CLINICAL STUDY PROTOCOL

A Phase 1/2a Open Label, Multicenter Study to Assess the Safety, Tolerability, Pharmacokinetics and Preliminary Efficacy of AFM24 in Patients with Advanced Solid Cancers

Protocol No.: AFM24-101

Version No: V10.0

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EudraCT No: 2019-003296-19

IND No.: 143500

Affimed GmbH

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PROTOCOL APPROVAL SIGNATURES

Sponsor's Approval:

This study will be conducted in compliance with International Council for Harmonisation (ICH) guidelines on Good Clinical Practice (GCP), the Declaration of Helsinki (with amendments), and in accordance with local legal and regulatory requirements, including data privacy laws.

This protocol, V10.0 dated 26 July, 2023, has been approved by Affimed GmbH.

Signature: ..... **Date:** .....

[redacted]

Signature: ..... **Date:** .....

[redacted]

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[redacted]

INVESTIGATOR'S DECLARATION AND APPROVAL

I have read this protocol and agree that it contains all the necessary details for carrying out this study. I will conduct the study as described in the current, approved protocol. I verify that I am suitably qualified by education, scientific, and medical training and experience to conduct the study. Documentation of my qualifications and professional affiliations are contained in my up-to-date curriculum vitae provided to the Sponsor.

I will provide the supplied copies of the protocol, including future protocol amendments, and all information relating to non-clinical and clinical experience when available (e.g., in updated editions of the Investigator's Brochure [IB]), to all staff involved in the conduct of this study. I will discuss this material with them to ensure that they are fully conversant with the investigational medicinal product and study design, and that they will handle the data and information generated in the study confidentially.

I will conduct the study in accordance with Good Clinical Practice, the Declaration of Helsinki, and the moral, ethical, and scientific principles that justify medical research. I acknowledge that the study will be conducted in accordance with the relevant laws and regulations relating to clinical studies and the protection of subjects, including data privacy laws. I confirm it is my duty and the duty of my study staff to ensure participating subjects are informed comprehensively about the nature of the study and will give their written consent to participate before entry into the study. Subjects will be informed that they may withdraw from the study at any time without jeopardizing their future care. I will use only the subject informed consent form approved by the Sponsor and the Ethics Committee/Institutional Review Board for this study. I will supply the Sponsor with any written material prepared by myself or my study staff, e.g., summary of study, which is given to the Ethics Committee/Institutional Review Board in support of the application.

Where applicable, the subject information contained in clinic records, reports, and manuscripts will be transcribed to the study case report forms. I (or my delegates as described in my Study File) will attest to the authenticity of the data and accuracy and completeness of the transcription by signing the case report forms. I agree to the audit and monitoring procedures to verify study records against original records. Should it be requested by government regulatory agencies, I will make available additional background data from my records and from the hospital or institution where the study was conducted (as permitted by the hospital or institution).

I understand that the case report forms and other data pertinent to this study are the property of Affimed GmbH and are confidential. I agree to only supply Affimed GmbH (or their delegates) with subject study data in such a way that the subject cannot be personally identified.

Investigator: …… ……..

Signature Date

Print Name: ……..

Institution Name: ……

Institution Address: ……

OTHER CONTACT INFORMATION

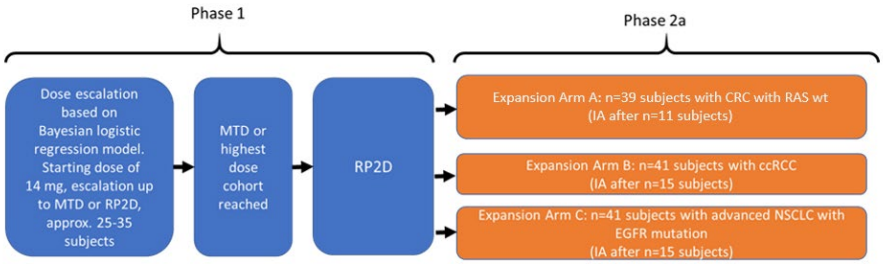
Full contact details for each Investigational site, the Sponsor, the Medical Monitor(s), and key coordinating and operational personnel will be maintained in the Trial Master File and in each site's Study File throughout the course of the study.

PROTOCOL SYNOPSIS

Study Title	A Phase 1/2a Open-Label, Multicenter Study to Assess the Safety, Tolerability, Pharmacokinetics and Preliminary Efficacy of AFM24 in Patients with Advanced Solid Cancers
Investigational Product	AFM24
Protocol Number	AFM24-101
EudraCT Number	2019-003296-19
IND Number	143500
Sponsor and Contract Research Organization	**Sponsor**: Affimed GmbH **Contract Research Organization**: PSI CRO AG
Study Phase	1/2a
Study Regions	Multicenter; United States, Europe, and Asia Pacific
Rationale	AFM24 is a first-in-class, tetravalent, bispecific, fragment crystallizable (Fc)-silenced antibody designed to target epidermal growth factor receptor-expressing ($EGFR^+$) solid tumors. Of its 4 binding sites, 2 binding sites are specific for EGFR; the other 2 binding sites are specific for CD16A, which is the Fcγ receptor expressed by natural killer (NK) cells and macrophages. AFM24 was designed to utilize the cytotoxic potential of NK cells and macrophages for the elimination of $EGFR^+$ cancer cells, offering a novel therapeutic approach to target $EGFR^+$ tumors with active immunotherapy. This bispecific innate immune cell recruiting antibody binds to both $EGFR^+$ cancer cells and $CD16A^+$ NK cells and macrophages with strong avidity, thus creating an immunological synapse. This results in antibody-dependent cellular cytotoxicity (ADCC; induced by NK cells) and antibody-dependent cellular phagocytosis (ADCP; induced by macrophages) of $EGFR^+$ tumor cells, thereby activating a potent antitumor immune response. At high concentrations, AFM24 can also down-modulate ligand-induced EGFR signaling. Due to its ADCC- and ADCP-related mode of actions, it is anticipated that AFM24 would be active in patients who harbor $EGFR^+$ cancers, potentially also including cancers that have intrinsic or acquired resistance to EGFR targeting monoclonal antibodies (mAbs) and tyrosine kinase inhibitors (TKIs). Therefore, AFM24 has the potential to overcome the limitations of EGFR-targeting standard of care (SOC) mAbs and TKIs. In addition, it is anticipated that AFM24 would have an improved safety profile compared with these SOC agents. Patients with previously treated advanced or metastatic solid tumor malignancies that express EGFR represent patient populations with high unmet medical need due to the associated poor prognosis and limited number of effective treatment options available. NK cells and macrophages have an intrinsic ability to eliminate tumor cells; however, innate immunity is often suppressed in cancer patients. By utilizing AFM24 to redirect and activate such immune cells it may be possible to release the antitumor potential of patients' own innate immunity to effectively control their cancers.

