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| **Document Type:** | Study Protocol |
| **Official Title:** | A randomized, open-label, active-controlled, Phase II study of intravenous anetumab ravtansine (BAY 94-9343) or vinorelbine in patients with advanced or metastatic malignant pleural mesothelioma overexpressing mesothelin and progressed on first line platinum/pemetrexed-based chemotherapy |
| **NCT Number:** | NCT02610140 |
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# Cover page of the integrated protocol

**A randomized, open-label, active-controlled, Phase II study of intravenous anetumab ravtansine (BAY 94-9343) or vinorelbine in patients with advanced or metastatic malignant pleural mesothelioma overexpressing mesothelin and progressed on first line platinum/pemetrexed-based chemotherapy**

This protocol version is an integration of the following documents / sections:

- **Original protocol,** Version 1.0, dated 17 AUG 2015
- **Amendment 02** (global amendment described in Section 15.1) forming integrated protocol Version 2.0, dated 09 FEB 2016
- **Amendment 04** (global amendment described in Section 15.2) forming integrated protocol Version 3.0, dated 11 AUG 2016
- **Amendment 05** (global amendment described in Section 15.3) forming integrated protocol Version 4.0, dated 18 APR 2017
- **Amendment 06** (global amendment described in Section 15.4) forming integrated protocol Version 5.0, dated 27 MAR 2018

Amendments not included in the consecutive numbering of amendments are local amendments not forming part of this integrated global protocol. This currently includes:

- **Amendment 01,** dated 04 DEC 2015 (local amendment valid for UK only)
- **Amendment 03,** dated 23 MAY 2016 (local amendment valid for Finland only)

# 1. Title page

**A randomized, open-label, active-controlled, Phase II study of intravenous anetumab ravtansine (BAY 94-9343) or vinorelbine in patients with advanced or metastatic malignant pleural mesothelioma overexpressing mesothelin and progressed on first line platinum/pemetrexed-based chemotherapy**

Phase II anetumab ravtansine as 2nd line treatment for malignant pleural mesothelioma (MPM)

ARCS-$M_{2L}$ (Anetumab Ravtansine Clinical Studies – Mesothelioma 2nd Line)

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| Test drug: | BAY 94-9343 / anetumab ravtansine | | |
| Study purpose: | Assess the efficacy and safety of anetumab ravtansine as 2nd line treatment in MPM | | |
| Clinical study phase: | II | Date: | 27 MAR 2018 |
| Registration: | EudraCT no.: 2012-003650-88 | Version no.: | 5.0 |
| Sponsor's study no.: | 15743 | | |
| Sponsor: | **Non-US: Bayer AG, D-51368 Leverkusen, Germany**<br>**US territory: Bayer HealthCare Pharmaceuticals Inc., 100 Bayer Boulevard, P.O. Box 915, Whippany NJ 07981-0915, USA** | | |
| Sponsor's medical expert: | PPD<br>PPD<br>PPD<br>Telephone no.: PPD<br>Mobile: PPD | | |

The study will be conducted in compliance with the protocol, ICH-GCP and any applicable regulatory requirements.

## Signature of the sponsor's medically responsible person

The signatory agrees to the content of the final integrated clinical study protocol as presented.

Name: PPD Role: PPD

Date: 9 April 2018 Signature: PPD

## Signature of principal investigator

The signatory agrees to the content of the final integrated clinical study protocol as presented.

Name:

Affiliation:

Date: Signature:

Signed copies of this signature page are stored in the sponsor's study file and in the respective center's investigator site file.

# 2. Synopsis

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| **Title** | A randomized, open-label, active-controlled, Phase II study of intravenous anetumab ravtansine (BAY 94-9343) or vinorelbine in patients with advanced or metastatic malignant pleural mesothelioma overexpressing mesothelin and progressed on first line platinum/pemetrexed-based chemotherapy |
| **Short title** | Phase II anetumab ravtansine as 2nd line treatment for malignant pleural mesothelioma (MPM) |
| **Clinical study phase** | II |
| **Study objective(s)** | The primary objective of this study is to:<br>• Test the superiority of anetumab ravtansine monotherapy over vinorelbine in progression-free survival (PFS)<br>The secondary objectives of this study are to:<br>• Test overall survival (OS)<br>S*econdary objective related to pulmonary function removed by amendment 2*<br>• Evaluate patient-reported outcomes (PROs) – symptom burden and health-related quality of life (QoL)<br>• Evaluate other indicators of treatment efficacy (indicators of tumor response)<br>• Evaluate safety<br><br>The other objectives of this study are to evaluate the:<br>• Pharmacokinetics (PK)<br>• Immunogenicity<br>• Biomarkers |
| **Test drug(s)** | Anetumab ravtansine |
| **Name of active ingredient** | Anetumab ravtansine / BAY 94-9343 |
| **Dose(s)** | 6.5 mg/kg every 3 weeks (Q3W) |
| **Route of administration** | Intravenous (IV) infusion over 1 h |
| **Duration of treatment** | Patients will continue on treatment until one of the following occurs:<br>• Progressive disease (PD) as defined by modified Response Evaluation Criteria in Solid Tumors (mRECIST) for mesothelioma as assessed by blinded central radiology review; however, treatment may be continued provided that the patient derives clinical benefit as determined by the treating physician.<br>• Clinical progression *(criteria related to progressive disease and clinical progression modified by amendment 2)*<br>• Death<br>• Any other criterion for withdrawal from study treatment. |

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| **Reference drug(s)** | Vinorelbine |
| **Name of active ingredient** | Vinorelbine |
| **Dose(s)** | 30 mg/m$^2$ once weekly (QW) |
| **Route of administration** | IV injection over 6 to 10 min |
| **Duration of treatment** | Patients will continue on treatment until one of the following occurs:<br>• PD as defined by mRECIST for mesothelioma as assessed by blinded central radiology review; however, treatment may be continued provided that the patient derives clinical benefit as determined by the treating physician<br>• Clinical progression *(criteria related to progressive disease and clinical progression modified by amendment 2)*<br>• Death<br>• Any other criterion for withdrawal from study treatment. |
| **Indication** | Advanced or metastatic MPM overexpressing mesothelin |
| **Diagnosis and main criteria for inclusion /exclusion** | Male or female patients (≥ 18 years of age) with unresectable locally advanced or metastatic MPM overexpressing mesothelin. Patients must have Eastern Cooperative Oncology Group Performance Status (ECOG PS) of 0 or 1, a life expectancy of at least 3 months and at least 1 measurable lesion per mRECIST per MPM (i.e. pleural lesion(s) measured using mRECIST or extra-pleural lesion(s) measurable per RECIST 1.1) as determined by the central reviewer *(modified by amendment 2)*. Patients must have received only 1 line of previous systemic anti-cancer treatment with platinum-pemetrexed with or without bevacizumab and must have no corneal epitheliopathy or any predisposing eye disorder. |
| **Study design** | A randomized, open-label, active-controlled, 2-arm, multicenter, Phase II study.<br>Approximately 210 patients *(changed by amendment 2)* who meet the eligibility criteria will be randomly assigned in a 2:1 ratio to receive anetumab ravtansine or vinorelbine, respectively. Patients will be stratified at randomization according to geographic region and per time to progression (TTP) on 1$^{st}$ line treatment.<br>The study is composed of the following periods:<br>• Screening<br>Note: A prescreening step, including the mesothelin expression level testing, can be performed without evidence of disease progression after the initial treatment cycles with platinum/pemetrexed (with or without bevacizumab) at the investigator's discretion after signing of informed consent.<br>• Treatment<br>• Safety-follow-up:<br>Patients who discontinue study treatment for any reason.<br>• Active follow-up (which also includes the safety follow-up period): |

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| | Patients who discontinue study treatment for any reason other than centrally confirmed radiological PD will be followed for progression during active follow-up until data maturation for the OS final analysis is reached (i.e. completion of number of events required for OS analysis), or until centrally confirmed progression, death, consent withdrawal or end of study, whichever occurs first *(modified by amendment 6)*.<br><br>• Long-term follow-up:<br>All patients who end study treatment for any reason will be followed for OS and any new anti-cancer treatment every 3 months until death, consent withdrawal, 24 months after the last patient's last treatment or end of study, whichever occurs first *(modified by amendment 6)*. |
| **Methodology** | Primary efficacy will be assessed based on radiological tumor evaluation by contrast-enhanced computed tomography (CT) or contrast-enhanced magnetic resonance imaging (MRI) of chest/abdomen/pelvis. The first tumor images will be obtained during full screening and will be sent to blinded central review to confirm radiological eligibility prior to randomization *(modified by amendment 2)*. During treatment as well as active follow-up, tumor imaging will be performed with the same modality every 6 weeks during the first 6 months after the start of study treatment, every 9 weeks until the end of year 2, and every 12 weeks thereafter, until the earlier of centrally confirmed radiological disease progression, OS analysis data maturation, or end of study *(modified by amendment 6)*. Primary analysis results will be based on central review.<br><br>*Description of forced vital capacity methodology removed by amendment 2*<br><br>Patients will be contacted to assess survival status every 3 months during long-term follow-up. In addition, extra survival sweep contacts will be conducted at the time of PFS final analysis and prior to OS final analysis to ensure that long-term follow-up data is current.<br><br>The effect of treatment on disease-specific symptoms and disease-specific health-related QoL will be assessed using the MD Anderson Symptom Inventory-Malignant Pleural Mesothelioma (MDASI-MPM) and the Lung Cancer Symptom Scale-Mesothelioma (LCSS-Meso), respectively, at full screening, at each cycle during treatment, at the safety follow-up visit, and during active follow-up *(paragraph clarified by amendment 4)*.<br><br>Safety evaluations will be done at full screening, at each clinic visit during the treatment, and at the safety follow-up visit. The National Cancer Institute's Common Terminology Criteria for Adverse Events (NCI-CTCAE) version 4.03 will be used to grade severity of adverse events (AEs). In addition, a Bayer grading system will be used to assess corneal epitheliopathy *(sentence added by amendment 2)*.<br><br>Sparse plasma sampling for PK will be performed on all patients.<br><br>Immunogenicity assessment will be performed for patients in the anetumab ravtansine arm only.<br><br>Obligatory biomarker sampling will be performed on all patients to measure mesothelin expression levels in tumor material at prescreening. In addition, plasma levels of soluble mesothelin will be studied to |

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| | evaluate whether plasma mesothelin levels may correlate with response rate and be of predictive value. Biomarker plasma will be collected to analyze circulating tumor DNA, too. Exploratory biomarker analysis may also be performed using additional fresh or archival tumor tissue to determine alterations in tumor-associated genes and to perform gene expression analysis *(modified by amendment 4)*.<br><br>An independent Data Monitoring Committee will periodically monitor patient safety *(clarification added by amendment 4)*.<br><br>Following OS data maturation, patients remaining on study will continue to be followed with reduced mandated assessments and data collection (although assessments can continue per investigator's judgement). Active follow-up, efficacy, and some safety assessments will no longer be required *(paragraph added by amendment 6)*. |
| **Type of control** | Patients in the comparator arm will receive vinorelbine 30 mg/m$^2$ IV QW. Vinorelbine is one of the drugs considered by various guidelines (e.g. National Comprehensive Cancer Network [NCCN], European Society of Medical Oncology [ESMO]) as a potential option for patients with advanced mesothelioma progressed after platinum-pemetrexed. Mechanistically, it is a spindle poison, therefore comparable with DM4, anetumab ravtansine metabolite. |
| **Data Monitoring Committee** | Yes |
| **Number of patients** | Approximately 210 patients will be randomized. Approximately 50% rate of screening failures is estimated, i.e. approximately 420 patients will be prescreened *(modified by amendments 2 and 4)*. |
| **Primary variable** | Progression-free survival (PFS), defined as time from randomization until disease progression (according to mRECIST for MPM, per blinded central radiology review) or death. |
| **Time point/frame of measurement for primary variable** | Primary analysis will be performed after approximately 117 PFS events are observed by central review in the study. |
| **Plan for statistical analysis** | The primary analysis set for the efficacy variables is the intent-to-treat set (ITT).<br><br>The primary variable, PFS based on assessment of central review, will be tested using a log-rank test stratified by geographic region and per TTP on 1$^{st}$ line treatment, with a 1-sided significance level of 0.0125. Kaplan-Meier survival curves will be plotted. Medians with Brookmeyer-Crowley confidence intervals will be calculated. The primary analysis will occur after approximately 117 PFS events are observed by central review.<br><br>Secondary efficacy variable OS will be tested using a 2-stage group-sequential testing procedure with an overall 1-sided significance level of 0.025 and 80% power. Each stage will utilize a 1-sided log-rank test stratified by geographic region and per TTP on 1$^{st}$ line treatment. A Lan-Demets alpha spending function with O'Brien-Fleming boundaries will be used. An interim analysis for OS will be performed at the same time as the final analysis for PFS, when approximately 80 OS events are expected to have been observed. The final analysis for OS will be performed after approximately 159 events have been observed *(paragraph modified by* |

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| | *amendment 2)*.<br><br>Additional secondary variables include objective response rate (ORR), disease control rate (DCR), duration of response (DOR), durable response rate (DRR) and analysis of the change in physical symptoms of MPM by PROs (as measured using the MDASI-MPM and LCSS-Meso) *(modified by amendment 2)*. In the event primary PFS and secondary OS hypothesis tests succeed, key secondary PRO variables will be tested at 1-sided significance level using an alpha-preserving hierarchy. A stratified log-rank test will be used for time-to-event endpoints, and a Cochran-Mantel-Haenszel test will be used for rate endpoints *(paragraph modified by amendment 4)*.<br><br>The 210 randomized patients are estimated to be accrued in approximately 19.8 months. Data for final PFS analysis are estimated to mature in 21.2 months. Data for final OS analysis are estimated to mature in 41.3 months *(paragraph modified by amendment 2)*. |

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## Table of tables



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# List of abbreviations

*List of abbreviations was updated by amendments 2, 4 and 5.*

| | |
|---|---|
| 5-HT3 | 5-hydroxytryptamine (serotonin) |
| AAG | Alpha-1 acid glycoprotein |
| ADA | Anti-drug antibody |
| ADC | Antibody-drug conjugate |
| AE | Adverse event |
| AG | Joint stock company, *Aktiengesellschaft* |
| ALP | Alkaline phosphatase |
| ALT | Alanine aminotransferase |
| ANC | Absolute neutrophil count |
| aPTT | Activated partial thromboplastin time |
| ARDS | Acute respiratory distress syndrome |
| ASCO | American Society of Clinical Oncology |
| AST | Aspartate aminotransferase |
| AUC | Area under the curve |
| BCVA | Best corrected visual acuity |
| β-HCG | β subunit of human chorionic gonadotropin |
| BIC | Best investigator choice |
| BIO | Biomarker set |
| BM | Biomarker |
| BP | Blood pressure |
| BSA | Body surface area |
| BUN | Blood urea nitrogen |
| °C | Celcius degree(s) |
| C | Cycle |
| CBC | Complete blood count |
| $C_{max}$ | Maximum drug concentration |
| CNS | Central nervous system |
| COA | Clinical Outcomes Assessment |
| CR | Complete response |
| CRF | Case report form |
| CRO | Contract research organization |
| CSF | Colony stimulating factor |
| CSR | Clinical Study Report |
| CT | Computed tomography |
| CTCAE | Common Terminology Criteria for Adverse Events |
| CTFG | Clinical Trial Facilitation Group |
| CYP2D6 | Cytochrome P450, family 2, subfamily D, polypeptide 6 |
| CYP3A4 | Cytochrome P450, family 3, subfamily A, polypeptide 4 |
| D | Day |
| DCR | Disease control rate |
| DICOM | Digital Imaging and Communications in Medicine |
| dL | Deciliter |
| DM4 | Derivatives of maytansine 4 |
| DM4-Me | Methyl-DM4 |
| DMC | Data Monitoring Committee |

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|---|---|
| DNA | Deoxyribonucleic acid |
| DOR | Duration of response |
| DRR | Durable response rate |
| ECG | Electrocardiogram |
| EchoCG | Echocardiogram |
| ECOG | Eastern Cooperative Oncology Group |
| ECOG PS | Eastern Cooperative Oncology Group Performance Status |
| EDC | Electronic data capture |
| eGFR | Estimated glomerular filtration rate |
| EMA | European Medicines Agency |
| ENR | Enrolled set |
| ESMO | European Society of Medical Oncology |
| ETDRS | Early Treatment Diabetic Retinopathy Study |
| EU | European Union |
| EudraCT | EU data repository for clinical trials |
| °F | Fahrenheit degree(s) |
| FDA | Food and Drug Administration |
| FFPE | Formalin-fixed, paraffin-embedded |
| FiH | First in Human |
| FSH | Follicle stimulating hormone |
| g | Gram(s) |
| GCL | Global Clinical Leader |
| GCP | Good Clinical Practice |
| G-CSF | Granulocyte-colony stimulating factor |
| GFR | Glomerular filtration rate |
| GGT | Gamma-glutamyl transferase |
| GMP | Good Manufacturing Practice |
| GPV | Global Pharmacovigilance |
| h | Hour(s) |
| H0 | Null hypothesis |
| HA | Alternative hypothesis |
| Hb | Hemoglobin |
| HDAC | Histone deacetylase |
| HIV | Human immunodeficiency virus |
| HR | Heart rate |
| IB | Investigator's brochure |
| ICF | Informed consent form |
| ICH | International Council for Harmonization |
| IEC | Independent Ethics Committee |
| IFCT | French Cooperative Thoracic Intergroup |
| IgG1 | Immunoglobulin G subclass 1 |
| IHC | Immunohistochemistry |
| ILD | Interstitial lung disease |
| IM | Immunogenicity |
| IMP | Investigational medicinal product |
| INR | International normalized ratio |
| IOP | Intraocular pressure |
| IRB | Institutional Review Board |
| IRC | Image Review Charter |

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|---|---|
| ITT | Intent-to-treat (set) |
| IUD | Intrauterine device |
| IUS | Intrauterine hormone-releasing system |
| IV | Intravenous |
| IxRS | Interactive Voice / Web Response System |
| kg | Kilogram(s) |
| LCSS | Lung Cancer Symptom Scale |
| LCSS-Meso | Lung Cancer Symptom Scale-Mesothelioma |
| LDH | Lactic dehydrogenase |
| LLN | Lower limit of normal |
| LPLV | Last patient last visit |
| LVEF | Left ventricular ejection fraction |
| $m^2$ | Square meter(s) |
| MAPS | Mesothelioma Avastin Plus Pemetrexed-cisplatin Study |
| MD | Doctor of Medicine |
| MDACC | MD Anderson Cancer Center |
| MDASI | MD Anderson Symptom Inventory |
| MDASI-LC | MD Anderson Symptom Inventory-Lung Cancer |
| MDASI-MPM | MD Anderson Symptom Inventory-Malignant Pleural Mesothelioma |
| MDRD | Modification of Diet in Renal Disease |
| MedDRA | Medical Dictionary for Regulatory Activities |
| mg | Milligram(s) |
| MHRA | Medicines and Healthcare Products Regulatory Agency |
| Min | Minute(s) |
| miRNA | Micro ribonucleic acid |
| mL | Milliliter(s) |
| $mm^3$ | Cubic millimeter(s) |
| mmHg | Millimeter of mercury |
| MoA | Mechanism of action |
| MPM | Malignant pleural mesothelioma |
| mRECIST | Modified Response Evaluation Criteria in Solid Tumors |
| MRI | Magnetic resonance imaging |
| M&S | Modelling and Simulation |
| MTD | Maximum tolerated dose |
| MUGA | Multiple gated acquisition |
| N | Number of patients |
| n | Number of non-missing values |
| N HCl | Normal hydrochloric acid |
| NAB | Neutralizing anti-drug antibody |
| NC | No change |
| NCCN | National Comprehensive Cancer Network |
| NCI-CTCAE | National Cancer Institute’s Common Terminology Criteria for Adverse Events |
| NE | Not evaluated |
| NGS | Next generation sequencing |
| NYHA | New York Heart Association |
| ORR | Objective response rate |
| OS | Overall survival |
| PD | Progressive disease |

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|---|---|
| PDX | Patient-derived xenograft |
| PET | Positron emission tomography |
| PFS | Progression-free survival |
| P-gp | Permeability glycoprotein |
| PGt | Pharmacogenetic |
| PhD | Doctor of Philosophy |
| PI | Patient information |
| PK(s) | Pharmacokinetic(s) |
| PopPBPK | Population, physiologically-based pharmacokinetic |
| PR | Partial response |
| PRO | Patient-reported outcome |
| PT | Prothrombin time |
| PTT | Partial thromboplastin time |
| Q3W | Every 3 weeks |
| QA | Quality assurance |
| QoL | Quality of life |
| QOL | Quality of life set |
| QW | Once weekly |
| RBC | Red blood cell count |
| RECIST | Response Evaluation Criteria in Solid Tumors |
| RNA | Ribonucleic acid |
| RoW | Rest of the world |
| RPIID | Recommended Phase II dose |
| RR | Respiratory rate |
| RT | Radiotherapy |
| SAE | Serious adverse event |
| SAF | Safety set |
| SAP | Statistical Analysis Plan |
| SAS | Statistical Analysis Software |
| SC | Steering Committee |
| SD | Stable disease |
| SmPC | Summary of product characteristics |
| SoC | Standard of care |
| SPDB | N-succinimidyl 4-(2-pyridyldithio)butyrate (reducible disulfide linker) |
| SPK | Superficial punctate keratitis |
| SQR RT | Square root (√) |
| SUSAR | Suspected, unexpected, serious adverse reaction |
| T1 | Tumor invades lamina propria |
| Ta | Non-invasive tumor |
| TEAE | Treatment-emergent adverse event |
| Temp | Body temperature |
| Tis | Carcinoma *in situ* |
| TMF | Trial master file |
| TTP | Time to progression |
| UK | United Kingdom |
| ULN | Upper limit of normal |
| US(A) | United States of America |
| VAS | Visual analogue scale |

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| WBC | White blood cell count |
| WOCBP | Women of childbearing potential |

# 3. Introduction

## 3.1 Background

Malignant pleural mesothelioma (MPM) is a locally invasive, usually fatal neoplasm arising from the mesothelial surfaces of the pleural cavity. The exact prevalence is unknown but it is estimated that mesotheliomas represent less than 1% of all cancers (1). A rare condition before 1950, its incidence rose following the increased use of asbestos with an expected peak in the next 10-20 years (2). Approximately 2500 new cases are recorded per year in the US (3) and the incidence of MPM shows marked variations from one country to another. Incidence is increasing in Russia, Western Europe (1.25/100000 per year in Great Britain, 1.1/100000 per year in Germany (4)), China and India. Mortality is highest in the UK, Netherlands, Australia; and is increasing in Japan, Argentina and Brazil (3). The link between occupational or environmental asbestos exposure and MPM was recognized in the early 1960s (5, 6). Since 1980 the use of asbestos was widely abandoned in the Western countries, but the incidence of MPM will continue to rise until approximately year 2020 (7) due to the long latency between asbestos exposure and development of MPM (8). Russia, China, Brazil and Canada are currently the top producers of asbestos (3).

Life expectancy in MPM is poor, with a median survival of approximately 1 year following diagnosis, also depending on the histological subtype (epithelioid and biphasic or mixed having a better prognosis than sarcomatoid), tumor stage and some patient-derived factors (general condition, age, weight loss, pain, platelets and asbestos exposure) (9). Typical presenting features of MPM are chest pain and dyspnea. Most people with MPM have pleural effusion evident on examination. Fatigue, profuse sweating, weight loss, anorexia and difficulty in swallowing become common as the disease progresses. The most suggestive computed tomography (CT) findings indicating malignant pleural disease are 1) a circumferential pleural rind, 2) nodular pleural thickening, 3) pleural thickening of > 1 cm and 4) mediastinal pleural involvement (10). Presentation and diagnosis often occur at an advanced stage and the prognosis for most patients is extremely poor (11).

### Treatment of MPM

Involvement of a multidisciplinary team is recommended to ensure prompt and appropriate management of disease, using a framework of radiotherapy, chemotherapy, surgery and symptom palliation with terminal care. However, few patients qualify for curative surgery, and the efficacy of radiotherapy is limited, hence the high need for effective systemic treatments. The combination of cisplatin and the antifolate pemetrexed proved superior to single cisplatin, respectively, in terms of overall survival (OS) (12.1 vs. 9.3 months), progression-free survival (PFS) (5.7 vs. 3.9 months), and response rate (41.3% vs. 16.7%) (12). The combination of cisplatin and pemetrexed is the worldwide current standard of care (SoC) for chemotherapy-naive patients (3). Data from the phase III, randomized, multicenter Mesothelioma Avastin Plus Pemetrexed-cisplatin Study (MAPS) (13) by the French Cooperative Thoracic Intergroup (IFCT) have been recently presented by Dr. Zalcman at 2015 ASCO annual meeting; this study was conducted to determine if the addition of bevacizumab 15 mg/kg every 3 weeks (Q3W) to standard cisplatin plus pemetrexed

chemotherapy would affect OS in patients with MPM. A total of 448 patients were enrolled, with 225 patients receiving SoC and 223 patients receiving bevacizumab plus SoC. In the intent-to-treat (ITT) population, the median OS in the bevacizumab arm was 18.8 months compared with 16.1 months in the SoC arm. Median PFS was 9.6 months in the bevacizumab arm compared with 7.5 months in the standard chemotherapy arm, also in the ITT population. Significantly more patients in the bevacizumab arm experienced Grade 3/4 events (71.2%) compared with standard chemotherapy arm (62.1%). In addition, significantly more Grade 3/4 hypertension (23.0% vs. 0%) and arterial and venous thrombotic events (5.8% vs. 0.9%) were reported in the bevacizumab arm. The overall conclusion was that the addition of bevacizumab to cisplatin and pemetrexed led to longer survival with acceptable toxicity in patients with MPM. However, discussant Dr. Nowak noted that whether the bevacizumab, cisplatin and pemetrexed triplet is widely adopted as a new SoC in this patient population will depend on several factors, particularly cost-effectiveness and reimbursement decisions made by health care systems in different parts of the world *(paragraph updated by amendment 2, see section 15.1.1.3)*.

There is no SoC for patients who relapse following a platinum-based treatment, as no single agent or combination has been shown to prolong survival. The largest study in relapsed patients with mesothelioma tested histone deacetylase (HDAC) inhibitor vorinostat against placebo (14). This Phase III study was conducted in 660 patients who had progressed after 1 or 2 systemic therapies, including cisplatin and pemetrexed. All patients received best supportive care, and were randomized to receive placebo or vorinostat 300 mg orally twice daily for 3 days each week of a 21-day cycle. There was no significant difference in median OS between the vorinostat and placebo groups (30.7 vs 27.1 weeks; hazard ratio 0.98; P = .858). Median PFS was comparable (6.3 vs. 6.1 weeks). Recently, another Phase III trial (NGR015) of NGR-hTNF plus best investigator choice (BIC) *versus* placebo plus BIC failed to meet the primary endpoint in 400 subjects enrolled: no OS benefit was found in previously treated patients in the experimental arm (median 8.4 vs 7.9 months) (15). Pemetrexed (if not given in 1$^{st}$ line), can be used in a 2$^{nd}$ line setting with median PFS and median OS of 3.6 and 8.4 months, respectively (16). Among other drugs used as single agents or in combination in MPM are vinorelbine and gemcitabine. The Phase II study to assess the safety and efficacy of weekly vinorelbine (30 mg/m$^2$ for 6 weeks) in 63 pre-treated patients showed an objective response rate (ORR) of 16% and an OS of 9.6 months (95% confidence interval: 7.3 - 11.8 months) (17). The main Grade 3/4 toxicity observed was neutropenia. Toxicity was similar to weekly vinorelbine when used in the 1$^{st}$ line setting. The authors concluded that weekly vinorelbine appeared to have a reasonable response rate with an acceptable toxicity profile in the 2$^{nd}$ line treatment of MPM (17). A Phase II study of gemcitabine monotherapy for 10 cycles (a 30-minute intravenous [IV] administration of 1250 mg/m$^2$ on Days 1, 8, and 15 of a 28-day cycle) involved 27 chemotherapy-naive patients (18). Neutropenia of ≥ Grade 3 occurred in 30% of patients, without episodes of febrile neutropenia. One case of hemolytic-uremic syndrome, most likely related to gemcitabine use, was observed. Overall, 2 objective responses were observed (ORR of 7%; 95% confidence interval: 1 - 24%) and the median OS was 8 months. The authors concluded that gemcitabine has limited activity in MPM.

### 3.1.1 Anetumab ravtansine (BAY 94-9343)

Anetumab ravtansine (BAY 94-9343) is an antibody-drug conjugate (ADC) targeting mesothelin, a protein normally present on mesothelial cells and overexpressed in the majority of mesotheliomas (both epithelioid and mixed histology for MPM), ductal pancreatic adenocarcinomas and adenocarcinomas of the ovary. The expression profile as well as the fact that mesothelin is an internalizing antigen suggest mesothelin as an adequate target for antibody-mediated delivery of cytotoxics. The biological function of mesothelin is unknown; mesothelin-deficient mice do not display a specific phenotype (19).

Anetumab ravtansine is composed of the human anti-mesothelin-monoclonal antibody BAY 86-1903 and the maytansinoid DM4 (BAY 100-6640), conjugated by a disulfide linker moiety to lysine residues of the antibody. DM4 is a spindle poison, and its mechanism of action (MoA) is inhibition of microtubule assembly (similar to that of vinca alkaloids).

*In vivo*, anetumab ravtansine showed potent inhibition of the growth of the human mesothelioma NCI-H226 cells (20). In a mouse xenograft model (subcutaneous NCI-H226), 2 cycles of triple IV inoculations of 0.2 mg/kg anetumab ravtansine (related to the concentration of DM4) significantly reduced tumor growth compared with the vehicle control (94%, $P < 0.001$) and achieved a 63% response rate (partial response [PR] in 5 out of 8 mice). In contrast, treatment with free active methyl-DM4 (DM4-Me) did not affect tumor growth significantly. Direct comparison of anetumab ravtansine at 0.2 mg/kg with cisplatin plus pemetrexed revealed a significantly higher efficacy of anetumab ravtansine, as cisplatin alone and in combination with pemetrexed resulted in 70% reduction of tumor growth ($P < 0.01$). The treatment groups were also compared by measuring the tumor weight at the end of the study: treatment with anetumab ravtansine resulted in a 14-fold lower tumor weight as compared with the combination of cisplatin and pemetrexed ($P < 0.05$).

Anetumab ravtansine has convincingly demonstrated monotherapy anti-tumor efficacy also in preclinical patient-derived xenograft (PDX) MPM tumor models (20). Evaluation of anetumab ravtansine in PDX models demonstrated tumor shrinkage and regression superior to several chemotherapies currently being used for the treatment of MPM in humans. Only 3 administrations of anetumab ravtansine at 0.2 mg/kg resulted in at least partial tumor regression in all mice using a Meso7212 PDX mesothelioma model ($P < 0.001$). Comparison with SoC revealed that the anti-tumor efficacy of anetumab ravtansine was more pronounced than cisplatin ($P < 0.05$) and pemetrexed ($P < 0.001$). The difference between the effects of a microtubule-targeting drug vinorelbine and anetumab ravtansine was not significant.

Further details can be found in the latest available version of the investigator's brochure (IB), which contains comprehensive information on the study drug.

### 3.1.2 Clinical experience

As of 18 JAN 2014, a total of 77 patients with advanced refractory solid tumors expressing mesothelin have been treated with the anti-mesothelin ADC anetumab ravtansine given as a single agent by 1-hour IV infusion in the Phase I First in Human (FiH) 15051 study with a Q3W schedule. Additional cohorts of patients have been enrolled in the 1.8 mg/kg or 2.2 mg/kg once weekly (QW) regimen.

The dose-escalation part of the FiH study 15051 was completed in FEB 2013 with 45 patients evaluated in 10 cohorts spanning the dose range from 0.15 mg/kg to 7.5 mg/kg given by 1-hour IV infusion Q3W. The maximum tolerated dose (MTD) was defined as 6.5 mg/kg Q3W. Subsequently 2 expansion cohorts (n=32) were treated at 6.5 mg/kg Q3W.

A total of 32 males and 45 females were treated, with a mean age of 61.4 years. Within the escalation cohorts (total 45 patients) the most common cancers were mesothelioma (n=21), pancreatic (n=9), breast (n=5), and ovarian cancer (n=4) whilst in the 6.5 mg/kg Q3W expansion cohorts (total 32 patients) patients had ovarian cancer (n=20) or mesothelioma (n=12).

Following IV administration, maximum ADC concentrations were typically observed around the end of infusion or within 1 h after the end of infusion. The pharmacokinetics (PK) parameters of interest, maximum drug concentration ($C_{max}$) and area under the curve (AUC) of the ADC, generally increased in a dose proportional manner in the 0.15 mg/kg to 7.5 mg/kg dose range studied. At the MTD, average half-life values of the ADC, total antibody and DM4-Me were approximately 5 to 6 days, and approximately 3 days for DM4, generally consistent with the range of half-life values reported for biologics and with no accumulation expected after Q3W dosing.

20 (53%) of 38 patients who started treatment at the MTD of 6.5 mg/kg Q3W had at least 1 dose modification due to a treatment-emergent adverse event (TEAE) deemed by the investigator to be causally related to anetumab ravtansine; 8 (40%) had the first dose modification in response to drug-related corneal morphology changes, and 7 (35%) had the first dose reduction due to drug-related peripheral neuropathy or symptoms commonly associated with it. 18 (90%) of 20 patients had a dose reduction to 5.5 mg/kg Q3W, and 5 (28%) of these 18 had another dose reduction to 4.5 mg/kg Q3W; both dose reductions were caused by a drug-related TEAE. It should be noted that none of the drug-related TEAEs that led to dose delay/interruption or dose reduction have been life-threatening or incapacitating, and all have been either fully reversible or resolved to a less severe grade upon interruption; very few drug-related TEAEs required permanent discontinuation of treatment. Nevertheless, only 3 (9%) of 35 patients who started treatment at doses ≤ 6.5 mg/kg Q3W had a dose modification due to a drug-related TEAE, and none of those required a dose reduction.

A significantly higher incidence of dose modifications due to drug-related TEAEs at the MTD of 6.5 mg/kg Q3W could be at least in part explained by the much longer drug exposure (duration of time on treatment) in patients who start treatment at this dose. The ORR, as determined by the incidence of PR, was notably better in patients who started at 6.5 mg/kg Q3W. 7 (18%) of 38 patients who started at 6.5 mg/kg Q3W had a long-lasting PR; these included 2 (10%) of 21 patients with ovarian cancer and 5 (31%) of 16 patients with mesothelioma (4 with pleural and 1 with peritoneal epithelial mesothelioma). 11 of the 16 patients with mesothelioma (8 with pleural mesothelioma and 3 with peritoneal mesothelioma) had received only 1 previous line of systemic cytotoxic chemotherapy before enrolling in the study. 5 of 11 patients in this group (45%) had a confirmed PR (4 PRs in pleural mesothelioma patients and 1 PR in peritoneal mesothelioma patients), which lasted for 11 months in 1 patient and ≥ 20 months in the other 4 patients.

Objective tumor responses persisted in 6 of 7 patients with PR in whom the starting dose of 6.5 mg/kg Q3W had to be reduced to 5.5 mg/kg Q3W due to a drug-related TEAE, and even in 2 of 4 patients who required a second dose reduction to 4.5 mg/kg Q3W due to another related TEAE. In contrast, none of the 35 patients who started at doses < 6.5 mg/kg Q3W had a PR, and only 1 of 9 patients who started at 5.5 mg/kg Q3W had an unconfirmed PR. If patients were to start treatment at doses < 6.5 mg/kg Q3W, the potential for clinical benefit could be reduced despite the lower risk of dose modification due to a drug-related TEAE.

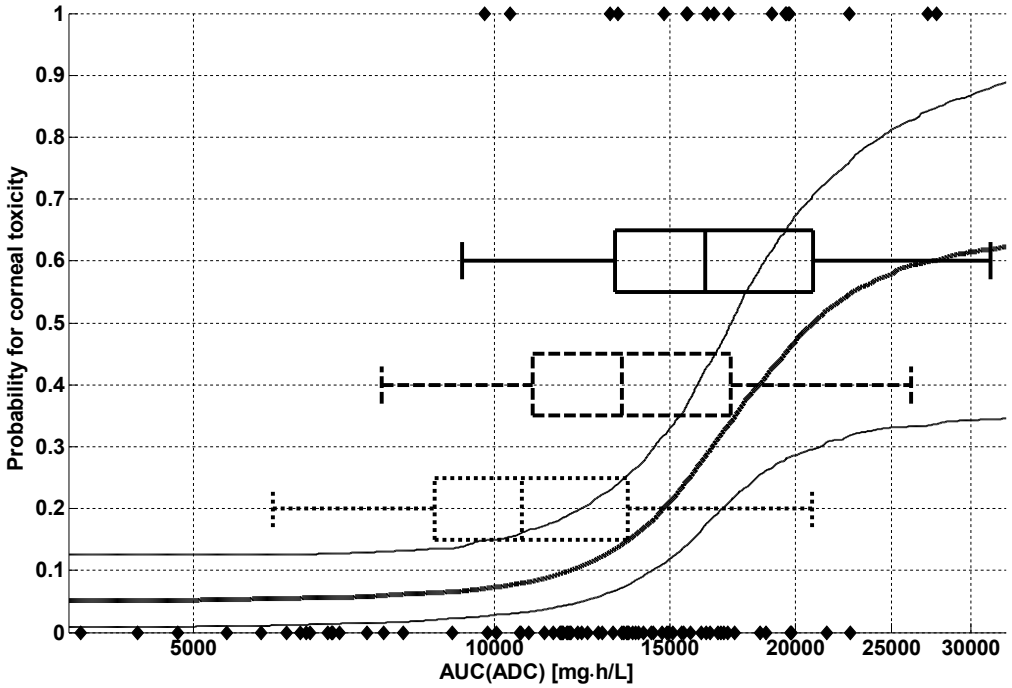
Objective responses or prolonged SD occurred only in patients with strong mesothelin expression (e.g. MPM of epithelioid and mixed histology).

Data from 15051 study indicate an overall acceptable and manageable safety profile. At the MTD of 6.5 mg/kg Q3W, the most common TEAEs that were assessed to be related to anetumab ravtansine were corneal epitheliopathy, peripheral neuropathy, myalgia, weakness, fatigue, anorexia, nausea, vomiting and diarrhea. The incidence of treatment-emergent serious adverse events (SAEs) that were considered to be related to anetumab ravtansine was low in all patients. There were no drug-related deaths throughout the study.

The safety finding of particular interest at the 6.5 mg/kg Q3W dose has been the corneal epitheliopathy and keratitis with and without blurred vision probably related to anetumab ravtansine: 11 of 38 patients (29%) developed corneal adverse events (AEs). None of these events affected the deep corneal stroma or were considered serious or led to drug discontinuation and all events were reversible.

Furthermore, population, physiologically-based pharmacokinetic (PopPBPK) modeling of preliminary data from the FiH study 15051, combined with a probabilistic regression analysis provided evidence that the area under the ADC plasma concentration-time curve at steady state, AUC(ADC), is a descriptor for the occurrence of corneal epitheliopathy, as shown in Figure 3–1. Based on the on average linear PK of anetumab ravtansine (see above in this section), it can be assumed that dose reduction will lead to a reduced total drug exposure, i.e. AUC(ADC), and thus, also to a reduced probability of corneal epitheliopathy (see Figure 3–1) *(paragraph and Figure 3-1 added by amendment 2, see section 15.1.1.23)*.

**Figure 3–1 Probability of corneal epitheliopathy versus model-predicted drug exposure –** ***figure added by amendment 2***




ADC = Antibody-drug conjugate; AUC = Area under the curve; N = Number of patients; PopPBPK = Population, physiologically-based pharmacokinetic; Q3W = Every 3 weeks
Drug exposure versus the probability of corneal toxicity relationship with AUC(ADC) equals the PopPBPK model-predicted area under the anetumab ravtansine plasma concentration-time curve at steady state.
The solid line indicates the median estimate and the thin lines represent the 90% confidence interval; data used for logistic regression model development are shown as diamonds.
The box plots represent simulated AUC(ADC) distributions in a virtual population of N=1000 subjects receiving either 4.5 mg/kg (dotted box), 5.5 mg/kg (dashed box) or 6.5 mg/kg (solid box) anetumab ravtansine given Q3W.

The other identified risks so far include peripheral neuropathy, liver function test increases and hypersensitivity reaction. In the Q3W MTD dose level, 16 of 38 patients (42%) experienced peripheral neuropathy and associated disorders (muscle spasms and cramps, gait disorder etc.); all but 1 case were Common Terminology Criteria for Adverse Events (CTCAE) Grade 1 or 2, 1 patient developed a Grade 3 event. It commonly led to dose interruption and reduction but it did not cause treatment discontinuation. The elevation on liver function test values was observed in patients treated at 6.5 mg/kg Q3W: aspartate aminotransferase (AST) increase in 7 patients (18%, with only 1 Grade 3, 3%), alanine aminotransferase (ALT) increase in 5 patients (13%, with no Grade 3), alkaline phosphatase (ALP) increase in 4 patients (10%, with only 1 Grade 3), and total bilirubin increase in 1 patient (3%, with no Grade 3). Only 1 patient required dose reduction due to drug-related Grade 3 AST increase. Finally, only 1 patient was reported with an infusion-related reaction (Grade 2) at the Q3W 6.5 mg/kg dose level.

In summary, anetumab ravtansine has demonstrated durable ORR when given at the MTD of 6.5 mg/kg Q3W in refractory metastatic mesothelioma. This preliminary potential for clinical benefit in an unmet medical need indication and overall safety profile lead to the selection of 6.5 mg/kg Q3W as the starting dose for anetumab ravtansine in the 2nd line treatment of patients with unresectable or metastatic pleural mesothelioma in this study.

No results are available from human interaction studies between anetumab ravtansine and other chemotherapies. No data are available to evaluate the potential interaction between anetumab ravtansine and radiation treatment.

Updated information on the safety profile including results from this study are available in the latest available version of the investigator's brochure (IB), which contains comprehensive information on the study drug *(sentence added by amendment 6, see section 15.4.1.5)*.

## 3.2 Rationale of the study

At the MTD of 6.5 mg/kg Q3W, anetumab ravtansine has demonstrated very strong efficacy in advanced, unresectable or metastatic epithelial mesothelioma (best objective response 31% overall or 45% in the 2nd line setting, with very durable responses) in a Phase I expansion cohort. Such high response rate and long lasting responses, if repeatable, would translate to the potential for anetumab ravtansine to impart large clinical benefit as the 2nd line treatment for advanced mesothelioma, which represents an indication of high unmet medical need for effective treatment options, as currently no approved SoC exists *(paragraph clarified by amendment 4, see section 15.2.1.19)*.

## 3.3 Benefit-risk assessment

Preliminary results from the ongoing 15051 FiH study demonstrated anti-tumor efficacy of anetumab ravtansine monotherapy in patients with MPM previously treated with platinum-based chemotherapy. Of the 38 patients treated at the MTD dose level of 6.5 mg/kg Q3W, 16 patients had mesothelioma, including 11 patients (8 with pleural mesothelioma and 3 with peritoneal mesothelioma) who received anetumab ravtansine as 2nd line treatment. Of these, 5 patients obtained PR as best objective response (4 PRs in pleural mesothelioma patients and 1 PR in peritoneal mesothelioma patients). 4 patients with objective responses and SD cases showed long response durations (> 20 months on study and ongoing).

Data from the ongoing 15051 FiH study indicate an overall acceptable and manageable safety profile. Drug-related TEAEs requiring dose reduction and/or interruption have been reported in approximately half of the patients treated at the MTD of 6.5 mg/kg Q3W (1 patient in cohort 9 and 16 patients in the expansion 6.5 mg/kg Q3W cohort). Treatment discontinuations due to drug-related TEAEs were rare. At the dose of 6.5 mg/kg Q3W, the safety finding of particular interest has been the corneal epitheliopathy in 11 patients; however, none of these events affected the deep corneal stroma or were considered serious or led to drug discontinuation and all events were fully reversible. An action plan has been developed for corneal epitheliopathy early detection and monitoring; prophylactic measures have been implemented (e.g. entry criteria, ocular lubricants, steroid eye drops) and a management algorithm including effective eye treatment and anetumab ravtansine dose adjustments has been set up in close collaboration with Bayer ophthalmologists (see Table 7–5). The other

TEAEs that would require diligent monitoring and management are hypersensitivity reaction, liver function abnormalities and peripheral neuropathy; however, these disorders were not either life-threatening and have been manageable and fully reversible and responded to dose reduction and/or symptomatic therapy.

In summary, a strong potential efficacy signal was obtained in the Phase I study (15051) in patients with mesothelioma treated with Q3W 6.5 mg/kg anetumab ravtansine. No approved SoC exists for 2nd line MPM, and drugs currently being used show a very limited response rate (16%) and a median PFS limited to 3.6 months (16). At the current state, 2nd line malignant mesothelioma is an indication of high unmet medical need for effective treatment options. Based on the available preclinical and clinical data, anetumab ravtansine has the potential to become the SoC in the 2nd line mesothelioma indication by significantly prolonging PFS and OS.

The overall safety profile of anetumab ravtansine is consistent with the employed class of toxophores and the underlying MoA. Most, if not all, reported AEs were manageable with short delays in drug administration and dose reductions. Therefore, the expected improvement in PFS, as seen in the Phase I FiH study, represents an important benefit that exceeds the risk from observed treatment-emergent adverse reactions.

The present study is acceptable after considering the risks and benefits associated with it.

# 4. Study objectives

The primary objective of this study is to:

- Test the superiority of anetumab ravtansine monotherapy over vinorelbine in progression-free survival (PFS)

The secondary objectives of this study are to:

- Test overall survival (OS)

  *Secondary objective related to pulmonary function removed by amendment 2*

- Evaluate patient-reported outcomes (PROs) – symptom burden and health-related quality of life (QoL)
- Evaluate other indicators of treatment efficacy (indicators of tumor response)
- Evaluate safety

The other objectives of this study are to evaluate the:

- Pharmacokinetics (PK)
- Immunogenicity
- Biomarkers
    - Further biomarkers to investigate the drug (i.e. mode-of-action-related effect and / or safety) and / or the pathomechanism of the disease (exploratory).

# 5. Study design

## 5.1 Design overview

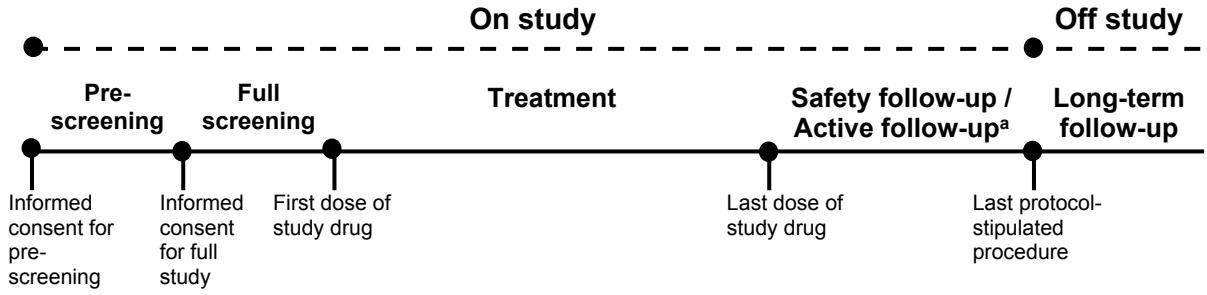
This is a randomized, open-label, active-controlled, 2-arm, multicenter, Phase II trial to evaluate the safety and efficacy of anetumab ravtansine as a single agent administered as an IV infusion Q3W in comparison to IV vinorelbine given according to the usual QW schedule.

At the time of the start of study treatment, the patients will have advanced or metastatic MPM recurrent/relapsing after a 1st line treatment with platinum in combination with pemetrexed with or without bevacizumab, and overexpressing mesothelin as determined by immunohistochemistry (IHC). Only patients who demonstrate mesothelin overexpression at the moderate and stronger membrane staining level by IHC in at least 30% of viable tumor cells can be randomized into the study *(modified by amendments 2 and 5, see section 15.1.1.6 and 15.3.1.2)*.

A prescreening step, including the mesothelin expression level testing, can be performed without evidence of disease progression after the initial treatment cycles with platinum/pemetrexed (with or without bevacizumab) at the investigator's discretion.

The overview of study periods is presented in Figure 5–1.

**Figure 5–1 Study periods**

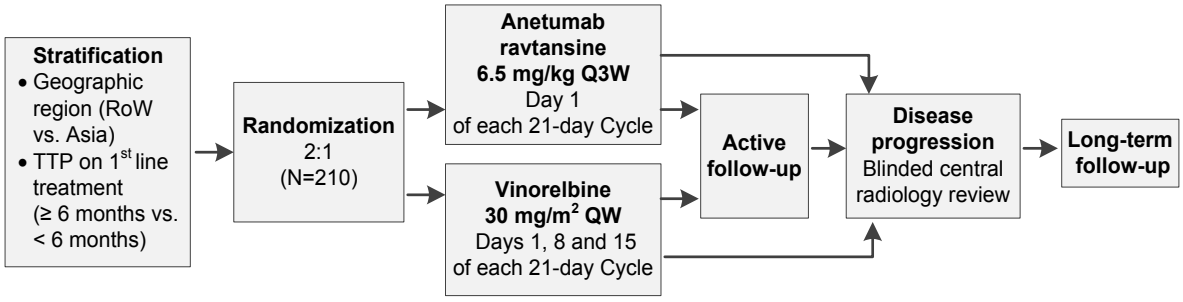



a If applicable.

The start of the study is defined by signing of the informed consent form (ICF) for prescreening. After meeting the eligibility criteria for prescreening and signing the ICF for full study (see Sections 6.1 and 6.2), approximately 210 patients who meet all of the inclusion and none of the exclusion criteria will be randomly assigned in a 2:1 ratio to receive anetumab ravtansine or vinorelbine, respectively. The anetumab ravtansine arm will consist of approximately 140 patients and the vinorelbine comparator arm of approximately 70 patients. Patients will be stratified at randomization according to geographic region (Rest of the world [RoW] *versus* Asia) and per time to progression (TTP) on 1st line treatment (≥ 6 months *versus* < 6 months). An approximately 50% screen fail rate is anticipated (25% at prescreening and a subsequent 33% among biomarker expressers). Approximately 420 patients are estimated to be required for prescreening to yield approximately 263 biomarker-positive patients, resulting in 210 randomized eligible patients (*paragraph modified by amendments 2 and 4, see section 15.1.1.2, 15.1.1.7 and 15.2.1.2*).

A graphical presentation of the overall study design is shown in Figure 5–2 *(figure modified by amendment 2, see section 15.1.1.2)*.

**Figure 5–2 Overall study design - amended**




N = Number of patients; Q3W = Every 3 weeks; QW = Once weekly; RoW = Rest of the world, TTP = Time to progression

The start of the treatment period is defined for efficacy purposes by randomization to study drug (anetumab ravtansine or vinorelbine), and for safety purposes by first administration of study drug. Start of treatment has to be within 24 hours after the randomization call. Patients in the anetumab ravtansine arm will receive anetumab ravtansine IV infusion at a dose of 6.5 mg/kg (recommended Phase II dose [RPIID]) on Day 1 of a 21-day cycle. Patients in the comparator arm will receive vinorelbine 30 mg/m$^2$ IV on Days 1, 8 and 15 of a 21-day cycle. Treatment will be continued until death or occurrence of PD as defined by Modified Response Evaluation Criteria in Solid Tumors (mRECIST) for mesothelioma (21) and assessed by blinded central radiology review, or clinical progression, or until another criterion for withdrawal from the study is met. In case of radiological progression, however, treatment may be continued provided that the patient derives clinical benefit as determined by the treating physician *(paragraph modified by amendment 2, see section 15.1.1.4, 15.1.1.19 and 15.1.1.22)*.

All patients who discontinue study treatment for any reason will enter the safety follow-up period. Safety follow-up visit will be performed 30 (+7) days after the last administration of study treatment.

Patients who discontinue study treatment for any reason other than centrally confirmed radiological PD will be followed for progression during active follow-up (which includes the safety follow-up period) until data maturation for the OS final analysis is reached (i.e. completion of number of events required for OS analysis), or until centrally confirmed progression, death, consent withdrawal or end of study, whichever occurs first *(modified by amendment 6, see section 15.4.1.1)*.

All patients who end study treatment for any reason will be followed for OS and any new anti-cancer treatment every 3 months during the long-term follow-up period until death, consent withdrawal, 24 months after the last patient's last treatment or end of study, whichever occurs first *(modified by amendment 6, see section 15.4.1.2)*.

Primary efficacy will be assessed based on radiological tumor evaluation by contrast-enhanced CT or contrast-enhanced magnetic resonance imaging (MRI) of chest/abdomen/pelvis (see Section 9.4.1). The first tumor images will be obtained during full screening and will be sent to blinded central review to confirm radiological eligibility prior to randomization *(modified by amendment 2, see section 15.1.1.15)*. During treatment as well as active follow-up, tumor imaging will be performed with the same modality every 6 weeks during the first 6 months after the start of study treatment, every 9 weeks until the end of year 2, and every 12 weeks thereafter, until the earlier of centrally confirmed radiological disease progression, OS analysis data maturation, or end of study *(modified by amendment 6, see section 15.4.1.1)*. Primary analysis results will be based on central review.

*Description of forced vital capacity removed by amendment 2*

Patients will be contacted to assess survival status every 3 months during long-term follow-up (see Section 9.4.2). In addition, extra survival sweep contacts will be conducted at the time of PFS final analysis and prior to OS final analysis to ensure that long-term follow-up data is current.

The effect of treatment on disease-specific symptoms and disease-specific health-related QoL will be assessed using the MD Anderson Symptom Inventory-Malignant Pleural Mesothelioma (MDASI-MPM) and the Lung Cancer Symptom Scale-Mesothelioma (LCSS-Meso), respectively, at full screening, at each cycle during treatment, at the safety follow-up visit, and during active follow-up as per Section 9.4.3 *(clarified by amendment 4, see section 15.2.1.17)*.

Safety evaluations will be done at full screening, at each clinic visit during the treatment, and at the safety follow-up visit as described in Section 9.6. The National Cancer Institute's Common Terminology Criteria for Adverse Events (NCI-CTCAE) version 4.03 will be used to grade severity of AEs. In addition, a Bayer grading system (see Table 7–5 and Table 7–6) will be used to assess corneal epitheliopathy *(sentence added by amendment 2, see section 15.1.1.26)*.

Sparse plasma sampling for PK will be performed on all patients as outlined in Section 9.5.

Immunogenicity assessment will be performed for patients in the anetumab ravtansine arm only as outlined in Section 9.7.2.

Obligatory biomarker sampling (see Section 9.7.1) will be performed on all patients to measure mesothelin expression levels in tumor material at prescreening. In addition, plasma levels of soluble mesothelin will be studied to evaluate whether plasma mesothelin levels may correlate with response rate and be of predictive value. Biomarker plasma will be collected to analyze circulating tumor DNA, too. Exploratory biomarker analysis may also be performed using additional fresh or archival tumor tissue to determine alterations in tumor-associated genes and to perform gene expression analysis *(modified by amendment 4, see section 15.2.1.11)*.

Following OS data maturation, patients remaining on study will continue to be followed with reduced mandated assessments and data collection (although assessments can continue per

investigator's judgement). Active follow-up, efficacy, and some safety assessments will no longer be required *(paragraph added by amendment 6, see section 15.4.1.1)*.

## 5.2 Primary variable

The primary variable of this study is progression-free survival (PFS) defined as time from randomization until disease progression (according to mRECIST for MPM, per blinded central radiology review) or death (for full definition, see Section 10.3.2 and Statistical Analysis Plan [SAP]).

## 5.3 Justification of the design

**Level of blinding.** This Phase II study will be open-label (see Section 7.5), because a double-blind, active-controlled study is not feasible due to different administration schedules, Q3W for anetumab ravtansine and QW for vinorelbine, and different safety profiles (e.g. corneal epitheliopathy *(modified by amendment 2, see section 15.1.1.5*) for the anetumab ravtansine arm and neutropenia for the comparator [vinorelbine] arm). The independent and central radiological review for the assessment of disease progression and other radiological imaging-based endpoints will be conducted in a blinded fashion. In addition, an independent PRO review committee of PRO, statistical, and psychometric experts, will conduct analyses in a blinded fashion to support validation of the MDASI-MPM instrument and determine endpoint definitional details *(sentence added by amendment 4, see section 15.2.1.16)*.

**Dosage.** At the RPIID of 6.5 mg/kg Q3W, anetumab ravtansine has demonstrated very strong efficacy in advanced, unresectable or metastatic epithelial mesothelioma (best objective response 31% overall or 45% in the 2$^{nd}$ line setting, with very durable responses) (see Section 3.1.2). Moreover, no drug-related deaths, only 5 drug-related SAEs and a low rate of drug-related Grade 3/4 AEs were reported from clinical experience with anetumab ravtansine at the RPIID. Based on the drug exposure corneal epitheliopathy relationship (see Section 3.1.2 and Figure 3–1) and the average linear PK of anetumab ravtansine, it can be assumed that dose reduction planned in this Phase II study will lead to a reduced total drug exposure, and thus, to a reduced probability of corneal epitheliopathy *(sentence modified by amendment 2, see section 15.1.1.5 and 15.1.1.23)*.

**Comparator.** Vinorelbine (see Section 7.2.2) is one of the drugs considered by various guidelines (e.g. National Comprehensive Cancer Network [NCCN], European Society of Medical Oncology [ESMO]) as a potential option for patients with advanced mesothelioma progressed after treatment with platinum and pemetrexed. Mechanistically, it is a spindle poison, therefore comparable with DM4.

**Study population.** Objective responses or prolonged SD cases in the 15051 study of anetumab ravtansine occurred in patients who demonstrated mesothelin overexpression at the moderate and stronger membrane staining level by IHC in at least 30% of viable tumor cells *(modified by amendments 2 and 5, see section 15.1.1.6 and 15.3.1.2)*. Because of the treatment's surface mesothelin targeting MoA, no clinical efficacy is expected in MPM patients with little or no mesothelin cell surface expression. Patients with a sarcomatoid histology are not expected to have mesothelin overexpression and should not enter

prescreening. Therefore, pre-selection based on mesothelin expression (see Section 6.1.1) is intended during recruitment of this study.

**Regimen/schedule of administration.** The choice of schedule (see Section 7.4.1.1) is based on exposure-response analysis based on clinical PK, efficacy and safety results from the 77 patients treated with anetumab ravtansine on the Q3W schedule in the study 15051 and, moreover, from the 38 patients treated with the MTD in the 6.5 mg/kg Q3W escalation cohort 9 (n=6) and the RPIID of 6.5 mg/kg Q3W expansion cohort (n=32).

**Randomization**. A 2:1 randomization ratio is used to provide an adequate safety database for evaluating anetumab ravtansine safety. This ratio also encourages study participation by providing an elevated probability of receiving experimental treatment. The sample size is adequate for efficacy, and the safety of vinorelbine is well-studied. The sample size includes a dropout rate of 3.4%/month (15.7% as of planned primary analysis) to address the possibility of dropouts (see Section 11.4) *(paragraph modified by amendment 2, see section 15.1.1.2)*.

For justification of study endpoints and measurements, see Section 9.8 *(cross-reference added by amendment 2, see section 15.1.1.26)*.

For **strategies to limit the amount and impact of missing data**, see Section 11.4.

### 5.4 End of study

*Section modified by amendment 6, see section 15.4.1.3.*

For each participating EU country, the end of the study according to the EU Clinical Trial Directive will be reached when the last visit of the last patient for all centers in the respective country has occurred within this study.

As for this study, important data will be collected after LPLV, the end of the study as a whole will be the date when the final clean database is available.

If the trial is stopped but benefits are observed for individual subjects and/or follow up of subjects is needed; treatment and/or follow up may be continued in a separate program upon agreement among the investigators, the sponsor, and appropriate regulatory authorities. Survival follow-up offered in a separate program will be offered to all surviving consenting patients.

### 5.5 Primary completion

Primary analysis will be performed after approximately 117 PFS events are observed by central review in the study *(clarified by amendment 2, see section 15.1.1.26)*.

The primary completion date for this study according to the FDA Amendment Act is specified in a separate document (not part of this study protocol).

## 6. Study population

### 6.1 Inclusion criteria

Patients eligible for inclusion into the study must meet the following inclusion criteria.

### 6.1.1 Eligibility criteria for prescreening

Overexpression of mesothelin at the moderate and stronger membrane staining level in at least 30% of viable tumor cells is a prerequisite to be eligible for this study *(modified by amendments 2 and 5, see section 15.1.1.6 and 15.3.1.2)*. Patients can only be randomized and start treatment in the study when there is a progression after 1st line treatment of platinum/pemetrexed (with or without bevacizumab). However, as part of prescreening, mesothelin expression level testing can be performed at the investigator's discretion as soon as the initial 1st line treatment cycles with platinum/pemetrexed (with or without bevacizumab) are administered, even without evidence of disease progression. Also if patients have ended this 1st line treatment and have not progressed yet, the mesothelin expression level test can be performed. The following criteria must be met at the time of prescreening.

1. Written informed consent for prescreening.
2. Unresectable locally advanced or metastatic MPM, confirmed by histology.
3. Availability of archival or fresh tissue for testing of mesothelin expression level.

   Note: Archival tissue is preferred and fresh biopsy should only be obtained if no archival tissue is available and if in the investigator's judgement, there is no additional risk for the patient's safety. Patients with a sarcomatoid histology are not expected to have mesothelin overexpression and should not enter prescreening.
4. Age ≥ 18 years (age limit may be higher if legally required in a country, e.g. in Japan adult age is considered ≥ 20 years).
5. Eastern Cooperative Oncology Group Performance Status (ECOG PS) of 0 or 1 (specified in Appendix 16.1).
6. Life expectancy of at least 3 months.
7. No prior treatment with anetumab ravtansine (or any other mesothelin-based therapy) or vinorelbine (or any other vinca-containing compound or spindle poison).
8. No prior use of targeted agents, experimental therapy or systemic anti-cancer treatment other than ongoing or completed 1st line platinum/pemetrexed (with or without bevacizumab).

**Besides these basic criteria, any criterion as outlined below under inclusion eligibility criteria for full study and exclusion criteria already known to prohibiting the patient's participation in the study should be considered. No study-related procedures should be performed which are not covered by the prescreening ICF.**

### 6.1.2 Eligibility criteria for full study

The following inclusion criteria must be met at the time of randomization call and on C1D1 unless otherwise specified *(this sentence was clarified by amendment 2, see section 15.1.1.19 and 15.1.1.26)*.

1. Written informed consent for full study.
2. Histological documentation of MPM overexpressing mesothelin at the moderate and stronger membrane staining level in at least 30% of viable tumor cells as determined by centrally performed IHC *(modified by amendments 2 and 5, see section 15.1.1.6 and 15.3.1.2)*.
3. Unresectable locally advanced or metastatic MPM after locally confirmed unequivocal progression on 1st line treatment with platinum (both cis- or carbo-platinum) in combination with pemetrexed. Last dose of previous therapy must be at least 28 days before the start of study treatment *(modified by amendment 4, see section 15.2.1.3)*.

   Note: Patients progressed on 1st line treatment with platinum plus pemetrexed in combination bevacizumab are allowed (13).
4. Patients must have at least 1 measurable lesion according to mRECIST for mesothelioma (specified in Appendix 16.3) i.e. pleural lesion(s) measured using mRECIST or extra-pleural lesion(s) measurable per RECIST 1.1. This will be confirmed by central review of images before the patient can be randomized into the study.

   Note: In case the only site of disease was previously treated with radiotherapy, there should be evidence of unequivocal PD in this site: measurable pleural disease should be assessed on a contrast enhanced CT/MRI done at the minimum 4 weeks after the end of radiotherapy and compared with previous imaging; unequivocal progression should be judged by the investigator as per mRECIST per MPM *(criterion 4 modified by amendment 2, see section 15.1.1.8 and 15.1.1.26)*.
5. ECOG PS of 0 or 1 (specified in Appendix 16.1).
6. Life expectancy of at least 3 months.
7. Women of childbearing potential (WOCBP) and fertile men must agree to use adequate contraception when sexually active from signing of the ICF for full study until at least 4 months after the last study drug administration. Men being treated with vinorelbine are advised not to father a child during and up to 6 months after treatment; for all male patients, prior to treatment with either study drug, advice should be sought for conserving sperm due to the chance of irreversible infertility as a consequence of treatment (22). The investigator or a designated associate is requested to advise the patient how to achieve highly effective birth control. Highly effective (failure rate of less than 1% per year) contraception methods (23) include:

   - Combined (estrogen and progesteron containing: oral, intravaginal, transdermal) and progesteron-only (oral, injectable, implantable) hormonal contraception associated with inhibition of ovulation.

- Intrauterine device (IUD) or intrauterine hormone-releasing system (IUS).
- Bilateral tubal occlusion or vasectomized partner (provided that partner is the sole sexual partner and has received medical assessment of the surgical success).
- Sexual abstinence (reliability to be evaluated in relation to the duration of the clinical trial and the preferred and usual lifestyle of the patient).

Male patients with a female partner of childbearing potential must use a condom and ensure that an additional form of contraception is also used during treatment and until 4 months after last study drug administration.

