males must not consider **fathering a child or donating sperm** during the study and for at least 4 months after the last dose of study drug.

Concomitant Medications/Therapies

- 31. Subjects must not have received any live vaccine within 30 days of the first dose of investigational product.
- 32. Treatment with any of the following therapies within the noted time intervals is excluded prior to the first dose of telisotuzumab vedotin:
  - Within 2 weeks (14 days): radiation not involving lungs.
- 33. Treatment with any of the following therapies does not require a washout period:
  - Palliative radiation therapy for bone, skin, or subcutaneous metastases for 10 fractions or less.
- 34. Subjects must not have had radiation therapy to the lung within 6 months prior to the first dose of study drug and until study drug is permanently discontinued.

5.2 Contraception Recommendations

Contraception Requirements for Females

Subjects must follow the following contraceptive guidelines as specified:

- Females, Non-Childbearing Potential

  Females do not need to use birth control during or following study drug treatment if considered of non-childbearing potential due to meeting any of the following criteria:

  1. Premenopausal female with permanent sterility or permanent infertility due to one of the following:
     - Permanent sterility due to a hysterectomy, bilateral salpingectomy, bilateral oophorectomy
     - Non-surgical permanent infertility due to Mullerian agenesis, androgen insensitivity, or gonadal dysgenesis; investigator discretion should be applied to determining study entry for these individuals.
  2. Postmenopausal female
     - Age > 55 years with no menses for 12 or more months without an alternative medical cause.

- Age ≤ 55 years with no menses for 12 or more months without an alternative medical cause AND a follicle-stimulating hormone (FSH) level ≥ 30 IU/L.

- Females, of Childbearing Potential
  - Female subjects should be provided information to seek advice about cryopreservation of eggs prior to treatment with study drug.
  - Review and document pregnancy avoidance recommendations with females of childbearing potential.
  - Females of childbearing potential must avoid pregnancy while taking study drug(s) and for at least 7 months after the last dose of study drug.
  - Females must commit to one of the following highly effective (with a failure rate of less than 1% per year, when used consistently and correctly) methods of birth control:
    - Combined (estrogen and progestogen containing) hormonal birth control (oral, intravaginal, transdermal, injectable) associated with inhibition of ovulation-initiated at least 30 days prior to study Baseline Day 1.
    - Progestogen-only hormonal birth control (oral, injectable, implantable) associated with inhibition of ovulation initiated at least 30 days prior to study Baseline Day 1.
    - Bilateral tubal occlusion/ligation (can be via hysteroscopy, provided a hysterosalpingogram confirms success of the procedure).
    - Intrauterine device (IUD).
    - Intrauterine hormone-releasing system (IUS).
    - Vasectomized partner (provided the partner has received medical confirmation of the surgical success of the vasectomy and is the sole sexual partner of the trial subject).
    - Practice true abstinence, defined as: Refraining from heterosexual intercourse when this is in line with the preferred and usual lifestyle of the subject (periodic abstinence [e.g., calendar, ovulation, symptothermal, post-ovulation methods] and withdrawal are not acceptable).
    - If required per local practices, male or female condom with or without spermicide OR cap, diaphragm or sponge with spermicide should be used in addition to one of the birth control methods listed above (excluding true abstinence).

Contraception recommendations related to use of concomitant therapies prescribed should be based on the local label.

Contraception Requirements for Males

Male subjects should be provided information to seek advice about cryopreservation of sperm prior to treatment with study drug.

Male subjects who are sexually active with a female partner of childbearing potential, must agree **to use male condoms, even if the male subject has undergone a successful vasectomy**, from Study Day 1 through at least 4 months after the last dose of study drug:

- His female partner(s) must also use at least 1 of the following highly effective (with a failure rate of less than 1% per year, when used consistently and correctly) methods of birth control:
  - Combined (estrogen and progestogen containing) hormonal birth control (oral, intravaginal, transdermal, injectable) associated with inhibition of ovulation initiated at least 30 days prior to study Baseline Day 1.
  - Progestogen-only hormonal birth control (oral, injectable, implantable) associated with inhibition of ovulation initiated at least 30 days prior to study Baseline Day 1.
  - bilateral tubal occlusion/ligation (can be via hysteroscopy, provided a hysterosalpingogram confirms success of the procedure).
  - intrauterine device (IUD).
  - Intrauterine hormone-releasing system (IUS).
  - Vasectomized partner (provided the partner has received medical confirmation of the surgical success of the vasectomy, and is the sole sexual partner of the trial subject).

5.3 Prohibited Medications and Therapy

No anti-cancer agents, investigational agents, or anti-cancer hormonal therapy may be taken concurrently while receiving telisotuzumab vedotin. For any subjects taking anti-cancer herbal remedies, documentation must be reviewed by the AbbVie Medical Monitor.

Since MMAE is metabolized primarily by the CYP3A4 enzyme, strong CYP3A4 inhibitors may increase the exposure of MMAE. Therefore, strong CYP3A4 inhibitors should be taken with caution and closely monitored for adverse reactions while subjects are undergoing telisotuzumab vedotin treatment.

Examples of clinical CYP3A inhibitors are provided on the Food and Drug Administration (FDA)'s website for Drug Development and Drug Interactions: https://www.fda.gov/drugs/drug-interactions-labeling/drug-development-and-drug-interactions-table-substrates-inhibitors-and-inducers.

P-glycoprotein (P-gp) inhibitors may also increase exposure to MMAE when co-administered with telisotuzumab vedotin. Subjects receiving P-gp inhibitors concomitantly should be closely monitored for adverse reactions.

Live vaccines are prohibited from 30 days prior to the first dose of study drug (telisotuzumab vedotin) until 90 days after study drug completion.

5.4 Prior and Concomitant Therapy

Any medication (including over-the-counter or prescription medicines, vitamins, and/or herbal products and dietary supplements) or vaccine that the subject is receiving from the time of signing the screening consent (or pre-screening consent if medication is received for study procedure-related serious adverse events [SAE] or non-serious AEs), through the course of the study, until 30 days after the last dose of study drug (refer to Operations Manual [Appendix I] Section 2.2 for details), must be recorded in the

electronic Case Report Form (eCRF). Reason for use, date(s) of administration including start and end dates, and dosage information including dose, route, and frequency should also be recorded.

There are limited clinical data on the concomitant use of hematopoietic growth factors with telisotuzumab vedotin. Therefore, caution should be used when telisotuzumab vedotin and haematopoietic growth factors are administered together.

Allowed concomitant medications/therapies include the following:

- Hormonal contraceptives and hormonal replacement therapy.
- After Cycle 1, palliative radiation therapy for bone or skin metastases or subcutaneous metastatic nodules for 10 fractions or less as long as the subject is otherwise stable.
- Best supportive care and treatment will be given as appropriate to each subject. For example, antiemetics, antibiotics, transfusions, growth factors, oxygen therapy, nutritional support, palliative treatment for pain or cough, and drugs for prevention of skeletal-related events or osteoporosis.
- Rescue concomitant medications/therapies including growth factors. Biologic response modifiers administered for erythropoiesis (e.g., erythropoietin, darbepoetin alpha) may be administered during protocol therapy. Granulocyte growth factors (e.g., granulocyte-colony stimulating factor [G-CSF], granulocyte-macrophage colony-stimulating factor [GM-CSF], etc.) are to be administered according to the Investigator's standard practice and/or National Comprehensive Cancer Network (NCCN) guidelines, 2021. Growth factors may be given prophylactically with the intent to prevent dose reductions or delays. Transfusion therapy, including red blood cells and platelets, is allowed.

Any questions regarding concomitant or prior therapy should be raised to the AbbVie emergency contact. Information regarding potential drug interactions with telisotuzumab vedotin can be located in the telisotuzumab vedotin Investigator's Brochure.

Subjects must be able to safely discontinue any prohibited medications prior to initial study drug administration, as detailed in Section 5.1, Concomitant Medications. Subjects must be consented for the study prior to discontinuing any prohibited medications for the purpose of meeting study eligibility.

Further details are provided in the Operations Manual (Appendix I) Section 3.3.

After discontinuation of study drug, post-treatment anti-cancer therapies (including both systemic therapies and radiation therapy) must be entered in the appropriate eCRFs.

For sites in China only as per local requirements, subjects must record concomitant medication daily on the subject paper diary cards (see Section 5.13).

COVID-19 Pandemic-Related Vaccination Guidance

Given the ongoing COVID-19 pandemic, selected non-live vaccines (e.g., mRNA, non-replicating viral vector, protein subunit, etc.) to prevent SARS-CoV-2 infection may be administered during screening, the treatment period, or follow-up, as long as components of the vaccine are not contraindicated.

The decision to receive a locally available vaccine should be based on local guidance and an individual discussion between the treating physician and the subject.

The potential impact of telisotuzumab vedotin on SARS-CoV-2 vaccination is unknown. Therefore, study drug should be administered as follows:

- The first dose of study drug (telisotuzumab vedotin), when possible, is preferred to be given approximately 7 days from the SARS-CoV-2 vaccine administration.

Note: The above guidance applies to all SARS-CoV-2 vaccine doses given as part of the complete treatment course.

These recommendations may be subject to change based on the evolving knowledge around the use of SARS-CoV-2 vaccines in patients with cancer and as more data are collected in real-world scenarios and clinical trials.

Any SARS-CoV-2 vaccine information must be documented on the COVID-19 vaccine eCRF. Refer to the Operations Manual (Appendix I) for instructions on reporting any AEs associated with the COVID-19 vaccine.

5.5 Withdrawal of Subjects and Discontinuation of Study

Subject treatments will continue until disease progression, intolerable toxicity, or subject meets other study discontinuation criteria.

Treatment with study drug should be discontinued (or maintained where specific exceptions exist) for any of the following reasons:

1. Progressive disease per RECIST v1.1.
    - Subjects with isolated CNS disease progression may continue treatment with telisotuzumab vedotin if the following conditions are met:
        - Disease control is maintained outside of the CNS.
        - The subject receives definitive local therapy to treat the CNS lesion (surgery or radiotherapy).
    - Subjects with locally determined radiographic disease progression may continue treatment until radiographic disease progression is confirmed by ICR, provided the subject does not require alternative anti-cancer therapy and is clinically stable per the following criteria:
        - Absence of emergent or worsening symptoms and signs indicating clinically significant progression of disease.
        - No decline in ECOG performance status.
        - Absence of progression of disease or progressive tumor at critical anatomical sites (e.g., cord compression) requiring urgent alternative medical intervention.
2. Any of the following AEs:

- The subject experiences an intolerable toxicity such that the Investigator believes further treatment would pose an unacceptable risk.
- The subject experiences an anaphylactic reaction that is attributed or suspected to be related to study drug exposure.
- The subject experiences a treatment-related AE that leads to delay in dosing telisotuzumab vedotin for > 42 days.
- Per discontinuation criteria in Toxicity Management section of protocol.
- Clinically significant abnormal laboratory results or AEs, which rule out continuation of the study drug, as determined by the investigator or the Sponsor.

3. The subject becomes pregnant while on study drug.
4. Eligibility criteria violation was noted after the subject started study drug and continuation of the study drug would place the subject at risk.
5. Introduction of prohibited medications or dosages and continuation of the study drug would place the subject at risk.

A subject may voluntarily withdraw or be withdrawn from the study at any time for reasons including, but not limited to, the following:

- The investigator believes it is in the best interest of the subject.
- The subject requests withdrawal from the study.
- Subject is significantly noncompliant with study procedures, which would put the subject at risk for continued participation in the trial.

For subjects to be considered lost to follow-up, reasonable attempts must be made to obtain information on the subject's final status. At a minimum, 2 telephone calls must be made and 1 certified letter must be sent and documented in the subject's source documentation.

AbbVie may terminate this study prematurely, either in its entirety or at any site. The investigator may also stop the study at their site if there are safety concerns. If AbbVie terminates the study for safety reasons, AbbVie will promptly notify the investigator.

COVID-19 Pandemic-Related Acceptable Protocol Modification

During the COVID-19 pandemic, it has been necessary to employ mitigation strategies to enable the investigator to ensure subject safety and continuity of care. Due to the COVID-19 pandemic, if an event occurs leading to difficulties in performing protocol-specified administration of PRO assessments, AbbVie may engage with site personnel to deploy alternate methods for assessments (e.g., phone contacts or virtual site visits). In all cases, these alternative measures must be allowed by local regulations and permitted by IRB/IEC. Details of acceptable mitigation strategies are identified and included in the Operations Manual in Appendix I.

The investigator should contact the sponsor medical contact before discontinuing a subject from the study for a reason other than described in the protocol to ensure all acceptable mitigation steps have been explored.

Refer to the Operations Manual in Appendix I Section 2 and Section 3 for details on how to handle study activities/procedures.

Interruption/Discontinuation of Study Drug Due to COVID-19 Infection

During the Study Drug Dosing Period, a subject with confirmed (viral test positive) or suspected COVID-19 infection can only be dosed with study drug if the following COVID-19 viral clearance criteria are met:

- At least 10 days since first positive test result have passed in asymptomatic patients or at least 10 days since recovery, defined as resolution of fever without use of antipyretics and improvement in symptoms.

Delays in study drug dosing due to the above COVID-19 testing guidance for subjects must be discussed with the AbbVie medical contact, along with the possibility of premature discontinuation from the study drug dosing period. Follow subsequent protocol Section 5.6 for subjects who discontinued study drug.

5.6 Follow-Up After Subject Discontinuation of Study Drug or from Study

To minimize missing data for efficacy and safety assessments, subjects who prematurely discontinue study drug treatment should continue to be followed for all regularly scheduled visits, unless subjects have decided to discontinue the study participation entirely (withdrawal of informed consent). Subjects should be advised on the continued scientific importance of their data even if they discontinue treatment with study drug early.

If a subject prematurely discontinues study participation (withdrawal of informed consent), the procedures outlined for the End of Treatment (EOT) visit should be completed as soon as possible, preferably within 7 days of documentation of the decision to discontinue study drug. In addition, if subject is willing, a 30-day follow-up phone call after the last dose of study drug may be completed to ensure all treatment-emergent AEs/SAEs have been resolved.

Subject must request to be withdrawn specifically from survival follow-up; this request must be documented in the subject's medical record and signed by the investigator; the eCRF should also be updated as appropriate. If a subject withdraws from study follow up or withdraws permission for the collection of their personal data, the study staff may still use available public records to obtain information about survival status only, as appropriate per local regulations.

In the event a subject withdraws consent from the clinical study, biomarker research will continue unless the subject explicitly requests analysis to be stopped. When AbbVie is informed the subject has withdrawn and no longer wishes biomarker samples research to continue, samples will not be analyzed and no new biomarker analysis data will be collected for the withdrawn subject or added to the existing data or database(s). A subject may withdraw consent for optional biomarker research at any time and

remain in the clinical study. Data generated from clinical study and/or optional biomarker research, before subject withdrawal of consent, will remain part of the study results.

5.7 Study Drug

Telisotuzumab vedotin will be supplied for IV administration at 1.9 mg/kg Q2W beginning on Cycle 1 Day 1.

Information about the study drug used in this study is presented in Table 2 in Section 6.1 of the Operations Manual (Appendix I).

AbbVie will supply telisotuzumab vedotin study drug. Telisotuzumab vedotin vials will be packaged with quantities sufficient to accommodate the study design. Each kit will be labeled per local requirements and this label must remain affixed to the kit.

Study drug will only be used for the conduct of this study.

Sites are responsible for obtaining emergency medications to manage infusion reaction, per institutional guidelines.

Sterile Investigational Product Dose Preparation guidelines must be followed for the preparation and administration of telisotuzumab vedotin. Further information on study drug, packaging, labeling, etc., is provided in the Operations Manual Appendix I, Section 6.

Upon completion of or discontinuation from study treatment, all original study drug units (containing unused study drugs) will be returned to the sponsor (or designee), or destroyed by third party vendor contracted with the site. All return or destruction procedures will be according to instructions from the sponsor and according to local regulations following completion of drug accountability procedures.

5.8 Randomization/Drug Assignment

All subjects will be assigned a unique identification number by the Interactive Response Technology (IRT) system during the Pre-Screening Period. For subjects who rescreen, the identification number assigned by the IRT at the initial Pre-Screening Visit should be used.

Randomization is not applicable to this study.

5.9 Re-PreScreening Activities

Subjects who initially prescreen fail due to a negative *MET* amplification testing result and have additional tumor material available may be permitted to re-prescreen following re-consent. Subjects can be re-prescreened in the IRT system as soon as additional tumor material is available to reassess *MET* amplification status.

5.10 Re-Screening Activities

Subjects that initially screen fail for the study may be permitted to re-screen following re-consent. All screening procedures will need to be repeated. The subject must meet all eligibility criteria at the time of re-screening in order to qualify for the study. There is no minimum period of time a subject must wait to re-screen for the study. If the subject had a complete initial screening evaluation including tumor assessment (CT scan/MRI) and the re-screen visit is more than 35 days since the initial screening assessment, tumor assessment should be repeated. As appropriate, sites are encouraged to contact the AbbVie Medical Monitor to confirm if subjects should or should not be re-screened.

Note that subjects are allowed to have certain laboratory samples re-drawn to meet eligibility within the same 28-day screening window, following consultation and written approval from the Medical Monitor/Therapeutic Area Medical Director.

Details regarding tumor assessments are provided in the Operations Manual Appendix I, Section 3.16.

5.11 Protocol Deviations

AbbVie does not allow intentional/prospective deviations from the protocol except when necessary to eliminate an immediate hazard to study subjects. The investigator is responsible for complying with all protocol requirements, written instructions, and applicable laws regarding protocol deviations. If a protocol deviation occurs (or is identified, including those that may be due to the COVID-19 pandemic), the investigator is responsible for notifying IEC/IRB, regulatory authorities (as applicable), and AbbVie.

5.12 Interstitial Lung Disease (ILD) Adjudication Committee (AC)

An external Interstitial Lung Disease (ILD) Adjudication Committee (AC) will be instituted for this study. Details on the membership, responsibilities, and working procedures of the external ILD AC will be described in its own charter, provided as a separate document in the study file.

- The ILD AC will adjudicate ILD cases (including potential ILD) on an ongoing basis. Adjudication of ILD cases will be based on evaluation of eCRFs and source documents including but not limited to chest high-resolution computed tomography (HRCT), arterial blood gases (ABG), and carbon monoxide diffusing capacity (DLCO).
- The ILD AC will review ongoing cases of ILD to make the final determination of ILD diagnoses to guide Sponsor decisions regarding trial suspension or trial discontinuation and to provide assessment of ILD prevalence at the end of study. Findings of the ILD AC with its recommendations will be provided to the Sponsor.

5.13 Paper Diary Cards for Sites in China Only

For sites in China only as per local requirements, a paper diary card will be provided at the Screening Visit. Subjects will be trained on how to complete the diary cards by site staff during the Screening Visit. For only those subjects undergoing a study-related clinical procedure (e.g., fresh biopsy) during the Pre-

Screening period, a paper diary card will be provided and training will occur at the Pre-Screening Visit. If subjects require re-training during the study, the site staff will accommodate this requirement.

All subjects should complete their paper diary cards throughout the entire study. Subjects will be instructed to bring their paper diary cards back to the site to be reviewed and collected at each visit, including at any visit at which a dose level change may be required. If COVID-19 circumstances warrant a virtual visit, diary cards should be reviewed virtually with the subject and site should collect the paper diary card at the next on-site visit.

Subjects will be instructed to record adverse events symptoms and concomitant medications in the paper diary cards. At each visit, the paper diary cards are to be reviewed by the investigator, assessed for any updates needed, and collected from the subject by study staff. Relevant information will be recorded as a new adverse event or concomitant medication, or used to update an existing adverse event or concomitant medication, in the eCRF as applicable. At each visit after Screening (or Pre-Screening, for subjects undergoing a study-related clinical procedure during the Pre-Screening period), up to and including the 30-Day Follow-Up Visit, the paper diary cards are to be returned to the site and appropriately filed with the subject's source documents for this study. At each visit after the paper diary card is initially dispensed (except the 30-Day Follow-Up Visit), the subject will be provided a new diary card.

In case of missing diary card information, or when discrepancies are discovered, site personnel should discuss with the subject and document changes to data in site records and eCRF forms, if applicable. The need for completion of the paper diary card will be reinforced with the subject during study visits, as necessary, by the site personnel.

6 SAFETY CONSIDERATIONS

6.1 Complaints and Adverse Events

Complaints

A complaint is any written, electronic, or oral communication that alleges deficiencies related to the physical characteristics, identity, quality, purity, potency, durability, reliability, safety, effectiveness, or performance of a product/device. Complaints associated with any component of this investigational product must be reported to AbbVie.

Product Complaint

A product complaint is any complaint related to the biologic or drug component of the product or to the medical device component(s).

For a product this may include, but is not limited to, damaged/broken product or packaging, product appearance whose color/markings do not match the labeling, labeling discrepancies/inadequacies in the labeling/instructions (e.g., printing illegible), missing components/product, device damage or not working properly, or packaging issues.

Product complaints concerning the investigational product and/or device must be reported to AbbVie within 24 hours of the study site's knowledge of the event.

Reporting will be done via electronic data capture (EDC). The date the product complaint details are entered into EDC and the form is saved represents the date reported to AbbVie. A back-up paper form will be provided for reporting complaints related to unassigned product or in the event of an EDC system issue. If a back-up paper form is used, the date the form is emailed to RD_PQC_QA@abbvie.com represents the date reported to AbbVie.

All follow-up information is to be reported to the sponsor (or an authorized representative) and documented in source as required by the sponsor. Product complaints associated with adverse events will be reported in the study summary. All other complaints will be monitored on an ongoing basis. Product complaints occurring during the study will be followed up to a satisfactory conclusion.

Medical Complaints/Adverse Events and Serious Adverse Events

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

Such an event can result from use of the drug as stipulated in the protocol or labeling, as well as from "special situation" such as accidental or intentional overdose, medication error, occupational or accidental exposure, off-label use, drug abuse, drug misuse, or drug withdrawal, all which must be reported whether associated with an adverse event or not. Any worsening of a pre-existing condition or illness is considered an adverse event. Worsening in severity of a reported adverse event should be reported as a new adverse event. Laboratory abnormalities and changes in vital signs are considered to be adverse events only if they result in discontinuation from the study, necessitate therapeutic medical intervention, meets protocol-specific criteria (see Section 6.2 regarding toxicity management), and/or if the investigator considers them to be AEs.

The investigators will monitor each subject for clinical and laboratory evidence of adverse events on a routine basis throughout the study. All adverse events will be followed to a satisfactory conclusion.

An elective surgery/procedure scheduled to occur during a study will not be considered an adverse event if the surgery/procedure is being performed for a pre-existing condition and/or the surgery/procedure has been pre-planned prior to study entry. However, if the pre-existing condition deteriorates unexpectedly during the study (e.g., surgery performed earlier than planned), then the deterioration of the condition for which the elective surgery/procedure is being done will be considered an AE.