Study Objectives	**PHASE 1** **Primary Objective:** • Determine the maximum tolerated dose (MTD), select one or more recommended phase 2 doses (RP2Ds), and investigate the safety and tolerability of AFM24 in subjects with advanced or metastatic solid malignancies. **Secondary Objectives:** • Characterize the safety and tolerability of AFM24, including both acute and chronic toxicities; • Characterize the pharmacokinetics (PK) of AFM24 administered intravenously (i.v.); • Characterize the immunogenicity of AFM24; and • Assess the preliminary antitumor efficacy of AFM24. **Exploratory:** • Assess the preliminary antitumor efficacy of AFM24, using Response Evaluation Criteria in Solid Tumors for immunotherapy (iRECIST) tumor response criteria; • Assess AFM24 pharmacodynamics **PHASE 2a** **Primary Objective:** • Assess the preliminary antitumor efficacy of AFM24, by local Response Evaluation Criteria in Solid Tumors (RECIST) v1.1. **Secondary Objectives:** • Characterize the safety and tolerability of AFM24, including both acute and chronic toxicities; • Characterize the PK of AFM24 administered i.v.; • Characterize the immunogenicity of AFM24; and • Assess the preliminary antitumor efficacy of AFM24. **Exploratory:** • Assess the preliminary antitumor efficacy of AFM24, using iRECIST tumor response criteria; • Assess AFM24 pharmacodynamics • Explore the predictive potential of biomarkers measured in blood and/or tumor tissue in response to AFM24
Methodology	AFM24-101 is a first in human (FIH), Phase 1/2a, open-label, non-randomized, multicenter, multiple ascending dose escalation/expansion study evaluating AFM24 as monotherapy in subjects with advanced or metastatic solid malignancies whose disease has progressed after treatment with previous anticancer therapies. There will be 2 parts to this study: a dose escalation phase (Phase 1) and a dose expansion phase (Phase 2a). The aim of the dose escalation phase is to determine the MTD and/or establish one or more RP2Ds. An adaptive 2-parameter Bayesian logistic regression model (BLRM) guided by the dose escalation with overdose control (EWOC) will be used in the escalation phase to guide determination of the MTD and/or RP2D in subjects with advanced or metastatic solid malignancies. The dose escalation phase (Phase 1) will be followed by the dose expansion phase (Phase 2a) once the MTD and/or at least one RP2D of AFM24 monotherapy has been determined. The dose expansion phase (Phase 2a) of the study is intended to collect preliminary evidence of antitumor efficacy and to further confirm the safety of AFM24 as monotherapy in distinct patient populations. The expansion phase will have 3 cohorts based on tumor type. An overview of study design is provided in Figure 1.

	The expansion cohorts may be opened in parallel or subsequently. Based on the findings in the Phase 1 part of the study, additional treatment schedules (i.e., every 2 weeks [q2w] dosing) may be explored in the Phase 2a expansion cohorts. An overview of the study scheme for each subject in weekly and q2w is described in Figure 5 and Figure 6 respectively. For each subject, the study starts with provision of written informed consent, followed by a screening phase lasting up to 21 days. For Phase 2a only, pre-screening will be required for subjects to determine whether eligibility criteria for EGFR expression (for subjects without a positive EGFR test) have been met prior to entering the screening phase (**Note:** if a positive EGFR test has been performed from a subject's tumor tissue, and the EGFR laboratory report is available, the subject can proceed directly to the screening activities). Following the up to 21-day screening phase, eligible subjects will be treated with AFM24 administered as an i.v. infusion for as long as they continue to show clinical benefit, as judged by the Investigator, or until disease progression, intolerable toxicity, Investigator discretion, subject withdrawal of consent, or other discontinuation criteria are met. After the end of treatment, subjects will be followed for duration of response (DOR), progression-free-survival (PFS) and overall survival (OS) until the end of the study, which is defined as the date the last subject ending treatment has completed the first Long-term Follow-Up interval. To minimize the number of subjects treated at potentially subtherapeutic dose levels in the dose escalation phase (Phase 1), cohorts 1 and 2 will enroll minimum 2 subjects, whereas cohorts 3 and above will enroll 3 to 4 subjects. In cohorts 3 and above, a fourth subject may be enrolled if treatment of the fourth subject is anticipated to begin within 14 days of treatment initiation of the third subject in the cohort. Treatment in each cohort will begin in a staggered approach with at least 7 days between the first dose of the first subject and the first dose of subsequent subjects. After the first subject in each cohort has begun treatment and been observed for at least 7 days, additional subjects within the cohort may begin treatment concurrently. In cohorts 1 and 2, a minimum of 2 subjects in each cohort need to be treated and complete the 28-day dose-limiting toxicity (DLT) observation period before the Safety Review Committee (SRC) may convene and decide on the dose level for the next cohort of subjects. In Cohorts 3 and above, a minimum of 3 subjects in each cohort need to be treated and be evaluable for DLT assessment to allow for a dose escalation decision by the SRC. All subjects who start treatment need to complete the 28-day DLT observation period or experience a DLT before the SRC meeting and dose escalation decision (minimum of 2 patients in cohorts 1/2 and 3 patients in cohorts 3/4). The dose cohorts might be escalated, de-escalated or expanded to up to 6 subjects based on the SRC decision. Dose escalation decisions will be made by the SRC, consisting of the Principal Investigators at each study center and the Sponsor's Medical representative(s), and additional clinical experts, as needed. The BLRM will be assessed for all subjects in the dose-determining set (DDS) consisting of all subjects who received at least 1 dose of AFM24, and either experienced a DLT at any time during Cycle 1 or met the minimum treatment and safety evaluation requirements without experiencing a DLT within Cycle 1. After completion of a given dose cohort, or at any time the BLRM is updated, the decision to dose escalate and the actual dose chosen will be based on the recommendation of the BLRM regarding the highest admissible dose according to the EWOC principle and the medical review of all available clinical, laboratory, and PK data. The outcome of these analyses and the respective datasets will be reviewed by the SRC. The SRC will then decide the dose level selection of the next dose cohort prior to enrollment. In the event of a Common Terminology Criteria for Adverse Events (CTCAE) Grade 5 adverse event (AE) or a second CTCAE Grade 4 AE at least possibly related to AFM24 at any time during Phase 1, the Sponsor will suspend further accrual and the Sponsor will perform a safety analysis that will be reviewed by an ad-hoc SRC meeting to decide on further progression of the study.