Note: a woman is considered WOCBP, i.e. fertile, following menarche and until becoming postmenopausal unless permanently sterile. Permanent sterilization methods include but are not limited to hysterectomy, bilateral salpingectomy and bilateral oophorectomy. A postmenopausal state is defined as no menses for 12 months without an alternative medical cause. A high follicle stimulating hormone (FSH) level in the postmenopausal range may be used to confirm a postmenopausal state in women not using hormonal contraception or hormonal replacement therapy. A man is considered fertile after puberty unless permanently sterile by bilateral orchiectomy (*criterion 7 modified by amendment 2, see section 15.1.1.9*).

8. Adequate bone marrow, liver and renal function as assessed by the following laboratory requirements conducted within 7 days before starting study treatment:

- Total bilirubin ≤ 1.5 x the upper limit of normal (ULN). Documented Gilbert syndrome is allowed if total bilirubin is mildly elevated (< 6 mg/dL).
- ALT and AST ≤ 3 x ULN (≤ 5 x ULN for patients with liver involvement of their cancer).
- ALP limit ≤ 2.5 x ULN (≤ 5 x ULN for patients with liver involvement of their cancer).
- Amylase and lipase ≤ 1.5 x ULN.
- Serum creatinine ≤ 1.5 x ULN.
- Glomerular filtration rate (GFR) ≥ 30 mL/min/1.73 $m^2$ according to the Modification of Diet in Renal Disease (MDRD) abbreviated formula (see Appendix 16.7).
- Adequate coagulation, as assessed by the following laboratory test results:
    - International normalized ratio (INR) or prothrombin time (PT) ≤ 1.5 x ULN (CTCAE Grade ≤ 1).
    - Partial thromboplastin time (PTT) or activated PTT (aPTT) ≤ 1.5 x ULN (CTCAE Grade ≤ 1).

      Note: Patients on stable dose of anti-coagulation therapy will be allowed to participate if they have no sign of bleeding or clotting and INR / PT and

PTT / aPTT test results are compatible with the acceptable benefit-risk ratio at the investigator's discretion (see Section 8.1).

- Platelet count ≥ 100000/mm$^3$, without platelet transfusion within 3 weeks before the start of study treatment (see Section 8.1).
- Hemoglobin (Hb) ≥ 9 g/dL, without blood transfusion or erythropoietin within 6 weeks before the start of study treatment (see Section 8.1).

  Note: Patients receiving chronic low-dose erythropoietin for chronic renal failure are allowed provided no dose adjustment is undertaken within 6 weeks before signing consent for full study and until safety follow-up visit and provided that they fulfill conditions of eligibility criteria (see also exclusion criterion number 18).
- Absolute neutrophil count (ANC) ≥ 1500/mm$^3$, without biologic response modifiers, such as G-CSF, within 6 weeks before the start of study treatment (see Section 8.1).

9. Left ventricular ejection fraction (LVEF) ≥ 50% or the lower limit of normal (LLN) according to local institution ranges of normality.

## 6.2 Exclusion criteria

Patients who meet the following criteria at the time of randomization call and on C1D1 will be excluded *(this sentence was modified by amendment 2, see section 15.1.1.19 and 15.1.1.26)*:

1. Previous assignment to treatment during this study. Patients permanently withdrawn from study participation will not be allowed to re-enter the study.
2. Previous (within 5 drug half-lives – if drug half-life in subjects is known - or 28 days, whichever is shorter, before the start of study treatment) or concomitant participation in another clinical study with investigational medicinal product(s) (IMP[s]).
3. Close affiliation with the investigational site; e.g. a close relative of the investigator, dependent person (e.g. employee or student of the investigational site).
4. More than 1 previous systemic anti-cancer therapy line for MPM (even if therapy used as neoadjuvant or adjuvant treatment) *(clarified by amendment 4, see section 15.2.1.19)*.

   Note: Patients pre-treated with systemic therapy other than platinum, pemetrexed, bevacizumab (13) (e.g. other cytotoxic drugs, immunotherapy, targeted therapy, hormonal therapy, or any other experimental or approved therapy or device) are not to be enrolled *(modified by amendment 4, see section 15.2.1.4)*.
5. Patients with corneal epitheliopathy or any eye disorder that may predispose the patients to this condition at the discretion of the investigator in consultation with the ophthalmologist/optometrist *(modified by amendment 2, see section 15.1.1.10)*.

Note: Low grades of superficial punctate keratitis, within the range seen in the normal population, should not lead to the exclusion of the patient *(note added by amendment 2, see section 15.1.1.11)*.

6. Previous or concurrent cancer that is distinct in primary site or histology from mesothelioma within 5 years before randomization.
   Exceptions: curatively treated
   - Cervical cancer *in situ*.
   - Non-melanoma skin cancer.
   - Superficial bladder tumors (Non-invasive tumor [Ta], Carcinoma *in situ* [Tis] and Tumor invades lamina propria [T1]).
7. Major surgery, open biopsy or significant traumatic injury within 28 days before the start of study treatment.
8. Pregnant or breast-feeding patients. WOCBP must have a serum pregnancy test performed a maximum of 7 days before the start of study treatment, and a negative result must be documented before the start of study treatment.
9. Pre-existing cardiac conditions as outlined below:
   - Congestive heart failure ≥ New York Heart Association (NYHA) class 2 (specified in Appendix 16.2).
   - Unstable angina (angina symptoms at rest), new-onset angina (begun within the last 3 months). Myocardial infarction less than 6 months before the start of study treatment.
   - Cardiac arrhythmias requiring anti-arrhythmic therapy (beta blockers or digoxin are permitted).
10. Clinically significant uncontrolled hypertension (systolic blood pressure > 150 mmHg or diastolic pressure > 90 mmHg despite optimal medical management).
11. Arterial thrombotic or embolic events such as cerebrovascular accident (including transient ischemic attacks), or venous pulmonary embolism within 6 months before the start of study treatment; venous thrombotic events such as deep vein thrombosis within 3 months before the start of study treatment.
12. Ongoing or active infection (bacterial, fungal, or viral) of NCI-CTCAE version 4.03 Grade > 2.
13. Known history of human immunodeficiency virus (HIV) infection.
14. Known history of chronic hepatitis B or C.
15. Patients with seizure disorder requiring medication.
16. Brain metastases or meningeal tumors or other metastases in the central nervous system (CNS). Patients with neurological symptoms must undergo a contrast CT scan or MRI of the brain and/or other areas of the CNS as applicable within 28 days before the start

of study treatment to exclude metastatic disease in the CNS *(criterion modified by amendment 4, see section 15.2.1.5)*.

17. History of organ allograft, stem cells or bone marrow transplant.
18. Patients with evidence or history of bleeding diathesis. Any hemorrhage or bleeding event ≥ CTCAE Grade 3 within 4 weeks before the start of study treatment.
19. Non-healing wound, ulcer, or bone fracture.
20. Renal failure requiring peritoneal or hemodialysis.
21. Known hypersensitivity to anetumab ravtansine or vinorelbine, study drug classes or excipients in the formulation.
22. Any illness or medical conditions that are unstable or could jeopardize the safety of the patient and his/her compliance in the study.
23. Unresolved toxicity higher than NCI-CTCAE version 4.03 Grade 1 attributed to any prior therapy/procedure excluding anemia Grade 2 (see Section 6.1.2, inclusion criterion 8) and alopecia of any Grade.
24. Any prohibited prior or concomitant therapy (see Table 8–1 in Section 8.1).

## 6.3 Withdrawal of patients from study

### 6.3.1 Withdrawal

#### 6.3.1.1 Screening failure

##### 6.3.1.1.1 Prescreening failure

A patient whose tumor tissue is centrally tested by IHC for mesothelin overexpression and whose result is not moderate and stronger membrane staining for mesothelin overexpression in at least 30% of viable tumor cells, or who fails to meet any of the other eligibility criteria for prescreening, is regarded as a “prescreening failure” *(modified by amendments 2 and 5, see section 15.1.1.6 and 15.3.1.2)*. These patients should not undergo any further screening procedures.

##### 6.3.1.1.2 Full screening failure

A patient who passes the prescreening, including the mesothelin overexpression testing, but for any other reason (e.g. failure to satisfy the remaining selection criteria) terminates the study before randomization is regarded as a “full screening failure”.

See Section 11.1 for data to be collected for screening failures.

##### 6.3.1.1.3 Re-screening

*The following text was modified and changed to appear as a separate subsection by amendment 4, see section 15.2.1.6.*

Re-screening is defined as re-starting the defined set of screening procedures following "screening failure" to allow a patient to participate at a later time point. This is not allowed except in the following circumstances:

- Equivocal screening test results that require repeat or further testing for clarification, which cannot for logistical reasons be performed within the screening period.
- Initial screening occurred too early to complete the required washout period after prior therapy.
- The in- / exclusion criteria preventing the patient's initial attempt to participate have been changed (via protocol amendment).
- The patient had successfully passed the screening procedures, but could not be randomized on schedule and the allocated time window for these tests has expired.

During re-screening, all expired tests must be repeated to fall within the protocol-defined time window.

The investigator has to ensure that the repeated screening procedures do not expose the patient to an unjustifiable health risk. Also, for re-screening, the patient has to re-sign the ICF, even if it was not changed after the patient's previous screening and a new patient identification number has to be requested via Interactive Voice / Web Response System (IxRS).

A patient can only be re-screened once and for all re-screening requests, the sponsor needs to be contacted to discuss before re-screening the patient.

Re-testing for mesothelin expression after obtaining an initial negative result is not allowed.

#### 6.3.1.2 Withdrawal criteria

All patients who enter the study should complete all phases of the study:

1. Prescreening
2. Full screening
3. Randomization
4. Treatment
5. Safety follow-up
6. Active follow-up
7. Long-term follow-up

Study treatment discontinuation (i.e. discontinuation during the treatment period) does not constitute withdrawal from the study.

Every effort should be made to retain patients who discontinue the treatment period for any reason. These patients are to be encouraged to remain on the study for follow-up of primary, secondary and other objectives (i.e. continue in the safety follow-up, active follow-up and/or long-term follow-up periods).

Patients are expected to participate in the follow-up unless they explicitly object. Withdrawal of consent to treatment should be documented in the patient's medical record. If the patient does not wish to be followed up further, this additional consent withdrawal for follow up would have to be documented, too.

**Withdrawal from study treatment, active follow-up and long-term follow-up**

Patients withdrawn from **the study treatment** phase of the study should be followed for primary, secondary and other objectives (i.e. continue in the safety follow-up, active follow-up and/or long-term follow-up periods) (see Figure 6–1 for withdrawal criteria).

**Figure 6–1 Withdrawal criteria - amended**

**PATIENTS MUST BE WITHDRAWN FROM THE STUDY TREATMENT IF ANY OF THE FOLLOWING OCCURS:**

- At their own request or at the request of their legally acceptable representative. At any time during the study and without giving reasons, a patient may decline to participate further. The patient will not suffer any disadvantage as a result.
- If, in the investigator's opinion, continuation of the study treatment would be harmful to the patient's well-being.
- At the specific request of the sponsor and in liaison with the investigator (e.g. obvious non-compliance, safety concerns).
- Centrally confirmed radiological PD as per mRECIST criteria; however, treatment may be continued provided that the patient derives clinical benefit as determined by the treating physician. Post OS maturation, central confirmation of radiological PD is no longer required; local assessment of radiological PD only is sufficient.
- Clinical progression.
- Occurrence of unacceptable toxicity to anetumab ravtansine or vinorelbine (see also Section 7.4.2).
- CTCAE Grade ≥ 3 hypersensitivity and acute infusion reaction.
- An adverse reaction deemed sufficiently serious to warrant discontinuation of treatment by the investigator or his designated associate(s).
- Development of a secondary malignancy.
- Patient starts treatment with any other anti-cancer therapy or any other prohibited medication as per Section 8.1.
- Positive serum β-HCG test consistent with pregnancy. Pregnancy should be reported along the same timelines as an SAE.
- Use of illicit drugs or other substances that may, in the opinion of the investigator or his designated associate(s), have a reasonable chance of contributing to toxicity or otherwise confound the results.
- Development of any intercurrent illness or situation which may, in the judgment of the investigator, affect assessments of clinical status and study endpoints to a relevant degree.
- Lost to follow-up.
- Death.

Patients must be withdrawn from **treatment with anetumab ravtansine** if any of the following occurs:

- Bayer Grade 4 corneal epitheliopathy (see Table 7–5).
- CTCAE Grade 4 non-hematological AE (see Table 7–4).
- If any type of TEAE requiring dose modification does not resolve to Grade ≤ 2(or Hb ≥ 9 g/dL in case of anemia) within 12 weeks after the last dose of anetumab ravtansine.
- Delay in anetumab ravtansine administration of 9 weeks (max. 12 weeks between 2 infusions of study drug).
- TEAE requiring dose reduction when already at the 4.5 mg/kg Q3W dose level (minimum dose).
- More than 2 dose reductions required due to a TEAE.

Patients must be withdrawn from **treatment with vinorelbine** if any of the following occurs:

- Development of CTCAE Grade ≥ 2 neurotoxicity.
- Confirmed interstitial pneumonitis or acute respiratory distress syndrome (ARDS).
- If 3 consecutive weekly doses are held because neutrophil granulocytes count is < 1,000 cells/mm3 in hematologic toxicity (27).

**SAFETY FOLLOW-UP VISIT**

**All patients** who discontinue study treatment must perform this visit, 30+7 days after the last administration of study treatment.

**Patients ending treatment without centrally confirmed radiological PD as per mRECIST criteria**

**Patients ending treatment with centrally confirmed radiological PD as per mRECIST criteria OR All patients ending treatment post OS maturation**

**ACTIVE FOLLOW-UP**

Imaging and QoL assessment will continue until centrally confirmed PD is observed or they withdraw consent to active follow-up, are lost to follow-up or due to death or until data maturation for the OS analysis is reached.

**LONG-TERM FOLLOW-UP**

Patients in long-term follow-up will have information on survival and new anti-cancer treatment collected. Patients must be withdrawn if they withdraw consent to long term follow-up, are lost to follow-up or due to death or at 24 months after the last patient's last treatment.

AE = Adverse event; ARDS = Acute respiratory distress syndrome; β-HCG = β subunit of human chorionic gonadotropin; CTCAE = Common Terminology Criteria for Adverse Events; Hb = Hemoglobin; mRECIST = Modified Response

Evaluation Criteria in Solid Tumors; OS = Overall survival; PD = Progressive disease; Q3W = Every 3 weeks; QoL = Quality of life; SAE = Serious adverse event; TEAE = Treatment-emergent adverse event

*Figure modified by amendment 2 (see section 15.1.1.3, 15.1.1.4, 15.1.1.5 and 15.1.1.26), amendment 4 (see section 15.2.1.8), and amendment 6 (see section 15.4.1.1, 15.4.1.2 and 15.4.1.4).*

**Patients randomized but not treated**

In the event a patient is randomized but never treated, a withdrawal from treatment CRF should be filled out for the patient articulating the date of and reason for not treating the patient. The patient should receive efficacy follow-up, active follow-up if feasible, otherwise long-term follow-up. No safety follow-up is required *(section added by amendment 2, see section 15.1.1.17)*.

**Lost to follow-up patients**

When a patient is lost to follow-up at any stage of the study, the site should try to contact the patient, the patient's relatives, or another doctor treating the patient, unless prohibited by local regulations. All attempts to contact the patient or relatives should be documented and sites are expected to perform at least 5 attempts to contact the patient over the course of 3 months. An additional contact attempt should be made at the time of each survival sweep *(sentence added by amendment 2, see section 15.1.1.18)*.

#### 6.3.1.3 General procedures

In all cases, the reason for withdrawal must be recorded in the CRF and in the patient's medical records.

The patient may object to the generation and processing of post-withdrawal data as specified in Section 13.4.

Details for the premature termination of the study as a whole (or components thereof) are provided in Section 12.

### 6.3.2 Replacement

No replacement of randomized patients will be allowed during this study.

## 6.4 Patient identification

After a patient has signed the prescreening ICF, the patient identification number will be provided to the investigators through an IxRS. Patients will be identified by a 9-digit patient identification number consisting of:

Digits 1 to 5 = Unique center number

Digits 6 to 9 = Current patient number within the center

When the patient is found eligible, a randomization contact to IxRS will be performed and the patient will be given a unique randomization number.

# 7. Treatment(s)

## 7.1 Treatments to be administered

All patients who meet the entry criteria will receive the test drug anetumab ravtansine considered to be an IMP, or vinorelbine.

The following treatment groups are defined for this study:

- Anetumab ravtansine arm: anetumab ravtansine 6.5 mg/kg IV Q3W
- Comparator arm: vinorelbine 30 mg/m$^2$ IV QW

## 7.2 Identity of study treatment

All study drugs will be labeled according to the requirements of local law and legislation. Label text will be approved according to the sponsor's agreed procedures, and a copy of the labels will be made available to the study site upon request.

Both anetumab ravtansine and vinorelbine will receive study-specific labeling and will be provided by the sponsor.

For all study drugs, a system of numbering in accordance with all requirements of GMP will be used, ensuring that each dose of study drug can be traced back to the respective bulk batch of the ingredients. Lists linking all numbering levels will be maintained by the sponsor's clinical supplies quality assurance (QA) group.

A complete record of batch numbers and expiry dates of all study treatment as well as the labels will be maintained in the sponsor's study file.

### 7.2.1 Test drug - anetumab ravtansine

Anetumab ravtansine is an ADC consisting of a fully human IgG1 antibody (MF T, BAY 86-1903) directed at the mesothelin antigen and conjugated to a synthetic maytansine derivative as toxophore (DM4, BAY 100-6640) through a reducible disulfide linker (SPDB linker).

The details of the investigational drug are given in Table 7–1.

**Table 7–1 Identity of anetumab ravtansine**

| | |
|---|---|
| Chemical name | Mesothelin antibody-drug conjugate: Immunoglobulin G1, anti-(human mesothelin) human monoclonal MF-T-IgG1 heavy chain, disulfide with human monoclonal MF-T-IgG1 λ-chain, dimer, triamide with N2´-[4-[(3-carboxypropyl) dithio]-4-methyl-1-oxopentyl]-N2´-deacetylmaytasine |
| Substance code number(s) | BAY 94-9343 |
| Appearance | |
| Freeze-dried drug product | White to off-white lyophilized cake or powder |
| Reconstituted solution | Clear or slightly opalescent solution |
| Formulation | Freeze-dried product in a 30 mL injection vial, containing 5 mg/mL of active ingredient after reconstitution |
| Composition | Anetumab ravtansine / BAY 94-9343 / L-histidine / glycine / sucrose / polysorbate 80 / 1 N HCl |
| Type of packaging and content | 30 mL injection vial |

IgG1 = Immunoglobulin G subclass 1; N HCl = Normal hydrochloric acid

The drug product is available as a lyophilizate. Each vial contains 62.5 mg of anetumab ravtansine; the amount available for administration, based on retractable volume of reconstituted solution, is 60 mg of anetumab ravtansine. It should be reconstituted in water for injection and diluted in 0.9% sodium chloride solution (normal saline) or dextrose 5% solution prior to administration as IV infusion *(modified by amendment 5, see section 15.3.1.1)*.

The drug product is to be stored at 2°C to 8°C (36°F to 46°F).

The reconstitution and dilution of the anetumab ravtansine solution and the associated stability information is described in detail in a separate manual “15743 Anetumab ravtansine storage and handling instructions” that will be maintained in the trial master file (TMF) and in each center’s investigator site file *(paragraph added to replace the sections of reconstitution and dilution of the anetumab ravtansine solution and the associated stability information by amendment 4)*.

Refer to IB for anetumab ravtansine for details regarding drug properties and formulation.

### 7.2.2 Comparator - vinorelbine

Vinorelbine formulation is a concentrate for infusion solution. It is available as concentrate with 10 mg/mL or 50 mg/5 mL vinorelbine (as tartrate) *(concentration corrected by amendment 2)*.

Vinorelbine should be prepared according to the manufacturer’s instructions.

The participating investigators are required to consult the SmPC/desk reference of vinorelbine, which contains details regarding drug properties, formulation, handling, reconstitution, contraindications, precautions and administration.

## 7.3 Treatment assignment

Patients with obtained written informed consents, who satisfy all eligibility criteria, will be stratified and randomized following a 2:1 ratio to either anetumab ravtansine or comparator (vinorelbine) arm.

Patients will be stratified according to geographic region (RoW *versus* Asia) and per TTP on 1st line treatment (≥ 6 months *versus* < 6 months). To accomplish random assignment, a computer-generated randomization list will be prepared by the sponsor and provided to an IxRS. Patients will be randomized using permuted-block randomization. The IxRS will assign each eligible patient to a treatment arm based on the stratification factors and randomization list and will provide a randomization number. The IxRS procedure is described in detail in a separate IxRS instruction manual that will be maintained in the TMF and in each center's investigator site file.

Confirmation of adequate level of mesothelin overexpression will be obtained from the central lab. Confirmation of radiological eligibility will be obtained from central radiological review *(modified by amendment 2, see section 15.1.1.15)*. Confirmation of other inclusion and exclusion requirements will be obtained from the investigator. After confirmation of patient eligibility in IxRS, a randomization code will be assigned.

## 7.4 Dosage and administration

### 7.4.1 Treatments to be administered

#### 7.4.1.1 Administration of anetumab ravtansine

After reconstitution and dilution (as described in Section 7.2.1), anetumab ravtansine will be administered as a 1-hour IV infusion every 3 weeks on Day 1 of each 21-day cycle until centrally confirmed radiological PD or any other criteria for withdrawal of treatment.

The individual dose will be 6.5 mg/kg per infusion from Cycle 1 onwards (see Section 5.3). In obese patients, anetumab ravtansine dose should be calculated considering a maximum weight of 100 kg.

Strict IV administration has to be ensured to avoid local intolerance reactions. After completion of the 1-hour anetumab ravtansine infusion, the infusion line will be rinsed with ≥ 100 mL of 0.9% saline solution to be administered as a short infusion.

See Section 9.1 for details on scheduled administrations.

Anetumab ravtansine infusion longer than 1 hour is permitted if following the dose modification guidelines. See Section 7.4.2.1 for details on dose modifications of anetumab ravtansine *(paragraph added by amendment 5, see section 15.3.1.6)*.

#### 7.4.1.2 Administration of vinorelbine

Vinorelbine will be administered as IV injection over 6 to 10 min; the dose will be 30 mg/m$^2$ to a maximum dose of 60 mg (17, 24, 25) weekly (i.e. on Days 1, 8 and 15 of each 21-day cycle) until centrally confirmed radiological PD or any other criteria for withdrawal of

treatment. Calculation of body surface area (BSA) will be done within the IxRS and the Mosteller equation will be used (see Appendix 16.8).

The participating investigators are required to consult the SmPC/desk reference of vinorelbine, which contains more details regarding drug contraindications, precautions and administration, the latter should be done according to local standards (see Section 7.2.2).

See Section 9.1 for details on scheduled administrations.

### 7.4.2 Dose modification

#### 7.4.2.1 Dose modifications of anetumab ravtansine

The NCI-CTCAE v4.03 will be used to assess toxicities; in addition, a Bayer grading system (see Table 7–5 and Table 7–6) will be used to assess corneal epitheliopathy *(modified by amendment 2, see section 15.1.1.5)*.

TEAE requiring dose modification (dose omission, infusion interruption, change in infusion rate, dose delay, dose reduction, or permanent discontinuation of study drug) will be defined as any of the events described below that is possibly, probably, or definitely related to anetumab ravtansine and occurs anytime during the study (not only in Cycle 1) *(clarified by amendment 4, see section 15.2.1.19)*.

The dose reduction levels of anetumab ravtansine will follow pre-defined dose levels shown in Table 7–2.

**Table 7–2 Dose levels of anetumab ravtansine**

| | |
|---|---|
| Dose level 1 (starting dose): | 6.5 mg/kg Q3W |
| Dose level -1: | 5.5 mg/kg Q3W |
| Dose level -2: | 4.5 mg/kg Q3W |

Q3W = Every 3 weeks

##### 7.4.2.1.1 Hematological toxicities

**Dose modifications for hematological toxicity**

- If treatment modification is required due to a hematological TEAE, and the continuation of treatment is appropriate, the anetumab ravtansine dose will be adjusted as described in Table 7–3 below *(cross-reference to Table 7-4 removed by amendment 4)*.
- G-CSF and other hematopoietic growth factors may be used during the study in the management of acute toxicity such as febrile neutropenia when clinically indicated per ASCO Recommendations for Therapeutic Use of CSF (26) or at the discretion of the investigator; however they may not be substituted for a required dose reduction.
- Blood transfusions and therapy with IV or subcutaneous erythropoietin-stimulating agents (epoetin alpha, darbepoetin alpha) are allowed per institution guidelines but may not be used as substitute for a required dose reduction (see also Table 8–1).

- Platelet transfusion may be used during the study in the management of acute toxicity such as hemorrhage or bleeding events, however they may not be used as substitute for a required dose reduction.

**Table 7–3 Dose modifications for anetumab ravtansine in response to hematological toxicities [a] for neutrophil and platelet nadir [b] counts – table added**

| Dose modifications | | Blood count |
|---|---|---|
| **Platelet count (/mm³)** | Start new cycle only if platelet count is | ≥ 75,000 (Grade ≤ 1) (pre-infusion) |
| | Dose reduce by 1 dose level [c] | < 25,000 (Grade 4) for ≥ 7 days (nadir [b]) |
| | | < 50,000 (Grade 3) for ≥ 7 days with bleeding [d] (nadir [b]) |
| **Absolute neutrophil count (/mm³)** | Start new cycle only if ANC is | ≥ 1000 (Grade ≤ 2) (pre-infusion) |
| | Dose reduce by 1 dose level [c] | < 500 (Grade 4) for 7 days (nadir [b]) |
| | | Febrile neutropenia (Grade 3) [e] (during previous cycle) |
| **Hemoglobin (g/dL)** | Start new cycle only if hemoglobin is | Hb ≥ 8 (pre-infusion) |
| | Re-start at the same dose or dose reduce by 1 dose level [c] (at investigator's discretion) | < 8 (nadir [b]) |
| **Any** | Discontinue | Grade 3 or 4 toxicity after 2 dose reductions |

ANC = Absolute neutrophil count; C = Cycle; CBC = Complete blood count; D = Day; Hb = Hemoglobin; Q3W = Every 3 weeks

a For any toxicity ≤ Grade 2 assessed as related to study drug(s) by the investigator, dose modification may be considered if investigator feels this is in the patients best interest. Such toxicities might be ≤ Grade 2 toxicities which interfere with the activities of daily life.

b Nadir: lowest value measured in previous cycle or pre-infusion. Site visits and blood test for CBC on D8 and D15 are mandatory for C1, C2 and C3 only. From C4 onwards, visits and procedures on D8 and D15 are no longer required.

c Dose reduction by 1 dose level translates to a change from 6.5 mg/kg Q3W to 5.5 mg/kg Q3W, or from 5.5 mg/kg Q3W to 4.5 mg/kg Q3W. Not more than 2 dose reductions from the starting dose level are permitted.

d Clinically significant bleeding, i.e. bleeding requiring platelet transfusion.

e Febrile neutropenia is defined as ANC < 1000/mm³ and fever (a single body temperature reading of > 38.3°C [101°F] or a sustained body temperature of ≥ 38°C [100.4°F] for more than 1 hour).

*Table 7-3 was added to combine the previous Tables 7-3 and 7-4 by amendment 4, see section 15.2.1.8. Consequently, the numbering of the subsequent tables in this section changed accordingly.*

#### 7.4.2.1.2 Non-hematological toxicities

**Non-hematological toxicities requiring dose modification**

*This subsection was modified by amendments 2 and 4, see section 15.1.1.5, 15.1.1.13, 15.1.1.26 and 15.2.1.8.*

- CTCAE Grade 2 anetumab ravtansine infusion-related reaction or other CTCAE Grade 2 hypersensitivity events (see Section 7.4.2.1.3)
- AST and/or ALT increase > 3.0 x ULN (CTCAE Grade ≥ 2) with concomitant increase in total bilirubin > 1.5 x ULN (CTCAE Grade ≥ 2)
- Bayer Grade ≥ 3 corneal epitheliopathy (see below and Table 7–5)
- Any other Grade ≥ 3 non-hematological toxicity that, in the investigator's opinion, warrants treatment modification (see Table 7–4), **excluding** the following:
    - Nausea, vomiting, or diarrhea if manageable with anti-emetics or anti-diarrheals within 7 days
    - Fatigue lasting ≤ 72 h
- Any other toxicity irrespective of the type or severity that represents a clinically significant risk to patient in the investigator's opinion.

**Dose modifications for non-hematological toxicity**

If treatment modification is required due to Grade ≥ 3 **non-hematological TEAE**, other than corneal epitheliopathy and infusion-related reaction/hypersensitivity events, and the continuation of treatment is appropriate, the anetumab ravtansine dose will be either reduced or maintained as is at investigator's discretion *(modified by amendment 2, see section 15.1.1.5 and 15.1.1.13)* (see Table 7–4).

**Table 7–4 Dose adjustments in response to non-hematologic toxicities - amended**

| CTCAE v4.03 grade | Anetumab ravtansine dose delay / interruption | Anetumab ravtansine dose modification |
|---|---|---|
| Grade 1 – 2 [a] | Treat on time | No change required |
| Grade 3 | 1st appearance: Delay/Interruption until Grade ≤ 2 [b]<br><br>2nd appearance: Delay/Interruption until Grade ≤ 2[b]<br><br>3rd appearance: Permanently discontinue | Re-start at the same dose or decrease by 1 dose level [c] (at investigator's discretion)<br>Decrease by 1 more dose level [c] |
| Grade 4 | Permanently discontinue | |

ALT = Alanine aminotransferase; AST = Aspartate aminotransferase; CTCAE = Common Terminology Criteria for Adverse Events; Q3W = Every 3 weeks; TEAE = Treatment-emergent adverse event

a AST and/or ALT increase of CTCAE Grade 2 with concomitant increase in total bilirubin of CTCAE Grade 2 will be treated as a CTCAE Grade 3 event.

b Treatment will be discontinued if the TEAE fails to resolve to Grade ≤ 2 within 12 weeks after the last dose of anetumab ravtansine *(clarified by amendment 4, see section 15.2.1.8, and modified by amendment 6, see section 15.4.1.4)*.

c Dose reduction by 1 dose level translates to a change from 6.5 mg/kg Q3W to 5.5 mg/kg Q3W, or from 5.5 mg/kg Q3W to 4.5 mg/kg Q3W. Not more than 2 dose reductions from the starting dose level are permitted.

The anetumab ravtansine dose reduction due to non-hematological TEAE will be done as described below:

- If the patient experienced a TEAE requiring dose reduction at the 6.5 mg/kg Q3W dose level, the subsequent anetumab ravtansine dose should be reduced to 5.5 mg/kg Q3W.
- If the patient experienced a TEAE requiring dose reduction at the 5.5 mg/kg Q3W dose level, the subsequent anetumab ravtansine dose should be reduced to 4.5 mg/kg Q3W.

After dose reduction for TEAE, there could be no intra-patient dose re-escalation irrespective of the type of TEAE that has led to dose reduction in this patient with the exception of grade 3 corneal epitheliopathy as per Table 7–5 *(sentence clarified by amendment 2, see section 15.1.1.16 and 15.1.1.21)*.

#### 7.4.2.1.3 Miscellaneous toxicities

**IV infusion-related reaction and other hypersensitivity events *(modified by amendment 2)***

*Subsection modified by amendments 2 and 4, see section 15.1.1.13 and 15.2.1.8.*

If a patient experiences a CTCAE Grade 2 anetumab ravtansine infusion-related reaction or other CTCAE Grade 2 hypersensitivity event deemed at least possibly related to anetumab ravtansine, the infusion of anetumab ravtansine will be interrupted.

If treatment interruption is caused by a CTCAE Grade 2 anetumab ravtansine **infusion-related reaction or other CTCAE Grade 2 hypersensitivity event** deemed at least possibly related to anetumab ravtansine, treatment may be re-started at the time determined at the investigator's discretion. Re-treatment should be at the infusion rate reduced by 50%, along with anti-allergic prophylaxis (e.g. anti-histamines, paracetamol, acetaminophen, and/or corticosteroids) chosen at the investigator's discretion or according to the institutional guidelines.

In case of a CTCAE Grade ≥ 3 hypersensitivity and acute infusion reaction, treatment must be permanently withdrawn.

**Miscellaneous toxicities requiring dose modification**

For any toxicity ≤ Grade 2 assessed as related to anetumab ravtansine by the investigator, dose modification should be considered. Such toxicities might be ≤ Grade 2 toxicities which interfere with the activities of daily life, such as long lasting fatigue, or anorexia, or corneal epitheliopathy with vision impairment etc. *(modified by amendment 2, see section 15.1.1.5)*. A dose change might be necessary in order to ensure the patient's compliance. These toxicities may be declared "TEAE requiring treatment modification" after consultation between the investigator and the sponsor.

**Dose modifications for corneal epitheliopathy *(modified by amendment 2)***

For the TEAE of corneal epitheliopathy and the best corrected visual acuity (BCVA) changes (blurred vision), the Bayer severity grading system (see Table 7–5 and Table 7–6) will be used to assess the severity of TEAEs requiring modification of anetumab ravtansine treatment *(modified by amendment 2, see section 15.1.1.5)*.

TEAE of corneal epitheliopathy deemed to be at least possibly related to anetumab ravtansine would require modification of anetumab ravtansine treatment (dose reduction or permanent discontinuation of treatment) according to the following principles *(modified by amendment 2, see section 15.1.1.5)* (see Table 7–5).

**Table 7–5 Bayer classification and management of corneal epitheliopathy - amended**

| | Grade 0 | Grade 1 | Grade 2 | Grade 3 | Grade 4 |
|---|---|---|---|---|---|
| **Corneal morphology** | No pathologic changes | Any stage of superficial punctate keratitis [a] | Epithelial opacities<br>Micro-cysts<br>Micro-deposits<br>Corneal erosion<br>Stromal opacity: non-central | Corneal ulcer without risk of acute rupture<br>Stromal opacity: central | Corneal ulcer more severe than Grade 3 |

| | Grade 0 | Grade 1 | Grade 2 | Grade 3 | Grade 4 |
|---|---|---|---|---|---|
| **Eye treatment** [b] | Ocular lubricants at the discretion of investigator in consultation with ophthalmologist / optometrist | Ocular lubricants; add topical steroids if superficial punctate keratitis shows treatment-emergent progression by ≥ 2 SPK Grades | Intensive treatment with ocular lubricants enhanced with ointments; topical steroids; therapeutic contact lens may be considered at the discretion of investigator in consultation with ophthalmologist/ optometrist | Intensive therapy with ointments; topical steroids; therapeutic contact lens or occlusion recommended at the discretion of investigator in consultation with ophthalmologist/ optometrist | Intensive therapy with lubricants, ointments, topical steroids and antibiotics as needed; occlusion or therapeutic contact lens recommended; amniotic membrane transplant and other locally approved therapies to be considered at the discretion of investigator in consultation with ophthalmologist/ optometrist |
| **Anetumab ravtansine** [c] | No change | No change | Keep treatment dose level and schedule if the ophthalmological exam can be performed as needed; otherwise consider dose reduction by -1 dose level without dose schedule change at the discretion of investigator in consultation with ophthalmologist/ optometrist | 1) Decrease dose to -1 dose level (or -2 dose level if event does not resolve to Grade ≤ 2 at the -1 dose level within 3 weeks)<br>2) Re-start at the original dose level if the first Grade 3 event resolves to Grade ≤ 2 within 3 weeks and does not recur<br>3) If not resolved within 3 weeks continue at reduced -1 dose level (or -2 dose level) | Discontinue treatment |

SPK = Superficial punctate keratitis

a Oxford Schema must be used for grading SPK from stage 0 to VI (see Section 16.9) *(cross-reference added by amendment 4)*.

b Other remedial therapies for corneal epitheliopathy may be added or substituted at investigator's discretion or according to the institutional standards.

c Treatment decisions are based on corneal epitheliopathy only, not on visual acuity changes *(modified by amendment 2, see section 15.1.1.5)*.

*Clarified that the ophthalmologist/optometrist will be consulted by the investigator by amendment 2*
*Optometrist added as an alternative to ophthalmologist by amendment 2*

**Table 7–6 Bayer classification of visual acuity changes**

| | Grade 0 | Grade 1 | Grade 2 | Grade 3 | Grade 4 |
|---|---|---|---|---|---|
| **Visual acuity** | No findings, no reporting from the patient | Symptomatic visual acuity loss < 3 lines (ETDRS equivalent [a]) | Visual acuity loss ≥ 3 lines, but < 6 lines (ETDRS equivalent [a]) | Visual acuity loss ≥ 6 lines (ETDRS equivalent [a] | Visual acuity loss ≥ 6 lines (ETDRS equivalent [a]) leading to blindness |

ETDRS = Early Treatment Diabetic Retinopathy Study
a In the ETDRS chart, each loss of 3 lines corresponds to halving the visual acuity. In other charts, an equivalent amount of visual acuity loss must be reached in order to meet this threshold.

**Recommended measures in case of eye dryness and ocular hypertension**

Changes in tear production as evaluated by the Schirmer test and in intraocular pressure (IOP) are not expected to occur as a direct consequence of anetumab ravtansine therapy. However, IOP may increase in some patients as a consequence of the therapy with topical steroid eye-drops. Since these drugs may be required to manage the corneal epitheliopathy syndrome, IOP will be monitored during this study for patients receiving topical steroid eye drops.

Changes in IOP should be managed by an ophthalmologist/optometrist *(modified by amendment 2, see section 15.1.1.10)*. The remedial therapy should be chosen at investigator's discretion or according to the institutional standards; therapeutic measures can include modification of the type or posology of topical steroid eye drop, initiation of topical IOP lowering drugs and any other therapeutic options according to the local SoC. Ophthalmological monitoring should be maintained until the IOP has returned to normal values.

Reductions in tear production evaluated by the Schirmer test, while not being a part of the corneal epitheliopathy syndrome, are a risk factor for developing ocular surface disease including corneal epithelial defects. Therefore, the tear production will be evaluated in this study to determine if changes in this parameter may be helpful to identify patients at higher risk of developing the corneal epitheliopathy syndrome. Abnormal values in the Schirmer test should be evaluated and managed by an ophthalmologist/optometrist to provide adequate protection to the corneal epithelium *(modified by amendment 2, see section 15.1.1.10)*. The remedial therapy for the treatment-emergent changes in the Schirmer test (dry eye) should be chosen at investigator's discretion or according to the institutional standards. These measures may include topical lubricants such as eye drops and ointments, punctual occlusion, use of therapeutic contact lenses and any other treatment approaches according to the local SoC.

#### 7.4.2.1.4 Continuation of treatment with anetumab ravtansine

Treatment with anetumab ravtansine could be re-started at the appropriate dose if the TEAE requiring dose modification has resolved to Grade ≤ 2 within 6 weeks after the last dose of anetumab ravtansine *(clarified by amendment 5, see section 15.3.1.5)*.

#### 7.4.2.1.5 Permanent discontinuation of anetumab ravtansine due to TEAEs

See Section 6.3.1.2 for withdrawal criteria.

### 7.4.2.2 Dose modifications of vinorelbine

The following dose modifications for vinorelbine, based on the US label guidance (27), are provided below as a general recommendation. After dose reduction for TEAE, there could be no intra-patient dose re-escalation irrespective of the type of TEAE that has led to dose reduction in this patient *(clarified by amendment 2, see section 15.1.1.16 and 15.1.1.21)*. All label specific instructions for treatment with vinorelbine will apply. Please refer to the local full prescribing information for further guidance.

**Dose modifications for hematological toxicity**

Neutrophil granulocyte counts should be ≥ 1,000 cells/mm$^3$ prior to the administration of vinorelbine. Some local prescribing information could require a treatment delay until recovery and observation of the patient if the neutrophil count is <1,500/mm$^3$ (22). Adjustments in the dosage of vinorelbine should be based on neutrophil granulocyte counts obtained on the day of treatment (or 1 day before) according to Table 7–7. G-CSF and other hematopoietic growth factors may be used during the study in the management of acute toxicity such as febrile neutropenia when clinically indicated per ASCO Recommendations for Therapeutic Use of CSF (26) or at the discretion of the investigator or according to local label guidance (if medically necessary, growth factors may be administered at recommended doses no earlier than 24 h after and not in the 24 h before vinorelbine administration; see also (27); however they may not be substituted for a required dose reduction).

**Table 7–7 Dose adjustments based on neutrophil granulocyte counts**

| Neutrophil granulocytes on day of treatment (cells/mm$^3$) | Percentage of starting dose of vinorelbine |
|---|---|
| ≥ 1500 | 100% |
| 1000-1499 | 50% |
| < 1000 | Do not administer. Repeat neutrophil granulocyte count in 1 week. If 3 consecutive weekly doses are held because granulocyte count is < 1,000 cells/mm$^3$, discontinue. |
| Note: For patients who, during treatment with vinorelbine, experienced fever and/or sepsis while granulocytopenic (< 1500) or had 2 consecutive weekly doses held due to granulocytopenia, subsequent doses of vinorelbine should be: | |
| ≥ 1500 | 75% |
| 1000-1499 | 37.5% |
| < 1000 | See above |

According to local prescribing information, treatment should be delayed until recovery and the patient should be observed if the thrombocyte count is below 100,000/mm$^3$ (or, in some countries, below 75,000/mm$^3$) (22). Platelet transfusion may be used during the study in the management of acute toxicity such as hemorrhage or bleeding events, however they may not be used as substitute for a required dose reduction (see also Table 8–1).

**Dose modifications for hepatic insufficiency**

Vinorelbine should be administered with caution to patients with hepatic insufficiency. In patients who develop hyperbilirubinemia during treatment with vinorelbine, the dose should be adjusted for total bilirubin according to Table 7–8.

**Table 7–8 Modifications based on total bilirubin**

| Total bilirubin (mg/dL) | Percentage of starting dose of vinorelbine |
|---|---|
| ≤ 2.0 | 100% |
| 2.1 - 3.0 | 50% |
| > 3 | 25% |

According to local prescribing information, in some countries, a reduced dose of 20 mg/m$^2$ is recommended in patients with severe liver impairment (22).

**Dose modifications for concurrent hematological toxicity and hepatic insufficiency**

In patients with both hematological toxicity and hepatic insufficiency, the lower of the doses based on the corresponding starting dose of vinorelbine determined from Table 7–7 and Table 7–8 should be administered.

**Dose modifications for renal insufficiency**

No dose adjustments for vinorelbine are required for renal insufficiency.

**Dose modifications for neurotoxicity**

If Grade ≥ 2 neurotoxicity develops, vinorelbine should be discontinued.

For further information on dose modifications for vinorelbine, see (27).

## 7.5 Blinding

This is an open-label study except for:

- The independent and central radiological review for the assessment of disease progression and other radiological imaging based endpoints, which will be conducted in a blinded fashion.
- The independent blinded PRO review committee which will conduct analyses to support validation of the MDASI-MPM instrument and determine endpoint definitional details *(bullet point added by amendment 4, see section 15.2.1.16)*.

## 7.6 Drug logistics and accountability

All study drugs will be stored at the investigational site in accordance with GCP and GMP requirements and the instructions given by the clinical supplies department of the sponsor, and will be inaccessible to unauthorized personnel. Special storage conditions and a complete record of batch numbers and expiry dates can be found in the sponsor's study file; the site-relevant elements of this information will be available in the investigator site file. On the day of receipt, the responsible site personnel will confirm receipt of study drug via IxRS. The

personnel will use the study drug only within the framework of this clinical study and in accordance with this protocol. Receipt, distribution, return and destruction (if any) of the study drug must be properly documented according to the sponsor's agreed and specified procedures.

Both for anetumab ravtansine and vinorelbine, the vials will all have a 2-panel standard label or booklet label affixed. 1 panel will be permanently attached to the vial while the second panel will be a tear-off section that will be appended to the dispensing documentation.

The number of vials used will be recorded on the appropriate treatment dispensing form. Reasons for dose delay and reduction will be recorded in the source documents and on the CRF.

Treatment accountability on patient level must be verified at every cycle, starting on C1D1. The monitor will review overall drug accountability and destruction per the site documentation only.

Written instructions on medication destruction will be made available to affected parties as applicable.

### 7.7 Treatment compliance

The administration of anetumab ravtansine or vinorelbine will be performed in the clinic on Day 1 of each 21-day cycle for anetumab ravtansine and on a weekly basis (Day 1, 8 and 15 of a 21-day cycle) for vinorelbine. Each administration must be recorded on the CRF and Drug Dispensing / Accountability Form.

Reasons for dose delay, reduction, or omission will also be recorded in the source documents and on the CRF.

An adequate record of receipt, distribution, and return of all study drugs must be kept in the form of a Drug Accountability Form.

The preparation and administration of anetumab ravtansine and vinorelbine will be performed by members of the investigator team during hospitalization and site visits. These persons will ascertain and document that the patient receives all treatments as planned.

Patient compliance with the treatment and protocol includes willingness to comply with all aspects of the protocol, and to have blood collected for all safety evaluations. At the discretion of the principal investigator or sponsor, a patient may be discontinued from the study treatment for non-compliance with visits or study drug.

## 8. Non-study therapy

### 8.1 Prior and concomitant therapy

Any medication which is considered necessary for the patient's welfare, and which is not expected to interfere with the evaluation of the study treatment, may be given at the discretion of the investigator. In general, patients should be closely monitored for side effects of all concomitant medications regardless of elimination path, especially those with narrow

therapeutic indices, such as warfarin, phenytoin, quinidine, carbamazepine, phenobarbital, cyclosporine and digoxin. From signing of ICF for full study to safety follow-up visit, all concomitant medications (including start/stop dates, dose, frequency, route of administration and indication) must be recorded in the patient's source documentation, as well as on the appropriate pages of the CRF. At prescreening and active follow-up period, only concomitant medications that are administered to treat AEs related to study-specific procedures are mandatory to be reported. Administration of contrast media for protocol-specified radiological procedures (CT scan or MRI) does not need to be reported on the concomitant medication CRF page, unless there is an AE related to the contrast medium injection (e.g. allergic reaction).

**Post OS maturation, only concomitant medication related to SAEs is required to be reported** *(sentence added by amendment 6, see section 15.4.1.1)*.

Prohibited prior and concomitant therapies and permitted concomitant therapies are listed in Table 8–1 and Table 8–2, respectively.

**Table 8–1 Prohibited prior and concomitant therapies - amended**

| Prohibited prior and concomitant therapy (see also Section 6.2) | Time period when prohibited | Comments |
|---|---|---|
| ***Prohibited for all patients*** | | |
| Anetumab ravtansine (or any other mesothelin-based therapy) | Prior to study treatment | |
| Vinorelbine (or any other vinca-containing compound) | Prior to study treatment | |
| Platinum/pemetrexed/ bevacizumab | Within 28 days before the start of study treatment until safety follow-up visit (*modified by amendment 4, see section 15.2.1.3*) | |
| Other systemic anticancer treatment (except study treatment) (cytotoxic therapy, targeted therapies, immunotherapy, hormonal therapy, or any other experimental or approved therapy) | Prior to study treatment until safety follow-up visit | |
| Use of biologic response modifiers, such as G-CSF | Within 6 weeks before the start of study treatment | G-CSF and other hematopoietic growth factors may be used during the study in the management of acute toxicity such as febrile neutropenia when clinically indicated per ASCO Recommendations for Therapeutic Use of CSF (26) or at the discretion of the investigator or according to local label guidance (if medically necessary, growth factors may be administered at recommended doses no earlier than 24 h after and not in the 24 h before vinorelbine administration; see also (27); however they may not be substituted for a required dose reduction). |

| Prohibited prior and concomitant therapy (see also Section 6.2) | Time period when prohibited | Comments |
|---|---|---|
| Blood transfusions and chronic therapy with IV or subcutaneous erythropoietin-stimulating agents (epoetin alpha, darbepoetin alpha) | Within 6 weeks before the start of study treatment. Thereafter, they are allowed per institution guidelines but may not be used as substitute for a required dose reduction. | Patients receiving chronic low-dose erythropoietin for chronic renal failure are allowed provided no dose adjustment is undertaken within 6 weeks before signing consent for full study and until safety follow-up visit and provided that they fulfill conditions of inclusion criterion number 8 (Section 6.1.2) and exclusion criterion number 20. |
| Platelet transfusions | Within 3 weeks before the start of study treatment. Thereafter, they may not be used as substitute for a required dose reduction. | |
| Anti-arrhythmic therapy other than beta blockers or digoxin | | |
| Radiotherapy | Within 4 weeks before the start of screening for full study | Except for pain control, see below in Table 8–2. Patients must have recovered from all therapy-related toxicities. The site of previous radiotherapy should have evidence of PD if this is the only site of disease: measurable pleural disease should be assessed on a contrast enhanced CT/MRI done at the minimum 4 weeks after the end of RT and compared with previous imaging; unequivocal progression should be judged by the investigator as per mRECIST per MPM. |
| Drugs with known bone marrow toxicity | | |
| Strong inhibitors and strong inducers of CYP3A4 (listed in Appendix 16.6), including:<br>- Herbal preparations containing CYP3A4 inducers (e.g. St John's Wort)<br>- Grapefruit and grapefruit juice (CYP3A4 inhibitor) | Within 2 weeks before the start of study treatment until the safety follow-up visit | DM4 and vinorelbine are substrates of CYP3A4.<br><br>During study treatment, moderate and weak CYP3A4 inducers should be used with caution as decrease in plasma concentrations of DM4 cannot be ruled out. |
| Concomitant live attenuated virus vaccines (e.g. yellow fever) | Within 2 weeks before the start of study treatment (for all patients, during screening, then from C1D1 until the safety follow-up visit for patients in vinorelbine arm only) *(modified by amendment 4, see section15.2.1.10)* | Contraindicated due to risk of generalized vaccine disease, possibly fatal |

ASCO = American Society of Clinical Oncology; C=Cycle; CSF = Colony stimulating factor; CT = Computed tomography; CYP3A4 = Cytochrome P450, family 3, subfamily A, polypeptide 4; D=Day; DM4 = Derivatives of maytansine 4; G-CSF = Granulocyte-colony stimulating factor; IV = Intravenous; MPM = Malignant pleural mesothelioma; mRECIST = Modified Response Evaluation Criteria in Solid Tumors; MRI = Magnetic resonance imaging; PD = Progressive disease; RT = Radiotherapy

*Acute steroid therapy or taper was removed by amendment 4. Concomitant live attenuated virus vaccines was transferred to under "prohibited for all patients" part of the table by amendment 4.*

**Table 8–2 Permitted concomitant therapies - amended**

| Permitted concomitant therapies | Comments |
|---|---|
| ***Permitted for all patients*** | |
| Oral and parenteral anti-coagulant agents, e.g. heparin, enoxaparin, warfarin, rivaroxaban, dabigatran, apixaban or aspirin at a dose ≤ 100 mg | Allowed if continued maintenance therapy is necessary at the investigator's discretion and provided that they fulfill conditions of inclusion criterion number 8 (Section 6.1.2). |
| Institutional standards for the management of infusion-related reactions or other hypersensitivity events *(modified by amendment 2, see section 15.1.1.13)* | May be utilized at the discretion of the investigator. |
| Chronic steroid therapy | Permitted provided that the dose is stable for one month prior to start of study drug. |
| Palliative radiotherapy for pain control | Allowed provided that:<br>- In the opinion of the investigator, the patient does not have PD,<br>- No more than 10% of the patient's bone marrow is irradiated,<br>- The radiation field does not encompass a non-pleural target lesion or a pleural measurable lesion,<br>- The radiation field does not encompass a lung field (to reduce the risk for interstitial lung disease [ILD] caused by irradiation pneumonitis), and<br>- Vinorelbine and anetumab ravtansine administration is interrupted during radiotherapy. Study treatment can be restarted after end of radiotherapy, provided all requirements outlined in Section 7.4 of this protocol are taken into account. The maximum interruption period for both drugs should not be exceeded.<br><br>Vinorelbine may result in radiosensitizing effects with prior or concomitant radiation therapy (27). |
| Standard therapies for concurrent medical conditions | |
| Prophylactic standard anti-emetics | May be administered according to standard practice: dexamethasone plus 5-HT3 blockers, such as granisetron, ondansetron, or an equivalent agent, are allowed on "as needed" basis. |
| Treatment with non-conventional therapies (for example herbs, except St John's Wort, or acupuncture), and vitamin/mineral supplements | Acceptable provided that they do not interfere with the study endpoints, in the opinion of the investigator. |
| Bisphosphonates or denosumab, with supplement of calcium and vitamin D | |
| Palliative (e.g. analgesics) and supportive care (e.g. nutritional therapy) for other disease-related symptoms and for toxicity associated with treatment | |
| Strong P-gp inhibitors (e.g. amiodarone, azithromycin, captopril, carvedilol, clarithromycin, conivaptan, cyclosporine, diltiazem, dronedarone, erythromycin,felodipine, itraconazole, ketoconazole, lopinavir and ritonavir, quercetin, quinidine, ranolazine, ticagrelor, verapamil) | DM4-Me (metabolite of DM4) and vinorelbine are P-gp substrates.<br>Caution should be exercised with concomitant administration of strong P-gp inhibitors. If anetumab ravtansine or vinorelbine must be co-administered with a strong P-gp inhibitor, then the patient should be carefully monitored or the strong P-gp inhibitor replaced at investigator's discretion. |

| | |
|---|---|
| Narrow therapeutic index medications | Patients taking narrow therapeutic index medications should be monitored proactively, if these medications cannot be avoided. |
| Beta blockers or digoxin | Permitted for patients with cardiac arrhythmias requiring therapy |

5-HT3 = 5-hydroxytryptamine (serotonin); DM4 = Derivatives of maytansine 4; DM4-Me = Methyl-DM4; ILD = Interstitial lung disease; PD = Progressive disease; P-gp = Permeability glycoprotein
*Chronic steroid therapy was added by amendment 4.*

All prior anti-cancer therapies, and all concomitant therapies including ophthalmological therapies as of full screening will be recorded on the CRF. At prescreening and active follow-up period, only concomitant medications that are administered to treat AEs related to study-specific procedures are mandatory to be reported.

## 8.2 Post-study therapy

At the end of study treatment, further therapy is at the discretion of the investigator.

No results are available from human interaction studies between anetumab ravtansine and other chemotherapies. No data are available to evaluate the potential interaction between anetumab ravtansine and radiation treatment. Therefore, when administering these agents after study treatment is withdrawn, it should be taken into consideration that anetumab ravtansine, DM4 or DM4-Me levels may be detectable for several weeks and could interact with chemotherapy and radiotherapy including palliative radiotherapy as outlined in Table 8–2 following discontinuation of anetumab ravtansine.

Once the expected final number of events is reached and results are available, the remaining patients on anetumab ravtansine treatment, who are considered by the investigator to benefit from continued anetumab ravtansine treatment, can be continued in the trial until disease progression. Patients still benefiting from vinorelbine treatment, in the investigator's opinion, should be transferred to commercial medication supply if available. There will be no cross-over between treatment arms.

# 9. Procedures and variables

## 9.1 Tabular schedule of evaluations

Schedule of procedures prior to OS maturation (i.e. prior to completion of number of events required for OS analysis) is presented in Table 9–1. Schedule of procedures following OS maturation is presented in Table 9–2 for anetumab ravtansine arm patients ongoing on treatment post OS maturation and in Table 9–3 for vinorelbine arm patients ongoing on treatment post OS maturation *(paragraph modified by amendment 6, see section 15.4.1.1)*.

**Table 9–1 Study flow chart – prior to OS maturation – amended**

| | Pre-screening | Full screening (maximum days before C1D1) | | | Treatment | | | | | | Safety follow-up period / visit | Active follow-up [a] | Long-term follow-up [a] |
|---|---|---|---|---|---|---|---|---|---|---|---|---|---|
| | | | | | Cycle 1 | | | Cycle 2 and higher | | | | | |
| **Days** | | **-28** | **-21** | **- 7** | **D1** | **D8** | **D15** | **D1** | **D8 [b]** | **D15 [b]** | **+30** (after last dose) | | **Every 3 months** |
| Acceptable time window (in days) (unless otherwise specified) | | | | | | +/-1 | +/-1 | +/-1 | +/-1 | +/-1 | +7 | | ±14 |
| **Screening and enrollment** | | | | | | | | | | | | | |
| Written informed consent for prescreening [c] | X | | | | | | | | | | | | |
| Written informed consent for full study [c] | | X | | | | | | | | | | | |
| Demographics | X | | | | | | | | | | | | |
| Study disease characteristics [d] | X | X | | | | | | | | | | | |
| Medical history [d] | | X | | | | | | | | | | | |
| Check eligibility criteria | X | X | | | X [z] | | | | | | | | |
| IxRS transaction [e] | X | X | | | X [z] | X | X | X | X | X | X | | |
| **Safety** | | | | | | | | | | | | | |
| Toxicity / AE assessment [f] | X [f] | X | | X | X [z] | X | X | X | X | X | X | X [f] | |
| Concomitant medication | X [f] | X | | | X [z] | X | X | X | X | X | X | X [f] | |
| Complete physical examination | | X | | | | | | | | | | | |
| Brief physical examination [g] | | | | | X [z] | X | X | X | X [g] | X [g] | X | | |
| Vital signs (BP, HR, RR, Temp) | | | | X | X [z] | X | X | X | X | X | X | | |
| Weight/height [h] | | X [h] | | | X [z] | X | X | X | X | X | X | | |
| 12-Lead ECG [i] | | X | | | X [i] | | | X [i] | | | X | | |
| ECOG PS assessment | X | X | | | X [z] | | | X | | | X | | |
| EchoCG or MUGA scan [j] | | X | | | | | | X [j] | | | | | |
| Ophthalmologic examination [k] | | | X | | | | | X | | | X | | |
| Complete blood count | | | | X | | X | X | X | X | X | X | | |
| Electrolyte and chemistry panel | | | | X | | X [l] | X [l] | X [aa] | X [l] | X [l] | X | | |
| eGFR | | | | X | | | | X | | | X | | |
| Coagulation panel | | | | X | | | | X | | | X | | |
| Urine dipstick [m] | | | | X | | | | X | | | | | |

| | Pre-screening | Full screening (maximum days before C1D1) | | | Treatment | | | | | | Safety follow-up period / visit | Active follow-up [a] | Long-term follow-up [a] |
|---|---|---|---|---|---|---|---|---|---|---|---|---|---|
| | | | | | Cycle 1 | | | Cycle 2 and higher | | | | | |
| **Days** | | **-28** | **-21** | **- 7** | **D1** | **D8** | **D15** | **D1** | **D8 [b]** | **D15 [b]** | **+30** (after last dose) | | **Every 3 months** |
| Acceptable time window (in days) (unless otherwise specified) | | | | | | +/-1 | +/-1 | +/-1 | +/-1 | +/-1 | +7 | | ±14 |
| Serum pregnancy test (if applicable) | | | | X [n] | | | | | | | X | | |
| **Efficacy** | | | | | | | | | | | | | |
| Radiological tumor evaluation with contrast-enhanced CT/MRI [o] | | X [bb] | | | Every 6 weeks (first 6 months), every 9 weeks (until end of year 2), every 12 weeks thereafter [o] | | | | | | | X [o] | |
| Disease and survival status [p] | | | | | | | | | | | | | X |
| **Pharmacokinetic sampling** [q] | | | | | | | | | | | | | |
| In anetumab ravtansine arm | | | | | X [r] | X | | X [r] | X [r] | X [r] | | | |
| In comparator (vinorelbine) arm | | | | | X [s] | | | | | | | | |
| **PGt blood for CYP2D6 analysis** (in anetumab ravtansine arm only) | | | | | X | | | | | | | | |
| **IM sampling** (in anetumab ravtansine arm only) [t] | | | | | X | | | X [t] | | | | | |
| **Biomarker sampling** | | | | | | | | | | | | | |
| BM archival or fresh biopsy tissue [u] | X [v] | | | | X [u] | | | | | | | | |
| BM plasma for soluble mesothelin [x] | | | | | X | | | | | | | | |
| BM plasma for exploratory analysis [x] | | | | | X | | | X [x] | | | X | | |
| **Patient-reported outcomes** | | | | | | | | | | | | | |
| LCSS-Meso [y] | | | | X | | | | X | | | X | X [y] | |
| MDASI-MPM [y] | | | | X | | X | X | X [y] | X [y] | X [y] | X | X [y] | |
| **Study drug IV infusion** | | | | | | | | | | | | | |
| Anetumab ravtansine arm | | | | | X | | | X | | | | | |
| Comparator (vinorelbine) arm | | | | | X | X | X | X | X | X | | | |
| **New anti-cancer treatment** | | | | | | | | | | | | X | X |

AE = Adverse event; ALT = Alanine aminotransferase; AST = Aspartate aminotransferase; BP = Blood pressure; BM = Biomarker; C = Cycle; CT = Computed tomography; CYP2D6 = Cytochrome P450, family 2, subfamily D, polypeptide 6; D = Day; ECG = Electrocardiogram; EchoCG = Echocardiogram; ECOG PS = Eastern Cooperative Oncology Group Performance Status; eGFR = Estimated glomerular filtration rate; HR = Heart rate; IHC = Immunohistochemistry; IM = Immunogenicity; IOP = Intraocular pressure; IV = Intravenous; IxRS = Interactive Voice / Web Response System; LCSS-Meso = Lung Cancer Symptom

Scale-Mesothelioma; MDASI-MPM = MD Anderson Symptom Inventory-Malignant Pleural Mesothelioma; mRECIST = Modified Response Evaluation Criteria in Solid Tumors; MRI = Magnetic resonance imaging; MUGA = Multiple gated acquisition; OS = Overall survival; PD = Progressive disease; PFS = Progression-free survival; PGt = Pharmacogenetic; PK = Pharmacokinetic(s); PR = Partial response; RR = Respiratory rate; SAE = Serious adverse event; Temp = Body temperature.

a Patients who discontinue study treatment due to any reason other than centrally confirmed radiological PD will enter active follow-up period. Patients who discontinue study treatment due to centrally confirmed PD will enter the long-term follow-up period immediately after the safety follow-up (safety follow-up visit). During active follow-up period, all assessments will be performed in parallel with CT/MRI.

b Patients in the anetumab ravtansine arm: Site visits on D8 and D15 will be performed only on C1, C2 and C3. From Cycle 4 onwards, visits on D8 and D15 are no longer required. Patients in the comparator arm: Site visits will be performed on D1, D8 and D15 of each cycle.

c Written patient informed consent must be obtained before any study-specific procedures.

d At prescreening, study disease characteristics and prior therapies for the study indication are collected (see Section 9.3.3). At full screening, study disease characteristics and prior therapies for the study indication are updated, and medical history (see Section 9.3.2) and non-study-indication-related medications collected (see Section 9.3.3).

e IxRS transaction to register the patient in the system will be done at prescreening. IxRS transaction to randomize the patient will take place maximum 24 hours before the administration of first dose of study drug and can only be done after all inclusion and exclusion criteria are checked and eligibility is confirmed *(modified by amendment 2, see section 15.1.1.19; IxRS transaction added also in the table at full screening -28 days by amendment 2)*. IxRS transactions for medication dispensing will be done on Day 1 of each cycle for the anetumab ravtansine arm and on Day 1, Day 8, and Day 15 for the comparator arm. IxRS transaction to register the end of treatment will be done at the safety follow-up visit.

f Any new finding or worsening of any ongoing medical history condition after the patient has signed the informed consent for full study must be recorded as an AE. At prescreening and active follow-up period, only AEs and SAEs related to study-specific procedures and concomitant medications that are administered to treat AEs related to study-specific procedures are mandatory to be reported. However, at the investigator's discretion, SAEs may be reported if considered potentially relevant. In such cases, the SAEs will be processed by the sponsor according to all applicable regulations.

g After C1, brief physical exams are only mandatory on D1 of each cycle and are optional as per local practice at D8 and D15 visits.

h Height is measured only at full screening.

i 12-Lead ECGs will be done during full screening, 30 min post-dose C1D1, pre-dose C2D1, pre-dose C3D1, pre-dose C4D1, pre-dose C5D1, pre-dose C6D1, and at safety follow-up visit.

j Cardiac function test is required during full screening and pre-dose C2D1, pre-dose C4D1, and afterwards at the investigator's discretion based on clinical need. During treatment, cardiac function test can be done up to 7 days before study drug administration. EchoCG shall be performed instead of MUGA when local regulations do not permit the use of MUGA as requested per protocol schedule *(footnote modified by amendment 4, see section 15.2.1.19)*.

k A detailed ophthalmologic examination (visual acuity, IOP, Schirmer test and slit lamp) will be done for all patients during full screening within 3 weeks before the start of study treatment. For patients treated in the anetumab ravtansine arm visual acuity and slit lamp exam will be repeated before infusion in every cycle except C1D1, and at safety follow-up visit, or more frequently at investigator's and ophthalmologist/optometrist's discretion (**important to refer to Table 7–5 and Table 7–6**) *(modified by amendment 2, see section 15.1.1.10)*. IOP measurement is to be repeated during anetumab ravtansine therapy if the patient receives steroid eye drops as treatment for corneal epitheliopathy; dry eye (Schirmer) test may be repeated during treatment at investigator's discretion (e.g. in case of eye dryness during anetumab ravtansine therapy) *(modified by amendment 2, see section 15.1.1.5)*. During treatment period, ophthalmologic examination can be done up to 7 days before anetumab ravtansine infusion.

l Only AST, ALT and bilirubin will be measured.

m During the study, complete urinalysis should be done when dipstick results are indicative or clinically indicated *(urine dipstick was removed from the table at visit C1D1 by amendment 2).*

n Serum pregnancy test should be repeated at least every 4 weeks until safety follow-up visit; only for women of childbearing potential.

o Pre-study CT/MRI may be acceptable as a baseline scan if done within 28 days before randomization, if centrally evaluable for mRECIST and if performed according to the Imaging Acquisition Guidance provided in the Imaging Manual. During treatment period as well as active follow-up period, tumor scans (contrast-enhanced CT/MRI of chest/abdomen/pelvis) will be performed with the same modality every 6 weeks during the first 6 months (24 weeks) after the start of study treatment, every 9 weeks until the end of year 2 (105 weeks), and every 12 weeks thereafter, until the earlier of centrally confirmed radiological disease progression, OS analysis data maturation, or end of study *(modified by amendment 6, see section 15.4.1.1)*. MRI shall be performed instead of CT when local regulations do not permit the use of CT as requested per protocol schedule. Visit window of +/- 7 days is allowed.

p Including survival status, date of death, and date of locally confirmed progression (only if no centrally confirmed PD was documented before starting long-term follow-up). Survival data will also be collected through survival sweep contact at the time of PFS final analysis and prior to OS final analysis.

q Time points of sampling are specified in Section 9.5.

r PK sampling will be performed for patients in the anetumab ravtansine arm on C1D1, C1D8, C2D1, C3D1, C3D8, C3D15, C4D1, C6D1, C9D1 and on Day 1 of every 3 cycles thereafter. Unscheduled PK samples are requested at the next clinic visit after the initial onset of corneal epitheliopathy and after the radiological assessment of the first PR (for details see Section 9.5) *(modified by amendment 2, see section 15.1.1.5)*.

s PK sampling will be performed for patients in the comparator arm on C1D1 and C1D2 (approximately 24 h after the start of C1D1 infusion) (for details see Section 9.5).

t Serum samples for immunogenicity assessment should be collected for patients in the anetumab ravtansine arm only and should always be collected before infusion. Sampling should be performed on C1D1, C2D1, C3D1, C6D1, C9D1 and on Day 1 of every 3 cycles thereafter.

u If additional archival tissue is available, optional archival tissue should be collected for patients who consent and sent when possible after C1D1. Fresh tumor tissue collection is optional after a local assessment of partial or complete response *(footnote modified and added to*

*C1D1 by amendment 4, see section 15.2.1.11)*.

v Archival tumor tissue should be used, fresh tissue should only be obtained when no archival tissue is available and when there is no additional risk for the patient in the investigator's judgement. Tissue will be used for central mesothelin expression testing via IHC.

x Biomarker plasma collection for soluble mesothelin will be done on C1D1 pre-dose. Biomarker plasma for exploratory analysis will be collected on C1D1 pre-dose, on C6D1, and at safety follow-up visit.

y MDASI-MPM and LCSS-Meso are to be completed before the patient meets with a clinician and before any examination or test is performed on that day. MDASI-MPM and LCSS-Meso are to be completed at full screening, on C2D1 and on Day 1 of every cycle thereafter (e.g. C3D1, C4D1 etc.), at safety follow-up visit, and during active follow-up period. During active follow-up period, MDASI-MPM and LCSS-Meso are to be taken in parallel with CT/MRI. In addition, the MDASI-MPM only is performed on Day 8 and Day 15 during Cycles 1, 2 and 3 *(footnote modified by amendment 2, see section 15.1.1.20)*.

z Eligibility criteria check, IxRS transaction to randomize the patient, toxicity / AE assessment, concomitant medication review, brief physical examination, vital signs and weight measurement, and ECOG PS assessment can be done within 24 hours before administration of the first dose of study drug. Eligibility must be confirmed prior to randomizing the patient in IxRS *(footnote added by amendment 2)*.

aa Lipase testing on Cycle 2 and higher Day 1 can be performed within 8 days before administration of the study treatment *(footnote added by amendment 4, see section 15.2.1.19)*.

bb Patients with neurological symptoms at screening must undergo a contrast CT or MRI scan of the brain and/or other areas of the CNS as applicable within 28 days before the start of study treatment to exclude metastatic disease in the CNS *(footnote added by amendment 4, see Section 15.2.1.5)*.