If an AE, whether associated with study drug or not, meets any of the following criteria, it is to be reported to AbbVie clinical pharmacovigilance as a serious adverse event within 24 hours of the site being made aware of the serious adverse event (refer to Section 4.3 of the Operations Manual [Appendix I] for reporting details and contact information):

Death of Subject	An event that results in the death of a subject.
Life-Threatening	An event that, in the opinion of the investigator, would have resulted in immediate fatality if medical intervention had not been taken. This does not include an event that would have been fatal if it had occurred in a more severe form.
Hospitalization or Prolongation of Hospitalization	An event that results in an admission to the hospital for any length of time or prolongs the subject's hospital stay. This does not include an emergency room visit or admission to an outpatient facility.
Congenital Anomaly	An anomaly detected at or after birth, or any anomaly that results in fetal loss.
Persistent or Significant Disability/Incapacity	An event that results in a condition that substantially interferes with the activities of daily living of a study subject. Disability is not intended to include experiences of relatively minor medical significance such as headache, nausea, vomiting, diarrhea, influenza, and accidental trauma (e.g., sprained ankle).
Important Medical Event Requiring Medical or Surgical Intervention to Prevent Serious Outcome	An important medical event that may not be immediately life-threatening or result in death or hospitalization, but based on medical judgment may jeopardize the subject and may require medical or surgical intervention to prevent any of the outcomes listed above (i.e., death of subject, life threatening, hospitalization, prolongation of hospitalization, congenital anomaly, or persistent or significant disability/incapacity). Additionally, any elective or spontaneous abortion or stillbirth is considered an important medical event. Examples of such events include allergic bronchospasm requiring intensive treatment in an emergency room or at home, blood dyscrasias or convulsions that do not result in inpatient hospitalization, or the development of drug dependency or drug abuse.

Adverse Event Collection Period

Serious and nonserious AEs occurring after the study-specific pre-screening informed consent is signed but prior to the initial dose of study drug will be collected only if they are considered by the investigator to be causally related to the study-required procedures.

All adverse events reported from the time of study drug administration until 30 days after discontinuation of study drug administration will be collected, whether solicited or spontaneously reported by the subject. After 30 days following the last dose of study drug or completion of study treatment only spontaneously reported SAEs will be collected (nonserious AEs will not be collected). In addition, study procedure-related serious and nonserious adverse events will be collected from the time the subject signs the study-specific informed consent.

The following definitions will be used for Serious Adverse Reactions (SAR) and Suspected Unexpected Serious Adverse Reaction (SUSAR):

SAR	Defined as all noxious and unintended responses to an IMP related to any dose administered that result in an SAE as defined above.
SUSAR	Refers to individual SAE case reports from clinical trials where a causal relationship between the SAE and the IMP was suspected by either the sponsor or the investigator, is unexpected (not listed in the applicable Reference Safety Information), and meets one of the above serious criteria.

AbbVie will be responsible for Suspected Unexpected Serious Adverse Reactions (SUSAR) reporting for the Investigational Medicinal Product (IMP) in accordance with global and local requirements.

Adverse events will be monitored throughout the study to identify any of special interest that may indicate a trend or risk to subjects.

Adverse Events of Special Interest

The following AEs of special interest will be monitored during the study:

- Peripheral neuropathy;
- Corneal toxicity;
- Hematological toxicities related to bone marrow suppression, especially neutropenia;
- Pneumonitis/interstitial lung disease (ILD).

If AEs of peripheral neuropathy, pneumonitis/ILD, corneal toxicity, or hematological toxicities related to bone marrow suppression, especially neutropenia, are reported, information must be reported on the appropriate eCRF until event resolution, return to baseline, or event is determined to be stable per investigator.

Other Safety Topic of Special Interest

Serious hepatobiliary toxicities, including hepatobiliary adverse events that lead to discontinuation/interruption of study drug, and significantly abnormal liver laboratory results (ALT/AST > 8 × ULN or ALT/AST > 3 × ULN with a total bilirubin > 2 × ULN), will be monitored as a safety topic of special interest during this study.

If any of the following events are reported, then the following supplemental report must be completed.

Event	Supplemental eCRF
Pneumonitis/Interstitial Lung Disease	Pneumonitis/ILD eCRF
Corneal (ocular) toxicity	Ophthalmology exam eCRF (as applicable, See Section 6.2)
Peripheral neuropathy	Peripheral neuropathy eCRF
Hepatobiliary toxicity (leading to discontinuation/interruption of study drug and/or ALT/AST > 8 × ULN and/or ALT/AST > 3 × ULN with a total bilirubin > 2 × ULN)	Hepatic AE eCRF

AE = adverse event; ALT = alanine aminotransferase; AST = aspartate aminotransferase; eCRF = electronic Case Report Form; ILD = interstitial lung disease; ULN = upper limit of normal

Adverse Event Severity and Relationship to Study Drug

The investigator will use the following definitions to assess the relationship of the adverse event to the use of study drug:

Reasonable Possibility	After consideration of factors including timing of the event, biologic plausibility, clinical judgment, and potential alternative causes, there is sufficient evidence (information) to suggest a causal relationship.
No Reasonable Possibility	After consideration of factors including timing of the event, biologic plausibility, clinical judgment, and potential alternative causes, there is insufficient evidence (information) to suggest a causal relationship.

For causality assessments, events assessed as having a reasonable possibility of being related to the study drug will be considered "associated" Events assessed as having no reasonable possibility of being related to study drug will be considered "not associated" In addition, when the investigator has not reported causality or deemed it not assessable, AbbVie will consider the event associated.

The investigator will rate the severity of each AE according to the National Cancer Institute (NCI) Common Terminology Criteria for Adverse Events (CTCAE) version 5.0. If a reported AE increases in severity, the initial AE should be given an outcome date and a new AE must be reported on a different onset date than the end date of the previous AE to reflect the change in severity. The dates on the AEs cannot overlap.

For AEs not captured by the NCI CTCAE, the following criteria should be used:

Grade 1	The AE is transient and easily tolerated by the subject (mild).
Grade 2	The AE causes the subject discomfort and interrupts the subject's usual activities (moderate).
Grade 3	The AE causes considerable interference with the subject's usual activities and may be incapacitating (moderate to severe).

Grade 4	The AE is life-threatening and requires urgent intervention (severe).
Grade 5	The AE results in the death of the subject (severe).

For all reported SAEs that increase in severity, the supplemental eCRFs also need to be updated to reflect any changes due to the increase in severity. For SAEs considered as having "no reasonable possibility" of being associated with study drug, the investigator will provide an "other" cause of the event.

Deaths

For SAEs with the outcome of death, the date and cause of death will be recorded in the appropriate eCRF.

Deaths due to disease progression that occur within the AE reporting period should be collected as an SAE on the eCRF and reported to AbbVie per SAE reporting timelines and processes. Deaths due to disease progression should be reported as such and not simply as the malignancy being treated. Any deaths which occur after the AE reporting period will be collected on the Death and Study Completion eCRF.

Death should be considered an outcome and not a distinct event. The event or condition that caused or contributed to the fatal outcome should be recorded as the single medical concept on the Adverse Event eCRF. Generally, only 1 such event should be reported.

The term "sudden death" should be used only for the occurrence of an abrupt and unexpected death in a subject, within 1 hour after the onset of acute symptoms or, in the case of an unwitnessed death, within 24 hours after the subject was last seen alive and stable. If death was due to presumed cardiac causes, the event should be reported as "sudden cardiac death."

If the cause of death is unknown and cannot be ascertained at the time of reporting, "unexplained death" should be recorded on the Adverse Event eCRF. If the cause of death later becomes available (e.g., after autopsy), "unexplained death" should be replaced by the established cause of death.

Pregnancy

While not an adverse event, pregnancy in a study subject must be reported to AbbVie within 24 hours after the site becomes aware of the pregnancy. Subjects who become pregnant during the study must be discontinued (Section 5.5). If a pregnancy occurs in a study subject or in the partner of a study subject, information regarding the pregnancy and the outcome will be collected.

In the event of pregnancy occurring in a subject's partner during the study, written informed consent from the partner must be obtained prior to collection of any such information. AbbVie will provide a separate consent form for this purpose. Pregnancy in a subject's partners will be collected from the date of the first dose through at least 4 months following the last dose of study drug.

The pregnancy outcome of an elective or spontaneous abortion, stillbirth or congenital anomaly is considered a SAE and must be reported to AbbVie within 24 hours after the site becomes aware of the event.

Recording of Adverse Events Symptoms on the Subject Paper Diary Cards

For sites in China only as per local requirements, subjects must record adverse event symptoms on the subject paper diary cards (see Section 5.13).

6.2 Toxicity Management

For the purpose of medical management, all AEs and laboratory abnormalities that occur during the study must be evaluated by the Investigator. National Cancer Institute (NCI) CTCAE, version 5.0 is to be used in the grading of AEs and laboratory abnormalities that are reported as AEs, each of which will be followed to satisfactory clinical resolution.

Toxicity Management for Telisotuzumab Vedotin

For observed toxicities, subjects should be assessed for inter-current illness or other causes and treated as appropriate. Hematological toxicities related to bone marrow suppression (neutropenia, anemia, and thrombocytopenia) and peripheral neuropathy have been commonly reported in clinical trials evaluating ADCs with MMAE, and have been observed with telisotuzumab vedotin.[11] Gastrointestinal toxicities such as nausea, vomiting, diarrhea, and constipation have also been observed with telisotuzumab vedotin in addition to fatigue, dyspnea, decreased appetite, and arthralgia. Telisotuzumab vedotin has displayed some of the toxicities associated with ABT-700, including peripheral edema, hypoalbuminemia, and decreased testosterone. These risks may be related to c-Met inhibition.

For subjects who have received the first dose of telisotuzumab vedotin and are clinically stable but have experienced a reversible toxicity, the dose of study drug can be delayed for up to 42 days after the scheduled dosing date.

Depending upon the nature and rapidity of the reversibility of the toxicity, the investigator can continue the subject on the same dose level or reduce the dose by 0.3 mg/kg (larger dose reductions are allowable after consultation with the AbbVie Medical Monitor). Up to 3 dose reductions down to a minimum dose of 1.0 mg/kg are allowed to manage toxicity after which the subject will be discontinued from therapy (refer to Table 1). Subjects who experience a treatment-related AE that leads to a delay in telisotuzumab vedotin dosing for > 42 days from the scheduled dose will be discontinued from study. For AEs considered not related to telisotuzumab vedotin leading to a dose delay > 42 days, the AbbVie medical monitor should be consulted prior to resuming treatment.

Table 1. Dose Reduction Guidelines

Initial Telisotuzumab Vedotin Dose	First Dose Reduction	Second Dose Reduction	Third Dose Reduction
1.9 mg/kg	1.6 mg/kg	1.3 mg/kg	1.0 mg/kg or discontinue study drug

Guidelines for toxicity management are given below.

Table 2. Management of Non-Hematologic Toxicity

Toxicity	Guidelines
Grade 3 or 4 non-hematologic toxicities	• First episode: Interrupt telisotuzumab vedotin. Once toxicity has resolved to Grade ≤ 1 or baseline, telisotuzumab vedotin may be resumed at the same dose. No dose modification is required. • For subsequent episodes: Interrupt telisotuzumab vedotin. Follow dose reduction guidelines when resuming treatment with telisotuzumab vedotin after resolution. A larger dose reduction is allowable after consultation with the AbbVie Therapeutic Area Medical Director. • Subjects who experience recurrent Grade 3 or 4 non-hematologic toxicities should be discussed with the AbbVie Medical Monitor as telisotuzumab vedotin may need to be permanently discontinued.

Acute Infusion Reactions

Appropriate medical therapy and support measures should be available for immediate use in case an acute infusion-related reaction (IRR) occurs. If a Grade 2, 3, or 4 IRR is observed either during or after an infusion, a local blood draw should be obtained (tryptase, total IgE, complement C3a and C5) approximately 2 hours after the first sign of the reaction. If the testing is not available at the local laboratory, please contact the AbbVie Medical Monitor.

Table 3. Management of Acute Infusion Reactions

Infusion Reaction Grade	Immediate Action	Modifications to Infusion Rate	Subsequent Prophylaxis
Grade 1 –- 2	• Interruption of telisotuzumab vedotin treatment if indicated • Administration of appropriate medical therapy (H1-receptor antagonist, systemic steroids, supplemental oxygen, fluid resuscitation) if indicated	• 50% reduction of the infusion rate if indicated • The rate can be increased in 50% increments every 30 minutes as tolerated until the infusion is completed. • Infusion duration can be increased as tolerated in subsequent cycles	**Recommended:** • H1-receptor antagonist • H2-receptor antagonist • Systemic steroids • Acetaminophen
Grade 3	• Immediate interruption of telisotuzumab vedotin treatment • Administration of appropriate medical therapy (H1-receptor antagonist, systemic steroids, supplemental oxygen, fluid resuscitation, subcutaneous epinephrine)	• 50% reduction of the infusion rate • The rate can be increased in 50% increments every 30 minutes as tolerated until the infusion is completed. • Infusion duration can be increased as tolerated in subsequent cycles	**Required:** • H1-receptor antagonist • H2-receptor antagonist • Systemic steroids • Acetaminophen
Grade 4	• Immediate interruption of telisotuzumab vedotin treatment • Urgent administration of appropriate medical therapy (H1-receptor antagonist, systemic steroids, supplemental oxygen, fluid resuscitation, subcutaneous epinephrine) • Hospitalization if indicated	• Permanent discontinuation of telisotuzumab vedotin is required.	• Not applicable

Peripheral Neuropathy

Subjects should be monitored for neuropathy which can be managed by a combination of dose delays and dose reductions (in increments of 0.3 mg/kg). Larger dose reductions are allowable after consultation with the AbbVie Medical Monitor (however, where confirmed as contrary to local regulations, larger dose reductions will not be allowed).

Table 4. Management of Peripheral Neuropathy

Toxicity	Guidelines
Grade 1	• Continue at same dose level.
Grade 2	• Interrupt telisotuzumab vedotin until Grade ≤ 1. Reduce telisotuzumab vedotin dose by at least one dose level when treatment resumes.
Grade 3	• Interrupt telisotuzumab vedotin until neuropathy is Grade ≤ 1. Reduce telisotuzumab vedotin dose by at least one dose level when treatment resumes.
Grade 4	• Permanent discontinuation of telisotuzumab vedotin is required.

- For subjects who have had a dose reduction due to peripheral neuropathy, the dose oftelisotuzumab vedotin may be increased to a maximum dose of 1.9 mg/kg Q2W if the neuropathy improves to Grade ≤ 1 for a period of at least 1 cycle (2 weeks).

Bone Marrow Suppression (neutropenia, anemia and thrombocytopenia)

Subjects should be monitored for bone marrow suppression which can be managed by a combination of dose delays and dose reductions (in increments of 0.3 mg/kg). Larger dose reductions are allowable after consultation with the AbbVie Medical Monitor (however, where confirmed as contrary to local regulations, larger dose reductions will not be allowed).

Table 5. Management of Bone Marrow Suppression

Toxicity	Guidelines
Grade 3 or Grade 4 Neutropenia with infection or fever	• Best medical practice for febrile neutropenia should be instituted immediately. • First episode: Interrupt telisotuzumab vedotin and once the toxicity has resolved to Grade 2 or baseline level, telisotuzumab vedotin may be resumed at the same dose. • For subsequent episodes: Interrupt telisotuzumab vedotin. Follow dose reduction guidelines when resuming treatment with telisotuzumab vedotin after resolution. A larger dose reduction may occur at the discretion of the investigator and according to the dose reduction guidelines. • Granulocyte colony stimulating factor (G-CSF) support may be administered with telisotuzumab vedotin if clinically indicated.
Grade 3 or Grade 4 Anemia or Thrombocytopenia	• Transfusions are allowed per best medical practice. • First episode: Interrupt telisotuzumab vedotin and once the toxicity has resolved to Grade 1 or baseline level, telisotuzumab vedotin may be resumed at the same dose. • For subsequent episodes: Interrupt telisotuzumab vedotin. Follow dose reduction guidelines when resuming treatment with telisotuzumab vedotin after resolution. A larger dose reduction may occur at the discretion of the investigator and according to the dose reduction guidelines.

Ocular Toxicities

Ocular adverse events, most commonly blurred vision, dry eye, and keratitis have been reported in telisotuzumab vedotin clinical trials. Generally, these ocular AEs have been low grade (Grade ≤ 2) and manageable with supportive care measures and, if necessary, ocular steroid eye drops.

If ocular adverse events occur, an evaluation by an ophthalmologist is required.

Table 6. Management of Ocular Toxicities

Toxicity	Guidelines
Grade 1 (mild symptoms)	• Treatment with telisotuzumab vedotin can continue without dose modification.
Grade 2 (moderate symptoms)	• Treatment with telisotuzumab vedotin may continue after ophthalmologist consult and consultation with the Medical Monitor.
Grade 3 or Grade 4 (severe symptoms)	• Permanent discontinuation of telisotuzumab vedotin is required.

Hypoalbuminemia and Edema

Table 7. Management of Hypoalbuminemia and Edema

Status	Guidelines
Subjects who are clinically stable (SD, PR, or CR) but have an albumin level < 2.5 g/dL or peripheral edema Grade ≥ 2	• Dosing of telisotuzumab vedotin may be held for up to 42 days (after the scheduled dose) if the Investigator considers that the delay is in the best interest of the subject to allow for recovery of albumin levels or resolution of edema. • The subject may resume dosing with telisotuzumab vedotin when albumin levels are ≥ 2.5 g/dL and any edema has resolved to Grade ≤ 1. • Subjects who have albumin levels of ≤ 2.5 g/dL or edema Grade ≥ 2 for > 42 days after the scheduled dose will be discontinued from study drug.

CR = complete response; PR = partial response; SD = stable disease

Decreased Testosterone

Preliminary laboratory results demonstrate a decrease in testosterone levels in male subjects treated with ABT-700. The reason for testosterone decrease remains unknown at this time but may be related to c-Met inhibition. Testosterone replacement therapy is allowed, when indicated, per Investigator discretion.

Pneumonitis/Interstitial Lung Disease (ILD)

If a subject develops symptoms of treatment-emergent pneumonitis/ILD, it is recommended that the latest published guidelines are followed to work-up, diagnose, and treat pneumonitis/ILD.[12,13] The following table is adapted from those guidelines. In particular, if a subject develops Grade ≥ 2 treatment-emergent pneumonitis/ILD, permanent discontinuation of telisotuzumab vedotin is required.

Table 8. Management of Pneumonitis/ILD

Grading	Guidelines
Grade 1: Asymptomatic, confined to one lobe of the lung or < 25% of lung parenchyma, clinical or diagnostic observations only	**Interruption of telisotuzumab vedotin until resolution to Grade 0 is required** • Repeat CT in 3 - 4 weeks; in subjects who have had baseline testing, may offer a repeat spirometry/DLCO in 3 - 4 weeks • May resume telisotuzumab vedotin with radiographic evidence of improvement or resolution. • If no improvement, should treat as Grade 2 • Monitor subjects weekly with history and physical examination and pulse oximetry; may also offer CXR
Grade 2: Symptomatic, involves more than one lobe of the lung or 25% - 50% of lung parenchyma, medical intervention indicated, limiting instrumental ADL	**Permanent discontinuation of telisotuzumab vedotin is required** • Prednisone 1 - 2 mg/kg/d and taper by 5 - 10 mg/wk over 4 - 6 weeks • Consider bronchoscopy with BAL • Consider empirical antibiotics • Monitor every 3 days with history and physical examination and pulse oximetry, consider CXR; no clinical improvement after 48 - 72 hours of prednisone, treat as Grade 3
Grade 3: Severe symptoms, hospitalization required, involves all lung lobes or > 50% of lung parenchyma, limiting self-care ADL, oxygen indicated **Grade 4: Life-threatening respiratory compromise**, urgent intervention indicated (intubation)	**Permanent discontinuation of telisotuzumab vedotin is required** • Empirical antibiotics; methylprednisolone IV 1 - 2 mg/kg/d; no improvement after 48 hours, may add infliximab 5 mg/kg or mycophenolate mofetil IV 1 g twice a day or IVIG for 5 days or cyclophosphamide; taper corticosteroids over 4 - 6 weeks • Pulmonary and infectious disease consults recommended • Bronchoscopy with BAL ± transbronchial biopsy • Subjects should be hospitalized for further management

ADL = activities of daily living; BAL = bronchoalveolar lavage; CT = computed tomography; CXR = chest x-ray; DLCO = diffusing capacity of lung for carbon monoxide; ILD = Interstitial Lung Disease; IV = intravenous; IVIG = intravenous immunoglobulin

6.3 Recording Data and Analyses of Safety Findings

Adverse events will be coded using the Medical Dictionary for Regulatory Activities (MedDRA). Details on the statistical analyses for safety will be provided in the SAP.

The number and percentage of subjects with TEAEs (i.e., any event that begins or worsens in severity after initiation of study drug through 30 days post-study drug dosing) will be tabulated by primary MedDRA System Organ Class (SOC) and preferred term. The tabulation of the number of subjects with TEAEs by severity grade and relationship to study drug also will be provided. Subjects reporting more than one AE for a given MedDRA preferred term will be counted only once for that term using the most severe grade according to the severity grade table and the most related according to the relationship to

study drug tables. Subjects reporting more than 1 type of event within an SOC will be counted only once for that SOC.

6.4 Recording Adverse Events and Intercurrent Illnesses

In the event of an SAE, whether associated with study drug or not, the investigator will notify Clinical Pharmacovigilance within 24 hours of the site being made aware of the SAE by entering the SAE data into the electronic data capture (EDC) RAVE® system. SAEs that occur prior to the site having access to the RAVE® system, or if RAVE is not operable, should be documented on the SAE non-CRF forms and emailed (preferred route) or faxed to Clinical Pharmacovigilance within 24 hours of the site being made aware of the SAE. Contact information for reporting AEs or any other safety concern or question is included in Appendix D.

AbbVie will be responsible for SUSAR reporting for the IMP in accordance with global and local guidelines and Appendix A of the Investigator Brochure will serve as the Reference Safety Information (RSI). The RSI in effect at the start of a Development Safety Update Report (DSUR) reporting period serves as the RSI during the reporting period. For follow-up reports, the RSI in place at the time of occurrence of the 'suspected' Serious Adverse Reaction will be used to assess expectedness.

7 STATISTICAL METHODS & DETERMINATION OF SAMPLE SIZE

7.1 Statistical and Analytical Plans

The statistical methods provided in this protocol will be focused on primary and key secondary analyses. Complete and specific details of the statistical analysis will be described in the Statistical Analysis Plan (SAP).

The final analysis will be conducted after all the subjects have had the chance to be followed for at least 6 months.

Interim analyses will occur as described in Section 4.1.

7.2 Definition for Analysis Populations

The Efficacy Evaluable analysis set includes all subjects who are *MET* amplified by local or central testing, and received at least 1 dose of study drug. The interim analyses will be conducted based on the number of subjects (i.e., information fraction) specified in Section 7.6. Details of the analysis sets will be provided in SAP.

The Safety Analysis Set consists of all subjects who received at least 1 dose of study drug and will be used for safety analyses.