	Prior to initiation of dose expansion phase (Phase 2a), an Independent Data Monitoring Committee (IDMC) will be established consisting of clinical experts who are not directly involved in this clinical study. The IDMC will review all safety data generated throughout the dose expansion phase (Phase 2a) part of the study on a regular basis. Based on the outcome of their review, the IDMC will provide recommendations to the Sponsor with regard to study conduct or study procedures. The set-up and operational process for this IDMC will be described in a separate IDMC charter. Once at least one RP2D dose has been determined, enrollment into 1 or more expansion cohorts for selected cancer indication in Phase 2a will begin (Figure 1). Other expansion cohorts may follow with the same or a different RP2D dose level. An optimum Simon's two-stage design will be applied for the preliminary efficacy analyses for the following expansion cohorts. • Expansion Cohort A will enroll up to a total of 39 subjects with microsatellite stable colorectal cancer (CRC) with rat sarcoma gene (RAS) wild-type tumor, the interim analysis (IA) will be conducted after 11 subjects; • Expansion Cohort B will enroll up to a total of 41 subjects with clear cell "renal cell carcinoma (ccRCC), the IA was planned after 15 subjects. However, Cohort A and C did not meet the criteria for continuation based on objective response (OR) and were stopped for futility. It is considered unlikely that the continuation criteria can be met in Cohort B. Hence it was decided to prematurely stop enrolment after 8 patients in Cohort B. • Expansion Cohort C will enroll up to a total of 41 subjects with advanced or metastatic non-small cell lung cancer (NSCLC) with an EGFR mutation, the IA will be conducted after 15 subjects **Figure 1: Overall Study Design**  approx. = approximately; ccRCC = clear cell renal cell carcinoma; CRC = colorectal cancer; EGFR = epidermal growth factor receptor; MTD = maximum tolerated dose; NSCLC = non-small cell lung cancer; RAS = rat sarcoma gene; RP2D = recommended phase 2 dose; wt = wild type.
Number of Subjects (planned)	Approximately 25 to 41 subjects will be enrolled in the dose escalation phase (Phase 1), dependent on the tested dose cohorts and the safety profile of AFM24. Additionally, 3 expansion cohorts, with up to a total of 39, 41, and 41 subjects in Cohorts A, B, and C, respectively, will be enrolled in the dose expansion phase (Phase 2a), for a maximum of 121 subjects. Depending on the preliminary efficacy observed in the dose escalation phase (Phase 1) of the study, additional expansion cohorts may be added by a protocol amendment.

Diagnosis and Main Criteria	Subjects will be considered eligible to be enrolled in the study if ALL of the inclusion criteria and NONE of the exclusion criteria are met as defined below. Prospective approval of protocol deviations to recruitment and enrollment criteria, also known as protocol waivers or exemptions, is not permitted. Please note that based on various guidelines (e.g., *NCCN Guidelines: Cancer and COVID-19 Vaccination Advisory Committee. Version 8.0;Jun 03, 2023 MHRA Guidance on Coronavirus [COVID-19]* [MHRA 2021]), COVID-19 vaccination should be prioritized for subjects with cancer with the understanding that there are limited safety and efficacy data in this subject group. These guidelines also state: • "Delay of vaccination until immunosuppressive therapy is reduced and/or based on immunophenotyping of T cell and B cell immunity can be considered." • "Systemic corticosteroids and targeted agents are expected to blunt immune responses to vaccination." This study utilizes a mandatory premedication regimen that contains corticosteroids (i.e., 20 mg of i.v. dexamethasone) for at least the duration of the first cycle (i.e., Cycle 1). Therefore, **for any new subjects to be enrolled in the study,** every effort should be made to vaccinate subjects prior to being considered for this study based on the Investigator's risk/benefit analysis for each subject. Any COVID-19 vaccination should be at least 2 weeks prior to C1D1; live attenuated vaccines at least 4 weeks prior to C1D1. **For subjects whose opportunity for COVID-19 vaccination arrives during the conduct of the study (i.e., ongoing subjects in the study)**, see instructions for COVID-19 vaccination provided in Section 5.6.1.1. INCLUSION CRITERIA The study will enroll subjects with advanced or metastatic solid malignancies whose disease has progressed after treatment with previous anticancer therapies. Subjects are eligible only if all the following criteria are met: 1) For the dose escalation phase (Phase 1): histologically or cytologically confirmed advanced or metastatic solid malignancies that are known to express EGFR. For the dose expansion phase (Phase 2a): histologically or cytologically confirmed advanced or metastatic $EGFR^{+}$ malignancies. EGFR expression is defined as positive staining for EGFR in ≥1% of tumor cells determined by a validated immunohistochemistry assay. Archived paraffin embedded tumor tissue is acceptable for EGFR determination– otherwise a fresh tumor biopsy must be performed. Local laboratory EGFR assessment is acceptable. 2) For dose escalation phase (Phase 1): Subjects must have been previously treated with 1 or more lines of anticancer therapy and have documented disease progression during or after their most recent line of anticancer therapy. In addition, either there is no further SOC therapy for the subject or the remaining SOC therapies are deemed not appropriate for the subject by the Investigator. 3) Subjects must have documented radiological progression during or after their latest therapy for all phases. 4) Voluntary provision and understanding of signed and dated, written informed consent prior to any mandatory study-specific procedures, sampling, or analysis.