*Forced vital capacity measurement was removed by amendment 2*

*A column for -21 days ophthalmologic examination was added by amendment 4*

*Vital signs was removed from the -28 day by amendment 4*

**Table 9–2 Study flow chart – anetumab ravtansine arm patients ongoing on treatment post OS maturation – added**

| | Treatment | | | Safety follow-up period / visit | Long-term follow-up |
|---|---|---|---|---|---|
| | Every cycle | Every 2 cycles | Every 3 cycles | | |
| **Days** | **D1** | **D1** | **D1** | **+30** (after last dose) | **Every 3 months** |
| Acceptable time window (in days) (unless otherwise specified) | -1 / +7 | -1 / +7 | -1 / +7 | +7 | ± 14 |
| **Safety** | | | | | |
| Toxicity / AE assessment[a] | X | | | X | |
| Concomitant medication (only report those related to SAEs) | X | | | X | |
| Brief physical examination | X | | | X | |
| Weight | X | | | X | |
| Ophthalmologic examination[b] | | X | | X | |
| Complete blood count | X | | | X | |
| AST/ALT/total bilirubin/creatinine | X[c] | | | X | |
| Urine dipstick[d] | X | | | | |
| Serum pregnancy test (if applicable)[e] | X | | | X | |
| **Efficacy** | | | | | |
| Survival status and new anti-cancer treatment[f] | | | | | X |
| **Biomarker/Pharmacokinetic sampling** | | | | | |
| BM plasma for exploratory analysis | | | | X | |
| IM sampling (pre-dose) | | | X | | |
| PK sampling (pre-dose) | | | X | | |
| **Study drug IV infusion** | | | | | |
| Anetumab ravtansine arm | X | | | | |
| IxRS transaction[g] | X | | | X | |

AE = Adverse event; ALT = Alanine aminotransferase; AST = Aspartate aminotransferase; BM = Biomarker; D = Day; IM = Immunogenicity; IOP = Intraocular pressure; IV = Intravenous; IxRS = Interactive Voice / Web Response System; OS = Overall survival; PK = Pharmacokinetic(s); SAE = Serious adverse event.

a New finding or worsening of any ongoing medical history condition after the patient has signed the informed consent for full study must be recorded as an AE.

b Patients treated in the anetumab ravtansine arm: visual acuity and slit lamp exam will be repeated before infusion in every other cycle or more frequently at investigator's and ophthalmologist/optometrist's discretion (e.g. for patients with corneal epitheliopathy ≥ Grade 2, ophthalmologic examination will occur at least at every cycle until resolution of corneal epitheliopathy to Grades 0 or 1; **important to refer to Table 7–5 and Table 7–6**) and at safety follow-up. IOP measurement is to be repeated during anetumab ravtansine therapy if the patient receives steroid eye drops as treatment for corneal epitheliopathy; dry eye (Schirmer) test may be repeated during treatment at investigator's discretion (e.g. in case of eye dryness during anetumab ravtansine therapy). During treatment period, ophthalmologic examination can be done up to 7 days before anetumab ravtansine infusion.

c Day 1 of every cycle: AST/ALT/total bilirubin/creatinine – other chemistry laboratory parameters can be performed at the investigator's discretion but do not need to be reported unless related to an SAE or a drug-related AE of Grade ≥ 3.

d During the study, complete urinalysis should be done when dipstick results are indicative or clinically indicated.

e Serum pregnancy test should be repeated at least every 4 weeks until the safety follow-up visit; only for women of childbearing potential.

f Including survival status and date of death.

g IxRS transactions for medication dispensing will be done on Day 1 of each cycle for the anetumab ravtansine arm. IxRS transaction to register the end of treatment will be done at the safety follow-up visit.

*Table added by amendment 6, see section 15.4.1.1.*

**Table 9–3 Study flow chart – vinorelbine arm patients ongoing on treatment post OS maturation – added**

| Days | Treatment - Every cycle | | | Safety follow-up period / visit | Long-term follow-up |
|---|---|---|---|---|---|
| | **D1** | **D8** | **D15** | **+30** (after last dose) | **Every 3 months** |
| Acceptable time window (in days) (unless otherwise specified) | +/-1 | +/-1 | +/-1 | +7 | ± 14 days |
| **Safety** | | | | | |
| Toxicity / AE assessment[a] | X | X | X | X | |
| Concomitant medication (only report those related to SAEs) | X | X | X | X | |
| Brief physical examination | X | X | X | X | |
| Weight | X | X | X | X | |
| Complete blood count | X | X | X | X | |
| AST/ALT/total bilirubin/creatinine | X[b] | X[b] | X[b] | X | |
| Urine dipstick[c] | X | | | | |
| Serum pregnancy test (if applicable)[d] | X | | | X | |
| **Efficacy** | | | | | |
| Survival status and new anti-cancer treatment[e] | | | | | X |
| **Study drug IV infusion** | | | | | |
| Comparator (vinorelbine) arm | X | X | X | | |
| IxRS transaction[f] | X | X | X | X | |

AE = Adverse event; ALT = Alanine aminotransferase; AST = Aspartate aminotransferase; D = Day; IV = Intravenous; IxRS = Interactive Voice / Web Response System; OS = Overall survival; SAE = Serious adverse event.

a New finding or worsening of any ongoing medical history condition after the patient has signed the informed consent for full study must be recorded as an AE.

b Day 1, 8 and 15 of every cycle: AST/ALT/total bilirubin/creatinine – other chemistry laboratory parameters can be performed at the investigator's discretion but do not need to be reported unless related to an SAE or a drug-related AE of Grade ≥ 3.

c During the study, complete urinalysis should be done when dipstick results are indicative or clinically indicated.

d Serum pregnancy test should be repeated at least every 4 weeks until the safety follow-up visit; only for women of childbearing potential.

e Including survival status and date of death.

f IxRS transactions for medication dispensing will be done on Day 1, Day 8, and Day 15 of each cycle for the comparator arm. IxRS transaction to register the end of treatment will be done at the safety follow-up visit.

*Table added by amendment 6, see section 15.4.1.1.*

## 9.2 Visit description

If not stated otherwise, the measurements listed in the following sections will be performed by or under the supervision of an investigator or a delegate.

### 9.2.1 Prescreening

A prescreening step, including mesothelin expression level testing, can be performed without evidence of disease progression after the initial treatment cycles with platinum/pemetrexed (with or without bevacizumab) at the investigator's discretion. Written patient informed consent for prescreening must be obtained before any prescreening or study-specific procedures. Enrollment in the study is defined as the signing of the ICF.

- Written informed consent for prescreening.
- Demographics (see Section 9.3.1).
- Study disease characteristics and prior therapies for the study indication (see Section 9.3.3).
- Check eligibility criteria for prescreening (see Section 6.1.1).
- IxRS transaction to register the patient (see Section 6.4)
- Toxicity/AE assessment (see Section 9.6.1). At prescreening, only AEs and SAEs that are related to study-specific procedures are mandatory to be reported.
- Concomitant medication review (see Section 8.1). At prescreening, only concomitant medications that are administered to treat AEs related to study-specific procedures are mandatory to be reported.
- ECOG PS assessment (see Section 9.6.3.3).
- Mandatory biomarker archival or fresh biopsy tissue (see Section 9.7.1).

All patients enrolled into the study will be listed on a patient enrollment log provided by the sponsor representatives.

### 9.2.2 Full screening period

Written patient informed consent for full study must be obtained before any study-specific procedures. The maximum interval allowed between signature of informed consent and the start of study treatment is 28 days. Certain results from diagnostic testing prior to the informed consent date and time may be used to fulfill screening criteria.

**Within 28 days before the start of study treatment:**

- Written informed consent for full study.
- IxRS transaction to register the patient's full screening (see Section 6.4) *(clarified by amendment 2, see section 15.1.1.26)*

- Updates of study disease characteristics and prior therapies for the study indication (see Section 9.3.3).
- Medical history (see Section 9.3.2) and non-study-indication-related medications (see Section 9.3.3).
- Check eligibility criteria for full study, and exclusion criteria (see Section 6.1.2 and 6.2, respectively).
- Radiological tumor evaluation with contrast-enhanced CT/MRI of chest/abdomen/pelvis (see Section 9.4.1). Pre-study CT/MRI may be acceptable as a baseline scan if done within 28 days before start of study drug, if centrally evaluable for mRECIST and if performed according to the Imaging Acquisition Guidance provided in the Imaging Manual. Patients with neurological symptoms at screening must undergo a contrast CT or MRI scan within 28 days before the start of study treatment to exclude brain metastases *(bullet point modified by amendments 2 and 4, see section 15.1.1.19 and 15.2.1.5)*.

  *Forced vital capacity measurement removed by amendment 2*
- Toxicity/AE assessment: any new finding or worsening of any ongoing medical history condition after the patient has signed the full study ICF must be recorded as an AE (see Section 9.6.1).
- Concomitant medication review (see Section 8.1).
- Complete physical examination (see Section 9.6.3.2.1).

  *Vital signs removed by amendment 4*
- Weight and height.
- 12-lead electrocardiogram (ECG) (see Section 9.6.3.5).
- ECOG PS assessment (see Section 9.6.3.3).
- Echocardiogram (EchoCG) or multiple gated acquisition (MUGA) scan (see Section 9.6.3.6).

**Within 21 days before the start of study treatment:**

*A separate subsection was created for the following bullet point by amendment 4.*

- A detailed ophthalmologic examination (visual acuity, IOP, Schirmer test and slit lamp) (see Section 9.6.3.7).

**Within 7 days before the start of study treatment:**

- PROs (LCSS-Meso and MDASI-MPM) (see Section 9.4.3) before the patient meets with a clinician and before any examination or test is performed *(clarified by amendment 2, see section 15.1.1.20)*.
- Toxicity/AE assessment (see Section 9.6.1).

- Vital signs (see Section 9.6.3.4).
- Laboratory (see Section 9.6.3.1).
    - Complete blood count.
    - Electrolyte and chemistry panel.
    - Measurement of estimated GFR (eGFR) (see Appendix 16.7).
    - Coagulation panel.
    - Urine dipstick. During the study, complete urinalysis should be done when dipstick results are indicative or clinically indicated.
    - Serum pregnancy test. Test should be repeated at least every 4 weeks until safety follow-up visit; only for WOCBP.

### 9.2.3 Treatment period

After all screening assessments have been completed and the patient's eligibility has been confirmed and documented (confirmation of mesothelin overexpression moderate and stronger membrane staining in at least 30% of viable tumor cells will be obtained from central lab and confirmation of radiological eligibility will be obtained from central radiological review), the patient may begin treatment *(paragraph modified by amendments 2 and 5, see section 15.1.1.6, 15.1.1.15 and 15.3.1.2)*.

#### 9.2.3.1 Treatment – Cycle 1

**Cycle 1 Day 1**

The following procedures should be performed on C1D1 **before receiving study treatment** unless otherwise specified in the protocol. Eligibility criteria check, IxRS transaction to randomize the patient, toxicity / AE assessment, concomitant medication review, brief physical examination, vital signs and weight measurement, and ECOG PS assessment can be done within 24 hours before administration of the first dose of study drug. Eligibility must be confirmed prior to randomizing the patient in IxRS *(modified by amendment 2, see section 15.1.1.19)*.

- Check eligibility criteria for full study, and exclusion criteria (see Section 6.1.2 and 6.2, respectively).
- IxRS transaction to randomize the patient (see Section 6.4) and for medication dispensing in both treatment arms (see Section 7.3) *(modified by amendment 2, see section 15.1.1.19)*.
- Toxicity/AE assessment (see Section 9.6.1).
- Concomitant medication review (see Section 8.1).
- Brief physical examination (see Section 9.6.3.2.2).
- Vital signs (see Section 9.6.3.4).

- Weight.
- ECOG PS assessment (see Section 9.6.3.3).

  *Laboratory test: urine dipstick was removed by amendment 2*
- PK sampling (see Section 9.5):
  - In the anetumab ravtansine arm: Pre-infusion (within 1 h before the start of infusion), end of infusion (within 5 min after the end of infusion) and approximately 3 h (range: 2 to 4 h) after the start of infusion.
  - In the comparator arm: Pre-infusion (within 1 h before the start of infusion), end of infusion (within 5 min after the end of infusion), approximately 3 h (range: 2 to 4 h) after the start of infusion.
- A pharmacogenetic sample (pre-dose) for determination of patient's CYP2D6 status (see Section 9.5) in the anetumab ravtansine arm.
- Serum collection for immunogenicity assessment (see Section 9.7.2) in the anetumab ravtansine arm.
- Biomarker plasma collection for soluble mesothelin (see Section 9.7.1).
- Biomarker plasma collection for exploratory analysis (see Section 9.7.1).
- Study treatment administration (IV infusion in both anetumab ravtansine and comparator arms [see Section 7.4]).
- 12-lead ECG (see Section 9.6.3.5), 30 min (+/- 5 min) post-dose *(modified by amendment 4, see section 15.2.1.19)*.

For patients who consent to provide optional additional archival tissue, this should be collected and sent to the central laboratory at any time post randomization *(added by amendment 4, see section 15.2.1.11)*.

**Cycle 1 Day 2**

- PK sampling (see Section 9.5) for patients in the comparator arm: Approximately 24 h after the start of C1D1 infusion.

**Cycle 1 Day 8**

For assessments of this visit, time windows of -1 day and +1 day are acceptable unless otherwise specified in the protocol.

The following procedures should be performed on C1D8 **before receiving study treatment** unless otherwise specified in the protocol:

- PRO (MDASI-MPM) (see Section 9.4.3) before the patient meets with a clinician and before any examination or test is performed *(added by amendment 2, see section 15.1.1.20)*.

- IxRS transaction for medication dispensing in the comparator arm (see Section 7.3).
- Toxicity/AE assessment (see Section 9.6.1).
- Concomitant medication review (see Section 8.1).
- Brief physical examination (see Section 9.6.3.2.2).
- Vital signs (see Section 9.6.3.4).
- Weight.
- Laboratory (see Section 9.6.3.1):
    - Complete blood count.
    - Electrolyte and chemistry panel (only AST, ALT and bilirubin).
- PK sampling (see Section 9.5) for patients in the anetumab ravtansine arm: Approximately 168 (± 24) h after the start of C1D1 infusion.
- Study treatment administration (IV infusion in the comparator arm [see Section 7.4]).

**Cycle 1 Day 15**

For assessments of this visit, time windows of -1 day and +1 day are acceptable unless otherwise specified in the protocol.

The following procedures should be performed on C1D15 **before receiving study treatment** unless otherwise specified in the protocol:

- PRO (MDASI-MPM) (see Section 9.4.3) before the patient meets with a clinician and before any examination or test is performed *(added by amendment 2, see section 15.1.1.20)*.
- IxRS transaction for medication dispensing in the comparator arm (see Section 7.3).
- Toxicity/AE assessment (see Section 9.6.1).
- Concomitant medication review (see Section 8.1).
- Brief physical examination (see Section 9.6.3.2.2).
- Vital signs (see Section 9.6.3.4).
- Weight.
- Laboratory (see Section 9.6.3.1):
    - Complete blood count.
    - Electrolyte and chemistry panel (only AST, ALT and bilirubin).
- Study treatment administration (IV infusion in the comparator arm [see Section 7.4]).

#### 9.2.3.2 Treatment – Cycle 2 and higher – prior to OS maturation

*Section heading modified by amendment 6, see section 15.4.1.1.*

**Cycle 2 and higher Day 1**

For assessments of this visit, time windows of -1 day and +1 day are acceptable unless otherwise specified in the protocol.

The following procedures should be performed on Cycle 2 and higher, Day 1 **before receiving study treatment** unless otherwise specified in the protocol.

- PROs (LCSS-Meso and MDASI-MPM) (see Section 9.4.3) before the patient meets with a clinician and before any examination or test is performed *(clarified by amendment 2, see section 15.1.1.20)*.
- IxRS transaction for medication dispensing in both treatment arms (see Section 7.3).
- Toxicity/AE assessment (see Section 9.6.1).
- Concomitant medication review (see Section 8.1).
- Brief physical examination (see Section 9.6.3.2.2).
- Vital signs (see Section 9.6.3.4).
- Weight.
- 12-lead ECG (see Section 9.6.3.5) on C2D1, C3D1, C4D1, C5D1 and C6D1.
- ECOG PS assessment (see Section 9.6.3.3).
- EchoCG or MUGA scan (see Section 9.6.3.6) on C2D1, C4D1, and afterwards at the investigator's discretion based on clinical need. During treatment, cardiac function test can be done up to 7 days before study drug administration *(bullet point modified by amendment 4, see section 15.2.1.19)*.
- Ophthalmologic examinations (visual acuity and slit lamp mandatory; IOP and Schirmer test optional) (see Section 9.6.3.7) for patients treated in the anetumab ravtansine arm in every cycle from C2D1 onwards, or more frequently at investigator's and ophthalmologist/optometrist's discretion (**important to refer to Table 7–5 and Table 7–6**) *(modified by amendment 2, see section 15.1.1.10)*. To be performed within 7 days before anetumab ravtansine infusion.
- Laboratory (see Section 9.6.3.1).
    - Complete blood count.
    - Electrolyte and chemistry panel (lipase testing can be performed within 8 days before administration of the study treatment) *(modified by amendment 4, see section 15.2.1.19)*.
    - Measurement of eGFR (see Appendix 16.7).

- Coagulation panel.
- Urine dipstick.

- PK sampling (see Section 9.5) for patients in the anetumab ravtansine arm will be done on C2D1, C3D1, C4D1, C6D1, C9D1 and on Day 1 of every 3 cycles thereafter:
  - C2D1: Pre-infusion (within 1 h before the start of infusion).
  - C3D1: Pre-infusion (within 1 h before the start of infusion), end of infusion (within 5 min after the end of infusion) and approximately 3 h (range: 2 to 4 h) after the start of infusion.
  - C4D1: Approximately 504 h after the start of C3D1 infusion (within 1 h before the start of infusion on C4D1).
  - C6D1, C9D1 and on Day 1 of every 3 cycles thereafter: Pre-infusion (within 1 h before the start of infusion) and end of infusion (within 5 min after the end of infusion).

  Unscheduled PK samples are requested at the next clinic visit after the initial onset of corneal epitheliopathy *(modified by amendment 2, see section 15.1.1.5)* and after the radiological assessment of the first PR (the first local observation of at least a 30% reduction in the total tumor measurement according to mRECIST).
- Serum for immunogenicity assessment (see Section 9.7.2) in the anetumab ravtansine arm will be collected on C2D1, C3D1, C6D1, C9D1 and on Day 1 of every 3 cycles thereafter.
- Biomarker plasma for exploratory analysis (see Section 9.7.1) will be collected on C6D1.
- Study treatment administration (IV infusion in both anetumab ravtansine and comparator arms [see Section 7.4]).

**Cycle 2 and higher Day 8**

Patients in the anetumab ravtansine arm: Site visits and below-described procedures on D8 will be performed on C1, C2 and C3 only. From Cycle 4 onwards, visits on D8 are no longer required. Patients in the comparator arm: Site visits and below-described procedures will be performed on D8 of each cycle.

For assessments of this visit, time windows of -1 day and +1 day are acceptable unless otherwise specified in the protocol.

The following procedures should be performed on Cycle 2 and higher, Day 8 **before receiving study treatment** unless otherwise specified in the protocol:

- PRO (MDASI-MPM) (only C2D8 and C3D8, see Section 9.4.3) before the patient meets with a clinician and before any examination or test is performed *(added by amendment 2, see section 15.1.1.20)*.

- IxRS transaction for medication dispensing in the comparator arm (see Section 7.3).
- Toxicity/AE assessment (see Section 9.6.1).
- Concomitant medication review (see Section 8.1).
- Brief physical examination (optional as per local practice and/or at investigator's discretion, see Section 9.6.3.2.2).
- Vital signs (see Section 9.6.3.4).
- Weight.
- Laboratory (see Section 9.6.3.1):
    - Complete blood count.
    - Electrolyte and chemistry panel (only AST, ALT and bilirubin).
- PK sampling (see Section 9.5) for patients in the anetumab ravtansine arm will be done on C3D8 only: Approximately 168 (± 24) h after the start of C3D1 infusion.
- Study treatment administration (IV infusion in the comparator arm [see Section 7.4]).

**Cycle 2 and higher Day 15**

Patients in the anetumab ravtansine arm: Site visits and below-described procedures on D15 will be performed on C1, C2 and C3 only. From Cycle 4 onwards, visits on D15 are no longer required. Patients in the comparator arm: Site visits and below-described procedures will be performed on D15 of each cycle.

For assessments of this visit, time windows of -1 day and +1 day are acceptable unless otherwise specified in the protocol.

The following procedures should be performed on Cycle 2 and higher, Day 15 **before receiving study treatment** unless otherwise specified in the protocol:

- PRO (MDASI-MPM) (only C2D15 and C3D15, see Section 9.4.3) before the patient meets with a clinician and before any examination or test is performed *(added by amendment 2, see section 15.1.1.20)*.
- IxRS transaction for medication dispensing in the comparator arm (see Section 7.3).
- Toxicity/AE assessment (see Section 9.6.1).
- Concomitant medication review (see Section 8.1).
- Brief physical examination (optional as per local practice and/or at investigator's discretion, see Section 9.6.3.2.2).
- Vital signs (see Section 9.6.3.4).
- Weight.
- Laboratory (see Section 9.6.3.1):

- Complete blood count.
- Electrolyte and chemistry panel (only AST, ALT and bilirubin).

- PK sampling (see Section 9.5) for patients in the anetumab ravtansine arm will be done on C3D15 only: Approximately 336 (± 24) h after the start of C3D1 infusion.
- Study treatment administration (IV infusion in the comparator arm [see Section 7.4]).

#### 9.2.3.3 Treatment post OS maturation – anetumab ravtansine arm - Day 1

*Section added by amendment 6, see section 15.4.1.1.*

For assessments of this visit, time windows of -1 day and +7 days are acceptable unless otherwise specified in the protocol.

The following procedures should be performed at Day 1 of each cycle **before receiving study treatment** unless otherwise specified in the protocol.

- IxRS transaction for medication dispensing (see Section 7.3).
- Toxicity/AE assessment (see Section 9.6.1).
- Concomitant medication review (see Section 8.1) – only medications related to SAEs are required to be reported.
- Brief physical examination (see Section 9.6.3.2.2).
- Weight.
- Ophthalmologic examinations (visual acuity and slit lamp mandatory; IOP and Schirmer test optional) (see Section 9.6.3.7) at every other cycle or more frequently at investigator's and ophthalmologist/optometrist's discretion (e.g. for patients with corneal epitheliopathy ≥ Grade 2, ophthalmologic examination will occur at least at every cycle until resolution of corneal epitheliopathy to Grades 0 or 1; **important to refer to Table 7–5 and Table 7–6)**. To be performed within 7 days before anetumab ravtansine infusion.
- Laboratory (see Section 9.6.3.1).
  - Complete blood count.
  - AST/ALT/total bilirubin/creatinine – other chemistry laboratory parameters can be performed at the investigator's discretion but do not need to be reported unless related to an SAE or a drug-related AE of Grade ≥ 3.
  - Urine dipstick.
- PK sampling (see Section 9.5) at Day 1 of every 3 cycles.
- Serum for immunogenicity assessment (see Section 9.7.2) at Day 1 of every 3 cycles
- Study treatment administration (IV infusion, see Section 7.4).

Serum pregnancy test should be repeated at least every 4 weeks until the safety follow-up visit for WOCBP.

#### 9.2.3.4 Treatment post OS maturation – vinorelbine arm – Days 1, 8 and 15

*Section added by amendment 6, see section 15.4.1.1.*

For assessments of this visit, time windows of -1 day and +1 day are acceptable unless otherwise specified in the protocol.

The following procedures should be performed at Day 1, Day 8 and Day 15 of each cycle **before receiving study treatment** unless otherwise specified in the protocol.

- IxRS transaction for medication dispensing (see Section 7.3).
- Toxicity/AE assessment (see Section 9.6.1).
- Concomitant medication review (see Section 8.1) – only medications related to SAEs are required to be reported.
- Brief physical examination (see Section 9.6.3.2.2).
- Weight.
- Laboratory (see Section 9.6.3.1).
    - Complete blood count.
    - AST/ALT/total bilirubin/creatinine – other chemistry laboratory parameters can be performed at the investigator's discretion but do not need to be reported unless related to an SAE or a drug-related AE of Grade ≥ 3.
    - Urine dipstick (**only at Day 1 of each cycle**).
- Study treatment administration (IV infusion, see Section 7.4).

Serum pregnancy test should be repeated at least every 4 weeks until the safety follow-up visit for WOCBP.

### 9.2.4 Efficacy assessments

**Radiological tumor evaluations *(modified by amendment 2)***

**Post OS maturation, tumor assessments should be performed as per local standard of care and will no longer be required to be performed per protocol scheduling or assessment requirements, or sent for central review** *(sentence added by amendment 6, see section 15.4.1.1)*.

Prior to OS maturation, radiological tumor evaluation with contrast-enhanced CT/MRI of chest/abdomen/pelvis will be performed at the following intervals (for further details, see Section 9.4.1) *(modified by amendments 2 and 6, see section 15.1.1.3 and 15.4.1.1)*.

Full screening (baseline):

- Within 28 days before the start of study treatment *(modified by amendment 2, see section 15.1.1.19)*.

Treatment and active follow-up:

- Every 6 weeks during the first 6 months after the start of study treatment.
- Every 9 weeks until the end of year 2.
- Every 12 weeks thereafter, until the earlier of centrally confirmed radiological disease progression, OS analysis data maturation, or end of study *(modified by amendment 6, see Section 15.4.1.1)*.

  Visit window of +/- 7 days is allowed.

### 9.2.5 Follow-up periods

#### 9.2.5.1 Safety follow-up prior to OS maturation

*Section heading modified by amendment 6, see section 15.4.1.1.*

When a patient discontinues the study treatment for any reason (except death, consent withdrawal or lost to follow-up) a safety follow-up visit will be performed 30 (+7) days after the last administration of study treatment. Scheduling should ensure that a minimum of 30 days have elapsed prior to the evaluation visit to ensure adequacy of safety follow-up period.

Prior to OS maturation, the following assessments should be performed at **the safety follow-up visit** *(modified by amendment 6, see section 15.4.1.1)*:

- PROs (LCSS-Meso and MDASI-MPM) (see Section 9.4.3) before the patient meets with a clinician and before any examination or test is performed *(clarified by amendment 2, see section 15.1.1.20)*.
- IxRS transaction to register the end of treatment.
- Toxicity/AE assessment (see Section 9.6.1).
- Concomitant medication review (see Section 8.1).
- Brief physical examination (see Section 9.6.3.2.2).
- Vital signs (see Section 9.6.3.4).
- Weight.
- 12-lead ECG (see Section 9.6.3.5).
- ECOG PS assessment (see Section 9.6.3.3).

- Ophthalmologic examinations (visual acuity and slit lamp mandatory; IOP and Schirmer test optional) (see Section 9.6.3.7) for patients treated in the anetumab ravtansine arm.
- Laboratory (see Section 9.6.3.1).
    - Complete blood count.
    - Electrolyte and chemistry panel.
    - Measurement of eGFR (see Appendix 16.7).
    - Coagulation panel.
    - Serum pregnancy test; only for WOCBP.
- Biomarker plasma collection for exploratory analysis (see Section 9.7.1).

#### 9.2.5.2 Safety follow-up post OS maturation

*Section added by amendment 6, see section 15.4.1.1.*

When a patient discontinues the study treatment for any reason (except death, consent withdrawal or lost to follow-up) a safety follow-up visit will be performed 30 (+7) days after the last administration of study treatment. Scheduling should ensure that a minimum of 30 days have elapsed prior to the evaluation visit to ensure adequacy of safety follow-up period.

The following assessments should be performed at **the safety follow-up visit**:

- IxRS transaction to register the end of treatment.
- Toxicity/AE assessment (see Section 9.6.1).
- Concomitant medication review (see Section 8.1) – only medications related to SAEs are required to be reported.
- Brief physical examination (see Section 9.6.3.2.2).
- Weight.
- Ophthalmologic examinations (visual acuity and slit lamp mandatory; IOP and Schirmer test optional) (see Section 9.6.3.7) for patients treated in the anetumab ravtansine arm.
- Laboratory (see Section 9.6.3.1).
    - Complete blood count.
    - AST/ALT/total bilirubin/creatinine.
    - Serum pregnancy test; only for WOCBP.
- Biomarker plasma for exploratory analysis (see Section 9.7.1) for patients treated in the anetumab ravtansine arm.

### 9.2.5.3 Active follow-up

**Following OS maturation, active follow-up is no longer required** *(sentence added by amendment 6, see section 15.4.1.1)*.

Prior to OS maturation, patients who discontinue study treatment due to any other reason than centrally confirmed radiological PD, will continue clinic visits during active follow-up for efficacy assessments including tumor response, disease-related-symptoms, and QoL *(modified by amendments 2, 4, and 6 see section 15.1.1.3, 15.2.1.17, and 15.4.1.1)*. These assessments will continue until disease progression, consent withdrawal, lost to follow-up or end of study.

- PROs (LCSS-Meso and MDASI-MPM) (see Section 9.4.3) before the patient meets with a clinician and before any examination or test is performed *(clarified by amendment 2, see section 15.1.1.20)*. During active follow-up period MDASI-MPM and LCSS-Meso are to be taken in parallel with CT/MRI.
- Radiological tumor evaluation with contrast-enhanced CT/MRI of chest/abdomen/pelvis. During active follow-up, tumor scans will be performed with the same modality every 6 weeks during the first 6 months after the start of study treatment, every 9 weeks until the end of year 2, and every 12 weeks thereafter, until the earlier of centrally confirmed radiological disease progression, OS analysis data maturation, or end of study (see Section 9.4.1) *(modified by amendment 6, see section 15.4.1.1)*. Visit window of +/- 7 days is allowed.

  *Forced vital capacity measurement removed by amendment 2*
- Toxicity/AE assessment (see Section 9.6.1), in parallel with CT/MRI. During active follow-up period, only AEs and SAEs that are related to study-specific procedures are mandatory to be reported. However, at the investigator's discretion, SAEs may be reported if considered potentially relevant. In such cases, the SAEs will be processed by the sponsor according to all applicable regulations.
- Concomitant medication review (see Section 8.1), in parallel with CT/MRI. During active follow-up period, only concomitant medications that are administered to treat AEs related to study-specific procedures are mandatory to be reported.
- New anti-cancer treatment, in parallel with CT/MRI.

### 9.2.5.4 Long-term follow-up

Patients enter the long-term follow-up period following centrally confirmed radiological progression, or withdrawal of consent to active follow-up. Patients with centrally confirmed PD during the treatment period enter long-term follow-up immediately after the safety follow-up visit.

Following OS maturation, all patients who discontinue treatment will enter the long-term follow-up period following the safety follow-up visit *(sentence added by amendment 6, see section 15.4.1.1 and 15.4.1.2)*.

All patients in the long-term follow-up period will be contacted every 3 months (±14 days) until death, withdrawal of consent, lost to follow-up, or 24 months after the last patient's last

treatment or end of study, whichever occurs first *(modified by amendment 6, see section 15.4.1.2)*. Patients or their health care providers will be contacted either in person or by telephone. In addition, extra survival sweep contacts will be conducted at the time of PFS final analysis and prior to OS final analysis to ensure that long-term follow-up data is current.

The information to be recorded at these contacts:

- Survival status.
- Date of death.
- New anti-cancer treatment.

  *Date of locally confirmed progression removed by amendment 6, see section 15.4.1.2.*

## 9.3 Population characteristics

Population characteristics including patient demographics, medical history, and other baseline characteristics listed in this section must be documented on the CRF by the investigator before the start of study treatment.

### 9.3.1 Demographic

Baseline patient data pertaining to demographic information will be collected at prescreening, including:

- Year of birth and age
- Sex
- Race (where legally allowed)
- Ethnicity (where legally allowed)
- Region.

### 9.3.2 Medical history

Medical history findings (i.e. previous diagnoses, diseases or surgeries) meeting all criteria listed below will be collected after consent for full study is signed as available to the investigator:

- Start before signing of the informed consent for full study
- Considered relevant for the patient's study eligibility.

Detailed instructions on the differentiation between (i) medical history and (ii) AEs can be found in Section 9.6.1.1.

### 9.3.3 Other baseline characteristics

The following **study disease characteristics** will be collected as of prescreening and will be updated if applicable during screening for full study:

- Date of MPM diagnosis

- Stage of MPM at diagnosis
- Treatment of MPM before enrollment (e.g. surgery, radiation and systemic therapy)

All prior medications and significant non-drug therapies **for the study indication** will be collected as of prescreening and will be updated if applicable during screening for full study, including:

- Trade name of medication
- Reason for medication (indication)
- Dose of medication
- Start date and end date or if continuing at patient's last visit

All **non-study-indication-related** medications and significant non-drug therapies taken within 30 days before ICF signature for full study will be documented, including:

- Trade name of medication
- Reason for medication (indication)
- Dose of medication
- Start date and end date or if continuing at patient's last visit.

## 9.4 Efficacy

The primary efficacy variable is progression-free survival (PFS) based on assessment of blinded independent central review. For definition and analysis of the primary variable and for description of secondary and other variables, please refer to Section 10.3.

### 9.4.1 Radiological tumor assessments

**Post OS maturation, tumor assessments should be performed as per local standard of care and will no longer be required to be performed per protocol scheduling or assessment requirements, or sent for central review** *(sentence added by amendment 6, see section 15.4.1.1)*.

The first radiological (contrast-enhanced CT/MRI of chest/abdomen/pelvis) tumor evaluation will be conducted during full screening within 28 days before the start of study treatment (see flow chart in Section 9.1). Pre-study CT/MRI may be acceptable as a baseline scan if done within 28 days before start of study drug *(modified by amendment 2, see section 15.1.1.19)*, if centrally evaluable for mRECIST and if performed according to the Imaging Acquisition Guidance provided in the Imaging Manual. Baseline CT/MRI should be obtained prior to randomization. A sole positron emission tomography (PET) scan without a diagnostic CT/MRI is not acceptable for radiological evaluation of target lesions; findings must be confirmed by CT or MRI. Although PET scan findings may be used as supportive evidence of tumor assessment, the CT or MRI results will be the definitive and documented data for the study. All subsequent scans should be done with the identical method and technique (e.g. slice thickness, field of view) to those obtained at baseline. These screening images will be

provided to blinded central review to assess radiological eligibility (central confirmation of radiological eligibility required before randomization) *(modified by amendment 2, see section 15.1.1.15)*. If focal neurological symptoms are present at screening, a CT scan or MRI of the brain and/or other areas of the CNS as applicable is required to rule out metastastic disease in the CNS within 28 days before the start of study treatment by the investigator. All additional suspected sites of disease should be imaged (e.g. cervical lymph nodes, bone etc.) *(paragraph modified by amendment 4, see section 15.2.1.5)*.

During treatment as well as active follow-up, tumor imaging and local assessments will be performed for the following time points: every 6 weeks for the first 6 months after the start of study treatment, every 9 weeks until the end of year 2, and every 12 weeks thereafter, until the earlier of centrally confirmed radiological disease progression, OS analysis data maturation, or end of study *(modified by amendment 6, see section 15.4.1.1)*. Visit window of +/- 7 days is allowed. MRI shall be performed instead of CT when local regulations do not permit the use of CT as requested per protocol schedule.

All images need to be sent to the central review service immediately after they are obtained.

Investigators will determine treatment response locally at each investigational site according to mRECIST criteria for MPM. Preferably all scans should be interpreted by the same radiologist/investigator during the study.

In the event of locally suspected progression, the site will inform the central review service and central review will start. Radiological real-time confirmation by central independent blinded evaluation is required before a final decision to stop the treatment is made. The site should also wait for the central review results before administering the next dose of treatment. In case of uncertain radiological disease progression, the patient may stay on treatment at the investigator's discretion until progression is definitely confirmed by central review on the subsequent tumor assessment.

When the central review assessment confirms progression, treatment may be continued if the patient derives clinical benefit as determined by the treating physician per the withdrawal criteria (see Section 6.3.1.2). Otherwise, study treatment should be stopped permanently and patient will enter safety follow-up (safety follow-up visit to be scheduled 30+7 days after the last administration of study treatment) and long-term follow-up period *(paragraph modified by amendment 5, see section 15.3.1.3)*.

Once centrally confirmed radiological progression is reported, protocol tumor assessment requirements end. Subsequent tumor imaging may be performed according to treating physician's discretion if study treatment is continued. The investigator is not required to send imaging taken following centrally confirmed PD to central review, and the central reviewer is not required to review any such imaging sent *(paragraph added by amendment 5, see section 15.3.1.3)*.

In the event the central review assessment does not find progression, the severity and clinical significance of local PD finding should be assessed. If patient has not significantly clinically deteriorated and has no toxicity requiring withdrawal, the patient should continue on treatment and further imaging should be conducted as per protocol required timelines. If patient has clinically deteriorated or has toxicity such that keeping patient on treatment would

be against patient's interest, the study treatment should be stopped permanently. The patient will enter the safety follow-up (safety follow-up visit to be scheduled 30+7 days after the last administration of study treatment) and active follow-up period.

The PD events for the primary endpoint of this study, and the time point and best response values for the secondary response endpoints, will be determined by independent blinded central reviewers according to mRECIST criteria (see Appendix 16.3) at the central image review. The blinded central reviewers including the adjudicator will be radiology board certified, experienced and independent radiologists with broad expertise in oncology, radiology and MPM as well as good knowledge of mRECIST criteria for MPM (21). The central reviewers must not be otherwise involved in this study, i.e. listed or identified investigator or subinvestigator who is directly involved in the treatment or evaluation of research patients is not accepted. The central reviewers will be blinded to patient identity and study treatment. Central reviewers will be isolated from knowledge of investigator PD assessments through read lock procedures and communication controls. All image sets, i.e. CT and MRI, must be anonymized by the study sites and provided digitally as Digital Imaging and Communications in Medicine (DICOM) format. The investigator must assure that the images are of acceptable diagnostic quality and fulfill the requirements outlined in the Imaging Manual. Additional specific information on the handling (i.e. collection, shipment, tracking) of the images for the central image review will be provided separately.

The final evaluation of treatment response for those patients not undergoing central review for PD confirmation will be done by central blinded review retrospectively. The central reviewer will determine the response per mRECIST criteria of each patient as of each time point. Responses of CR and PR will be confirmed by repeated observation per mRECIST criteria. Confirmed responses of CR and PR will be dated per mRECIST criteria *(paragraph modified by amendment 4, see section 15.2.1.12)*.

In case a patient discontinues study for reasons other than centrally confirmed disease progression and doesn't want to enter or stay in the active-follow-up, information on locally confirmed date of progression should be collected during long-term follow-up. Progression results not documented by centrally collected imaging will be classified as clinical progression and used in sensitivity analysis.

*Section Pulmonary function assessment removed by amendment 2; numbering of the following sections changed accordingly*.

### 9.4.2 Survival

Patients will be contacted for survival every 3 months (±14 days) during long-term follow-up until death, withdrawal of consent, lost to follow-up, or 24 months after the last patient's last treatment or the end of study, whichever occurs first (see flow chart in Section 9.1) *(modified by amendment 6, see section 15.4.1.2)*. In addition, extra survival sweep contacts will be conducted prior to PFS final analysis and prior to OS final analysis to ensure that long-term follow-up data is current *(clarified by amendment 2, see section 15.1.1.26)*.

### 9.4.3 Patient-reported outcomes

**PRO will no longer be collected after OS maturation** *(sentence added by amendment 6, see section 15.4.1.1)*.

The effect of treatment on disease-related symptoms and disease-specific health-related quality of life (QoL) will be assessed using the MD Anderson Symptom Inventory-Malignant Pleural Mesothelioma (MDASI-MPM) and the Lung Cancer Symptom Scale-Mesothelioma (LCSS-Meso), respectively *(clarified by amendment 4, see section 15.2.1.17)*.

The LCSS-Meso will be used to assess change in thoracic cancer symptoms and health-related Quality of Life (HRQoL). In addition to the LCSS-Meso, the MDASI-MPM will be used to assess change in thoracic cancer symptoms and interference of these symptoms with daily activities *(paragraph clarified by amendment 4, see section 15.2.1.17)*.

The MDASI-MPM questionnaires will be completed at full screening (within 7 days before the start of study treatment), on C1D8, C1D15, C2D1, C2D8, C2D15, C3D1, C3D8, C3D15 and on Day 1 of every cycle thereafter (i.e. C4D1, C5D1 etc.), at safety follow-up visit and during active follow-up period. The LCSS-Meso questionnaires will be completed at full screening (within 7 days before the start of study treatment), C2D1 and on Day 1 of every cycle thereafter (i.e. C3D1, C4D1 etc.), at safety follow-up visit and during active follow-up period. During active follow-up period, MDASI-MPM and LCSS-Meso are to be taken in parallel with tumor scans i.e. with the same modality every 6 weeks during the first 6 months after the start of study treatment, every 9 weeks until the end of year 2, and every 12 weeks thereafter, until the earlier of centrally confirmed radiological disease progression, OS analysis data maturation, or end of study *(modified by amendment 6, see section 15.4.1.1)*. MDASI-MPM and LCSS-Meso are to be completed before the patient meets with a clinician and before any examination or test is performed on that day. A PRO information sheet will be provided and completed by the study personnel for each questionnaire at each visit at which the LCSS-Meso and the MDASI-MPM are to be administered, regardless of whether or not the LCSS-Meso or the MDASI-MPM are completed by the patient *(paragraph modified by amendment 2, see section 15.1.1.20)*.

Questionnaires should be completed by all patients at the time points described in the flow chart of Section 9.1, except when not logistically possible.

#### 9.4.3.1 MDASI-MPM

The MDASI-MPM has been derived from the MD Anderson Symptom Inventory-Lung Cancer (MDASI-LC). The MDASI-MPM was developed for use in mesothelioma through qualitative interviews with 20 patients with MPM. This questionnaire, the MDASI-MPM, asks patients to rate a list of symptoms (at the worst) and activities (amount of interference from symptoms) on a 0 (symptom not present or no interference) to 10 (symptom as bad as can be imagined or complete interference) numeric scale in the last 24 hours. The MDASI-MPM contains the 13 symptom items (those found to have the highest frequency and/or severity in patients with various cancers and treatment types) and 6 interference items of the validated MDASI-Core and an additional 6 symptom items developed by qualitative

interviews of 20 patients with pleural mesothelioma and 6 patients with different types of cancer receiving anetumab ravtansine (see Appendix 16.5.1).

Patient interviews containing open-ended questions were conducted by trained MD Anderson Cancer Center (MDACC) research staff. Analysis of the qualitative interviews produced a list of symptom and interference items for the content domain of the MDASI-MPM. An expert panel composed of physicians, nurses, patients, and family caregivers familiar with pleural mesothelioma rated the symptom list for relevance to reduce the number of items to the provisional list.

Psychometric characteristics will be obtained from patients in the Thoracic Medical Oncology Clinic at MD Anderson, and qualitative and psychometric results will be presented to FDA/COA reviewers for consultation. Input is being sought concerning the conceptual framework of the measure, recall period, and a sub-set of disease-related symptoms that might be included in a composite score for a responder analysis.

The MDASI-MPM will be used to assess the severity of multiple symptoms and the impact of symptoms on daily functioning.

#### 9.4.3.2 LCSS-Meso

The LCSS-Meso (28) is designed as a site-specific measure of QoL, particularly for use in clinical trials (see Appendix 16.5.2). It evaluates 5 major symptoms associated with mesothelioma and their effect on overall symptomatic distress, functional activities, and global QoL. It captures in detail those dimensions most likely to be influenced by therapeutic interventions and evaluates other dimensions globally.

The patient questionnaire consists of visual analogue scales (VAS) (100 mm horizontal line). The patient is instructed to put a mark on the line to indicate intensity of response to the items in question (0 = lowest rating; 100 = highest rating). Completion of the patient scale takes approximately 8 min initially, including demonstration of the VAS and 3-5 min for subsequent administrations.

### 9.5 Pharmacokinetics / pharmacodynamics

**Anetumab ravtansine arm**

PK samples will be collected for the analysis of the ADC and total antibody, DM4 and DM4-Me. Sparse PK samples will be collected as follows (see Sections 9.1 and 9.2):

- C1D1: Pre-infusion (within 1 h before the start of infusion), end of infusion (within 5 min after the end of infusion) and approximately 3 h (range: 2 to 4 h) after the start of infusion. A pharmacogenetic sample should be collected on C1D1 (pre-dose) for determination of patient's CYP2D6 status. Results will be used to correlate to DM4 exposure.
- C1D8: Approximately 168 (± 24) h after the start of C1D1 infusion (sample collection to coincide with the clinic safety visit).
- C2D1: Pre-infusion (within 1 h before the start of infusion).

- C3D1: Pre-infusion (within 1 h before the start of infusion), end of infusion (within 5 min after the end of infusion) and approximately 3 h (range: 2 to 4 h) after the start of infusion.
- C3D8 and C3D15: Approximately 168 (± 24) h and 336 (± 24) h after the start of C3D1 infusion (sample collection to coincide with the clinic safety visit).
- C4D1: Approximately 504 h after the start of C3D1 infusion (within 1 h before the start of infusion on C4D1).
- C6D1, C9D1 and on Day 1 of every 3 cycles thereafter: Pre-infusion (within 1 h before the start of infusion) and end of infusion (within 5 min after the end of infusion).

Unscheduled PK samples are requested at the next clinic visit after the initial onset of corneal epitheliopathy *(modified by amendment 2, see section 15.1.1.5)* and after the radiological assessment of the first PR (the first local observation of at least a 30% reduction in the total tumor measurement according to mRECIST). The date and actual clock time of this unscheduled PK sample and of the last dose of anetumab ravtansine has to be recorded on the CRF as an Unscheduled Procedure.

Unscheduled PK will no longer be performed after OS maturation *(sentence added by amendment 6, see section 15.4.1.1)*.

Measurement of alpha-1 acid glycoprotein (AAG) may be performed in select pharmacokinetic samples to estimate unbound DM4 and DM4-Me exposure *(sentence added by amendment 5, see section 15.3.1.4)*.

**Comparator (vinorelbine) arm**

Sparse PK samples will be collected for vinorelbine as follows (see Sections 9.1 and 9.2):

- C1D1: Pre-infusion (within 1 h before the start of infusion), end of infusion (within 5 min after the end of infusion), approximately 3 h (range: 2 to 4 h) after the start of infusion.
- C1D2: Approximately 24 h after the start of C1D1 infusion.

For all PK samples collected in this study, sampling times outside the suggested intervals will not be considered as protocol deviations. It is important that the actual date and time of blood sampling and start and stop times of study drug administration are documented on the CRF and patient's source document because PK calculations will be based on the actual sampling times relative to dosing times. Details about the collection, processing, storage and shipment of samples will be provided in a separate document (e.g. laboratory manual).

Plasma concentrations of all analytes will be measured using a validated method. If required, other metabolites may be measured. Exploratory measurements of other moieties may be performed, if needed.

## 9.6 Safety

### 9.6.1 Adverse events

#### 9.6.1.1 Definitions

**Definition of adverse event (AE)**

In a clinical study, an AE is any untoward medical occurrence (i.e. any unfavorable and unintended sign [including abnormal laboratory findings], symptom or disease) in a patient or clinical investigation subject after providing written informed consent for participation in the study. Therefore, an AE may or may not be temporally or causally associated with the use of a medicinal (investigational) product.

A surgical procedure that was planned prior to the start of the study by any physician treating the patient should not be recorded as an AE (however, the condition for which the surgery is required may be an AE).

New lesions or disease progression per se should not be regarded as AEs. Instead, the associated signs and symptoms should be recorded as AEs.

In the following differentiation between medical history and AEs, the term “condition” may include abnormal e.g. physical examination findings, symptoms, diseases, laboratory, ECG.

- Conditions that started before signing of informed consent for full study and for which no symptoms or treatment are present until signing of informed consent for full study are recorded as medical history (e.g. seasonal allergy without acute complaints).
- Conditions that started before signing of informed consent for full study and for which symptoms or treatment are present after signing of informed consent for full study, at unchanged intensity, are recorded as medical history (e.g. allergic pollinosis).
- Conditions that started or deteriorated after signing of informed consent for full study will be documented as AEs. This includes intercurrent illnesses.

**Definition of serious adverse event (SAE)**

An SAE is classified as any untoward medical occurrence that, at any dose, meets any of the following criteria (a – f):

a. Results in death.

b. Is life-threatening.

   The term ‘life-threatening’ in the definition refers to an event in which the patient was at risk of death at the time of the event, it does not refer to an event which hypothetically might have caused death if it were more severe.

c. Requires inpatient hospitalization or prolongation of existing hospitalization.

A hospitalization or prolongation of hospitalization will not be regarded as an SAE if at least one of the following exceptions is met:

– The admission results in a hospital stay of less than 12 hours.

– The admission is pre-planned.

(e.g. elective or scheduled surgery arranged prior to the start of the study; admission is part of the study procedures as described in Section 9.2).

– The admission is not associated with an AE
(e.g. social hospitalization for purposes of respite care).

However, it should be noted that invasive treatment during any hospitalization may fulfill the criterion of 'medically important' and as such may be reportable as an SAE dependent on clinical judgment. In addition, where local regulatory authorities specifically require a more stringent definition, the local regulation takes precedence.

d. Results in persistent or significant disability / incapacity.

Disability means a substantial disruption of a person's ability to conduct normal life's functions.

e. Is a congenital anomaly / birth defect.

f. Is another serious or important medical event as judged by the investigator.

#### 9.6.1.2 Classifications for adverse event assessment

All AEs will be assessed and documented by the investigator according to the categories detailed below.

##### 9.6.1.2.1 Seriousness

For each AE, the seriousness must be determined according to the criteria given in Section 9.6.1.1.

##### 9.6.1.2.2 Intensity

The intensity of an AE should be documented using the NCI-CTCAE v4.03 or by the Bayer grading system (see Table 7–5 and Table 7–6) for corneal epitheliopathy *(sentence added by amendment 2, see section 15.1.1.26)*. For events not listed in the NCI-CTCAE, the following scale will be used:

- Grade 1: Mild
- Grade 2: Moderate
- Grade 3: Severe
- Grade 4: Life-threatening
- Grade 5: Fatal

#### 9.6.1.2.3 Causal relationship

The assessment of the causal relationship between an AE and the administration of treatment is a decision to be made by the investigator, who is a qualified physician, based on all information available at the time of the completion of the CRF.

The assessment is based on the question whether there was a “reasonable causal relationship” to the study treatment in question.

Possible answers are “yes” or “no”

An assessment of “no” would include:

1. The existence of a highly likely alternative explanation, e.g. mechanical bleeding at surgical site.

or

2. Non-plausibility, e.g. the patient is struck by an automobile when there is no indication that the drug caused disorientation that may have caused the event; cancer developing a few days after the first drug administration.

An assessment of “yes” indicates that that the AE is reasonably associated with the use of the study treatment.

Important factors to be considered in assessing the relationship of the AE to study treatment include:

- The temporal sequence from drug administration: The event should occur after the drug is given. The length of time from drug exposure to event should be evaluated in the clinical context of the event.
- Recovery on drug discontinuation (de-challenge), recurrence on drug re-introduction (re-challenge): Patient’s response after de-challenge or re-challenge should be considered in view of the usual clinical course of the event in question.
- Underlying, concomitant, intercurrent diseases:
  Each event should be evaluated in the context of the natural history and course of the disease being treated and any other disease the patient may have.
- Concomitant medication or treatment:
  The other drugs the patient is taking or the treatment the patient receives should be examined to determine whether any of them might have caused the event in question.
- Known response pattern for this class of drug: Clinical/preclinical.
- Exposure to physical and/or mental stresses: The exposure to stress might induce adverse changes in the recipient and provide a logical and better explanation for the event.
- The pharmacology and pharmacokinetics of the study treatment:
  The pharmacokinetic properties (absorption, distribution, metabolism and excretion)

of the study treatment, coupled with the individual patient's pharmacodynamics should be considered.

- The assessment is not possible.

**Causal relationship to protocol-required procedure(s)**

The assessment of a possible causal relationship between the AE and protocol-required procedure(s) is based on the question whether there was a "reasonable causal relationship" to protocol-required procedure(s).

Possible answers are "yes" or "no".

#### 9.6.1.2.4 Action taken with study treatment

Any action on study treatment to resolve the AE is to be documented using the categories listed below.

- Drug withdrawn
- Drug interrupted
- Dose reduced
- Dose not changed
- Dose increased *(added by amendment 2, see section 15.1.1.21)*
- Not applicable
- Unknown

#### 9.6.1.2.5 Other specific treatment(s) of adverse events

- None
- Remedial drug therapy
- Other

#### 9.6.1.2.6 Outcome

The outcome of the AE is to be documented as follows:

- Recovered/resolved
- Recovering/resolving
- Recovered/resolved with sequelae
- Not recovered/not resolved
- Fatal
- Unknown

### 9.6.1.3 Assessments and documentation of adverse events

AEs observed, mentioned upon open questioning by a member of the investigator team or spontaneously reported by the patient will be documented in the patient's records and on the appropriate CRF. AEs will be documented in an event-based manner, using NCI-CTCAE version 4.03 guidelines. In addition, since the NCI-CTCAE may not adequately capture the severity of new corneal epitheliopathy, an alternative severity grading system for corneal epitheliopathy will be used (see Table 7–5 and Table 7–6) *(modified by amendment 2, see section 15.1.1.5)*.

All AE's occurring in the period between the signing of the informed consent for the full study and the end of the safety follow-up phase (safety follow-up visit) have to be recorded on the respective CRF pages by the investigator. After the end of the safety follow-up phase there is no requirement to actively collect AEs including deaths. An AE (irrespective of causal relationship) not completely resolved at the end of the pre-defined collection period must be followed up until resolution (chronicity, baseline grade or complete resolution) or until the investigator considers the event will not improve further. At prescreening and during active follow-up period, only AEs and SAEs that are **related to study-specific procedures** have to be reported. The type of information that should be assessed and recorded by the investigator for each AE is listed in Section 9.6.1.2.

"Death" should not be recorded as an AE on the AE page. Instead, "death" is the outcome of underlying AE(s).

For all SAEs the sponsor has to carry out a separate assessment for expectedness, seriousness and causal relationship to study drug.

### 9.6.1.4 Reporting of serious adverse events

The definition of SAEs is given in Section 9.6.1.1. Each SAE must be followed up until resolution or stabilization by submission of updated reports to the designated recipient.

It is not mandatory to report new SAEs occurring after the protocol-defined observation period, however, at the investigator's discretion these may be reported if considered potentially relevant. In such cases, the SAEs will be processed by the sponsor according to all applicable regulations.

#### Investigator's notification of the sponsor

All investigators will be thoroughly instructed and trained on all relevant aspects of the investigator's reporting obligations for SAEs. This information, including all relevant contact details, is summarized in the investigator site file. This information will be updated as needed.

The investigator must report immediately (within 24 hours of the investigator's awareness) all SAEs occurring during the observation period defined in Section 9.6.1.3 to the recipient detailed in the instructions for SAE reporting included in the Investigator File. For this, an AE page in the CRF as well as the complementary pages provided in the Investigator File must be completed for each SAE.

SAEs occurring after the protocol-defined observation period will be processed by the sponsor according to all applicable regulations.

If disease progression leads to signs and symptoms that meet the criteria for seriousness (see Section 9.6.1.1), the associated signs and symptoms should be reported as SAE, not the underlying cause (i.e. "progressive disease" should not be recorded as SAE**). In this case, disease progression should be mentioned on the SAE form as "alternative explanation".**

If a new primary malignancy is noted at any time before end of active follow-up, it must be reported as an SAE, whether or not it is assessed as related to study treatment.

For documentation of laboratory findings as SAE, please refer to Section 9.6.3.1.

**Notification of the IECs / IRBs**

Notification of the IECs / IRBs about all relevant events (e.g. SAEs, suspected, unexpected, serious adverse reactions [SUSARs]) will be performed by the sponsor and/or by the investigator according to all applicable regulations.

**Notification of the authorities**

The processing and reporting of all relevant events (e.g. SAEs, SUSARs) to the authorities will be done by the sponsor according to all applicable regulations.

**Sponsor's notification of the investigational site**

The sponsor will inform all investigational sites about reported relevant events (e.g. SUSARs) according to all applicable regulations.

### 9.6.1.5 Expected adverse events

For this study, the applicable reference document for anetumab ravtansine is the most current version of the IB. For vinorelbine, applicable product information leaflets will be used.

Overview listings of frequent events that have occurred so far in the clinical development are shown in the current IB. If relevant new safety information is identified, the information will be integrated into an update of the IB and distributed to all participating sites.

The expectedness of AEs will be determined by the sponsor according to the applicable reference document and according to all local regulations.

### 9.6.1.6 Adverse events of special safety interest

Anetumab ravtansine is an investigational drug and current knowledge of the AEs associated with this compound is limited.

As with any new chemical entity, there is always potential for unexpected AEs, including hypersensitivity reactions.

Corneal epitheliopathy is considered as AE of special interest. Specific dose modification schemes are defined in Section 7.4.2.1. An alternative severity grading system for corneal epitheliopathy will be used in addition to NCI-CTCAE version 4.03 criteria, since the NCI-

CTCAE may not adequately capture the severity of these novel adverse reactions (see Table 7–5 and Table 7–6) *(paragraph modified by amendment 2, see section 15.1.1.5)*.

There is no need for expedited reporting or use of complementary pages to report corneal epitheliopathy, unless it meets the criteria for an SAE as defined in Section 9.6.1.1 *(modified by amendment 2, see section 15.1.1.14)*; however these events will need to be closely monitored and reviewed, and documented timely and accurately both in source data and on the CRF. Details of ophthalmologic examination will be documented on the "ophthalmologic examination" and "slit lamp" CRF pages and in case AEs occur, also on "AE" CRF page, ensuring the reporting terminology used on those pages matches and reflects the source.

### 9.6.2 Pregnancies

The investigator must report to the sponsor any pregnancy occurring in a female study patient during her participation in this study. The outcome of the pregnancy should be followed up carefully, and any outcome of the mother and the child at delivery should be reported.

The child's health should be followed up until 4 weeks after birth.

For a pregnancy in the partner of a male study patient, all efforts will be made to obtain similar information on course and outcome, subject to the partner's consent.

For all reports, the forms provided are to be used. The investigator should submit them within the same timelines as an SAE.

Only those pregnancies with abnormal outcome need to be reported as SAEs. All pregnancies must be reported on additional pregnancy report forms provided to the site *(paragraph added by amendment 4, see section 15.2.1.19)*.

### 9.6.3 Further safety

#### 9.6.3.1 Laboratory evaluations

Safety laboratory analyses will be performed locally according to the schedule summarized in the flow charts of Section 9.1.

- Complete blood count: Hemoglobin, hematocrit, platelet count, red blood cell count (RBC), white blood cell count (WBC). WBC must include differential including neutrophil, lymphocyte, monocyte, basophil, and eosinophil counts *(bullet point modified by amendment 4, see section 15.2.1.19)*.
- Electrolyte and chemistry panel: sodium, potassium, chloride, calcium (total, corrected, or ionized), phosphorus, glucose (fasting or random/unspecified), AST, ALT, gamma-glutamyl transferase (GGT), bilirubin (total and direct), ALP, uric acid, total protein, albumin, lipase, amylase, lactic dehydrogenase (LDH), blood urea nitrogen (BUN) or urea, and creatinine *(bullet point modified by amendment 4, see section 15.2.1.19)*.
- **Post OS maturation, only AST, ALT, total bilirubin and creatinine are required;** other chemistry laboratory parameters can be performed at the investigator's discretion but do not need to be reported unless related to an SAE or a drug-related AE of Grade ≥ 3 *(bullet point added by amendment 6, see section 15.4.1.1)*.

- Coagulation panel: PTT or aPTT or PTT ratio, and PT or PT-INR or PT ratio.
- Urinalysis: Only dipstick test will be done, and complete urinalysis (e.g. microscopic analysis of the urine sediment) will only be done if the dipstick results are indicative or clinically indicated.
- Serum pregnancy test in WOCBP. Test should be repeated at least every 4 weeks until safety follow-up visit. Postmenopausal women who have not had periods for more than 1 year without an alternative medical cause or surgically sterilized women will not be required to undergo a serum pregnancy test (this information should be recorded under medical history on the CRF).
- eGFR according to the MDRD abbreviated formula (see Appendix 16.7).

An isolated laboratory abnormality that meets the criteria for a CTCAE Grade 4 classification is not reportable as an SAE, unless the investigator assesses that the event meets standard International Council for Harmonization (ICH) criteria for an SAE (see SAE definition in Section 9.6.1.1) *(updated by amendment 2, see section 15.1.1.26)*. All laboratory abnormalities, including CTCAE Grade 4 abnormalities, will be documented on the laboratory CRF.

#### 9.6.3.2 Physical examination

Physical examinations will be performed according to the schedule summarized in the flow charts of Section 9.1. Clinically significant abnormal physical examination findings are recorded either as medical history or as AEs (see Section 9.6.1.1).