7.3 Handling Potential Intercurrent Events for the Primary and Key Secondary Endpoints

The corresponding estimand for the primary endpoint of ORR per ICR according to RECIST v1.1 is defined as follows:

- Population: Previously untreated subjects with MET amplified non-squamous NSCLC.
- Variable: Whether patients achieved a confirmed objective response (i.e., complete response or partial response confirmed by a repeat assessment ≥ 4 weeks apart).
- Treatments: Telisotuzumab vedotin at 1.9 mg/kg every 2 weeks IV.
- Intercurrent events:
  - Premature discontinuation of study drug: treatment policy strategy- all available disease assessments, including those after the study drug discontinuation, will be used for the analysis of the endpoint.
  - Use of new anticancer therapy: while on treatment (not on new anti-cancer therapy) strategy – all available disease assessment prior to or on the date of initiation of new anti-cancer therapy will be used for the analysis of ORR.
- Summary measure: proportions of patients achieved confirmed objective response.

The corresponding estimand of the key secondary endpoint of DoR is defined as follows:

- Population: Previously untreated subjects with MET amplified non-squamous NSCLC who achieved a confirmed objective response by ICR according to RECIST v1.1.
- Variable: Time interval from the date of the first occurrence of a confirmed objective response until the first date of progressive disease or death from any cause, whichever occurs first.
- Treatments: Telisotuzumab vedotin at 1.9 mg/kg every 2 weeks IV.
- Intercurrent events:
  - Premature discontinuation of study drug: treatment policy strategy–- all available disease assessments, including those after the study drug discontinuation, will be used for the analysis of the endpoint.
  - Use of new anticancer therapy: treatment policy strategy–- all available disease assessments, including those after the initiation of the new anticancer therapy, will be used for the analysis of the endpoint
- Summary measure: Distribution for duration of response.

7.4 Statistical Analyses for Efficacy

Summary and Analysis of the Primary Endpoint

Analysis of the primary endpoint of ORR per ICR (as defined in Section 3.2) will be conducted on the efficacy evaluable analysis set. The ORR per ICR will be summarized, along with 2-sided 95% exact confidence intervals based on the binomial distribution. Subjects without a post-baseline ICR disease assessment will be considered as non-responders in the calculation of ORR. The primary endpoint of ORR per ICR is used to test the clinical hypothesis that the ORR of telisotuzumab vedotin in previously untreated patients with *MET* amplified non-squamous NSCLC exceeds 40%. The exact binomial test will be used for the ORR comparison, and stopping boundaries for the two interim and final analyses are computed using O'Brien-Fleming function in Table 9.

Sensitivity analysis for primary endpoint of ORR will include ORR per investigator assessment. Details will be provided in the SAP.

Summary and Analysis of Secondary Endpoints

Summary and Analysis of Key Secondary Endpoint

The key secondary endpoint of DoR (as defined in Section 3.3) will be analyzed based on the confirmed responders by ICR. The distribution of the DoR will be estimated using Kaplan-Meier methodology.

Sensitivity analysis for key secondary endpoint of DoR will include DoR per investigator assessment. Details will be provided in the SAP.

Summary and Analysis of Other Secondary Endpoints

Other secondary endpoints include DCR, PFS, OS, time to deterioration in cough or pain or dyspnea as measured by the cough, pain, and dyspnea items of the EORTC QLQ-LC13, time to deterioration of physical functioning as measured by the physical functioning domain of the EORTC QLQ-C30, change from baseline in quality of life as measured by the global health status/quality of life domain of the EORTC QLQ-C30. Details will be provided in the SAP.

7.5 Statistical Analyses for Safety

Safety and tolerability of telisotuzumab vedotin will be assessed by evaluating AEs, physical examinations, and changes in laboratory data and vital signs, as well as drug discontinuation or dosing modification due to adverse events, for the entire study duration. Details on the safety analyses will be provided in the SAP.

7.6 Interim Analyses

There will be 2 interim analyses.

The first interim analysis (IA1) for efficacy will take place after approximately 20 efficacy evaluable subjects have had the chance to be followed for at least 6 months. A second interim analysis (IA2) for efficacy will take place after approximately 50 efficacy evaluable subjects have had the chance to be

followed for at least 6 months. The stopping boundaries are provided in Table 9 Section 7.8. Additional details will be provided in the statistical analysis plan (SAP).

7.7 Overall Type I Error Control

Family-wise type 1 error for testing ORR will be controlled with 1-sided 0.025 significance level. Group sequential design for a single arm study with 2 interim analyses for efficacy at approximately 20 subjects (information fraction of 0.286) and approximately 50 subjects (IF of 0.714), respectively will be carried out using O'Brien-Fleming boundaries (O'Brien 1979).[14]

7.8 Sample Size Determination

The planned sample size is approximately 70 efficacy evaluable subjects with 2 interim analyses. This sample size will provide approximately 91% overall power to rule out an ORR of 40% using an exact binomial test assuming the true ORR for telisotuzumab vedotin is 60%.

The stopping boundaries, cumulative α and power are provided in Table 9.

Table 9. Power and Planned Efficacy Stopping Boundaries at IA1, IA2, and Final Analysis (FA) for ORR

Analysis	Information Fraction (No. of subjects)	Cumulative α (1-sided)	Cumulative power	Efficacy Stopping Boundaries (No. of responders)
ORR IA1	28.6% (20)	0.000027	0.4%	18
ORR IA2	71.4% (50)	0.008	67.0%	29
ORR FA	100% (70)	0.025	91.3%	37

FA = final analysis; ORR = Objective Response Rate; IA1 = interim analysis 1; IA2= interim analysis 2

8 ETHICS

8.1 Independent Ethics Committee/Institutional Review Board (IEC/IRB)

The protocol, informed consent form(s), recruitment materials, and all subject materials will be submitted to the IEC/IRB for review and approval. Approval of both the protocol and the informed consent form(s) must be obtained before any subject is enrolled. Any amendment to the protocol will require review and approval by the IEC/IRB before the changes are implemented to the study. In addition, all changes to the consent form(s) will be IEC/IRB approved.

8.2 Ethical Conduct of the Study

The study will be conducted in accordance with the protocol, Operations Manual (Appendix I), International Council for Harmonisation (ICH) guidelines, applicable regulations, and guidelines governing clinical study conduct and the ethical principles that have their origin in the Declaration of Helsinki. Responsibilities of the investigator are specified in Appendix B. Investigators should notify AbbVie if any urgent safety measures are taken to protect the subjects against any immediate hazard.

8.3 Subject Confidentiality

For personal data that AbbVie controls and maintains, AbbVie has developed a robust security program to protect subject personal data focused on due diligence in design, managed change, and information security governance. Information security policies govern the information security functions including identity and access management, operations, infrastructure, application, and third-party security requirements. The risk-based AbbVie Data Classification Tool dictates the level of scrutiny and control required for the relevant activities per AbbVie's information security policies taking into account the sensitivity of the data.

Before subject data is shared with AbbVie, the study doctor and staff will replace any information that could directly identify a subject (such as name, address, and contact information) with a generic code which AbbVie cannot link to that subject's identity in order to protect the confidentiality of the data.

AbbVie has a data protection impact assessment (DPIA) program to ensure and document the appropriate controls and safeguards stated above are in place for clinical trial data that it controls and maintains, and these processing activities respect privacy of clinical trial subjects. AbbVie also maintains robust security incident response policies and procedures, including requirements for the containment of any data related incidents, the mitigations measures where needed, and notification to authorities or affected individuals where required.

9 SOURCE DOCUMENTS AND CASE REPORT FORM COMPLETION

The investigator is responsible for ensuring the accuracy, completeness, legibility, and timeliness of the data reported. All source documents should be attributable, legible, contemporaneous, original, accurate, and complete to ensure accurate interpretation of data. Clinical site monitoring is conducted to ensure that the rights and well-being of human subjects are protected, that the reported trial data are accurate, complete, and verifiable, and that the conduct of the trial is in compliance with the currently approved protocol, ICH Good Clinical Practice (GCP), and applicable local regulatory requirement(s). During the COVID-19 pandemic, and geo-political conflict in Ukraine and surrounding impacted regions, remote data review/verification may be employed if allowed by the local regulatory authority, IRB/IEC, and the study site.

10 DATA QUALITY ASSURANCE

AbbVie will ensure that the clinical trial is conducted with a quality management system that will define quality tolerance limits in order to ensure human subject protection and reliability of study results. Data will be generated, documented, and reported in compliance with the protocol, ICH GCP, and applicable regulatory requirements.

11 COMPLETION OF THE STUDY

The start-of-study is defined as the date of the first site activated.

The end-of-study is defined as the date of the end of study participation by the last subject in the last country where the study was conducted.

12 REFERENCES

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APPENDIX A. STUDY-SPECIFIC ABBREVIATIONS AND TERMS

Abbreviation	Definition
ABG	Arterial blood gases
AC	Adjudication Committee
ADA	Anti-drug antibodies
ADC	Antibody-drug conjugate
AE	Adverse event
ALT	Alanine aminotransferase
ANC	Absolute neutrophil count
AST	Aspartate aminotransferase
CNS	Central nervous system
COVID-19	Coronavirus Disease - 2019
CR	Complete response
CrCl	Creatinine clearance
CT	Computed tomography
CTCAE	Common Terminology Criteria for Adverse Events
ctDNA	Circulating Tumor Deoxyribonucleic Acid
DCR	Disease control rate
DLCO	Carbon monoxide diffusing capacity
DNA	Deoxyribonucleic acid
DoR	Duration of Response
DPIA	Data protection impact assessment
DSUR	Development Safety Update Report
ECG	Electrocardiogram
ECMO	Extracorporeal membrane oxygenation
ECOG	Eastern Cooperative Oncology Group
eCRF	Electronic Case Report Form
EDC	Electronic data capture
EORTC	European Organization for Research and Treatment of Cancer
EORTC QLQC30	European Organization for Research and Treatment of Cancer Quality of Life Questionnaire Core 30
EORTC QLQ-LC13	European Organization for Research and Treatment of Cancer Quality of Life Questionnaire Lung Cancer Module 13

EOT	End of Treatment
EQ-5D-5L	EuroQoL 5 Dimension 5 Level
EU	European Union
FDA	Food and Drug Administration
FSH	Follicle-stimulating hormone
GCP	Good clinical practice
G-CSF	Granulocyte-colony stimulating factor
GM-CSF	Granulocyte-macrophage colony-stimulating factor
HBV	Hepatitis B virus
HCV	Hepatitis C virus
HGF	Hepatocyte growth factor
HIV	Human immunodeficiency virus
HRCT	High-resolution computed tomography
IA1	First interim analysis
IA2	Second interim analysis
ICE	Intercurrent event
ICH	International Council for Harmonisation of Technical Requirements for Pharmaceuticals for Human Use
ICR	Independent central review
IEC	Independent ethics committee
IgG	Immunoglobulin G
IHC	Immunohistochemistry
ILD	Interstitial Lung Disease
IMP	Investigational Medicinal Product
IRB	Institutional review board
IRR	Infusion-related reaction
IRT	Interactive response technology
IUD	Intrauterine device
IUS	Intrauterine hormone-releasing system
IV	Intravenous
IVDR	In Vitro Medical Device Regulation
MedDRA	Medical Dictionary for Regulatory Activities
MMAE	Monomethylauristatin E
MRI	Magnetic resonance imaging

nADA	Neutralizing anti-drug antibodies
NCCN	National Comprehensive Cancer Network
NCI	National Cancer Institute
NSCLC	Non-small cell lung cancer
ORR	Objective response rate
OS	Overall survival
PCR	Polymerase chain reaction
PD	Progressive disease
PDx	Pharmacodynamic
PFS	Progression Free Survival
PGIC	Patient Global Impression of Change
PGIS	Patient Global Impression of Severity
P-gp	P-glycoprotein
PK	Pharmacokinetic(s)
PR	Partial response
PRO	Patient-Reported Outcome
PRO-CTCAE	Patient-Reported Outcome Common Terminology Criteria for Adverse Events
Q2W	Every 2 weeks
Q3W	Every 3 weeks
QLQ	Quality of Life Questionnaire
RECIST	Response Evaluation Criteria in Solid Tumors
RSI	Reference Safety Information
QTc	QT interval corrected for heart rate
QTcF	QT interval corrected for heart rate using Fridericia's formula
SAE	Serious adverse event
SAP	Statistical analysis plan
SAR	Serious adverse reactions
SARS-CoV-2	Severe acute respiratory syndrome coronavirus 2
SD	Stable disease
SDAC	Statistical Data Analysis Center
SOC	System Organ Class
SUSAR	Suspected unexpected serious adverse reactions
TEAE	Treatment-emergent adverse event
TK	Tyrosine kinase

ULN	Upper limit of normal
VAS	Visual Analog Scale
vc	Valine-citrulline

APPENDIX B. RESPONSIBILITIES OF THE INVESTIGATOR

Protocol M22-137: Phase 2, Open-Label Study in Subjects with Previously Untreated *MET* Amplified Locally Advanced/Metastatic Non-Squamous Non-Small Cell Lung Cancer (NSCLC)

Protocol Date: 07 March 2023

Clinical research studies sponsored by AbbVie are subject to the International Council for Harmonisation of Technical Requirements for Pharmaceuticals for Human Use (ICH) Good Clinical Practices (GCP) and local laws and regulations and guidelines governing the study at the site location. In signing the Investigator Agreement, the investigator is agreeing to the following:

1. Conducting the study in accordance with ICH GCP, the applicable regulatory requirements, current protocol and operations manual, and making changes to a protocol only after notifying AbbVie and the appropriate Institutional Review Board (IRB)/Independent Ethics Committee (IEC), except when necessary to protect the subject from immediate harm.
2. Personally conducting or supervising the described investigation(s).
3. Informing all subjects, or persons used as controls, that the drug is being used for investigational purposes and complying with the requirements relating to informed consent and ethics committees (e.g., IEC or IRB) review and approval of the protocol and its amendments.
4. Reporting complaints that occur in the course of the investigation(s) to AbbVie.
5. Reading the information in the Investigator's Brochure/safety material provided, including the instructions for use and the potential risks and side effects of the investigational product(s).
6. Informing all associates, colleagues, and employees assisting in the conduct of the study about their obligations in meeting the above commitments.
7. Maintaining adequate and accurate records of the conduct of the study, making those records available for inspection by representatives of AbbVie and/or the appropriate regulatory agency, and retaining all study-related documents until notification from AbbVie.
8. Maintaining records demonstrating that an ethics committee reviewed and approved the initial clinical protocol and all of its amendments.
9. Reporting promptly (within one [1] calendar day) to AbbVie, the ethics committees/institutional review boards (as required) and other appropriate individuals (e.g., coordinating investigator, institution director):
    - All changes in the research activity and all unanticipated problems involving risks to human subjects or others
    - Any departure from relevant clinical trial law or regulation, GCP, or the trial protocol that has the potential to affect the following:
        - Rights, safety, physical or mental integrity of the subjects in the clinical trial
        - Scientific value of the clinical trial, reliability or robustness of data generated
10. Providing direct access to source data documents for study-related monitoring, audits, IEC/IRB review, and regulatory inspection(s).

Signature of Principal Investigator | Date

Name of Principal Investigator (printed or typed)

APPENDIX C. LIST OF PROTOCOL SIGNATORIES

Name	Title	Functional Area
[redacted]	[redacted]	[redacted]
[redacted]	[redacted]	[redacted]
[redacted]	[redacted]	[redacted]
[redacted]	[redacted]	[redacted]

APPENDIX D. SAFETY REPORTING CONTACT INFORMATION

For SAE reporting outside RAVE:

Email: PPDINDPharmacovigilance@abbvie.com
FAX to: +1 (847) 938-0660

For safety concerns, contact the Oncology Safety Team at:

AbbVie Oncology Safety Team
1 North Waukegan Road
North Chicago, Illinois 60064
Toll Free: +1 (833) 942-2226
Email: SafetyManagement_Oncology@abbvie.com

For any subject safety concerns, please contact the physician listed below:

Primary Therapeutic Area Medical Director
EMERGENCY MEDICAL CONTACT:
[redacted]
AbbVie
Wegalaan 9
2132JD Hoofddorp
The Netherlands

Contact Information:

Office: [redacted]
Mobile:
Email:

In emergency situations involving study subjects when the primary Therapeutic Area Medical Director is not available by phone, please contact the 24-hour AbbVie Medical Escalation Hotline where your call will be re-directed to a designated backup AbbVie Therapeutic Area Medical Director:

HOTLINE: +1 (973) 784-6402

The sponsor will be responsible for Suspected Unexpected Serious Adverse Reactions (SUSAR) reporting for the Investigational Medicinal Product (IMP) in accordance with global and local requirements.

APPENDIX E. ACTIVITY SCHEDULE

The following table shows the required activities. The individual activities are described in detail in the **Operations Manual**. Allowed modifications due to COVID-19 and/or the geo-political conflict in Ukraine and surrounding impacted regions are detailed within the Operations Manual.

Study Activities Table

Activity	Pre-screening for *MET* amplification	Screening	Cycle 1		Cycle ≥ 2	Every ~ 6 Weeks (± 7 Days)	End of Treatment	30-Day Follow-Up (+ 7 Days)	Post-Treatment Follow-Up	Survival Follow-Up
		Day –28 to Day –1	Day 1	Day 8 (± 2 Days)	Day 1 (+ 2 Days)				Every 6 Weeks Until Disease Progression	
INTERVIEWS & QUESTIONNAIRES										
Subject Information and Informed Consent	✓	✓								
Eligibility Criteria	✓	✓								
Medical and Cancer History	✓	✓	✓							
Adverse Event Assessment	✓	✓	✓	✓	✓		✓	✓		
Prior/Concomitant Therapy	✓	✓	✓	✓	✓		✓	✓		
Post-treatment Anti-Cancer Therapy Information								✓	✓	✓
Survival Status								✓		✓
PRO Assessments		✓	✓		✓		✓	✓	✓	
For China sites only, dispense subject paper diary cards for adverse event symptoms and concomitant therapy. Previously dispensed diaries will be collected and reviewed. At the 30 day follow-up visit, the final diary will be collected and no additional diaries will be dispensed.	✓	✓	✓	✓	✓		✓	✓		
LOCAL LABORATORY TESTS & EXAMINATIONS										
12-lead ECG		✓	✓		✓		✓			
Vital signs, including pulse oximetry		✓	✓	✓	✓		✓	✓		
Physical examination (complete or limited)		✓	✓	✓	✓		✓	✓		

Activity	Pre-screening for *MET* amplification	Screening	Cycle 1		Cycle ≥ 2	Every ~ 6 Weeks (± 7 Days)	End of Treatment	30-Day Follow-Up (+ 7 Days)	Post-Treatment Follow-Up	Survival Follow-Up
		Day –28 to Day –1	Day 1	Day 8 (± 2 Days)	Day 1 (+ 2 Days)				Every 6 Weeks Until Disease Progression	
Pregnancy test (urine)			✓		✓		✓	✓	✓ Monthly for 7 months after last dose of study drug	
ECOG Performance Status		✓	✓		✓		✓	✓		
Ophthalmological exam		✓								
Tumor Assessment (CT Scan/MRI)		✓ (Day-35 to -1)				✓	✓		✓	
MRI of brain (or CT scan if MRI contraindicated)		✓ (Day -35 to -1)								
CENTRAL LABORATORY TESTS										
Pregnancy test		✓								
Hematology		✓	✓	✓	✓		✓	✓		
Chemistry		✓	✓	✓	✓		✓	✓		
Urinalysis		✓	✓				✓			
Testosterone, sex hormone binding globulin (males only)		✓			✓		✓	✓		
aPTT/PT/INR		✓								
Tumor Material FFPE block/slides/wet tissue	✓	✓								
Plasma (ctDNA) for central assay evaluation (Screening)		✓								
Plasma (ctDNA) (C1D1, C2D1 and every other odd cycle after Cycle 2, e.g., C3D1, C5D1, until end of treatment)			✓		✓		✓			
Tumor Material at Disease Progression (Optional) FFPE block/wet tissue/slides							✓			

Activity	Pre-screening for *MET* amplification	Screening	Cycle 1		Cycle ≥ 2	Every ~ 6 Weeks (± 7 Days)	End of Treatment	30-Day Follow-Up (+ 7 Days)	Post-Treatment Follow-Up	Survival Follow-Up
		Day –28 to Day –1	Day 1	Day 8 (± 2 Days)	Day 1 (+ 2 Days)				Every 6 Weeks Until Disease Progression	
Biomarker Samples (plasma) (C1D1, C2D1 and every other odd cycle after Cycle 2, e.g., C3D1, C5D1, etc.)			✓		✓		✓			
Biomarker Sample (whole blood) *MET* gene analysis and optional genetic testing (or at any visit after Cycle 1 Day 1)			✓							
PK Samples			✓	✓	✓					
ADA and nADA Samples			✓	✓	✓					
℞ TREATMENT										
Enrollment			✓ Day –3 to Day 1							
Telisotuzumab vedotin dosing			✓		✓					

APPENDIX F. PROTOCOL SUMMARY OF CHANGES

Previous Protocol Versions

Protocol	Date
Version 1.0	09 December 2021
Version 2.0	25 May 2022
Version 2.1 (China Only)	19 August 2022
Version 2.2 (Japan Only)	01 November 2022
Version 2.3 (EU Only)	21 December 2022

The purpose of this version is to apply the following changes:

In the study protocol Section 5.4 (Prior and Concomitant Therapy), Section 5.13 (Paper Diary Cards for Sites in China Only), Section 6.1 (Complaints and Adverse Events), Appendix E (Activity Schedule), Operations Manual Section 2.1 (Individual Treatment Period Visit Activities), Section 2.2 (Individual Post-Treatment Period Visit Activities), Operations Manual Section 3.18 (Paper Diary Cards for Sites in China Only), and Operations Manual Section 5.5 (China-Specific Requirements):

- Added the use of subject paper diary cards for sites in China.

  Rationale: To be in alignment with local requirements as per the China Center for Food and Drug Inspections (CFDI).

In the study protocol Section 2.1 (Background and Rationale) and Section 2.2 (Benefits and Risks):

- Additional context added describing standard of care options, benefit/risk of the study, to update study data, to correct a typographical error, and to add a minor revision of the description of the characterization to support the initiation of the trial.

  Rationale: To provide additional and updated information.

In the study protocol Synopsis, and Section 3.3 (Secondary Endpoints):

- The definition for time to first deterioration in cough, pain or dyspnea as measured by the EORTC-QLQ-LC13 has been updated.
- The definition for time to first deterioration in physical functioning as measured by EORTC-QLQ-Core 30 has been updated.

  Rationale: To clarify the definition for the intended assessment.

In the study protocol Synopsis, and Section 3.4 (Additional Efficacy Endpoints):

- A description of the analysis method for PRO CTCAE has been removed.

  Rationale: To remove the analysis method.