	5) Male or female aged ≥18 years on the day of signing informed consent (or of an acceptable age according to local regulations, whichever is older). 6) Eastern Cooperative Oncology Group (ECOG) Performance Score (PS) 0 or 1 7) Adequate organ function, assessed within 14 and within 7 days before first AFM24 infusion, defined as follows: **Note: transfusions and hematopoietic growth factors to help meet eligibility are not allowed.** • Bone marrow: Absolute neutrophil count ≥1.5×10^9/L, platelet count ≥100×10^9/L, and hemoglobin ≥8 g/dL; ▪ Hepatic: total bilirubin ≤1.5× upper limit of normal (ULN) (or ≤3×ULN in participants with Gilbert's syndrome), alanine aminotransferase and aspartate aminotransferase ≤2.5×ULN for subjects without liver metastasis, and alanine aminotransferase and aspartate aminotransferase ≤5×ULN for subjects with liver metastasis; ▪ Renal: If serum creatinine concentration ≥1.5×ULN, then estimated creatinine clearance must be ≥50 mL/min (Cockcroft-Gault formula). 8) Serum potassium, calcium, magnesium, and phosphate within normal limits or not worse than CTCAE v5.0 Grade 1 and asymptomatic. If values are low on the initial screening assessment, supplements may be given, if clinically appropriate, and values repeated to confirm within CTCAE v5.0 Grade 1 limits. 9) For dose escalation phase (Phase 1): Subjects must have (mandatory) at least 1 tumor site that is accessible to biopsy and that is considered by the Investigator to be low risk and of sufficient size to undergo a core biopsy procedure on at least 2 separate occasions. 10) For the dose expansion phase (Phase 2a) only: Subjects must have measurable disease per RECIST v1.1 (i.e., at least 1 measurable lesion ≥10 mm by computed tomography [CT] scan or magnetic resonance imaging (MRI) or ≥20 mm by chest X-ray, malignant lymph nodes are considered measurable if short axis is ≥15 mm assessed by CT scan), with the last imaging performed within 28 days before Cycle 1 Day 1 (C1D1). 11) Subjects in dose expansion phase (Phase 2a) must have histologically confirmed advanced or metastatic EGFR-positive malignancy for each expansion cohort as listed below: • Cohort A: Subjects with RAS wild type, microsatellite stable CRC whose disease has progressed after having received ≥2 prior lines of therapy, which must have included oxaliplatin, irinotecan, and fluoropyrimidine. If available, prior therapy must also have included an anti-vascular endothelial growth factor (anti-VEGF) or anti-vascular endothelial growth factor and its receptor (anti-VEGFR) therapy (e.g., bevacizumab, aflibercept, or ramucirumab), and an anti-EGFR therapy (e.g., cetuximab or panitumumab). • Cohort B: Subjects with ccRCC whose disease has progressed after having received ≥1 prior line(s) of therapy, which must have included a TKI (e.g., sunitinib, pazopanib) and a checkpoint inhibitor (e.g., pembrolizumab, avelumab, nivolumab). • Cohort C: Subjects with advanced or metastatic NSCLC harboring a targetable EGFR kinase domain mutation and whose disease has progressed on or after having received ≥1 prior lines of therapy for advanced disease including ≥1 prior TKI approved for EGFR mutated NSCLC, such as gefitinib, erlotinib, afatinib, dacomitinib or osimertinib. Subjects who were treated with a 1st or 2nd generation TKI in 1st line and developed a documented T790M mutation must have

	received a TKI targeting this mutation such as osimertinib or lazertinib to be eligible. Subjects must have documentation of EGFR mutated NSCLC as assessed by an approved test using genomic sequencing of tumor or circulating free tumor DNA. 12) Female subjects must have a negative urine or serum pregnancy test within 7 days prior to first dose of AFM24 if of childbearing potential or be of non-childbearing potential. If the urine pregnancy test is positive or cannot be confirmed as negative, a serum pregnancy test will be required. The serum pregnancy test must be negative for the subject to be eligible. Non-childbearing potential is defined as: • Postmenopausal, 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 post-menopausal state in women not using hormonal contraception or hormonal replacement therapy. However, in the absence of 12 months of amenorrhea, a single FSH measurement is insufficient. • Surgically sterile. Surgical sterilization methods include hysterectomy, bilateral salpingectomy, and bilateral oophorectomy. 13) Females of childbearing potential must agree to sexual abstinence (defined below) or be willing to use a highly effective method of contraception for the course of the study from 14 days prior to the first dose of study drug through 120 days after the last dose of study drug. Acceptable highly effective birth control methods include: • Oral, intravaginal, or transdermal combined (estrogen and progestogen containing) hormonal contraception associated with inhibition of ovulation; • Oral, injectable, or implantable progestogen-only hormonal contraception associated with inhibition of ovulation; • Intrauterine device; • Intrauterine hormone-releasing system; • Bilateral tubal occlusion; • Vasectomized partner (provided that partner is the sole sexual partner of the female of reproductive potential and that the vasectomized partner has received medical assessment of the surgical success); and • Sexual abstinence. In the context of this study, sexual abstinence is considered a highly effective method only if defined as refraining from heterosexual intercourse from 14 days prior to the first dose of study drug up to 120 days after the last dose of study drug. The reliability of sexual abstinence needs to be evaluated in relation to the duration of the clinical study and the preferred and usual lifestyle of the subject. 14) Males who have female partners of childbearing potential must agree to use a highly effective method of contraception as described in inclusion criterion 13, starting with the first dose of study drug through 120 days after the last dose of study drug. <u>EXCLUSION CRITERIA</u> Subjects are eligible only if none of the following criteria are met: 1) Currently participating in a study and receiving study therapy or participated in a study of an investigational agent and received study therapy or used an investigational device within 4 weeks of the first dose of study drug.

	2) Treatment with systemic anticancer therapy within 4 weeks (6 weeks if therapy was mitomycin C and/or nitrosoureas), or within 5 half-lives of the agent if half-life is known and it is shorter, before first dose of study drug. Anticancer therapies include cytotoxic chemotherapy, targeted inhibitors, and immunotherapies, but do not include hormonal therapy or radiotherapy. 3) Radiation therapy within 2 weeks before first dose of study drug or unresolved (National Cancer Institute [NCI] CTCAE v5.0 >Grade 1) toxicity from previous radiotherapy (eg, radiation dermatitis). **Note**: Palliative (limited field) radiotherapy for managing pain associated with bone metastases present at baseline is permitted during the study. 4) Major surgical procedure, open biopsy, or significant traumatic injury within 4 weeks before first dose of study drug or anticipation of need of a major surgical procedure during the course of study. **Note**: Procedures that are considered to be minimally invasive (eg, peripherally inserted central catheters lines and/or port placements) will be exceptions. 5) Subjects with toxicities (as a result of prior anticancer therapy) which have not recovered to baseline or CTCAE v5.0 ≤Grade 2, except for AEs not considered a likely safety risk (eg, alopecia, specific laboratory abnormalities). 6) History of any other invasive malignancy, unless previously treated with curative intent and the subject has been disease free for 3 years or longer. Examples for acceptable previous malignancies include: completely removed in situ cervical intra-epithelial neoplasia, non-melanoma skin cancer, ductal carcinoma in situ, and early-stage prostate cancer that has been adequately treated 7) One or more of the following cardiac criteria: • Unstable angina; • Myocardial infarction within 6 months prior to screening; • New York Heart Association Class III to IV heart failure; • Corrected QT interval >470 msec obtained as the mean from 3 consecutive resting electrocardiograms (ECGs) using the Fridericia's formula; • Clinically important abnormalities in rhythm, conduction, or morphology of resting ECG (eg, complete left bundle branch block or third-degree heart block); • Congenital long QT syndrome; • Uncontrolled hypertension (≥150/100 mmHg based on accurate measurement and average of ≥2 readings which are ≥5 minutes apart on ≥2 occasions) despite maximum antihypertensive therapy. **Note**: Patients who initially fail screening due to uncontrolled hypertension as defined above, but who then attain controlled hypertension with intensified antihypertensive therapy are allowed to undergo rescreening. 8) Stroke or transient ischemic attack within 6 months prior to screening. 9) History of leptomeningeal disease or spinal cord compression.