##### 9.6.3.2.1 Complete physical examination

Complete physical examination of all organ systems includes:

- General appearances
- Skin
- Eyes
- Ears, nose and throat
- Head and neck
- Pulmonary/thoracic
- Cardiovascular
- Abdomen
- Lymph nodes
- Musculoskeletal system (including extremities and spine)
- Genito-urinary system

If indicated by the patient's history, the following will be examined by specialists, if applicable:

- Gynecological organs
- Rectum

#### 9.6.3.2.2 Brief physical examination

Brief physical examination includes, but is not limited to, review of organ systems and physical areas of symptomatic concern or investigator's degree of suspicion for any abnormality. After Cycle 1, brief physical examinations are only mandatory on Day 1 of each cycle and are optional as per local practice at Day 8 and Day 15 visits.

### 9.6.3.3 ECOG Performance Status

**ECOG PS will no longer be collected after OS maturation** *(sentence added by amendment 6, see section 15.4.1.1)*.

Change of ECOG PS will be measured for safety reason; grading definitions are given in Appendix 16.1. ECOG PS will be assessed at prescreening, full screening, on Day 1 of each cycle and at safety follow-up visit (see flow chart in Section 9.1).

### 9.6.3.4 Vital signs

**Vital signs will no longer be collected after OS maturation apart from body weight for dose calculation** *(sentence added by amendment 6, see section 15.4.1.1)*.

Body weight/height, heart rate, blood pressure, body temperature, and respiratory rate will be assessed according to the schedule summarized in the flow chart of Section 9.1. Height is measured in centimeters (cm) and obtained only at full screening. Body weight will be measured in kilograms (kg), measurement units 0.1 kg, and should be obtained without shoes. If clinically indicated (e.g. excessive weight loss), it is at the investigator's discretion to perform these measurements more frequently. Blood pressure has to be measured in a consistent manner throughout the study (preferably using a manual cuff at the same arm with the patient sitting for 5 min before the measurement). Any clinically relevant measurements or changes are to be reported as AEs (e.g. weight gain or loss, hypertension, tachycardia, bradycardia, etc.).

### 9.6.3.5 12-lead ECG

**ECGs will no longer be performed after OS maturation** *(sentence added by amendment 6, see section 15.4.1.1)*.

12-lead ECGs will be performed according to the schedule summarized in the flow chart of Section 9.1. The overall interpretation of the ECG (normal/abnormal, clinical relevance) and the ECG diagnosis will be documented in the source documents and on the CRF. This review should be completed by a qualified physician and signed and dated at the time of review.

### 9.6.3.6 Cardiac function

Cardiac function test is mandatory. It will be measured by EchoCG or MUGA scan at full screening and on C2D1, C4D1, and afterwards at the investigator's discretion based on clinical need (see flow chart in Section 9.1). During treatment, cardiac function test can be done up to 7 days before study drug administration. EchoCG shall be performed instead of

MUGA when local regulations do not permit the use of MUGA as requested per protocol schedule *(paragraph modified by amendment 4, see section 15.2.1.19)*.

#### 9.6.3.7 Ophthalmologic examinations

Corneal epitheliopathy has been identified as a TEAE of special interest for which a causal relationship with anetumab ravtansine has been deemed probable by the investigators in Phase I trial. A detailed ophthalmologic examination (visual acuity [BCVA according to ETDRS, or Snellen, or Landolt C or other charts], IOP, dry eye test [Schirmer test] and slit lamp) will be done for all patients during full screening within 3 weeks before the start of study treatment (see flow chart in Section 9.1). For patients treated in the anetumab ravtansine arm, visual acuity test and slit lamp examination will be repeated before infusion in every cycle except C1D1 **(and every other cycle after OS maturation)**, and at safety follow-up visit, or more frequently at investigator's and ophthalmologist/optometrist's discretion (e.g. for patients with corneal epitheliopathy ≥ Grade 2, ophthalmologic examination will occur at least at every cycle until resolution of corneal epitheliopathy to Grades 0 or 1) (**important to refer to Table 7–5 and Table 7–6**). IOP measurement is to be repeated during anetumab ravtansine therapy if the patient receives steroid eye drops as treatment for corneal epitheliopathy; dry eye (Schirmer) test may be repeated during treatment at investigator's discretion (e.g. in case of eye dryness during anetumab ravtansine therapy). During treatment, ophthalmologic examination can be done up to 7 days before anetumab ravtansine infusion *(paragraph modified by amendments 2 and 6, see section 15.1.1.5, 15.1.1.10 and 15.4.1.1)*.

In certain countries, an optometrist or equivalent specialist may be licensed to perform the eye examinations as detailed above; as per ICH-GCP, at the Principal Investigator's discretion, a chosen specialist can perform required eye exams *(added by amendment 2, see section 15.1.1.10)*.

## 9.7 Other procedures and variables

### 9.7.1 Biomarkers

Preclinical and Phase I evidence suggests that mesothelin expression (or expression level above a certain threshold) in human tumors may be required for binding, internalization, and anti-tumor activity of anetumab ravtansine. All patients will have formalin-fixed, paraffin-embedded (FFPE) tumor samples available for IHC determination of mesothelin expression at prescreening as a potential predictive biomarker (see also flow chart in Section 9.1). In the absence of archival tissue, fresh biopsies may be used if deemed safe by the investigator and there is no additional risk for the patient in the investigator's judgement. Only patients whose tumors express mesothelin at membrane staining intensity of moderate and stronger in at least 30% of viable tumor cells will participate further in this study *(modified by amendments 2 and 5, see section 15.1.1.6 and 15.3.1.2)*. Mesothelin levels will be determined using a validated IHC assay (clone SP74).

In addition to obligatory measurement of mesothelin expression levels, plasma levels of soluble mesothelin at baseline (whole blood on C1D1 pre-dose) will be studied to evaluate whether plasma mesothelin levels may correlate with response rate and be of predictive value.

Biomarker plasma (from whole blood) will be collected on C1D1 pre-dose, on C6D1, and at safety follow-up visit to analyze circulating tumor DNA, too.

For patients who provide optional consent, exploratory biomarker analysis may also be performed using additional fresh or archival tumor tissue to determine alterations in tumor-associated genes and to perform gene expression analysis. If additional archival tissue is available after randomization, tissue should be sent for analysis to the central laboratory. Fresh tumor tissue should be collected after a local assessment of response (complete response [CR] or partial response [PR]) for patients who consent to this procedure. The exploratory biomarkers may include, but are not limited to, DNA sequencing of tumor-associated genes and gene expression profiling. Next generation sequencing (NGS), and RNA, protein or miRNA expression analysis may be performed. The analysis of changes in the genomic and expression profile (e.g. mesothelin expression) in tumor tissue over time on drug treatment may elucidate the underlying molecular mechanism of drug response and intrinsic and acquired resistance to anetumab ravtansine *(paragraph modified by amendment 4, see section 15.2.1.11)*.

In addition to the biomarkers listed above, other biomarkers deemed relevant to gain further knowledge about the pathomechanism of the disease or about the drug (i.e. mode of action-related effect or safety of the drug) may be measured, based on newly emerging data from other ongoing studies and/or literature data *(clarified by amendment 5, see section 15.3.1.7)*.

Details on the collection, processing, storage and shipment of biomarker samples will be provided in separate documents (e.g. sample handling sheets or lab manual).

### 9.7.2 Immunogenicity

Serum samples for immunogenicity assessment should be collected for patients in the anetumab ravtansine arm on C1D1, C2D1, C3D1, C6D1, C9D1 and on Day 1 of every 3 cycles thereafter (see flow charts in Section 9.1). On all days, serum sample for immunogenicity assessment should be collected before infusion. Immunogenicity assessment will include a determination of binding and neutralizing anti-drug antibodies (ADAs and NABs, respectively) and a titer determination.

## 9.8 Appropriateness of procedures / measurements

The efficacy assessments used in the study include those considered SoC to evaluate anti-tumor activity in patients with advanced or metastatic MPM.

The safety assessments are appropriate and standard to monitor safety and assess toxicity.

**Appropriateness of PFS as primary endpoint**. OS is generally recognized as the gold standard for establishing treatment efficacy in late-stage cancer. However, MPM is a rare disease. The 10.5 patients/month accrual rate with 8-months ramp-up estimated as feasible in this study would be insufficient to support the sample sizes needed to reliably power an OS study in a time period reasonable for a Phase II study in the context of an unmet medical need. PFS represents a widely-used and accepted clinical endpoint achievable in the present context. Accordingly, PFS represents an appropriate primary endpoint in this study.

**Appropriateness of mRECIST criteria**. RECIST 1.1 criteria, designed to assess spherically shaped solid tumors, may be an unreliable method in the context of the lens/crescent-shaped pleural lesions found in MPM (29). mRECIST criteria were designed and validated to measure the specific context of MPM (21, 30). Accordingly, mRECIST criteria are appropriate for the study context.

*Appropriateness of forced vital capacity measurement removed by amendment 2*

**Appropriateness of PROs.** The Lung Cancer Symptom Scale (LCSS) modified for patients with mesothelioma (LCSS-Meso) is a potentially appropriate instrument for clinical trials of mesothelioma therapies. The original model underpinning the psychometric testing of the LCSS was modified slightly and tested in 495 patients who had MPM. The LCSS-Meso is an 8-item patient scale (the item evaluating hemoptysis was dropped from the original LCSS; the rest of the items remain the same). The findings of the validation study support the use of the LCSS-Meso as a sensitive instrument for serial measurement during clinical trials and yields reproducible results for patients with mesothelioma (31, 32).

In addition to the LCSS-Meso, the MDASI-MPM will be completed by patients (according to Table 9–1). The MDASI contains 13 “core” symptoms that are reported with high frequency or unusual severity in an outpatient cancer patient population. The measure also has 6 items that describe how much the symptoms have interfered with different aspects of the patient’s life during the past 24 h. These include: general activity, mood, walking ability, normal work (including both work outside the home and housework), relations with other people, and enjoyment of life, with 0 being “did not interfere,” and 10 being “interfered completely”. This questionnaire has been used extensively to measure symptoms and symptom interference in patients with different types of cancer. In addition to the 13 core symptom items, and the 6 interference items, the MDASI-MPM includes 6 mesothelioma-specific and treatment-specific items: Mesothelioma-specific symptom items are being identified through qualitative interviews with patients with MPM and will be used in this study. This questionnaire is intended to be a “fit for purpose” questionnaire to assess the symptoms most common to patients with locally advanced or metastatic MPM.

# 10. Statistical methods and determination of sample size

## 10.1 General considerations

Statistical analysis will be performed using SAS version 9.2 or later; the version used will be specified in the SAP.

In general, continuous variables will be summarized using number of non-missing values (n), number of missing values, means, standard deviations, medians, maximum, minimum, and interquartile range.

Ordinal variables will be summarized using n, number of missing values, medians, maximum, minimum, and interquartile range.

Categorical variables will be summarized using n, number of missing values, and percentages.

Time-to-event variables will be summarized using Kaplan-Meier estimates.

Further details on the statistical analyses will be provided in the SAP.

Reports of data updated following the cut-off for the final OS analysis will be descriptive in character, and may consist of listings *(sentence added by amendment 6, see section 15.4.1.1)*.

## 10.2 Analysis sets

The statistical analysis sets are defined as follows:

**Intent-to-treat set (ITT)**. All randomized patients will be included in the ITT. Patients in this set will be reported by treatment arm as randomized. This set will be used for patient characteristics, demographic, and efficacy evaluations.

**PK set.** All patients with at least one valid PK sample for anetumab ravtansine will be included in the analysis set for the anetumab ravtansine PK analysis. All patients with at least one valid PK sample for vinorelbine will be included in the analysis set for the PK analysis of vinorelbine. PK samples will be considered valid under the following conditions: known dose, known duration of treatment, known time of sample collection *(paragraph modified by amendment 4, see section 15.2.1.13)*.

**Immunogenicity set.** All patients who have received at least one dose of anetumab ravtansine and have valid post-baseline measurement of ADAs or NABs will be included in the analysis set for the immunogenicity analysis of anetumab ravtansine which is defined as the immunogenicity set.

**Safety set (SAF).** All treated patients, that is, all randomized patients receiving any amount of any study treatment, will be included in the SAF. Patients in this set will be reported by treatment arm as treated. The SAF will be used for safety evaluations.

**Quality of life set (QOL).** All randomized patients with a non-missing LCSS-Meso evaluation at baseline will be included in the QOL dataset. Patients in this set will be reported by treatment arm as randomized. The QOL set will be used for QoL evaluations *(paragraph clarified by amendment 4, see section 15.2.1.17)*.

**Biomarker set (BIO).** All patients evaluated for mesothelin expression at prescreening will be included in the biomarker set. The biomarker set will be used for biomarker analyses. Evaluability for analyses of efficacy and safety by biomarker status will be described in the SAP.

**Enrolled set (ENR).** All patients who signed the informed consent for any portion of the study including prescreening *(clarified by amendment 2, see section 15.1.1.26)*. Enrolled patients will be used for patient disposition.

Further details on analysis sets will be described in the SAP.

## 10.3 Variables and planned statistical analyses

For missing data, please refer to Section 11.4.

### 10.3.1 Population characteristics

Population characteristics (see Section 9.3) will be reported by summary statistics and listings. Further details will be described in the SAP.

### 10.3.2 Primary efficacy variable

**Progression-free survival (PFS)** is defined as time from randomization until disease progression (according to mRECIST for MPM, per blinded central radiology review) or death. Patients not experiencing death or progression will be censored at the last tumor assessment.

Additional details, including additional censoring rules, will be described in the SAP.

**Primary efficacy analysis**

The primary efficacy analysis tests the following hypotheses:

H0: In patients with advanced or metastatic MPM overexpressing mesothelin and progressed on 1st line platinum/pemetrexed-based chemotherapy, PFS under treatment with anetumab ravtansine at 6.5 mg/kg Q3W is not superior to PFS under treatment with 30 mg/m$^2$ QW vinorelbine.

*versus*

HA: In patients with advanced or metastatic MPM overexpressing mesothelin and progressed on 1st line platinum/pemetrexed-based chemotherapy, PFS under treatment with anetumab ravtansine at 6.5 mg/kg Q3W is superior to PFS under treatment with 30 mg/m$^2$ QW vinorelbine.

These hypotheses will be tested at the primary efficacy final analysis using a 1-sided log-rank test at significance level of 0.0125, stratified by geographic region (RoW *versus* Asia) and per TTP on 1st line treatment (≥ 6 months *versus* < 6 months).

Assuming true median PFS of 3.6 months under vinorelbine treatment and constant hazards, the study primary hypothesis test is designed to detect a 100% prolongation of true PFS (median 7.2 months) in the anetumab ravtansine arm in comparison to the comparator arm (hazard ratio 0.5) with 90% power with a 1-sided significance level of 0.0125 *(sentence clarified by amendment 2, see section 15.1.1.26).*

The final primary endpoint analysis will be performed after approximately 117 PFS events have been observed. In addition to the stratified log-rank test described above, PFS will be summarized using Kaplan-Meier (33) estimates. Plots will be produced by treatment arm. Medians and Brookmeyer-Crowley (34) confidence intervals will be reported. Hazard ratios (anetumab ravtansine regimen/vinorelbine) will be estimated using Cox proportional hazards models (35) stratified by the same factors. Subgroup analyses will be performed as described in the SAP. Additional details will be described in the SAP.

Assumption-checking and sensitivity analyses will be performed, consistent with regulatory guidance on progression-free survival endpoints including Appendix 1 to the EMA guideline on the evaluation of anti-cancer medicinal products in man (36) and the FDA guidance on

clinical trial endpoints for the approval of non-small cell lung cancer drugs and biologics (37), including analyses to assess the impact of missing data; the possibility of informative censoring, survivorship, and selection biases; the proportional hazards assumption; and the impact of clinical progression and subsequent therapy. Investigator progression will be evaluated as a sensitivity analysis, and concordance between investigator and independent central review determinations will be evaluated. Details will be described in the SAP *(paragraph modified by amendment 4, see section 15.2.1.15)*.

An updated analysis of PFS will be performed at the time of the final Overall Survival analysis (See Section 10.3.3.1). Details will be described in the SAP *(paragraph added by amendment 4, see section 15.2.1.14)*.

### 10.3.3 Secondary variables

#### 10.3.3.1 Secondary efficacy variables

Additional details, including additional censoring rules for time-to-event variables, will be described in the SAP *(sentence added by amendment 2, see section 15.1.1.26)*.

**Overall survival (OS)**, defined as time from randomization until death from any cause. Patients lost to follow-up or alive at the time of analysis will be censored at the last known alive date.

*Forced vital capacity response rate was removed by amendment 2*

**Objective response rate (ORR)**: A patient is a responder if the patient has a confirmed tumor response on-study of CR or PR, as determined by the central radiological reviewer per mRECIST criteria. The ORR in each arm is the number of responders divided by the number of randomized patients.

**Disease control rate (DCR)**: A patient has disease control if the patient has a confirmed tumor response of CR or PR or a tumor response of SD as determined by the central radiological reviewer per mRECIST criteria. The DCR in each arm is defined as the number of patients with disease control divided by the number of randomized patients (*definition modified by amendment 4, see section 15.2.1.19*).

**Duration of response (DOR)** is defined in responders as the time from documentation of tumor response to disease progression or death without documented progression, as determined by the central radiological reviewer.

**Durable response rate (DRR)**: A durable responder is defined as a responder with a duration of response (CR or PR per mRECIST criteria, as determined by the central radiological reviewer) of 180 days or more. The DRR in each arm is the number of durable responders divided by the number of randomized patients *(variable added by amendment 4)*.

**Patient-reported outcomes**

*Subsection modified by amendment 4, see section 15.2.1.16.*

Patient-reported outcomes (PROs) will be evaluated based on the MD Anderson Symptom Inventory-Malignant Pleural Mesothelioma (MDASI-MPM).

An independent PRO review committee of PRO, statistical, and psychometric experts, blinded to study treatment, will conduct analyses based on regulatory feedback, data from independent studies, and pooled study data from this study following database lock at primary analysis, to support validation of the MDASI-MPM instrument and determine key definitions and details as described below.

**Time to worsening of symptoms characteristic of mesothelioma** is defined in patients **evaluable for assessing worsening of symptoms**, as the time from randomization until the first **worsening of symptoms** characteristic of mesothelioma. Worsening must be confirmed by a second MDASI-MPM assessment. Patients who died, were lost to follow-up, or ended MDASI-MPM assessments without confirmed worsening of symptoms will be censored at the date of their last MDASI-MPM assessment with a non-missing **total subset score**.

**Time to worsening of pain** is defined in patients **evaluable for assessing worsening of pain**, as time from randomization until the first **worsening of pain**. Worsening must be confirmed by a second MDASI-MPM assessment. Patients who died, were lost to follow-up, or ended MDASI-MPM assessments without confirmed worsening of pain will be censored at the date of their last MDASI-MPM assessment with a non-missing pain score.

**Improvement rate of symptoms characteristic of mesothelioma** is defined in each randomized study arm as the number of patients with confirmed **improvement of symptoms** characteristic of mesothelioma, divided by the number of patients **evaluable for improvement** of symptoms characteristic of mesothelioma. Improvement in each patient must be confirmed by a second MDASI-MPM assessment.

**Improvement rate of pain** is defined in each randomized study arm as the number of patients with confirmed **improvement of pain**, divided by the number of patients **evaluable for improvement of pain**. Improvement in each patient must be confirmed by a second MDASI-MPM assessment.

For analyses of the above PRO endpoints, the following terms will be defined by the independent blinded PRO review committee:

- **Worsening of symptoms characteristic of mesothelioma** as measured by the MDASI-MPM questionnaire total score of the subset of symptoms.
- **Improvement of symptoms characteristic of mesothelioma** as measured by the MDASI-MPM questionnaire total score of the subset of symptoms.
- **Worsening of pain** as measured by the “pain at its worst” item of the MDASI-MPM.
- **Improvement of pain** as measured by the “pain at its worst” item of the MDASI-MPM.

For each term, the independent blinded PRO review committee will determine the specific change from baseline constituting improvement or worsening, and will define the minimum and/or maximum baseline score and other criteria constituting **evaluability** to determine improvement or worsening for the respective term.

For symptoms characteristic of mesothelioma, the independent blinded PRO review committee will also define the applicable subset of MDASI-MPM items, and the calculation

algorithm to calculate **the total subset score** on that subset at each assessment, including handling of missing or partially missing data.

The independent blinded PRO review committee and its analyses will be further described in the Independent Blinded PRO Review Committee Charter and/or the Independent Blinded PRO Review Analysis Plan.

**Secondary efficacy analysis**

*Subsection modified by amendment 4, see section 15.2.1.18 and 15.2.1.14.*

For regulatory label claim purposes, to preserve the overall Type I error rate, secondary endpoint hypothesis testing will be performed for the following key secondary efficacy variables in the event of primary endpoint superiority, according to the following hierarchy:

- Overall survival
- Time to worsening of symptoms characteristic of mesothelioma
- Time to worsening of pain
- Improvement rate of symptoms characteristic of mesothelioma
- Improvement rate of pain

Secondary OS will be evaluated separately in a 2-stage group sequential procedure as further described below, with final analysis expected to occur after the primary endpoint analysis.

Final analysis for duration of response and durable response rate will be performed at the time of the final OS analysis. An interim analysis of these variables will be performed at time of the final PFS analysis. Details will be described in the SAP.

Final analysis for other secondary variables will occur at the same time as the primary endpoint analysis. To preserve the validity of the secondary endpoint hierarchy and control of overall study-wide secondary Type I error, superiority for secondary endpoint hypothesis tests ranking below OS in the hierarchy cannot be declared for regulatory label claim purposes until OS hypothesis testing succeeds. Accordingly, unless OS superiority is found at the interim OS analysis, the hypothesis testing outcome of endpoints ranking below it will not be fully effective, and any superiority for these endpoints cannot be declared for regulatory label claim purposes, until the outcome of the OS hypothesis test is determined and OS superiority found at the final OS analysis. An updated analysis of these secondary variables will occur at time of the final OS analysis.

The secondary efficacy OS analysis tests the following hypotheses:

H0: In patients with advanced or metastatic MPM overexpressing mesothelin and progressed on 1$^{st}$ line platinum/pemetrexed-based chemotherapy, OS under treatment with anetumab ravtansine at 6.5 mg/kg Q3W is not superior to OS under treatment with 30 mg/m$^2$ QW vinorelbine.

*versus*

HA: In patients with advanced or metastatic MPM overexpressing mesothelin and progressed on 1st line platinum/pemetrexed-based chemotherapy, OS under treatment with anetumab ravtansine at 6.5 mg/kg Q3W is superior to OS under treatment with 30 mg/m$^2$ QW vinorelbine.

These hypotheses will be tested using a 2-stage group sequential hypothesis test procedure. Each stage will utilize a 1-sided log-rank test, stratified by geographic region (RoW *versus* Asia) and per TTP on 1st line treatment (≥ 6 months *versus* < 6 months).

Assuming true median OS of 9.6 months under vinorelbine treatment and constant hazards, the 2-stage group sequential hypothesis test is designed to detect a 60% prolongation of true OS (median 15.4 months) in the anetumab ravtansine arm in comparison to the comparator arm with an overall 80% power and an overall 1-sided significance level of 0.025 (hazard ratio 0.625) *(modified by amendment 2, see section 15.1.1.1)*.

The interim OS analysis will be performed at the time of the final primary endpoint (PFS) analysis, when an estimated 80 OS events will be observed. If the study is not stopped for superiority at the interim analysis, the final OS analysis will occur when approximately 159 OS events have been observed. A Lan-Demets alpha spending function (38) with O'Brien-Fleming boundaries (39) will be used, based on actual events at the time of the interim analysis. Approximately 0.00158 alpha is estimated to be spent at the interim analysis and 0.02342 at the final if 80 OS events are observed at the interim analysis. The actual alpha levels will be based on the actual number of events included in the interim analysis. The group sequential testing procedure is further described in Section 10.4, and additional details will be described in the SAP *(paragraph modified by amendment 2, see section 15.1.1.1)*.

At each analysis, OS will also be evaluated be summarized using Kaplan-Meier (33) estimates. Plots will be produced by treatment arm. Medians and Brookmeyer-Crowley (34) confidence intervals will be reported.

Other key secondary time-to-event variables (time to worsening of symptoms characteristic of mesothelioma, time to worsening of pain) will be tested using a 1-sided log-rank test stratified by geographic region (RoW versus Asia) and per TTP on 1st line treatment (≥ 6 months versus < 6 months), with a 1-sided significance level of 0.025. In addition, all other secondary time-to-event variables (time to worsening of symptoms characteristic of mesothelioma, time to worsening of pain, DOR) will be summarized using Kaplan-Meier (33) estimates. Plots will be produced by treatment arm. Medians and Brookmeyer-Crowley (34) confidence intervals will be reported. Further details will be described in the SAP.

Select secondary response rate variables (improvement rate of symptoms characteristic of mesothelioma, improvement rate of pain) will be tested using a Cochran-Mantel-Haenszel test (40) stratified by geographic region (RoW versus Asia) and per TTP on 1st line treatment (≥ 6 months versus < 6 months), with a 1-sided significance level of 0.025. In addition, all secondary response rate variables (ORR, DCR, DRR, improvement rate of symptoms characteristic of mesothelioma, improvement rate of pain) will be summarized by treatment arm including number of patients (N), response rates, and Clopper-Pearson (41) exact binomial confidence intervals. In addition, each response category will be summarized. Further details will be described in the SAP.

Sensitivity analyses will be performed, including analyses to assess the impact of missing data and the possibility of survivorship and selection biases. Further details will be described in the SAP.

Further details on secondary efficacy analyses will be described in the SAP.

#### 10.3.3.2 Other efficacy variables

- MDASI-MPM symptom interference score
- LCSS-Meso total score
- LCSS-Meso 3 summary item score

Other efficacy variables will be summarized descriptively. Plots of mean MDASI-MPM symptom interference score, LCSS-Meso total score, and LCSS-Meso 3 summary item score will be produced over time.

The complete list of variables to be analyzed for this study will be provided in the SAP.

#### 10.3.3.3 Safety variables

Safety variables will include AEs, infusion-related reactions (IRRs), laboratory changes (hematology, clinical chemistry and clinical urinalysis), abnormal findings in physical examination, changes in ECOG PS, changes in vital signs (weight, blood pressure, heart rate, respiratory rate, and body temperature), changes in ECG, changes in cardiac function test (EchoCG or MUGA scan) and changes in ophthalmologic examinations (visual acuity and slit lamp examination, IOP and Schirmer test if repeated). All AEs whether considered drug-related or not, will be reported on the CRF with a diagnosis, start/stop dates, action taken, whether treatment was discontinued, any corrective measures taken, outcome and other possible causes. For all events, the relationship to treatment and the intensity of the event according to CTCAE v4.03 will be determined by the investigator, using the terms and definitions given in Section 9.6.1.2 *(paragraph modified by amendments 2 and 4, see section 15.1.1.3 and 15.2.1.19)*.

**Definition of treatment-emergent safety events**

The treatment period for safety purposes is defined as the start of study treatment until 30 days after the last day of study treatment.

Treatment-emergent safety events (e.g. TEAEs) are safety events which arise or worsen during the treatment period.

Additional details will be described in the SAP.

**Safety analysis**

The final safety analysis will be performed at the time of the final primary endpoint analysis.

An updated safety analysis will be performed at the time of the final analysis of the secondary endpoint OS.

All randomized patients who receive at least 1 dose of treatment will be valid for safety analysis.

All observations pertinent to the safety of treatment will be recorded on the CRF and included in the Clinical Study Report (CSR).

Descriptive summary tables will be presented for all safety parameters. All TEAEs, treatment-emergent and hematological/biochemical toxicities based on laboratory measurements, as well as drug-related AEs and SAEs, will be graded by CTCAE v4.03 and categorized by MedDRA.

Results of physical examination, vital signs, ECG, and other safety variables as described in the SAP will be summarized. The number (%) of patients who discontinue study drug due to AE or for whom a dose reduction or interruption is needed due to AE will also be summarized.

### 10.3.4 Other variables

#### 10.3.4.1 Pharmacokinetic variables

PK data for all or selected analytes collected during the study will be analyzed at the end of study using nonlinear mixed effects models. Mixed effects models, or population type models, describe the relationship between e.g. dose, time and pharmacological observations such as plasma drug concentrations. Both structural and random effects are involved in this relationship. A population PK model will be developed to characterize the PK of all or selected analytes over the entire treatment period using individual drug concentration data. Individual PK parameters of all or selected analytes will be calculated. Furthermore, pharmacokinetic / pharmacodynamic modeling using population approaches to relate parameters of clinical safety and efficacy response with plasma concentrations of all or selected analytes will be investigated.

The details of the modeling analysis will be described in a separate Modelling and Simulation (M&S) Analysis Plan and the results will be reported in a separate M&S Report.

Plasma concentration data for all analytes will be listed in the CSR.

#### 10.3.4.2 Biomarker variables

An analysis of mesothelin expression levels in all patients evaluated for mesothelin expression will be performed. For randomized patients, biomarker parameters that may predict response, e.g. mesothelin expression levels in tumors and in plasma, may be analyzed by patient, summarized by mesothelioma subtype, and associated with tumor response using descriptive statistics, if appropriate. The association between biomarker and selected safety, efficacy, or PK parameters may be graphically displayed. Further exploratory statistical analyses may be performed. Biomarker variables and analyses will be further described in the SAP and/or in a separate document *(clarified by amendment 4, see section 15.2.1.19)*.

#### 10.3.4.3 Immunogenicity variables

For both ADAs and NABs, the number and percent of patients with the positive immunogenicity result will be summarized by time point. The individual patient's immunogenicity results for ADAs and NABs (positive or not applicable) will be listed by time point for each patient. Further details may be described in the SAP.

## 10.4 Determination of sample size

The sample size is primarily designed to support hypothesis test of the primary endpoint PFS, and to provide a limited formal evaluation of secondary endpoint OS *(paragraph modified by amendment 2, see section 15.1.1.1)*.

Power calculations were performed using East 6.3 software.

### 10.4.1 Primary endpoint progression-free survival

The sample size is designed to test the following hypotheses for primary endpoint PFS:

H0: In patients with advanced or metastatic MPM overexpressing mesothelin and progressed on 1st line platinum/pemetrexed-based chemotherapy, PFS under treatment with anetumab ravtansine at 6.5 mg/kg Q3W is not superior to PFS under treatment with 30 mg/m$^2$ QW vinorelbine.

*versus*

HA: In patients with advanced or metastatic MPM overexpressing mesothelin and progressed on 1st line platinum/pemetrexed-based chemotherapy, PFS under treatment with anetumab ravtansine at 6.5 mg/kg Q3W is superior to PFS under treatment with 30 mg/m$^2$ QW vinorelbine.

These hypotheses will be tested using a 1-sided log-rank test, stratified by geographic region (RoW *versus* Asia) and per TTP on 1st line treatment (≥ 6 months *versus* < 6 months).

Assuming median PFS of 3.6 months under vinorelbine treatment and constant hazards and a 2:1 treatment:comparator randomization, a 100% prolongation of PFS in the anetumab ravtansine arm in comparison to the comparator arm can be detected at a 1-sided significance level of 0.0125 with 90% power, with a single-stage trial with approximately 117 PFS events (hazard ratio 0.5). Assuming a maximum accrual rate of 12.5 patients/month (25 patients/ month prescreened with 50% overall pre-screening and screening failure rate) with 6-month linear accrual ramp-up, and a 3.4%/month dropout (loss to follow-up and unevaluable for tumor assessment) rate, 210 patients be will accrued in approximately 19.8 months and reach endpoint maturation of 117 events in approximately 22.0 months. The total number of unevaluable/dropout patients over the duration of the study through final PFS analysis is estimated at 33 (15.7%) *(paragraph modified by amendments 2 and 4, see section 15.1.1.2 and 15.2.1.2)*.

### 10.4.2 Secondary endpoint overall survival

The sample size is also designed to test the following hypotheses in secondary endpoint OS *(modified by amendment 2, see section 15.1.1.2)*:

H0: In patients with advanced or metastatic MPM overexpressing mesothelin and progressed on 1st line platinum/pemetrexed-based chemotherapy, OS under treatment with anetumab ravtansine at 6.5 mg/kg Q3W is not superior to OS under treatment with 30 mg/m$^2$ QW vinorelbine.

*versus*

HA: In patients with advanced or metastatic MPM overexpressing mesothelin and progressed on 1st line platinum/pemetrexed-based chemotherapy, OS under treatment with anetumab ravtansine at 6.5 mg/kg Q3W is superior to OS under treatment with 30 mg/m$^2$ QW vinorelbine.

Assuming true median OS of 9.6 months under vinorelbine treatment and constant hazards, a 60% prolongation of true OS (median 15.4 months) in the anetumab ravtansine arm in comparison to the comparator arm (median 9.6 months) can be detected with an overall 80% power and an overall 1-sided significance level of 0.025 (hazard ratio 0.625), with a 2-stage group sequential test with a total of 159 events *(modified by amendment 2, see section 15.1.1.1)*.

The OS analysis assumes the same accrual as for primary endpoint PFS, with 210 patients accrued in approximately 19.8 months. A 0.3% per month loss to OS follow-up rate is assumed. An interim OS analysis will be performed at the time of the final primary endpoint (PFS) analysis at an estimated 22 months from first patient randomized, when an estimated 80 OS events will have been observed. If the study is not stopped for superiority at the OS interim analysis, the final OS analysis will occur after approximately159 OS events have been observed, at approximately 41.3 months from first patient randomized. A Lan-Demets alpha spending function (38) with O'Brien-Fleming boundaries (39) will be used, based on actual events at the time of the interim analysis. Under the null hypothesis of no anetumab ravtansine OS superiority, approximately 0.00158 alpha is estimated to be spent at the interim analysis and 0.02342 at the final (0.025 alpha overall). Under the alternative hypothesis of 60% OS improvement under anetumab ravtansine treatment, the chance of finding superiority is estimated at 16.9% at the interim analysis and 63.2% at the final analysis (80% power overall). The total number of patients lost to OS follow-up over the duration of the study through final OS analysis is estimated at 10 (4.8%) *(paragraph modified by amendment 2, see section 15.1.1.2)*.

### 10.5 Planned interim analyses

An interim analysis for OS will be performed, by the sponsor, at the same time as the final primary endpoint analysis, as described in Section 10.4 *(clarified by amendment 2, see section 15.1.1.26)*.

In addition, the study will be monitored periodically for safety by a Data Monitoring Committee (DMC). Further details will be described in the DMC charter.

## 11. Data handling and quality assurance

### 11.1 Data recording

The data collection tool for this study will be a validated electronic data capture (EDC) system called RAVE. Patient data necessary for analysis and reporting will be entered/transmitted into a validated database or data system (e.g. TOSCA; SAS).

Data required according to this protocol will be recorded by investigational site personnel via data entry into the internet based EDC software system RAVE, which Bayer has licensed

from Medidata Solutions Worldwide. RAVE has been validated by Medidata Solutions Worldwide and Bayer for use in its clinical studies. RAVE allows for the application of software logic to set-up data entry screens and data checks to ensure the completeness and accuracy of the data entered by the site personnel. Bayer extensively applies the logic to ensure data are complete and reflect the clinical data requirements of the study. Data queries resulting from the application of the software logic are resolved by the site personnel. The data are stored at a secure host facility maintained by Medidata Solutions Worldwide and transferred on a periodic basis to Bayer's internal computer system via a secure Virtual Private Network.

All access to the RAVE system is through a password-protected security system that is part of the RAVE software. All internal Bayer and external investigator site personnel seeking access must go through a thorough RAVE training process before they are granted access to RAVE for use in Bayer's clinical studies. Training records are maintained. Study-specific RAVE training will be provided at the investigator’s meetings, and a study-specific manual (CRF completion guidelines) will be provided to all sites.

All personnel with access to the RAVE system are supported by a Service Desk staffed with trained personnel to answer questions and ensure access is maintained such that data entry can proceed in a timely manner.

The RAVE System contains a system-generated audit trail that captures any changes made to a data field, including who made the change, why the change was made and the date and time it was made. This information is available both at the investigator’s site and at Bayer. Data entries made in the RAVE EDC screens are supported by source documents maintained for all patients enrolled in this study.

**Source documentation**

The site must implement processes to ensure availability of all required source documentation. A source document checklist (not part of this protocol) will be used at the site to identify the source data for key data points collected and the monitor will work with the site to complete this.

It is the expectation of the sponsor that all data entered into the CRF has source documentation available at the site.

**Data recorded from prescreening and full screening failures**

At minimum, the following data should be recorded in the CRF:

- Demographic information (patient number; year of birth / age; sex; if applicable race / ethnicity)
- Disease characteristics *(added by amendment 4, see section 15.2.1.19)*
- Date of all informed consent(s)that were signed
- Relevant inclusion/exclusion criteria for prescreening and for full study (if available)
- Reason for premature discontinuation
- Result of mesothelin overexpression level testing (if available)
- Date of last visit.

These data will be transferred to the respective database.

For prescreening failures who experienced an SAE related to prescreening procedures, and for full screening failures who had signed consent for full study and who experienced an SAE, the following data should be collected in the CRF in addition to the data specified above:

- All information related to the SAE such as:
  - The SAE itself
  - Concomitant medication
  - Medical history
  - Other information needed for SAE complementary page.

## 11.2 Monitoring

In accordance with applicable regulations, GCP, and sponsor's/CRO's procedures, monitors will contact the site prior to the start of the study to review with the site staff the protocol, study requirements, and their responsibilities to satisfy regulatory, ethical, and sponsor's requirements. When reviewing data collection procedures, the discussion will also include identification and documentation of source data items.

The sponsor/designee will monitor the site activity to verify that the:

- Data are authentic, accurate and complete.
  Supporting data may be requested (example: blood glucose readings to support a diagnosis of diabetes).
- Safety and rights of patients are being protected.
- Study is conducted in accordance with the currently approved protocol (including study treatment being used in accordance with the protocol).
- Any other study agreements, GCP, and all applicable regulatory requirements are met.

The investigator and the head of the medical institution (where applicable) agrees to allow the monitor direct access to all relevant documents.

## 11.3 Data processing

Data will be collected as described in Section 11.1. Clinical data management will be performed in accordance with applicable sponsor's/CRO's standards and data cleaning procedures. This is applicable for data recorded on CRF as well as for data from other sources (e.g. IxRS, laboratory, ECG, adjudication committees).

For data coding (e.g. AEs, medication), internationally recognized and accepted dictionaries will be used.

After its initial release for biometrical analysis, the clinical database is planned to be re-opened for the inclusion of the following additional data: PK data, antibody data.

## 11.4 Missing data

For primary endpoint PFS, strategies to reduce the dropout rate (loss to follow-up and unevaluable for tumor assessment) include:

- Seriousness of disease condition results in patients highly motivated to continue treatment and assessments.
- Study regimen is continued indefinitely, during clinical benefit. Because the primary endpoint of progression is a well-accepted key indicator of presence of clinical benefit, use of progression or death as primary endpoint tends to encourage patients to continue coming to the clinic for continued treatment until the endpoint is met.
- Patients who must withdraw from treatment early (e.g. due to toxicity) are required to continue to come to the clinic for tumor assessments until documented radiological progression per central review.
- Use of real-time central review following investigator finding of progression provides consistent read quality, and reduces likelihood of censoring in the event investigator finds documented progression but central review does not, and increases likelihood patient will continue tumor assessments.
- Requirement of real-time review of screening tumor assessments assures patients have measurable disease per central reviewer prior to randomization, reducing unevaluable rate.
- Quality control and training program reduces likelihood of spoiled/unusable imaging.
- Frequent imaging visit schedule (every 6 weeks during the first 6 months, every 9 weeks until the end of year 2, and every 12 weeks thereafter) reduces likelihood of dropout prior to documented progression.

Strategies to reduce the dropout rate for secondary endpoints include:

- For OS, every effort will be made to continue contacting study patients in long-term follow-up and to determine death status and dates. A survival sweep contact will be

conducted at the time of PFS final analysis and prior to OS final analysis to ensure that long-term follow-up data is current *(paragraph modified by amendment2, see section 15.1.1.26)*.

- For other secondary efficacy endpoints, patients will continue to be assessed during active follow-up to mitigate bias due to differences in treatment withdrawal timing on results. Tumor response-related endpoints will be conducted by central review, and centrally determined measurable disease will be required prior to randomization to minimize inclusion of unevaluable patients.
- For all endpoints and study data, clinical data will be closely monitored by strict clinical monitoring and data management. Missing data will trigger queries and follow-up. Active training of study personnel on study and data procedures will stress the importance of complete data.

Strategies to reduce impact of missing data when present include:

- Time-to-event analysis approaches maximize available data and reduce impact of censoring, with unbiased results when censoring is uninformative.
- Study is powered assuming a ~16% total dropout rate (3.4% per month) for PFS and a ~5% total (0.3% per month) dropout rate for OS, ensuring a moderate dropout will not degrade reliability of study results *(paragraph modified by amendment 2, see section 15.1.1.2)*.
- Analyses will ensure conservative treatment of missing values. For tumor response endpoints, missing assessments will count as non-responders *(modified by amendment 2, see section 15.1.1.3)*. For non-time-to-event disease symptom and QoL endpoints, time point analysis will include patients present both at baseline and at the time point, mitigating survivorship bias *(bullet point clarified by amendment 4, see section 15.2.1.17)*.

## 11.5 Audit and inspection

To ensure compliance with GCP and regulatory requirements, a member of the sponsor's (or a designated CRO's) QA unit may arrange to conduct an audit to assess the performance of the study at the study site and of the study documents originating there. The investigator/institution will be informed of the audit outcome.

In addition, inspections by regulatory health authority representatives and IEC(s)/IRB(s) are possible. The investigator should notify the sponsor immediately of any such inspection.

The investigator/institution agrees to allow the auditor or inspector direct access to all relevant documents and allocate his/her time and the time of his/her staff to the auditor/inspector to discuss findings and any issues. Audits and inspections may occur at any time during or after completion of the study.

## 11.6 Archiving

Essential documents shall be archived safely and securely in such a way that ensures that they are readily available upon authorities' request.

Patient (hospital) files including tumor images will be archived according to local regulations and in accordance with the maximum period of time permitted by the hospital, institution or private practice. Where the archiving procedures do not meet the minimum timelines required by the sponsor, alternative arrangements must be made to ensure the availability of the source documents for the required period.

The central reading institution will archive the data for at least 15 years.

The investigator/institution notifies the sponsor if the archival arrangements change (e.g. relocation or transfer of ownership).

The investigator site file is not to be destroyed without the sponsor's approval.

The contract with the investigator/institution will contain all regulations relevant for the study center.

# 12. Premature termination of the study

The sponsor has the right to close this study (or, if applicable, individual segments thereof [e.g. treatment arms; dose steps; centers]) at any time, which may be due but not limited to the following reasons:

- If risk-benefit ratio becomes unacceptable owing to, for example,
  - Safety findings from this study (e.g. SAEs)
  - Results of parallel clinical studies
  - Results of parallel animal studies
    (on e.g. toxicity, teratogenicity, carcinogenicity or reproduction toxicity).
- If the study conduct (e.g. recruitment rate; dropout rate; data quality; protocol compliance) does not suggest a proper completion of the trial within a reasonable time frame.

The investigator has the right to close his/her center at any time.

For any of the above closures, the following applies:

- Closures should occur only after consultation between involved parties. Final decision on the closure must be in writing.
- All affected institutions (e.g. IEC(s)/IRB(s); competent authority(ies); study center; head of study center) must be informed as applicable according to local law.
- All study materials (except documentation that has to remain stored at site) must be returned to the sponsor. The investigator will retain all other documents until notification is given by the sponsor for destruction.
- In the event of a partial study closure, ongoing patients, including those in post-study follow-up, must be taken care of in an ethical manner.

Details for individual patient's withdrawal can be found in Section 6.3.1.

# 13. Ethical and legal aspects

## 13.1 Investigator(s) and other study personnel

**Sponsor's medical expert**

*Study medical expert was changed by amendment 4.*

Name: PPD
Address: PPD
PPD
Telephone: PPD
Mobile: PPD

**Co-ordinating investigators**

Name: PPD
Title: PPD
Address: PPD
PPD
PPD
PPD

Name: PPD
Title: PPD
Address: PPD
PPD
PPD
PPD

All other study personnel not included in this section are identified in a separate personnel list (not part of this clinical study protocol) as appropriate. This list will be updated as needed; an abbreviated version with personnel relevant for the centers will be available in each center's investigator site file.

Whenever the term 'investigator' is noted in the protocol text, it may refer to either the principal investigator at the site, or an appropriately qualified, trained and delegated individual of the investigational site.

The principal investigator of each center must sign the protocol signature page and must receive all required external approvals (e.g. health authority, ethics committee, sponsor) before patient recruitment may start at the respective center. Likewise, all amendments to the protocol must be signed by the principal investigator and must have received all required external approvals before coming into effect at the respective center.

A complete list of all participating centers and their investigators, as well as all required signature documents, will be maintained in the sponsor's study file.

The global sponsor of this study is identified on the title page of this protocol. If required by local law, local co-sponsors will be nominated; they will be identified on the respective country-specific signature pages.

**External data evaluation bodies**

**Data Monitoring Committee (DMC)**

A DMC will be established which will closely interact with the sponsor's Global Pharmacovigilance (GPV) department in order to assess all safety-relevant information.

The DMC will include at least 3 members, including an independent Statistician and Oncologist. Safety review meetings will be held periodically as per separate DMC Charter. Enrollment to the study will continue throughout the scheduled meetings of the DMC.

Decisions on trial termination, amendment, or cessation of patient recruitment based on risk/benefit assessment will be made after recommendations from the DMC have been assessed by the sponsor.

**Steering Committee (SC)**

An SC will support the sponsor during the conduct of the study in all aspects of safety and efficacy.

Decisions on continuation, trial termination, amendment, or cessation of patient recruitment based on risk/benefit assessment will be made after recommendations from the SC have been assessed by the sponsor.

**Central radiological evaluation**

Radiological evaluation of contrast-enhanced CT/MRI scans will be performed by an independent blinded central review. Further details will be provided in a separate Image Review Charter (IRC).

**Central laboratory**

Biomarker, PK, immunogenicity, mesothelin expression, and CYP2D6 pharmacogenetic tests will be performed centrally. Further details will be provided in the Laboratory Manual.

**Independent blinded PRO review committee**

An independent PRO review committee of PRO, statistical, and psychometric experts, blinded to study treatment, will conduct analyses based on regulatory feedback, data from independent studies, and pooled study data from this study following database lock at primary analysis, to support validation of the MDASI-MPM instrument and determine key definitions and details regarding secondary PRO endpoints *(subsection added by amendment 5, see section 15.3.1.7)*.

## 13.2 Funding and financial disclosure

**Funding**

This study will be funded by its sponsor.

**Financial disclosure**

Each investigator (including principal and/or any sub investigators) who is directly involved in the treatment or evaluation of research patients has to provide a financial disclosure according to all applicable legal requirements. All relevant documentation will be filed in the TMF.

## 13.3 Ethical and legal conduct of the study

The procedures set out in this protocol, pertaining to the conduct, evaluation, and documentation of this study, are designed to ensure that the sponsor and investigator abide by GCP guidelines and the guiding principles detailed in the Declaration of Helsinki. The study will also be carried out in keeping with applicable local law(s) and regulation(s).

Documented approval from appropriate IEC(s)/IRBs will be obtained for all participating centers/countries before start of the study, according to GCP, local laws, regulations and organizations. When necessary, an extension, amendment or renewal of the IEC/IRB approval must be obtained and also forwarded to the sponsor. The responsible unit (e.g. IEC/IRB, head of the study center/medical institution) must supply to the sponsor, upon request, a list of the

IEC/IRB members involved in the vote and a statement to confirm that the IEC/IRB is organized and operates according to GCP and applicable laws and regulations.

Strict adherence to all specifications laid down in this protocol is required for all aspects of study conduct; the investigator may not modify or alter the procedures described in this protocol.

Modifications to the study protocol will not be implemented by either the sponsor or the investigator without agreement by both parties. However, the investigator or the sponsor may implement a deviation from, or a change of, the protocol to eliminate an immediate hazard(s) to the trial patients without prior IEC/IRB/sponsor approval/favorable opinion. As soon as possible, the implemented deviation or change, the reasons for it and if appropriate the proposed protocol amendment should be submitted to the IEC/IRB/head of medical institution/sponsor. Any deviations from the protocol must be explained and documented by the investigator.

Details on discontinuation of the entire study or parts thereof can be found in Section 12.

## 13.4 Patient information and consent

**Patient information and informed consent form for prescreening**

A patient information (PI) and ICF with brief information on the study will be provided to patients with unresectable locally advanced or metastatic MPM who would like to participate in this study.

The PI/ICF for prescreening provided by the sponsor or the study center includes the general aspects of the study conduct, details on the tissue samples required to perform the mesothelin overexpression test, and information on risks in case a fresh biopsy is needed. A sample PI/ICF for prescreening is provided as a document separate to this protocol.

The patient has the right to ask the investigator to explain the study in detail and the right to withdraw from the study at any time without any disadvantage and without having to provide reasons for this decision.

**Patient information and informed consent form for full study**

A PI/ICF for screening of study treatment eligibility (ICF for full study) will be provided no longer than 28 days prior to start of study treatment to the patient who passes the prescreening, including mesothelin overexpression level test, and who still has interest to participate in this study. The PI/ICF for full study should be provided prior to activities related to the screening for full study.

All relevant information on the study will be summarized in the PI/ICF for full study provided by the sponsor or the study center. A sample PI/ICF for full study is provided as a document separate to this protocol.

Based on this PI sheet, the investigator or designee will explain all relevant aspects of the study to each patient / legal representative or proxy consenter (if the patient is under legal protection), prior to his/her entry into the full study (i.e. before any examinations and

procedures associated with the selection for the full study are performed excluding the prescreening procedures or further study-specific data is recorded on study-specific forms).

The following applies to PI/ICF for prescreening and for full study:

The investigator will also mention that written approval of the IRB/IEC has been obtained.

Each patient / legal representative or proxy consenter will be informed about the following aspects of premature withdrawal:

- Each patient has the right to withdraw from the study at any time without any disadvantage and without having to provide reasons for this decision.
- The patient's consent covers end-of-study examinations as specified in the visit description described in Section 9.2 to be conducted after withdrawal of consent.
- The patient's data that have been collected until the time of withdrawal will be retained and statistically analyzed in accordance with the SAP.
- Patient-specific data on the basis of material obtained before withdrawal may be generated after withdrawal (e.g. image reading, analysis of biological specimen such as blood, urine or tissues); these data would also be retained and statistically analyzed in accordance with the SAP. The patient has the right to object to the generation and processing of this post-withdrawal data. The patient's oral objection must be documented in the patient's source data.

Each patient / legal representative or proxy consenter will have ample time and opportunity to ask questions.

Only if the patient / legal representative or proxy consenter voluntarily agrees to sign the ICF and has done so, may he/she enter the study. Additionally, the investigator will personally sign and date the form. The patient / legal representative or proxy consenter will receive a copy of the signed and dated form.

The signed informed consent statement is to remain in the investigator site file or, if locally required, in the patient's note/file of the medical institution.

In the event that informed consent is obtained on the date that screening study procedures are performed, the study record or patient´s clinical record must clearly show that informed consent was obtained prior to these procedures.

- If the patient is not capable of providing a signature, a verbal statement of consent can also be given in the presence of an impartial witness (independent of the sponsor and the investigator). This is to be documented by a signature from the informing physician as well as by a signature from the witness.
- For adults under legal protection, consent shall be given by the legal guardian(s). The consent of an adult under legal protection shall also be requested where such a person is able to express his/her own will. His/her refusal or the withdrawal of his/her consent may not be disregarded.

The ICF and any other written information provided to patients / legal representatives or proxy consenters will be revised whenever important new information becomes available that may be relevant to the patient's consent, or there is an amendment to the protocol that necessitates a change to the content of the PI and/or the written ICF. The investigator will inform the patient / legal representative or proxy consenter of changes in a timely manner and will ask the patient to confirm his/her participation in the study by signing the revised ICF. Any revised written ICF and written information must receive the IEC/IRB`s approval / favorable opinion in advance of use.

## 13.5 Publication policy and use of data

The sponsor has made the information regarding the study protocol publicly available on the internet at www.clinicaltrials.gov.

All data and results and all intellectual property rights in the data and results derived from the study will be the property of the sponsor who may utilize them in various ways, such as for submission to government regulatory authorities or disclosure to other investigators.

Regarding public disclosure of study results, the sponsor will fulfill its obligations according to all applicable laws and regulations. The sponsor is interested in the publication of the results of every study it performs.

The sponsor recognizes the right of the investigator to publish the results upon completion of the study. However, the investigator, whilst free to utilize study data derived from his/her center for scientific purposes, must obtain written consent of the sponsor on the intended publication manuscript before its submission. To this end, the investigator must send a draft of the publication manuscript to the sponsor within a time period specified in the contract. The sponsor will review the manuscript promptly and will discuss its content with the investigator to reach a mutually agreeable final manuscript.

## 13.6 Compensation for health damage of patients / insurance

The sponsor maintains clinical trial insurance coverage for this study in accordance with the laws and regulations of the country in which the study is performed.

## 13.7 Confidentiality

All records identifying the patient will be kept confidential and, to the extent permitted by the applicable laws and/or regulations, will not be made publicly available.

Patient names will not be supplied to the sponsor. Only the patient number will be recorded in the CRF, and if the patient name appears on any other document (e.g. pathologist report), it must be obliterated before a copy of the document is supplied to the sponsor. Study findings stored on a computer will be stored in accordance with local data protection laws. As part of the informed consent process, the patients will be informed in writing that representatives of the sponsor, IEC/IRB, or regulatory authorities may inspect their medical records to verify the information collected, and that all personal information made available for inspection will be handled in strictest confidence and in accordance with local data protection laws.

If the results of the study are published, the patient's identity will remain confidential.

The investigator will maintain a list to enable patients to be identified.

# 14. Reference list

*Reference list was updated by amendments 2 and 4. The numbering of the references was changed accordingly.*

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# 15. Protocol amendments

## 15.1 Amendment 2

Amendment 2 is a global amendment dated 09 FEB 2016.

### 15.1.1 Overview of changes to the study

#### 15.1.1.1 Modification 1: Change in OS analysis design

The study design was changed to increase the power of the OS analysis to 80%, with a corresponding increase in sample size and number of required OS events. The revised design also incorporates assumptions changes, including an increase in the accrual rate, more conservative PFS dropout assumptions, and a lower OS dropout assumption.

Sections affected by this modification: Section 2 Synopsis, Section 10.3.3.1 Secondary efficacy variables, Section 10.4 Determination of sample size, Section 10.4.2 Secondary endpoint overall survival

#### 15.1.1.2 Modification 2: Changes in determination of sample size

Number of randomized patients was changed from 183 to 210 (total), from 122 to 140 (anetumab ravtansine arm) and 61 to 70 (comparator arm). The sample size was increased to support the OS evaluation. Increased number of patients supports powering OS analysis at 80%.

The accrual rate was increased to reflect improved assessment of accrual capabilities.

PFS dropout rate was increased to reflect provision for additional PFS dropouts afforded by larger number of patients. OS dropout rate was decreased to reflect improved OS follow-up effort.

As a result, the estimates of the times for patients to be accrued and to reach endpoint maturation were updated.

Information was updated on the estimated number of prescreened and screened patients needed to reach 210 randomized patients.

Sections affected by this modification: Section 2 Synopsis, Section 5.1 Design overview, Section 5.3 Justification of the design, Section 10.3.3.1 Secondary efficacy variables, Section 10.4.1 Primary endpoint progression-free survival, Section 10.4.2 Secondary endpoint overall survival, Section 11.4 Missing data.

#### 15.1.1.3 Modification 3: Pulmonary function evaluation removed

Pulmonary function evaluation by forced vital capacity measurement was removed from the secondary endpoints since spirometry schedule could be a significant burden for the patients.

Sections affected by this modification: Section 2 Synopsis, Section 3.1 Background, Section 4 Study objectives, Section 5.1 Design overview, Section 6.3.1.2 Withdrawal criteria, Section 9.1 Tabular schedule of evaluations, Section 9.2.2 Full screening period, Section 9.2.4 Efficacy assessments, Section 9.2.5.2 Active follow-up, Section 9.4 Efficacy, Section 9.8

Appropriateness of procedures / measurements, Section 10.3.3.1 Secondary efficacy variables, Section 10.3.3.3 Safety variables, Section 11.4 Missing data, Section 14 Reference list

#### 15.1.1.4 Modification 4: Clarification of progression as withdrawal criterion

Language in withdrawal criteria regarding duration of treatment after disease progression has been clarified.

Sections affected by this modification: Section 2 Synopsis, Section 5.1 Design overview, Section 6.3.1.2 Withdrawal criteria

#### 15.1.1.5 Modification 5: Definition of corneal epitheliopathy introduced

“Corneal epitheliopathy” has been introduced throughout the protocol to replace other wordings “corneal toxicity”, “eye toxicity”, “corneal morphology changes”, “ocular adverse drug reactions”, and “corneal disorder” for consistency.

Sections affected by this modification: Section 5.3 Justification of the design, Section 6.3.1.2 Withdrawal criteria, Section 7.4.2.1 Dose modifications of anetumab ravtansine, Section 7.4.2.1.2 Non-hematological toxicities, Section 7.4.2.1.3 Miscellaneous toxicities, Section 9.1 Tabular schedule of evaluations, Section 9.2.3.2 Treatment – Cycle 2 and higher, Section 9.5 Pharmacokinetics / pharmacodynamics, Section 9.6.1.3 Assessments and documentation of adverse events, Section 9.6.1.6 Adverse events of special safety interest, Section 9.6.3.7 Ophthalmologic examinations

#### 15.1.1.6 Modification 6: Redefinition of mesothelin overexpression

Mesothelin overexpression was redefined as “moderate” and “stronger” and reference to the expression levels of ‘2+’ and ‘3+’ was removed for consistency with the language used by the central laboratory Ventana in their protocol and in their communication to Authorities.

Sections affected by this modification: Section 5.1 Design overview, Section 5.3 Justification of the design, Section 6.1.1 Eligibility criteria for prescreening, Section 6.1.2 Eligibility criteria for full study, Section 6.3.1.1.1 Prescreening failure, Section 9.2.3 Treatment period, Section 9.7.1 Biomarkers

#### 15.1.1.7 Modification 7: Clarification of start of full study

Wording regarding the start of full study phase was updated for clarity by adding language on full study ICF to be signed prior to entering the screening phase.

Sections affected by this modification: Section 5.1 Design overview

#### 15.1.1.8 Modification 8: Clarification of radiological eligibility

Radiological eligibility criterion (inclusion criterion number 4) was updated to allow inclusion of patients who have pleural non-measurable lesions per mRECIST but at the same have non-pleural measurable disease (per RECIST 1.1). This was done after consultation and approval of the Steering Committee.

Sections affected by this modification: Section 2 Synopsis, Section 6.1.2 Eligibility criteria for full study

#### 15.1.1.9 Modification 9: Clarification of contraception duration and use

In the eligibility criteria for the full study, the duration of contraception was corrected from 3 to 4 months after the last dose to provide consistency throughout the document. Advice on the use of additional contraception was strengthened in the protocol for male patients with a female partner of childbearing potential in line with the relevant EU Clinical Trial Facilitation Group (CTFG) guideline. Male patients with a female partner of childbearing potential must use a condom and ensure that an additional form of contraception is also used. Sperm conservation advice has been extended to all male patients (both arms) These changes were made due the request of the Medicines and Healthcare Products Regulatory Agency (MHRA) in United Kingdom (UK).

Sections affected by this modification: Section 6.1.2 Eligibility criteria for full study

#### 15.1.1.10 Modification 10: Addition of optometrist as an alternative to ophthalmologist

Optometrist was added as an alternative to ophthalmologist as in some countries optometrist is licensed to perform the eye examinations requested in this Clinical Study Protocol. It was also clarified that the ophthalmologist/optometrist will be consulted by the investigator.

Sections affected by this modification: Section 6.2 Exclusion criteria, Section 7.4.2.1.3 Miscellaneous toxicities, Section 9.1 Tabular schedule of evaluations, Section 9.2.3.2 Treatment – Cycle 2 and higher, Section 9.6.3.7 Ophthalmologic examinations

#### 15.1.1.11 Modification 11: Clarification of ocular eligibility

A note about low grades of superficial punctate keratitis was added to exclusion criterion number 5 to give appropriate guidance on ocular assessment during screening as a clarification.

Sections affected by this modification: Section 6.2 Exclusion criteria

#### 15.1.1.12 Modification 12: Vinorelbine formulation corrected

The data about vinorelbine formulations available was corrected.

Sections affected by this modification: Section 7.2.2 Comparator - vinorelbine

#### 15.1.1.13 Modification 13: Dose modification due to hypersensitivity corrected

Language on dose modification for anetumab ravtansine infusion-related reaction/other hypersensitivity events was corrected.

Sections affected by this modification: Section 7.4.2.1.2 Non-hematological toxicities, Section 7.4.2.1.3 Miscellaneous toxicities, Section 8.1 Prior and concomitant therapy

#### 15.1.1.14 Modification 14: Clarification of reporting of AE of special interest

Language on reporting of AE of special interest updated for clarity.

Sections affected by this modification: Section 9.6.1.6 Adverse events of special safety interest

#### 15.1.1.15 Modification 15: Clarification of blinded central review during screening

Language on blinded central review during screening was modified for completeness since during screening, blinded central review will not only check if at least 1 measurable lesion is present, but it will review the radiological eligibility in its entirety as defined in inclusion criterion number 4.

Sections affected by this modification: Section 2 Synopsis, Section 5.1 Design overview, Section 7.3 Treatment assignment, Section 9.2.3 Treatment period, Section 9.4.1 Radiological tumor assessments

#### 15.1.1.16 Modification 16: Clarification of intra-patient dose escalation for study drugs

The language was modified ("for TEAE" added) to clarify that there can be no intra-patient dose escalation for study drugs when medication was previously reduced for TEAE. In case dose reduction occurred by mistake or logistical difficulty, this can be corrected in the following cycles.

Sections affected by this modification: Section 7.4.2.1.2 Non-hematological toxicities, Section 7.4.2.2 Dose modifications of vinorelbine

#### 15.1.1.17 Modification 17: Clarification on follow-up of patients who are randomized but not treated

Clarification was added on follow-up of patients who are randomized but not treated. Change clarifies how to process patients who are randomized but received no treatment, clarifying that all ITT patients should be followed for efficacy to the extent feasible.

Sections affected by this modification: Section 6.3.1.2 Withdrawal criteria

#### 15.1.1.18 Modification 18: Additional contact attempt added at the time of each survival sweep

A requirement for an additional contact attempt at the time of each survival sweep was added, to clarify that a further attempt should be made to contact patients previously lost to follow-up.

Sections affected by this modification: Section 6.3.1.2 Withdrawal criteria

#### 15.1.1.19 Modification 19: Time window between randomization and treatment start added

A time window between the IxRS transaction and the start of study drug has been introduced: start of treatment has to be within 24 hours after randomization call, provided the patient is seen at site prior to randomization, all in- and exclusion criteria are checked and patient is considered eligible before the randomization call is made. This change was introduced to fit in better with site logistical procedures.

Sections affected by this modification: Section 5.1 Design overview, Section 6.1.2 Eligibility criteria for full study, Section 6.2 Exclusion criteria, Section 9.1 Tabular schedule of

evaluations, Section 9.2.2 Full screening period, Section 9.2.3.1 Treatment – Cycle 1, Section 9.4.1 Radiological tumor assessments, Section 9.2.4 Efficacy assessments

#### 15.1.1.20 Modification 20: PROs schedule updated

PROs schedule was updated with MDASI-MPM questionnaires at C1D8, C1D15, C2D8, C2D15, C3D8 and C3D15. The reason for this change is to address the FDA/COA feedback on the PROs evidence and endpoint strategy.

In addition, it was clarified that MDASI-MPM and LCSS-Meso are to be completed before the patient meets with a clinician and before any examination or test is performed on that day.

Sections affected by this modification: Section 9.1 Tabular schedule of evaluations, Section 9.2.2 Full screening period, Section 9.2.3.1 Treatment – Cycle 1, Section 9.2.3.2 Treatment – Cycle 2 and higher, Section 9.2.5.1 Safety follow-up, Section 9.2.5.2 Active follow-up, Section 9.4.3 Patient-reported outcomes

#### 15.1.1.21 Modification 21: Inconsistency in dose re-escalation clarified

Inconsistency in dose re-escalation between dose modifications for non-hematological toxicities (Section 7.4.2.1.2 Non-hematological toxicities) and Table 7-6 (7.4.2.1.3 Miscellaneous toxicities) was clarified. Accordingly, “dose increased” was added in the list of actions taken on study treatment to resolve the AE.

Sections affected by this modification: Section 7.4.2.1.2 Non-hematological toxicities, Section 7.4.2.2 Dose modifications of vinorelbine, Section 9.6.1.2.4 Action taken with study treatment

#### 15.1.1.22 Modification 22: Clarification on start of treatment period

It was clarified that the start of treatment for efficacy purposes is defined as the randomization, and the start of treatment for safety purposes is defined as the first administration of study drug.