In the study protocol Synopsis, Section 3.7 (Biomarker Research), Section 5.1 (Eligibility Criteria), Appendix E (Activity Schedule); and in the Operations Manual Section 2.1 (Screening), Section 3.7 (Sample Collection for MET Amplification and Biomarker Testing), and Section 8.1 (Flowchart):

- To specify that the additional tumor material and plasma are requested to allow for central assay evaluation.

  Rationale: To clarify the intended use of the requested material.

In the study protocol Synopsis, Section 5.1 (Eligibility Criteria):

- Eligibility #3: Clarification that the central assay is a *MET* FISH Assay, and that as applicable, the central assay can only be utilized after IVDR certification is obtained.

  Rationale: To provide additional clarification regarding the central assay.

- Eligibility #6: Clarification that only non-squamous adenocarcinoma histology is allowed in the study.

  Rationale: To provide clarification regarding the allowed histology.

- Eligibility #8: Clarification that subjects with actionable mutations, including EGFR, ALK, ROS1, and BRAF are only excluded if therapy is available.

  Rationale: To provide clarified guidance.

- Eligibility #11: Updated eligibility criterion to allow no more than 1 cycle of chemotherapy prior to receiving the first dose of study drug is allowed. To clarify that immunotherapy in the adjuvant or neoadjuvant setting is allowed.

  Rationale: To allow flexibility regarding treatment with 1 cycle of chemotherapy and to broaden allowed therapies in the adjuvant/neoadjuvant setting.

- Eligibility #16: Removed consultation with AbbVie medical monitor for clinically insignificant imaging findings

  Rationale: To clarify the eligibility criterion.

- Eligibility #18: Removed clinically significant from the definition of unresolved AEs.

  Rationale: To clarify the eligibility criterion.

- Eligibility #21: To remove active corneal disorder.

  Rationale: To clarify the eligibility criterion.

In the study protocol Section 5.1 (Eligibility Criteria):

- Eligibility #20: To broaden the criterion to allow for HBsAg positivity associated with HBV DNA ≥ 500 IU/mL.

  Rationale: To clarify the definition for active hepatitis B infection.

- Eligibility #27: To add consideration for a positive pregnancy test in a subject who is not pregnant.

  Rationale: To provided updated guidance.

- Eligibility #28-31: To update the contraception requirement durations for female subjects and male subjects.

  Rationale: To clarify the duration of required contraception.

In the study protocol Section 5.2 (Contraception Recommendations)

- To clarify that female subjects should be provided information regarding cryopreservation of eggs prior to study drug treatment.
- To clarify that females of childbearing potential and female partners of male subjects must use highly effective birth control defined as a failure rate of less than 1% per year.
- To clarify that male subjects must use condoms from Day 1 of treatment to 4 months after the last dose of study drug.

  Rationale: To provide additional guidance to the subjects.

In the study protocol Section 5.3 (Prohibited Medication and Therapy):

- To clarify that live vaccines are prohibited 30 days prior to the first dose until 90 days after study drug completion, and to remove clinical inhibitors of transporters from the example list provided.
  Rationale: To provide clarification.

In the study protocol Section 5.5 (Withdrawal of Subjects and Discontinuation of Study), Section 9 (Source Documents and Case Report Form Completion), Operations Manual Section 5.6 (Geo-Political Conflict):

- To clarify the allowed alternate methods of administering PROs
- To update COVID-specific and geo-political conflict-specific protocol verbiage

  Rationale: To update COVID-19 specific considerations.

In the study protocol Section 5.5 (Withdrawal of Subjects and Discontinuation of Study)

- To clarify that study drug should be discontinued if a subject experiences a treatment-related AE that leads to delay in dosing telisotuzumab vedotin for > 42 days.
  Rationale: For consistency

In the study protocol Section 5.7 (Study Drug):

- To allow drug to be destroyed by third-party vendor contracted with the site
  Rationale: To provide flexibility for drug destruction.

In the study protocol Section 6.1 (Complaints and Adverse Events):

- To update the required reporting period for pregnancies in female partners of male subjects, and to clarify that only spontaneously reported SAEs will be collected 30 days following the last dose of study drug or completion of study treatment.
  Rationale: To provide consistent guidance in the protocol.

In the study protocol Section 6.2 (Toxicity Management):

- Specified minimum dose of 1.0 mg/kg for telisotuzumab vedotin.

  Rationale: To clarify lowest dose of telisotuzumab vedotin allowed.
- Revised "Recommended Action" to "Guidelines" in Table 2, Table 4, Table 5, Table 6, Table 7, and Table 8, and revised language preceding Table 2 introducing the guidelines.

  Rationale: To provide clarity and consistent language regarding action to be taken for toxicity management.
- Table 3: Grade 4 infusion reactions require permanent discontinuation of telisotuzumab vedotin is required.

  Rationale: To provide clarification.
- Table 4: Revised guideline for management of peripheral neuropathy.

  Rationale: To provide guidance to investigators.
- Table 6: Revised text to state that permanent discontinuation of telisotuzumab vedotin is required if a subject develops Grade 3 or Grade 4 ocular toxicities.

  Rationale: To provide more specific instructions on management of ocular toxicities.
- Table 8: Revised text to state that permanent discontinuation of telisotuzumab vedotin is required if a subject develops Grade ≥ 2 treatment-emergent pneumonitis/ILD, and interruption of telisotuzumab vedotin until resolution to Grade 0 is required if a subject develops Grade 1 treatment-emergent pneumonitis/ILD.

  Rationale: To provide more specific instructions on management of pneumonitis/ILD.

In the study protocol Section 8.3 (Subject Confidentiality):

- Updated text throughout section regarding subject confidentiality.

  Rationale: To comply with EU CTR requirements.

In the study protocol Appendix D (Safety Reporting Contact Information) and operations manual Section 4.2 (Reporting Adverse Events and Intercurrent Illnesses):

- Revised text "in accordance with Directive 2001/20/EC" to "in accordance with global and local requirements."

  Rationale: To remove reference to EU Directive to align with EU CTR submission process

In the protocol Synopsis, Section 3.3 (Secondary Endpoint), and Section 7.4 (Statistical Analyses for Efficacy)

- Added by ICR to qualify that DoR will be based on the confirmed responders by ICR.

  Rationale: To clarify that confirmed responders are per ICR assessment.

In the protocol Synopsis, Section 3.3 (Secondary Endpoint) and Section 3.4 (Additional Efficacy Endpoints)

- Updated text to read "cough or pain or dyspnea as measured respectively."

  Rationale: To clarify that each domain would be analyzed separately.

In the protocol Synopsis and Section 3.7 (Biomarker Research)

- Removed "Endpoints" from "Biomarker Research Endpoints"

  Rationale: To clarify that the use of the data received for exploratory biomarker research are not part of any primary or secondary study endpoints.

In the protocol Section 7.2 (Definition of Analysis Populations):

- To remove measurable disease as part of the efficacy evaluable analysis set definition.

  Rationale: To simplify the definition for efficacy evaluable.

In the protocol Section 3.1 (Objectives, Hypotheses and Estimands), and Section 7.3 (Handling Potential Intercurrent Events for the Primary and Key Secondary Endpoints):

- To revise the confirmation of response from 2 consecutive occasions to confirmed by a repeat assessment.
- To clarify that all available disease assessments prior to or on the date of the initiation of new anti-cancer therapy will be used for the ORR analysis.

  Rationale: To incorporate HA feedback and to provide clarification.

In the protocol Synopsis, Section 4.1 (Overall Study Design and Plan), Section 7.1 (Statistical & Analytical Plans), Section 7.6 (Interim Analyses) and Section 7.8 (Sample Size Determination):

- To update the description of the follow-up period to reflect that it is for subjects that have had the chance to be followed for at least 6 months.
- To include a table outlining the power and planned efficacy stopping boundaries at IA1, IA2, and FA.

  Rationale: To simplify the description and to incorporate HA feedback.

In the study protocol Appendix E (Activity Schedule), Operations Manual Section 2.1 (Individual Treatment Period Visit Activities), Operations Manual Section 3.7 (Sample Collection for MET Amplification Central Assay Evaluation and Biomarker Testing):

- Added the allowance of tissue slide submission for end of treatment.

  Rationale: To align with specific regulatory requirements

In the study protocol Appendix E (Activity Schedule) and operations manual Section 2.1 (Individual Treatment Period Visit Activities) and Section 3.16 (Tumor Assessments):

- Added that the window for CT/MRI collection is Day -35 to Day -1 and that if standard of care the image must meet the study imaging requirements.

  Rationale: To provide additional flexibility and limit radiation exposure for subjects.

In the study protocol Appendix E (Activity Schedule) and Operations Manual Section 2.1 (Individual Treatment Period Visit Activities)

- To remove the requirement for imaging to be obtained prior to dosing

  Rationale: For clarification and completeness.

In Appendix E (Activity Schedule), and Operations Manual Section 2.1 (Individual Treatment Period Visit Activities), Section 2.2 (Individual Post-treatment Period Visit Activities), and Section 3.13 (Clinical Laboratory Tests):

- Edited to indicate monthly urine pregnancy testing will occur through 7 months after last dose.

  Rationale: Required time period was changed from 6 to 7 months to reflect 6 months (period of folliculogenesis) plus 5 half-lives of study drug.

In the study protocol Appendix G (IVDR Specific Appendix to Protocol M22-137)

- Added Appendix G to the protocol.

  Rationale: To be consistent with current European standards and IVDR.

In the study protocol Appendix H (Adverse Event Reporting for the IVD)

- Added Appendix H to the protocol.

  Rationale: To provide clarity and specific instruction on ADEs to be collected globally to be compliant with IVDR.

In the protocol operations manual Section 1 (Contacts):

- Added and updated contact information for the PK Sample Lab and Central *MET* Amplification Testing Lab

  Rationale: To provide the latest contact information.

In the protocol operations manual Section 2.1 (Individual Treatment Period Visit Activities):

- To specify testosterone and sex-hormone binding globulin testing must be repeated up to 3 days prior to dosing if screening is > 14 days from Cycle 1 Day 1

  Rationale: For consistency

- To clarify that a serum pregnancy test in place of the urine pregnancy test is allowed provided that it can be resulted prior to the study drug administration for Cycle 1 Day 1 and Cycle ≥ 2 Day 1.

  Rationale: To allow flexibility to align with site standard process, where applicable.

In the protocol operations manual Section 2.1 (Individual Treatment Period Visit Activities), Section 3.6 (Pharmacokinetics):

- To clarify the 2 day window for the PK draw at C1D8, and the 5 minute infusion window for the 30 minute post-dose PK draw for Cycles 2-18

  Rationale: For clarification and completeness

In the protocol operations manual Section 2.1 (Pre-screening) and Section 3.7 (Sample Collection for MET Amplification Central Assay Evaluation and Biomarker Testing):

- To clarify the two-step process for submitting tissue samples with the timeframe

  Rationale: For clarification.

In the protocol operations manual Section 3.7 (Sample Collection for *MET* Amplification Central Assay Evaluation and Biomarker Testing):

- Specified that if a subject has submitted a tissue/plasma sample for local *MET* amplification testing or has a documented MET amplification result, they must be registered in the IRT system (pre-screening registration step) before entering the pre-screening period.

  Rationale: To clarify the timing of IRT registration for subjects that have submitted a sample for local *MET* amplification testing.

In the protocol operations manual Section 6.5 (Dosage Preparations) and protocol operations manual Table 2:

- To clarify that telisotuzumab vedotin in a solution for infusion/injection.

  Rationale: To incorporate HA recommended clarification.

In the protocol operations manual Section 3.3 (Concomitant Medications):

- To clarify that any conmed or prior therapy question should be addressed prior to enrolment or initiation of conmeds in question.

  Rationale: To clarify the requirements for Therapeutic Area Medical Director review

In the protocol Operations Manual Section 3.5 (Patient-Reported Outcomes):

- To clarify that PROs may be completed up to 72 hours prior to dosing, and to allow the use of interview transcripts for virtual PRO administration due to COVID-19

  Rationale: To clarify the appropriate window for administration of PROs and use of interview transcripts for remote administration.

In the protocol operations manual:

- Section 3.8 (12-Lead Electrocardiogram): To clarify that ECG is to be performed prior to dosing, to clarify that ECG should be performed at earliest feasible visit if delayed due to COVID-19.
- Section 3.9 (Height and Weight): To clarify that weight will be assessed at all study visits prior to dosing.
- Section 3.10 (Vital Signs): To clarify that vital signs are to be collected prior to study drug administration, and to clarify that vital signs may be obtained remotely due to COVID-19
- Section 3.11 (Physical Exam): To clarify that physical exam should be performed prior to dosing.
- Section 3.13 (Clinical Laboratory Tests): To clarify that blood samples should be collected prior to dosing, to clarify that borderline pregnancy test should be repeated 48-72 hours later for eligibility, and to clarify the actions to take based on pregnancy test results.
- Section 3.16 (Tumor Assessments): To clarify the imaging schedule following treatment discontinuation for reasons other than progression.
- Section 6.1 (Treatment Administration): To clarify that IRT transactions should occur as close to D1 of each cycle as possible.

  Rationale: To provide clarifications.
- In the protocol operations manual Section 5.4 (Japan-Specific Requirements): Removed text regarding the age of consent being 20 years of age or older
- To add pulse oximetry for all visits where vital signs are obtained.

  Rationale: To update the age of consent per the PMDA guidance and to add pulse oximetry.
- In the protocol operations manual Section 5.5 (China-Specific Requirements): Remove "at screening" from the list of ctDNA samples not collected in China

  Rationale: To clarify that screening ctDNA samples are requested for confirmatory assessments to support current and future CDx development.

In the protocol operations manual Section 2.1 (Screening) and protocol operations manual Section 3.16 (Tumor Assessments)

- Clarified that for subjects receiving one cycle of systemic chemotherapy, the baseline radiographic tumor assessment should be performed after the completion of the chemotherapy cycle.

  Rationale: To clarify the imaging schedule for subjects who receive one cycle of chemotherapy prior to receiving the first dose of study drug

APPENDIX G. IVDR SPECIFIC APPENDIX TO PROTOCOL M22-137

Part 1: Investigators Agreement Statement

ACKNOWLEDGMENT FORM

FOR INVESTIGATORS

I herewith acknowledge that I will be acting as [an investigator/the National Coordinating Investigator] in the following clinical study, a pharmaceutical clinical trial involving an IVD for patient selection.

- The pharmaceutical clinical trial M22-137 is sponsored by AbbVie and includes investigation sites in Europe. This pharmaceutical clinical trial is authorised under Clinical Trials Regulation EU No 536/2014.
- In association with the pharmaceutical clinical trial, an investigational IVD will be used for patient selection under the *MET* FISH Assay Clinical Performance Study Plan which is sponsored by the diagnostic service provider, NeoGenomics. The study will be authorised under IVDR (2017/746).

I understand that the pharmaceutical clinical trial M22-137 is combined with an in vitro diagnostic (IVD) device. The investigational NeoGenomics *MET* FISH Assay will be used to determine *MET* amplification in NSCLC tumor specimens from patients screened for enrolment in M22-137. A MET/CEP7 ratio of ≥ 1.8 has been analytically validated and is an inclusion criterion for the pharmaceutical clinical trial.

I acknowledge that I will be responsible as an investigator for performing the study in accordance with IVDR, including the processing and transfer of NSCLC tumor specimens that will be obtained from patients in the course of the screening for the pharmaceutical clinical trial. These specimens will be collected under the protocol of the pharmaceutical clinical trial but tested for *MET* amplification under the *MET* FISH Assay Clinical Performance Study Plan. The diagnostic tests with the specimens will be executed for the study sites by a specialized and appropriately accredited diagnostic laboratory. The study subjects will be accordingly informed in the consent forms.

I have read and understood the study protocol of the pharmaceutical clinical trial of the sponsor M22-137 and the separate *MET* FISH Assay Clinical Performance Study Plan provided by NeoGenomics. I will use all investigational products only for the purposes explicitly described in the respective *MET* FISH Assay Clinical Performance Study Plan. I acknowledge that even if the NeoGenomics *MET* FISH assay is delegated and performed by a specialized external laboratory, I am responsible for the study participants, including the indication, ordering and initiation of the assay and the review and communication of the results. In case of an authority audit of the clinical trial, I will provide all relevant information pertaining to the studies as required by IVDR or other applicable laws.

I acknowledge that I will act as [an investigator/the National Coordinating Investigator] in the study and I agree to conduct the study in strict compliance with the study protocols and the applicable laws and regulations.

Role in the study:	
Name and title:	
Address including postal code:	
Site/Centre Number (if available):	
Signature:	
Date of signature:	

This document contains confidential information, which should not be copied, referred to, released, or published without written approval from AbbVie and NeoGenomics. Investigators are cautioned that the information in the protocol may be subject to change and revision.

Part 2: Responsibilities for Pharmaceutical Clinical Trial Investigators and Diagnostic Study Investigators

The clinical trial is designed in such a way that all possible residual risks associated with the use of the CDx investigational product is acceptable.

The responsibilities associated with the diagnostic device between the pharmaceutical clinical trial investigators and the diagnostic testing site investigators are provided in Table 10 below.

Table 10. Responsibilities for Pharmaceutical Clinical Trial Investigators and Diagnostic Study Investigators

Clinical Study M22-137 Investigator Responsibilities **(EudraCT #)**	**IVD Testing MET FISH Assay Clinical Performance Study Plan Investigator Responsibilities**
Consent of patients, where the informed consent form informs the patients about the use of the investigational device and the associated risks	
• Procure tumor specimens (this may include invasive sampling to obtain fresh specimens for the purpose of testing with the NeoGenomics MET FISH assay) • Submit the specimen to designated diagnostic testing site	
	Receive NSCLC tumor specimens from Pharma Study screening sites
	• Prepare received tumor specimens • Execute NeoGenomics MET FISH assay • Interpret stained slides for {biomarker} status
	Provide the diagnostic test result for screened patient
Manage patient enrollment decision based on the diagnostic test result from diagnostic testing site	

APPENDIX H. ADVERSE EVENT REPORTING FOR THE IVD

The NeoGenomics MET FISH assay is a dual color, spot counting FISH test utilizing probes for the MET gene (7q31.2) and CEP7. The MET FISH assay is intended to be used as a clinical trial assay (CTA) to assess for MET amplification in formalin-fixed paraffin embedded (FFPE) specimens from study subjects with a confirmed diagnosis of non-small cell lung cancer (NSCLC) as part of eligibility criteria within the AbbVie clinical study (Protocol No. AbbVie M22-137). The M22-137 clinical trial is designed in such a way that all possible residual risks associated with the use of the NeoGenomics MET FISH assay are acceptable.

NeoGenomics will report all laboratory operator related Adverse Device Effects and Serious Adverse Device Effects related to the use of the device to AbbVie. Adverse Device Effects/Serious Adverse Device Effects related to use of the device in the Sponsor designated FISH testing laboratory, which do not lead to a patient Adverse Event, will not be further discussed in the appendix below. NeoGenomics will report any erroneous assay result to AbbVie within 24 hours of awareness. Patient-related Adverse Events and Serious Adverse Device Effects for subjects will be handled and reported by AbbVie according to this protocol.

For this M22-137 study in which subjects are enrolled, AbbVie will determine whether an event has led to inappropriate patient management.

The clinical trial is designed in such a way that all possible residual risks associated with the use of the investigational product are acceptable.

Adverse Event

An AE is defined as any untoward medical occurrence, inappropriate patient management decision, unintended disease or injury or any untoward clinical signs (including an abnormal laboratory finding) in subjects, users or other persons whether or not related to the investigational medical device. This definition includes events that are anticipated as well as unanticipated, events related to the investigational device, or events related to the procedures involved.

- Subjects may experience AEs while on a study if a patient management decision is based on an incorrectly reported test result from the clinical trial assay (e.g., a subject was inappropriately enrolled into the corresponding pharmaceutical study based on a test result initially reported as positive that is subsequently determined to be a suspected false positive).

If an AE meets any of the following criteria below, without taking into account whether the event was caused by the IVD medical device, it is to be reported to AbbVie as an SAE within 24 hours after the site is made aware of the SAE:

- Led to a patient management decision resulting in death or an imminent life-threatening situation for the individual being tested, or in the death of the individual's offspring,
- Led to death, injury, or permanent impairment to a body structure or body function
- Led to a serious deterioration in the health of a subject that either resulted in:
  - a life-threatening illness or injury, or

- a permanent impairment of a body structure or a body function, or
- inpatient hospitalization or prolongation of existing hospitalization, or
- medical or surgical intervention to prevent life threatening illness

- Led to fetal distress, fetal death, or a congenital abnormality or birth defect.

A planned hospitalization for a preexisting condition, or a procedure required by the protocol, without a serious deterioration in health, is not considered an SAE.

Adverse Device Effects

Adverse device effects are AEs related to the use of an investigational IVD medical device. This includes any AE resulting from insufficiencies or inadequacies in the instructions for use, the deployment, the implantation, the installation, the operation, or any malfunction of the investigational medical device. This includes any event that is a result of a use error or intentional abnormal use of the investigational medical device.

Serious Adverse Device Effects

Serious adverse device effects are adverse device effects that have resulted in any of the consequences characteristic of an SAE or that might have led to any of these consequences if suitable action had not been taken or intervention had not been made or if circumstances had been less opportune.

Unanticipated Serious Adverse Device Effects

Serious adverse device effect which by its nature, incidence, severity or outcome has not been identified in the current version of the risk analysis report.

Device Deficiency

A device deficiency is an inadequacy of an investigational medical device related to its identity, quality, durability, reliability, safety, or performance. This may include malfunctions, use error, or inadequacy in the information supplied by the manufacturer.

The sponsor shall review all device deficiencies and determine and document in writing whether they could have led to an SAE. The Sponsor designated IHC laboratory will report all Device Deficiencies to AbbVie.

Any device deficiency that is associated with an SAE must be reported to the sponsor within 24 hours after the clinical site investigator determines that the event meets the definition of a device deficiency, by entering the data into the EDC system. Device deficiencies determined to have caused an AE or SAE that occur prior to the clinical site having access to the EDC system, or if EDC is not operable, should be documented on the AE or SAE non-CRF forms and emailed (preferred route) or faxed to sponsor within either 24 hours (for SAEs) or 5 calendar days (for AEs) of the site being made aware of the AE or SAE.

In accordance with the safety reporting requirements for IVDs (in-vitro diagnostics) under Article 76 of the In Vitro Diagnostic Regulation (2017/746) and in accordance with ISO 20916:2019, if a device deficiency meets any of the following criteria, it is to be reported to AbbVie immediately after the clinical site is made aware:

- Any SAE
- Any device deficiency that may have led to an SAE if:
  - Suitable action had not been taken or
  - Intervention had not been made or
  - Circumstances had been less fortunate
- New findings/updates in relation to already reported events

Anticipated ADEs Due to Sampling

- In the M22-137 protocol, invasive sampling is not required for each patient screened for MET amplification; archival tissue from a prior biopsy may be used to determine MET amplification. If an archival specimen is not available, a fresh biopsy will be collected according to routine standard of care medical procedures that carry minimal risk to the patient.
- According ISO20916:2019
  - "When the clinical performance study uses leftover/archived specimens, subjects will not be at risk from adverse events of any kind."
  - "Where the study uses specimen collection procedures that pose no additional risk to the subject, in exceptional cases, there might be adverse events impacting the subjects."
- Therefore we do not anticipate sample collection procedures to pose additional risk to the subject except for exceptional cases.
- In the event that any adverse events occur as a consequence of fresh sample collection, they will be recorded and reported according to all applicable regulations.