	10) Known brain metastases unless asymptomatic and not requiring steroids for at least 4 weeks prior to start of study drug. 11) Subjects with primary brain tumor who require high dose steroids (defined as ≥30 mg prednisolone or equivalent per day) or who received high dose steroids within 4 weeks prior to first dose of study drug. 12) Diagnosis of immunodeficiency or active infection including known hepatitis B, hepatitis C, or human immunodeficiency virus (HIV). A negative confirmatory test within 3 months of treatment start does not have to be repeated during the screening period 13) Active autoimmune disease that requires systemic treatment with steroids or other immunosuppressive agents, or subjects who have received such agents within 4 weeks prior to first dose of study drug: Exceptions: • Topical (≤20% of the skin surface area), ocular, intra-articular, intranasal, or inhalation corticosteroids with minimal systemic absorption • A short course (≤7 days) of corticosteroids prescribed prophylactically (eg, for contrast dye allergy or antiemetic therapy) or for treatment of non-autoimmune causes (eg, delayed hypersensitivity reaction caused by contact allergen) • Physiological replacement doses of corticosteroids for adrenal or pituitary insufficiency 14) Has received a live vaccine administered within 28 days of planned treatment start (C1D1) or while participating in the study. Seasonal vaccines for influenza are generally inactivated vaccines and are allowed. Intranasal vaccines are live vaccines and are not allowed. 15) Subjects who require systemic steroid treatment or any other immunosuppressive therapy, or subjects who received such therapy within 4 weeks prior to the first dose of study drug, with the exceptions as outlined under exclusion criterion #13. 16) Pregnant, breastfeeding, or expecting to conceive or father children within the projected duration of the study, starting with the Screening visit (females) or first dose of study drug (males) through 120 days after the last dose of study drug. 17) Subject's unwillingness to comply with the protocol or inability to appreciate the nature, meaning, and consequences of the study and to formulate his/her own wishes correspondingly. 18) Any medical, psychological, or social condition that would interfere with the subject's participation in the study.
Investigational product, dosage and mode of administration	During the dose escalation phase (Phase 1) AFM24 will be administered as weekly infusion. Based on results from the dose escalation phase (Phase 1), additional dosing regimen (ie, every 2 weeks) may be explored in the dose expansion phase (Phase 2a) **only**. For dose escalation phase (Phase 1) and dose expansion phase (Phase 2a) • Weekly dosing regimen (every 1 week [q1w]): ie, on Day 1, Day 8, Day 15, and Day 22 of a 28-day cycle (see APPENDIX A [Section 14.1]). For dose expansion phase (Phase 2a) **only** In addition to the weekly dosing regimen mentioned above, the following dosing regimen may be used:

	• Every 2 weeks dosing regimen: i.e., on Day 1 and Day 15 of a 28-day cycle (see APPENDIX B [Section 14.2]). If the drug is given on a q2w schedule, the daily dose will not be higher than the highest daily dose that was tested in Phase 1 part of the study and was considered safe. The baseline infusion time should not take less than approximately 4 hours (**Note**: infusion time is approximately 4 hours, any infusion time ≥3 hour 50 minutes will not be a deviation) for at least the first 2 AFM24 infusions. It should also be noted that as the dose escalation continues into the higher dosing cohorts, the baseline infusion time may increase to >4 hours and as long as over 2 days (i.e., split day dosing) based on a given subject's tolerability as detailed in the Pharmacy Manual for each cohort. For infusion times that span over 2 days (i.e., split day dosing), timepoints for different assessments may be affected and the Schedule of Assessment (SoA) tables should be referenced for details (See APPENDIX A [Section 14.1] and APPENDIX B [Section 14.2] for SoA tables for weekly and q2w dosing schedules, respectively). If the first 2 consecutive AFM24 infusions are well tolerated (defined as no infusion-related reaction (IRR)/cytokine release syndrome (CRS) >Grade 1), then the infusion time may be decreased to <4 hours to a minimum of 1 hour starting with the third subsequent infusion (i.e., C1D15 for weekly dosing regimen and C2D1 for q2w dosing regimen) at the discretion of the Investigator along with a potential reduction of post infusion- observation period from 4 hours to a minimum of 2 hours and a taper of corticosteroid premedication. Investigators should only make 1 modification per infusion at 1 time (See APPENDIX F [Section 14.6] for details regarding treatment management for symptoms of IRR/CRS due to study drug). Refer to the Pharmacy Manual for full details regarding study drug administration. Subjects may receive AFM24 as long as they continue to show clinical benefit, as judged by the Investigator, or until disease progression, other treatment discontinuation criteria are met, or withdrawal of consent. For the dose escalation phase (Phase 1), the starting first in human dose for AFM24 will be 14 mg. Five provisional dose levels are defined for the dose escalation (increasing incrementally at 200% per dose to 40 mg, 120 mg, 360 mg, and 1000 mg). If the first dose level of 14 mg is not well tolerated, a 50% lower dose (7 mg) may be evaluated. It is possible for additional, intermediate dose levels to be tested during the study.
Criteria for evaluation	Safety will be assessed by periodic vital signs, physical examinations, ECOG PS, 12--lead ECGs, clinical laboratory assessments, and monitoring of AEs. Adverse events will be graded using the NCI CTCAE, v5.0. Disease response will be assessed by the Investigator, using local RECIST v1.1 and iRECIST (Eisenhauer et al., 2009; Schwartz et al., 2016). In Phase 1 and 2a, imaging results will also be sent for independent central review. Tumor assessment with CT and/or MRI will occur at Screening as well as at timepoints specified in the respective SoA tables for weekly and every-2-week dose regimens (see APPENDIX A [Section 14.1] and APPENDIX B [Section 14.2], respectively). Partial or complete response needs to be confirmed with repeated assessment at least 4 weeks after the initial assessment. The PK profile will be assessed by determining serum levels of AFM24 at intervals throughout the study. The pharmacodynamics (PD) will be assessed by measuring cytokine levels and various lymphocyte subsets including NK cells, activated NK cells, and macrophages in peripheral blood.
Statistical methods	The safety set will consist of all subjects who received at least 1 dose of AFM24. The safety set will be the primary population for all safety related endpoints except determination of the dose-DLT relationship, and for all efficacy related endpoints.