Sections affected by this modification: Section 5.1 Design overview

#### 15.1.1.23 Modification 23: Clarification of the study background with data on probability of corneal epitheliopathy versus model-predicted drug exposure

The background of the study was clarified with data on probability of corneal epitheliopathy versus model-predicted drug exposure. In addition, the sentence in Section 5.3 Justification of the design referring to this data was clarified and a cross-reference added.

Sections affected by this modification: Section 3.1.2 Clinical experience, Section 5.3 Justification of the design

#### 15.1.1.24 Modification 24: Urine dipstick test removed from visit C1D1

Urine dipstick test removed from visit C1D1 because this test is already performed within 7 days before C1D1.

Sections affected by this modification: Section 9.1 Tabular schedule of evaluations, Section 9.2.3.1 Treatment – Cycle 1

#### 15.1.1.25 Modification 25: Appendix regarding response assessment updated

Appendix regarding the response assessment was updated to correctly reflect mRECIST criteria.

Sections affected by this modification: Section 16.3 Response assessment

#### 15.1.1.26 Other modifications and corrections

In addition to the modifications specified above, there have been minor corrections for better clarity and consistency.

- List of abbreviations has been updated. ICH was also updated in the text to International Council for Harmonization as it had changed the name. Sections affected by this modification: List of abbreviations, Section 9.6.3.1 Laboratory evaluations
- Bayer corneal epitheliopathy grading system was referenced in additional sections in the text. Sections affected by this modification: Section 2 Synopsis, Section 5.1 Design overview, Section 9.6.1.2.2 Intensity
- A cross-reference to Section 9.8 Appropriateness of procedures / measurements was added in section 5.3 Justification of the design for clarity. Sections affected by this modification: Section 5.3 Justification of the design
- It was clarified that the primary analysis will take place after 117 PFS events are observed rather than at that time. Sections affected by this modification: Section 5.5 Primary completion
- It was clarified that the eligibility criteria must be met and the exclusion criteria must be not met at the time of randomization call. Sections affected by this modification: Section 6.1.2 Eligibility criteria for full study, Section 6.2 Exclusion criteria
- Cross-reference to Appendix 16.3 Response assessment was inserted instead of cross-reference to Section 9.4.1 Radiological tumor assessments in inclusion criterion number 4. Sections affected by this modification: Section 6.1.2 Eligibility criteria for full study
- It was clarified that if the anetumab ravtansine solution is frozen or stored above room temperature, it should be discarded. Sections affected by this modification: Section 7.2.1 Test drug - anetumab ravtansine
- As a clarification, the first withdrawal criterion for treatment with anetumab ravtansine in Figure 6-1 was divided into 2 criteria. In addition, the language regarding the exceptions to the withdrawal and to the treatment modification in Figure 6-1 and in subsection “Non-hematological toxicities requiring dose modification”, respectively, were removed as per request of French Authorities. Sections affected by this modification: Section 6.3.1.2 Withdrawal criteria, Section 7.4.2.1.2 Non-hematological toxicities

- IxRS transaction was added in the Study flow chart and visit descriptions at full screening -28 days as a correction. Sections affected by this modification: Section 9.1 Tabular schedule of evaluations, Section 9.2.2 Full screening period
- It was clarified that the extra survival sweep contacts will be conducted prior to PFS final analysis rather than at the time of PFS final analysis. Sections affected by this modification: Section 9.4.2 Survival
- It was clarified that patients who sign the informed consent for prescreening will be included in the ENR. Sections affected by this modification: Section 10.2 Analysis sets
- The location of the language "hazard ratio" was changed in the section describing the primary efficacy analysis to grammatically correct the sentence. Sections affected by this modification: Section 10.3.2 Primary efficacy variable
- A sentence referring to SAP was added in the Section 10.3.3.1 Secondary efficacy variables for consistency with the Section 10.3.2 Primary efficacy variable. Sections affected by this modification: Section 10.3.3.1 Secondary efficacy variables
- It was clarified that the sponsor will perform the interim analysis for OS. Sections affected by this modification: Section 10.5 Planned interim analyses
- The sentence referring to the analysis methods described for PFS was removed from the paragraph describing the strategies to reduce the dropout rate for secondary endpoint OS for clarity. Sections affected by this modification: Section 11.4 Missing data
- Reference list been updated. Sections affected by this modification: Section 14 Reference list

### 15.1.2 Changes to the protocol text

In the sections on changes to the protocol text, all protocol sections affected by the respective amendment are detailed; the sequence of the sections follows the structure of the most recent previous protocol version. As applicable, changes to the protocol text are highlighted as follows:

- Addition of a whole new portion: Brief identification of the new portion
- Removal of a whole portion: Complete display of the removed portion, formatted as ~~crossed out~~
- Editing of an existing portion: Comparative presentation of "*old text*" versus "*new text*", with "*old text*" referring to the most recent previous protocol version. Deletions are ~~crossed out~~ in the "*old text*". Additions are <u>underlined</u> in the "*new text*".
- Tables / figures: The term "*amended*" is added to the caption.
- Terminological changes: Brief specification of the terminological change

Correction of typos or omissions are not highlighted.

## 15.1.2.1 Section 2 Synopsis

*Old text:*

| | |
|---|---|
| **Study objective(s)** | […]<br>The secondary objectives of this study are to:<br>• Test overall survival (OS)<br>• ~~Evaluate pulmonary function~~<br>• Evaluate patient-reported outcomes (PROs) – symptom burden and health-related quality of life (QoL)<br>• Evaluate other indicators of treatment efficacy (indicators of tumor response)<br>• Evaluate safety<br>[…] |
| **Test drug(s)**<br>[…]<br>**Duration of treatment** | Anetumab ravtansine<br><br>Patients will continue on treatment until one of the following occurs:<br>• Progressive disease (PD) as defined by modified Response Evaluation Criteria in Solid Tumors (mRECIST) for mesothelioma as assessed by blinded central radiology review<br>• Clinical progression ~~(continuation of treatment until centrally confirmed radiological PD could be allowed if in the investigator's judgement this would provide clinical benefit to the patient)~~<br>• Death<br>• Any other criterion for withdrawal from study treatment. |
| **Reference drug(s)**<br>[…]<br>**Duration of treatment** | Vinorelbine<br><br>Patients will continue on treatment until one of the following occurs:<br>• PD as defined by mRECIST for mesothelioma as assessed by blinded central radiology review<br>• Clinical progression ~~(continuation of treatment until centrally confirmed radiological PD could be allowed if in the investigator's judgement this would provide clinical benefit to the patient)~~<br>• Death<br>• Any other criterion for withdrawal from study treatment. |

[…]

| | |
|---|---|
| **Diagnosis and main criteria for inclusion /exclusion** | Male or female patients (≥ 18 years of age) with unresectable locally advanced or metastatic MPM overexpressing mesothelin. Patients must have Eastern Cooperative Oncology Group Performance Status (ECOG PS) of 0 or 1, a life expectancy of at least 3 months and at least 1 measurable lesion per mRECIST per MPM as determined by the central reviewer. Patients must have received only 1 line of previous systemic anti-cancer treatment with platinum-pemetrexed with or without bevacizumab and must have no corneal epitheliopathy or any predisposing eye disorder. |
| **Study design** | A randomized, open-label, active-controlled, 2-arm, multicenter, Phase II study. |

| | |
|---|---|
| | Approximately ~~183~~ patients who meet the eligibility criteria will be randomly assigned in a 2:1 ratio to receive anetumab ravtansine or vinorelbine, respectively. Patients will be stratified at randomization according to geographic region and per time to progression (TTP) on 1st line treatment.<br>[…] |
| **Methodology** | Primary efficacy will be assessed based on radiological tumor evaluation by contrast-enhanced computed tomography (CT) or contrast-enhanced magnetic resonance imaging (MRI) of chest/abdomen/pelvis. The first tumor images will be obtained during full screening and will be sent to blinded central review to confirm ~~that at least 1 measurable lesion is present~~ prior to randomization. During treatment as well as active follow-up, tumor imaging will be performed with the same modality every 6 weeks during the first 6 months after the start of study treatment, every 9 weeks until the end of year 2, and every 12 weeks thereafter until centrally confirmed radiological disease progression or end of study. Primary analysis results will be based on central review.<br>~~Determination of forced vital capacity (FVC) will be performed as a reproducible measure of pulmonary function, by a spirometry test until centrally confirmed radiological progression or end of study.~~<br>Patients will be contacted to assess survival status every 3 months during long-term follow-up. In addition, extra survival sweep contacts will be conducted at the time of PFS final analysis and prior to OS final analysis to ensure that long-term follow-up data is current.<br>The effect of treatment on disease-specific health-related QoL and disease-specific symptoms will be assessed using the MD Anderson Symptom Inventory-Malignant Pleural Mesothelioma (MDASI-MPM) and the Lung Cancer Symptom Scale-Mesothelioma (LCSS-Meso) at full screening, at each cycle during treatment, at the safety follow-up visit, and during active follow-up.<br>Safety evaluations will be done at full screening, at each clinic visit during the treatment, and at the safety follow-up visit. The National Cancer Institute's Common Terminology Criteria for Adverse Events (NCI-CTCAE) version 4.03 will be used to grade severity of adverse events (AEs).<br>[…] |

[…]

| | |
|---|---|
| **Number of patients** | Approximately ~~183~~ patients will be randomized. Approximately 40% rate of screening failures is estimated, i.e. approximately ~~305~~ patients will be screened. |

[…]

| | |
|---|---|
| **Plan for statistical analysis** | […]<br>Secondary efficacy variable OS will be tested using a 2-stage group-sequential testing procedure with an overall 1-sided significance level of 0.025 and ~~73~~% power. Each stage will utilize a 1-sided log-rank test |

| | |
|---|---|
| | stratified by geographic region and per TTP on 1st line treatment. A Lan-Demets alpha spending function with O'Brien-Fleming boundaries will be used. An interim analysis for OS will be performed at the same time as the final analysis for PFS, when approximately ~~85~~ OS events are expected to have been observed. The final analysis for OS will be performed after approximately ~~135~~ events have been observed.<br><br>Additional secondary variables include ~~FVC response rate~~, objective response rate (ORR), disease control rate (DCR), duration of response (DOR), and analysis of the change in physical symptoms of MPM by PROs (as measured using the MDASI-MPM and LCSS-Meso). The final analysis for all these additional secondary variables will occur at the time of primary endpoint analysis.<br><br>The ~~183~~ randomized patients are estimated to be accrued in approximately ~~20.4~~ months. Data for final PFS analysis are estimated to mature in ~~23.9~~ months. Data for final OS analysis are estimated to mature in ~~41.4~~ months. |

*New text:*

| | |
|---|---|
| **Study objective(s)** | […]<br>The secondary objectives of this study are to:<br>• Test overall survival (OS)<br>• Evaluate patient-reported outcomes (PROs) – symptom burden and health-related quality of life (QoL)<br>• Evaluate other indicators of treatment efficacy (indicators of tumor response)<br>• Evaluate safety<br>[…] |
| **Test drug(s)**<br>[…]<br>**Duration of treatment** | Anetumab ravtansine<br><br>Patients will continue on treatment until one of the following occurs:<br>• Progressive disease (PD) as defined by modified Response Evaluation Criteria in Solid Tumors (mRECIST) for mesothelioma as assessed by blinded central radiology review; however, treatment may be continued provided that the patient derives clinical benefit as determined by the treating physician.<br>• Clinical progression<br>• Death<br>• Any other criterion for withdrawal from study treatment. |

| | |
|---|---|
| **Reference drug(s)**<br>[…]<br>**Duration of treatment** | Vinorelbine<br><br>Patients will continue on treatment until one of the following occurs:<br>• PD as defined by mRECIST for mesothelioma as assessed by blinded central radiology review; however, treatment may be continued provided that the patient derives clinical benefit as determined by the treating physician<br>• Clinical progression<br>• Death<br>• Any other criterion for withdrawal from study treatment. |

[…]

| | |
|---|---|
| **Diagnosis and main criteria for inclusion /exclusion** | Male or female patients (≥ 18 years of age) with unresectable locally advanced or metastatic MPM overexpressing mesothelin. Patients must have Eastern Cooperative Oncology Group Performance Status (ECOG PS) of 0 or 1, a life expectancy of at least 3 months and at least 1 measurable lesion per mRECIST per MPM (i.e. pleural lesion(s) measured using mRECIST or extra-pleural lesion(s) measurable per RECIST 1.1) as determined by the central reviewer. Patients must have received only 1 line of previous systemic anti-cancer treatment with platinum-pemetrexed with or without bevacizumab and must have no corneal epitheliopathy or any predisposing eye disorder. |
| **Study design** | A randomized, open-label, active-controlled, 2-arm, multicenter, Phase II study.<br><br>Approximately 210 patients who meet the eligibility criteria will be randomly assigned in a 2:1 ratio to receive anetumab ravtansine or vinorelbine, respectively. Patients will be stratified at randomization according to geographic region and per time to progression (TTP) on 1st line treatment.<br><br>[…] |

| | |
|---|---|
| **Methodology** | Primary efficacy will be assessed based on radiological tumor evaluation by contrast-enhanced computed tomography (CT) or contrast-enhanced magnetic resonance imaging (MRI) of chest/abdomen/pelvis. The first tumor images will be obtained during full screening and will be sent to blinded central review to confirm radiological eligibility prior to randomization. During treatment as well as active follow-up, tumor imaging will be performed with the same modality every 6 weeks during the first 6 months after the start of study treatment, every 9 weeks until the end of year 2, and every 12 weeks thereafter until centrally confirmed radiological disease progression or end of study. Primary analysis results will be based on central review.<br><br>Patients will be contacted to assess survival status every 3 months during long-term follow-up. In addition, extra survival sweep contacts will be conducted at the time of PFS final analysis and prior to OS final analysis to ensure that long-term follow-up data is current.<br><br>The effect of treatment on disease-specific health-related QoL and disease-specific symptoms will be assessed using the MD Anderson Symptom Inventory-Malignant Pleural Mesothelioma (MDASI-MPM) and the Lung Cancer Symptom Scale-Mesothelioma (LCSS-Meso) at full screening, at each cycle during treatment, at the safety follow-up visit, and during active follow-up.<br><br>Safety evaluations will be done at full screening, at each clinic visit during the treatment, and at the safety follow-up visit. The National Cancer Institute's Common Terminology Criteria for Adverse Events (NCI-CTCAE) version 4.03 will be used to grade severity of adverse events (AEs). In addition, a Bayer grading system will be used to assess corneal epitheliopathy.<br><br>[…] |

[…]

| | |
|---|---|
| **Number of patients** | Approximately 210 patients will be randomized. Approximately 40% rate of screening failures is estimated, i.e. approximately 350 patients will be prescreened. |

[…]

| | |
|---|---|
| **Plan for statistical analysis** | […]<br><br>Secondary efficacy variable OS will be tested using a 2-stage group-sequential testing procedure with an overall 1-sided significance level of 0.025 and 80% power. Each stage will utilize a 1-sided log-rank test stratified by geographic region and per TTP on 1st line treatment. A Lan-Demets alpha spending function with O'Brien-Fleming boundaries will be used. An interim analysis for OS will be performed at the same time as the final analysis for PFS, when approximately 80 OS events are expected to have been observed. The final analysis for OS will be performed after approximately 159 events have been observed<br><br>Additional secondary variables include objective response rate (ORR), disease control rate (DCR), duration of response (DOR), and analysis of the change in physical symptoms of MPM by PROs (as measured using |

| | |
|---|---|
| | the MDASI-MPM and LCSS-Meso). The final analysis for all these additional secondary variables will occur at the time of primary endpoint analysis.<br><br>The 210 randomized patients are estimated to be accrued in approximately 19.8 months. Data for final PFS analysis are estimated to mature in 21.2 months. Data for final OS analysis are estimated to mature in 41.3 months. |

### 15.1.2.2 List of abbreviations

*Old text:*

| | |
|---|---|
| ~~FVC~~ | ~~Forced vital capacity~~ |
| […] | |
| ICH | International ~~Conference on~~ Harmonization |
| […] | |
| ~~PFT~~ | ~~Pulmonary function test~~ |

*New text:*

| | |
|---|---|
| CTFG | Clinical Trial Facilitation Group |
| […] | |
| FSH | Follicle stimulating hormone |
| […] | |
| ICH | International Council for Harmonization |
| […] | |
| MHRA | Medicines and Healthcare Products Regulatory Agency |
| […] | |
| PopPBPK | Population, physiologically-based pharmacokinetic |

### 15.1.2.3 Section 3.1 Background

*Old text:*

[…]

**Treatment of MPM**

Involvement of a multidisciplinary team is recommended to ensure prompt and appropriate management of disease, using a framework of radiotherapy, chemotherapy, surgery and symptom palliation with terminal care. However, few patients qualify for curative surgery, and the efficacy of radiotherapy is limited, hence the high need for effective systemic treatments. The combination of cisplatin and the antifolate pemetrexed proved superior to single cisplatin, respectively, in terms of overall survival (OS) (12.1 vs. 9.3 months), progression-free survival (PFS) (5.7 vs. 3.9 months), and response rate (41.3% vs. 16.7%) (12). ~~The regimen also proved superior with respect to improvement in respiratory function. Results indicate that patients who had a tumor response had consistently better pulmonary~~

~~function tests (PFTs) than patients with stable disease (SD), and patients with SD had better PFTs than patients with progressive disease (PD) (12).~~ […]

*New text:*

[…]

**Treatment of MPM**

Involvement of a multidisciplinary team is recommended to ensure prompt and appropriate management of disease, using a framework of radiotherapy, chemotherapy, surgery and symptom palliation with terminal care. However, few patients qualify for curative surgery, and the efficacy of radiotherapy is limited, hence the high need for effective systemic treatments. The combination of cisplatin and the antifolate pemetrexed proved superior to single cisplatin, respectively, in terms of overall survival (OS) (12.1 vs. 9.3 months), progression-free survival (PFS) (5.7 vs. 3.9 months), and response rate (41.3% vs. 16.7%) (12). […]

## 15.1.2.4 Section 3.1.2 Clinical experience

*Old text:*

[…]

The safety finding of particular interest at the 6.5 mg/kg Q3W dose has been the corneal epitheliopathy and keratitis with and without blurred vision probably related to anetumab ravtansine: 11 of 38 patients (29%) developed corneal adverse events (AEs). None of these events affected the deep corneal stroma or were considered serious or led to drug discontinuation and all events were reversible.

[…]

*New text:*

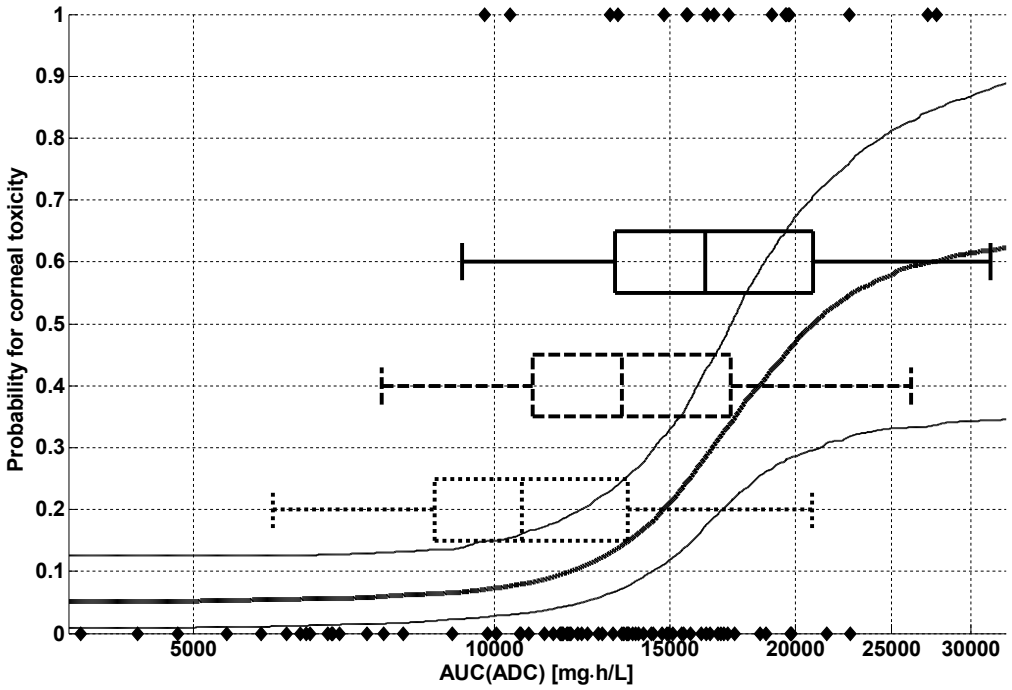
[…]

The safety finding of particular interest at the 6.5 mg/kg Q3W dose has been the corneal epitheliopathy and keratitis with and without blurred vision probably related to anetumab ravtansine: 11 of 38 patients (29%) developed corneal adverse events (AEs). None of these events affected the deep corneal stroma or were considered serious or led to drug discontinuation and all events were reversible.

Furthermore, population, physiologically-based pharmacokinetic (PopPBPK) modeling of preliminary data from the FiH study 15051, combined with a probabilistic regression analysis provided evidence that the area under the ADC plasma concentration-time curve at steady state, AUC(ADC), is a descriptor for the occurrence of corneal epitheliopathy, as shown in Figure 3-1. Based on the on average linear PK of anetumab ravtansine (see above in this

section), it can be assumed that dose reduction will lead to a reduced total drug exposure, i.e. AUC(ADC), and thus, also to a reduced probability of corneal epitheliopathy (see Figure 3-1).

**Figure 3-1 Probability of corneal epitheliopathy versus model-predicted drug exposure**




ADC = Antibody-drug conjugate; AUC = Area under the curve; N = Number of patients; PopPBPK = Population, physiologically-based pharmacokinetic; Q3W = Every 3 weeks
Drug exposure versus the probability of corneal toxicity relationship with AUC(ADC) equals the PopPBPK model-predicted area under the anetumab ravtansine plasma concentration-time curve at steady state.
The solid line indicates the median estimate and the thin lines represent the 90% confidence interval; data used for logistic regression model development are shown as diamonds.
The box plots represent simulated AUC(ADC) distributions in a virtual population of N=1000 subjects receiving either 4.5 mg/kg (dotted box), 5.5 mg/kg (dashed box) or 6.5 mg/kg (solid box) anetumab ravtansine given Q3W.

[…]

### 15.1.2.5 Section 4 Study objectives

*Old text:*

[…]

The secondary objectives of this study are to:

- Test overall survival (OS)
- ~~Evaluate pulmonary function~~
- Evaluate patient-reported outcomes (PROs) – symptom burden and health-related quality of life (QoL)
- Evaluate other indicators of treatment efficacy (indicators of tumor response)
- Evaluate safety

[…]

*New text:*

[…]

The secondary objectives of this study are to:

- Test overall survival (OS)
- Evaluate patient-reported outcomes (PROs) – symptom burden and health-related quality of life (QoL)
- Evaluate other indicators of treatment efficacy (indicators of tumor response)
- Evaluate safety

[…]

### 15.1.2.6 Section 5.1 Design overview

*Old text:*

[…]

At the time of the start of study treatment, the patients will have advanced or metastatic MPM recurrent/relapsing after a 1st line treatment with platinum in combination with pemetrexed with or without bevacizumab, and overexpressing mesothelin as determined by immunohistochemistry (IHC). Only patients who demonstrate mesothelin overexpression at the moderate ~~(2+)~~ and strong ~~(3+)~~ level by IHC in at least 30% of tumor cells can be randomized into the study.

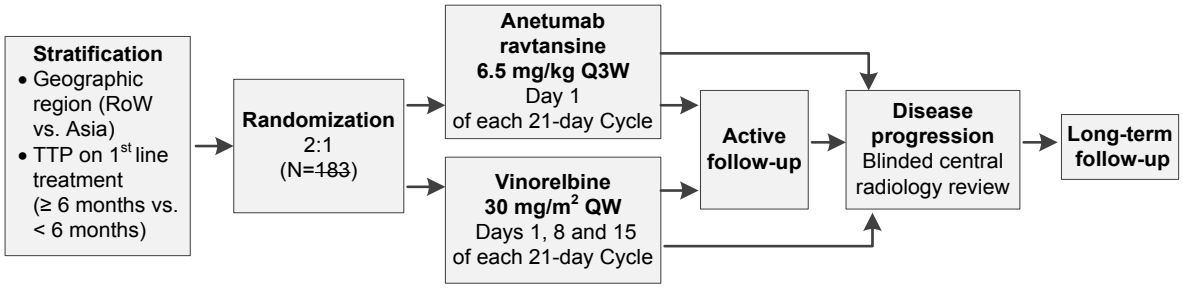
[…]

The start of the study is defined by signing of the informed consent form (ICF) for prescreening. After meeting the eligibility criteria for prescreening and for full study (see

Sections 6.1 and 6.2), approximately ~~183~~ patients will be randomly assigned in a 2:1 ratio to receive anetumab ravtansine or vinorelbine, respectively. The anetumab ravtansine arm will consist of approximately ~~122~~ patients and the vinorelbine comparator arm of approximately ~~61~~ patients. Patients will be stratified at randomization according to geographic region (Rest of the world [RoW] *versus* Asia) and per time to progression (TTP) on 1st line treatment (≥ 6 months *versus* < 6 months).

A graphical presentation of the overall study design is shown in Figure 5-2.

**Figure 5-2 Overall study design**




N = Number of patients; Q3W = Every 3 weeks; QW = Once weekly; RoW = Rest of the world, TTP = Time to progression

The start of the treatment period is defined by ~~first administration of~~ study drug (anetumab ravtansine or vinorelbine). Patients in the anetumab ravtansine arm will receive anetumab ravtansine IV infusion at a dose of 6.5 mg/kg (recommended Phase II dose [RPIID]) on Day 1 of a 21-day cycle. Patients in the comparator arm will receive vinorelbine 30 mg/m$^2$ IV on Days 1, 8 and 15 of a 21-day cycle. Treatment will be continued until death or occurrence of PD as defined by Modified Response Evaluation Criteria in Solid Tumors (mRECIST) for mesothelioma (21) and assessed by blinded central radiology review, or clinical progression, or until another criterion for withdrawal from the study is met. In case of ~~clinical~~ progression, however, ~~continuation of treatment until centrally confirmed radiological PD could be allowed if in the investigator's judgement this would provide clinical benefit to the patient~~.

[…]

Primary efficacy will be assessed based on radiological tumor evaluation by contrast-enhanced CT or contrast-enhanced magnetic resonance imaging (MRI) of chest/abdomen/pelvis (see Section 9.4.1). The first tumor images will be obtained during full screening and will be sent to blinded central review to confirm ~~that at least 1 measurable lesion is present~~ prior to randomization. During treatment as well as active follow-up, tumor imaging will be performed with the same modality every 6 weeks during the first 6 months after the start of study treatment, every 9 weeks until the end of year 2, and every 12 weeks thereafter until centrally confirmed radiological disease progression or end of study. Primary analysis results will be based on central review.

~~Determination of forced vital capacity (FVC) will be performed as a reproducible measure of pulmonary function, by a spirometry test as described in Section 9.4.2 until centrally confirmed radiological progression or end of study.~~

[…]

Safety evaluations will be done at full screening, at each clinic visit during the treatment, and at the safety follow-up visit as described in Section 9.6. The National Cancer Institute's Common Terminology Criteria for Adverse Events (NCI-CTCAE) version 4.03 will be used to grade severity of AEs.

*New text:*

[…]

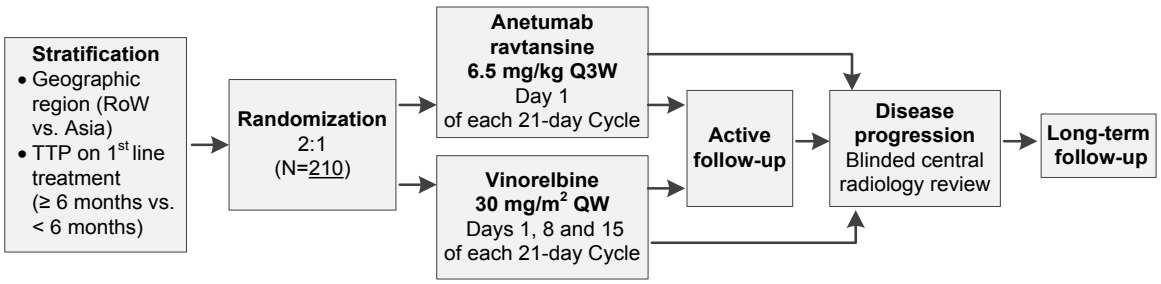
At the time of the start of study treatment, the patients will have advanced or metastatic MPM recurrent/relapsing after a 1st line treatment with platinum in combination with pemetrexed with or without bevacizumab, and overexpressing mesothelin as determined by immunohistochemistry (IHC). Only patients who demonstrate mesothelin overexpression at the moderate and stronger level by IHC in at least 30% of tumor cells can be randomized into the study.

[…]

The start of the study is defined by signing of the informed consent form (ICF) for prescreening. After meeting the eligibility criteria for prescreening and signing the ICF for full study (see Sections 6.1 and 6.2), approximately 210 patients who meet all of the inclusion and none of the exclusion criteria will be randomly assigned in a 2:1 ratio to receive anetumab ravtansine or vinorelbine, respectively. The anetumab ravtansine arm will consist of approximately 140 patients and the vinorelbine comparator arm of approximately 70 patients. Patients will be stratified at randomization according to geographic region (Rest of the world [RoW] *versus* Asia) and per time to progression (TTP) on 1st line treatment (≥ 6 months *versus* < 6 months). An approximately 40% screen fail rate is anticipated (25% at prescreening and a subsequent 20% among biomarker expressers. Approximately 350 patients are estimated to be required for prescreening to yield approximately 263 biomarker-positive patients, resulting in 210 randomized eligible patients).

A graphical presentation of the overall study design is shown in Figure 5-2.

**Figure 5-2 Overall study design**




N = Number of patients; Q3W = Every 3 weeks; QW = Once weekly; RoW = Rest of the world, TTP = Time to progression

The start of the treatment period is defined for efficacy purposes by randomization to study drug (anetumab ravtansine or vinorelbine), and for safety purposes by first administration of study drug. Start of treatment has to be within 24 hours after the randomization call. Patients in the anetumab ravtansine arm will receive anetumab ravtansine IV infusion at a dose of 6.5 mg/kg (recommended Phase II dose [RPIID]) on Day 1 of a 21-day cycle. Patients in the comparator arm will receive vinorelbine 30 mg/m$^2$ IV on Days 1, 8 and 15 of a 21-day cycle. Treatment will be continued until death or occurrence of PD as defined by Modified Response Evaluation Criteria in Solid Tumors (mRECIST) for mesothelioma (21) and assessed by blinded central radiology review, or clinical progression, or until another criterion for withdrawal from the study is met. In case of radiological progression, however, treatment may be continued provided that the patient derives clinical benefit as determined by the treating physician.

[…]

Primary efficacy will be assessed based on radiological tumor evaluation by contrast-enhanced CT or contrast-enhanced magnetic resonance imaging (MRI) of chest/abdomen/pelvis (see Section 9.4.1). The first tumor images will be obtained during full screening and will be sent to blinded central review to confirm radiological eligibility prior to randomization. During treatment as well as active follow-up, tumor imaging will be performed with the same modality every 6 weeks during the first 6 months after the start of study treatment, every 9 weeks until the end of year 2, and every 12 weeks thereafter until centrally confirmed radiological disease progression or end of study. Primary analysis results will be based on central review.

[…]

Safety evaluations will be done at full screening, at each clinic visit during the treatment, and at the safety follow-up visit as described in Section 9.6. The National Cancer Institute's Common Terminology Criteria for Adverse Events (NCI-CTCAE) version 4.03 will be used to grade severity of AEs. In addition, a Bayer grading system (see Table 7-6 and Table 7-7) will be used to assess corneal epitheliopathy.

[…]

### 15.1.2.7 Section 5.3 Justification of the design

*Old text:*

**Level of blinding.** This Phase II study will be open-label (see Section 7.5), because a double-blind, active-controlled study is not feasible due to different administration schedules, Q3W for anetumab ravtansine and QW for vinorelbine, and different safety profiles (e.g. corneal ~~toxicity~~ for the anetumab ravtansine arm and neutropenia for the comparator [vinorelbine] arm). The independent and central radiological review for the assessment of disease progression and other radiological imaging-based endpoints will be conducted in a blinded fashion.

**Dosage.** At the RPIID of 6.5 mg/kg Q3W, anetumab ravtansine has demonstrated very strong efficacy in advanced, unresectable or metastatic epithelial mesothelioma (best objective response 31% overall or 45% in the 2nd line setting, with very durable responses) (see Section 3.1.2). Moreover, no drug-related deaths, only 5 drug-related SAEs and a low rate of drug-related Grade 3/4 AEs were reported from clinical experience with anetumab ravtansine at the RPIID. Based on the ~~on~~ average linear PK of anetumab ravtansine, it can be assumed that dose reduction planned in this Phase II study will lead to a reduced total drug exposure and thus, to a reduced probability of corneal ~~toxicity~~.

[…]

**Study population.** Objective responses or prolonged SD cases in the 15051 study of anetumab ravtansine occurred in patients with moderate to strong mesothelin expression ~~(2+ and 3+)~~. Because of the treatment's surface mesothelin targeting MoA, no clinical efficacy is expected in MPM patients with little or no mesothelin cell surface expression. Patients with a sarcomatoid histology are not expected to have mesothelin overexpression and should not enter prescreening. Therefore, pre-selection based on mesothelin expression (see Section 6.1.1) is intended during recruitment of this study.

[…]

**Randomization**. A 2:1 randomization ratio is used to provide an adequate safety database for evaluating anetumab ravtansine safety. This ratio also encourages study participation by providing an elevated probability of receiving experimental treatment. The sample size is adequate for efficacy, and the safety of vinorelbine is well-studied. The sample size includes a ~~margin of 14.8~~% to address the possibility of dropouts (see Section 11.4).

For **strategies to limit the amount and impact of missing data**, see Section 11.4.

*New text:*

**Level of blinding.** This Phase II study will be open-label (see Section 7.5), because a double-blind, active-controlled study is not feasible due to different administration schedules, Q3W for anetumab ravtansine and QW for vinorelbine, and different safety profiles (e.g. corneal epitheliopathy for the anetumab ravtansine arm and neutropenia for the comparator [vinorelbine] arm). The independent and central radiological review for the assessment of

disease progression and other radiological imaging-based endpoints will be conducted in a blinded fashion.

**Dosage.** At the RPIID of 6.5 mg/kg Q3W, anetumab ravtansine has demonstrated very strong efficacy in advanced, unresectable or metastatic epithelial mesothelioma (best objective response 31% overall or 45% in the 2nd line setting, with very durable responses) (see Section 3.1.2). Moreover, no drug-related deaths, only 5 drug-related SAEs and a low rate of drug-related Grade 3/4 AEs were reported from clinical experience with anetumab ravtansine at the RPIID. Based on the drug exposure corneal epitheliopathy relationship (see Section 3.1.2 and Figure 3-1) and the average linear PK of anetumab ravtansine, it can be assumed that dose reduction planned in this Phase II study will lead to a reduced total drug exposure, and thus, to a reduced probability of corneal epitheliopathy.

[…]

**Study population.** Objective responses or prolonged SD cases in the 15051 study of anetumab ravtansine occurred in patients with moderate to stronger mesothelin expression. Because of the treatment's surface mesothelin targeting MoA, no clinical efficacy is expected in MPM patients with little or no mesothelin cell surface expression. Patients with a sarcomatoid histology are not expected to have mesothelin overexpression and should not enter prescreening. Therefore, pre-selection based on mesothelin expression (see Section 6.1.1) is intended during recruitment of this study.

[…]

**Randomization**. A 2:1 randomization ratio is used to provide an adequate safety database for evaluating anetumab ravtansine safety. This ratio also encourages study participation by providing an elevated probability of receiving experimental treatment. The sample size is adequate for efficacy, and the safety of vinorelbine is well-studied. The sample size includes a dropout rate of 3.4%/month (15.7% as of planned primary analysis) to address the possibility of dropouts (see Section 11.4).

For justification of study endpoints and measurements, see Section 9.8.

For **strategies to limit the amount and impact of missing data**, see Section 11.4.

### 15.1.2.8 Section 5.5 Primary completion

*Old text:*

Primary analysis will be performed ~~when~~ approximately 117 PFS events are observed by central review in the study.

[…]

*New text:*

Primary analysis will be performed after approximately 117 PFS events are observed by central review in the study.

[…]

### 15.1.2.9 Section 6.1.1 Eligibility criteria for prescreening

*Old text:*

Overexpression of mesothelin at the moderate ~~(2+)~~ and strong ~~(3+)~~ level in at least 30% of tumor cells is a prerequisite to be eligible for this study. […]

*New text:*

Overexpression of mesothelin at the moderate and stronger level in at least 30% of tumor cells is a prerequisite to be eligible for this study. […]

### 15.1.2.10 Section 6.1.2 Eligibility criteria for full study

*Old text:*

The following inclusion criteria must be met at the time of ~~full screening~~ and on C1D1 unless otherwise specified.

1. Written informed consent for full study.
2. Histological documentation of MPM overexpressing mesothelin at the moderate ~~(2+)~~ and strong ~~(3+)~~ level in at least 30% of tumor cells as determined by centrally performed IHC.

[…]

4. Patients must have at least 1 measurable lesion according to mRECIST for mesothelioma (specified in ~~Section 9.4.1~~). This will be confirmed by central review of images before the patient can be randomized into the study.

   ~~Note: Patients with non-pleural disease as the only relapse site after a pleural surgery (e.g. subcutaneous lesions, nodal lesions, lung lesions etc.) will be eligible if at least 1 measurable lesion according to RECIST 1.1 is present.~~

   Note: In case the only site of disease was previously treated with radiotherapy, there should be evidence of unequivocal PD in this site: measurable pleural disease should be assessed on a contrast enhanced CT/MRI done at the minimum 4 weeks after the end of radiotherapy and compared with previous imaging; unequivocal progression should be judged by the investigator as per mRECIST per MPM.

[…]

7. Women of childbearing potential (WOCBP) and fertile men must agree to use adequate contraception when sexually active from signing of the ICF for full study until at least ~~3~~ months after the last study drug administration. Men being treated with vinorelbine are advised not to father a child during and up to 6 months after treatment; prior to treatment, advice should be sought for conserving sperm due to the chance of irreversible infertility as a consequence of treatment ~~with vinorelbine~~ (22)~~(~~.The

investigator or a designated associate is requested to advise the patient how to achieve highly effective birth control. Highly effective (failure rate of less than 1% per year) contraception methods (23) include:

- Combined (estrogen and progesteron containing: oral, intravaginal, transdermal) and progesteron-only (oral, injectable, implantable) hormonal contraception associated with inhibition of ovulation.
- Intrauterine device (IUD) or intrauterine hormone-releasing system (IUS).
- Bilateral tubal occlusion or vasectomized partner (provided that partner is the sole sexual partner and has received medical assessment of the surgical success).
- Sexual abstinence (reliability to be evaluated in relation to the duration of the clinical trial and the preferred and usual lifestyle of the patient).

Male patients ~~should~~ use a condom during treatment and until ~~the end of relevant systemic exposure (this is 1 month~~ after last study drug administration~~), plus a further 3 months period, unless the female partner is permanently sterile. When a male study patient has a female partner of childbearing potential, contraception recommendations to the female partner should also be considered~~.

Note: a woman is considered WOCBP, i.e. fertile, following menarche and until becoming postmenopausal unless permanently sterile. Permanent sterilization methods include but are not limited to hysterectomy, bilateral salpingectomy and bilateral oophorectomy. A postmenopausal state is defined as no menses for 12 months without an alternative medical cause. A high follicle stimulating hormone (FSH) level in the postmenopausal range may be used to confirm a postmenopausal state in women not using hormonal contraception or hormonal replacement therapy. A man is considered fertile after puberty unless permanently sterile by bilateral orchiectomy.

[…]

*New text:*

The following inclusion criteria must be met at the time of <u>randomization call</u> and on C1D1 unless otherwise specified.

1. Written informed consent for full study.
2. Histological documentation of MPM overexpressing mesothelin at the moderate and strong<u>er</u> level in at least 30% of tumor cells as determined by centrally performed IHC.

[…]

4. Patients must have at least 1 measurable lesion according to mRECIST for mesothelioma (specified in <u>Appendix 16.3) i.e. pleural lesion(s) measured using mRECIST or extra-pleural lesion(s) measurable per RECIST 1.1</u>. This will be confirmed by central review of images before the patient can be randomized into the study.

Note: In case the only site of disease was previously treated with radiotherapy, there should be evidence of unequivocal PD in this site: measurable pleural disease should be assessed on a contrast enhanced CT/MRI done at the minimum 4 weeks after the end of radiotherapy and compared with previous imaging; unequivocal progression should be judged by the investigator as per mRECIST per MPM.

[…]

7. Women of childbearing potential (WOCBP) and fertile men must agree to use adequate contraception when sexually active from signing of the ICF for full study until at least 4 months after the last study drug administration. Men being treated with vinorelbine are advised not to father a child during and up to 6 months after treatment; for all male patients, prior to treatment with either study drug, advice should be sought for conserving sperm due to the chance of irreversible infertility as a consequence of treatment (22). The investigator or a designated associate is requested to advise the patient how to achieve highly effective birth control. Highly effective (failure rate of less than 1% per year) contraception methods (23) include:

   - Combined (estrogen and progesteron containing: oral, intravaginal, transdermal) and progesteron-only (oral, injectable, implantable) hormonal contraception associated with inhibition of ovulation.
   - Intrauterine device (IUD) or intrauterine hormone-releasing system (IUS).
   - Bilateral tubal occlusion or vasectomized partner (provided that partner is the sole sexual partner and has received medical assessment of the surgical success).
   - Sexual abstinence (reliability to be evaluated in relation to the duration of the clinical trial and the preferred and usual lifestyle of the patient).

   Male patients with a female partner of childbearing potential must use a condom and ensure that an additional form of contraception is also used during treatment and until 4 months after last study drug administration.

   Note: a woman is considered WOCBP, i.e. fertile, following menarche and until becoming postmenopausal unless permanently sterile. Permanent sterilization methods include but are not limited to hysterectomy, bilateral salpingectomy and bilateral oophorectomy. A postmenopausal state is defined as no menses for 12 months without an alternative medical cause. A high follicle stimulating hormone (FSH) level in the postmenopausal range may be used to confirm a postmenopausal state in women not using hormonal contraception or hormonal replacement therapy. A man is considered fertile after puberty unless permanently sterile by bilateral orchiectomy.

[…]

### 15.1.2.11 Section 6.2 Exclusion criteria

*Old text:*

Patients who meet the following criteria at the time of ~~full screening~~ and on C1D1 will be excluded:

[…]

5. Patients with corneal epitheliopathy or any eye disorder that may predispose the patients to this condition at the discretion of the ophthalmologist.

[…]

*New text:*

Patients who meet the following criteria at the time of randomization call and on C1D1 will be excluded:

5. Patients with corneal epitheliopathy or any eye disorder that may predispose the patients to this condition at the discretion of the investigator in consultation with the ophthalmologist/optometrist.

   Note: Low grades of superficial punctate keratitis, within the range seen in the normal population, should not lead to the exclusion of the patient.

### 15.1.2.12 Section 6.3.1.1.1 Prescreening failure

*Old text:*

A patient whose tumor tissue is centrally tested by IHC for mesothelin overexpression and whose result is not moderate ~~(2+)~~ and strong ~~(3+)~~ mesothelin overexpression in at least 30% of the tumor cells, or who fails to meet any of the other eligibility criteria for prescreening, is regarded as a “prescreening failure”. These patients should not undergo any further screening procedures.

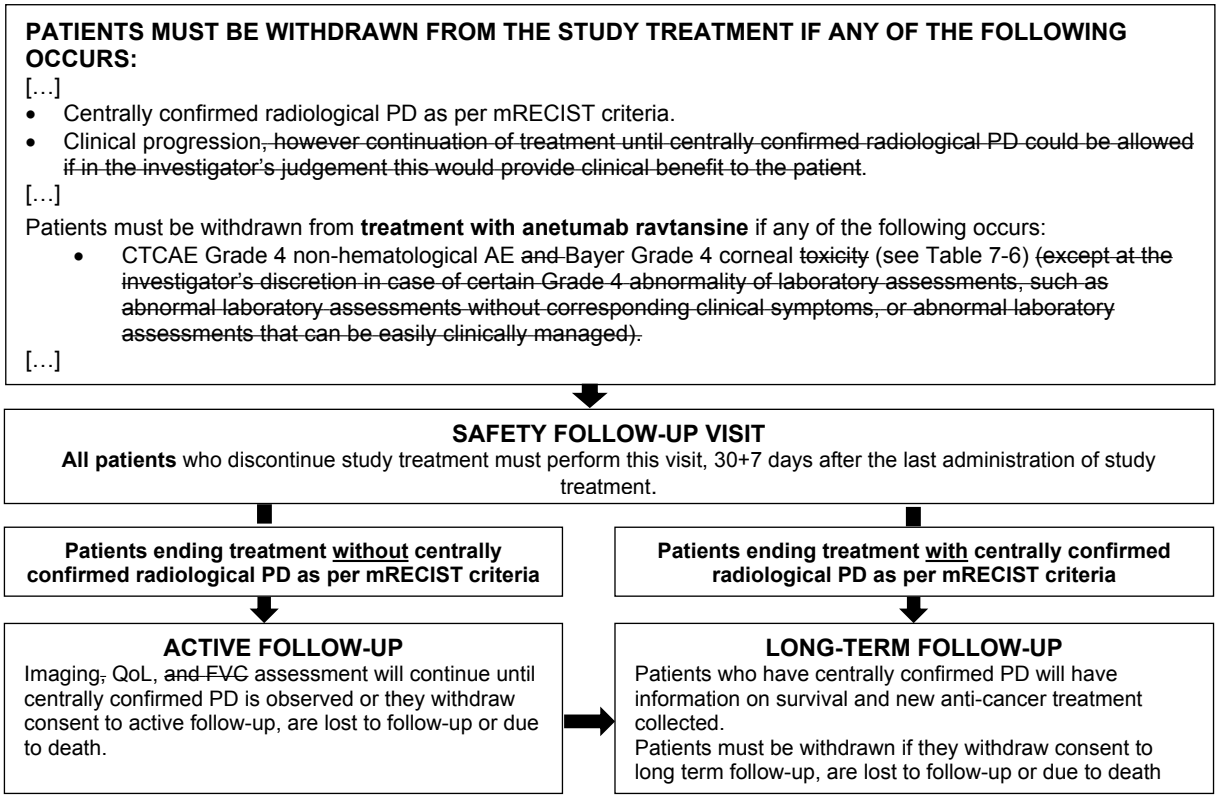
*New text:*

A patient whose tumor tissue is centrally tested by IHC for mesothelin overexpression and whose result is not moderate and stronger mesothelin overexpression in at least 30% of the tumor cells, or who fails to meet any of the other eligibility criteria for prescreening, is regarded as a “prescreening failure”. These patients should not undergo any further screening procedures.

## 15.1.2.13 Section 6.3.1.2 Withdrawal criteria

*Old text:*

**Figure 6-1 Withdrawal criteria**



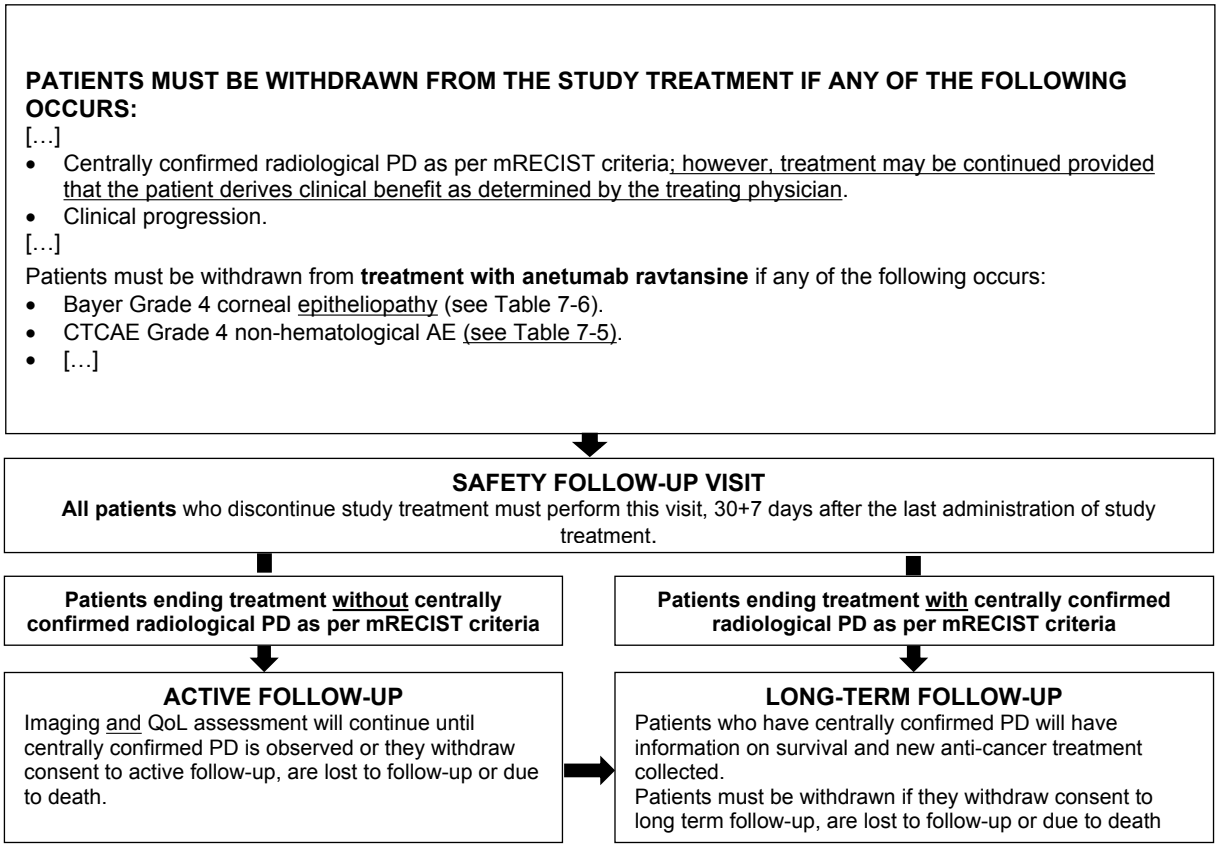

AE = Adverse event; ARDS = Acute respiratory distress syndrome; β-HCG = β subunit of human chorionic gonadotropin; CTCAE = Common Terminology Criteria for Adverse Events; FVC = Forced vital capacity; Hb = Hemoglobin; mRECIST = Modified Response Evaluation Criteria in Solid Tumors; PD = Progressive disease; Q3W = Every 3 weeks; QoL = Quality of life; SAE = Serious adverse event; TEAE = Treatment-emergent adverse event

### Lost to follow-up patients

When a patient is lost to follow-up at any stage of the study, the site should try to contact the patient, the patient's relatives, or another doctor treating the patient, unless prohibited by local regulations. All attempts to contact the patient or relatives should be documented and sites are expected to perform at least 5 attempts to contact the patient over the course of 3 months.

*New text:*

**Figure 6-1 Withdrawal criteria**




AE = Adverse event; ARDS = Acute respiratory distress syndrome; β-HCG = β subunit of human chorionic gonadotropin; CTCAE = Common Terminology Criteria for Adverse Events; Hb = Hemoglobin; mRECIST = Modified Response Evaluation Criteria in Solid Tumors; PD = Progressive disease; Q3W = Every 3 weeks; QoL = Quality of life; SAE = Serious adverse event; TEAE = Treatment-emergent adverse event

## Patients randomized but not treated

In the event a patient is randomized but never treated, a withdrawal from treatment CRF should be filled out for the patient articulating the date of and reason for not treating the patient. The patient should receive efficacy follow-up, active follow-up if feasible, otherwise long-term follow-up. No safety follow-up is required.

### Lost to follow-up patients

When a patient is lost to follow-up at any stage of the study, the site should try to contact the patient, the patient's relatives, or another doctor treating the patient, unless prohibited by local regulations. All attempts to contact the patient or relatives should be documented and sites are expected to perform at least 5 attempts to contact the patient over the course of 3 months. An additional contact attempt should be made at the time of each survival sweep.

### 15.1.2.14 Section 7.2.1 Test drug - anetumab ravtansine

*Old text:*

**Stability of the reconstituted solution**

[…]

If frozen or stored above ~~25°C (77°F)~~, the solution should be discarded.

[…]

**Stability of the diluted solution**

[…]

If frozen or stored above ~~25°C~~, the solution should be discarded.

[…]

*New text:*

**Stability of the reconstituted solution**

[…]

If frozen or stored above room temperature, the solution should be discarded.

[…]

**Stability of the diluted solution**

[…]

If frozen or stored above room temperature, the solution should be discarded.

[…]

### 15.1.2.15 Section 7.2.2 Comparator - vinorelbine

*Old text:*

Vinorelbine formulation is a concentrate for infusion solution. It is available as concentrate with 10 mg/mL or 50 mg/mL vinorelbine (as tartrate).

[…]

*New text:*

Vinorelbine formulation is a concentrate for infusion solution. It is available as concentrate with 10 mg/mL or 50 mg/5 mL vinorelbine (as tartrate).

[…]

### 15.1.2.16 Section 7.3 Treatment assignment

*Old text:*

[…]

Confirmation of adequate level of mesothelin overexpression will be obtained from the central lab. Confirmation of ~~at least 1 measurable lesion present~~ will be obtained from central radiological review. Confirmation of other inclusion and exclusion requirements will be obtained from the investigator. After confirmation of patient eligibility in IxRS, a randomization code will be assigned.

*New text:*

[…]

Confirmation of adequate level of mesothelin overexpression will be obtained from the central lab. Confirmation of radiological eligibility will be obtained from central radiological review. Confirmation of other inclusion and exclusion requirements will be obtained from the investigator. After confirmation of patient eligibility in IxRS, a randomization code will be assigned.

### 15.1.2.17 Section 7.4.2.1 Dose modifications of anetumab ravtansine

*Old text:*

The NCI-CTCAE v4.03 will be used to assess toxicities; in addition, a Bayer grading system (see Table 7-6 and Table 7-7) will be used to assess corneal ~~toxicity~~.

[…]

*New text:*

The NCI-CTCAE v4.03 will be used to assess toxicities; in addition, a Bayer grading system (see Table 7-6 and Table 7-7) will be used to assess corneal epitheliopathy.

[…]

### 15.1.2.18 Section 7.4.2.1.2 Non-hematological toxicities

*Old text:*

**Non-hematological toxicities requiring dose modification**

- CTCAE Grade ≥ 2 anetumab ravtansine infusion reaction or other CTCAE Grade ≥ 2 hypersensitivity events
- AST and/or ALT increase > 5.0 x ULN (CTCAE Grade ≥ 3)
- AST and/or ALT increase > 3.0 x ULN (CTCAE Grade ≥ 2) with concomitant increase in total bilirubin > 1.5 x ULN (CTCAE Grade ≥ 2)

- Total bilirubin > 3.0 x ULN (CTCAE Grade ≥ 3)
- Bayer Grade ≥ 3 corneal ~~toxicity~~ (see below and Table 7-6)
- Any other Grade ≥ 3 non-hematological toxicity that, in the investigator's opinion, warrants treatment modification (see Table 7-5), **excluding** the following:
    - Nausea, vomiting, or diarrhea if manageable with anti-emetics or anti-diarrheals within 7 days
    - Hair loss
    - Fatigue lasting ≤ 72 h
    - ~~Certain asymptomatic laboratory assessments without a clear clinical correlate, if the investigator determines that this TEAE would not require treatment modification~~

[…]

**Dose modifications for non-hematological toxicity**

If treatment modification is required due to Grade ≥ 3 **non-hematological TEAE**, other than corneal ~~toxicity~~ and infusion reaction/hypersensitivity events, and the continuation of treatment is appropriate, the anetumab ravtansine dose will be either reduced or maintained as is at investigator's discretion (see Table 7-5).

[…]

After dose reduction, there could be no intra-patient dose escalation irrespective of the type of TEAE that has led to dose reduction in this patient.

*New text:*

**Non-hematological toxicities requiring dose modification**

- CTCAE Grade 2 anetumab ravtansine infusion-related reaction or other CTCAE Grade 2 hypersensitivity events (see Section 7.4.2.1.3)
- AST and/or ALT increase > 5.0 x ULN (CTCAE Grade ≥ 3)
- AST and/or ALT increase > 3.0 x ULN (CTCAE Grade ≥ 2) with concomitant increase in total bilirubin > 1.5 x ULN (CTCAE Grade ≥ 2)
- Total bilirubin > 3.0 x ULN (CTCAE Grade ≥ 3)
- Bayer Grade ≥ 3 corneal epitheliopathy (see below and Table 7-6)
- Any other Grade ≥ 3 non-hematological toxicity that, in the investigator's opinion, warrants treatment modification (see Table 7-5), **excluding** the following:
    - Nausea, vomiting, or diarrhea if manageable with anti-emetics or anti-diarrheals within 7 days

- Hair loss
- Fatigue lasting ≤ 72 h

[…]

**Dose modifications for non-hematological toxicity**

If treatment modification is required due to Grade ≥ 3 **non-hematological TEAE**, other than corneal epitheliopathy and infusion-related reaction/hypersensitivity events, and the continuation of treatment is appropriate, the anetumab ravtansine dose will be either reduced or maintained as is at investigator's discretion (see Table 7-5).

[…]

After dose reduction for TEAE, there could be no intra-patient dose re-escalation irrespective of the type of TEAE that has led to dose reduction in this patient with the exception of grade 3 corneal epitheliopathy as per Table 7-6.

## 15.1.2.19 Section 7.4.2.1.3 Miscellaneous toxicities

*Old text:*

**IV infusion reaction and other hypersensitivity events**

If a patient experiences a CTCAE Grade ≥ 2 anetumab ravtansine infusion reaction or other CTCAE Grade ≥ 2 hypersensitivity event deemed at least possibly related to anetumab ravtansine, the infusion of anetumab ravtansine will be interrupted.

If treatment interruption is caused by a CTCAE Grade ≥ 2 anetumab ravtansine **infusion reaction or other CTCAE Grade ≥ 2 hypersensitivity event** deemed at least possibly related to anetumab ravtansine, treatment may be re-started at the time determined at the investigator's discretion. Re-treatment should be at the infusion rate reduced by 50%, along with anti-allergic prophylaxis (e.g. anti-histamines, acetaminophen, and/or corticosteroids) chosen at the investigator's discretion or according to the institutional guidelines.

**Miscellaneous toxicities requiring dose modification**

For any toxicity ≤ Grade 2 assessed as related to anetumab ravtansine by the investigator, dose modification should be considered. Such toxicities might be ≤ Grade 2 toxicities which interfere with the activities of daily life, such as long lasting fatigue, or anorexia, or corneal ~~toxicity~~ with vision impairment etc. A dose change might be necessary in order to ensure the patient's compliance. These toxicities may be declared "TEAE requiring treatment modification" after consultation between the investigator and the sponsor.

**Dose modifications for corneal ~~toxicity~~**

For the TEAE of corneal ~~morphology changes~~ and the best corrected visual acuity (BCVA) changes (blurred vision), the Bayer severity grading system (see Table 7-6 and Table 7-7) will

be used to assess the severity of TEAEs requiring modification of anetumab ravtansine treatment.

TEAE of corneal ~~morphology changes~~ deemed to be at least possibly related to anetumab ravtansine would require modification of anetumab ravtansine treatment (dose reduction or permanent discontinuation of treatment) according to the following principles (see Table 7-6).

**Table 7-6 Bayer classification and management of corneal epitheliopathi~~es~~**

| | Grade 0 | Grade 1 | Grade 2 | Grade 3 | Grade 4 |
|---|---|---|---|---|---|
| **Corneal morphology** | No pathologic changes | Any stage of superficial punctate keratitis [a] | Epithelial opacities<br>Micro-cysts<br>Micro-deposits<br>Corneal erosion<br>Stromal opacity: non-central | Corneal ulcer without risk of acute rupture<br>Stromal opacity: central | Corneal ulcer more severe than Grade 3 |
| **Eye treatment** [b] | Ocular lubricants at the discretion of investigator ~~and~~ ophthalmologist | Ocular lubricants; add topical steroids if superficial punctate keratitis shows treatment-emergent progression by ≥ 2 SPK Grades | Intensive treatment with ocular lubricants enhanced with ointments; topical steroids; therapeutic contact lens may be considered at the discretion of investigator ~~and~~ ophthalmologist | Intensive therapy with ointments; topical steroids; therapeutic contact lens or occlusion recommended at the discretion of investigator ~~and~~ ophthalmologist | Intensive therapy with lubricants, ointments, topical steroids and antibiotics as needed; occlusion or therapeutic contact lens recommended; amniotic membrane transplant and other locally approved therapies to be considered at the discretion of investigator ~~and~~ ophthalmologist |
| **Anetumab ravtansine** [c] | No change | No change | Keep treatment dose level and schedule if the ophthalmological exam can be performed as needed; otherwise consider dose reduction by -1 dose level without dose schedule change at the discretion of investigator ~~and~~ ophthalmologist | 1) Decrease dose to -1 dose level (or -2 dose level if event does not resolve to Grade ≤ 2 at the -1 dose level within 3 weeks)<br>2) Re-start at the original dose level if the first Grade 3 event resolves to Grade ≤ 2 within 3 weeks and does not recur<br>3) If not resolved within 3 weeks continue at reduced -1 dose level (or -2 dose level) | Discontinue treatment |

SPK = Superficial punctate keratitis

a Oxford Schema must be used for grading SPK from stage 0 to VI.

**Table 7-6 Bayer classification and management of corneal epitheliopathies**

| | Grade 0 | Grade 1 | Grade 2 | Grade 3 | Grade 4 |
|---|---|---|---|---|---|

b Other remedial therapies for corneal epitheliopathy may be added or substituted at investigator's discretion or according to the institutional standards.
c Treatment decisions are based on corneal ~~morphology changes~~ only, not on visual acuity changes.

[…]

**Recommended measures in case of eye dryness and ocular hypertension**

[…]

Changes in IOP should be managed by an ophthalmologist. The remedial therapy should be chosen at investigator's discretion or according to the institutional standards; therapeutic measures can include modification of the type or posology of topical steroid eye drop, initiation of topical IOP lowering drugs and any other therapeutic options according to the local SoC. Ophthalmological monitoring should be maintained until the IOP has returned to normal values.

Reductions in tear production evaluated by the Schirmer test, while not being a part of the corneal epitheliopathy syndrome, are a risk factor for developing ocular surface disease including corneal epithelial defects. Therefore, the tear production will be evaluated in this study to determine if changes in this parameter may be helpful to identify patients at higher risk of developing the corneal epitheliopathy syndrome. Abnormal values in the Schirmer test should be evaluated and managed by an ophthalmologist to provide adequate protection to the corneal epithelium. The remedial therapy for the treatment-emergent changes in the Schirmer~~'s~~ test (dry eye) should be chosen at investigator's discretion or according to the institutional standards. These measures may include topical lubricants such as eye drops and ointments, punctual occlusion, use of therapeutic contact lenses and any other treatment approaches according to the local SoC.

*New text:*

**IV infusion-related reaction and other hypersensitivity events**

If a patient experiences a CTCAE Grade 2 anetumab ravtansine infusion-related reaction or other CTCAE Grade 2 hypersensitivity event deemed at least possibly related to anetumab ravtansine, the infusion of anetumab ravtansine will be interrupted.

If treatment interruption is caused by a CTCAE Grade 2 anetumab ravtansine **infusion-related reaction or other CTCAE Grade 2 hypersensitivity event** deemed at least possibly related to anetumab ravtansine, treatment may be re-started at the time determined at the investigator's discretion. Re-treatment should be at the infusion rate reduced by 50%, along with anti-allergic prophylaxis (e.g. anti-histamines, acetaminophen, and/or corticosteroids) chosen at the investigator's discretion or according to the institutional guidelines.

In case of a CTCAE Grade ≥ 3 hypersensitivity and acute infusion reaction, treatment must be permanently withdrawn.

**Miscellaneous toxicities requiring dose modification**

For any toxicity ≤ Grade 2 assessed as related to anetumab ravtansine by the investigator, dose modification should be considered. Such toxicities might be ≤ Grade 2 toxicities which interfere with the activities of daily life, such as long lasting fatigue, or anorexia, or corneal epitheliopathy with vision impairment etc. A dose change might be necessary in order to ensure the patient's compliance. These toxicities may be declared "TEAE requiring treatment modification" after consultation between the investigator and the sponsor.

**Dose modifications for corneal epitheliopathy**

For the TEAE of corneal epitheliopathy and the best corrected visual acuity (BCVA) changes (blurred vision), the Bayer severity grading system (see Table 7-6 and Table 7-7) will be used to assess the severity of TEAEs requiring modification of anetumab ravtansine treatment.

TEAE of corneal epitheliopathy deemed to be at least possibly related to anetumab ravtansine would require modification of anetumab ravtansine treatment (dose reduction or permanent discontinuation of treatment) according to the following principles (see Table 7-6).