Anticipated ADEs Due to Inaccurate Testing Results

- In the case of a false negative result from the NeoGenomics MET FISH assay, the subject would not be eligible for enrollment into the study and would be managed in accordance with standard of care. This situation presents no additional risks compared to a subject who chooses not to participate in the study.
- In the case of a false positive result from the NeoGenomics MET FISH assay, a subject with tumor MET amplification below the 1.8 MET/CEP7 ratio cutoff may be inappropriately enrolled into the study and may experience less clinical benefit compared to a subject whose tumor has higher MET/CEP7 ratio (≥ 1.8). However, the current standard of care for advanced NSCLC has limited efficacy. In addition, the risk of adverse events from the study drug is not expected to exceed risks associated with standard of care, and all enrolled patients will be closely monitored for adverse events and evidence of disease progression.
- The analytical performance of the NeoGenomics MET FISH assay has been validated for its intended use within the context of this study. The results of the analytical performance testing demonstrate that the NeoGenomics MET FISH assay has satisfied all validation testing criteria

including accuracy, sensitivity, specificity, and precision. Therefore, the risk of a false-positive test result is considered extremely low.

- In addition, the NeoGenomics MET FISH assay incorporates evaluation of normal cells within the specimen to serve as internal controls. Normal cells should be present in all cases and probes should be clearly visible in the expected pattern. The potential for a false NeoGenomics MET FISH assay result is minimized to the fullest extent. Therefore, the potential for serious risk to study subjects due to false positive result is unlikely.
- Results from the NeoGenomics MET FISH assay will not expose study subjects to safety risks (e.g., adverse events from the investigational therapeutic product) that exceed the risks encountered with non-trial standard of care. Results from NeoGenomics MET FISH assay do not influence the assignment of the patient into a particular study arm (experimental vs control) because there is not a control arm in this study; therefore, a false test result would not expose the subjects to safety risks that exceed the risks encountered with standard of care therapies. .
- Overall, the risks associated with the study drug are not expected to be greater than those expected during chemotherapy. Therefore, results from the NeoGenomics MET FISH assay will not expose a subject to a greater risk than treatment with non-trial standard of care. All risks associated with the investigational drug are defined within the AbbVie patient informed consent form.
- If a patient is enrolled due to a false positive result and experience any AEs during study, the clinical site will assess the relationship between the AE/SAE and the study device and well as the study device procedure (i.e., fresh biopsy for enrollment testing).

Adverse Event Causality Assessment

The clinical enrollment site investigator will use the following definitions to assess the relationship of the adverse event.

Not Related – Relationship to the device can be excluded when:

- the event is not a known side effect of the product category the device belongs to or of similar devices and procedures;
- the event has no temporal relationship with the use of the investigational device or the procedures;
- the event does not follow a known response pattern to the medical device (if the response pattern is previously known) and is biologically implausible;
- the event involves a body site or an organ not expected to be affected by the device or procedure;
- the event can be attributed to another cause (e.g., an underlying or concurrent illness/clinical condition, an effect of another device, drug, treatment, or other risk factors);
- the event does not depend on a false result given by the investigational device use for diagnosis when applicable;
- harms to the subject are not clearly due to use error.

For non-relatedness to be established, not all the criteria listed above might be met at the same time, depending on the type of device/procedures and the serious event.

Possible – the relationship with the use of the investigational device is weak but cannot be ruled out completely. Alternative causes are also possible (e.g., an underlying or concurrent illness/clinical condition or/and an effect of another device, drug, or treatment). Cases where relatedness cannot be assessed or no information has been obtained should also be classified as possible.

Probable – the relationship with the use of the investigational device seems relevant and/or the even cannot be reasonably explained by another cause, but additional information may be obtained.

Causal relationship – the event is associated with the investigational device or with procedures beyond reasonable doubt when:

- the event is a known side effect of the product category the device belongs to or of similar devices and procedures;
- the event has a temporal relationship with investigational device use/application or procedures;
- the event involves a body site or organ that
  - the investigational device or procedures are applied to;
  - the investigational device or procedures have an effect on;
- the event follows a known response pattern to the medical device (if the response pattern is previously known);
- other possible causes (e.g., an underlying or concurrent illness/clinical condition and/or an effect of another device, drug or treatment) have been adequately ruled out;
- harm to the subject is due to error in use;
- the event depends on a false result given by the investigational device used for diagnosis, when applicable.

For relatedness to be established, not all the criteria listed above might be met at the same time, depending on the type of device/procedures and the event.

Reporting SADEs

SADE Reporting from Sponsor or Designee
In accordance with the safety reporting requirements for IVDs (in-vitro diagnostics) under Article 76 of the In Vitro Diagnostic Regulation (2017/746) and in accordance with ISO20916: 2019, the sponsor will report without delay the following events to the relevant authorities: a. any SAE that has a causal or reasonably possible causal relationship with the investigational device, or the investigation procedure; b. any device deficiency that might have led to a serious adverse event if appropriate action had not been taken, intervention had not occurred, or circumstances had been less fortunate; c. any new findings in relation to any event referred to in points a) and b). AbbVie will also submit relevant periodic reports per country specific requirements. **Timelines for Reporting:** • For all reportable events according Article 76 of IVDR, which indicate an imminent risk of death, serious injury, or serious illness and that requires prompt remedial action for other patients/subjects, users or other persons or a new finding to it: Immediately, but not later than 2 calendar days after awareness by sponsor of a new reportable event or of new information in relation with an already reported event. This includes events that are of significant and unexpected nature such that they become alarming as a potential public health hazard. It also includes the possibility of multiple deaths occurring at short intervals. • Any other reportable events or a new finding/update to it: Immediately, but not later than 7 calendar days following the date of awareness by the sponsor of the new reportable event or of new information in relation with an already reported event.

Serious Adverse Device Effect Reporting from Sponsor or Designee for Germany
In accordance with the safety reporting requirements for IVDs (in-vitro diagnostics) under Article 76 of the In Vitro Diagnostic Regulation (2017/746) and in accordance with ISO20916:2019 the sponsor will report without delay the following events to the Federal Institute for Drugs and Medical Devices (BfArM) using the individual SAE report form (for SAEs from German investigational sites only) and the MDCG Clinical Investigation Summary Safety Reporting Form: a. any SAE that has a causal or reasonably possible causal relationship with the investigational device, the comparator or the investigation procedure; b. any device deficiency that might have led to a serious adverse event; c. any new findings in relation to any event referred to in points a) and b). AbbVie will also report all SAEs to BfArM quarterly using the Summary Evaluation of Serious Adverse Events form/table. The email address to which SAE reports (individual and collective forms) will be sent is MPSAE@BFARM.de. **Timelines for Reporting:** 1. For all reportable events according Article 76 of IVDR, which indicate an imminent risk of death, serious injury, or serious illness and that requires prompt remedial action for other patients/subjects, users or other persons or a new finding to it: Immediately, but not later than 2 calendar days after awareness by sponsor of a new reportable event or of new information in relation with an already reported event. This includes events that are of significant and unexpected nature such that they become alarming as a potential public health hazard. It also includes the possibility of multiple deaths occurring at short intervals. 2. Any other reportable events or a new finding/update to it: Immediately, but not later than 7 calendar days following the date of awareness by the sponsor of the new reportable event or of new information in relation with an already reported event.

APPENDIX I. OPERATIONS MANUAL

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Operations Manual for Clinical Study Protocol M22-137

Non-Small Cell Lung Cancer: Telisotuzumab Vedotin (ABBV-399) Phase 2 Study

SPONSOR:	AbbVie	ABBVIE INVESTIGATIONAL PRODUCT:	Telisotuzumab vedotin (ABBV-399)

FULL TITLE: Phase 2, Open-Label Study in Subjects with Previously Untreated *MET* Amplified Locally Advanced/Metastatic Non-Squamous Non-Small Cell Lung Cancer (NSCLC)

1 CONTACTS

Sponsor/ Emergency Medical Contact	[redacted] AbbVie Wegalaan 9 2132JD Hoofddorp The Netherlands **EMERGENCY 24 hour Number:** **+1 (973) 784-6402**	Office: Mobile: Email: [redacted]
Safety Concerns	Oncology Safety Team AbbVie Inc. 1 North Waukegan Road North Chicago, IL 60064	Toll Free: +1 (833) 942-2226 Email: SafetyManagement_Oncology@abbvie.com
SAE Reporting outside of EDC	Email: PPDINDPharmacovigilance@abbvie.com	Fax: +1 (847) 938-0660
Protocol Deviations and Product complaints	[redacted] AbbVie 1 N Waukegan Road North Chicago, IL 60064, USA	Phone: Email: [redacted]
Certified Clinical Lab	USA and Canada Labcorp Central Laboratory Services L.P. 8211 Scicor Drive Indianapolis, IN 46214, USA	Phone: (317) 271 1200 (local calls) Fax: (317) 273 4030
	Europe Labcorp Central Laboratory Services SARL Rue Moïse-Marcinhes 7 CH-1217 Meyrin/Genève Switzerland	Phone: +41 58 822 7901 Fax: +41 58 822 7521
	Asia and Australia Labcorp Development (Asia) Pte. Ltd. 1, International Business Park #01-03 They Synergy Singapore 609917	Phone: +65 6560 8793 Fax: +65 6565 5901

Certified Clinical Lab (Continued)	China Clinical Center Lab Labcorp Pharmaceutical Research and Development (Shanghai) Co. Limited Building 9 No. 338 Jialilue Road Zhangjiang Hi-Tech Park Shanghai 201203 China	Phone: +86 21 51371111 Fax: +86 21 51371301
	Japan CB Lab c/o BML General Laboratory 1361-1 Matoba Kawagoe-shi Saitama 350-1101, Japan	Japan toll free: 0120 123 905 Direct line: +81 3 6837 9536 Fax: +81 3 5250 0360
Biomarker Sample Lab	AbbVie Inc. 1 North Waukegan Road North Chicago, IL 60064, USA	Email: bpm@abbvie.com
PK Sample Lab	ABBV-399 conjugated antibody, ADA and nADA: AbbVie Deutschland GmbH and Co KG Regulated Bioanalysis Knollstrasse 67061 Ludwigshafen, Germany	Phone: +49 621-589-3978 Email: ulrike.graab@abbvie.com Email: gprd_lupet@abbvie.com
	Free MMAE toxin: Abbvie Inc. Dept. R46W, Bldg. AP13A, Rm. 2310 c/o: Delivery Services 1150 S. Northpoint Boulevard Waukegan, Illinois 60085, USA	Phone: +(847) 937-0889 Fax: +(847) 938-9898 Email: sample.receiving@abbvie.com
Central MET Amplification Testing Lab	NeoGenomics Laboratories, Inc. Attn: Pharma Services Dept 4570 Executive Drive, Suite 250 San Diego, CA 92121, USA	Phone: +949 445-7300 ext 5043 Fax: Email: LJ_Pharma_Services@neogenomics.com
	China NeoGenomics Laboratories, Inc. Attn: Pharma Services Division Building 6, Block 19, Yong' An Road Huguan Industrial Park, Suzhou New District Suzhou Shi Jiang Sheng, 215600 CHINA	Phone: Fax: Email: [redacted]

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2 PROTOCOL ACTIVITIES BY VISIT

Study visits may be impacted due to the COVID-19 pandemic. This may include changes such as phone or virtual visits (if allowed by local regulations), visits at alternative locations, or changes in the visit frequency and timing of study procedures, among others. Additional details are provided in the subsequent section. Every effort should be made to ensure the safety of subjects and site staff, while maintaining the integrity of the study. If visits cannot be conducted onsite due to travel restrictions or other pandemic-related reasons, follow the updates below on how to proceed.

2.1 Individual Treatment Period Visit Activities

This section presents a list of activities performed during each visit, organized by visit. The dot pattern on the upper right indicates the place of the visit in the overall Treatment Period Activity Schedule.

Activities are grouped by category (Interview, Exam, etc.). Further information about each activity is provided in Section 3.

COVID-19 Pandemic-Related Acceptable Protocol Modifications

During the COVID-19 pandemic, if it is not possible for all study procedures to be performed as specified due to travel restrictions or other reasons, the following modifications are allowed:

- Some study visits and/or activities may be performed by phone/virtually if allowed by local regulations. These are indicated by a hashtag (#) in the appropriate visit table(s) below.
- Some study visits and/or activities may be performed by a local clinic/hospital/laboratory. These are indicated by a plus sign (+) in the appropriate visit table(s) below. All procedures performed at local facilities must be performed by appropriately qualified personnel.
- Study Visits and/or activities should be performed as scheduled whenever possible. If it is not possible to do so due to the pandemic, the following modifications are allowed:
    - If an activity is missed during a virtual visit, perform the activity at the earliest feasible opportunity. Laboratory draws should be obtained within 24 hours from the scheduled visit.

PRE-SCREENING FOR MET AMPLIFICATION:

INTERVIEW & QUESTIONNAIRES	• Subject information and informed consent[#,a] • Adverse event assessment[#,+,b] • For China sites only, dispense subject diary cards for adverse event symptoms and concomitant therapy [d]	• Eligibility criteria • Medical and cancer history[#] • Prior/concomitant therapy[#]
CENTRAL LAB	• Tumor material; FFPE block/slides/wet tissue[c]	

Study visits/activities may be performed by phone/virtually if allowed by local regulations.

\+ Study visits/activities may be performed by a local clinic/hospital/laboratory.

a. Informed consent form (ICF) may be a pre-screening only ICF or it could be a general ICF, depending on local regulations.

b. Study procedure-related SAEs and study procedure-related nonserious AEs only.

c. For subjects without local documentation of *MET* amplification, tumor material (FFPE block or wet tissue) must be sent to an AbbVie designated laboratory for testing of *MET* amplification (refer to the laboratory manual for details). If the two-step pre-screening tumor material submission process is used (as detailed in the Laboratory manual), Step 1 must be completed during pre-screening, but Step 2 can be completed up to 2 weeks after C1D1. If site or country policy only allow slides to be sent, freshly cut slides can be sent instead of tissue block. This material will be used to determine subject eligibility. If the subject has a local documentation of *MET* amplification, the results should be submitted for Sponsor approval. With Sponsor approval, the subject will be eligible based upon the local result, and tissue does not need to be submitted at pre-screening.

d. Dispensed at Pre-Screening only for subjects undergoing a study-related clinical procedure during the Pre-Screening period.

SCREENING (Day -28 to Day -1):

INTERVIEW & QUESTIONNAIRES	• Subject information and informed consent[a] • Adverse event assessment • Eligibility criteria •	• Medical and cancer history • Prior/concomitant therapy • PRO assessments[b] • For China sites only, dispense subject paper diary cards for adverse event symptoms and concomitant therapy. Previously dispensed diaries will be collected and reviewed.[i]
LOCAL LABS & EXAMS	• 12-lead electrocardiogram • Vital signs, including pulse oximetry • Complete physical examination (including height)	• ECOG performance status • Tumor assessment (CT scan/MRI)[c] • MRI of brain[d] • Ophthalmological exam
CENTRAL LAB	• Hematology[e] • Chemistry[e] • Urinalysis[e] • aPTT/PT/INR • Pregnancy test (serum)	• Testosterone, sex hormone binding globulin (males only)[f,e] • Tumor material; FFPE block/slides/wet tissue[g] • Plasma (ctDNA) for central assay evaluation [h]

a. The types of ICFs available are: main, optional genetic testing/tissue and pregnant partner; main and optional ICFs could be 1 or 2 different ICFs, depending on local regulations.

b. The EORTC QLQ-C30, EORTC QLQ-LC13, and PGIS will be administered at Screening. All PRO assessments must be completed at the study visit prior to any other procedures or clinical assessments.

c. The screening tumor assessment should be completed as close as possible to enrollment. The window for tumor assessments by CT/MRI is Day -35 to Day -1. For subjects receiving one cycle of systemic chemotherapy, the baseline radiographic tumor assessment should be performed after the completion of the chemotherapy cycle.

d. Or computed tomography (CT) scan (only if MRI is contraindicated). The window for CT/MRI collection is day -35 to Day -1.

e. Chemistry, hematology, urinalysis, testosterone, and sex hormone binding globulin must be repeated up to 3 days prior to dosing if screening is > 14 days from Cycle 1 Day 1.

f. Collection must be concurrent with collection for other clinical chemistry laboratories.

g. For subjects who will be enrolled in the study, tumor material (FFPE block, slides, or wet tissue) is requested at Screening for central assay evaluation and biomarker testing. If the tumor material submitted at Pre-screening is sufficient for central assay evaluation and

biomarker testing, additional material does not need to be submitted at Screening. Biopsy should occur before telisotuzumab vedotin administration.

h. For subjects who will be enrolled in the study, plasma (ctDNA) is requested at Screening for central assay evaluation.

i. Collect and review at Screening only for subjects undergoing a study-related clinical procedure during the Pre-Screening period.

NOTE: Subjects are allowed to have certain laboratory samples re-drawn to meet eligibility within the same 28-day screening window, following consultation and written approval from the Medical Monitor/Therapeutic Area Medical Director (further details in Protocol Section 5.10).

CYCLE 1 DAY 1:

INTERVIEWS & QUESTIONNAIRES	• Adverse event assessment • Prior/concomitant therapy • Medical and cancer history[a] •	• PRO assessments[b] • For China sites only, dispense subject paper diary cards for adverse event symptoms and concomitant therapy. Previously dispensed diaries will be collected and reviewed.
LOCAL LABS & EXAMS	• Vital signs, including pulse oximetry • Limited physical examination • 12-lead electrocardiogram	• ECOG performance status • Pregnancy test (urine)[c,+]
CENTRAL LAB	• Hematology[d,+] • Chemistry[d,+] • Urinalysis[d,+] • ADA and nADA samples (serum)[e]	• Biomarker samples (plasma)[f] • Biomarker Sample (whole blood) *MET* gene analysis and genetic testing[g] • PK samples (serum and plasma)[h] • Plasma (ctDNA)[i]
TREATMENT	• Enrollment[j]	• Telisotuzumab vedotin dosing[k]

\+ Study visits/activities may be performed by a local clinic/hospital/laboratory.

a. On Cycle 1 Day 1, any additional medical history observed after signing of the informed consent but prior to initial study drug administration and not considered related to study-required procedures will be recorded in the subject's medical history.

b. The EORTC QLQ-C30, EORTC QLQ-LC13, EQ-5D-5L, select items of the PRO-CTCAE, and PGIS will be administered at Cycle 1 Day 1. All PRO assessments should be completed at the study visit prior to any other procedures, clinical assessments, or dosing. On Cycle 1 Day 1, PRO assessments may be done within 72 hours prior to dosing.

c. A urine pregnancy test is required prior to study drug administration. A serum pregnancy test in place of the urine pregnancy test is allowed provided that it can be resulted prior to the study drug administration.

d. Chemistry, hematology, and urinalysis must be repeated up to 3 days prior to dosing if screening is > 14 days from Cycle 1 Day 1.
e. ADA and nADA samples for telisotuzumab vedotin will be collected (pre-dose on Day 1 of every cycle up to Cycle 18 and Cycle 1 Day 8).
f. Biomarker samples will be collected pre-dose.
g. Sample may be collected at Cycle 1 Day 1 or at any visit after Cycle 1 Day 1. It is mandatory for *MET* gene analysis and optional for genetic testing.
h. PK blood samples for telisotuzumab vedotin and free monomethyl auristatin E (MMAE) toxin will be collected prior to telisotuzumab vedotin infusion and 30 minutes (± 5 min) after the end of the telisotuzumab vedotin infusion on Cycle 1 Day 1.
i. Plasma (ctDNA) samples will be collected pre-dose Cycle 1 Day 1, Cycle 2 Day 1, every other odd cycle after Cycle 2 (e.g., Cycle 3 Day 1, Cycle 5 Day 1, until end of treatment).
j. Enrollment should occur as close as possible to Cycle 1 Day 1, but no more than 3 days prior to Cycle 1 Day 1.
k. Telisotuzumab vedotin dosing will be weight-based and will be given as an IV infusion over 30 ± 10 minutes every 2 weeks (Q2W).

CYCLE 1 DAY 8 (± 2 DAYS)

INTERVIEW & QUESTIONNAIRES	• Adverse event assessment[#,+] •	• Prior/concomitant therapy[#] • For China sites only, dispense subject paper diary cards for adverse event symptoms and concomitant therapy. Previously dispensed diaries will be collected and reviewed.
LOCAL LABS & EXAMS	• Vital signs, including pulse oximetry[+]	• Limited physical examination[+]
CENTRAL LAB	• Hematology[+] • Chemistry[+] • ADA and nADA samples (serum)[a]	• PK samples (serum and plasma)[b]

Study visits/activities may be performed by phone/virtually if allowed by local regulations.
+ Study visits/activities may be performed by a local clinic/hospital/laboratory.
a. ADA/nADA blood samples for telisotuzumab vedotin will be collected (pre-dose on Day 1 of every cycle up to Cycle 18 and Cycle 1 Day 8).
b. PK blood samples for telisotuzumab vedotin and free MMAE toxin will be collected.