	The DDS will consist of all subjects in the safety set who have either (a) experienced DLT at any time during Cycle 1, or (b) met the minimum treatment and safety evaluation requirements without experiencing DLT within Cycle 1. During the study, for the first 2 dose levels of AFM24 treatment, at least 2 subjects need to be evaluable for dose escalation to occur. For the remaining cohorts, a minimum of 3 subjects evaluable for the DDS will be treated per dose cohort until determination of the MTD and/or one or more RP2Ds. Subjects must receive ≥80% of their assigned AFM24 dose in Cycle 1 and complete the 28-day DLT observation period or have had a DLT within the first cycle of treatment to be considered evaluable for DLT. The DDS will be used in the BLRM to estimate the dose-DLT relationship. The PK set consists of all subjects who have received at least 1 adequately documented dose of study drug and have at least 1 adequately documented post dose PK measurement. Data will be summarized with respect to demographic and baseline characteristics, medical history, prior cancer history and anticancer therapies, prior medication, safety measurements, efficacy measurements and all relevant PK and PD measurements using descriptive statistics (quantitative data) and contingency (frequency and percentages) tables (qualitative data) by dose cohort. **Primary Analysis** **Phase 1 (Dose Escalation)** The safety analysis will consist of listings and summaries of AEs (frequency tables based on CTCAE grades), summaries of laboratory abnormalities (CTCAE grade shift tables, low/normal/high shift tables based on laboratory normal ranges, and summary statistics tables) and flagging of notable values in listings, with results of other tests (eg, ECG, vital signs) being listed and summarized. A 2-parameter BLRM guided by the EWOC principle will be used for dose escalation of the AFM24 therapy. Standardized doses will be used such that 1 of the doses (d*) equals 1, eg, doses are rescaled as d/d*. Consequently, α is equal to the odds of the probability of toxicity at d*. All information currently available about the dose-DLT relationship of AFM24 is summarized in a prior distribution. For this study, this includes preclinical data about the starting dose and predicted MTD of AFM24 within different animal species. This prior distribution is then updated after each cohort of subjects with all the DLT data available in the DDS from the current study. Once updated, the distribution summarizes the probability that the true rate of DLT for each dose lies in the following categories: • 0% to <16%: under-dosing; • ≥16% to <33%: targeted toxicity; and • ≥33% to 100%: excessive toxicity. The frequency of DLTs will be tabulated by dose for subjects in the dose escalation phase (Phase 1) (especially for Cycle 1 and subjects in the DDS as the primary endpoint tabulation) and information about all DLTs will be listed by dose. **Phase 2a (Dose Expansion)** Once the MTD and/or at least one RP2D is determined, enrollment of subjects into 1 of several expansion cohorts for selected tumor indications can begin. The primary objective of the expansion phase is to determine preliminary efficacy as objective response (OR) using a Simon's two-stage design. The primary endpoint is based on the objective response assessed by local Investigator according to RECIST v1.1. The primary analysis will take place once all subjects per cohort had at least 1 confirmed response assessment (ie, ≥12 weeks post-baseline) or have been withdrawn from the study.

	Secondary Analyses **Phase 1 (Dose Escalation) & Phase 2a (Dose Expansion)** Overall response as defined by achieving confirmed complete response (CR) and/or partial response (PR) will be assessed by RECIST v1.1. DOR, PFS, and OS will be summarized using descriptive statistics and Kaplan-Meier estimates. The PK analysis plan will be described in a separate Data Analysis Plan. Where feasible, non-compartmental analysis will be conducted using concentration-time data of AFM24. Summary statistics of PK parameters such as area under the concentration-time curve over the dose interval, maximum plasma concentration, time to maximum plasma concentration, and minimum plasma concentration, will be reported by dose group. Additional parameters or model-based analysis may be calculated depending on the available data. In the expansion cohorts, owing to sparse data sampling an exploratory population PK analysis may be conducted to provide more comprehensive PK parameters for these subjects. If a population PK analysis is conducted, all available clinical PK data from AFM24 will be used. Immunogenicity parameters will be summarized by descriptive statistics. Exploratory analyses will be summarized by descriptive or summary statistics. Potential relationships between dose, safety, PK, and exploratory PD endpoints will be examined. NK cells, macrophages, and molecular tumor markers will be examined for possible correlations with Investigator assessed RECIST efficacy endpoints where appropriate. **Interim Analyses** **Phase 1 (Dose Escalation)** An interim analysis (IA) will be conducted at each dose escalation step. The BLRM will be updated with the respective number of subjects treated and the number of DLTs observed in the last cohort. The updated model will then give a statistical recommendation for the next escalation step. In addition, a risk-benefit assessment that includes a comprehensive analysis of safety and available clinical information will be done to decide on the next escalation steps. In the event of a CTCAE Grade 5 AE or a second CTCAE Grade 4 AE at least possibly related to AFM24 at any time during Phase 1, the Sponsor will suspend further enrollment and an interim safety analysis will be done. The interim safety analysis will be reviewed by an ad-hoc SRC meeting to decide on further progression of the study. At least 1 IA (end of Phase 1) will be performed after all subjects treated in Phase 1 have completed their first post-baseline disease assessment and its confirmation (2nd post-baseline assessment, i.e., ≥12 weeks post-baseline) or have withdrawn from the study. In case several RP2Ds will be determined, additional IAs might be performed after the respective dose level. No formal interim report will be written. All subjects still ongoing at this timepoint will continue until disease progression, intolerable toxicity, Investigator discretion, or subject's withdrawal of consent and all assessments will be included in final analysis at the end of study. **Phase 2a (Dose Expansion)** An IA, without a formal IA report, will be performed for each cohort independently, once the defined number of subjects (11, 15, and 15 subjects for Cohorts A, B, and C, respectively) in the respective cohort have completed a confirmed disease assessment or have withdrawn from the study. In case of a negative result, the respective cohort may be stopped for futility. The results of the IA will be non-binding. Safety criteria will also be evaluated to guide the decision to continue the study cohorts. During the conduct of the study, after the interim analysis of Cohort A and C and stopping these cohorts for futility, it was considered unlikely that the continuation criteria can be met

	in Cohort B. Hence it was decided to prematurely stop enrolment after 8 patients in Cohort B.