**Table 7-6 Bayer classification and management of corneal epitheliopathy**

| | Grade 0 | Grade 1 | Grade 2 | Grade 3 | Grade 4 |
|---|---|---|---|---|---|
| **Corneal morphology** | No pathologic changes | Any stage of superficial punctate keratitis [a] | Epithelial opacities<br><br>Micro-cysts<br>Micro-deposits<br>Corneal erosion<br>Stromal opacity: non-central | Corneal ulcer without risk of acute rupture<br><br>Stromal opacity: central | Corneal ulcer more severe than Grade 3 |
| **Eye treatment [b]** | Ocular lubricants at the discretion of investigator in consultation with ophthalmologist /optometrist | Ocular lubricants; add topical steroids if superficial punctate keratitis shows treatment-emergent progression by ≥ 2 SPK Grades | Intensive treatment with ocular lubricants enhanced with ointments; topical steroids; therapeutic contact lens may be considered at the discretion of investigator in consultation with ophthalmologist/ optometrist | Intensive therapy with ointments; topical steroids; therapeutic contact lens or occlusion recommended at the discretion of investigator in consultation with ophthalmologist/ optometrist | Intensive therapy with lubricants, ointments, topical steroids and antibiotics as needed; occlusion or therapeutic contact lens recommended; amniotic membrane transplant and other locally approved therapies to be considered at the discretion of investigator in consultation with ophthalmologist/ optometrist |
| **Anetumab ravtansine [c]** | No change | No change | Keep treatment dose level and schedule if the ophthalmological exam can be performed as | 1) Decrease dose to -1 dose level (or -2 dose level if event does not resolve to Grade ≤ 2 at the -1 dose | Discontinue treatment |

**Table 7-6 Bayer classification and management of corneal epitheliopathy**

| Grade 0 | Grade 1 | Grade 2 | Grade 3 | Grade 4 |
|---|---|---|---|---|
| | | needed; otherwise consider dose reduction by -1 dose level without dose schedule change at the discretion of investigator in consultation with ophthalmologist/ optometrist | level within 3 weeks) 2) Re-start at the original dose level if the first Grade 3 event resolves to Grade ≤ 2 within 3 weeks and does not recur 3) If not resolved within 3 weeks continue at reduced -1 dose level (or -2 dose level) | |

SPK = Superficial punctate keratitis
a Oxford Schema must be used for grading SPK from stage 0 to VI.
b Other remedial therapies for corneal epitheliopathy may be added or substituted at investigator's discretion or according to the institutional standards.
c Treatment decisions are based on corneal epitheliopathy only, not on visual acuity changes.

[…]

**Recommended measures in case of eye dryness and ocular hypertension**

[…]

Changes in IOP should be managed by an ophthalmologist/optometrist. The remedial therapy should be chosen at investigator's discretion or according to the institutional standards; therapeutic measures can include modification of the type or posology of topical steroid eye drop, initiation of topical IOP lowering drugs and any other therapeutic options according to the local SoC. Ophthalmological monitoring should be maintained until the IOP has returned to normal values.

Reductions in tear production evaluated by the Schirmer test, while not being a part of the corneal epitheliopathy syndrome, are a risk factor for developing ocular surface disease including corneal epithelial defects. Therefore, the tear production will be evaluated in this study to determine if changes in this parameter may be helpful to identify patients at higher risk of developing the corneal epitheliopathy syndrome. Abnormal values in the Schirmer test should be evaluated and managed by an ophthalmologist/optometrist to provide adequate protection to the corneal epithelium. The remedial therapy for the treatment-emergent changes in the Schirmer test (dry eye) should be chosen at investigator's discretion or according to the institutional standards. These measures may include topical lubricants such as eye drops and ointments, punctual occlusion, use of therapeutic contact lenses and any other treatment approaches according to the local SoC.

## 15.1.2.20 Section 7.4.2.2 Dose modifications of vinorelbine

*Old text:*

The following dose modifications for vinorelbine, based on the US label guidance (27), are provided below as a general recommendation. After dose reduction, there could be no intra-patient dose escalation irrespective of the type of TEAE that has led to dose reduction in this patient. All label specific instructions for treatment with vinorelbine will apply. Please refer to the local full prescribing information for further guidance.
[…]

*New text:*

The following dose modifications for vinorelbine, based on the US label guidance (27), are provided below as a general recommendation. After dose reduction <u>for TEAE</u>, there could be no intra-patient dose <u>re-</u>escalation irrespective of the type of TEAE that has led to dose reduction in this patient. All label specific instructions for treatment with vinorelbine will apply. Please refer to the local full prescribing information for further guidance.
[…]

## 15.1.2.21 Section 8.1 Prior and concomitant therapy

*Old text:*

[…]

**Table 8-2 Permitted concomitant therapies**

| Permitted concomitant therapies | Comments |
|---|---|
| ***Permitted for all patients*** | |
| […] | |
| Institutional standards for the management of infusion reactions | May be utilized at the discretion of the investigator. |
| […] | |

[…]

*New text:*

[…]

**Table 8-2 Permitted concomitant therapies**

| Permitted concomitant therapies | Comments |
|---|---|
| ***Permitted for all patients*** | |
| […] | |
| Institutional standards for the management of infusion-related reactions or other hypersensitivity events | May be utilized at the discretion of the investigator. |
| […] | |

[…]

## 15.1.2.22 Section 9.1 Tabular schedule of evaluations

*Old text:*

Schedule of procedures is presented in Table 9-1.

**Table 9-1 Study flow chart**

| | Pre-screening | Full screening (maximum days before C1D1) | | Treatment | | | | | | Safety follow-up period / visit | Active follow-up [a] | Long-term follow-up [a] |
|---|---|---|---|---|---|---|---|---|---|---|---|---|
| | | | | Cycle 1 | | | Cycle 2 and higher | | | | | |
| **Days** | | **-28** | **- 7** | **D1** | **D8** | **D15** | **D1** | **D8 [b]** | **D15 [b]** | **+30** (after last dose) | | **Every 3 months** |
| Acceptable time window (in days) (unless otherwise specified) | | | | | +/-1 | +/-1 | +/-1 | +/-1 | +/-1 | +7 | | ±14 |
| **Screening and enrollment** | | | | | | | | | | | | |
| Written informed consent for prescreening [c] | X | | | | | | | | | | | |
| Written informed consent for full study [c] | | X | | | | | | | | | | |
| Demographics | X | | | | | | | | | | | |
| Study disease characteristics [d] | X | X | | | | | | | | | | |
| Medical history [d] | | X | | | | | | | | | | |
| Check eligibility criteria | X | X | | X | | | | | | | | |
| IxRS transaction [e] | X | | | X | X | X | X | X | X | X | | |
| **Safety** | | | | | | | | | | | | |
| Toxicity / AE assessment [f] | X [f] | X | X | X | X | X | X | X | X | X | X [f] | |
| Concomitant medication | X [f] | X | | X | X | X | X | X | X | X | X [f] | |
| Complete physical examination | | X | | | | | | | | | | |
| Brief physical examination [g] | | | | X | X | X | X | X [g] | X [g] | X | | |
| Vital signs (BP, HR, RR, Temp) | | X | X | X | X | X | X | X | X | X | | |
| Weight/height [h] | | X [h] | | X | X | X | X | X | X | X | | |
| 12-Lead ECG [i] | | X | | X [i] | | | X [i] | | | X | | |
| ECOG PS assessment | X | X | | X | | | X | | | X | | |
| EchoCG or MUGA scan [j] | | X | | | | | X [j] | | | | | |
| Ophthalmologic examination [k] | | X | | | | | X | | | X | | |
| Complete blood count | | | X | | X | X | X | X | X | X | | |
| Electrolyte and chemistry panel | | | X | | X [l] | X [l] | X | X [l] | X [l] | X | | |
| eGFR | | | X | | | | X | | | X | | |
| Coagulation panel | | | X | | | | X | | | X | | |

**Table 9-1 Study flow chart**

| | Pre-screening | Full screening (maximum days before C1D1) | | Treatment | | | | | | Safety follow-up period / visit | Active follow-up [a] | Long-term follow-up [a] |
|---|---|---|---|---|---|---|---|---|---|---|---|---|
| | | | | Cycle 1 | | | Cycle 2 and higher | | | | | |
| **Days** | | **-28** | **- 7** | **D1** | **D8** | **D15** | **D1** | **D8 [b]** | **D15 [b]** | **+30** (after last dose) | | **Every 3 months** |
| Acceptable time window (in days) (unless otherwise specified) | | | | | +/-1 | +/-1 | +/-1 | +/-1 | +/-1 | +7 | | ±14 |
| Urine dipstick [m] | | | X | ~~X~~ | | | X | | | | | |
| Serum pregnancy test (if applicable) | | | X [n] | | | | | | | X | | |
| **Efficacy** | | | | | | | | | | | | |
| Radiological tumor evaluation with contrast-enhanced CT/MRI [o] | | X | | Every 6 weeks (first 6 months), every 9 weeks (until end of year 2), every 12 weeks thereafter [o] | | | | | | | X [o] | |
| ~~Forced vital capacity (FVC) [o]~~ | | ~~X~~ | | ~~In parallel with CT/MRI [o]~~ | | | | | | | ~~X [o]~~ | |
| Disease and survival status [p] | | | | | | | | | | | | X |
| […] | | | | | | | | | | | | |
| **Patient-reported outcomes** | | | | | | | | | | | | |
| LCSS-Meso [y] | | | X | | | | X | | | X | X [y] | |
| MDASI-MPM [y] | | | X | | | | X | | | X | X [y] | |
| […] | | | | | | | | | | | | |

AE = Adverse event; ALT = Alanine aminotransferase; AST = Aspartate aminotransferase; BP = Blood pressure; BM = Biomarker; C = Cycle; CT = Computed tomography; CYP2D6 = Cytochrome P450, family 2, subfamily D, polypeptide 6; D = Day; ECG = Electrocardiogram; EchoCG = Echocardiogram; ECOG PS = Eastern Cooperative Oncology Group Performance Status; eGFR = Estimated glomerular filtration rate; ~~FVC = Forced vital capacity;~~ HR = Heart rate; IHC = Immunohistochemistry; IM = Immunogenicity; IOP = Intraocular pressure; IV = Intravenous; IxRS = Interactive Voice / Web Response System; LCSS-Meso = Lung Cancer Symptom Scale-Mesothelioma; MDASI-MPM = MD Anderson Symptom Inventory-Malignant Pleural Mesothelioma; mRECIST = Modified Response Evaluation Criteria in Solid Tumors; MRI = Magnetic resonance imaging; MUGA = Multiple gated acquisition; OS = Overall survival; PD = Progressive disease; PFS = Progression-free survival; PGt = Pharmacogenetic; PK = Pharmacokinetic(s); PR = Partial response; RR = Respiratory rate; SAE = Serious adverse event; Temp = Body temperature.

[…]

e IxRS transaction to register the patient in the system will be done at prescreening. IxRS transaction to randomize the patient will take place ~~on the day of the~~ first dose of study drug. IxRS transactions for medication dispensing will be done on Day 1 of each cycle for the anetumab ravtansine arm and on Day 1, Day 8, and Day 15 for the comparator arm. IxRS transaction to register the end of treatment will be done at the

safety follow-up visit.

[…]

k A detailed ophthalmologic examination (visual acuity, IOP, Schirmer test and slit lamp) will be done for all patients during full screening within 3 weeks before the start of study treatment. For patients treated in the anetumab ravtansine arm visual acuity and slit lamp exam will be repeated before infusion in every cycle except C1D1, and at safety follow-up visit, or more frequently at investigator's and ophthalmologist's discretion (**important to refer to Table 7-6 and Table 7-7**). IOP measurement is to be repeated during anetumab ravtansine therapy if the patient receives steroid eye drops as treatment for ~~eye toxicity~~; dry eye (Schirmer) test may be repeated during treatment at investigator's discretion (e.g. in case of eye dryness during anetumab ravtansine therapy). During treatment period, ophthalmologic examination can be done up to 7 days before anetumab ravtansine infusion.

[…]

o Pre-study CT/MRI may be acceptable as a baseline scan if done within 28 days before randomization, if centrally evaluable for mRECIST and if performed according to the Imaging Acquisition Guidance provided in the Imaging Manual. During treatment period as well as active follow-up period, tumor scans (contrast-enhanced CT/MRI of chest/abdomen/pelvis) ~~and FVC~~ will be performed with the same modality every 6 weeks during the first 6 months (24 weeks) after the start of study treatment, every 9 weeks until the end of year 2 (105 weeks), and every 12 weeks thereafter until centrally confirmed radiological disease progression or end of study. MRI shall be performed instead of CT when local regulations do not permit the use of CT as requested per protocol schedule. Visit window of +/- 7 days is allowed.

[…]

r PK sampling will be performed for patients in the anetumab ravtansine arm on C1D1, C1D8, C2D1, C3D1, C3D8, C3D15, C4D1, C6D1, C9D1 and on Day 1 of every 3 cycles thereafter. Unscheduled PK samples are requested at the next clinic visit after the initial onset of corneal ~~toxicity~~ and after the radiological assessment of the first PR (for details see Section 9.5).

[…]

y MDASI-MPM and LCSS-Meso are to be completed before the patient meets with a clinician ~~or~~ before any examination or test is performed on that day. MDASI-MPM and LCSS-Meso are to be completed at full screening, on C2D1 and on Day 1 of every cycle thereafter (e.g. C3D1, C4D1 etc.), at safety follow-up visit, and during active follow-up period. During active follow-up period, MDASI-MPM and LCSS-Meso are to be taken in parallel with CT/MRI.

*New text:*

Schedule of procedures is presented in Table 9-1.

**Table 9-1 Study flow chart**

| | Pre-screening | Full screening (maximum days before C1D1) | | Treatment | | | | | | Safety follow-up period / visit | Active follow-up [a] | Long-term follow-up [a] |
|---|---|---|---|---|---|---|---|---|---|---|---|---|
| | | | | Cycle 1 | | | Cycle 2 and higher | | | | | |
| **Days** | | **-28** | **- 7** | **D1** | **D8** | **D15** | **D1** | **D8** [b] | **D15** [b] | **+30** (after last dose) | | **Every 3 months** |
| Acceptable time window (in days) (unless otherwise specified) | | | | | +/-1 | +/-1 | +/-1 | +/-1 | +/-1 | +7 | | ±14 |
| **Screening and enrollment** | | | | | | | | | | | | |
| Written informed consent for prescreening [c] | X | | | | | | | | | | | |
| Written informed consent for full study [c] | | X | | | | | | | | | | |
| Demographics | X | | | | | | | | | | | |
| Study disease characteristics [d] | X | X | | | | | | | | | | |
| Medical history [d] | | X | | | | | | | | | | |
| Check eligibility criteria | X | X | | X[z] | | | | | | | | |
| IxRS transaction [e] | X | X | | X[z] | X | X | X | X | X | X | | |
| **Safety** | | | | | | | | | | | | |
| Toxicity / AE assessment [f] | X [f] | X | X | X[z] | X | X | X | X | X | X | X [f] | |
| Concomitant medication | X [f] | X | | X[z] | X | X | X | X | X | X | X [f] | |
| Complete physical examination | | X | | | | | | | | | | |
| Brief physical examination [g] | | | | X[z] | X | X | X | X [g] | X [g] | X | | |
| Vital signs (BP, HR, RR, Temp) | | X | X | X[z] | X | X | X | X | X | X | | |
| Weight/height [h] | | X [h] | | X[z] | X | X | X | X | X | X | | |
| 12-Lead ECG [i] | | X | | X [i] | | | X [i] | | | X | | |
| ECOG PS assessment | X | X | | X[z] | | | X | | | X | | |
| EchoCG or MUGA scan [j] | | X | | | | | X [j] | | | | | |
| Ophthalmologic examination [k] | | X | | | | | X | | | X | | |
| Complete blood count | | | X | | X | X | X | X | X | X | | |

**Table 9-1 Study flow chart**

| Days | Pre-screening | Full screening (maximum days before C1D1) | | Treatment | | | | | | Safety follow-up period / visit | Active follow-up [a] | Long-term follow-up [a] |
|---|---|---|---|---|---|---|---|---|---|---|---|---|
| | | | | Cycle 1 | | | Cycle 2 and higher | | | | | |
| | | -28 | - 7 | D1 | D8 | D15 | D1 | D8 [b] | D15 [b] | +30 (after last dose) | | Every 3 months |
| Acceptable time window (in days) (unless otherwise specified) | | | | | +/-1 | +/-1 | +/-1 | +/-1 | +/-1 | +7 | | ±14 |
| Electrolyte and chemistry panel | | | X | | X [l] | X [l] | X | X [l] | X [l] | X | | |
| eGFR | | | X | | | | X | | | X | | |
| Coagulation panel | | | X | | | | X | | | X | | |
| Urine dipstick [m] | | | X | | | | X | | | | | |
| Serum pregnancy test (if applicable) | | | X [n] | | | | | | | X | | |
| **Efficacy** | | | | | | | | | | | | |
| Radiological tumor evaluation with contrast-enhanced CT/MRI [o] | | X | | Every 6 weeks (first 6 months), every 9 weeks (until end of year 2), every 12 weeks thereafter [o] | | | | | | | X [o] | |
| Disease and survival status [p] | | | | | | | | | | | | X |
| […] | | | | | | | | | | | | |
| **Patient-reported outcomes** | | | | | | | | | | | | |
| LCSS-Meso [y] | | | X | | | | X | | | X | X [y] | |
| MDASI-MPM [y] | | | X | | X | X | X [y] | X [y] | X [y] | X | X [y] | |
| […] | | | | | | | | | | | | |

AE = Adverse event; ALT = Alanine aminotransferase; AST = Aspartate aminotransferase; BP = Blood pressure; BM = Biomarker; C = Cycle; CT = Computed tomography; CYP2D6 = Cytochrome P450, family 2, subfamily D, polypeptide 6; D = Day; ECG = Electrocardiogram; EchoCG = Echocardiogram; ECOG PS = Eastern Cooperative Oncology Group Performance Status; eGFR = Estimated glomerular filtration rate; HR = Heart rate; IHC = Immunohistochemistry; IM = Immunogenicity; IOP = Intraocular pressure; IV = Intravenous; IxRS = Interactive Voice / Web Response System; LCSS-Meso = Lung Cancer Symptom Scale-Mesothelioma; MDASI-MPM = MD Anderson Symptom Inventory-Malignant Pleural Mesothelioma; mRECIST = Modified Response Evaluation Criteria in Solid Tumors; MRI = Magnetic resonance imaging; MUGA = Multiple gated acquisition; OS = Overall survival; PD = Progressive disease; PFS = Progression-free survival; PGt = Pharmacogenetic; PK = Pharmacokinetic(s); PR = Partial response; RR = Respiratory rate; SAE = Serious adverse event; Temp = Body temperature.

[…]

e IxRS transaction to register the patient in the system will be done at prescreening. IxRS transaction to randomize the patient will take place

maximum 24 hours before the administration of first dose of study drug and can only be done after all inclusion and exclusion criteria are checked and eligibility is confirmed. IxRS transactions for medication dispensing will be done on Day 1 of each cycle for the anetumab ravtansine arm and on Day 1, Day 8, and Day 15 for the comparator arm. IxRS transaction to register the end of treatment will be done at the safety follow-up visit.

[…]

k A detailed ophthalmologic examination (visual acuity, IOP, Schirmer test and slit lamp) will be done for all patients during full screening within 3 weeks before the start of study treatment. For patients treated in the anetumab ravtansine arm visual acuity and slit lamp exam will be repeated before infusion in every cycle except C1D1, and at safety follow-up visit, or more frequently at investigator's and ophthalmologist/optometrist's discretion (**important to refer to Table 7-6 and Table 7-7**). IOP measurement is to be repeated during anetumab ravtansine therapy if the patient receives steroid eye drops as treatment for corneal epitheliopathy; dry eye (Schirmer) test may be repeated during treatment at investigator's discretion (e.g. in case of eye dryness during anetumab ravtansine therapy). During treatment period, ophthalmologic examination can be done up to 7 days before anetumab ravtansine infusion.

[…]

o Pre-study CT/MRI may be acceptable as a baseline scan if done within 28 days before randomization, if centrally evaluable for mRECIST and if performed according to the Imaging Acquisition Guidance provided in the Imaging Manual. During treatment period as well as active follow-up period, tumor scans (contrast-enhanced CT/MRI of chest/abdomen/pelvis) will be performed with the same modality every 6 weeks during the first 6 months (24 weeks) after the start of study treatment, every 9 weeks until the end of year 2 (105 weeks), and every 12 weeks thereafter until centrally confirmed radiological disease progression or end of study. MRI shall be performed instead of CT when local regulations do not permit the use of CT as requested per protocol schedule. Visit window of +/- 7 days is allowed.

[…]

r PK sampling will be performed for patients in the anetumab ravtansine arm on C1D1, C1D8, C2D1, C3D1, C3D8, C3D15, C4D1, C6D1, C9D1 and on Day 1 of every 3 cycles thereafter. Unscheduled PK samples are requested at the next clinic visit after the initial onset of corneal epitheliopathy and after the radiological assessment of the first PR (for details see Section 9.5).

[…]

y MDASI-MPM and LCSS-Meso are to be completed before the patient meets with a clinician and before any examination or test is performed on that day. MDASI-MPM and LCSS-Meso are to be completed at full screening, on C2D1 and on Day 1 of every cycle thereafter (e.g. C3D1, C4D1 etc.), at safety follow-up visit, and during active follow-up period. During active follow-up period, MDASI-MPM and LCSS-Meso are to be taken in parallel with CT/MRI. In addition, the MDASI-MPM only is performed on Day 8 and Day 15 during Cycles 1, 2 and 3.

z Eligibility criteria check, IxRS transaction to randomize the patient, toxicity / AE assessment, concomitant medication review, brief physical examination, vital signs and weight measurement, and ECOG PS assessment can be done within 24 hours before administration of the first dose of study drug. Eligibility must be confirmed prior to randomizing the patient in IxRS.

### 15.1.2.23 Section 9.2.2 Full screening period

*Old text:*

**Within 28 days before the start of study treatment:**

- Written informed consent for full study.
- Updates of study disease characteristics and prior therapies for the study indication (see Section 9.3.3).
- Medical history (see Section 9.3.2) and non-study-indication-related medications (see Section 9.3.3).
- Check eligibility criteria for full study, and exclusion criteria (see Section 6.1.2 and 6.2, respectively).
- Radiological tumor evaluation with contrast-enhanced CT/MRI of chest/abdomen/pelvis (see Section 9.4.1). Pre-study CT/MRI may be acceptable as a baseline scan if done within 28 days before ~~randomization~~, if centrally evaluable for mRECIST and if performed according to the Imaging Acquisition Guidance provided in the Imaging Manual.
- ~~FVC measurement (see Section 9.4.2).~~
- Toxicity/AE assessment: any new finding or worsening of any ongoing medical history condition after the patient has signed the full study ICF must be recorded as an AE (see Section 9.6.1).

[…]

**Within 7 days before the start of study treatment:**

- PROs (LCSS-Meso and MDASI-MPM) (see Section 9.4.4) before the patient meets with a clinician ~~or~~ before any examination or test is performed.

[…]

*New text:*

**Within 28 days before the start of study treatment:**

- Written informed consent for full study.
- <u>IxRS transaction to register the patient's full screening (see Section 6.4)</u>
- Updates of study disease characteristics and prior therapies for the study indication (see Section 9.3.3).
- Medical history (see Section 9.3.2) and non-study-indication-related medications (see Section 9.3.3).
- Check eligibility criteria for full study, and exclusion criteria (see Section 6.1.2 and 6.2, respectively).

- Radiological tumor evaluation with contrast-enhanced CT/MRI of chest/abdomen/pelvis (see Section 9.4.1). Pre-study CT/MRI may be acceptable as a baseline scan if done within 28 days before start of study drug, if centrally evaluable for mRECIST and if performed according to the Imaging Acquisition Guidance provided in the Imaging Manual.
- Toxicity/AE assessment: any new finding or worsening of any ongoing medical history condition after the patient has signed the full study ICF must be recorded as an AE (see Section 9.6.1).

[…]

**Within 7 days before the start of study treatment:**

- PROs (LCSS-Meso and MDASI-MPM) (see Section 9.4.3) before the patient meets with a clinician and before any examination or test is performed.

[…]

### 15.1.2.24 Section 9.2.3 Treatment period

*Old text:*

After all screening assessments have been completed and the patient's eligibility has been confirmed and documented (confirmation of mesothelin overexpression moderate ~~[2+]~~ and strong ~~[3+]~~ in at least 30% of tumor cells will be obtained from central lab and confirmation of ~~at least 1 measurable lesion present~~ will be obtained from central radiological review), the patient may begin treatment.

*New text:*

After all screening assessments have been completed and the patient's eligibility has been confirmed and documented (confirmation of mesothelin overexpression moderate and stronger in at least 30% of tumor cells will be obtained from central lab and confirmation of radiological eligibility will be obtained from central radiological review), the patient may begin treatment.

### 15.1.2.25 Section 9.2.3.1 Treatment – Cycle 1

*Old text:*

The following procedures should be performed on C1D1 **before receiving study treatment** unless otherwise specified in the protocol:

- Check eligibility criteria for full study, and exclusion criteria (see Section 6.1.2 and 6.2, respectively).
- IxRS transaction to randomize the patient (see Section 6.4) ~~on the day of the first dose of study drug~~ and for medication dispensing in both treatment arms (see Section 7.3).
- Toxicity/AE assessment (see Section 9.6.1).

- Concomitant medication review (see Section 8.1).
- Brief physical examination (see Section 9.6.3.2.2).
- Vital signs (see Section 9.6.3.4).
- Weight.
- ECOG PS assessment (see Section 9.6.3.3).
- ~~Laboratory (see Section 9.6.3.1):~~
    - ~~Urine dipstick.~~
- PK sampling (see Section 9.5):
    - In the anetumab ravtansine arm: Pre-infusion (within 1 h before the start of infusion), end of infusion (within 5 min after the end of infusion) and approximately 3 h (range: 2 to 4 h) after the start of infusion.
    - In the comparator arm: Pre-infusion (within 1 h before the start of infusion), end of infusion (within 5 min after the end of infusion), approximately 3 h (range: 2 to 4 h) after the start of infusion.

[…]

**Cycle 1 Day 8**

[…]

The following procedures should be performed on C1D8 **before receiving study treatment** unless otherwise specified in the protocol:

- IxRS transaction for medication dispensing in the comparator arm (see Section 7.3).

[…]

**Cycle 1 Day 15**

[…]

The following procedures should be performed on C1D15 **before receiving study treatment** unless otherwise specified in the protocol:

- IxRS transaction for medication dispensing in the comparator arm (see Section 7.3).

[…]

*New text:*

The following procedures should be performed on C1D1 **before receiving study treatment** unless otherwise specified in the protocol. Eligibility criteria check, IxRS transaction to randomize the patient, toxicity / AE assessment, concomitant medication review, brief physical examination, vital signs and weight measurement, and ECOG PS assessment can be done within 24 hours before administration of the first dose of study drug. Eligibility must be confirmed prior to randomizing the patient in IxRS.

- Check eligibility criteria for full study, and exclusion criteria (see Section 6.1.2 and 6.2, respectively).
- IxRS transaction to randomize the patient (see Section 6.4) and for medication dispensing in both treatment arms (see Section 7.3).
- Toxicity/AE assessment (see Section 9.6.1).
- Concomitant medication review (see Section 8.1).
- Brief physical examination (see Section 9.6.3.2.2).
- Vital signs (see Section 9.6.3.4).
- Weight.
- ECOG PS assessment (see Section 9.6.3.3).
- PK sampling (see Section 9.5):
    - In the anetumab ravtansine arm: Pre-infusion (within 1 h before the start of infusion), end of infusion (within 5 min after the end of infusion) and approximately 3 h (range: 2 to 4 h) after the start of infusion.
    - In the comparator arm: Pre-infusion (within 1 h before the start of infusion), end of infusion (within 5 min after the end of infusion), approximately 3 h (range: 2 to 4 h) after the start of infusion.

[…]

**Cycle 1 Day 8**

[…]

The following procedures should be performed on C1D8 **before receiving study treatment** unless otherwise specified in the protocol:

- PRO (MDASI-MPM) (see Section 9.4.3) before the patient meets with a clinician or before any examination and test is performed.
- IxRS transaction for medication dispensing in the comparator arm (see Section 7.3).

[…]

**Cycle 1 Day 15**

[…]

The following procedures should be performed on C1D15 **before receiving study treatment** unless otherwise specified in the protocol:

- PRO (MDASI-MPM) (see Section 9.4.3) before the patient meets with a clinician and before any examination or test is performed.
- IxRS transaction for medication dispensing in the comparator arm (see Section 7.3).

[…]

## 15.1.2.26 Section 9.2.3.2 Treatment – Cycle 2 and higher

*Old text:*

**Cycle 2 and higher Day 1**

[…]

- PROs (LCSS-Meso and MDASI-MPM) (see Section 9.4.4) before the patient meets with a clinician ~~or~~ before any examination or test is performed.

[…]

- Ophthalmologic examinations (visual acuity and slit lamp mandatory; IOP and Schirmer test optional) (see Section 9.6.3.7) for patients treated in the anetumab ravtansine arm in every cycle from C2D1 onwards, or more frequently at investigator's and ophthalmologist's discretion (**important to refer to Table 7-6 and Table 7-7)**. To be performed within 7 days before anetumab ravtansine infusion.

[…]

- PK sampling (see Section 9.5) for patients in the anetumab ravtansine arm will be done on C2D1, C3D1, C4D1, C6D1, C9D1 and on Day 1 of every 3 cycles thereafter:
    - C2D1: Pre-infusion (within 1 h before the start of infusion).
    - C3D1: Pre-infusion (within 1 h before the start of infusion), end of infusion (within 5 min after the end of infusion) and approximately 3 h (range: 2 to 4 h) after the start of infusion.
    - C4D1: Approximately 504 h after the start of C3D1 infusion (within 1 h before the start of infusion on C4D1).
    - C6D1, C9D1 and on Day 1 of every 3 cycles thereafter: Pre-infusion (within 1 h before the start of infusion) and end of infusion (within 5 min after the end of infusion).

  Unscheduled PK samples are requested at the next clinic visit after the initial onset of corneal ~~toxicity~~ and after the radiological assessment of the first PR (the first local

observation of at least a 30% reduction in the total tumor measurement according to mRECIST).

[…]

**Cycle 2 and higher Day 8**

[…]

The following procedures should be performed on Cycle 2 and higher, Day 8 **before receiving study treatment** unless otherwise specified in the protocol:

- IxRS transaction for medication dispensing in the comparator arm (see Section 7.3).

[…]

**Cycle 2 and higher Day 15**

[…]

The following procedures should be performed on Cycle 2 and higher, Day 15 **before receiving study treatment** unless otherwise specified in the protocol:

- IxRS transaction for medication dispensing in the comparator arm (see Section 7.3).

[…]

*New text:*

**Cycle 2 and higher Day 1**

[…]

- PROs (LCSS-Meso and MDASI-MPM) (see Section 9.4.3) before the patient meets with a clinician and before any examination or test is performed.

[…]

- Ophthalmologic examinations (visual acuity and slit lamp mandatory; IOP and Schirmer test optional) (see Section 9.6.3.7) for patients treated in the anetumab ravtansine arm in every cycle from C2D1 onwards, or more frequently at investigator's and ophthalmologist/optometrist's discretion (**important to refer to Table 7-6 and Table 7-7)**. To be performed within 7 days before anetumab ravtansine infusion.

[…]

- PK sampling (see Section 9.5) for patients in the anetumab ravtansine arm will be done on C2D1, C3D1, C4D1, C6D1, C9D1 and on Day 1 of every 3 cycles thereafter:
    - C2D1: Pre-infusion (within 1 h before the start of infusion).

- C3D1: Pre-infusion (within 1 h before the start of infusion), end of infusion (within 5 min after the end of infusion) and approximately 3 h (range: 2 to 4 h) after the start of infusion.
- C4D1: Approximately 504 h after the start of C3D1 infusion (within 1 h before the start of infusion on C4D1).
- C6D1, C9D1 and on Day 1 of every 3 cycles thereafter: Pre-infusion (within 1 h before the start of infusion) and end of infusion (within 5 min after the end of infusion).

Unscheduled PK samples are requested at the next clinic visit after the initial onset of corneal epitheliopathy and after the radiological assessment of the first PR (the first local observation of at least a 30% reduction in the total tumor measurement according to mRECIST).

[…]

**Cycle 2 and higher Day 8**

[…]

The following procedures should be performed on Cycle 2 and higher, Day 8 **before receiving study treatment** unless otherwise specified in the protocol:

- PRO (MDASI-MPM) (only C2D8 and C3D8, see Section 9.4.3) before the patient meets with a clinician and before any examination or test is performed.
- IxRS transaction for medication dispensing in the comparator arm (see Section 7.3).

[…]

**Cycle 2 and higher Day 15**

[…]

The following procedures should be performed on Cycle 2 and higher, Day 15 **before receiving study treatment** unless otherwise specified in the protocol:

- PRO (MDASI-MPM) (only C2D15 and C3D15, see Section 9.4.3) before the patient meets with a clinician and before any examination or test is performed.
- IxRS transaction for medication dispensing in the comparator arm (see Section 7.3).

[…]

## 15.1.2.27 Section 9.2.4 Efficacy assessments

*Old text:*

**Radiological tumor evaluations ~~and forced vital capacity measurements~~**

Radiological tumor evaluation with contrast-enhanced CT/MRI of chest/abdomen/pelvis ~~and FVC measurement~~ will be performed at the following intervals (for further details, see Section~~s~~ 9.4.1 ~~and 9.4.2, respectively~~).

Full screening (baseline):

- Within 28 days before the start of study treatment ~~and randomization~~.

[…]

*New text:*

**Radiological tumor evaluations**

Radiological tumor evaluation with contrast-enhanced CT/MRI of chest/abdomen/pelvis will be performed at the following intervals (for further details, see Section 9.4.1).

Full screening (baseline):

- Within 28 days before the start of study treatment.

[…]

## 15.1.2.28 Section 9.2.5.1 Safety follow-up

*Old text:*

[…]

- PROs (LCSS-Meso and MDASI-MPM) (see Section 9.4.4) before the patient meets with a clinician ~~or~~ before any examination or test is performed.

[…]

*New text:*

[…]

- PROs (LCSS-Meso and MDASI-MPM) (see Section 9.4.3) before the patient meets with a clinician and before any examination or test is performed.

[…]

### 15.1.2.29 Section 9.2.5.2 Active follow-up

*Old text:*

Patients who discontinue study treatment due to any other reason than centrally confirmed radiological PD will continue clinic visits during active follow-up for efficacy assessments including tumor response~~, FVC~~ and QoL. These assessments will continue until disease progression, consent withdrawal, lost to follow-up or end of study.

- PROs (LCSS-Meso and MDASI-MPM) (see Section 9.4.4) before the patient meets with a clinician ~~or~~ before any examination or test is performed. During active follow-up period MDASI-MPM and LCSS-Meso are to be taken in parallel with CT/MRI.

[…]

- ~~FVC measurement (see Section 9.4.2), in parallel with CT/MRI.~~
- Toxicity/AE assessment (see Section 9.6.1), in parallel with CT/MRI. During active follow-up period, only AEs and SAEs that are related to study-specific procedures are mandatory to be reported. However, at the investigator's discretion, SAEs may be reported if considered potentially relevant. In such cases, the SAEs will be processed by the sponsor according to all applicable regulations.

[…]

*New text:*

Patients who discontinue study treatment due to any other reason than centrally confirmed radiological PD will continue clinic visits during active follow-up for efficacy assessments including tumor response and QoL. These assessments will continue until disease progression, consent withdrawal, lost to follow-up or end of study.

- PROs (LCSS-Meso and MDASI-MPM) (see Section 9.4.3) before the patient meets with a clinician and before any examination or test is performed. During active follow-up period MDASI-MPM and LCSS-Meso are to be taken in parallel with CT/MRI.

[…]

- Toxicity/AE assessment (see Section 9.6.1), in parallel with CT/MRI. During active follow-up period, only AEs and SAEs that are related to study-specific procedures are mandatory to be reported. However, at the investigator's discretion, SAEs may be reported if considered potentially relevant. In such cases, the SAEs will be processed by the sponsor according to all applicable regulations.

[…]

### 15.1.2.30 Section 9.4.1 Radiological tumor assessments

*Old text:*

The first radiological (contrast-enhanced CT/MRI of chest/abdomen/pelvis) tumor evaluation will be conducted during full screening within 28 days before the start of study treatment (see

flow chart in Section 9.1). Pre-study CT/MRI may be acceptable as a baseline scan if done within 28 days before ~~randomization~~, if centrally evaluable for mRECIST and if performed according to the Imaging Acquisition Guidance provided in the Imaging Manual. Baseline CT/MRI should be obtained prior to randomization. A sole positron emission tomography (PET) scan without a diagnostic CT/MRI is not acceptable for radiological evaluation of target lesions; findings must be confirmed by CT or MRI. Although PET scan findings may be used as supportive evidence of tumor assessment, the CT or MRI results will be the definitive and documented data for the study. All subsequent scans should be done with the identical method and technique (e.g. slice thickness, field of view) to those obtained at baseline. These screening images will be provided to blinded central review to assess radiological eligibility (central confirmation ~~of at least 1 measurable lesion~~ required before randomization). If focal neurological symptoms are present at screening, a CT scan or MRI of the brain is required to rule out brain metastasis by the investigator. All additional suspected sites of disease should be imaged (e.g. cervical lymph nodes, bone etc.).

[…]

*New text:*

The first radiological (contrast-enhanced CT/MRI of chest/abdomen/pelvis) tumor evaluation will be conducted during full screening within 28 days before the start of study treatment (see flow chart in Section 9.1). Pre-study CT/MRI may be acceptable as a baseline scan if done within 28 days before <u>start of study drug</u>, if centrally evaluable for mRECIST and if performed according to the Imaging Acquisition Guidance provided in the Imaging Manual. Baseline CT/MRI should be obtained prior to randomization. A sole positron emission tomography (PET) scan without a diagnostic CT/MRI is not acceptable for radiological evaluation of target lesions; findings must be confirmed by CT or MRI. Although PET scan findings may be used as supportive evidence of tumor assessment, the CT or MRI results will be the definitive and documented data for the study. All subsequent scans should be done with the identical method and technique (e.g. slice thickness, field of view) to those obtained at baseline. These screening images will be provided to blinded central review to assess radiological eligibility (central confirmation <u>of radiological eligibility</u> required before randomization). If focal neurological symptoms are present at screening, a CT scan or MRI of the brain is required to rule out brain metastasis by the investigator. All additional suspected sites of disease should be imaged (e.g. cervical lymph nodes, bone etc.).

[…]

## 15.1.2.31 Section 9.4 Efficacy

*Old text:*

**~~9.4.2 Pulmonary function assessment~~**

~~Forced vital capacity (FVC) as a measure of pulmonary function in chemotherapy pre-treated patients will be evaluated by a spirometry machine at full screening within 28 days before the start of study treatment (see flow chart in Section 9.1). During treatment period as well as active follow-up period FVC will be performed in parallel with tumor scans i.e. with the same~~

~~modality every 6 weeks during the first 6 months after the start of study treatment, every 9 weeks until the end of year 2, and every 12 weeks thereafter until centrally confirmed radiological disease progression or end of study. Visit window of +/- 7 days is allowed.~~

*New text:*

*Section 9.4.2 Pulmonary function assessment removed by amendment 2; numbering of the following sections changed accordingly*

## 15.1.2.32 Section 9.4.2 Survival

*Old text:*

Patients will be contacted for survival every 3 months (±14 days) during long-term follow-up until data maturation for the OS final analysis is reached, death, withdrawal of consent, lost to follow-up or the end of study, whichever occurs first (see flow chart in Section 9.1). In addition, extra survival sweep contacts will be conducted ~~at the time of~~ PFS final analysis and prior to OS final analysis to ensure that long-term follow-up data is current.

*New text:*

Patients will be contacted for survival every 3 months (±14 days) during long-term follow-up until data maturation for the OS final analysis is reached, death, withdrawal of consent, lost to follow-up or the end of study, whichever occurs first (see flow chart in Section 9.1). In addition, extra survival sweep contacts will be conducted <u>prior to</u> PFS final analysis and prior to OS final analysis to ensure that long-term follow-up data is current.

## 15.1.2.33 Section 9.4.3 Patient-reported outcomes

*Old text:*

[…]

The ~~LCSS-Meso and~~ MDASI-MPM questionnaires will be completed at full screening (within 7 days before the start of study treatment), on C2D1 and on Day 1 of every cycle thereafter (i.e. ~~C3D1,~~ C4D1 etc.), at safety follow-up visit and during active follow-up period. During active follow-up period, MDASI-MPM and LCSS-Meso are to be taken in parallel with tumor scans i.e. with the same modality every 6 weeks during the first 6 months after the start of study treatment, every 9 weeks until the end of year 2, and every 12 weeks thereafter until centrally confirmed radiological disease progression or end of study. MDASI-MPM and LCSS-Meso are to be completed before the patient meets with a clinician ~~or~~ before any examination or test is performed on that day. A PRO information sheet will be provided and completed by the study personnel for each questionnaire at each visit at which the LCSS-Meso and the MDASI-MPM are to be administered, regardless of whether or not the LCSS-Meso or the MDASI-MPM are completed by the patient.

[…]

*New text:*

[…]

The MDASI-MPM questionnaires will be completed at full screening (within 7 days before the start of study treatment), on C1D8, C1D15, C2D1, C2D8, C2D15, C3D1, C3D8, C3D15 and on Day 1 of every cycle thereafter (i.e. C4D1, C5D1 etc.), at safety follow-up visit and during active follow-up period. The LCSS-Meso questionnaires will be completed at full screening (within 7 days before the start of study treatment), C2D1 and on Day 1 of every cycle thereafter (i.e. C3D1, C4D1 etc.), at safety follow-up visit and during active follow-up period. During active follow-up period, MDASI-MPM and LCSS-Meso are to be taken in parallel with tumor scans i.e. with the same modality every 6 weeks during the first 6 months after the start of study treatment, every 9 weeks until the end of year 2, and every 12 weeks thereafter until centrally confirmed radiological disease progression or end of study. MDASI-MPM and LCSS-Meso are to be completed before the patient meets with a clinician and before any examination or test is performed on that day. A PRO information sheet will be provided and completed by the study personnel for each questionnaire at each visit at which the LCSS-Meso and the MDASI-MPM are to be administered, regardless of whether or not the LCSS-Meso or the MDASI-MPM are completed by the patient.

[…]

### 15.1.2.34 Section 9.5 Pharmacokinetics / pharmacodynamics

*Old text:*

**Anetumab ravtansine arm**

[…]

Unscheduled PK samples are requested at the next clinic visit after the initial onset of corneal ~~toxicity~~ and after the radiological assessment of the first PR (the first local observation of at least a 30% reduction in the total tumor measurement according to mRECIST). The date and actual clock time of this unscheduled PK sample and of the last dose of anetumab ravtansine has to be recorded on the CRF as an Unscheduled Procedure.

[…]

*New text:*

**Anetumab ravtansine arm**

[…]

Unscheduled PK samples are requested at the next clinic visit after the initial onset of corneal epitheliopathy and after the radiological assessment of the first PR (the first local observation of at least a 30% reduction in the total tumor measurement according to mRECIST). The date and actual clock time of this unscheduled PK sample and of the last dose of anetumab ravtansine has to be recorded on the CRF as an Unscheduled Procedure.

[…]

### 15.1.2.35 Section 9.6.1.2.2 Intensity

*Old text:*

The intensity of an AE should be documented using the NCI-CTCAE v4.03. For events not listed in the NCI-CTCAE, the following scale will be used:

[…]

*New text:*

The intensity of an AE should be documented using the NCI-CTCAE v4.03 or by the Bayer grading system (see Table 7-6 and Table 7-7) for corneal epitheliopathy. For events not listed in the NCI-CTCAE, the following scale will be used:

[…]

### 15.1.2.36 Section 9.6.1.2.4 Action taken with study treatment

*Old text:*

Any action on study treatment to resolve the AE is to be documented using the categories listed below.

- Drug withdrawn
- Drug interrupted
- Dose reduced
- Dose not changed
- Not applicable
- Unknown

*New text:*

Any action on study treatment to resolve the AE is to be documented using the categories listed below.

- Drug withdrawn
- Drug interrupted
- Dose reduced
- Dose not changed
- Dose increased
- Not applicable
- Unknown

### 15.1.2.37 Section 9.6.1.3 Assessments and documentation of adverse events

*Old text:*

AEs observed, mentioned upon open questioning by a member of the investigator team or spontaneously reported by the patient will be documented in the patient's records and on the appropriate CRF. AEs will be documented in an event-based manner, using NCI-CTCAE version 4.03 guidelines. In addition, since the NCI-CTCAE may not adequately capture the severity of new corneal epitheliopathy, an alternative severity grading system for ~~ocular adverse drug reactions~~ will be used (see Table 7-6 and Table 7-7).

[…]

*New text:*

AEs observed, mentioned upon open questioning by a member of the investigator team or spontaneously reported by the patient will be documented in the patient's records and on the appropriate CRF. AEs will be documented in an event-based manner, using NCI-CTCAE version 4.03 guidelines. In addition, since the NCI-CTCAE may not adequately capture the severity of new corneal epitheliopathy, an alternative severity grading system for corneal epitheliopathy will be used (see Table 7-6 and Table 7-7).

[…]

### 15.1.2.38 Section 9.6.1.6 Adverse events of special safety interest

*Old text:*

[…]

Corneal ~~disorders are~~ considered as AE~~s~~ of special interest. Specific dose modification schemes are defined in Section 7.4.2.1. An alternative severity grading system for ~~ocular adverse drug reactions~~ will be used in addition to NCI-CTCAE version 4.03 criteria, since the NCI-CTCAE may not adequately capture the severity of these novel adverse reactions (see Table 7-6 and Table 7-7).

There is no need to report corneal ~~toxicities as SAEs~~ unless ~~they~~ meet the criteria for an SAE as defined in Section 9.6.1.1; however these events will need to be closely monitored and reviewed, and documented timely and accurately both in source data and on the CRF. Details of ophthalmologic examination will be documented on the "ophthalmologic examination" and "slit lamp" CRF pages and in case AEs occur, also on "AE" CRF page, ensuring the reporting terminology used on those pages matches and reflects the source.

*New text:*

[…]

Corneal epitheliopathy is considered as AE of special interest. Specific dose modification schemes are defined in Section 7.4.2.1. An alternative severity grading system for corneal epitheliopathy will be used in addition to NCI-CTCAE version 4.03 criteria, since the NCI-

CTCAE may not adequately capture the severity of these novel adverse reactions (see Table 7-6 and Table 7-7).

There is no need for expedited reporting or use of complementary pages to report corneal epitheliopathy, unless it meets the criteria for an SAE as defined in Section 9.6.1.1; however these events will need to be closely monitored and reviewed, and documented timely and accurately both in source data and on the CRF. Details of ophthalmologic examination will be documented on the "ophthalmologic examination" and "slit lamp" CRF pages and in case AEs occur, also on "AE" CRF page, ensuring the reporting terminology used on those pages matches and reflects the source.

### 15.1.2.39 Section 9.6.3.1 Laboratory evaluations

*Old text:*

[…]

An isolated laboratory abnormality that meets the criteria for a CTCAE Grade 4 classification is not reportable as an SAE, unless the investigator assesses that the event meets standard International ~~Conference on~~ Harmonization (ICH) criteria for an SAE (see SAE definition in Section 9.6.1.1). All laboratory abnormalities, including CTCAE Grade 4 abnormalities, will be documented on the laboratory CRF.

*New text:*

[…]

An isolated laboratory abnormality that meets the criteria for a CTCAE Grade 4 classification is not reportable as an SAE, unless the investigator assesses that the event meets standard International Council for Harmonization (ICH) criteria for an SAE (see SAE definition in Section 9.6.1.1). All laboratory abnormalities, including CTCAE Grade 4 abnormalities, will be documented on the laboratory CRF.

### 15.1.2.40 Section 9.6.3.7 Ophthalmologic examinations

*Old text:*

Corneal ~~toxicity~~ has been identified as a TEAE of special interest for which a causal relationship with anetumab ravtansine has been deemed probable by the investigators in Phase I trial. A detailed ophthalmologic examination (visual acuity [BCVA according to ETDRS, or Snellen, or Landolt C or other charts], IOP, dry eye test [Schirmer test] and slit lamp) will be done for all patients during full screening within 3 weeks before the start of study treatment (see flow chart in Section 9.1). For patients treated in the anetumab ravtansine arm, visual acuity test and slit lamp examination will be repeated before infusion in every cycle except C1D1, and at safety follow-up visit, or more frequently at investigator's and ophthalmologist's discretion (**important to refer to Table 7-6 and Table 7-7**). IOP measurement is to be repeated during anetumab ravtansine therapy if the patient receives steroid eye drops as treatment for ~~eye toxicity~~; dry eye (Schirmer) test may be repeated during treatment at investigator's discretion (e.g. in case of eye dryness during anetumab ravtansine

therapy). During treatment, ophthalmologic examination can be done up to 7 days before anetumab ravtansine infusion.

*New text:*

Corneal epitheliopathy has been identified as a TEAE of special interest for which a causal relationship with anetumab ravtansine has been deemed probable by the investigators in Phase I trial. A detailed ophthalmologic examination (visual acuity [BCVA according to ETDRS, or Snellen, or Landolt C or other charts], IOP, dry eye test [Schirmer test] and slit lamp) will be done for all patients during full screening within 3 weeks before the start of study treatment (see flow chart in Section 9.1). For patients treated in the anetumab ravtansine arm, visual acuity test and slit lamp examination will be repeated before infusion in every cycle except C1D1, and at safety follow-up visit, or more frequently at investigator's and ophthalmologist/optometrist's discretion (**important to refer to Table 7-6 and Table 7-7**). IOP measurement is to be repeated during anetumab ravtansine therapy if the patient receives steroid eye drops as treatment for corneal epitheliopathy; dry eye (Schirmer) test may be repeated during treatment at investigator's discretion (e.g. in case of eye dryness during anetumab ravtansine therapy). During treatment, ophthalmologic examination can be done up to 7 days before anetumab ravtansine infusion.

In certain countries, an optometrist or equivalent specialist may be licensed to perform the eye examinations as detailed above; as per ICH-GCP, at the Principal Investigator's discretion, a chosen specialist can perform required eye exams.

## 15.1.2.41 Section 9.7.1 Biomarkers

*Old text:*

Preclinical and Phase I evidence suggests that mesothelin expression (or expression level above a certain threshold) in human tumors may be required for binding, internalization, and anti-tumor activity of anetumab ravtansine. All patients will have formalin-fixed, paraffin-embedded (FFPE) tumor samples available for IHC determination of mesothelin expression at prescreening as a potential predictive biomarker (see also flow chart in Section 9.1). In the absence of archival tissue, fresh biopsies may be used if deemed safe by the investigator and there is no additional risk for the patient in the investigator's judgement. Only patients whose tumors express mesothelin at staining intensity of moderate ~~(2+)~~ and strong ~~(3+)~~ in at least 30% of tumor cells will participate further in this study. Mesothelin levels will be determined using a validated IHC assay (clone SP74).

[…]

*New text:*

Preclinical and Phase I evidence suggests that mesothelin expression (or expression level above a certain threshold) in human tumors may be required for binding, internalization, and anti-tumor activity of anetumab ravtansine. All patients will have formalin-fixed, paraffin-embedded (FFPE) tumor samples available for IHC determination of mesothelin expression at prescreening as a potential predictive biomarker (see also flow chart in Section 9.1). In the

absence of archival tissue, fresh biopsies may be used if deemed safe by the investigator and there is no additional risk for the patient in the investigator's judgement. Only patients whose tumors express mesothelin at staining intensity of moderate and stronger in at least 30% of tumor cells will participate further in this study. Mesothelin levels will be determined using a validated IHC assay (clone SP74).

[…]

### 15.1.2.42 Section 9.8 Appropriateness of procedures / measurements

*Old text:*

[…]

**Appropriateness of mRECIST criteria**. RECIST 1.1 criteria, designed to assess spherically shaped solid tumors, may be an unreliable method in the context of the lens/crescent-shaped pleural lesions found in MPM (29). mRECIST criteria were designed and validated to measure the specific context of MPM (21, 30). Accordingly, mRECIST criteria are appropriate for the study context.

~~**Appropriateness of FVC**. The degree of improvement of pulmonary function assessed by FVC has been chosen as surrogate measure of patient benefit and parameter to demonstrate validity of mRECIST. Pulmonary function tests (PFT) correlate with tumor response: in the cisplatin-pemetrexed Phase III trial, patients who had a tumor response had consistently better PFT than patients with SD, and patients with SD had better PFTs than patients with PD (12).The FVC test has already been used and validated in the Phase III VANTAGE trial (31) and previously by Nowak et al. (32), as mentioned by Byrne in the mRECIST criteria (21).~~

[…]

*New text:*

**Appropriateness of mRECIST criteria**. RECIST 1.1 criteria, designed to assess spherically shaped solid tumors, may be an unreliable method in the context of the lens/crescent-shaped pleural lesions found in MPM (29). mRECIST criteria were designed and validated to measure the specific context of MPM (21, 30). Accordingly, mRECIST criteria are appropriate for the study context.

[…]

### 15.1.2.43 Section 10.2 Analysis sets

*Old text:*

[…]

**Enrolled set (ENR).** All patients who signed the informed consent for any portion of the study. Enrolled patients will be used for patient disposition.

[…]

*New text:*

[…]

**Enrolled set (ENR).** All patients who signed the informed consent for any portion of the study including prescreening. Enrolled patients will be used for patient disposition.

[…]

## 15.1.2.44 Section 10.3.2 Primary efficacy variable

*Old text:*

[…]

Assuming true median PFS of 3.6 months under vinorelbine treatment and constant hazards, the study primary hypothesis test is designed to detect a 100% prolongation of true PFS (median 7.2 months) in the anetumab ravtansine arm in comparison to the comparator arm with 90% power with a 1-sided significance level of 0.0125 ~~(hazard ratio 0.5)~~.

[…]

*New text:*

[…]

Assuming true median PFS of 3.6 months under vinorelbine treatment and constant hazards, the study primary hypothesis test is designed to detect a 100% prolongation of true PFS (median 7.2 months) in the anetumab ravtansine arm in comparison to the comparator arm (hazard ratio 0.5) with 90% power with a 1-sided significance level of 0.0125.

[…]

## 15.1.2.45 Section 10.3.3.1 Secondary efficacy variables

*Old text:*

**Overall survival (OS)**, defined as time from randomization until death from any cause. Patients lost to follow-up or alive at the time of analysis will be censored at the last known alive date.

~~**Forced vital capacity (FVC) response rate**: An improvement of ≥ 30% FVC is defined as PR, an improvement of < 30% to a deterioration of < 20% is defined as no change (NC), and a deterioration of ≥ 20% is defined as PD (30). A patient is a responder if the patient has a best spirometrically-evaluated FVC improvement on-study of PR, as determined by the investigator. No confirmation of FVC response is required. The FVC response rate in each arm is the number of responders divided by the number of randomized patients.~~

**Objective response rate (ORR)**: A patient is a responder if the patient has a confirmed tumor response on-study of CR or PR, as determined by the central radiological reviewer per

mRECIST criteria. The ORR in each arm is the number of responders divided by the number of randomized patients.

[…]

**Secondary efficacy analysis**

[…]

Assuming true median OS of 9.6 months under vinorelbine treatment and constant hazards, the 2-stage group sequential hypothesis test is designed to detect a 60% prolongation of true OS (median 15.4 months) in the anetumab ravtansine arm in comparison to the comparator arm with an overall ~~73~~% power and an overall 1-sided significance level of 0.025 (hazard ratio 0.625).

The interim OS analysis will be performed at the time of the final primary endpoint (PFS) analysis, when an estimated ~~85~~ OS events will be observed. If the study is not stopped for superiority at the interim analysis, the final OS analysis will occur when approximately ~~135~~ OS events have been observed. A Lan-Demets alpha spending function (~~38~~) with O'Brien-Fleming boundaries (~~39~~) will be used, based on actual events at the time of the interim analysis. Approximately ~~0.005~~ alpha is estimated to be spent at the interim analysis and ~~0.020~~ at the final if ~~85~~ OS events are observed at the interim analysis. The actual alpha levels will be based on the actual number of events included in the interim analysis. The group sequential testing procedure is further described in Section 10.4, and additional details will be described in the SAP.

[…]

Response rate variables (~~FVC response rate,~~ ORR, DCR) will be summarized by treatment arm including number of patients (N), response rates, and Clopper-Pearson (~~40~~) exact binomial confidence intervals. In addition, each response category will be summarized. ~~FVC response rate will be tested for association with treatment using a 1-sided Fisher's Exact Test (41, 42) with significance level of 0.025.~~ Further details will be described in the SAP.

[…]

*New text:*

Additional details, including additional censoring rules for time-to-event variables, will be described in the SAP.

**Overall survival (OS)**, defined as time from randomization until death from any cause. Patients lost to follow-up or alive at the time of analysis will be censored at the last known alive date.

**Objective response rate (ORR)**: A patient is a responder if the patient has a confirmed tumor response on-study of CR or PR, as determined by the central radiological reviewer per mRECIST criteria. The ORR in each arm is the number of responders divided by the number of randomized patients.

[…]

**Secondary efficacy analysis**

[…]

Assuming true median OS of 9.6 months under vinorelbine treatment and constant hazards, the 2-stage group sequential hypothesis test is designed to detect a 60% prolongation of true OS (median 15.4 months) in the anetumab ravtansine arm in comparison to the comparator arm with an overall 80% power and an overall 1-sided significance level of 0.025 (hazard ratio 0.625).

The interim OS analysis will be performed at the time of the final primary endpoint (PFS) analysis, when an estimated 80 OS events will be observed. If the study is not stopped for superiority at the interim analysis, the final OS analysis will occur when approximately 159 OS events have been observed. A Lan-Demets alpha spending function (36) with O'Brien-Fleming boundaries (37) will be used, based on actual events at the time of the interim analysis. Approximately 0.00158 alpha is estimated to be spent at the interim analysis and 0.02342 at the final if 80 OS events are observed at the interim analysis. The actual alpha levels will be based on the actual number of events included in the interim analysis. The group sequential testing procedure is further described in Section 10.4, and additional details will be described in the SAP.

[…]

Response rate variables (ORR, DCR) will be summarized by treatment arm including number of patients (N), response rates, and Clopper-Pearson (38) exact binomial confidence intervals. In addition, each response category will be summarized. Further details will be described in the SAP.

[…]

## 15.1.2.46 Section 10.3.3.3 Safety variables

*Old text:*

Safety variables will include AEs, laboratory changes (hematology, clinical chemistry and clinical urinalysis), abnormal findings in physical examination, changes in ECOG PS, changes in vital signs (weight, blood pressure, heart rate, respiratory rate, and body temperature), ~~changes in FVC,~~ changes in ECG, changes in cardiac function test (EchoCG or MUGA scan) and changes in ophthalmologic examinations (visual acuity and slit lamp examination, IOP and Schirmer test if repeated). […]

*New text:*

Safety variables will include AEs, laboratory changes (hematology, clinical chemistry and clinical urinalysis), abnormal findings in physical examination, changes in ECOG PS, changes in vital signs (weight, blood pressure, heart rate, respiratory rate, and body temperature), changes in ECG, changes in cardiac function test (EchoCG or MUGA scan) and changes in ophthalmologic examinations (visual acuity and slit lamp examination, IOP and Schirmer test if repeated). […]

### 15.1.2.47 Section 10.4 Determination of sample size

*Old text:*

The sample size is primarily designed to support hypothesis test of the primary endpoint PFS. ~~Statistical power for the analysis of the secondary endpoint of OS is also evaluated~~.

[…]

*New text:*

The sample size is primarily designed to support hypothesis test of the primary endpoint PFS, and to provide a limited formal evaluation of secondary endpoint OS.

[…]

### 15.1.2.48 Section 10.4.1 Primary endpoint progression-free survival

*Old text:*

[…]

Assuming median PFS of 3.6 months under vinorelbine treatment and constant hazards and a 2:1 treatment:comparator randomization, a 100% prolongation of PFS in the anetumab ravtansine arm in comparison to the comparator arm can be detected at a 1-sided significance level of 0.0125 with 90% power, with a single-stage trial with approximately 117 PFS events (hazard ratio 0.5). Assuming a maximum accrual rate of ~~10.5~~ patients/month (~~17.5~~ patients/ month screened with 40% overall screening failure rate) with ~~8~~-month linear accrual ramp-up, and a ~~2.7~~%/month dropout (loss to follow-up and unevaluable for tumor assessment) rate, ~~183~~ patients be will accrued in approximately ~~20.4~~ months and reach endpoint maturation of 117 events in approximately ~~23.9~~ months. The total number of unevaluable/dropout patients over the duration of the study through final PFS analysis is estimated at ~~27~~ (~~14.8~~%).

*New text:*

[…]

Assuming median PFS of 3.6 months under vinorelbine treatment and constant hazards and a 2:1 treatment:comparator randomization, a 100% prolongation of PFS in the anetumab ravtansine arm in comparison to the comparator arm can be detected at a 1-sided significance level of 0.0125 with 90% power, with a single-stage trial with approximately 117 PFS events

(hazard ratio 0.5). Assuming a maximum accrual rate of 12.5 patients/month (20.83 patients/ month screened with 40% overall screening failure rate) with 6-month linear accrual ramp-up, and a 3.4%/month dropout (loss to follow-up and unevaluable for tumor assessment) rate, 210 patients be will accrued in approximately 19.8 months and reach endpoint maturation of 117 events in approximately 22.0 months. The total number of unevaluable/dropout patients over the duration of the study through final PFS analysis is estimated at 33 (15.7%).

### 15.1.2.49 Section 10.4.2 Secondary endpoint overall survival

*Old text:*

The sample size is also ~~evaluated for~~ test~~ing~~ the following hypotheses in secondary endpoint OS:

[…]

Assuming true median OS of 9.6 months under vinorelbine treatment and constant hazards, a 60% prolongation of true OS (median 15.4 months) in the anetumab ravtansine arm in comparison to the comparator arm (median 9.6 months) can be detected with an overall ~~73~~% power and an overall 1-sided significance level of 0.025 (hazard ratio 0.625), with a 2-stage group sequential test with a total of ~~135~~ events.

The OS analysis assumes the same accrual as for primary endpoint PFS, with ~~183~~ patients accrued in approximately ~~20.4~~ months. A 0.~~5~~% per month loss to OS follow-up rate is assumed. An interim OS analysis will be performed at the time of the final primary endpoint (PFS) analysis at an estimated ~~23.9~~ months from first patient randomized, when an estimated 8~~5~~ OS events will have been observed. If the study is not stopped for superiority at the OS interim analysis, the final OS analysis will occur after approximately ~~135~~ OS events have been observed, at approximately ~~41.4~~ months from first patient randomized. A Lan-Demets alpha spending function (~~38~~) with O'Brien-Fleming boundaries (~~39~~) will be used, based on actual events at the time of the interim analysis. Under the null hypothesis of no anetumab ravtansine OS superiority, approximately 0.00~~5~~ alpha is estimated to be spent at the interim analysis and 0.02~~0~~ at the final (0.025 alpha overall). Under the alternative hypothesis of 60% OS improvement under anetumab ravtansine treatment, the chance of finding superiority is estimated at ~~29.4~~% at the interim analysis and ~~43.6~~% at the final analysis (~~73~~% power overall). The total number of patients lost to OS follow-up over the duration of the study through final OS analysis is estimated at ~~13~~ (~~7.1~~%)

*New text:*

The sample size is also designed to test the following hypotheses in secondary endpoint OS:

[…]

Assuming true median OS of 9.6 months under vinorelbine treatment and constant hazards, a 60% prolongation of true OS (median 15.4 months) in the anetumab ravtansine arm in comparison to the comparator arm (median 9.6 months) can be detected with an overall 80% power and an overall 1-sided significance level of 0.025 (hazard ratio 0.625), with a 2-stage group sequential test with a total of 159 events.

The OS analysis assumes the same accrual as for primary endpoint PFS, with 210 patients accrued in approximately 19.8 months. A 0.3% per month loss to OS follow-up rate is assumed. An interim OS analysis will be performed at the time of the final primary endpoint (PFS) analysis at an estimated 22 months from first patient randomized, when an estimated 80 OS events will have been observed. If the study is not stopped for superiority at the OS interim analysis, the final OS analysis will occur after approximately 159 OS events have been observed, at approximately 41.3 months from first patient randomized. A Lan-Demets alpha spending function (36) with O'Brien-Fleming boundaries (37) will be used, based on actual events at the time of the interim analysis. Under the null hypothesis of no anetumab ravtansine OS superiority, approximately 0.00158 alpha is estimated to be spent at the interim analysis and 0.02342 at the final (0.025 alpha overall). Under the alternative hypothesis of 60% OS improvement under anetumab ravtansine treatment, the chance of finding superiority is estimated at 16.9% at the interim analysis and 63.2% at the final analysis (80% power overall). The total number of patients lost to OS follow-up over the duration of the study through final OS analysis is estimated at 10 (4.8%).

### 15.1.2.50 Section 10.5 Planned interim analyses

*Old text:*

An interim analysis for OS will be performed at the same time as the final primary endpoint analysis, as described in Section 10.4.

[…]

*New text:*

An interim analysis for OS will be performed, by the sponsor, at the same time as the final primary endpoint analysis, as described in Section 10.4.