CYCLE ≥ 2 DAY 1 (+ 2 DAYS):

INTERVIEWS & QUESTIONNAIRES	• Adverse event assessment[#,+] •	• Prior/concomitant therapy[#] • PRO assessments[j] • For China subjects only, dispense subject paper diary cards for adverse event symptoms and concomitant therapy. Previously dispensed diaries will be collected and reviewed.
LOCAL LABS & EXAMS	• Vital signs, including pulse oximetry • Limited physical examination	• ECOG performance status • Pregnancy test (urine)[a,+] • 12-lead electrocardiogram[b]
CENTRAL LAB	• Hematology[c,+] • Chemistry[c,+] • Testosterone, sex hormone binding globulin (males only)[c,d,+]	• ADA and nADA samples (serum)[e] • Biomarker samples (plasma)[f] • PK samples (serum and plasma)[g] • Plasma (ctDNA)[h]
TREATMENT	• Telisotuzumab vedotin dosing[i]	

#	Study visits/activities may be performed by phone/virtually if allowed by local regulations.
+	Study visits/activities may be performed by a local clinic/hospital/laboratory.
a.	A urine pregnancy test is required before dosing on Cycle 2 Day 1 and on Day 1 of every subsequent cycle. A serum pregnancy test in place of the urine pregnancy test is allowed provided that it can be resulted prior to the study drug administration.
b.	To be performed at Cycle 2 Day 1 and Cycle 3 Day 1.
c.	Chemistry, hematology, testosterone, and sex hormone binding globulin tests may occur up to 3 days prior to Cycle 2 Day 1 and beyond.
d.	Collection must be concurrent with collection for other clinical chemistry laboratories. Collection will occur every 3 cycles starting with Cycle 2 (i.e., Cycle 2, Cycle 5, etc.).
e.	ADA and nADA samples (serum) for telisotuzumab vedotin will be collected (pre-dose on Day 1 of every cycle up to Cycle 18 and Cycle 1 Day 8).
f.	Biomarker samples will be collected pre-dose on Cycle 2 Day 1 and every other odd cycle thereafter (e.g., Cycle 3 Day 1, Cycle 5 Day 1, until end of treatment).
g.	PK blood samples for telisotuzumab vedotin and free MMAE toxin will be collected prior to telisotuzumab vedotin infusion and 30 minutes (± 5 min) after the end of the telisotuzumab vedotin infusion on Day 1 of every cycle up to Cycle 18.
h.	Plasma (ctDNA) samples will be collected pre-dose on Cycle 2 Day 1 and every other odd cycle after Cycle 2 (e.g., Cycle 3 Day 1, Cycle 5 Day 1, until end of treatment).
i.	Telisotuzumab vedotin dosing will be based on the subject's weight at Cycle 1 Day 1. The dose does not need to be adjusted unless the subject's weight changes by > 10% from baseline. However, the dose may be adjusted for weight changes ≤ 10% at the discretion of the investigator. It is not necessary to calculate dosing based on ideal body weight. The

dose for subjects with weight > 100 kg should be calculated for 100 kg. Telisotuzumab vedotin will be given over 30 ± 10 minutes Q2W.

j. The EORTC QLQ-C30, EORTC QLQ-LC13, EQ-5D-5L, select items of the PRO-CTCAE, PGIS and PGIC will be administered every cycle prior to dosing for the first 26 cycles and every other cycle thereafter. All PRO assessments should be completed at the study visit prior to any other procedures and clinical assessments. PRO assessments may be done within 72 hours prior to dosing. If there is a dosing delay, the PRO administration should remain on the dosing day.

EVERY ~ 6 WEEKS (± 7 DAYS):

LOCAL LABS & EXAMS	• Tumor assessments (CT/MRI)[a,b,+]

\+ Study visits/activities may be performed by a local clinic/hospital/laboratory.

a. Post-baseline tumor assessment will be conducted every 6 weeks (± 7 days) from Cycle 1 Day 1 until radiographic progression (i.e., at Weeks 6, 12, 18, etc., from Cycle 1 Day 1). After 1 year, CT or MRIs will be performed approximately every 8 weeks (± 7 days) and after 2 years, approximately every 12 weeks (± 14 days).

b. All subjects should continue to have per protocol scans until disease progression is confirmed by ICR.

END OF TREATMENT:

INTERVIEWS & QUESTIONNAIRES	• Adverse event assessment[#,+] •	• Prior/concomitant therapy[#] • PRO assessments[a,#] • For China sites only, dispense subject paper diary cards for adverse event symptoms and concomitant therapy. Previously dispensed diaries will be collected and reviewed.
LOCAL LABS & EXAMS	• Vital signs, including pulse oximetry[+] • Limited physical examination[+]	• ECOG performance status • Pregnancy test (urine)[+] • Tumor assessment (CT/MRI)[b,+] • 12-lead electrocardiogram
CENTRAL LAB	• Hematology[+] • Chemistry[+] • Urinalysis[+] • Testosterone, sex hormone binding globulin (males only)[+,d]	• Biomarker samples (plasma) • Tumor material at disease progression (optional) (FFPE block/wet tissue/slides)[c] • Plasma (ctDNA)

Study visits/activities may be performed by phone/virtually if allowed by local regulations.

\+ Study visits/activities may be performed by a local clinic/hospital/laboratory.

a. The EORTC QLQ-C30, EORTC QLQ-LC13, EQ-5D-5L, select items of the PRO-CTCAE, PGIS and PGIC will be administered at End of Treatment. All PRO assessments should be completed at the study visit prior to any other procedures and clinical assessments. PRO assessments may be done within 72 hours prior to the study visit.

b. Tumor assessment may be omitted if performed within the last 6 weeks.

c. Optional fresh tumor material at time of disease progression (FFPE block/wet tissue) may be obtained from subjects if it is deemed safe to do so by the investigator at the End of Treatment (EOT) Visit and if the subject has agreed to optional tissue testing.

d. Samples should be collected concurrently with samples for other chemistry laboratories.

NOTE: The EOT visit is the last visit during the Treatment Phase before subjects begin the Post-Treatment Follow-Up and/or Survival Follow-Up Phase. This visit should occur within 7 days of documentation of the decision to discontinue study drug due to disease progression or other criteria for discontinuing study drug and prior to subjects beginning any new anti-cancer therapy, if possible.

2.2 Individual Post-Treatment Period Visit Activities

This section presents a list of activities performed during each visit, organized by visit. The dot pattern on the upper right indicates the place of the visit in the overall Post-Treatment Period Activity Schedule.

Activities are grouped by category (Interview, Exam, etc.). Further information about the activities is presented in Section 3.

30-DAY FOLLOW-UP (+ 7 DAYS)

INTERVIEW & QUESTIONNAIRES	• Adverse event assessment[#,+] • Post-treatment Anti-Cancer Therapy Information[#]	• Prior/concomitant therapy[#] • Survival Status[#] • PRO assessments[a,#] • For China sites only, collect subject paper diary cards and review adverse event symptoms and concomitant therapy
LOCAL LABS & EXAMS	• Vital signs, including pulse oximetry[+] • Limited physical examination[+]	• ECOG performance status • Pregnancy test (urine)[+]
CENTRAL LAB	• Hematology[+] • Chemistry[+]	• Testosterone, sex hormone binding globulin (males only)[+,b]

Study visits/activities may be performed by phone/virtually if allowed by local regulations.

\+ Study visits/activities may be performed by a local clinic/hospital/laboratory.

a. The EORTC QLQ-C30, EORTC QLQ-LC13, EQ-5D-5L, select items of the PRO-CTCAE, PGIS and PGIC will be administered at 30-day Follow-up. All PRO assessments should be completed at the study visit prior to any other procedures and clinical assessments. PRO assessments may be done within 72 hours prior to the study visit.

b. Samples should be collected concurrently with samples for other chemistry laboratories.

NOTE: A follow-up visit is required 30 days (+ 7 days) after the last dose of study drug. If the EOT Visit is more than 30 days from the last dose of study drug the 30-Day Follow-Up Visit is not required.

POST-TREATMENT FOLLOW-UP:

INTERVIEW & QUESTIONNAIRES	• Post-treatment Anti-Cancer Therapy Information[#]	• PRO assessments[a,#]
LOCAL LABS & EXAMS	• Tumor assessment (CT/MRI)[b,+]	• Pregnancy test (urine)[c,+]

Study visits/activities may be performed by phone/virtually if allowed by local regulations.

\+ Study visits/activities may be performed by a local clinic/hospital/laboratory.

a. The EORTC QLQ-C30, EORTC QLQ-LC13, and EQ-5D-5L will be administered during the Post Treatment period. All PRO assessments should be completed at the study visit prior to any other procedures and clinical assessments. All subjects will continue to complete the PROs until disease progression is confirmed by independent central review. During post-treatment follow up, PRO assessments will occur on the same schedule as the tumor assessments. PRO assessments may be done within 72 hours prior to the study visit.

b. Subjects who discontinue study drug for any reason other than progressive disease demonstrated by imaging will continue to be followed per study imaging schedule as outlined below until they have progressive disease documented by imaging, death, or withdraw consent. Following study drug discontinuation, these subjects will continue to be followed by assessments every 6 weeks. The first Post-Treatment Follow-Up (PTFU) Visit will occur at 6 weeks (± 7 days) after the last scan, then every 6 weeks (± 7 days) until disease progression. After 1 year, CT or MRIs will be performed approximately every 8 weeks (± 7 days) and after 2 years, approximately every 12 weeks (± 14 days). All subjects, whenever possible, should continue to have per protocol scans until disease progression is confirmed by independent central review. Subsequent anti-cancer therapy information (dates and responses) will also be collected during Post-Treatment Follow-Up.

c. A urine pregnancy test must be completed monthly (± 7 days) for 7 months after the last dose of study drug. Subjects may perform test at home using a urine pregnancy kit.

SURVIVAL FOLLOW-UP:

INTERVIEW & QUESTIONNAIRES	• Post-treatment Anti-Cancer Therapy Information[#]	• Survival Status[a,#]

Study visits/activities may be performed by phone/virtually if allowed by local regulations.

a. Survival Follow up will be performed every 3 months starting from the time subject progressed or last dose of drug or as required for data analysis for subject's survival information and post-treatment cancer information. Survival Follow-up will continue until the endpoint of death via subject contact, phone call or medical chart review as appropriate.

3 STUDY PROCEDURES

3.1 Study Subject Information and Informed Consent

The investigator or their representative will explain the nature of the study to the subject, the benefits and risks anticipated from participation in the study, and answer all questions regarding this study. Prior to any study-related pre-screening/screening procedures being performed on the subject or any medications being discontinued by the subject in order to participate in this study, the informed consent statement will be reviewed, signed, and dated by the subject or their legally authorized representative, the person who administered the informed consent, and any other signatories according to local requirements. A copy of the signed informed consent will be given to the subject and the original will be placed in the subject's medical record. An entry must also be made in the subject's dated source documents to confirm that informed consent was obtained prior to any study-related procedures and that the subject received a signed copy.

The informed consent for *MET* amplification testing (pre-screening informed consent) and the informed consent for the study procedures (main study informed consent) may be used separately or combined as a single informed consent document where allowed by local regulation and the independent ethics committee (IEC)/institutional review board (IRB).

The IEC/IRB-approved informed consent must be signed and dated by each subject or the subject's legally acceptable representative prior to the submission of tumor material for pre-screening, undergoing any study procedures, or before any prohibited medications are withheld from the subject in order to participate in this study. Where confirmed as a local requirement, the subject (not a representative) must provide the written consent. For subjects without local documentation of *MET* amplification, tumor material testing will be conducted to determine *MET* amplification status, which is required for subject eligibility. No screening procedures should proceed while tissue testing results are pending and until *MET* amplification status is obtained.

Information regarding benefits for subjects and information regarding provisions for treating and/or compensating subjects who are harmed because of participation in the study can be found in the informed consent form.

Additional genetic analysis will only be done on the sample collected for *MET* gene analysis if the subject consents. The optional tumor material (at the time of disease progression) may be collected if it is deemed safe to do so by the investigators. This biomarker research sample will only be collected if the subject has voluntarily signed and dated a written consent form describing the exploratory research. The written consent may be part of the main consent form. If consent for optional samples is not provided, the subject will still be allowed to participate in the study.

There will be no impact on the subject's participation in the study if he/she does not consent to the collection of tumor material at the time of disease progression or to additional genetic analysis.

In the event of pregnancy occurring in a subject's partner during the study, written informed consent from the partner must be obtained prior to collection of information regarding the pregnancy and the outcome.

Due to the COVID-19 pandemic, it is possible that additional protocol modifications not outlined in this protocol may become necessary. If this situation arises, in addition to the study informed consent, additional verbal consent may be obtained prior to these adaptations or substantial changes in study conduct in accordance with local regulations. An appropriately signed and dated informed consent form should be obtained from the subject afterwards, as soon as possible.

3.2 Medical History

A complete medical history including demographics, history of tobacco, alcohol, and drug use will be taken at screening. The subject's medical history will be recorded at pre-screening and screening visits (Section 2.1).

The subject's medical history will be updated before the first dose of study drug (Cycle 1 Day 1). On Cycle 1 Day 1, any additional medical history observed after signing of the informed consent form but before initial study drug administration and not considered related to study-required procedures will be recorded in the subject's medical history. This updated medical history will serve as the baseline for clinical assessment.

COVID-19 Pandemic-Related Acceptable Protocol Modifications

Medical and cancer history can be obtained virtually.

3.3 Concomitant Medication

If a subject reports taking any over-the-counter, prescription medications, or if administration of any medication becomes necessary from signature of the screening consent (or pre-screening consent if medication is for study procedure-related serious or non-serious AEs) through 30 days after last dose of study drug, the name of the medication, dosage information including dose, route, and frequency, date(s) of administration including start and end dates, and reason for use must be recorded on the appropriate electronic Case Report Form (eCRF).

No anti-cancer agents, investigational agents, or anti-cancer hormonal therapy may be taken concurrently while receiving telisotuzumab vedotin.

Since monomethylauristatin E (MMAE) is metabolized primarily by the CYP3A4 enzyme, strong CYP3A4 inhibitors may increase the exposure of MMAE. Therefore, strong CYP3A4 inhibitors should be taken with caution and closely monitored for adverse reactions while subjects are undergoing telisotuzumab vedotin treatment.

P-glycoprotein (P-gp) inhibitors may also increase exposure to MMAE when co-administered with telisotuzumab vedotin. Subjects receiving P-gp inhibitors concomitantly should be closely monitored for adverse reactions.

The AbbVie Therapeutic Area Medical Director identified in Section 1 should be contacted if there are any questions regarding concomitant or prior therapies prior to subject enrollment and/or initiation of the concomitant medication in question.

Further details regarding prohibited, cautionary, and allowed concomitant medications are provided in the Protocol Section 5.3 and Section 5.4.

COVID-19 Pandemic-Related Acceptable Protocol Modifications

Concomitant medication information can be obtained virtually.

3.4 Adverse Event Assessment

Please refer to Protocol Section 6.

COVID-19 Pandemic-Related Acceptable Protocol Modifications

Adverse events can be assessed at alternate locations or virtually.

3.5 Patient-Reported Outcomes

All PRO assessments should be completed at the study visit prior to any other procedures, clinical assessments, or dosing. Subjects should be instructed to follow the instructions provided with the instrument and to provide the best possible response to each item. Site personnel shall not provide interpretation or assistance to subjects other than encouragement to complete the tasks. Subjects who are functionally unable to read any of the instruments may have site personnel read the questionnaire to them. Site personnel will encourage completion of the instrument at all specified visits and will ensure that a response is entered for all items.

Subjects will complete self-administered Patient-Reported Outcome (PRO) questionnaires on a tablet as specified in Section 2.1, and COVID-related protocol modifications are detailed below.

- The EORTC QLQ-C30, EORTC QLQ-LC13, and PGIS will be administered at Screening.
- The EORTC QLQ-C30, EORTC QLQ-LC13, EQ-5D-5L, select items of the PRO-CTCAE, and PGIS will be administered at Cycle 1 Day 1.
- Following Cycle 1 Day 1, the EORTC QLQ-C30, EORTC QLQ-LC13, EQ-5D-5L, select items of the PRO-CTCAE, PGIS and PGIC will be administered every cycle prior to dosing for the first 26 cycles and every other cycle thereafter, End of Treatment and 30-day Follow-up. If there is a dosing delay, the PRO administration should remain on the dosing day (i.e., Day 1 of cycle). The EORTC QLQC30, EORTC QLQ-LC13, and EQ5D-5L will be administered during the Post Treatment period. All PRO assessments will need to be administered within 72 hours prior to dosing at all cycles.

The following (electronic) PROs will be administered:

- EORTC QLQ-C30
- EORTC QLQ-LC13
- EQ-5D-5L
- PGIS and PGIC
- Select items from the PRO-CTCAE

The EORTC QLQ-C30 assesses the HRQoL in cancer patients participating in clinical trials.[1] This instrument was developed and validated for use in a cancer patient population, and its reliability and validity are highly consistent across different language and cultural groups. The EORTC QLQ-C30 comprises 5 functional scales (physical, role, emotional, social, cognitive), 8 single-item symptom scales (fatigue, pain, nausea/vomiting, appetite loss, constipation, diarrhea, insomnia, and dyspnea), as well as subscales assessing global health/quality of life and financial impact. Most items use a 4-point Likert scale from "not at all" to "very much" and a 1-week recall period except for the final 2 items, which use a 7-point scale response. Raw scores are transformed to a scale of 0 to 100, with higher scores representing better functioning/quality of life and greater symptom burden.

The EORTC QLQ-LC13 is the lung cancer specific module of the core EORTC QLQ-C30.[2] The QLQ-LC13 includes 13 questions that include both multi-item and single-item scales of lung cancer-associated symptoms (e.g., pain, coughing, hemoptysis, and dyspnea) and side-effects from chemo- and radiotherapy (e.g., hair loss, neuropathy, sore mouth and dysphagia). With the exception of 2 pain questions, which have dichotomous response categories (no or yes) and a free response if 'yes' is selected, all items on the QLQ-LC13 are scored on a 4-point Likert scale ranging from 1 (not at all) to 4 (very much). The items have a 1-week recall period. All scale and item scores are linearly transformed to a 0 to 100 scale, with higher scores representing increasing symptom levels or impacts.

The EQ-5D-5L is a generic preference instrument that has been validated in numerous populations.[3,4] The EQ-5D-5L consists of 2 components: the EQ-5D descriptive system and the EQ visual analog scale (VAS). The EQ-5D descriptive system comprises 5 dimensions: mobility, self-care, usual activities, pain/discomfort and anxiety/depression. Each dimension has 5 levels: no problems, slight problems, moderate problems, severe problems, and extreme problems. The subject is asked to indicate their health state in each of the 5 dimensions. Based on the subject's response, a 1-digit number is created that expresses the level selected for each dimension. The digits for the 5 dimensions can be combined into a 5-digit number that describes the subject's health state. The EQ VAS records the subject's self-rated health on a vertical VAS where the endpoints are labeled "The best health you can imagine" and "The worst health you can imagine." The VAS can be used as a quantitative measure of health outcome that reflects the subject's own judgment.

The PGIC scale assesses patients' perceptions of change in their NSCLC symptoms, cough, shortness of breath, pain and overall quality of life as well as difficulty with physical activities due to NSCLC since the start of treatment in the study. All questions employ the following response options: Much better, A little better, No change, A little worse, and Much worse.

The PGIS scale asks the patient to assess the severity of their NSCLC symptoms, cough, shortness of breath, and pain, as well as difficulty of doing physical activities, and interference with daily life due to NSCLC over the past 7 days. The questions related to NSCLC symptoms employ the following 5 response options: None, Mild, Moderate, Severe, and Very Severe. The physical activities and daily life questions employ the following response options: Not at all, Slightly, Moderately, Very much, and Extremely.

PRO-CTCAE is a patient-reported outcome (PRO) measurement system developed to evaluate symptomatic toxicity in patients on cancer clinical trials. The PRO-CTCAE Item Library includes 124 items representing 78 symptomatic toxicities drawn from the CTCAE. All questions employ a 7-day recall period and are scored from 0 to 4 (or 0/1 for absent/present). Select items from the PRO-CTCAE will be included in the trial.

PRO assessments including the order of administration are listed in Table 1.

Table 1. Patient-Reported Outcome Assessments

Administration Order	Measure	Administration Time
1	EORTC QLQ-C30	approximately 12 minutes
2	EORTC QLQ-LC13	approximately 5 minutes
3	EQ-5D-5L	approximately 3 minutes
4	PGIS and PGIC	approximately 5 minutes
5	Select items from PRO-CTCAE	approximately 5 minutes
	Total administration time: approximately 30 minutes	

EORTC QLQ-C30 = European Organization for Research and Treatment of Cancer Quality of Life Questionnaire Core 30 Palliative; EORTC QLQ-LC13 = EORTC QLQ Lung Cancer Module 13; EQ-5D-5L = EuroQoL 5 Dimension 5 Level; PGIC = patient global impression of change; PGIS = patient global impression of severity; PRO-CTCAE = patient-reported outcomes Common Terminology Criteria for Adverse Events

COVID-19 Pandemic-Related Acceptable Protocol Modifications

Due to the COVID-19 pandemic, some procedures may be conducted via phone or video conference. PROs eligible for completion by interview via phone or video conference are EORTC QLQ-C30, EORTC QLQ-LC13, EQ-5D-5L, select items of the PRO-CTCAE, PGIS and PGIC. Interview transcripts will be used when available and for PROs where interview transcripts are not available, sites will be provided specific guidance for administering the PROs virtually in a way that preserves the intent of the questions and response options. Sites may share the questionnaire by videoconference or send the questionnaires (email or hard copy) to the subjects to allow them to read/understand the questions and responses when the subject is providing responses over the phone.

3.6 Pharmacokinetic Sampling

Blood samples for assay of telisotuzumab vedotin conjugate (ABBV-399) in serum and free cytotoxin monomethyl auristatin E (MMAE) toxin levels in plasma will be collected at specified time-points, and results will be tabulated and summarized. Samples may be used for additional exploratory analyses and/or assay development and validation as deemed appropriate. PK samples will be collected at the designated study visits as specified in Section 2.1. PK blood samples for telisotuzumab vedotin and free MMAE toxin will be collected as follows:

- Prior to telisotuzumab vedotin infusion
- 30 minutes (± 5 minutes) after the end of the telisotuzumab vedotin infusion on Cycle 1 Day 1
- Cycle 1 Day 8 (± 2 days);
- Pre-dose and 30 minutes (± 5 minutes) after the end of the telisotuzumab vedotin infusion on Day 1 of Cycle 2 up to Cycle 18

Serum samples for assay of telisotuzumab vedotin anti-drug antibodies (ADA) and neutralizing anti-drug antibodies (nADA) will also be collected as follows:

- Pre-dose on Day 1 of every cycle up to Cycle 18
- Cycle 1 Day 8

Blood samples will be collected by venipuncture from the arm contralateral to the arm used for dose administration. The time that each blood sample is collected will be recorded to the minute.

nADA samples may be used for the analysis of neutralizing anti-drug antibodies, if useful for the interpretation of the data.

Refer to the study-specific central laboratory manual for detailed instructions on sample collection, processing, and sample shipment information. Samples will be analyzed at or under the supervision of the AbbVie Bioanalysis department in Lake County, IL (MMAE) and Ludwigshafen, Germany (telisotuzumab vedotin conjugate, ADA and nADA).

3.7 Sample Collection for MET Amplification Central Assay Evaluation and Biomarker Testing

Biospecimens (plasma, whole blood and tumor tissue) will be collected as specified in Section 2.1 to support subject pre-screening, central assay evaluation, and the biomarker research objectives of the study. Assessments may include, but are not limited to, biomarkers related to the pathway(s) targeted by the study drug, or those believed to be related to the disease(s) being studied. The information learned from analyzing these samples may be used to investigate factors influencing response to treatment, scientific questions related to NSCLC, and/or in the development of new therapies and diagnostic tests.

Sample Collection at Pre-Screening and Screening

For subjects without local documentation of *MET* amplification, tumor material (FFPE block or wet tissue) must be sent to an AbbVie designated central laboratory for testing of *MET* amplification at Pre-screening (refer to the laboratory manual for details), following signature of informed consent. If site or country policy only allow slides to be sent, freshly cut slides can be sent instead of tissue block. This sample will be used to make a decision on enrollment. These subjects must be registered in the interactive response technology (IRT) system (pre-screening registration step) before entering the pre-screening period. For subjects who will be enrolled in the study, tumor material (FFPE block, slides, or wet tissue) and plasma (ctDNA) are requested at Screening for central assay evaluation and biomarker testing. If the tumor material submitted at Pre-screening is sufficient for central assay evaluation and biomarker testing, additional tissue material does not need to be submitted at Screening. If the two-step prescreening tumor material submission process is used (as detailed in the Laboratory Manual), Step 1 must be completed during pre-screening, but Step 2 can be completed up to 2 weeks after C1D1.