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LIST OF ABBREVIATIONS

Abbreviation	Explanation
ADCC	antibody-dependent cellular cytotoxicity
ADCP	antibody-dependent cellular phagocytosis
AE	adverse event
AESI	adverse event of special interest
BLRM	Bayesian logistic regression model
BRAF	v-raf murine sarcoma viral oncogene homolog B1
ccRCC	clear cell renal cell carcinoma
CD16A	Fcγ receptor IIIA
CFR	Code of Federal Regulations
CI	confidence interval
CR	complete response
CRA	clinical research associate
CRC	colorectal cancer
CRS	cytokine release syndrome
CSR	clinical study report
CT	computed tomography
CTCAE	Common Terminology Criteria for Adverse Events
ctDNA	circulating tumor DNA
DDS	dose-determining set
DLT	dose-limiting toxicity
DOR	duration of response
EC	Ethics Committee
EC_{50}	half maximal effective concentration
ECG	electrocardiogram
ECOG	Eastern Cooperative Oncology Group
eCRF	electronic Case Report Form
EDC	Electronic Data Capture
EGFR	epidermal growth factor receptor
EOI	end of infusion
EWOC	escalation with overdose control
Fc	fragment crystallizable
FcRn	neonatal Fc receptor
FDA	Food and Drug Administration
FIH	first in human
FSH	follicle-stimulating hormone
GCP	Good Clinical Practice
GLP	Good Laboratory Practice
HER	human epidermal growth factor receptor
HIV	human immunodeficiency virus
IA	interim analysis
IB	Investigator's Brochure
ICF	Informed Consent Form
ICH	International Council for Harmonisation
IEC	Independent Ethics Committee
IDMC	Independent Data Monitoring Committee
IgG	immunoglobulin G

Abbreviation	Explanation
IL	interleukin
IND	Investigational New Drug
IRB	Institutional Review Board
iRECIST	Response Evaluation Criteria in Solid Tumors for immunotherapy
IRR	infusion-related reaction
i.v.	intravenously
KRAS	Kirsten rat sarcoma genes
LOEL	lowest observed effect level
mAb	monoclonal antibodies
MABEL	minimum anticipated biological effect level
MRI	magnetic resonance imaging
MTD	maximum tolerated dose
NCI	National Cancer Institute
NK	natural killer
NOAEL	no observed adverse effect level
NSCLC	non-small cell lung cancer
OS	overall survival
PD	pharmacodynamic(s)
PFS	progression-free survival
PK	pharmacokinetic
PR	partial response
q7d	every 7 days
q1w	every 1 week
q2w	every 2 weeks
RAS	rat sarcoma gene
RECIST	Response Evaluation Criteria in Solid Tumors
RP2D	recommended phase 2 dose
SAE	serious adverse event
SD	stable disease
SoA	schedule of assessments
SOC	standard of care
SRC	Safety Review Committee
SUSAR	suspected unexpected serious adverse reaction
TKI	tyrosine kinase inhibitor
ULN	upper limit of normal
US	United States
VEGF	vascular endothelial growth factor
VEGFR	vascular endothelial growth factor and its receptor

1.0 INTRODUCTION

AFM24 is a first-in-class, tetravalent, bispecific, fragment crystallizable (Fc)-silenced antibody designed to target epidermal growth factor receptor-expressing ($EGFR^+$) solid tumors. Of its 4 binding sites, 2 binding sites are specific for EGFR; the other 2 binding sites are specific for CD16A, which is the Fcγ receptor expressed by natural killer (NK) cells and macrophages. AFM24 was designed to specifically utilize the cytotoxic potential of NK cells and macrophages for the specific, potent, and efficient elimination of $EGFR^+$ cancer cells, offering a novel therapeutic approach to target EGFR+ tumors with active immunotherapy.

This bispecific innate immune cell recruiting antibody binds to both, $EGFR^+$ cancer cells and $CD16A^+$ NK cells and macrophages with strong avidity, thus creating an immunological synapse. This results in antibody-dependent cellular cytotoxicity (ADCC; induced by NK cells) and antibody-dependent cellular phagocytosis (ADCP; induced by macrophages) of $EGFR^+$ tumor cells, thereby activating a potent antitumor immune response.

Due to its ADCC- and ADCP-related mode of actions, it is anticipated that AFM24 would be active in patients who harbor $EGFR^+$ cancers, potentially also including those cancers that have intrinsic or acquired resistance to EGFR targeting monoclonal antibodies (mAbs) and tyrosine kinase inhibitors (TKIs). Therefore, AFM24 has the potential to overcome the limitations of EGFR-targeting standard of care (SOC) agents, such as mAbs and TKIs that target EGFR.

In addition, AFM24 may offer an improved safety profile compared with current EGFR-targeting SOC agents. At high concentrations, AFM24 can also down-modulate ligand-induced EGFR signaling. However, the inhibitory effect of AFM24 on ligand-induced EGFR signaling is substantially lower relative to the anti-EGFR-targeting mAb cetuximab.

Patients with previously treated advanced or metastatic solid tumor malignancies that express EGFR represent patient populations with high unmet medical need due to the associated poor prognosis and limited number of treatment options available. NK cells and macrophages have an intrinsic ability to eliminate tumor cells; however, innate immunity is often suppressed in cancer patients. By utilizing AFM24 to redirect and activate such immune cells, it may be possible to release the antitumor potential of a patient's own innate immune system to effectively control their cancers.

AFM24 may offer a much-needed alternative to current therapeutic approaches for patients with a variety of solid cancers with high unmet needs, such as colorectal, lung, gastric, esophageal, pancreatic, head and neck, breast, ovarian, cervical, urothelial and renal cancers, and glioblastoma multiforme (AFM24 also binds to EGFR variant III with similar affinity).

1.1 EGFR and Description of Disease

EGFR is a member of the human epidermal growth factor receptor (HER) family of receptor tyrosine kinases and is typically activated through ligand binding and homo- or heterodimerization resulting in intracellular tyrosine phosphorylation and signal transduction. It is expressed in a variety of different cell types (Huang & Harari, 1999) and is involved in the regulation of cellular differentiation and proliferation (Salomon et al., 1995).