[…]

### 15.1.2.51 Section 11.4 Missing data

*Old text:*

[…]

Strategies to reduce the dropout rate for secondary endpoints include:

- For OS, every effort will be made to continue contacting study patients in long-term follow-up and to determine death status and dates. A survival sweep contact will be conducted at the time of PFS final analysis and prior to OS final analysis to ensure that long-term follow-up data is current. ~~Analysis methods as described for PFS help mitigate the impact of missing data.~~

[…]

Strategies to reduce impact of missing data when present include:

- Time-to-event analysis approaches maximize available data and reduce impact of censoring, with unbiased results when censoring is uninformative.
- Study is powered assuming a ~1~~5~~% total dropout rate (3% per month) for PFS and a 0.~~5~~% per month dropout rate for OS, ensuring a moderate dropout ~~rate~~ will not degrade reliability of study results.
- Analyses will ensure conservative treatment of missing values. For tumor ~~and FVC~~ response endpoints, missing assessments will count as non-responders. For non-time-to-event QoL endpoints, time point analysis will include patients present both at baseline and at the time point, mitigating survivorship bias.

*New text:*

[…]

Strategies to reduce the dropout rate for secondary endpoints include:

- For OS, every effort will be made to continue contacting study patients in long-term follow-up and to determine death status and dates. A survival sweep contact will be conducted at the time of PFS final analysis and prior to OS final analysis to ensure that long-term follow-up data is current.

[…]

Strategies to reduce impact of missing data when present include:

- Time-to-event analysis approaches maximize available data and reduce impact of censoring, with unbiased results when censoring is uninformative.
- Study is powered assuming a ~1<u>6</u>% total dropout rate (3<u>.4</u>% per month) for PFS and a <u>~5% total</u> (0.<u>3</u>% per month<u>)</u> dropout rate for OS, ensuring a moderate dropout will not degrade reliability of study results.
- Analyses will ensure conservative treatment of missing values. For tumor response endpoints, missing assessments will count as non-responders. For non-time-to-event QoL endpoints, time point analysis will include patients present both at baseline and at the time point, mitigating survivorship bias.

### 15.1.2.52 Section 14 Reference list

*Old text:*

~~31. Krug LM, Arduino JM, Sun X, Kindler HL, Manegold C, Fennell D, et al. Forced vital capacity (FVC) as a reproducible measure of pulmonary function (PF) in chemotherapy-pretreated patients with malignant pleural mesothelioma (MPM). J Clin Oncol. 2011;29(suppl; abstr 7028).~~

~~32. Nowak AK, Byrne MJ, Williamson R, Ryan G, Segal A, Fielding D, et al. A multicentre phase II study of cisplatin and gemcitabine for malignant mesothelioma. Br J Cancer. 2002;87(5):491-6.~~
~~41. Fisher RA. Statistical Methods for Research Workers. Edinburgh: Oliver and Boyd. 1954.~~
~~42. Agresti A. Categorical Data Analysis. Third Edition. New Jersey: John Wiley & Sons. 2013.~~

*New text:*

*Reference list was updated by amendment 2. The numbering of the references was changed accordingly.*

### 15.1.2.53 Section 16.3 Response assessment

*Old text:*

Tumor response will be evaluated in this study using the mRECIST criteria for MPM (21).

At baseline, the pleural disease to be measured should have a short-axis diameter of at least 1 cm for ~~each~~ of the 6 measurements, as lesions < 1 cm are considered non-measurable.

Uni-dimensional measurements of tumor thickness perpendicular to the chest wall or mediastinum should be performed, measured in 2 sites (or positions) at 3 separate levels on transverse cuts of contrast-enhanced CT scan (or MRI). The sum of the ~~6~~ measurements defines a pleural unidimensional measure: sum of 6 pleural thickness measurements = 1 univariate diameter.

[…]

Nodal, subcutaneous and other bidimensionally measurable lesions (e.g. lung) are measured unidimensionally as per the RECIST 1.1 criteria. Unidimensional measurements are added to obtain the total tumor measurement.

*New text:*

Tumor response will be evaluated in this study using the mRECIST criteria for MPM (21).

At baseline, the pleural disease to be measured should have a short-axis diameter of at least 1 cm for <u>at minimum one</u> of the 6 measurements, as lesions < 1 cm are considered non-measurable.

Unidimensional measurements of tumor thickness perpendicular to the chest wall or mediastinum should be performed, measured in 2 sites (or positions) at 3 separate levels on transverse cuts of contrast-enhanced CT scan (or MRI). The sum of the measurements <u>which meet the definition of measurable disease</u> defines a pleural unidimensional measure: sum of <u>up to</u> 6 pleural thickness measurements = 1 univariate diameter.

[…]

Nodal, subcutaneous and other bidimensionally measurable non-pleural lesions (e.g. lung) are measured unidimensionally as per the RECIST 1.1 criteria. Unidimensional measurements are added to obtain the total tumor measurement.

## 15.2 Amendment 4

Amendment 4 is a global amendment dated 11 AUG 2016.

### 15.2.1 Overview of changes to the study

#### 15.2.1.1 Modification 1: Addition of durable response rate (DRR) as a secondary variable

Durable response rate was added as a secondary variable as it could be a key in the context of the regulatory environment surrounding this trial.

Sections affected by this modification: Section 2 Synopsis, Section 10.3.3.1 Secondary efficacy variables

#### 15.2.1.2 Modification 2: Change in the number of patients planned to be prescreened

The screen failure rate was increased from 40% to 50% based on current data. Subsequently, the number of patients planned to be prescreened was increased from 350 to 420 and the number of patients to be prescreened / month from 20.83 to 25.

Sections affected by this modification: Section 2 Synopsis, Section 5.1 Design overview, Section 10.4.1 Primary endpoint progression-free survival

#### 15.2.1.3 Modification 3: Change in inclusion/exclusion criteria: Amendment of time window for prior participation in another clinical study

The option for 5 drug half lives was removed from the time window for prior treatment with platinum in combination with pemetrexed before start of study treatment (full study inclusion criterion 3). This was done due to the short half life of pemetrexed (3.5 hours) as one of the first line therapies to allow for any toxicities to resolve before the start of study treatment.

Sections affected by this modification: Section 6.1.2 Eligibility criteria for full study, Section 8.1 Prior and concomitant therapy

#### 15.2.1.4 Modification 4: Change in exclusion criteria: Exclusion of prior experimental device therapy

Patients having received prior device therapy were excluded in order to have a homogenous first line population (exclusion criterion 4). There is no internal or literature data available explaining how signaling pathways are modified after treatment with devices, and particularly whether patients may respond differentially after treatment with these devices in combination with standard of care compared to standard of care alone.

Sections affected by this modification: Section 6.2 Exclusion criteria

#### 15.2.1.5 Modification 5: Change in exclusion criteria: Exclusion of patients with CNS metastasis

Patients with CNS metastasis were excluded from the study population for this trial since the incidence of brain metastases is very low in pleural mesothelioma population (42, 43) and

prognosis for patients with existing brain or other CNS metastases is generally poor (exclusion criterion 16).

Sections affected by this modification: Section 6.2 Exclusion criteria, Section 9.1 Tabular schedule of evaluations, Section 9.2.2 Full screening period, Section 9.4.1 Radiological tumor assessments

#### 15.2.1.6 Modification 6: Clarification on re-screening criteria

Clarification was added around the circumstances where re-screening would be permitted to align with other studies in the program.

Sections affected by this modification: Section 6.3.1.1.3 Re-screening

#### 15.2.1.7 Modification 7: Removal of details around reconstitution and dilution of anetumab ravtansine

Information about reconstitution and dilution of the anetumab ravtansine solution and the associated stability information was removed from the protocol and included in a standalone document. This update was made to provide the investigational sites with the most current guidance in the most effective and efficient way.

Sections affected by this modification: Section 7.2.1 Test drug – anetumab ravtansine

#### 15.2.1.8 Modification 8: Changes to dose modifications of anetumab ravtansine

- Previous Tables 7-3 (Dose adjustments in response to neutrophil and platelet nadir counts of the previous cycle) and 7-4 (Dose adjustments in response to pre-infusion values) were combined into one table (Table 7-3) for clarity and ease of use and to align with other studies in the program. The numbering of the subsequent tables in the Section 7 was changed accordingly.
- In Table 7-3, criteria for dose modification based on platelet nadir count of the previous cycle were modified to be in line with other studies in the program (for ≥ 7 days added for platelets < 25,000 $mm^3$ and < 50,000/$mm^3$ with clinically significant bleeding instead of ≥ 25,000/$mm^3$).
- Requirement of dose reduction for ANC < 1,000/$mm^3$ and/or platelets < 75,000/$mm^3$ was replaced with requirement to adjust dose by nadir counts in previous cycle.
- The following were removed from the section non-hematological toxicities requiring dose modification for clarity and to remove duplication in line with other studies in the program:
    - AST and/or ALT increase > 5.0 x ULN (CTCAE Grade ≥ 3) – this is duplication of information in Table 7-4.
    - Total bilirubin > 3.0 x ULN (CTCAE Grade ≥ 3) – this is duplication of information in Table 7-4.
    - Hair loss CTCAE Grade ≥ 3 as alopecia grade 3 does not exist.

- In Table 7-4 an inconsistency between a footnote and the table was corrected i.e. treatment should be interrupted/delayed unless TEAE resolves to Grade ≤ 2. This was corrected also in Figure 6-1.
- Paracetamol was added as an example of anti-allergic prophylaxis for infusion-related reaction or other hypersensitivity event. This is in line with guidance used in other studies in the program.

Sections affected by this modification: Section 6.3.1.2 Withdrawal criteria, Section 7.4.2.1.1 Hematological toxicities, Section 7.4.2.1.2 Non-hematological toxicities, Section 7.4.2.1.3 Miscellaneous toxicities

#### 15.2.1.9 Modification 9: Addition of Oxford Schema

Oxford Schema and the respective reference were added as an appendix for completeness. A cross-reference to the appendix was added in Table 7-5. Oxford Schema is used for the grading of superficial punctate keratitis if observed during the slit lamp examination.

Sections affected by this modification: Section 7.4.2.1.3 Miscellaneous toxicities, Section 16.9 Grading staining: Oxford Schema (new addition)

#### 15.2.1.10 Modification 10: Corrections to prior and concomitant therapies

- Acute steroids were removed from prohibited prior and concomitant therapies (Table 8-1) since the use of these medications for conditions such as pain control, dyspnea and nausea was more widely spread than anticipated after a determination was made that there were no pharmacokinetic, safety or medical concerns. The use of chronic steroids was added to the permitted concomitant therapies (Table 8-2).
- Concomitant live attenuated virus vaccines (e.g. yellow fever) were added as prohibited for patients in both arms rather than just in the vinorelbine arm within 2 weeks before the start of study treatment as the treatment assignment is only performed at randomization. After C1D1, these therapies are only prohibited for patients in the vinorelbine arm.

Sections affected by these modifications: Section 8.1 Prior and concomitant therapy

#### 15.2.1.11 Modification 11: Addition of collection of optional archival tumor tissue for exploratory analysis

Optional collection of archival tumor tissue for patients who consent post randomization was added in order to perform the analysis of changes in the genomic and expression profile (e.g. mesothelin expression) in tumor tissue over time on drug treatment. This may elucidate the underlying molecular mechanism of drug response and intrinsic and acquired resistance to anetumab ravtansine.

Sections affected by this modification: Section 2 Synopsis, Section 5.1 Design overview, Section 9.1 Tabular schedule of evaluations, Section 9.2.3.1 Treatment – Cycle 1, Section 9.7.1 Biomarkers

#### 15.2.1.12 Modification 12: Clarification regarding central review for determination of progressive disease

Language to state that only patients who have not undergone central review for PD confirmation will undergo retrospective central blinded review was added for clarity.

Sections affected by this modification: Section 9.4.1 Radiological tumor assessments

#### 15.2.1.13 Modification 13: Clarification to PK validity criteria

Language was added in the description of the analysis set “PK set” for clarity.

Sections affected by this modification: Section 10.2 Analysis sets

#### 15.2.1.14 Modification 14: Timing of analysis of DRR, DOR and updated PFS

Because the PFS analysis is expected to mature shortly after accrual ends, it may not be sufficiently mature to assess duration of response or the newly added durable response rate endpoint. Accordingly, final analysis of this newly added endpoint is deferred until the final OS analysis to permit greater data maturity.

Following patients for tumor assessments through OS analysis to obtain duration of response makes an updated analysis of PFS and of DOR at time of OS analysis appropriate.

Sections affected by this modification: Section 10.3.2 Primary efficacy variable, Section 10.3.3.1 Secondary efficacy variables

#### 15.2.1.15 Modification 15: Addition of mention of sensitivity analyses and citations

Addition of mention of sensitivity analyses and site to 2012 EU and 2015 FDA guidances for primary variable PFS. This change is to ensure that the study design is up to date with the FDA and EU guidance for conducting the primary variable PFS analysis.

Sections affected by this modification: Section 10.3.2 Primary efficacy variable

#### 15.2.1.16 Modification 16: Addition of further details to the analysis of the patient-reported outcomes

In response to FDA feedback and scientific advice from MD Anderson Cancer Center, the MDASI-MPM developer, the definitions of the PRO endpoints were modified and further details surrounding the analysis of the PROs were added. Based on feedback from MD Anderson Cancer Center, radiological progression was decoupled from PRO endpoint definitions. To enable this Phase II study to be used both to help validate the MDASI-MPM and perform hypothesis testing on MDASI-MPM-based endpoints, an independent blinded PRO review committee is being established to perform validation-related analyses and determine key endpoint details based on blinded analyses of pooled data, including the degree of change from baseline constituting clinically meaningful improvement and worsening in symptoms and pain.

Sections affected by this modification: Section 5.3 Justification of the design, Section 7.5 Blinding, Section 10.3.3.1 Secondary efficacy variables

#### 15.2.1.17 Modification 17: Clarification of patient-reported outcomes instrument use

Clarification was added referring to the LCSS-Meso as a disease-related QoL or HRQoL assessment instrument, and referring to the MDASI-MPM as a disease-related symptom assessment instrument.

Sections affected by this modification: Section 2 Synopsis, Section 5.1 Design overview, Section 9.2.5.2 Active follow-up, Section 9.4.3 Patient-reported outcomes, Section 10.2 Analysis sets, Section 11.4 Missing data

#### 15.2.1.18 Modification 18: Addition of hypothesis tests and hierarchy for selected secondary variables

Hypothesis tests and hierarchy for selected secondary variables including addressing the timing were added. Regulatory guidance and feedback requires formal hypothesis tests and establishing a gatekeeping strategy for secondary variables to ensure control of overall study Type I error. A hierarchy was specified. Language was added to clarify analysis timing. Although additional secondary variables will be analyzed at primary endpoint analysis, the Type I error control strategy requires that secondary variables ranking below OS in the hierarchy to wait until the OS analysis completes to determine superiority.

Sections affected by this modification: Section 2 Synopsis, Section 10.3.3.1 Secondary efficacy variables

#### 15.2.1.19 Other modifications and corrections

In addition to the modifications specified above, there have been minor corrections for better clarity and consistency.

- Due to sponsor name change, sponsor information and sponsor logo were changed. In addition, Bayer HealthCare Pharmaceuticals Inc. was added as a sponosr for US territory since it is and has at any time been the sponsor for the US territory for this trial as set forth in FDA IND form 1571. Sections affected by this modification: Section 1 Title page
- Study acronym (ARCS-$M_{2L}$) was added. Sections affected by this modification: Section 1 Title page
- Study medical expert was changed. Sections affected by this modification: Section 1 Title page, Section 13.1 Investigator(s) and other study personnel
- A sentence about Data Monitoring Committee was added in the protocol synopsis for consistency with the rest of the document. Sections affected by this modification: Section 2 Synopsis
- List of abbreviations was updated. Sections affected by this modification: List of abbreviations
- Limitation of data was clarified based on a Phase I expansion cohort. Sections affected by this modification: Section 3.2 Rationale of the study

- A clarification was added to the exclusion criterion 4 to make it clear that only patients with more than 1 line of previous systemic anti-cancer therapy for MPM are excluded. Sections affected by this modification: Section 6.2 Exclusion criteria
- Dose omission, infusion interruption and change in infusion rate were added as options for anetumab ravtansine dose modifications for consistency with the rest of the section. In addition, wording "temporary treatment interruption" was changed to "dose delay". Sections affected by this modification: Section 7.4.2.1 Dose modifications of anetumab ravtansine
- A column for ophthalmologic examination within 21 days before the start of study treatment was added to the Study flow chart for ease of use and clarity. In addition, a separate section was created for the respective bullet point in the Visit description section. Sections affected by this modification: Section 9.1 Tabular schedule of evaluations, Section 9.2.2 Full screening period
- Vitals signs was removed from the -28 day prior to screening time window as this was a duplication and should only be in the – 7 day prior to screening time window. Sections affected by this modification: Section 9.1 Tabular schedule of evaluations, Section 9.2.2 Full screening period
- Time window for lipase testing at Cycle 2 Day 1 and higher Day 1 visits was increased as due to logistical issues in different countries with national or referral laboratory turnaround times, it is not always possible to obtain lipase analysis results prior to dosing within the 1 day window for Cycle 2 and higher Day 1. A safety risk assessment was performed and it was determined that there will be no additional risk to the patient by referring to lipase analysis results which are up to 8 days old before dosing. Therefore the time window for lipase testing on Cycle 2 and higher Day 1 was extended to 8 days before administration of the study treatment. Sections affected by this modification: Section 9.1 Tabular schedule of evaluations, Section 9.2.3.2 Treatment – Cycle 2 and higher
- Time window for cardiac function testing during treatment was increased to 7 days due to logistical issues in different countries where due to availability of the appointments for these tests, it is not always possible to obtain the results prior to dosing within the 1 day window for on treatment visits. A safety risk assessment was performed and it was determined that there will be no additional risk to the patient by referring to cardiac function results which are up to 7 days old before administration of the study treatment. Sections affected by this modification are: Section 9.1 Tabular schedule of evaluations, Section 9.2.3.2 Treatment – Cycle 2 and higher, Section 9.6.3.6 Cardiac function
- A time window of +/- 5 min was added for 12-lead ECG on C1D1 at 30 min post-dose to allow flexibility at the site level. Sections affected by this modification: Section 9.2.3.1 Treatment – Cycle 1

- Language was added to specify in which situation pregnancies should be reported as SAEs (i.e. only those with abnormal outcome). Sections affected by this modification: Section 9.6.2 Pregnancies
- Red blood cell count was added to the list of laboratory assessments as this had been mistakenly omitted. Sections affected by this modification: Section 9.6.3.1 Laboratory evaluations
- Specification of calcium type collected was added to the list of laboratory assessment as CTCAE 4.03 requires specification of calcium type to grade hypercalcemia and hypocalcemia severity. Sections affected by this modification: Section 9.6.3.1 Laboratory evaluations
- Definition of disease control rate was clarified to define patients with disease control. Sections affected by this modification: Section 10.3.3.1 Secondary efficacy variables
- Infusion-related reactions (IRRs) were added to the list of safety variables to clarify separate reporting of infusion-related reactions and associated symptoms. Sections affected by this modification: Section 10.3.3.3 Safety variables
- It was added that biomarker analyses may be specified in a separate document. Sections affected by this modification: Section 10.3.4.2 Biomarker variables
- "Disease characteristics" was added to the data required from prescreening and full screening failures for consistency with Section 9.1 Tabular schedule of evaluations. Sections affected by this modification: Section 11.1 Data recording
- Reference list was updated. Sections affected by this modification: Section 14 Reference list

### 15.2.2 Changes to the protocol text

In the sections on changes to the protocol text, all protocol sections affected by the respective amendment are detailed; the sequence of the sections follows the structure of the most recent previous protocol version. As applicable, changes to the protocol text are highlighted as follows:

- Addition of a whole new portion: Brief identification of the new portion
- Removal of a whole portion: Complete display of the removed portion, formatted as ~~crossed out~~
- Editing of an existing portion: Comparative presentation of "*old text*" versus "*new text*", with "*old text*" referring to the most recent previous protocol version. Deletions are ~~crossed out~~ in the "*old text*". Additions are <u>underlined</u> in the "*new text*".
- Tables / figures: The term "*amended*" is added to the caption.
- Terminological changes: Brief specification of the terminological change

Correction of typos or omissions are not highlighted.

### 15.2.2.1 Section 1 Title page

*Old text:*

[…]

Phase II anetumab ravtansine as 2nd line treatment for malignant pleural mesothelioma (MPM)

Test drug: BAY 94-9343 / anetumab ravtansine

[…]

Sponsor: **Bayer ~~HealthCare~~ AG, D-51368 Leverkusen, Germany**

Sponsor's medical expert: PPD
PPD
PPD

Telephone no.: PPD

Mobile: PPD

[…]

*New text:*

[…]

Phase II anetumab ravtansine as 2nd line treatment for malignant pleural mesothelioma (MPM)

ARCS-$M_{2L}$ (Anetumab Ravtansine Clinical Studies – Mesothelioma 2nd Line)

Test drug: BAY 94-9343 / anetumab ravtansine

[…]

Sponsor: **Non-US: Bayer AG, D-51368 Leverkusen, Germany**
**US territory: Bayer HealthCare Pharmaceuticals Inc., 100 Bayer Boulevard, P.O. Box 915, Whippany NJ 07981-0915, USA**

Sponsor's medical expert: PPD
PPD
PPD

Telephone no.: PPD

Mobile: PPD

[…]

### 15.2.2.2 Section 2 Synopsis

*Old text:*

| | |
|---|---|
| **[…]** | |
| **Methodology** | […]<br>The effect of treatment on disease-specific health-related QoL ~~and disease-specific symptoms~~ will be assessed using the MD Anderson Symptom Inventory-Malignant Pleural Mesothelioma (MDASI-MPM) and the Lung Cancer Symptom Scale-Mesothelioma (LCSS-Meso) at full screening, at each cycle during treatment, at the safety follow-up visit, and during active follow-up.<br>[…]<br>Obligatory biomarker sampling will be performed on all patients to measure mesothelin expression levels in tumor material at prescreening. In addition, plasma levels of soluble mesothelin will be studied to evaluate whether plasma mesothelin levels may correlate with response rate and be of predictive value. Biomarker plasma will be collected to analyze circulating tumor DNA, too. Exploratory biomarker analysis may also be performed using additional fresh tumor tissue to determine alterations in tumor-associated genes and to perform gene expression analysis. |
| […] | |
| **Number of patients** | Approximately 210 patients will be randomized.<br>Approximately ~~40~~% rate of screening failures is estimated, i.e. approximately ~~350~~ patients will be prescreened. |
| […] | |
| **Plan for statistical analysis** | […]<br>Additional secondary variables include objective response rate (ORR), disease control rate (DCR), duration of response (DOR), and analysis of the change in physical symptoms of MPM by PROs (as measured using the MDASI-MPM and LCSS-Meso). ~~The final analysis for all these additional secondary variables will occur at the time of primary endpoint analysis.~~<br>[…] |

*New text:*

| | |
|---|---|
| **[…]** | |
| **Methodology** | […]<br>The effect of treatment on disease-specific symptoms and disease-specific health-related QoL will be assessed using the MD Anderson Symptom Inventory-Malignant Pleural Mesothelioma (MDASI-MPM) and the Lung Cancer Symptom Scale-Mesothelioma (LCSS-Meso), respectively, at full screening, at each cycle during treatment, at the safety follow-up visit, and during active follow-up.<br>[…]<br>Obligatory biomarker sampling will be performed on all patients to measure mesothelin expression levels in tumor material at prescreening. In addition, plasma levels of soluble mesothelin will be studied to evaluate whether plasma mesothelin levels may correlate with response rate and be of predictive value. Biomarker plasma will be collected to analyze circulating tumor DNA, too. Exploratory biomarker analysis may also be performed using additional fresh or archival tumor tissue to determine alterations in tumor-associated genes and to perform gene expression analysis.<br>An independent Data Monitoring Committee will periodically monitor patient safety. |
| […] | |
| **Number of patients** | Approximately 210 patients will be randomized. Approximately 50% rate of screening failures is estimated, i.e. approximately 420 patients will be prescreened. |
| […] | |
| **Plan for statistical analysis** | […]<br>Additional secondary variables include objective response rate (ORR), disease control rate (DCR), duration of response (DOR), durable response rate (DRR) and analysis of the change in physical symptoms of MPM by PROs (as measured using the MDASI-MPM and LCSS-Meso). In the event primary PFS and secondary OS hypothesis tests succeed, key secondary PRO variables will be tested at 1-sided significance level using an alpha-preserving hierarchy. A stratified log-rank test will be used for time-to-event endpoints, and a Cochran-Mantel-Haenszel test will be used for rate endpoints.<br>[…] |

### 15.2.2.3 List of abbreviations

*Old text:*

| | |
|---|---|
| […] | |
| ~~USP~~ | ~~United States Pharmacopeia~~ |
| […] | |

*New text:*

| | |
|---|---|
| […] | |
| DRR | Durable response rate |
| […] | |
| EMA | European Medicines Agency |
| […] | |
| RBC | Red blood cell count |
| […] | |

### 15.2.2.4 Section 3.2 Rationale of the study

*Old text:*

At the MTD of 6.5 mg/kg Q3W, anetumab ravtansine has demonstrated very strong efficacy in advanced, unresectable or metastatic epithelial mesothelioma (best objective response 31% overall or 45% in the 2nd line setting, with very durable responses). Such high response rate and long lasting responses would translate to the potential for anetumab ravtansine to impart large clinical benefit as the 2nd line treatment for advanced mesothelioma, which represents an indication of high unmet medical need for effective treatment options, as currently no approved SoC exists.

*New text:*

At the MTD of 6.5 mg/kg Q3W, anetumab ravtansine has demonstrated very strong efficacy in advanced, unresectable or metastatic epithelial mesothelioma (best objective response 31% overall or 45% in the 2nd line setting, with very durable responses) in a Phase I expansion cohort. Such high response rate and long lasting responses, if repeatable, would translate to the potential for anetumab ravtansine to impart large clinical benefit as the 2nd line treatment for advanced mesothelioma, which represents an indication of high unmet medical need for effective treatment options, as currently no approved SoC exists.

### 15.2.2.5 Section 5.1 Design overview

*Old text:*

[…]

An approximately 40% screen fail rate is anticipated (25% at prescreening and a subsequent ~~20~~% among biomarker expressers. Approximately ~~350~~ patients are estimated to be required

for prescreening to yield approximately 263 biomarker-positive patients, resulting in 210 randomized eligible patients).

[…]

The effect of treatment on ~~disease-specific health-related QoL and~~ disease-specific symptoms will be assessed using the MD Anderson Symptom Inventory-Malignant Pleural Mesothelioma (MDASI-MPM) and the Lung Cancer Symptom Scale-Mesothelioma (LCSS-Meso) at full screening, at each cycle during treatment, at the safety follow-up visit, and during active follow-up as per Section 9.4.3.

[…]

Exploratory biomarker analysis may also be performed using additional fresh tumor tissue to determine alterations in tumor-associated genes and to perform gene expression analysis.

*New text:*

[…]

An approximately 50% screen fail rate is anticipated (25% at prescreening and a subsequent 33% among biomarker expressers. Approximately 420 patients are estimated to be required for prescreening to yield approximately 263 biomarker-positive patients, resulting in 210 randomized eligible patients).

[…]

The effect of treatment on disease-specific symptoms and disease-specific health-related QoL will be assessed using the MD Anderson Symptom Inventory-Malignant Pleural Mesothelioma (MDASI-MPM) and the Lung Cancer Symptom Scale-Mesothelioma (LCSS-Meso), respectively, at full screening, at each cycle during treatment, at the safety follow-up visit, and during active follow-up as per Section 9.4.3.

[…]

Exploratory biomarker analysis may also be performed using additional fresh or archival tumor tissue to determine alterations in tumor-associated genes and to perform gene expression analysis.

### 15.2.2.6 Section 5.3 Justification of the design

*Old text:*

**Level of blinding**. […] The independent and central radiological review for the assessment of disease progression and other radiological imaging-based endpoints will be conducted in a blinded fashion.

[…]

*New text:*

**Level of blinding**. […] The independent and central radiological review for the assessment of disease progression and other radiological imaging-based endpoints will be conducted in a

blinded fashion. In addition, an independent PRO review committee of PRO, statistical, and psychometric experts, will conduct analyses in a blinded fashion to support validation of the MDASI-MPM instrument and determine endpoint definitional details.

[…]

### 15.2.2.7 Section 6.1.2 Eligibility criteria for full study

*Old text:*

[…]

3. Unresectable locally advanced or metastatic MPM after locally confirmed unequivocal progression on 1st line treatment with platinum (both cis- or carbo-platinum) in combination with pemetrexed. Last dose of previous therapy must be at least ~~5 drug half-lives or~~ 28 days~~, whichever is shorter,~~ before the start of study treatment.

[…]

*New text:*

[…]

3. Unresectable locally advanced or metastatic MPM after locally confirmed unequivocal progression on 1st line treatment with platinum (both cis- or carbo-platinum) in combination with pemetrexed. Last dose of previous therapy must be at least 28 days before the start of study treatment.

[…]

### 15.2.2.8 Section 6.2 Exclusion criteria

*Old text:*

[…]

4. More than 1 previous systemic anti-cancer therapy line (even if therapy used as neoadjuvant or adjuvant treatment).

   Note: Patients pre-treated with systemic therapy other than platinum, pemetrexed, bevacizumab (13) (e.g. other cytotoxic drugs, immunotherapy, targeted therapy, hormonal therapy, or any other experimental or approved therapy) are not to be enrolled.

   […]

~~16. Symptomatic brain metastases or meningeal tumors or other uncontrolled metastases in the central nervous system (CNS) unless the patient~~

- ~~Is > 6 months from definitive therapy,~~
- ~~Has a negative imaging study within 4 weeks before study entry (ICF signature for full study) and~~

- ~~Is clinically stable with respect to the tumor at the time of study entry.~~

[…]

*New text:*

[…]

4. More than 1 previous systemic anti-cancer therapy line <u>for MPM</u> (even if therapy used as neoadjuvant or adjuvant treatment).

   Note: Patients pre-treated with systemic therapy other than platinum, pemetrexed, bevacizumab (13) (e.g. other cytotoxic drugs, immunotherapy, targeted therapy, hormonal therapy, or any other experimental or approved therapy <u>or device</u>) are not to be enrolled.

   […]

16. <u>Brain metastases or meningeal tumors or other metastases in the central nervous system (CNS). Patients with neurological symptoms must undergo a contrast CT scan or MRI of the brain and/or other areas of the CNS as applicable within 28 days before the start of study treatment to exclude metastastic disease in the CNS.</u>

    […]

## 15.2.2.9 Section 6.3.1.1.3 Re-screening

*Old text:*

~~Re-starting the defined set of screening procedures to enable the "screening failure" patient's participation at a later time point is not allowed – with the following exceptions:~~

- ~~The patient had successfully passed the screening procedures, but could not start subsequent treatment on schedule.~~
- ~~Initial screening occurred too early to complete the required washout period after prior therapy.~~
- ~~The in- / exclusion criteria preventing the patient's initial attempt to participate have been changed (via protocol amendment).~~
- ~~Equivocal screening results require further testing for clarification even if, for logistical reasons, the further testing cannot be performed within the allocated time window (e.g. equivocal laboratory creatinine clearance requiring formal creatinine clearance measurement).~~

~~In any case, the investigator has to ensure that the repeated screening procedures do not expose the patient to an unjustifiable health risk. Also, for re-screening, the patient has to re-sign the ICF, even if it was not changed after the patient's previous screening.~~

~~Re-testing for mesothelin expression after obtaining an initial negative result is not allowed.~~

~~A patient can only be re-screened once and for all re-screening requests, the sponsor needs to be contacted to discuss before re-screening the patient.~~

*New text:*

Re-screening is defined as re-starting the defined set of screening procedures following "screening failure" to allow a patient to participate at a later time point. This is not allowed except in the following circumstances:

- Equivocal screening test results that require repeat or further testing for clarification, which cannot for logistical reasons be performed within the screening period.
- Initial screening occurred too early to complete the required washout period after prior therapy.
- The in- / exclusion criteria preventing the patient's initial attempt to participate have been changed (via protocol amendment).
- The patient had successfully passed the screening procedures, but could not be randomized on schedule and the allocated time window for these tests has expired.

During re-screening, all expired tests must be repeated to fall within the protocol-defined time window.

The investigator has to ensure that the repeated screening procedures do not expose the patient to an unjustifiable health risk. Also, for re-screening, the patient has to re-sign the ICF, even if it was not changed after the patient's previous screening and a new patient identification number has to be requested via Interactive Voice / Web Response System (IxRS).

A patient can only be re-screened once and for all re-screening requests, the sponsor needs to be contacted to discuss before re-screening the patient.

Re-testing for mesothelin expression after obtaining an initial negative result is not allowed.

## 15.2.2.10 Section 6.3.1.2 Withdrawal criteria

*Old text:*

[…]

**Withdrawal from study treatment, active follow-up and long-term follow-up**

[…]

**Figure 6-1 Withdrawal criteria**

[…]

Patients must be withdrawn from **treatment with anetumab ravtansine** if any of the following occurs:

[…]

- If any type of TEAE requiring dose modification does not resolve to Grade ≤ ~~1~~ (or Hb ≥ 9 g/dL in case of anemia) within 6 weeks after the last dose of anetumab ravtansine.

[…]

[…]

*New text:*

[…]

## Withdrawal from study treatment, active follow-up and long-term follow-up

[…]

**Figure 6-1 Withdrawal criteria**

[…]

Patients must be withdrawn from **treatment with anetumab ravtansine** if any of the following occurs:

[…]

- If any type of TEAE requiring dose modification does not resolve to Grade ≤ 2 (or Hb ≥ 9 g/dL in case of anemia) within 6 weeks after the last dose of anetumab ravtansine.

[…]

[…]

## 15.2.2.11 Section 7.2.1 Test drug – anetumab ravtansine

*Old text:*

[…]

The drug product is to be stored at 2°C to 8°C (36°F to 46°F).

~~**Reconstitution**~~

~~The drug product should be reconstituted and processed under aseptic conditions (i.e. qualified laminar flow unit and trained personnel) to preclude microbial contamination.~~

~~Using a sterile syringe, gently add 11.9 mL of water for injection through the middle of the stopper to the freeze-dried product into the 30 mL injection vial to obtain a solution (approximate reconstituted volume is 12.5 mL). During reconstitution, make sure that the needle does not come into contact with the cake or resulting solution; avoid shaking. The lyophilizate should dissolve completely.~~

~~The reconstituted lyophilizate may be diluted only after the solution is clear.~~

~~**Dilution of the reconstituted solution**~~

~~Dilution of the reconstituted solution with 0.9% sodium chloride solution (normal saline) should be done under aseptic conditions (i.e. qualified laminar flow unit and trained personnel) to preclude microbial contamination. A slight turbidity may occur during the dilution which does not affect the quality of the drug product.~~

~~**Stability of the reconstituted solution**~~

~~Exposure to bright light should be avoided; standard room illumination does not necessitate any precautions.~~

~~The reconstituted solution is physically and chemically stable for 24 h at room temperature and between 2°C and 8°C. However, unless administered immediately, for microbiologic consideration, the reconstituted solution should be stored between 2°C and 8°C and used within 6 h according to USP 797 "Pharmaceutical Compounding – Sterile preparations".~~

~~If not reconstituted under aseptic conditions, the solution should be used immediately or stored at 2°C to 8°C and used within 1 h, according to USP 797.~~

~~If frozen or stored above room temperature, the solution should be discarded.~~

~~**Stability of the diluted solution**~~

~~Exposure to bright light should be avoided; standard room illumination does not necessitate any precautions.~~

~~Stability investigations have shown that if diluted under aseptic conditions, concentrations between 0.1 and 3.0 mg/mL are stable for the period of use (24 h) at room temperature and between 2°C and 8°C. However, unless administered immediately, for microbiologic consideration, diluted solution should be stored between 2°C and 8°C and used within 6 h according to USP 797 "Pharmaceutical Compounding – Sterile preparations".~~

~~If not diluted under aseptic conditions, the solution should be used immediately or stored at 2°C to 8°C and used within 1 h, according to USP 797.~~

~~If frozen or stored above room temperature, the solution should be discarded.~~

Refer to IB for anetumab ravtansine for details regarding drug properties and formulation.

*New text:*

[…]

The drug product is to be stored at 2°C to 8°C (36°F to 46°F).

The reconstitution and dilution of the anetumab ravtansine solution and the associated stability information is described in detail in a separate manual "15743 Anetumab ravtansine storage and handling instructions" that will be maintained in the trial master file (TMF) and in each center's investigator site file.

Refer to IB for anetumab ravtansine for details regarding drug properties and formulation.

## 15.2.2.12 Section 7.4.2.1 Dose modifications of anetumab ravtansine

*Old text:*

[…]

TEAE requiring dose modification (~~temporary treatment interruption,~~ dose reduction, or permanent discontinuation of ~~treatment~~) will be defined as any of the events described below that is possibly, probably, or definitely related to anetumab ravtansine and occurs anytime during the study (not only in Cycle 1).

[…]

*New text:*

[…]

TEAE requiring dose modification (dose omission, infusion interruption, change in infusion rate, dose delay, dose reduction, or permanent discontinuation of study drug) will be defined as any of the events described below that is possibly, probably, or definitely related to anetumab ravtansine and occurs anytime during the study (not only in Cycle 1).

[…]

## 15.2.2.13 Section 7.4.2.1.1 Hematological toxicities

*Old text:*

**Dose modifications for hematological toxicity**

- If treatment modification is required due to a hematological TEAE, and the continuation of treatment is appropriate, the anetumab ravtansine dose will be adjusted as described in Table 7-3 ~~and Table 7-4~~ below.

[…]

**Table 7-3 Dose adjustments in response to neutrophil and platelet nadir a counts of the previous cycle**

| Absolute neutrophil nadir count of the previous cycle (/mm³) | | Platelet nadir count of the previous cycle (/mm³) | Anetumab ravtansine dose adjustment [b] |
|---|---|---|---|
| ≥ 500 or < 500 for < 7 days | and | ≥ 25,000 | No change |
| < 500 for ≥ 7 days | and/or | < 25,000 regardless of the presence of active bleeding (or ≥ 25,000 with clinically significant bleeding, i.e. bleeding requiring platelet transfusion) | Decrease 1 dose level [b] |
| Febrile neutropenia [c] | and/or | < 25,000 regardless of the presence of active bleeding (or ≥ 25,000 with clinically significant bleeding, i.e. bleeding requiring platelet transfusion) | Decrease 1 dose level [b] |

ANC = Absolute neutrophil count; C = Cycle; CBC = Complete blood count; D = Day; Q3W = Every 3 weeks

a Site visits and blood test for CBC (and biochemistry) on D8 and D15 will be performed on C1, C2 and C3 only. From Cycle 4 onwards, visits and procedures on D8 and D15 are no longer required.

b Dose reduction by 1 dose level translates to a change from 6.5 mg/kg Q3W to 5.5 mg/kg Q3W, or from 5.5 mg/kg Q3W to 4.5 mg/kg Q3W. Not more than 2 dose reductions from the starting dose level are permitted.

c Febrile neutropenia is defined as ANC < 1000/mm³ and fever (a single body temperature reading of > 38.3°C [101°F] or a sustained body temperature of ≥ 38°C [100.4°F] for more than 1 hour).

**Table 7-4 Dose adjustments in response to pre-infusion values**

| Absolute neutrophil count (/mm³) | | Platelets (/mm³) | Hemoglobin (g/dL) | Timing | Anetumab ravtansine dose adjustment |
|---|---|---|---|---|---|
| ≥ 1,000 | and | ≥ 75,000 | | Treat on time | Adjust dose by nadir [a] counts in previous cycle per investigator's discretion |
| < 1,000 | and/or | < 75,000 | | Delay until ANC ≥ 1.0 and platelets ≥ 75,000 [b] | Decrease by 1 dose level [c] |
| | | | < 8 | Delay until Hb ≥ 8 [b] | Re-start at the same dose or decrease by 1 dose level [c] (at investigator's discretion) |

ANC = Absolute neutrophil count; C = Cycle; CBC = Complete blood count; D = Day; Hb = Hemoglobin; Q3W = Every 3 weeks; TEAE = Treatment-emergent adverse event

a Site visits and blood test for CBC (and biochemistry) on D8 and D15 will be performed on C1, C2 and C3 only. From Cycle 4 onwards, visits and procedures on D8 and D15 are no longer required.

b Treatment will be discontinued if the TEAE fails to resolve to Grade ≤ 1 (or Hb ≥ 9 g/dL in case of anemia) within 6 weeks after the last dose of anetumab ravtansine.

c Dose reduction by 1 dose level translates to a change from 6.5 mg/kg Q3W to 5.5 mg/kg Q3W, or from 5.5 mg/kg Q3W to 4.5 mg/kg Q3W. Not more than 2 dose reductions from the starting dose level are permitted.

*New text:*

**Dose modifications for hematological toxicity**

- If treatment modification is required due to a hematological TEAE, and the continuation of treatment is appropriate, the anetumab ravtansine dose will be adjusted as described in Table 7-3 below.

[…]

**Table 7–3 Dose modifications for anetumab ravtansine in response to hematological toxicities [a] for neutrophil and platelet nadir [b] counts – table added**

| Dose modifications | | Blood count |
|---|---|---|
| **Platelet count (/mm³)** | Start new cycle only if platelet count is | ≥ 75,000 (Grade ≤1) (pre-infusion) |
| | Dose reduce by 1 dose level [c] | < 25,000 (Grade 4) for ≥ 7 days (nadir [b]) |
| | | < 50,000 (Grade 3) for ≥ 7 days with bleeding [d] (nadir [b]) |
| **Absolute neutrophil count (/mm³)** | Start new cycle only if ANC is | ≥ 1000 (Grade ≤ 2) (pre-infusion) |
| | Dose reduce by 1 dose level [c] | < 500 (Grade 4) for 7 days (nadir [b]) |
| | | Febrile neutropenia (Grade 3) [e] (during previous cycle) |
| **Hemoglobin (g/dL)** | Start new cycle only if hemoglobin is | Hb ≥ 8 (pre-infusion) |
| | Re-start at the same dose or dose reduce by 1 dose level [c] (at investigator's discretion) | < 8 (nadir [b]) |
| **Any** | Discontinue | Grade 3 or 4 toxicity after 2 dose reductions |

ANC = Absolute neutrophil count; C = Cycle; CBC = Complete blood count; D = Day; Hb = Hemoglobin; Q3W = Every 3 weeks

a For any toxicity ≤ Grade 2 assessed as related to study drug(s) by the investigator, dose modification may be considered if investigator feels this is in the patients best interest. Such toxicities might be ≤ Grade 2 toxicities which interfere with the activities of daily life.

b Nadir: lowest value measured in previous cycle or pre-infusion. Site visits and blood test for CBC on D8 and D15 are mandatory for C1, C2 and C3 only. From C4 onwards, visits and procedures on D8 and D15 are no longer required.

c Dose reduction by 1 dose level translates to a change from 6.5 mg/kg Q3W to 5.5 mg/kg Q3W, or from 5.5 mg/kg Q3W to 4.5 mg/kg Q3W. Not more than 2 dose reductions from the starting dose level are permitted.

d Clinically significant bleeding, i.e. bleeding requiring platelet transfusion.

e Febrile neutropenia is defined as ANC < 1000/mm³ and fever (a single body temperature reading of > 38.3°C [101°F] or a sustained body temperature of ≥ 38°C [100.4°F] for more than 1 hour).

## 15.2.2.14 Section 7.4.2.1.2 Non-hematological toxicities

*Old text:*

**Non-hematological toxicities requiring dose modification**

- CTCAE Grade 2 anetumab ravtansine infusion-related reaction or other CTCAE Grade 2 hypersensitivity events (see Section 7.4.2.1.3)
- ~~AST and/or ALT increase > 5.0 x ULN (CTCAE Grade ≥ 3)~~
- AST and/or ALT increase > 3.0 x ULN (CTCAE Grade ≥ 2) with concomitant increase in total bilirubin > 1.5 x ULN (CTCAE Grade ≥ 2)
- ~~Total bilirubin > 3.0 x ULN (CTCAE Grade ≥ 3)~~
- Bayer Grade ≥ 3 corneal epitheliopathy (see below and Table 7-~~6~~)
- Any other Grade ≥ 3 non-hematological toxicity that, in the investigator's opinion, warrants treatment modification (see Table 7-~~5~~), **excluding** the following:
  - Nausea, vomiting, or diarrhea if manageable with anti-emetics or anti-diarrheals within 7 days
  - ~~o~~ ~~Hair loss~~
  - Fatigue lasting ≤ 72 h
- Any other toxicity irrespective of the type or severity that represents a clinically significant risk to patient in the investigator's opinion.

**Dose modifications for non-hematological toxicity**

[…]

**Table 7-~~5~~ Dose adjustments in response to non-hematologic toxicities**

| CTCAE v4.03 grade | Anetumab ravtansine dose delay / interruption | Anetumab ravtansine dose modification |
|---|---|---|
| […] | | |
| […] | 1st appearance: Delay/Interruption until Grade ≤ 2 [b]<br><br>2nd appearance: Delay/Interruption until Grade ≤ 2[b]<br><br>[…] | […] |
| […] | | |

[…]

b Treatment will be discontinued if the TEAE fails to resolve to Grade ≤ ~~1~~ within 6 weeks after the last dose of anetumab ravtansine.

[…]

[…]

*New text:*

**Non-hematological toxicities requiring dose modification**

- CTCAE Grade 2 anetumab ravtansine infusion-related reaction or other CTCAE Grade 2 hypersensitivity events (see Section 7.4.2.1.3)
- AST and/or ALT increase > 3.0 x ULN (CTCAE Grade ≥ 2) with concomitant increase in total bilirubin > 1.5 x ULN (CTCAE Grade ≥ 2)
- Bayer Grade ≥ 3 corneal epitheliopathy (see below and Table 7-5)
- Any other Grade ≥ 3 non-hematological toxicity that, in the investigator's opinion, warrants treatment modification (see Table 7-4), **excluding** the following:
    - Nausea, vomiting, or diarrhea if manageable with anti-emetics or anti-diarrheals within 7 days
    - Fatigue lasting ≤ 72
- Any other toxicity irrespective of the type or severity that represents a clinically significant risk to patient in the investigator's opinion.

**Dose modifications for non-hematological toxicity**

[…]

**Table 7-4 Dose adjustments in response to non-hematologic toxicities**

| CTCAE v4.03 grade | Anetumab ravtansine dose delay / interruption | Anetumab ravtansine dose modification |
|---|---|---|
| […] | | |
| | 1st appearance: Delay/Interruption until Grade ≤ 2 [b]<br><br>2nd appearance: Delay/Interruption until Grade ≤ 2[b]<br><br>[…] | |
| […] | | |

[…]

b Treatment will be discontinued if the TEAE fails to resolve to Grade ≤ 2 within 6 weeks after the last dose of anetumab ravtansine.

[…]

[…]

## 15.2.2.15 Section 7.4.2.1.3 Miscellaneous toxicities

*Old text:*

**IV infusion-related reaction and other hypersensitivity events**

[…]

Re-treatment should be at the infusion rate reduced by 50%, along with anti-allergic prophylaxis (e.g. anti-histamines, acetaminophen, and/or corticosteroids) chosen at the investigator's discretion or according to the institutional guidelines.

[…]

**Dose modifications for corneal epitheliopathy**

[…]

**Table 7-~~6~~ Bayer classification and management of corneal epitheliopathy**

[…]

[…]
a Oxford Schema must be used for grading SPK from stage 0 to VI.
[…]

[…]

*New text:*

**IV infusion-related reaction and other hypersensitivity events**

[…]

Re-treatment should be at the infusion rate reduced by 50%, along with anti-allergic prophylaxis (e.g. anti-histamines, paracetamol, acetaminophen, and/or corticosteroids) chosen at the investigator's discretion or according to the institutional guidelines.

[…]

**Dose modifications for corneal epitheliopathy**

[…]

**Table 7-5 Bayer classification and management of corneal epitheliopathy**

[…]

[…]
a Oxford Schema must be used for grading SPK from stage 0 to VI (see Section 16.9).
[…]

[…]

### 15.2.2.16 Section 7.5 Blinding

*Old text:*

This is an open-label study except for the independent and central radiological review for the assessment of disease progression and other radiological imaging based endpoints, which will be conducted in a blinded fashion.

*New text:*

This is an open-label study except for:

- The independent and central radiological review for the assessment of disease progression and other radiological imaging based endpoints, which will be conducted in a blinded fashion.
- The independent blinded PRO review committee which will conduct analyses to support validation of the MDASI-MPM instrument and determine endpoint definitional details.

### 15.2.2.17 Section 8.1 Prior and concomitant therapy

*Old text:*

[…]

**Table 8-1 Prohibited prior and concomitant therapies**

| Prohibited prior and concomitant therapy (see also Section 6.2) | Time period when prohibited | Comments |
|---|---|---|
| ***Prohibited for all patients*** | | |
| […] | | |
| Platinum/pemetrexed/ bevacizumab | Within ~~5 drug half-lives or~~ 28 days~~, whichever is shorter,~~ before the start of study treatment until safety follow-up visit | |
| […] | | |
| Anti-arrhythmic therapy other than beta blockers or digoxin | | |
| ~~Acute steroid therapy or taper~~ | | ~~Chronic steroid therapy is acceptable, provided that the dose is stable for 1 month before the start of study treatment and thereafter.~~ |
| Radiotherapy | Within 4 weeks before the start of screening for full study | Except for pain control, see below in Table 8-2. […] |
| Drugs with known bone marrow toxicity | | |
| Strong inhibitors and strong inducers of CYP3A4 (listed in Appendix 16.6), including: - Herbal preparations | Within 2 weeks before the start of study treatment until the safety follow-up visit | DM4 and vinorelbine are substrates of CYP3A4.<br><br>During study treatment, moderate and weak CYP3A4 inducers should be used with caution as decrease in |

**Table 8-1 Prohibited prior and concomitant therapies**

| Prohibited prior and concomitant therapy (see also Section 6.2) | Time period when prohibited | Comments |
|---|---|---|
| containing CYP3A4 inducers (e.g. St John's Wort)<br>- Grapefruit and grapefruit juice (CYP3A4 inhibitor) | | plasma concentrations of DM4 cannot be ruled out. |
| ~~***Prohibited for patients in the comparator (vinorelbine) arm***~~ | | |
| Concomitant live attenuated virus vaccines (e.g. yellow fever) | Within 2 weeks before the start of study treatment until the safety follow-up visit | Contraindicated due to risk of generalized vaccine disease, possibly fatal |

ASCO = American Society of Clinical Oncology; CSF = Colony stimulating factor; CT = Computed tomography; CYP3A4 = Cytochrome P450, family 3, subfamily A, polypeptide 4; DM4 = Derivatives of maytansine 4; G-CSF = Granulocyte-colony stimulating factor; IV = Intravenous; MPM = Malignant pleural mesothelioma; mRECIST = Modified Response Evaluation Criteria in Solid Tumors; MRI = Magnetic resonance imaging; PD = Progressive disease; RT = Radiotherapy

**Table 8-2 Permitted concomitant therapies**

| Permitted concomitant therapies | Comments |
|---|---|
| ***Permitted for all patients*** | |
| […] | |
| Institutional standards for the management of infusion-related reactions or other hypersensitivity events | May be utilized at the discretion of the investigator. |
| Palliative radiotherapy for pain control | Allowed provided that:<br>- In the opinion of the investigator, the patient does not have PD, […] |
| […] | |

[…]

*New text:*

[…]

**Table 8-1 Prohibited prior and concomitant therapies**

| Prohibited prior and concomitant therapy (see also Section 6.2) | Time period when prohibited | Comments |
|---|---|---|
| ***Prohibited for all patients*** | | |
| […] | | |
| Platinum/pemetrexed/ bevacizumab | Within 28 days before the start of study treatment until safety follow-up visit | |

**Table 8-1 Prohibited prior and concomitant therapies**

| Prohibited prior and concomitant therapy (see also Section 6.2) | Time period when prohibited | Comments |
|---|---|---|
| […] | | |
| Anti-arrhythmic therapy other than beta blockers or digoxin | | |
| Radiotherapy | Within 4 weeks before the start of screening for full study | Except for pain control, see below in Table 8-2. […] |
| Drugs with known bone marrow toxicity | | |
| Strong inhibitors and strong inducers of CYP3A4 (listed in Appendix 16.6), including:<br>- Herbal preparations containing CYP3A4 inducers (e.g. St John's Wort)<br>- Grapefruit and grapefruit juice (CYP3A4 inhibitor) | Within 2 weeks before the start of study treatment until the safety follow-up visit | DM4 and vinorelbine are substrates of CYP3A4.<br><br>During study treatment, moderate and weak CYP3A4 inducers should be used with caution as decrease in plasma concentrations of DM4 cannot be ruled out. |
| Concomitant live attenuated virus vaccines (e.g. yellow fever) | Within 2 weeks before the start of study treatment (for all patients, during screening, then from C1D1 until the safety follow-up visit for patients in vinorelbine arm only) | Contraindicated due to risk of generalized vaccine disease, possibly fatal |

ASCO = American Society of Clinical Oncology; C=Cycle; CSF = Colony stimulating factor; CT = Computed tomography; CYP3A4 = Cytochrome P450, family 3, subfamily A, polypeptide 4; D=Day; DM4 = Derivatives of maytansine 4; G-CSF = Granulocyte-colony stimulating factor; IV = Intravenous; MPM = Malignant pleural mesothelioma; mRECIST = Modified Response Evaluation Criteria in Solid Tumors; MRI = Magnetic resonance imaging; PD = Progressive disease; RT = Radiotherapy

**Table 8-2 Permitted concomitant therapies**

| Permitted concomitant therapies | Comments |
|---|---|
| ***Permitted for all patients*** | |
| […] | |
| Institutional standards for the management of infusion-related reactions or other hypersensitivity events | May be utilized at the discretion of the investigator. |
| Chronic steroid therapy | Permitted provided that the dose is stable for one month prior to start of study drug. |
| Palliative radiotherapy for pain control | Allowed provided that:<br>- In the opinion of the investigator, the patient does not have PD, […] |
| […] | |

[…]

## 15.2.2.18 Section 9.1 Tabular schedule of evaluations

*Old text:*

**Table 9-1 Study flow chart**

| | Pre-screening | Full screening (maximum days before C1D1) | | Treatment | | | | | | Safety follow-up period / visit | Active follow-up [a] | Long-term follow-up [a] |
|---|---|---|---|---|---|---|---|---|---|---|---|---|
| | | | | Cycle 1 | | | Cycle 2 and higher | | | | | |
| **Days** | | **-28** | **- 7** | **D1** | **D8** | **D15** | **D1** | **D8** [b] | **D15** [b] | **+30** (after last dose) | | **Every 3 months** |
| Acceptable time window (in days) (unless otherwise specified) | | | | | +/-1 | +/-1 | +/-1 | +/-1 | +/-1 | +7 | | ±14 |
| […] | | | | | | | | | | | | |
| **Safety** | | | | | | | | | | | | |
| […] | | | | | | | | | | | | |
| Vital signs (BP, HR, RR, Temp) | | ~~X~~ | X | X [z] | X | X | X | X | X | X | | |
| […] | | | | | | | | | | | | |
| Ophthalmologic examination [k] | | ~~X~~ | | | | | X | | | X | | |
| […] | | | | | | | | | | | | |
| Electrolyte and chemistry panel | | | X | | X [l] | X [l] | X | X [l] | X [l] | X | | |
| […] | | | | | | | | | | | | |
| **Efficacy** | | | | | | | | | | | | |
| Radiological tumor evaluation with contrast-enhanced CT/MRI [o] | | X | | Every 6 weeks (first 6 months), every 9 weeks (until end of year 2), every 12 weeks thereafter [o] | | | | | | | X [o] | |
| […] | | | | | | | | | | | | |
| **Biomarker sampling** | | | | | | | | | | | | |
| BM archival or fresh biopsy tissue [u] | X [v] | | | | | | | | | | | |
| […] | | | | | | | | | | | | |

**Table 9-1 Study flow chart**

| | Pre-screening | Full screening (maximum days before C1D1) | | Treatment | | | | | | Safety follow-up period / visit | Active follow-up [a] | Long-term follow-up [a] |
|---|---|---|---|---|---|---|---|---|---|---|---|---|
| | | | | Cycle 1 | | | Cycle 2 and higher | | | | | |
| **Days** | | **-28** | **- 7** | **D1** | **D8** | **D15** | **D1** | **D8** [b] | **D15** [b] | **+30** (after last dose) | | **Every 3 months** |
| Acceptable time window (in days) (unless otherwise specified) | | | | | +/-1 | +/-1 | +/-1 | +/-1 | +/-1 | +7 | | ±14 |

[…]

j Cardiac function test is required during full screening and pre-dose C2D1, pre-dose C4D1, and afterwards at the investigator's discretion based on clinical need. EchoCG shall be performed instead of MUGA when local regulations do not permit the use of MUGA as requested per protocol schedule.

[…]

u Fresh tumor tissue collection is optional after a local assessment of partial or complete response.

[…]

z Eligibility criteria check, IxRS transaction to randomize the patient, toxicity / AE assessment, concomitant medication review, brief physical examination, vital signs and weight measurement, and ECOG PS assessment can be done within 24 hours before administration of the first dose of study drug. Eligibility must be confirmed prior to randomizing the patient in IxRS.

*New text:*

**Table 9-1 Study flow chart**

| Days | Pre-screening | Full screening (maximum days before C1D1) | | | Treatment | | | | | | Safety follow-up period / visit | Active follow-up [a] | Long-term follow-up [a] |
|---|---|---|---|---|---|---|---|---|---|---|---|---|---|
| | | | | | Cycle 1 | | | Cycle 2 and higher | | | | | |
| | | -28 | -21 | - 7 | D1 | D8 | D15 | D1 | D8 [b] | D15 [b] | +30 (after last dose) | | Every 3 months |
| Acceptable time window (in days) (unless otherwise specified) | | | | | | +/-1 | +/-1 | +/-1 | +/-1 | +/-1 | +7 | | ±14 |
| […] | | | | | | | | | | | | | |
| **Safety** | | | | | | | | | | | | | |
| […] | | | | | | | | | | | | | |
| Vital signs (BP, HR, RR, Temp) | | | | X | X [z] | X | X | X | X | X | X | | |
| […] | | | | | | | | | | | | | |
| Ophthalmologic examination [k] | | | X | | | | | X | | | X | | |
| […] | | | | | | | | | | | | | |
| Electrolyte and chemistry panel | | | | X | | X [l] | X [l] | X [aa] | X [l] | X [l] | X | | |
| […] | | | | | | | | | | | | | |
| **Efficacy** | | | | | | | | | | | | | |
| Radiological tumor evaluation with contrast-enhanced CT/MRI [o] | | X [bb] | | | Every 6 weeks (first 6 months), every 9 weeks (until end of year 2), every 12 weeks thereafter [o] | | | | | | | X [o] | |
| […] | | | | | | | | | | | | | |
| **Biomarker sampling** | | | | | | | | | | | | | |
| BM archival or fresh biopsy tissue [u] | X [v] | | | | X [u] | | | | | | | | |
| […] | | | | | | | | | | | | | |

[…]

j Cardiac function test is required during full screening and pre-dose C2D1, pre-dose C4D1, and afterwards at the investigator's discretion based on clinical need. During treatment, cardiac function test can be done up to 7 days before study drug administration. EchoCG shall be performed instead of MUGA when local regulations do not permit the use of MUGA as requested per protocol schedule.

[…]

u If additional archival tissue is available, optional archival tissue should be collected for patients who consent and sent when possible after C1D1. Fresh tumor tissue collection is optional after a local assessment of partial or complete response.

[…]

**Table 9-1 Study flow chart**

| | Pre-screening | Full screening (maximum days before C1D1) | | | Treatment | | | | | | Safety follow-up period / visit | Active follow-up [a] | Long-term follow-up [a] |
|---|---|---|---|---|---|---|---|---|---|---|---|---|---|
| | | | | | Cycle 1 | | | Cycle 2 and higher | | | | | |
| **Days** | | **-28** | **-21** | **- 7** | **D1** | **D8** | **D15** | **D1** | **D8 [b]** | **D15 [b]** | **+30** (after last dose) | | **Every 3 months** |
| Acceptable time window (in days) (unless otherwise specified) | | | | | | +/-1 | +/-1 | +/-1 | +/-1 | +/-1 | +7 | | ±14 |

z Eligibility criteria check, IxRS transaction to randomize the patient, toxicity / AE assessment, concomitant medication review, brief physical examination, vital signs and weight measurement, and ECOG PS assessment can be done within 24 hours before administration of the first dose of study drug. Eligibility must be confirmed prior to randomizing the patient in IxRS.

aa Lipase testing on Cycle 2 and higher Day 1 can be performed within 8 days before administration of the study treatment.

bb Patients with neurological symptoms at screening must undergo a contrast CT or MRI scan of the brain and/or other areas of the CNS as applicable within 28 days before the start of study treatment to exclude metastatic disease in the CNS.

### 15.2.2.19 Section 9.2.2 Full screening period

*Old text:*

[…]

**Within 28 days before the start of study treatment:**

[…]

- Radiological tumor evaluation with contrast-enhanced CT/MRI of chest/abdomen/pelvis (see Section 9.4.1). Pre-study CT/MRI may be acceptable as a baseline scan if done within 28 days before start of study drug, if centrally evaluable for mRECIST and if performed according to the Imaging Acquisition Guidance provided in the Imaging Manual.

[…]

- Complete physical examination (see Section 9.6.3.2.1).
- ~~Vital signs (see Section 9.6.3.4).~~
- Weight and height.

[…]

- A detailed ophthalmologic examination (visual acuity, IOP, Schirmer test and slit lamp) (see Section 9.6.3.7) will be done within 3 weeks before the start of study treatment.

[…]

*New text:*

[…]

**Within 28 days before the start of study treatment:**

[…]

- Radiological tumor evaluation with contrast-enhanced CT/MRI of chest/abdomen/pelvis (see Section 9.4.1). Pre-study CT/MRI may be acceptable as a baseline scan if done within 28 days before start of study drug, if centrally evaluable for mRECIST and if performed according to the Imaging Acquisition Guidance provided in the Imaging Manual. Patients with neurological symptoms at screening must undergo a contrast CT or MRI scan within 28 days before the start of study treatment to exclude brain metastases

[…]

- Complete physical examination (see Section 9.6.3.2.1).
- Weight and height.

[…]

**Within 21 days before the start of study treatment:**

- A detailed ophthalmologic examination (visual acuity, IOP, Schirmer test and slit lamp) (see Section 9.6.3.7)

[…]

### 15.2.2.20 Section 9.2.3.1 Treatment – Cycle 1

*Old text:*

**Cycle 1 Day 1**

[…]

- 12-lead ECG (see Section 9.6.3.5), 30 min post-dose.

*New text:*

**Cycle 1 Day 1**

[…]

- 12-lead ECG (see Section 9.6.3.5), 30 min (+/- 5 min) post-dose.

For patients who consent to provide optional additional archival tissue, this should be collected and sent to the central laboratory at any time post randomization.

### 15.2.2.21 Section 9.2.3.2 Treatment – Cycle 2 and higher

*Old text:*

**Cycle 2 and higher Day 1**

[…]

- EchoCG or MUGA scan (see Section 9.6.3.6) on C2D1, C4D1, and afterwards at the investigator's discretion based on clinical need.

[…]

- Laboratory (see Section 9.6.3.1).

  […]

  - Electrolyte and chemistry panel.

[…]

*New text:*

**Cycle 2 and higher Day 1**

[…]

- EchoCG or MUGA scan (see Section 9.6.3.6) on C2D1, C4D1, and afterwards at the investigator's discretion based on clinical need. During treatment, cardiac function test can be done up to 7 days before study drug administration.

[…]

- Laboratory (see Section 9.6.3.1).

  […]

  - Electrolyte and chemistry panel (lipase testing can be performed within 8 days before administration of the study treatment).

[…]

### 15.2.2.22 Section 9.2.5.2 Active follow-up

*Old text:*

Patients who discontinue study treatment due to any other reason than centrally confirmed radiological PD will continue clinic visits during active follow-up for efficacy assessments including tumor response and QoL.

[…]

*New text:*

Patients who discontinue study treatment due to any other reason than centrally confirmed radiological PD will continue clinic visits during active follow-up for efficacy assessments including tumor response, disease-related-symptoms, and QoL.

[…]

### 15.2.2.23 Section 9.4.1 Radiological tumor assessments

*Old text:*

[…]

If focal neurological symptoms are present at screening, a CT scan or MRI of the brain is required to rule out ~~brain~~ metastas~~is~~ by the investigator. All additional suspected sites of disease should be imaged (e.g. cervical lymph nodes, bone etc.).

[…]

The final evaluation of treatment response will be done by central blinded review retrospectively.

[…]

*New text:*

[…]

If focal neurological symptoms are present at screening, a CT scan or MRI of the brain and/or other areas of the CNS as applicable is required to rule out metastastic disease in the CNS within 28 days before the start of study treatment by the investigator. All additional suspected sites of disease should be imaged (e.g. cervical lymph nodes, bone etc.)

[…]

The final evaluation of treatment response for those patients not undergoing central review for PD confirmation will be done by central blinded review retrospectively.