If a subject has submitted a tissue/plasma sample for local *MET* amplification testing or has a documented *MET* amplification result, they must be registered in the IRT system (pre-screening registration step) before entering the pre-screening period. In order to confirm *MET* amplification,

documentation must be provided to and reviewed by the Sponsor. All subject identifying information must be de-identified. With Sponsor approval, local documentation of *MET* amplification can be used for eligibility, and tumor material does not need to be submitted at Pre-screening. For subjects who will be enrolled in the study, sufficient tumor material (FFPE block, slides, or wet tissue) and plasma (ctDNA) are requested at Screening for central assay evaluation and biomarker testing.

Tumor Material at Time of Disease Progression

For all countries except China, optional tumor material at time of disease progression (FFPE block/wet tissue/slides) may be obtained from subjects if it is deemed safe to do so by the investigator at the EOT Visit.

Biomarker Sample Collection and Assessments (Cycle 1 Day 1 and Beyond)

For all countries except China, plasma collection for biomarker analysis will be collected pre-dose on Cycle 1 Day 1, pre-dose on Cycle 2 Day 1, pre-dose on every other odd cycle thereafter (e.g., Cycle 3 Day 1, Cycle 5 Day 1, etc.) and at the final (EOT) visit.

ctDNA Sample Collection and Assessments (C1D1 and Beyond)

For all countries except China, plasma collection for ctDNA analysis will be collected at pre-dose on Cycle 1 Day 1, pre-dose on Cycle 2 Day 1, pre-dose on every other odd cycle thereafter (e.g., Cycle 3 Day 1, Cycle 5 Day 1, etc.) and at the final (EOT) visit.

MET Gene Analysis Sampling

For all countries except China, the whole blood sample for *MET* gene analysis (including amplification and sequencing) may be collected on Cycle 1 Day 1 or at any visit after Cycle 1 Day 1. The whole blood sample for *MET* gene analysis may be used for additional genetic testing as part of biomarker research only if the subject consents. No additional blood sample will be collected.

Sample Handling, Storage, and Shipping

All biomarker samples should be labeled and shipped as outlined in the study-specific Study M22-137 laboratory manual. AbbVie (or people or companies working with AbbVie) will store the samples and data in a secure storage space with adequate measures to protect confidentiality. The samples may be retained while research on c-Met antibody-drug conjugates (ADCs) (or drugs of this class) or non-small cell lung cancer (NSCLC) and related conditions continues, but for no longer than 20 years after study completion, or per local requirement.

3.8 12-Lead Electrocardiogram

12-Lead Electrocardiogram (Single Only)

A 12-lead electrocardiogram (ECG) will be performed at the designated study visits as specified in Section 2.1 and should be performed prior to dosing on study dosing visits. Standard 12-lead safety ECG will be performed at Screening, Cycle 1 Day 1, Cycle 2 Day 1, Cycle 3 Day 1, and EOT.

ECG Safety Review

The ECGs will be evaluated by an appropriately trained physician at the study site (the "local reader"). The local reading of the ECG will be used by the investigator for subject safety assessments, including adverse event determination and management, and decision on whether a subject will be discontinued from the study.

The local reader from the site will sign and date all ECG tracings and will provide their global interpretation as a written comment on the tracing using the following categories:

- Normal ECG
- Abnormal ECG – Not clinically significant (NCS)
- Abnormal ECG – Clinically significant (CS)

Only the local reader's evaluation of the ECG will be collected and documented in the subject's source folder. The automatic machine reading (i.e., machine-generated measurements and interpretation that are automatically printed on the ECG tracing) will not be collected.

Clinically significant ECG changes should be captured as adverse events (AEs) on the appropriate eCRF.

COVID-19 Pandemic-Related Acceptable Protocol Modifications

In the event this may not be performed due to study modifications related to the COVID-19 pandemic, perform the 12-lead ECG at the next earliest feasible visit or arrange to have an alternative acceptable local facility perform the ECG for the subject.

3.9 Height and Weight

Subject weight will be assessed at all study visits, for study drug dosing visits it should be assessed prior to dosing; height will only be assessed at the Screening Visit (Section 2.1). The subject will wear lightweight clothing and no shoes during weighing.

3.10 Vital Signs

Vital sign determinations of systolic and diastolic blood pressure, pulse rate, respiratory rate, and body temperature will be obtained at visits as specified in Section 2.1. Blood pressure and pulse rate should be measured after the subject has been sitting for at least 3 minutes.

Vital sign measurements taken just prior to dosing on Cycle 1 Day 1 will serve as the baseline measurement for clinical assessments. Where these are being performed on a dosing day, vital signs measurements should be completed prior to study drug administration.

COVID-19 Pandemic-Related Acceptable Protocol Modifications

Due to the COVID-19 pandemic, subject visits may be conducted via phone or video conference. In these situations, vital signs may be obtained by the subject or caregiver as needed.

3.11 Physical Examination

A physical examination will be performed at the designated study visits as specified in Section 2.1. A complete physical examination will be performed at the Screening Visit. Symptom-directed limited physical examinations will be performed at all other visits. Where these are being performed on a dosing day, the examination should be performed prior to study drug administration.

The physical examination performed at Screening will serve as the baseline physical examination for the entire study. Physical examination abnormalities noted at the Cycle 1 Day 1 visit prior to the first dose of study drug should be recorded in the subject's medical history. Any significant physical examination findings after the first dose will be recorded as AE. All findings, whether related to an AE or part of each subject's medical history, will be captured on the appropriate electronic Case Report Form (eCRF) page.

At any time, a symptom-directed physical examination can be performed as deemed necessary by the investigator.

COVID-19 Pandemic-Related Acceptable Protocol Modifications

Due to the COVID-19 pandemic, for non-treatment visits, the subject may have the physical examination performed at a local clinic/hospital/laboratory.

3.12 Study Drug Administration

Study drug will be administered to subjects on visits as specified in Section 2.1. Further details regarding study drug, dosing, etc. are provided in Section 6.1.

3.13 Clinical Laboratory Tests

Where blood samples for serum chemistry, hematology, and urinalysis tests are collected on a dosing day, they should be collected prior to study drug administration. The baseline laboratory test results for clinical assessment for a particular test will be defined as the last measurement prior to the initial dose of study drug.

All laboratory samples (chemistry, hematology, and urinalysis) will be assessed using a certified central laboratory. The central laboratory for this study will provide instructions regarding the collection, processing, and shipping of samples.

A qualified (e.g., certification or accreditation) local reference laboratory may perform laboratory testing for immediate subject management (e.g., to determine eligibility, to continue study drug administration) or when central laboratory results may not be available prior to dosing; however, split or concurrent samples must be drawn and sent to the central laboratory as per the protocol schedule for data analysis.

Local laboratory values should not be captured in the eCRF, unless:

- the local laboratory result is contradictory and supports eligibility or treatment decision that would be prohibited based on the central laboratory result

- the local laboratory result is used to evaluate an adverse event
- when the central laboratory result is not available (e.g., sample not evaluable) and local laboratory results have been drawn

In the instances listed above, local laboratory results must be recorded in the eCRF to be included in the data analysis. The appropriate documents will be collected for both the central and local laboratories, as needed.

Collection of samples for screening and Cycle 1 Day 1 chemistry, hematology, and urinalysis is as follows:

- If screening > 14 days prior to Cycle 1 Day 1: screening labs must be repeated within 3 days of Cycle 1 Day 1.

These tests may be obtained up to 3 days prior to Cycle 2 Day 1 and beyond (Section 2.1).

For a laboratory test value outside the reference range that the investigator considers clinically significant:

- The investigator will repeat the test to verify the out-of-range value;
- The investigator will follow the out-of-range value to a satisfactory clinical resolution;
- A laboratory test value that requires discontinuation of study drug dose/schedule or necessitate medical/therapeutic intervention will be recorded as an AE (details provided in the Protocol Section 6).

Instructions regarding the collection, processing, and shipping of these samples will be provided by the central laboratory and sent to the region-specific certified laboratory address (Section 1).

Hematology	Clinical Chemistry
Hematocrit Hemoglobin Red blood cell (RBC) count White blood cell (WBC) count Neutrophils Bands Lymphocytes Monocytes Basophils Eosinophils Absolute platelet count Mean corpuscular volume (MCV) Activated partial thromboplastin time (aPTT) International normalized ratio (INR) or prothrombin time (PT)	Blood urea nitrogen (BUN) Creatinine Total bilirubin Alanine aminotransferase (ALT) Aspartate aminotransferase (AST) Total alkaline phosphatase (ALP) Sodium Potassium Calcium Inorganic phosphorus Uric acid Cholesterol Total protein Glucose Triglycerides Albumin Lactate dehydrogenase (LDH) Magnesium Chloride Bicarbonate Testosterone[a] Sex hormone binding globulin[a]
Urinalysis	
Specific gravity Ketones pH Protein Blood Glucose Microscopic examination if dipstick results are positive	

a. Male subjects only.

Pregnancy Tests (Serum and Urine)

A pregnant or breastfeeding female is not eligible for participation or continuation in this study.

A negative pregnancy test for all female subjects of child-bearing potential is required at the Screening Visit and a negative urine pregnancy test for all female subjects of child-bearing potential is required at baseline prior to the first dose of study drug. A urine pregnancy test will be performed up to 3 days prior to Cycle 1 Day 1 (Day –3) and up to 3 days prior to Day 1 of every subsequent dosing cycle. The pregnancy test results must be reviewed and determined to be negative prior to dosing with study drug. Serum or urine pregnancy tests can be performed at the discretion of the investigator or per local guidelines.

Pregnancy testing should not be performed for females of Non-Childbearing Potential (See Protocol Section 5.2 for criteria defining females of non-childbearing potential in this study).

The pregnancy test will be sent to and performed by the central laboratory. If the serum pregnancy test is positive the subject is considered a screen failure. If the serum pregnancy test is borderline, it should be repeated 48-72 hours days later to determine eligibility.

If the repeat serum pregnancy test is:

- Positive, follow requirements below on ruling out pregnancy in the case of a positive test prior to inclusion in the trial;
- Negative, the subject can be enrolled into the trial;
- Still borderline, the AbbVie Therapeutic Area Medical Director will be consulted prior to the subject being enrolled in the study.

If serum pregnancy test is positive, it should be repeated within 48-72 hours. If the repeat serum pregnancy test remains positive, pregnancy must be ruled out prior to inclusion in trial (i.e., referral to Ob/Gyn) and in consultation with the investigator and AbbVie Therapeutic Area Medical Director. If pregnancy cannot be ruled out, the subject will be considered a screen failure. In the absence of a pregnancy, the subject can be enrolled into the study.

Additional urine pregnancy tests will be performed at visits as specified in Section 2.1. Urine pregnancy testing should be completed monthly (± 7 days) for 7 months after the date of the last dose of study drug. Subjects may perform test at home using a urine pregnancy test at End of Treatment, 30-day follow up, and for the monthly tests for 7 months after the date of the last dose of study drug.

Urinalysis

Dipstick urinalysis will be completed by the central laboratory at all required visits. Specified abnormal macroscopic urinalyses defined as protein, ketones, or blood greater than negative, or glucose greater than normal will be followed up with a microscopic analysis at the central laboratory.

Coagulation Tests

Activated partial thromboplastin time/prothrombin time/international normalized ratio (aPTT/PT/INR) coagulations tests will be performed at study visits as specified in Section 2.1.

Testosterone and Sex Hormone Binding Globulin

Testosterone and sex hormone binding globulin will be evaluated at study visits as specified in Section 2.1. At applicable study visits, samples for these tests should be drawn concurrently with those for the other clinical chemistry laboratory tests.

COVID-19 Pandemic-Related Acceptable Protocol Modifications

If travel restrictions or other changes in local regulations in light of the COVID-19 pandemic prevent the subject from having blood drawn for laboratory testing at the study site, if possible, arrange for subjects to have laboratory work done at a local laboratory, hospital, or other facility. Local laboratory results should be obtained along with reference ranges and kept within the subjects' source documentation. Local laboratory results should be reviewed by the investigator as soon as possible.

3.14 ECOG Assessment

Eastern Cooperative Oncology Group (ECOG) scale will be used to assess performance status at visit.

Grade	ECOG
0	Fully active, able to carry on all pre-disease performance without restriction.
1	Restricted in physically strenuous activity but ambulatory and able to carry out work of a light or sedentary nature, e.g., light housework, office work.
2	Ambulatory and capable of all self-care but unable to carry out any work activities. Up and about more than 50% of waking hours.
3	Capable of only limited self-care, confined to bed or chair more than 50% of waking hours.
4	Completely disabled. Cannot carry on any self-care. Totally confined to bed or chair.

3.15 Ophthalmologic Exam

Subjects will have an Ophthalmologic Exam at Screening (Section 2.1). Post-baseline ophthalmologic exams are required for ocular side effects occur (Protocol Section 6.2). Ophthalmologic exams should include assessment of visual acuity, intra ocular pressure, funduscopic examination, and slit lamp examination, and any other finding or observation, according to the standard procedures of the ophthalmologist.

3.16 Tumor Assessments

The primary measure of response and disease progression will be determined by central review according to the RECIST version 1.1 criteria. Subject evaluations and treatment management will be made based on the investigator and/or qualified site staff review. In addition, imaging scans should be sent to an independent central imaging vendor. In cases where verification of PD is requested to support a treatment decision, scans should be sent within 5 business days from imaging acquisition. AbbVie may discontinue this requirement at any time during the course of the study. The central imaging vendor will provide instructions regarding the preparation and shipment/upload of images. All images obtained throughout the time a subject is on study should be saved and provided upon request. All subjects, whenever possible, should continue to have per protocol scans until disease progression is confirmed by the independent central imaging vendor.

Tumor assessments should be performed at the visits as specified in Section 2.1 and Section 2.2.

Baseline radiographic tumor assessment (contrast computed tomography [CT] or magnetic resonance imaging [MRI]) must be performed within 35 days prior to Cycle 1 Day 1. The tumor assessment performed at screening will serve as the baseline for clinical assessment. For subjects receiving one cycle

of systemic chemotherapy, the baseline radiographic tumor assessment should be performed after the completion of the chemotherapy cycle. Changes in measurable lesions over the course of therapy will be assessed using RECIST version 1.1, as described in Section 8.2. The same imaging technique should be used throughout the study if possible.

Baseline radiographic tumor assessment will include chest and abdomen, and any other sites clinically indicated (such as neck and pelvis). In addition, a baseline MRI of the brain is required for all subjects during screening. A CT scan of the brain with contrast may be done if an MRI scan is contraindicated or unavailable. A standard of care MRI or CT scan of brain may be used for all required sites of disease as the baseline scan as long as it was performed within 35-day prior to Cycle 1 Day 1 and meets study imaging requirements.

Imaging while on study will occur approximately every 6 weeks (± 7 days) from Cycle 1 Day 1 during the first year. After 1 year, the scans will be performed approximately every 8 weeks (± 7 days); after 2 years, approximately every 12 weeks (+/- 14 days). These pre-determined visits are all relative to Cycle 1 Day 1. If the visit is off schedule from these pre-assigned visits, the site should consult the sponsor. Imaging will also be performed at the EOT Visit (± 7 days). Tumor assessment at the EOT Visit may be omitted if performed within the last 6 weeks.

Subjects who discontinue study drug for any reason other than progressive disease (PD) demonstrated by imaging will be followed until they have PD documented by imaging, death, or withdraw consent. Following study drug discontinuation, subjects will continue to be followed according to the same tumor assessment schedule until progression. Imaging will continue approximately every 6 weeks (± 7 days) until disease progression or until 1 year since Cycle 1 Day 1. After 1 year, CT or MRIs will be performed approximately every 8 weeks (± 7 days) and after 2 years, approximately every 12 weeks (± 14 days).

Subjects who continue study drug after isolated CNS disease progression (Section 5.5 of protocol) should continue following the study imaging schedule as outlined above.

Subjects with locally determined radiographic disease progression may continue treatment until radiographic disease progression is confirmed by ICR provided the subject does not require alternative anti-cancer therapy and is clinically stable per the following criteria:

- Absence of emergent or worsening symptoms and signs indicating clinically significant progression of disease.
- No decline in ECOG performance status.
- Absence of progression of disease or progressive tumor at critical anatomical sites (e.g., cord compression) requiring urgent alternative medical intervention.

Imaging may also be performed at other times if the investigator suspects tumor progression.

A CT/MRI scan of the full chest, abdomen (with image of liver and adrenal glands), neck and pelvis (when clinically indicated), and other locations as clinically indicated, will be used in the evaluation of tumor responses. The estimated amount of radiation per CT scan would be 1700 mrem [17mSv] (700 mrem [7mSv] for chest + 1000 mrem [10mSv] for abdomen and pelvis) as per http://www.ans.org/pi/resources/dosechart. All sites of disease identified at Screening should be imaged as part of tumor assessments and all sites of suspected progression should be imaged for tumor

assessments. All lesions identified at Screening should continue to be followed by the same imaging technique (if possible).

If the subject is unable to undergo a CT scan with intravenous (IV) contrast due to allergy or renal insufficiency, a non-contrast CT may be performed. An MRI can be conducted in cases where local laws/requirements mandate but should have Sponsor approval prior to performing.

The CT portion of positron emission tomography (PET–CT) can be used for RECIST measurements only if the site can document that the CT performed as part of the PET–CT is of diagnostic quality. Bone scan and PET scan are not considered adequate for tumor measurements but can be used to confirm the presence or disappearance of bone lesions. Fluorodeoxyglucose - positron emission tomography (FDG-PET) scans may be used to determine PD according to the RECIST1.1 algorithm for identifying new lesions based on FDG-PET (see Section 8.2).

COVID-19 Pandemic-Related Acceptable Protocol Modifications

If travel restrictions or other changes in local regulations in light of the COVID-19 pandemic prevent the subject from having tumor assessments completed at the study site, if possible, arrange for subjects to have them done at a local laboratory, hospital, or other facility.

3.17 Subject Withdrawal

All attempts must be made to determine the primary reason for discontinuation of study drug or study participation. The information will be recorded in the source documents and on the appropriate eCRF page. However, these procedures should not interfere with the initiation of any new treatments or therapeutic modalities that the investigator feels are necessary to treat the subject's condition. Following discontinuation of study drug, the subject will be treated in accordance with the investigator's best clinical judgment, irrespective of whether the subject decides to continue participation in the study.

3.18 Paper Diary Cards for Sites in China Only

For sites in China only as per local requirements, at the visits specified in Section 2.1, the investigator will review the paper diary card. Study staff will record relevant information in existing adverse event and concomitant medication forms in the eCRF as applicable. Study staff will collect the paper diary card and dispense a new paper diary card at the visits specified in Section 2.1.

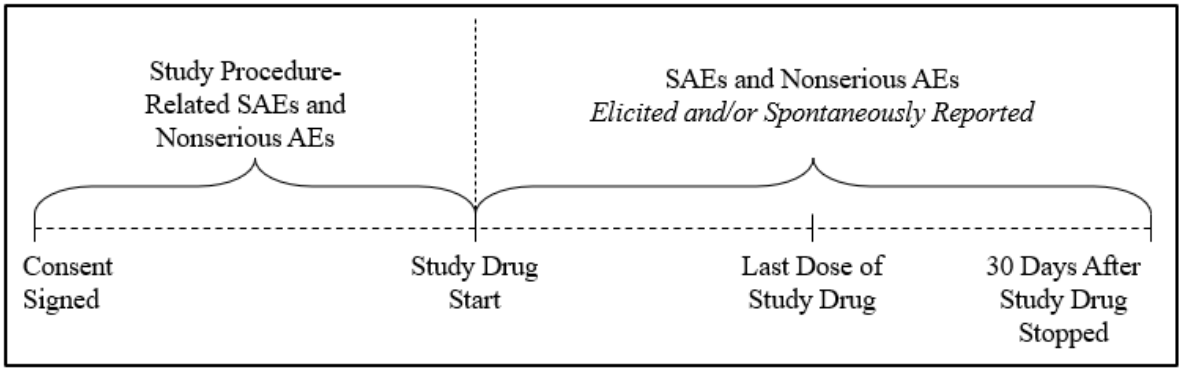
In the event that a subject withdraws or is discontinued from the study, the subject paper diary cards are to be returned to the site and appropriately filed with the subject's source documents for this study.

4 SAFETY MANUAL

4.1 Methods and Timing of Safety Assessment

All serious and nonserious AEs which could be related to study procedures, (e.g., infection at liver biopsy site, done during screening) will be collected from the time the subject signed the study-specific informed consent until study drug administration. From the time of study drug administration until

30 days after discontinuation of study treatment, all AEs and SAEs will be collected whether solicited or spontaneously reported by the subject. After 30 days following completion of study treatment and throughout the Post-Treatment Period, all spontaneously reported SAEs will be collected (nonserious AEs will not be collected).



4.2 Reporting Adverse Events and Intercurrent Illnesses

In the event of an SAE, whether associated with study drug or not, the investigator will notify Clinical Pharmacovigilance within 24 hours of the site being made aware of the SAE by entering the SAE data into the electronic data capture (EDC) system. SAEs that occur prior to the site having access to the RAVE® system, or if RAVE is not operable, should be documented on the SAE nonCRF forms and emailed (preferred route) or faxed to Clinical Pharmacovigilance within 24 hours of the site being made aware of the SAE.

Email: PPDINDPharmacovigilance@abbvie.com
FAX to: +1 (847) 938-0660

For safety concerns, contact the Oncology Safety Team at:

Oncology Safety Team
AbbVie Inc
1 North Waukegan Road
North Chicago, Illinois 60064
Toll Free: +1 (833) 942-2226
Email: SafetyManagement_Oncology@abbvie.com

For any subject safety concerns, please contact the physician listed below:

Primary Therapeutic Area Medical Director
EMERGENCY MEDICAL CONTACT:
[redacted]
AbbVie
Wegalaan 9
2132JD Hoofddorp
The Netherlands

Contact Information:

Office: [redacted]
Mobile:
Email:

In emergency situations involving study subjects when the primary Therapeutic Area Medical Director is not available by phone, please contact the 24-hour AbbVie Medical Escalation Hotline where your call will be re-directed to a designated backup AbbVie Therapeutic Area Medical Director:

HOTLINE: +1 (973) 784-6402

The sponsor will be responsible for Suspected Unexpected Serious Adverse Reactions (SUSAR) reporting for the Investigational Medicinal Product (IMP) in accordance with global and local requirements.

COVID-19 Pandemic-Related Acceptable Protocol Modifications

Supplemental study case report forms should be completed in the event of COVID-19 related missed/virtual visits, study drug interruptions or discontinuations, vaccines, or adverse events (including capture of specific signs/symptoms of infection and testing results).