[…]

### 15.2.2.24 Section 9.4.3 Patient-reported outcomes

*Old text:*

The effect of treatment on disease-specific health-related quality of life (QoL) ~~and disease-specific symptoms~~ will be assessed using the MD Anderson Symptom Inventory-Malignant Pleural Mesothelioma (MDASI-MPM) and the Lung Cancer Symptom Scale-Mesothelioma (LCSS-Meso).

The LCSS-Meso will be used to assess change in thoracic cancer symptoms. In addition to the LCSS-Meso, the MDASI-MPM will be used to assess change in thoracic cancer symptoms and interference of these symptoms with daily activities.

[…]

*New text:*

The effect of treatment on disease-related symptoms and disease-specific health-related quality of life (QoL) will be assessed using the MD Anderson Symptom Inventory-Malignant Pleural Mesothelioma (MDASI-MPM) and the Lung Cancer Symptom Scale-Mesothelioma (LCSS-Meso), respectively.

The LCSS-Meso will be used to assess change in thoracic cancer symptoms and health-related Quality of Life (HRQoL). In addition to the LCSS-Meso, the MDASI-MPM will be used to assess change in thoracic cancer symptoms and interference of these symptoms with daily activities.

[…]

### 15.2.2.25 Section 9.6.2 Pregnancies

*Old text:*

[…]

For all reports, the forms provided are to be used. The investigator should submit them within the same timelines as an SAE.

*New text:*

[…]

For all reports, the forms provided are to be used. The investigator should submit them within the same timelines as an SAE.

Only those pregnancies with abnormal outcome need to be reported as SAEs. All pregnancies must be reported on additional pregnancy report forms provided to the site.

### 15.2.2.26 Section 9.6.3.1 Laboratory evaluations

*Old text:*

Safety laboratory analyses will be performed locally according to the schedule summarized in the flow chart of Section 9.1.

- Complete blood count: Hemoglobin, hematocrit, platelet count, white blood cell count (WBC). WBC must include differential including neutrophil, lymphocyte, monocyte, basophil, and eosinophil counts.
- Electrolyte and chemistry panel: sodium, potassium, chloride, calcium, phosphorus, glucose (fasting or random/unspecified), AST, ALT, gamma-glutamyl transferase (GGT), bilirubin (total and direct), ALP, uric acid, total protein, albumin, lipase, amylase, lactic dehydrogenase (LDH), blood urea nitrogen (BUN) or urea, and creatinine.

[…]

*New text:*

Safety laboratory analyses will be performed locally according to the schedule summarized in the flow chart of Section 9.1.

- Complete blood count: Hemoglobin, hematocrit, platelet count, red blood cell count (RBC), white blood cell count (WBC). WBC must include differential including neutrophil, lymphocyte, monocyte, basophil, and eosinophil counts.
- Electrolyte and chemistry panel: sodium, potassium, chloride, calcium (total, corrected, or ionized), phosphorus, glucose (fasting or random/unspecified), AST, ALT, gamma-glutamyl transferase (GGT), bilirubin (total and direct), ALP, uric acid, total protein, albumin, lipase, amylase, lactic dehydrogenase (LDH), blood urea nitrogen (BUN) or urea, and creatinine.

[…]

### 15.2.2.27 Section 9.6.3.6 Cardiac function

*Old text:*

Cardiac function test is mandatory. It will be measured by EchoCG or MUGA scan at full screening and on C2D1, C4D1, and afterwards at the investigator's discretion based on clinical need (see flow chart in Section 9.1). EchoCG shall be performed instead of MUGA when local regulations do not permit the use of MUGA as requested per protocol schedule.

*New text:*

Cardiac function test is mandatory. It will be measured by EchoCG or MUGA scan at full screening and on C2D1, C4D1, and afterwards at the investigator's discretion based on clinical need (see flow chart in Section 9.1). During treatment, cardiac function test can be done up to 7 days before study drug administration. EchoCG shall be performed instead of MUGA when local regulations do not permit the use of MUGA as requested per protocol schedule.

### 15.2.2.28 Section 9.7.1 Biomarkers

*Old text:*

[…]

~~E~~Exploratory biomarker analysis may also be performed using additional fresh tumor tissue to determine alterations in tumor-associated genes and to perform gene expression analysis. Fresh tumor tissue should be collected after a local assessment of response (complete response [CR] or partial response [PR]) for patients who consent to this procedure. The exploratory biomarkers may include, but are not limited to, DNA sequencing of tumor-associated genes and gene expression profiling. Next generation sequencing (NGS), and RNA, protein or miRNA expression analysis may be performed.

[…]

*New text:*

[…]

For patients who provide optional consent, exploratory biomarker analysis may also be performed using additional fresh or archival tumor tissue to determine alterations in tumor-associated genes and to perform gene expression analysis. If additional archival tissue is available after randomization, tissue should be sent for analysis to the central laboratory. Fresh tumor tissue should be collected after a local assessment of response (complete response [CR] or partial response [PR]) for patients who consent to this procedure. The exploratory biomarkers may include, but are not limited to, DNA sequencing of tumor-associated genes and gene expression profiling. Next generation sequencing (NGS), and RNA, protein or miRNA expression analysis may be performed. The analysis of changes in the genomic and expression profile (e.g. mesothelin expression) in tumor tissue over time on drug treatment may elucidate the underlying molecular mechanism of drug response and intrinsic and acquired resistance to anetumab ravtansine.

[…]

### 15.2.2.29 Section 10.2 Analysis sets

*Old text:*

[…]

**PK set.** All patients with valid PK ~~profile~~ for anetumab ravtansine will be included in the analysis set for the anetumab ravtansine PK analysis. All patients with valid PK ~~profile~~ for vinorelbine will be included in the analysis set for the PK analysis of vinorelbine.

[…]

**Quality of life set (QOL).** All randomized patients with a non-missing ~~QoL~~ evaluation at baseline will be included in the QOL dataset. Patients in this set will be reported by treatment arm as randomized. The QOL set will be used for QoL evaluations.

[…]

*New text:*

[…]

**PK set.** All patients with at least one valid PK sample for anetumab ravtansine will be included in the analysis set for the anetumab ravtansine PK analysis. All patients with at least one valid PK sample for vinorelbine will be included in the analysis set for the PK analysis of vinorelbine. PK samples will be considered valid under the following conditions: known dose, known duration of treatment, known time of sample collection.

[…]

**Quality of life set (QOL).** All randomized patients with a non-missing LCSS-Meso evaluation at baseline will be included in the QOL dataset. Patients in this set will be reported by treatment arm as randomized. The QOL set will be used for QoL evaluations.

[…]

### 15.2.2.30 Section 10.3.2 Primary efficacy variable

*Old text:*

[…]

**Primary efficacy analysis**

[…]

~~S~~ensitivity analyses will be performed, ~~including analyses to assess the impact of missing data and the possibility of~~ survivorship and selection biases. ~~Further d~~details will be described in the SAP.

*New text:*

[…]

**Primary efficacy analysis**

[…]

Assumption-checking and sensitivity analyses will be performed, consistent with regulatory guidance on progression-free survival endpoints including Appendix 1 to the EMA guideline on the evaluation of anti-cancer medicinal products in man (36) and the FDA guidance on clinical trial endpoints for the approval of non-small cell lung cancer drugs and biologics (37), including analyses to assess the impact of missing data; the possibility of informative censoring, survivorship, and selection biases; the proportional hazards assumption; and the impact of clinical progression and subsequent therapy. Investigator progression will be evaluated as a sensitivity analysis, and concordance between investigator and independent central review determinations will be evaluated. Details will be described in the SAP.

An updated analysis of PFS will be performed at the time of the final Overall Survival analysis (See Section 10.3.3.1). Details will be described in the SAP.

## 15.2.2.31 Section 10.3.3.1 Secondary efficacy variables

*Old text:*

[…]

**Disease control rate (DCR)**, defined as ~~proportion~~ of patients ~~achieving CR, PR, or SD per mRECIST criteria, as determined by the central radiological reviewer.~~

**Duration of response (DOR)** is defined in responders as the time from documentation of tumor response to disease progression or death without documented progression, as determined by the central radiological reviewer.

**Patient-reported outcomes**

~~**Time to worsening of symptoms characteristic of mesothelioma**, as measured by the MDASI-MPM questionnaire total score of the subset of symptoms. Patients will be considered as "censored" at the date of their last tumor evaluation, if the reason for stopping treatment is not related to PD. Patients dropping out due to progression-related reason or experiencing a PD event or death due to any reason will be considered as having had their deterioration in symptoms at the date of their last tumor evaluation.~~

~~**Time to worsening of pain** based on a 1 or 2 point increase in the "pain at its worst" item of the MDASI-MPM repeated over 2 assessment time points.~~

~~**Time to improvement of symptoms characteristic of mesothelioma**, as measured by the MDASI-MPM questionnaire total score of the subset of symptoms will be evaluated for patients who still have room for improvement in symptoms. Patients will be considered as "censored" at the date of their last MDASI-MPM questionnaire on or before the date of their last tumor evaluation, if the reason for stopping treatment is not related to PD. Patients dropping out due to progression-related reason or experiencing a PD event or death due to any~~

~~reason will be considered censored at the largest observation time (of events and censoring in all patients evaluated for improvement), plus 1 day.~~

~~**Time to improvement of pain** based on a 1 or 2 point decrease in the "pain at its worst" item of the MDASI-MPM repeated over 2 assessment time points.~~

~~Further sensitivity analyses for the MDASI-MPM and the LCSS-Meso will be described in the SAP (e.g. might involve different handling of the last response status for that patient or considering PD and death as censored).~~

**Secondary efficacy analysis**

The secondary efficacy OS analysis tests the following hypotheses:

[…]

At each analysis, OS will also be evaluated be summarized using Kaplan-Meier (33) estimates. Plots will be produced by treatment arm. Medians and Brookmeyer-Crowley (34) confidence intervals will be reported.

~~The final efficacy analysis for other secondary endpoints will be conducted at the time of the primary endpoint analysis.~~

~~Other secondary time-to-event variables (time to worsening of symptoms characteristic of mesothelioma, time to worsening of pain, time to improvement of symptoms characteristic of mesothelioma, time to improvement of pain, DOR) will be summarized using Kaplan-Meier (33) estimates. Plots will be produced by treatment arm. Medians and Brookmeyer-Crowley (34) confidence intervals will be reported.~~

~~Response rate variables (ORR, DCR) will be summarized by treatment arm including number of patients (N), response rates, and Clopper-Pearson (38) exact binomial confidence intervals. In addition, each response category will be summarized. Further details will be described in the SAP.~~

Sensitivity analyses will be performed, including analyses to assess the impact of missing data and the possibility of survivorship and selection biases. Further details will be described in the SAP.

[…]

*New text:*

[…]

**Disease control rate (DCR)**: A patient has disease control if the patient has a confirmed tumor response of CR or PR or a tumor response of SD as determined by the central radiological reviewer per mRECIST criteria. The DCR in each arm is defined as the number of patients with disease control divided by the number of randomized patients.

**Duration of response (DOR)** is defined in responders as the time from documentation of tumor response to disease progression or death without documented progression, as determined by the central radiological reviewer.

**Durable response rate (DRR)**: A durable responder is defined as a responder with a duration of response (CR or PR per mRECIST criteria, as determined by the central radiological reviewer) of 180 days or more. The DRR in each arm is the number of durable responders divided by the number of randomized patients.

**Patient-reported outcomes**

Patient-reported outcomes (PROs) will be evaluated based on the MD Anderson Symptom Inventory-Malignant Pleural Mesothelioma (MDASI-MPM).

An independent PRO review committee of PRO, statistical, and psychometric experts, blinded to study treatment, will conduct analyses based on regulatory feedback, data from independent studies, and pooled study data from this study following database lock at primary analysis, to support validation of the MDASI-MPM instrument and determine key definitions and details as described below.

**Time to worsening of symptoms characteristic of mesothelioma** is defined in patients **evaluable for assessing worsening of symptoms**, as the time from randomization until the first **worsening of symptoms** characteristic of mesothelioma. Worsening must be confirmed by a second MDASI-MPM assessment. Patients who died, were lost to follow-up, or ended MDASI-MPM assessments without confirmed worsening of symptoms will be censored at the date of their last MDASI-MPM assessment with a non-missing **total subset score**.

**Time to worsening of pain** is defined in patients **evaluable for assessing worsening of pain**, as time from randomization until the first **worsening of pain**. Worsening must be confirmed by a second MDASI-MPM assessment. Patients who died, were lost to follow-up, or ended MDASI-MPM assessments without confirmed worsening of pain will be censored at the date of their last MDASI-MPM assessment with a non-missing pain score.

**Improvement rate of symptoms characteristic of mesothelioma** is defined in each randomized study arm as the number of patients with confirmed **improvement of symptoms** characteristic of mesothelioma, divided by the number of patients **evaluable for improvement** of symptoms characteristic of mesothelioma. Improvement in each patient must be confirmed by a second MDASI-MPM assessment.

**Improvement rate of pain** is defined in each randomized study arm as the number of patients with confirmed **improvement of pain**, divided by the number of patients **evaluable for improvement of pain**. Improvement in each patient must be confirmed by a second MDASI-MPM assessment.

For analyses of the above PRO endpoints, the following terms will be defined by the independent blinded PRO review committee:

- **Worsening of symptoms characteristic of mesothelioma** as measured by the MDASI-MPM questionnaire total score of the subset of symptoms.

- **Improvement of symptoms characteristic of mesothelioma** as measured by the MDASI-MPM questionnaire total score of the subset of symptoms.
- **Worsening of pain** as measured by the "pain at its worst" item of the MDASI-MPM.
- **Improvement of pain** as measured by the "pain at its worst" item of the MDASI-MPM.

For each term, the independent blinded PRO review committee will determine the specific change from baseline constituting improvement or worsening, and will define the minimum and/or maximum baseline score and other criteria constituting **evaluability** to determine improvement or worsening for the respective term.

For symptoms characteristic of mesothelioma, the independent blinded PRO review committee will also define the applicable subset of MDASI-MPM items, and the calculation algorithm to calculate **the total subset score** on that subset at each assessment, including handling of missing or partially missing data.

The independent blinded PRO review committee and its analyses will be further described in the Independent Blinded PRO Review Committee Charter and/or the Independent Blinded PRO Review Analysis Plan.

**Secondary efficacy analysis**

For regulatory label claim purposes, to preserve the overall Type I error rate, secondary endpoint hypothesis testing will be performed for the following key secondary efficacy variables in the event of primary endpoint superiority, according to the following hierarchy:

- Overall survival
- Time to worsening of symptoms characteristic of mesothelioma
- Time to worsening of pain
- Improvement rate of symptoms characteristic of mesothelioma
- Improvement rate of pain

Secondary OS will be evaluated separately in a 2-stage group sequential procedure as further described below, with final analysis expected to occur after the primary endpoint analysis.

Final analysis for duration of response and durable response rate will be performed at the time of the final OS analysis. An interim analysis of these variables will be performed at time of the final PFS analysis. Details will be described in the SAP.

Final analysis for other secondary variables will occur at the same time as the primary endpoint analysis. To preserve the validity of the secondary endpoint hierarchy and control of overall study-wide secondary Type I error, superiority for secondary endpoint hypothesis tests ranking below OS in the hierarchy cannot be declared for regulatory label claim purposes until OS hypothesis testing succeeds. Accordingly, unless OS superiority is found at the interim OS analysis, the hypothesis testing outcome of endpoints ranking below it will not be fully effective, and any superiority for these endpoints cannot be declared for regulatory label

claim purposes, until the outcome of the OS hypothesis test is determined and OS superiority found at the final OS analysis. An updated analysis of these secondary variables will occur at time of the final OS analysis.

The secondary efficacy OS analysis tests the following hypotheses:

[…]

At each analysis, OS will also be evaluated be summarized using Kaplan-Meier (33) estimates. Plots will be produced by treatment arm. Medians and Brookmeyer-Crowley (34) confidence intervals will be reported.

Other key secondary time-to-event variables (time to worsening of symptoms characteristic of mesothelioma, time to worsening of pain) will be tested using a 1-sided log-rank test stratified by geographic region (RoW versus Asia) and per TTP on 1st line treatment (≥6 months versus < 6 months), with a 1-sided significance level of 0.025. In addition, all other secondary time-to-event variables (time to worsening of symptoms characteristic of mesothelioma, time to worsening of pain, DOR) will be summarized using Kaplan-Meier (33) estimates. Plots will be produced by treatment arm. Medians and Brookmeyer-Crowley (34) confidence intervals will be reported. Further details will be described in the SAP.

Select secondary response rate variables (improvement rate of symptoms characteristic of mesothelioma, improvement rate of pain) will be tested using a Cochran-Mantel-Haenszel test (40) stratified by geographic region (RoW versus Asia) and per TTP on 1st line treatment (≥6 months versus < 6 months), with a 1-sided significance level of 0.025. In addition, all secondary response rate variables (ORR, DCR, DRR, improvement rate of symptoms characteristic of mesothelioma, improvement rate of pain) will be summarized by treatment arm including number of patients (N), response rates, and Clopper-Pearson (41) exact binomial confidence intervals. In addition, each response category will be summarized. Further details will be described in the SAP.

Sensitivity analyses will be performed, including analyses to assess the impact of missing data and the possibility of survivorship and selection biases. Further details will be described in the SAP.

[…]

### 15.2.2.32 Section 10.3.3.3 Safety variables

*Old text:*

Safety variables will include AEs, laboratory changes (hematology, clinical chemistry and clinical urinalysis), abnormal findings in physical examination, changes in ECOG PS, changes in vital signs (weight, blood pressure, heart rate, respiratory rate, and body temperature), changes in ECG, changes in cardiac function test (EchoCG or MUGA scan) and

changes in ophthalmologic examinations (visual acuity and slit lamp examination, IOP and Schirmer test if repeated).

[…]

*New text:*

Safety variables will include AEs, infusion-related reactions (IRRs), laboratory changes (hematology, clinical chemistry and clinical urinalysis), abnormal findings in physical examination, changes in ECOG PS, changes in vital signs (weight, blood pressure, heart rate, respiratory rate, and body temperature), changes in ECG, changes in cardiac function test (EchoCG or MUGA scan) and changes in ophthalmologic examinations (visual acuity and slit lamp examination, IOP and Schirmer test if repeated).

[…]

### 15.2.2.33 Section 10.3.4.2 Biomarker variables

*Old text:*

[…]

Biomarker variables and analyses will be further described in the SAP.

*New text:*

[…]

Biomarker variables and analyses will be further described in the SAP and/or in a separate document.

### 15.2.2.34 Section 10.4.1 Primary endpoint progression-free survival

*Old text:*

[…]

Assuming a maximum accrual rate of 12.5 patients/month (~~20.83~~ patients/ month screened with ~~40~~% overall screening failure rate) with 6-month linear accrual ramp-up, and a 3.4%/month dropout (loss to follow-up and unevaluable for tumor assessment) rate, 210 patients be will accrued in approximately 19.8 months and reach endpoint maturation of 117 events in approximately 22.0 months.

[…]

*New text:*

[…]

Assuming a maximum accrual rate of 12.5 patients/month (25 patients/ month prescreened with 50% overall pre-screening and screening failure rate) with 6-month linear accrual ramp-up, and a 3.4%/month dropout (loss to follow-up and unevaluable for tumor assessment) rate,

210 patients be will accrued in approximately 19.8 months and reach endpoint maturation of 117 events in approximately 22.0 months.

[…]

## 15.2.2.35 Section 11.1 Data recording

*Old text:*

[…]

**Data recorded from prescreening and full screening failures**

At minimum, the following data should be recorded in the CRF:

- Demographic information (patient number; year of birth / age; sex; if applicable race / ethnicity)
- Date of all informed consent(s)that were signed

[…]

*New text:*

[…]

**Data recorded from prescreening and full screening failures**

At minimum, the following data should be recorded in the CRF:

- Demographic information (patient number; year of birth / age; sex; if applicable race / ethnicity)
- Disease characteristics
- Date of all informed consent(s)that were signed

[…]

## 15.2.2.36 Section 11.4 Missing data

*Old text:*

[…]

Strategies to reduce impact of missing data when present include:

[…]

- Analyses will ensure conservative treatment of missing values. For tumor response endpoints, missing assessments will count as non-responders. For non-time-to-event QoL endpoints, time point analysis will include patients present both at baseline and at the time point, mitigating survivorship bias.

*New text:*

[…]

Strategies to reduce impact of missing data when present include:

[…]

- Analyses will ensure conservative treatment of missing values. For tumor response endpoints, missing assessments will count as non-responders. For non-time-to-event disease symptom and QoL endpoints, time point analysis will include patients present both at baseline and at the time point, mitigating survivorship bias.

### 15.2.2.37 Section 13.1 Investigator(s) and other study personnel

*Old text:*

**Sponsor's medical expert**

Name: PPD
Address: PPD
PPD
Telephone: PPD
Mobile: PPD

[…]

*New text:*

**Sponsor's medical expert**

Name: PPD
Address: PPD
PPD
Telephone: PPD
Mobile: PPD

[…]

### 15.2.2.38 Section 14 Reference list

*Old text:*

4. Stahel RA, Weder W, Lievens Y, Felip E, Group EGW. Malignant pleural mesothelioma: ESMO Clinical Practice Guidelines for diagnosis, treatment and follow-up. Ann Oncol. 2010;21 Suppl 5:v126-8.

*New text:*

4. Stahel RA, Weder W, Lievens Y, Felip E, ESMO Guidelines Working Group. Malignant pleural mesothelioma: ESMO Clinical Practice Guidelines for diagnosis, treatment and follow-up. Ann Oncol. 2010;21 Suppl 5:v126-8.

*New references added by amendment 4:*

36. EMA. Appendix 1 to the guideline on the evaluation of anticancer medicinal products in man, 2012. Available online: http://www.google.fi/url?sa=t&rct=j&q=&esrc=s&source=web&cd=1&cad=rja&uact=8&ved=0ahUKEwi12K62sbbNAhUGbhQKHS-BD5UQFggiMAA&url=http%3A%2F%2Fwww.ema.europa.eu%2Fema%2Fpages%2Fincludes%2Fdocument%2Fopen_document.jsp%3FwebContentId%3DWC500137126&usg=AFQjCNEOUdPPE1LoZOiaWFaz_8VfRiM1mA.

37. FDA. Clinical Trial Endpoints for the Approval of Non-Small Cell Lung Cancer Drugs and Biologics Guidance for Industry, April 2015. Available online: www.fda.gov/downloads/Drugs/.../Guidances/UCM259421.pdf.

40. Agresti A. Categorical Data Analysis. Third Edition. New Jersey: John Wiley & Sons. 2013.

42. Miller AC, Miettinen M, Schrump DS, Hassan R. Malignant mesothelioma and central nervous system metastases. Report of two cases, pooled analysis, and systematic review. Annals of the American Thoracic Society. 2014;11(7):1075-81.

43. Yamagishi T, Fujimoto N, Miyamoto Y, Asano M, Fuchimoto Y, Wada S, et al. Brain metastases in malignant pleural mesothelioma. Clinical & experimental metastasis. 2016;33(3):231-7.

49. Bron AJ, Evans VE, Smith JA. Grading of corneal and conjunctival staining in the context of other dry eye tests. Cornea. 2003;22(7):640-50.

### 15.2.2.39 Section 16.9 Grading staining: Oxford Schema (new addition)

*Old text:*

Not applicable.

*New text:*

*Oxford Schema was added by amendment 4.*

[Oxford Schema not repeated here, see the respective Appendix]

Reference: (49)

## 15.3 Amendment 5

Amendment 5 is a global amendment dated 18 APR 2017.

### 15.3.1 Overview of changes to the study

#### 15.3.1.1 Modification 1: Addition of dextrose as alternative diluent for anetumab ravtansine

Dextrose was added as an alternative diluent for anetumab ravtansine. As anetumab ravtansine is in development, further testing has been performed following feedback on the preparation of the drug and this alternative diluent has been developed.

Sections affected by this modification: Section 7.2.1 Test drug - anetumab ravtansine

#### 15.3.1.2 Modification 2: Clarification regarding the definition of mesothelin overexpression

The definition of mesothelin overexpression was clarified with the addition of moderate and stronger referring to “membrane staining” in at least 30% of “viable” tumor cells for consistency with the language used by Ventana in their protocol and in their communication to Authorities.

Sections affected by this modification: Section 5.1 Design overview, Section 5.3 Justification of the design, Section 6.1.1 Eligibility criteria for prescreening, Section 6.1.2 Eligibility criteria for full study, Section 6.3.1.1.1 Prescreening failure, Section 9.2.3 Treatment period, Section 9.7.1 Biomarkers

#### 15.3.1.3 Modification 3: Clarification regarding continued treatment after centrally confirmed progression and tumor assessment requirements

Clarification was added to the Section of Radiological tumor assessments that patients who have centrally confirmed progression may continue on treatment provided that the patient derives clinical benefit as determined by the treating physician to ensure consistency with the witdrawal criteria for the study. Further details were added to confirm the requirements for tumor assessments for these patients.

Sections affected by this modification: Section 9.4.1 Radiological tumor assessments

#### 15.3.1.4 Modification 4: Addition of parameter for pharmacokinetics samples

Addition of alpha-1 acid glycoprotein (AAG) as a test that may be performed on pharmacokinetic samples to estimate unbound DM4 and DM4-Me exposure.

Sections affected by this modification: Section 9.5 Pharmacokinetics / pharmacodynamics

#### 15.3.1.5 Modification 5: Clarification regarding criteria on continuation of treatment with anetumab ravtansine

In the Section of Continuation of treatment with anetumab ravtansine, a correction has been made to align with the withdrawal criteria and dose modifications to confirm that anetumab

ravtansine can be re-started if the TEAE requiring dose modification has resolved to "Grade ≤ 2" within 6 weeks after the last dose of anetumab ravtansine.

Sections affected by this modification: Section 7.4.2.1.4 Continuation of treatment with anetumab ravtansine

#### 15.3.1.6 Modification 6: Clarification regarding anetumab ravtansine infusion duration

A clarification has been added to confirm that the anetumab ravtansine infusion can be longer than the stipulated 1 hour if following the dose modification guidelines outlined in the protocol.

Sections affected by this modification: Section 7.4.1.1 Administration of anetumab ravtansine

#### 15.3.1.7 Other modifications and corrections

In addition to the modifications specified above, there have been minor corrections for better clarity and consistency.

- List of abbreviations has been updated. Sections affected by this modification: List of abbreviations
- A duplication was removed regarding pathomechanism of the disease in the description of additional biomarkers that may be measured. Sections affected by this modification: Section 9.7.1 Biomarkers
- The PRO review committee was added to the list of external data evaluation bodies since it was mistakenly not added to the list when added to other sections of the protocol by amendment 4. Sections affected by this modification: Section 13.1 Investigator(s) and other study personnel

### 15.3.2 Changes to the protocol text

In the sections on changes to the protocol text, all protocol sections affected by the respective amendment are detailed; the sequence of the sections follows the structure of the most recent previous protocol version. As applicable, changes to the protocol text are highlighted as follows:

- Addition of a whole new portion: Brief identification of the new portion
- Removal of a whole portion: Complete display of the removed portion, formatted as ~~crossed out~~
- Editing of an existing portion: Comparative presentation of "*old text*" versus "*new text*", with "*old text*" referring to the most recent previous protocol version. Deletions are ~~crossed out~~ in the "*old text*". Additions are underlined in the "*new text*".
- Tables / figures: The term "*amended*" is added to the caption.
- Terminological changes: Brief specification of the terminological change

Correction of typos or omissions are not highlighted.

### 15.3.2.1 List of abbreviations

*Old text:*

| | |
|---|---|
| 5-HT3 | 5-hydroxytryptamine (serotonin) |

[…]

*New text:*

| | |
|---|---|
| 5-HT3 | 5-hydroxytryptamine (serotonin) |
| AAG | Alpha-1 acid glycoprotein |

[…]

### 15.3.2.2 Section 5.1 Design overview

*Old text:*

[…]

At the time of the start of study treatment, the patients will have advanced or metastatic MPM recurrent/relapsing after a 1st line treatment with platinum in combination with pemetrexed with or without bevacizumab, and overexpressing mesothelin as determined by immunohistochemistry (IHC). Only patients who demonstrate mesothelin overexpression at the moderate and stronger level by IHC in at least 30% of tumor cells can be randomized into the study.

[…]

*New text:*

[…]

At the time of the start of study treatment, the patients will have advanced or metastatic MPM recurrent/relapsing after a 1st line treatment with platinum in combination with pemetrexed with or without bevacizumab, and overexpressing mesothelin as determined by immunohistochemistry (IHC). Only patients who demonstrate mesothelin overexpression at the moderate and stronger membrane staining level by IHC in at least 30% of viable tumor cells can be randomized into the study.

[…]

### 15.3.2.3 Section 5.3 Justification of the design

*Old text:*

[…]

**Study population.** Objective responses or prolonged SD cases in the 15051 study of anetumab ravtansine occurred in patients ~~with moderate-to-stronger mesothelin expression~~.
[…]

*New text:*

[…]

**Study population.** Objective responses or prolonged SD cases in the 15051 study of anetumab ravtansine occurred in patients who demonstrated mesothelin overexpression at the moderate and stronger membrane staining level by IHC in at least 30% of viable tumor cells. […]

### 15.3.2.4 Section 6.1.1 Eligibility criteria for prescreening

*Old text:*

Overexpression of mesothelin at the moderate and stronger level in at least 30% of tumor cells is a prerequisite to be eligible for this study. […]

*New text:*

Overexpression of mesothelin at the moderate and stronger membrane staining level in at least 30% of viable tumor cells is a prerequisite to be eligible for this study. […]

### 15.3.2.5 Section 6.1.2 Eligibility criteria for full study

*Old text:*

[…]

2. Histological documentation of MPM overexpressing mesothelin at the moderate and stronger level in at least 30% of tumor cells as determined by centrally performed IHC.

[…]

*New text:*

[…]

2. Histological documentation of MPM overexpressing mesothelin at the moderate and stronger membrane staining level in at least 30% of viable tumor cells as determined by centrally performed IHC.

[…]

### 15.3.2.6 Section 6.3.1.1.1 Prescreening failure

*Old text:*

A patient whose tumor tissue is centrally tested by IHC for mesothelin overexpression and whose result is not moderate and stronger mesothelin overexpression in at least 30% of ~~the~~ tumor cells, or who fails to meet any of the other eligibility criteria for prescreening, is regarded as a “prescreening failure”. These patients should not undergo any further screening procedures.

*New text:*

A patient whose tumor tissue is centrally tested by IHC for mesothelin overexpression and whose result is not moderate and stronger membrane staining for mesothelin overexpression in at least 30% of viable tumor cells, or who fails to meet any of the other eligibility criteria for prescreening, is regarded as a "prescreening failure". These patients should not undergo any further screening procedures.

### 15.3.2.7 Section 7.2.1 Test drug - anetumab ravtansine

*Old text:*

[…]

The drug product is available as a lyophilizate. Each vial contains 62.5 mg of anetumab ravtansine; the amount available for administration, based on retractable volume of reconstituted solution, is 60 mg of anetumab ravtansine. It should be reconstituted in water for injection and diluted in 0.9% sodium chloride solution (normal saline) prior to administration as IV infusion.

[…]

*New text:*

[…]

The drug product is available as a lyophilizate. Each vial contains 62.5 mg of anetumab ravtansine; the amount available for administration, based on retractable volume of reconstituted solution, is 60 mg of anetumab ravtansine. It should be reconstituted in water for injection and diluted in 0.9% sodium chloride solution (normal saline) or dextrose 5% solution prior to administration as IV infusion.

[…]

### 15.3.2.8 Section 7.4.1.1 Administration of anetumab ravtansine

*Old text:*

[…]

See Section 9.1 for details on scheduled administrations.

*New text:*

[…]

See Section 9.1 for details on scheduled administrations.

Anetumab ravtansine infusion longer than 1 hour is permitted if following the dose modification guidelines. See Section 7.4.2.1 for details on dose modifications of anetumab ravtansine.

### 15.3.2.9 Section 7.4.2.1.4 Continuation of treatment with anetumab ravtansine

*Old text:*

Treatment with anetumab ravtansine could be re-started at the appropriate dose if the TEAE requiring dose modification has resolved to Grade ≤ 2 within 6 weeks after the last dose of anetumab ravtansine.

*New text:*

Treatment with anetumab ravtansine could be re-started at the appropriate dose if the TEAE requiring dose modification has resolved to Grade ≤ 2 within 6 weeks after the last dose of anetumab ravtansine.

### 15.3.2.10 Section 9.2.3 Treatment period

*Old text:*

After all screening assessments have been completed and the patient's eligibility has been confirmed and documented (confirmation of mesothelin overexpression moderate and stronger in at least 30% of tumor cells will be obtained from central lab and confirmation of radiological eligibility will be obtained from central radiological review), the patient may begin treatment.

*New text:*

After all screening assessments have been completed and the patient's eligibility has been confirmed and documented (confirmation of mesothelin overexpression moderate and stronger membrane staining in at least 30% of viable tumor cells will be obtained from central lab and confirmation of radiological eligibility will be obtained from central radiological review), the patient may begin treatment.

### 15.3.2.11 Section 9.4.1 Radiological tumor assessments

*Old text:*

[…]

In the event of locally suspected progression, the site will inform the central review service and central review will start. Radiological real-time confirmation by central independent blinded evaluation is required before a final decision to stop the treatment is made. The site should also wait for the central review results before administering the next dose of treatment. In case of uncertain radiological disease progression, the patient may stay on treatment at the investigator's discretion until progression is definitely confirmed by central review on the subsequent tumor assessment.

~~When the central review assessment confirms progression, study treatment should be stopped permanently and patient will enter safety follow-up (safety follow-up visit to be scheduled 30+7 days after the last administration of study treatment) and long-term follow-up period.~~

[…]

*New text:*

[…]

In the event of locally suspected progression, the site will inform the central review service and central review will start. Radiological real-time confirmation by central independent blinded evaluation is required before a final decision to stop the treatment is made. The site should also wait for the central review results before administering the next dose of treatment. In case of uncertain radiological disease progression, the patient may stay on treatment at the investigator's discretion until progression is definitely confirmed by central review on the subsequent tumor assessment.

When the central review assessment confirms progression, treatment may be continued if the patient derives clinical benefit as determined by the treating physician per the withdrawal criteria (see Section 6.3.1.2). Otherwise, study treatment should be stopped permanently and patient will enter safety follow-up (safety follow-up visit to be scheduled 30+7 days after the last administration of study treatment) and long-term follow-up period.

Once centrally confirmed radiological progression is reported, protocol tumor assessment requirements end. Subsequent tumor imaging may be performed according to treating physician's discretion if study treatment is continued. The investigator is not required to send imaging taken following centrally confirmed PD to central review, and the central reviewer is not required to review any such imaging sent.

[…]

### 15.3.2.12 Section 9.5 Pharmacokinetics / pharmacodynamics

*Old text:*

[…]

Unscheduled PK samples are requested at the next clinic visit after the initial onset of corneal epitheliopathy and after the radiological assessment of the first PR (the first local observation of at least a 30% reduction in the total tumor measurement according to mRECIST). The date and actual clock time of this unscheduled PK sample and of the last dose of anetumab ravtansine has to be recorded on the CRF as an Unscheduled Procedure.

[…]

*New text:*

[…]

Unscheduled PK samples are requested at the next clinic visit after the initial onset of corneal epitheliopathy and after the radiological assessment of the first PR (the first local observation of at least a 30% reduction in the total tumor measurement according to mRECIST). The date and actual clock time of this unscheduled PK sample and of the last dose of anetumab ravtansine has to be recorded on the CRF as an Unscheduled Procedure.

Measurement of alpha-1 acid glycoprotein (AAG) may be performed in select pharmacokinetic samples to estimate unbound DM4 and DM4-Me exposure.

[…]

### 15.3.2.13 Section 9.7.1 Biomarkers

*Old text:*

Preclinical and Phase I evidence suggests that mesothelin expression (or expression level above a certain threshold) in human tumors may be required for binding, internalization, and anti-tumor activity of anetumab ravtansine. All patients will have formalin-fixed, paraffin-embedded (FFPE) tumor samples available for IHC determination of mesothelin expression at prescreening as a potential predictive biomarker (see also flow chart in Section 9.1). In the absence of archival tissue, fresh biopsies may be used if deemed safe by the investigator and there is no additional risk for the patient in the investigator's judgement. Only patients whose tumors express mesothelin at staining intensity of moderate and stronger in at least 30% of tumor cells will participate further in this study. Mesothelin levels will be determined using a validated IHC assay (clone SP74).

[…]

In addition to the biomarkers listed above, other biomarkers deemed relevant to gain further knowledge about the pathomechanism of the disease or about the drug (i.e. mode of action-related effect or safety of the drug) ~~and/or the pathomechanism of the disease~~ may be measured, based on newly emerging data from other ongoing studies and/or literature data.

[…]

*New text:*

Preclinical and Phase I evidence suggests that mesothelin expression (or expression level above a certain threshold) in human tumors may be required for binding, internalization, and anti-tumor activity of anetumab ravtansine. All patients will have formalin-fixed, paraffin-embedded (FFPE) tumor samples available for IHC determination of mesothelin expression at prescreening as a potential predictive biomarker (see also flow chart in Section 9.1). In the absence of archival tissue, fresh biopsies may be used if deemed safe by the investigator and there is no additional risk for the patient in the investigator's judgement. Only patients whose tumors express mesothelin at membrane staining intensity of moderate and stronger in at least

30% of viable tumor cells will participate further in this study. Mesothelin levels will be determined using a validated IHC assay (clone SP74).

[…]

In addition to the biomarkers listed above, other biomarkers deemed relevant to gain further knowledge about the pathomechanism of the disease or about the drug (i.e. mode of action-related effect or safety of the drug) may be measured, based on newly emerging data from other ongoing studies and/or literature data.

[…]

## 15.3.2.14 Section 13.1 Investigator(s) and other study personnel

*Old text:*

[…]

**Central laboratory**

Biomarker, PK, immunogenicity, mesothelin expression, and CYP2D6 pharmacogenetic tests will be performed centrally. Further details will be provided in the Laboratory Manual.

*New text:*

[…]

**Central laboratory**

Biomarker, PK, immunogenicity, mesothelin expression, and CYP2D6 pharmacogenetic tests will be performed centrally. Further details will be provided in the Laboratory Manual.

**Independent blinded PRO review committee**

An independent PRO review committee of PRO, statistical, and psychometric experts, blinded to study treatment, will conduct analyses based on regulatory feedback, data from independent studies, and pooled study data from this study following database lock at primary analysis, to support validation of the MDASI-MPM instrument and determine key definitions and details regarding secondary PRO endpoints.

## 15.4 Amendment 6

Amendment 6 is a global amendment dated 27 MAR 2018.

### 15.4.1 Overview of changes to the study

#### 15.4.1.1 Modification 1: Evaluations and data collection reduced for patients ongoing on treatment post OS maturation

Following OS data maturation, patients remaining on study will continue to be followed with reduced mandated assessments and data collection. Active follow-up, efficacy, and some safety assessments will no longer be required. New study flow charts (Table 9–2 and Table 9–3) were added for patients ongoing on treatment post OS maturation in anetumab ravtansine and vinorelbine arms, respectively.

The intent of this modification is to continue to treat patients who are benefitting from treatment with a more limited assessment schedule removing all non-essential procedures to reduce the burden on patients.

Sections affected by this modification: Section 2 Synopsis, Section 5.1 Design overview, Section 6.3.1.2 Withdrawal criteria, Section 8.1 Prior and concomitant therapy, Section 9.1 Tabular schedule of evaluations, Section 9.2.3.2 Treatment – Cycle 2 and higher – prior to OS maturation, Section 9.2.3.3 Treatment post OS maturation – anetumab ravtansine arm – Day 1, Section 9.2.3.4 Treatment post OS maturation – vinorelbine arm – Days 1, 8 and 15, Section 9.2.4 Efficacy assessments, Section 9.2.5.1 Safety follow-up prior to OS maturation, Section 9.2.5.2 Safety follow-up post OS maturation, Section 9.2.5.3 Active follow-up, Section 9.2.5.4 Long-term follow-up, Section 9.4.1 Radiological tumor assessments, Section 9.4.3 Patient-reported outcomes, Section 9.5 Pharmacokinetics / pharmacodynamics, Section 9.6.3.1 Laboratory evaluations, Section 9.6.3.3 ECOG Performance Status, Section 9.6.3.4 Vital signs, Section 9.6.3.5 12-lead ECG, Section 9.6.3.7 Ophthalmologic examinations, Section 10.1 General considerations

#### 15.4.1.2 Modification 2: Continuation of collection of survival data post OS maturation

The sponsor will continue to assess survival data on patients after OS data maturation until 24 months after last patient's last treatment. The rationale for this survival data collection is to better understand the total duration of potential clinical benefit and treatment experience of patients with anetumab ravtansine.

Sections affected by this modification: Section 2 Synopsis, Section 5.1 Design overview, Section 6.3.1.2 Withdrawal criteria, Section 9.2.5.4 Long-term follow-up, Section 9.4.2 Survival

#### 15.4.1.3 Modification 3: Clarification of end of study definition

Clarification that end of study is defined by last visit of the last patient within the 15743 study and addition of possibility that treatment or follow up of subjects could continue within a separate program were included. This caveat was added in the event that such a program

would be launched and approved to allow patients to continue treatment and/or be followed up.

Sections affected by this modification: Section 5.4 End of study

#### 15.4.1.4 Modification 4: Modification of withdrawal criteria

Removal of requirement for radiological progression to be centrally confirmed prior to withdrawal as central review will no longer be performed.

Allow delay in administration of anetumab ravtansine for up to 12 weeks as the previous maximum allowed gap of 6 weeks was due to the efficacy endpoint and patients should be allowed to continue as per investigator's discretion if they are benefitting from treatment.

Sections affected by this modification: Section 6.3.1.2 Withdrawal criteria, Section 7.4.2.1.2 Non-hematological toxicities

#### 15.4.1.5 Modification 5: Addition of reference to the investigator's brochure to Clinical experience section

Reference to investigator's brochure for updated safety information and results from this study was added to indicate where this information is available.

Sections affected by this modification: Section 3.1.2 Clinical experience

### 15.4.2 Changes to the protocol text

The detailed description of changes compared to the previous integrated protocol v. 4.0 (amendment 5) is replaced by a "tracked changes" version of the protocol, separate from this document. Changes to the protocol body are tracked in this separate document using strike-through for deleted text and underline for new text.

# 16. Appendices

## 16.1 ECOG Performance Status

| Grade | Description |
|---|---|
| 0 | Fully active, able to carry on all pre-diseases performance without restriction.<br>(Karnofsky 90-100) |
| 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).<br>(Karnofsky 70-80) |
| 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.<br>(Karnofsky 50-60) |
| 3 | Capable of only limited self-care, confined to bed or chair more than 50% of waking hours.<br>(Karnofsky 30-40) |
| 4 | Completely disabled. Cannot carry on any self-care. Totally confined to bed or chair.<br>(Karnofsky 10-20) |

## 16.2 New York Heart Association (NYHA) functional classification

| NYHA Class | Symptoms |
|---|---|
| I | No symptoms and no limitation in ordinary physical activity, e.g. shortness of breath when walking, climbing stairs etc. |
| II | Mild symptoms (mild shortness of breath and/or angina) and slight limitation during ordinary activity. |
| III | Marked limitation in activity due to symptoms, even during less-than-ordinary activity, e.g. walking short distances (20–100 m).<br>Comfortable only at rest. |
| IV | Severe limitations. Experiences symptoms even while **at rest**. Mostly bedbound patients. |

Source (44)

## 16.3 Response assessment

Tumor response will be evaluated in this study using the mRECIST criteria for MPM (21).

At baseline, the pleural disease to be measured should have a short-axis diameter of at least 1 cm for at minimum one of the 6 measurements, as lesions < 1 cm are considered non-measurable *(modified by amendment 2, see section 15.1.1.25)*.

Unidimensional measurements of tumor thickness perpendicular to the chest wall or mediastinum should be performed, measured in 2 sites (or positions) at 3 separate levels on transverse cuts of contrast-enhanced CT scan (or MRI). The sum of the measurements which meet the definition of measurable disease defines a pleural unidimensional measure: sum of up to 6 pleural thickness measurements = 1 univariate diameter. Transverse cuts used for measurements must be at least 1 cm apart and related to anatomical landmarks in the thorax as determined by the reviewer during baseline assessment by means of appropriate markers these cuts are chosen to allow reproducible assessment at later time points. If measureable tumor is present, transverse cuts in the upper thorax, above the level of division of the main bronchi are preferred. At reassessment, pleural thickness must be measured at the same position at the same level and by the same observer, whenever possible. This is not necessarily the greatest tumor thickness at that level *(paragraph modified by amendment 2, see section 15.1.1.25)*.

Nodal, subcutaneous and other bidimensionally non-pleural measurable lesions (e.g. lung) are measured unidimensionally as per the RECIST 1.1 criteria *(modified by amendment 2, see section 15.1.1.25)*. Unidimensional measurements are added to obtain the total tumor measurement.

Due to the natural evolution of disease, an isolated new pleural or pericardial effusion should be only considered as a new lesion and thus calling for PD in case it is substantial, cytological malignancy is confirmed and the patient had not had any pleural or pericardial effusion history before treatment. However, any isolated new or significant increases in existing pleural or pericardial effusions in a stable or responding patient, without any other evidence of progression, is insufficient evidence to call progression.

Additional detailed instruction on the measurement process and on the assessment of tumor response will be provided in the Imaging Manual.

### Response Criteria

**Complete response (CR):** Disappearance of all target lesions. Disappearance of all non-target lesions and normalization of tumor marker level, if applicable. Any pathological lymph nodes (whether target or non-target) must have decreased in size to have a short axis of < 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. No appearance of new lesions. Non-target lesions must be stable or can be not evaluable.

**Progressive disease (PD):** At least a 20% increase in the sum of diameters of target lesions, taking as reference the smallest sum on study = nadir (this includes the baseline sum if that is the smallest on study). In addition to the relative increase of 20%, the sum must also demonstrate an absolute increase of at least 5 mm. For non-target lesions, unequivocal progression of existing lesions represents PD.
*Note: the appearance of one or more new lesions is also considered progression.*

**Stable disease (SD):** Neither sufficient shrinkage to qualify for PR nor sufficient increase to qualify for PD, taking as reference the smallest sum diameters while on study.

Table below provides an overview how the overall response is assessed.

**Overall Response Assessment**

| Target lesions | Non-target lesions | New lesions | Overall response |
|---|---|---|---|
| CR | CR | No | CR |
| CR | Non-CR/Non-PD | No | PR |
| CR | NE | | |
| PR | Non-PD or not all evaluated | | |
| SD | Non-PD or not all evaluated | No | SD |
| NE | Non-PD | No | NE |
| PD | Any | Yes or No | PD |
| Any | PD | Yes or No | |
| Any | Any | Yes | |

CR = Complete response; NE = Not evaluated; PD = Progressive disease; PR = Partial response; SD = Stable disease
Adapted from (45)

## 16.4 National Cancer Institute's Common Terminology Criteria for Adverse Events, version 4.03

This study will utilize the NCI-CTCAE v4.03 for toxicity and SAE reporting by sites. A copy of the CTCAE v4.03 can be downloaded from the website (46).

## 16.5 Patient-reported outcomes

### 16.5.1 MDASI-MPM

**M. D. Anderson Symptom Inventory (MDASI - MPM)**

**Part I.** How **severe** are your symptoms?

People with cancer frequently have symptoms that are caused by their disease or by their treatment. We ask you to rate how severe the following symptoms have been in the ***last 24 hours***. Please select a number from 0 (symptom has not been present) to 10 (the symptom was as bad as you can imagine it could be) for each item.

| | NOT PRESENT 0 | 1 | 2 | 3 | 4 | 5 | 6 | 7 | 8 | 9 | AS BAD AS YOU CAN IMAGINE 10 |
|---|---|---|---|---|---|---|---|---|---|---|---|
| 1. Your **pain** at its WORST? | ○ | ○ | ○ | ○ | ○ | ○ | ○ | ○ | ○ | ○ | ○ |
| 2. Your **fatigue (tiredness)** at its WORST? | ○ | ○ | ○ | ○ | ○ | ○ | ○ | ○ | ○ | ○ | ○ |
| 3. Your **nausea** at its WORST? | ○ | ○ | ○ | ○ | ○ | ○ | ○ | ○ | ○ | ○ | ○ |
| 4. Your **disturbed sleep** at its WORST? | ○ | ○ | ○ | ○ | ○ | ○ | ○ | ○ | ○ | ○ | ○ |
| 5. Your feeling of being **distressed (upset)** at its WORST? | ○ | ○ | ○ | ○ | ○ | ○ | ○ | ○ | ○ | ○ | ○ |
| 6. Your **shortness of breath** at its WORST? | ○ | ○ | ○ | ○ | ○ | ○ | ○ | ○ | ○ | ○ | ○ |
| 7. Your problem with **remembering things** at its WORST? | ○ | ○ | ○ | ○ | ○ | ○ | ○ | ○ | ○ | ○ | ○ |
| 8. Your problem with **lack of appetite** at its WORST? | ○ | ○ | ○ | ○ | ○ | ○ | ○ | ○ | ○ | ○ | ○ |
| 9. Your feeling **drowsy (sleepy)** at its WORST? | ○ | ○ | ○ | ○ | ○ | ○ | ○ | ○ | ○ | ○ | ○ |
| 10. Your having a **dry mouth** at its WORST? | ○ | ○ | ○ | ○ | ○ | ○ | ○ | ○ | ○ | ○ | ○ |
| 11. Your feeling **sad** at its WORST? | ○ | ○ | ○ | ○ | ○ | ○ | ○ | ○ | ○ | ○ | ○ |
| 12. Your **vomiting** at its WORST? | ○ | ○ | ○ | ○ | ○ | ○ | ○ | ○ | ○ | ○ | ○ |
| 13. Your **numbness or tingling** at its WORST? | ○ | ○ | ○ | ○ | ○ | ○ | ○ | ○ | ○ | ○ | ○ |

| | NOT PRESENT 0 | 1 | 2 | 3 | 4 | 5 | 6 | 7 | 8 | 9 | AS BAD AS YOU CAN IMAGINE 10 |
|---|---|---|---|---|---|---|---|---|---|---|---|
| 14. Your **coughing** at its WORST? | ○ | ○ | ○ | ○ | ○ | ○ | ○ | ○ | ○ | ○ | ○ |
| 15. Your **feeling of malaise (not feeling well)** at its WORST? | ○ | ○ | ○ | ○ | ○ | ○ | ○ | ○ | ○ | ○ | ○ |
| 16. Your trouble with your **balance or falling** at its WORST? | ○ | ○ | ○ | ○ | ○ | ○ | ○ | ○ | ○ | ○ | ○ |
| 17. Your **chest heaviness or tightness** at its WORST? | ○ | ○ | ○ | ○ | ○ | ○ | ○ | ○ | ○ | ○ | ○ |
| 18. Your **muscle weakness** at its WORST? | ○ | ○ | ○ | ○ | ○ | ○ | ○ | ○ | ○ | ○ | ○ |
| 19. Your **eye problems** at its WORST? | ○ | ○ | ○ | ○ | ○ | ○ | ○ | ○ | ○ | ○ | ○ |

**Part II. How have your symptoms interfered with your life?**

**Symptoms frequently interfere with how we feel and function. How much have your symptoms interfered with the following items in the last 24 hours:**

| | DID NOT INTERFERE 0 | 1 | 2 | 3 | 4 | 5 | 6 | 7 | 8 | 9 | INTERFERED COMPLETELY 10 |
|---|---|---|---|---|---|---|---|---|---|---|---|
| 20. **General activity?** | ○ | ○ | ○ | ○ | ○ | ○ | ○ | ○ | ○ | ○ | ○ |
| 21. **Mood?** | ○ | ○ | ○ | ○ | ○ | ○ | ○ | ○ | ○ | ○ | ○ |
| 22. **Work (including work around the house)?** | ○ | ○ | ○ | ○ | ○ | ○ | ○ | ○ | ○ | ○ | ○ |
| 23. **Relations with other people?** | ○ | ○ | ○ | ○ | ○ | ○ | ○ | ○ | ○ | ○ | ○ |
| 24. **Walking?** | ○ | ○ | ○ | ○ | ○ | ○ | ○ | ○ | ○ | ○ | ○ |
| 25. **Enjoyment of life?** | ○ | ○ | ○ | ○ | ○ | ○ | ○ | ○ | ○ | ○ | ○ |

## 16.5.2 LCSS-Meso

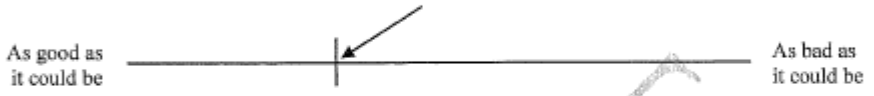
**LCSS-Meso: Patient Scale**

Quality of Life Research Associates, LLC © 2013

*Directions:* Please place a mark along each line where it would best describe the symptoms of your lung illness DURING THE PAST DAY (within the last 24 hours).

**Example Question:**

**How good is the weather?**




**1. How good is your appetite?**


**2. How much fatigue do you have?**


**3. How much coughing do you have?**


**4. How much shortness of breath do you have?**

**5. How much pain do you have?**

None |_____| As much as it could be

**6. How bad are your symptoms from your lung illness?**

I have none |_____| As bad as they could be

**7. How much has your lung illness affected your ability to carry out normal activities?**

Not at all |_____| So much that I can do nothing for myself

**8. How would you rate the quality of your life today?**

Very high |_____| Very low

## 16.6 CYP3A4 inhibitors and inducers

Table below provides an overview of strong CYP3A4 inhibitors and inducers.

| Strong CYP3A4 inhibitors | Strong CYP3A4 inducers |
|---|---|
| Boceprevir | Avasimibe |
| Clarithromycin | Carbamazepine |
| Conivaptan | Phenytoin |
| Grapefruit juice | Rifampin |
| Indinavir | St. John's wort |
| Itraconazole | |
| Ketoconazole | |
| Lopinavir / Ritonavir | |
| Mibefradil (withdrawn in the US) | |
| Nefazodone | |
| Nelfinavir | |
| Posaconazole | |
| Ritonavir | |
| Saquinavir | |
| Telaprevir | |
| Telithromycin | |
| Voriconazole | |

CYP3A4 = Cytochrome P450, family 3, subfamily A, polypeptide 4
Source (47)

## 16.7 Calculation of glomerular filtration rate by the Modification of Diet in Renal Disease formula

In accordance with established nephrology practice and guidelines, renal function at baseline and throughout the study will be assessed by means of the estimated GFR, calculated using the abbreviated MDRD study formula.

This equation of 4 variables (serum creatinine level, age, sex, and ethnicity) is recommended by the National Kidney Foundation for use in individuals 18 years or older. The formula can be found at the following website (48).

Patients with a baseline GFR < 30 mL/min/1.73 $m^2$ calculated by this method will not be allowed to participate in the study.

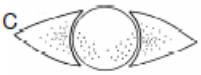
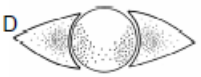
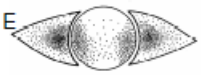
## 16.8 Mosteller Equation for calculation of body surface area (BSA)

BSA ($m^2$) = SQR RT ([Height(cm) x Weight(kg) ]/ 3600 )

Where SQR RT is square root (√).

## 16.9 Grading staining: Oxford Schema

*Oxford Schema was added by amendment 4.*

<table>
<tr><td>DEWS</td><td>DRY EYE: DIAGNOSTIC TEST TEMPLATE</td><td></td></tr>
<tr><td>RAPPORTEUR</td><td>A.J.Bron</td><td>21st Oct 2004</td></tr>
<tr><td>TEST</td><td>Grading staining: Oxford Schema</td><td></td></tr>
<tr><td>TO DIAGNOSE</td><td>The scheme is used to estimate surface damage in dry eye.</td><td>REFERENCES</td></tr>
<tr><td>VERSION of TEST</td><td>[ V 1 ]</td><td></td></tr>
<tr><td>DESCRIPTION</td><td>Surface damage to the exposed eye, assessed by staining, is graded against standard charts.</td><td></td></tr>
<tr><td>NATURE of STUDY</td><td>N. A.</td><td></td></tr>
<tr><td>CONDUCT of TESTS</td><td>Grading Schema:<br>Staining is represented by punctate dots on a series of panels (A-E). Staining ranges from 0-5 for each panel and 0-15 for the total exposed inter-palpebral conjunctiva and cornea. The dots are ordered on a log scale
<table>
<tr><th>PANEL</th><th>GRADE</th><th>CRITERIA</th></tr>
<tr><td>A  </td><td>0</td><td>Equal to or less than panel A</td></tr>
<tr><td>B  </td><td>I</td><td>Equal to or less than panel B, greater than A</td></tr>
<tr><td>C  </td><td>II</td><td>Equal to or less than panel C, greater than B</td></tr>
<tr><td>D  </td><td>III</td><td>Equal to or less than panel D, greater than C</td></tr>
<tr><td>E  </td><td>IV</td><td>Equal to or less than panel E, greater than D</td></tr>
<tr><td>>E</td><td>V</td><td>Greater than panel E</td></tr>
</table>
Conduct of Test:<br>• Dye is instilled.<br>• Slit-lamp is set (eg.16 magnification with x10 oculars with Haag-Streit).<br>• Cornea: The upper eyelid is lifted slightly to grade the whole corneal surface,<br>• Conjunctiva: To grade the temporal zone, the subject looks nasally; to grade the nasal zone the subject looks temporally.<br>• (The upper and lower conjunctiva can also be</td><td>Bron Evans Smith 2003.</td></tr>
</table>

| | | |
|---|---|---|
| | graded).<br>**Selection of dyes:**<br>A list dyes and filters can be found in the original paper.<br>With fluorescein, staining must be graded as quickly as possible after instillation, since the dye then diffuses rapidly into the tissue and its high luminosity blurring the stain margin.<br>Staining after rose bengal or lissamine green, persists at high contrast and may therefore be observed for a considerable period. This is convenient for both grading and photography.<br><br>**Fluorescein sodium**<br>**1. Quantified drop instillation**<br>eg 2 µl of 2 % sterile fluorescein instilled into each conjunctival sac with a micro-pipette (using a sterile tip). In very dry eye, larger volumes risk the possibility of inadequate dilution into the fluorescent range.<br>**2. Unquantified instillation – impregnated paper strips**<br>This is a convenient approach in the clinic using the following method of application:<br>• A single drop of unit dose saline is instilled onto a fluorescein-impregnated strip.<br>• When the drop has saturated the impregnated tip, the excess is shaken into a waste bin with a sharp flick.<br>• The right lower lid is then pulled down and the strip is tapped onto the lower tarsal conjunctiva. A similar procedure is carried out on the left.<br>If too large a volume is delivered then the concentration in the tear film will be too high, and the tear film and staining pattern will be non-fluorescent.<br>**3.Timing**<br>The fluorescein break-up time (FBUT) is usually performed prior to grading. Since fluorescein diffuses rapidly into tissues, punctate staining blurs after a short period. It is therefore essential to assess staining rapidly, in sequence, in the right and then the left eye, so that the staining patterns observed are equally crisp.<br>If it is intended to photograph the staining pattern for grading, then photography should follow immediately after each instillation.<br><br>**Exciter and Barrier Filters**<br>The absorption peak of fluorescein sodium occurs between 465 - 490 nm and the emission peak between 520 - 530 nm A suggested filter pair for detection of fluorescein staining is a yellow, Kodak Wratten 12 barrier filter (transmitting above 495 nm) or an orange Wratten 15 filter (transmitting above 510 nm) in combination with a blue Wratten 47 or 47A exciter filter. The 47A shows greater transmittance than the Wratten 47 over the absorption range. The 'cobalt' filter of many slit-lamps is suitable to use with a Wratten 12 or 15 | |

| | | |
|---|---|---|
| | barrier.<br><br>Where more light is required for photographic purposes, narrow band-pass, interference filters can be used.<br><br>The use of both exciter and barrier filters allows both the cornea and conjunctiva to be assessed using a single stain. This is a major advantage in clinical trials where it is otherwise customary to employ fluorescein to grade corneal staining and rose bengal or lissamine green to grade conjunctival staining.<br><br>**Disadvantages of Fluorescein Staining**<br>Blurred pattern if reading is delayed. Delay in photographing fluorescein staining results in blurred images of the staining pattern.<br><br>**Rose Bengal**<br>The intensity of rose bengal staining is dose dependent. If drop size or concentration is reduced to minimize stinging, the amount of staining is also reduced. Use of impregnated strips will give weaker staining than use of a full drop of 1% solution. Best results are achieved with, eg. 25 µl 1%, instilled into the conjunctival sac. Because rose bengal stings, instillation is best preceded by a topical anesthetic.<br><br>**Instillation Technique**<br>1) eg. A drop of Proxymetacaine is instilled into the conjunctival sac followed, after recovery, by;<br>2) A drop of rose bengal 1.0%. This is instilled onto the upper bulbar conjunctiva with the upper lid retracted and the patient looking down.<br>3) Since both anaesthetic and drop may stimulate reflex tearing, the test should follow measurement of the FBUT and of the Schirmer test. (Conjunctival staining due to insertion of the Schirmer paper can usually be distinguished from that due to dry eye disease).<br><br>Both eyes may be stained prior to grading, since there is no risk of the staining pattern in the first eye being obscured by the time the second eye is graded.<br><br>The cited paper gives advice about avoidance of overspill.<br><br>**Visibility**<br>Rose bengal staining on the conjunctiva shows up well against the sclera and may be enhanced using a red-free (green) light source. Corneal staining may show up well against a blue iris, but is difficult to see against a dark brown iris.<br><br>**Phototoxicity**<br>Photo-activation of rose bengal by sunlight increases post-instillation symptoms, especially in severe dry eye with heavy staining. This post-instillation pain can be minimised | |

<table>
<tr><td></td><td>by liberal irrigation with normal saline at the end of the test.<br><br>Lissamine green stains the eye in a similar manner to rose bengal but is as well tolerated as fluorescein. Visibility and dose-dependency are the same as rose bengal and staining is persistant so that photography need not be performed immediately after instillation.<br>Lissamine green is available as impregnated strips or may be ordered as a pre-prepared solution. A 25 µl 1% drop will give more intense staining. Because the drop is well tolerated, no anaesthetic is required.<br><br>Visibility<br>As with rose bengal, lissamine green staining is easily visible on the conjunctiva. On the cornea, staining is seen well against a light blue iris background but is poorly visible against a dark brown iris background. For both rose bengal and lissamine green, because the dyes are poorly seen within the tear film, the dye in the tear film does not obscure the staining pattern. Also, since both dyes do not diffuse into the substantia propria of the conjunctiva, the staining pattern is retained for longer.<br><br>Visibility of staining may be enhanced using a white light source and a red barrier filter, to give a black pattern on a red ground. A suitable filter is a Hoya 25A, or a Kodak Wratten 92.</td><td></td></tr>
<tr><td>Web Video</td><td>Not available</td><td></td></tr>
<tr><td>Materials:</td><td>Oxford Grading Charts - available from A J Bron anthony.bron@eye.ox.ac.uk</td><td></td></tr>
<tr><td>Standardization</td><td>Nil additional</td><td></td></tr>
<tr><td>Variations of technique</td><td></td><td></td></tr>
<tr><td>Diagnostic value</td><td>No stats supplied.</td><td></td></tr>
<tr><td>Repeatability</td><td>A small intra-interobserver study was carried out in 1986 and was presented but not published:<br><br>Intra-observer study: This study asked two trained ophthalmologists to grade a series of standard slides, showing corneal and conjunctival fluorescein staining, on 2 separate occasions. [note: -this study is only relevant to grading photographic records not patients.]<br><br>Intra-observer κ for grading photographs of staining, using the Oxford scheme. Two observers.<br><table><tr><td></td><td>Cornea</td><td>Conjunctiva</td></tr><tr><td>Observer 1</td><td>0.86</td><td>0.69</td></tr><tr><td>Observer 2</td><td>0.65</td><td>0.83</td></tr></table><br>Not that values are in the good to excellent range.<br><br>Inter-observer study: In this study, the same 2 observers</td><td>Hardman Lea et al. 1986 AER abstract.</td></tr>
</table>

<table>
<tr><td></td><td>graded fluorescein staining (blue exciter; yellow filter) in 13 dry eye patients at an interval within 2-3 weeks.<br><br>Inter-observer κ for grading patients with dry eye, using the Oxford scheme. Two observers. Fluorescein; bengal rose<br><table><tr><td>Observer 1 v 2</td><td>Cornea</td><td>Conjunctiva</td></tr><tr><td>Fluorescein</td><td>0.88</td><td>0.48</td></tr><tr><td>Bengal rose</td><td>0.87</td><td>0.54</td></tr></table><br>It is of interest that observations are in the excellent category for cornea, with either stain and in the fair category for conjunctiva.</td><td></td></tr>
<tr><td>Sensitivity</td><td>(true positives) [ - ]</td><td></td></tr>
<tr><td>Specificity</td><td>(100 – false positives) [ - ]</td><td></td></tr>
</table>

**References:**

Bron A, Evans VE, Smith JA. (2003). Grading of corneal and conjunctival staining in the context of other dry eye tests. *Cornea* 22(7): 640-50.

Reference: (49)