SARS-CoV-2 infections should be captured as adverse events. If the event meets the criteria for a serious adverse event (SAE), then follow the SAE reporting directions per the protocol and above. The following COVID-19 related supplemental eCRFs should be completed (for both serious and nonserious events):

- COVID-19 Supplemental Signs/Symptoms
- COVID-19 Status Form

If a subject has a confirmed or suspected SARS-CoV-2 infection and study drug was interrupted, the investigator should contact the sponsor emergency medical contact listed above before reintroducing study drug.

Reactions known to be associated with the SARS-CoV-2 vaccine should be reported as adverse events. If the event meets the criteria for an SAE, then follow the SAE reporting directions. All adverse events associated with the SARS-CoV-2 vaccine will be linked to the vaccine on the COVID-19 Vaccine eCRF.

4.3 Reporting of ILD Adverse Events

ILD cases and potential cases will be reviewed by an ILD Adjudication Committee. Details on clinical data and imaging that will be transferred to the AC for adjudication of ILD cases/potential cases will be outlined in an ILD AC procedure manual, provided as a separate document in the study file.

5 COUNTRY-SPECIFIC REQUIREMENTS

5.1 Sample Retention Requirements

Samples collected for Study M22-137 may be retained for no longer than 20 years after study completion or per local requirements.

5.2 SUSAR Reporting

AbbVie will be responsible for Suspected Unexpected Serious Adverse Reactions (SUSAR) reporting for the Investigational Medicinal Product (IMP) in accordance with global and local guidelines and Appendix A of the Investigator Brochure will serve as the Reference Safety Information (RSI). The RSI in effect at the start of a DSUR reporting period serves as the RSI during the reporting period. For follow-up reports, the RSI in place at the time of occurrence of the 'suspected' Serious Adverse Reaction will be used to assess expectedness.

5.3 Treatment After End of Study

For active subjects on telisotuzumab vedotin, subjects will continue on study treatment until disease progression or discontinuation of study drug. At the subject's last study visit, the investigator will discuss the appropriate subsequent treatment with the subject.

5.4 Japan-Specific Requirements

Vital Signs

Pulse oximetry (oxygen saturation) is required during each vital signs exam.

Protocol Deviations

Investigators must record all protocol deviations in the appropriate medical records. The principal investigator must report protocol deviations that were necessary to eliminate an immediate hazard to study subjects, including the reason(s) for protocol deviation(s), to both AbbVie and the head of the medical institution.

5.5 China-Specific Requirements

Hepatitis virus infection in eligibility criteria

Hepatitis B serology is required at screening for subjects in China, per local standard of care.

Additional Endpoints

Not applicable to mainland China.

Exploratory Research

Not applicable to mainland China.

Biomarker research endpoints

The sample for *MET* gene analysis will not be collected in mainland China.

The plasma biomarker samples (collected pre-dose on Cycle 1 Day 1, pre-dose on Cycle 2 Day 1 and pre-dose on every odd cycle thereafter [e.g., Cycle 3 Day 1, Cycle 5 Day 1, etc.] and at the EOT Visit) will not be collected for subjects in mainland China.

ctDNA Sample Collection

The plasma (ctDNA) samples (collected at Screening, pre-dose Cycle 1 Day 1, pre-dose on Cycle 2 Day 1, pre-dose on every other odd cycle thereafter [e.g., Cycle 3 Day 1, Cycle 5, Day 1, etc.], and at the EOT visit) will not be collected for subjects in mainland China.

Paper Diary Cards

For sites in China only as per local requirements, subject paper diary cards will be used to record adverse event symptoms and concomitant medications (see Section 3.18).

5.6 Geo-Political Conflict In Ukraine and Surrounding Impacted Countries - Acceptable Protocol Modifications

The geo-political conflict in Ukraine and surrounding impacted regions has posed significant challenges in performing protocol-specified procedures. To ensure the safety of study participants and minimize risks to the integrity of the study, alternative methods for study assessments, activities, data collection, or study drug shipment are being implemented for impacted sites and study participants in these regions/countries. Protocol modifications employed due to the COVID-19 pandemic may be followed for study sites and participants impacted by the geo-political conflict in these regions as well.

Alternative methods or protocol modifications that may be employed include the following:

Study Subject Information and Informed Consent

It is possible that additional protocol modifications not outlined in this protocol may become necessary. If this situation arises, in addition to the study informed consent, additional temporary verbal consent

may be obtained prior to these adaptations or substantial changes in study conduct in accordance with local regulations. An appropriately signed and dated informed consent form should be obtained from the subject afterwards, as soon as possible.

Study Drug/Device Interruption or Discontinuation:

Delays in study drug dosing must be discussed with the sponsor medical contact, along with the possibility of premature discontinuation from study drug. The investigator should contact the sponsor medical contact before discontinuing a subject from the study for a reason other than described in the protocol to ensure all acceptable mitigation steps have been explored.

Study Visits:

Study visits may be impacted and include changes such as phone or virtual visits, visits at alternative locations, or changes in the visit frequency and timing of study procedures, among others. Every effort should be made to ensure the safety of subjects and site staff, while maintaining the integrity of the study. If visits cannot be conducted, discuss the next steps with the sponsor medical contact.

Follow the instructions in Section 2, Protocol Activities by Visit, above for the COVID-19 Pandemic-Related Acceptable Protocol Modifications instructions.

Laboratory Tests, Exams, and Activities:

Subjects may have laboratory testing performed at a local laboratory, hospital, or other facility as needed. Follow the instructions in Section 3.13, Clinical Laboratory Tests, above for the COVID-19 Pandemic-Related Acceptable Protocol Modifications instructions on how to obtain local laboratory samples or if samples cannot be obtained.

6 STUDY DRUG

6.1 Treatments Administered

The study drug (telisotuzumab vedotin) will be administered on visits as described in Section 2.1. General study drug information is provided in Table 2.

Table 2. Description of Study Drug

Study Drug	Dosage Form	Strength	Route of Administration	Manufacturer
Telisotuzumab vedotin (ABBV-399)	Powder for solution for infusion/for injection	100 mg (20mg/mL after reconstitution)	Intravenous infusion	AbbVie

The first dose of study drug will be administered after all other procedures are completed.

Study drug must not be dispensed without contacting the IRT system. Study drug may only be administered to subjects enrolled in the study through the IRT system. IRT transactions for study kit assignment should occur as close as possible to Day 1 of each cycle and no more than 3 days prior to the

Day 1 visit. At the end of the Treatment Period or if a subject is prematurely discontinued, the site will contact the IRT system to provide visit date information and study drug return information for each kit.

6.2 Packaging and Labeling

Telisotuzumab vedotin in vial form will be packaged in cartons. Each vial and carton will be labeled per country requirements. Labels must remain affixed to the vial and carton. Upon receipt, study drugs should be stored as specified on the label and kept in a secure location. Each kit will contain a unique kit number. This kit number is assigned to a subject via Interactive Response Technology (IRT) and encodes the appropriate study drug to be dispensed at the subject's corresponding study visit. Study drug must not be dispensed without contacting the IRT system. All blank spaces on the label should be completed by site staff prior to dispensing to subject.

Storage and Disposition of Study Drug

Study drug must be stored at controlled temperature (telisotuzumab vedotin: 2 to 8°C/35.6 to 46.4°F). Please refer to the clinical labels for detailed storage conditions.

The investigational products are for investigational use only and are to be used only within the context of this study. The study drug supplied for this study must be maintained under adequate security and stored under the conditions specified on the label until dispensed for subject use or destroyed on site as appropriate.

Sites are responsible for maintaining the investigational study drug and devices according to the storage conditions specified on the clinical label and monitoring for temperature excursions with the use of a calibrated continuous temperature monitoring device (for example, chart recorders and/or acceptable calibrated min /max thermometers) or continuous monitoring systems. Specific guidance on appropriate temperature monitoring and temperature excursions reporting requirements will be provided separately.

All original study drug units (containing unused study drugs) will be returned to the Sponsor (or designee) or destroyed on site. All destruction procedures will be according to instructions from the Sponsor and according to local regulations following completion of drug accountability procedure.

6.3 Method of Assigning Subjects to Treatment Groups

This is a Phase 2, open-label, non-randomized study. All eligible subjects will receive the same dose of telisotuzumab vedotin until disease progression, intolerable toxicity, or other study discontinuation criteria are met.

At the pre-screening visit, all subjects will be assigned a unique subject number using the IRT. For subjects who do not meet the study selection criteria, the site personnel must contact the IRT system and identify the subject as a screen failure.

Subjects who are enrolled will retain their subject number assigned at the pre-screening visit throughout the study. Upon receipt of study drug, the site will acknowledge receipt in the IRT system.

Contact information and user guidelines for IRT use will be provided to each site.

6.4 Selection and Timing of Dose for Each Subject

Telisotuzumab vedotin dosing will be based on the subject's weight at Cycle 1 Day 1. The dose of telisotuzumab vedotin does not need to be adjusted unless the subject's weight changes by > 10% from baseline. However, the dose may be adjusted for weight changes ≤ 10% at the discretion of the investigator. It is not necessary to calculate dosing based on ideal body weight. The dose for subjects with weight > 100 kg should be calculated for 100 kg. Telisotuzumab vedotin will be given via IV administration over 30 ± 10 minutes Q2W on study visits as specified in Section 2.1.

6.5 Preparation/Reconsitution of Dosage Form

Written instructions for the preparation of telisotuzumab vedotin (ABBV-399) solutions for infusion/for injection will be provided as a separate document from the protocol.

7 REFERENCES

1. Aaronson NK, Ahmedzai S, Bergman B, et al. The European Organization for Research and Treatment of Cancer QLQ-C30: a quality-of-life instrument for use in international clinical trials in oncology. J Natl Cancer Inst. 1993;85(5):365-76.

2. Bergman B, Aaronson NK, Ahmedzai S, et al. The EORTC QLQ-LC13: a modular supplement to the EORTC Core Quality of Life Questionnaire (QLQ-C30) for use in lung cancer clinical trials. EORTC Study Group on Quality of Life. Eur J Cancer. 1994;30a(5):635-42.

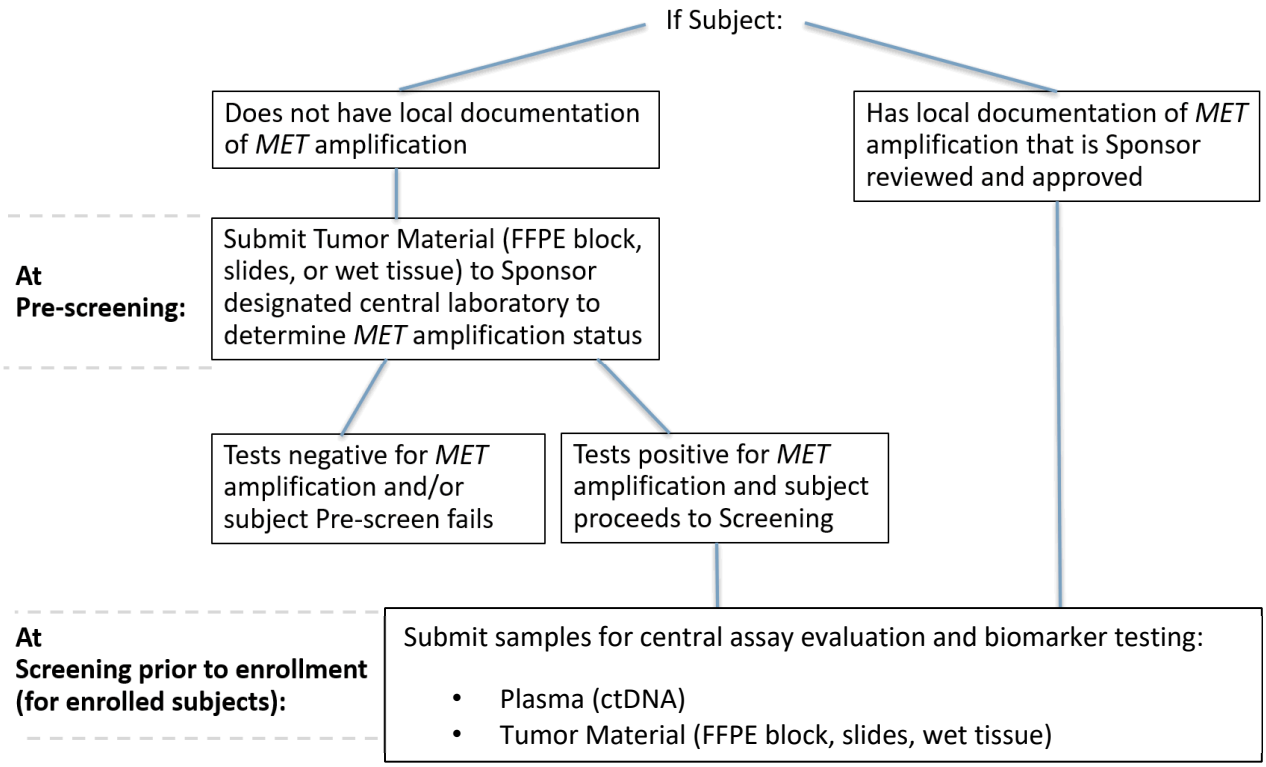
3. Herdman M, Gudex C, Lloyd A, et al. Development and preliminary testing of the new five-level version of EQ-5D (EQ-5D-5L). Qual Life Res. 2011;20(10):1727-36.

4. Oppe M, Devlin NJ, van Hout B, et al. A program of methodological research to arrive at the new international EQ-5D-5L valuation protocol. Value Health. 2014;17(4):445-53.

5. Eisenhauer EA, Therasse P, Bogaerts J, et al. New response evaluation criteria in solid tumours: revised RECIST guideline (version 1.1). Eur J Cancer. 2009;45(2):228-47.

8 APPENDICES

8.1 PRE-SCREENING AND SCREENING SAMPLE COLLECTION FLOWCHART FOR MET AMPLIFICATION CONFIRMATION AND BIOMARKER TESTING



8.2 RESPONSE EVALUATION CRITERIA FOR SOLID TUMORS (RECIST) VERSION 1.1

Response criteria will be assessed using RECIST (version 1.1; see literature reference for complete guidelines[5]). An overview is presented below.

Eligibility

Subjects with measurable disease at baseline can have objective tumor response evaluated by RECIST (version 1.1). Measurable disease is defined by the presence of at least one measurable lesion. If the measurable disease is restricted to a solitary lesion, its neoplastic nature should be confirmed by cytology/histology if possible.

Measurability

Measurable Lesions	Lesions accurately measured in at least one dimension with a minimum size of: Longest diameter ≥ 10 mm (CT scan slice thickness no greater than 5 mm) 10 mm caliper measurement by clinical exam
Non-Measurable Lesions	All other lesions, including small lesions (longest diameter < 10 mm) as well as truly non-measurable lesions. Lesions considered truly non-measurable include: leptomeningeal disease, ascites, pleural/pericardial effusion, inflammatory breast disease, lymphangitic involvement of skin or lung and also abdominal masses that are not confirmed and followed by imaging techniques.
Measurable Malignant Lymph Nodes	To be considered pathologically enlarged and measurable, a lymph node must be ≥ 15 mm in short axis when assessed by CT scan (CT scan slice thickness recommended to be no greater than 5 mm). At baseline and in follow-up, only the short axis will be measured and followed.
Non-Measurable Malignant Lymph Nodes	Pathological lymph nodes with ≥ 10 to < 15 mm short axis.
Special Considerations Regarding Lesion Measurability	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 MRI/CT 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 in an area subjected to other loco-regional therapy, are usually not considered measurable unless there has been demonstrated progression in the lesion.

All measurements should be taken and recorded in metric notation, using calipers if clinically assessed. All baseline evaluations should be performed as closely as possible to the beginning of treatment and not more than 28 days before the beginning of the treatment.

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.

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

Methods of Measurement

Conventional CT should be performed with cuts of 5 mm or less in slice thickness contiguously. This applies to tumors of the chest and abdomen. A scale should be incorporated into all radiographic measurements. MRI can be performed if required by local law but should have sponsor approval.

If prior to enrollment, it is known a subject is not able to undergo CT scans with IV contrast due to allergy or renal insufficiency, the decision as to whether a non-contrast CT or MRI should be used to evaluate the subject at baseline and follow-up should be guided by the tumor type under investigation and the anatomic location of the disease. For subjects who develop contraindications to contrast after baseline contrast CT is done, the decision as to whether non-contrast CT or MRI should be made based upon discussion with the AbbVie Therapeutic Area Medical Director.

For accurate objective response evaluation, ultrasound should not be used to measure tumor lesions.

The utilization of endoscopy and laparoscopy for objective tumor evaluation is not advised. However, such techniques can be useful in confirming complete pathological response when biopsies are obtained.

Cytology and histology can be used to differentiate between partial response (PR) and complete response (CR) in rare cases.

Baseline Documentation of "Target" and "Non-Target" Lesions

All measurable lesions up to a maximum of 2 lesions per organ and 5 lesions in total, representative of all involved organs should be identified as target lesions and recorded and measured at baseline. Target lesions should be selected on the basis of their size (lesions with the longest diameter), be representative of all involved organs, but in addition should be those that lend themselves to reproducible repeated measurements. Tumor lesions situated in a previously irradiated area, or in an area subjected to other loco-regional therapy, are usually not considered measurable unless there has been demonstrated progression in the lesion.

Lymph nodes merit special mention since they are normal anatomical structures which may be visible by imaging even if not involved by tumor. Pathological nodes which are defined as measurable and may be identified as target lesions must meet the criterion of a short axis of ≥ 15 mm by CT scan. Only the short axis of these nodes will contribute to the baseline sum. The short axis of the node is the diameter normally used by radiologists to judge if a node is involved by solid tumor. Nodal size is normally reported as two dimensions in the plane in which the image is obtained (for CT scan this is almost always the axial plane). The smaller of these measures is the short axis. For example, an abdominal node which is reported as being 20 mm × 30 mm has a short axis of 20 mm and qualifies as a malignant, measurable node. In this example, 20 mm should be recorded as the node measurement. All other pathological nodes (those with short axis ≥ 10 mm but < 15 mm) should be considered non-target

lesions. Nodes that have a short axis < 10 mm are considered non-pathological and should not be recorded or followed.

A sum of the longest diameter (LD) for all target lesions will be calculated and reported as the baseline sum LD. If lymph nodes are to be included in the sum, then as noted above, only the short axis is added into the sum. The baseline sum LD will be used as reference by which to characterize the objective tumor response.

All other lesions (or sites of disease) including pathological lymph nodes should be identified as non-target lesions and should also be recorded at baseline. Measurements of these lesions are not required, but the presence (stable, increasing or decreasing) or absence of each should be noted throughout follow-up.

Evaluation of Target Lesions

Complete Response (CR):

The 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 the LD of target lesions, taking as reference the smallest sum LD recorded since the treatment started (baseline or after) or the appearance of one or more new lesions. In addition to the relative increase of 20%, the sum must also demonstrate an absolute increase of at least 5 mm.

Stable Disease (SD):

Neither sufficient shrinkage to qualify for PR nor sufficient increase to qualify for PD, taking as reference the smallest sum LD since the treatment started (baseline or after).

Assessment of Target Lesions:

Lymph nodes identified as target lesions should always have the actual short axis measurement recorded (measured in the same anatomical plane as the baseline examination), even if the nodes regress to below 10 mm on study. This means that when lymph nodes are included as target lesions, the 'sum' of lesions may not be zero even if complete response criteria are met, since a normal lymph node is defined as having a short axis of < 10 mm. For PR, SD and PD, the actual short axis measurement of the nodes is to be included in the sum of target lesions.

All lesions (nodal and non-nodal) recorded at baseline should have their actual measurements recorded at each subsequent evaluation, even when very small (< 5 mm). However, sometimes target lesions or lymph nodes become too small to measure. If it is in the opinion of the radiologist that the lesion has likely disappeared, the measurement should be recorded as 0 mm. If the lesion is believed to be

present, but too small to measure, a default value of 5 mm should be assigned (as derived from the 5 mm CT slice thickness). The measurement of these lesions is potentially non-reproducible; therefore, providing this default value will prevent false responses or progression based upon measurement error.

Evaluation of Non-Target Lesions

Complete Response (CR):

The 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).

Non-CR/Non-PD:

Persistence of one or more non-target lesion(s) and/or maintenance of tumor marker level above the normal limits.

Progressive Disease (PD):

Unequivocal progression of existing non-target lesions.

In this setting, to achieve 'unequivocal progression' on the basis of non-target disease, there must be an overall level of substantial worsening in non-target disease such that, even in the presence of SD or PR in target disease, the overall tumor burden has increased sufficiently to merit discontinuation of therapy. A modest 'increase' in the size of one or more non-target lesions is usually not sufficient to qualify for unequivocal progression status. The designation of overall progression solely on the basis of change in non-target disease in the face of SD or PR of target disease will therefore be extremely rare.

New Lesions

The appearance of new malignant lesions denotes disease progression. While there are no specific criteria for the identification of new radiographic lesions, the findings of a new lesion should be unequivocal; i.e., not attributable to differences in scanning technique, timing of scanning, phase of contrast administration, change in imaging modality or finding thought to represent something other than tumor (e.g., some 'new' bone lesions may be simply healing or flare of pre-existing lesions). A lesion identified on a follow-up study in an anatomical location that was not scanned at baseline is considered a new lesion and will indicate disease progression. An example of this is the patient who has visceral disease at baseline and while on study has a CT or MRI brain ordered which reveals metastases. The patient's brain metastases are considered evidence of progressive disease even if he/she did not have brain imaging at baseline.

If a new lesion is equivocal (e.g., too small to measure), continued therapy and follow-up evaluation will clarify if it represents truly new disease. If repeat scans confirm there is a new lesion, then progression should be declared using the date of the initial scan.

New lesions can be identified on the basis of FDG-PET imaging according to the following algorithm:

- Negative FDG-PET at baseline, with a positive FDG-PET at follow-up is a sign of PD based on a new lesion.
- No FDG-PET at baseline and a positive FDG-PET at follow-up:

- If the positive FDG-PET at follow-up corresponds to a new site of disease confirmed by CT, this is PD;
- If the positive FDG-PET at follow-up is not confirmed as a new site of disease on CT, additional follow-up CT scans are needed to determine if there is truly progression occurring at that site (if so, the date of PD will be the date of the initial abnormal FDG-PET scan);
- If the positive FDG-PET at follow-up corresponds to a pre-existing site of disease on CT that is not progressing on the basis of the anatomic images, this is not PD.

Calculating Overall Response

Response of Combined Lesion Type			
Target Lesion	**Non-Target Lesion**	**New Lesion**	**Overall Response**
CR	CR	No	CR
CR	Non-CR/non-PD	No	PR
CR	Not evaluated	No	PR
PR	Non-PD or not evaluated	No	PR
SD	Non-PD or not evaluated	No	SD
Not all evaluated	Non-PD	No	NE
PD	Any	Yes or No	PD
Any	PD	Yes or No	PD
Any	Any	Yes	PD

CR = complete response; PR = partial response; SD = stable disease; PD = progressive disease; NE = Unable to evaluate

Document Approval

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