EGFR is known to be overexpressed in multiple tumor types (eg, colorectal cancer [CRC], non-small cell lung cancer [NSCLC], head and neck squamous cell carcinoma, glioblastoma multiforme, and prostate, kidney, cervical, bladder, ovarian, and triple-negative breast cancers) (Bast et al., 1993; Ishikawa et al., 1990; Itakura et al., 1994; Kim et al., 1996; Rikimaru et al.,

1992; Robertson 1996; Sargent et al., 1989). In many cases, aberrant EGFR activation, mediated primarily through changes in gene amplification, gene mutations, and autocrine ligand stimulation, is an important factor in tumorigenesis.

1.2 Mode of Action of AFM24

AFM24 is a first-in-class, tetravalent, bispecific, Fc-silenced antibody designed to target $EGFR^+$ solid tumors. Of its 4 binding sites, 2 binding sites are specific for EGFR and the other 2 binding sites are specific for CD16A, which is the Fcγ receptor mainly expressed by NK cells and macrophages. The antigen binding domains are fused to a human Fc portion to facilitate neonatal Fc receptor (FcRn) binding and to achieve serum half-life comparable to classical immunoglobulin G (IgG) antibodies. The Fc portion was engineered to eliminate binding to all Fcγ receptors but allows fixing of complement and complement-dependent cytotoxicity (CDC) on $EGFR^+$ cells.

By design, AFM24 binds to both $EGFR^+$ cancer cells and $CD16A^+$ NK cells and macrophages with strong avidity, thus creating an immunological synapse. This results in ADCC (induced by NK cells) and ADCP (induced by macrophages) of $EGFR^+$ tumor cells, thereby activating a potent antitumor immune response.

It is anticipated that AFM24 would be active in patients who harbor $EGFR^+$ cancers, including, but not limited to those cancers that have intrinsic or acquired resistance to EGFR targeting mAbs and TKIs. AFM24 has also the potential to overcome the limitations of EGFR-targeting standard of care (SOC) mAbs and TKIs.

In addition, it is anticipated that AFM24 would demonstrate an improved safety profile compared with these SOC agents. At high concentrations, AFM24 can also down-modulate ligand-induced EGFR signaling. However, the inhibitory effect of AFM24 on ligand-induced EGFR signaling is substantially lower relative to the anti-EGFR-targeting mAb cetuximab.

1.3 Nonclinical Studies

The preclinical characterization of AFM24 described below demonstrates the ability of AFM24 to redirect innate immune cells to $EGFR^+$ malignancies through a mutation-independent mechanism of action to be active across a range of human cancers as well as to overcome resistance to current SOC therapies, while conferring a favorable safety profile. Please refer to the Investigator's Brochure (IB) for additional details.

1.3.1 Pharmacology

1.3.1.1 Primary Pharmacodynamics

Binding of AFM24 to effector cells (NK cells and macrophages) via CD16A has been demonstrated. The EGFR binding specificity of AFM24 was established by demonstrating the inability of AFM24 to bind to other members of the EGFR family (HER2, HER3, and HER4). Binding was shown to recombinant human CD16A, cynomolgus CD16, as well as human and cynomolgus recombinant EGFR, human and cynomolgus NK cells, human macrophages, and human tumor cell lines with low and high EGFR copy number. Furthermore, AFM24 was shown to bind to EGFR in the presence of the ligands EGF and TGF-α. In line with the silenced Fc region of AFM24, no binding to Fcγ receptors other than CD16A was observed.

In the presence of NK cells, AFM24 induced ADCC in all investigated human tumor cell lines expressing EGFR, including those bearing the Kirsten rat sarcoma genes (KRAS) or BRAF

(v-raf murine sarcoma viral oncogene homolog B1) mutation. In the presence of macrophages, AFM24 induced ADCP of $EGFR^+$ tumor cells. In addition, complement-dependent cytotoxicity of $EGFR^+$ cells could be induced in the presence of complement factors.

Dose-dependent *in vivo* efficacy was demonstrated using the A-431 mouse tumor model growing in humanized mice (ie, mice engrafted with human $CD34^+$ cells, forming human immune cells) in both the prophylactic and therapeutic settings. AFM24-treated mice frequently showed increased intratumoral NK cell numbers when compared with vehicle-treated control animals.

1.3.1.2 Secondary Pharmacodynamics

In line with the mode of action of AFM24, a dose-dependent cytokine release of interleukin 6 (IL-6), tumor necrosis factor-alpha, and interferon-gamma, was detected in cultures of peripheral blood mononuclear cells in the presence of target cells *in vitro*. These data are consistent with the IL-6 release observed in the nonclinical toxicity studies (Section 1.3.3).

NK cell fratricide by AFM24 was observed only at high antibody concentrations. Compared to daratumumab, an anti-CD38 mAb with reported NK cell fratricide *in vitro* and *in vivo*, the half maximal effective concentration (EC_{50}) of AFM24-induced NK cell fratricide was 190-fold lower. AFM24 increased NK cell activation marker CD69 in the presence of target tumor cells with a mean EC_{50} of 8.3 pM. In the absence of target tumor cells, the EC_{50} of NK cell activation, most likely because of NK-NK cell lysis, was substantially lower (mean EC_{50}: 4545 pM).

1.3.2 Pharmacokinetics

The pharmacokinetics (PK) of AFM24 was investigated in mice and in cynomolgus monkeys. Although AFM24 does not bind to mouse CD16A or mouse EGFR, humanized mice bearing subcutaneous human $EGFR^+$ tumors were used for pharmacodynamics (PD) experiments. In this context, key PK parameters of AFM24 in immunocompetent normal mice were determined to better understand the *in vivo* efficacy (see the IB for details).

AFM24 binds to human, cynomolgus monkey and mouse FcRn. The half-life of AFM24 in tumor-free mice (14 days) is longer than in monkeys (range 33.4 to 154 hours), which is within the expectations for a human IgG1 due to the 2.6-fold higher relative binding of human IgG1 to mouse FcRn versus human FcRn (Ober et al., 2001).

In cynomolgus monkeys, a more-than-dose-proportional increase in AFM24 exposure was noted in a single dose PK study and a pilot toxicity study with low animal numbers. However, in a pivotal Good Laboratory Practice (GLP) toxicity study with large animal number (n = 6 or n = 10 in recovery-controlled groups), exposure, as assessed by mean AFM24 maximum plasma concentration and AUC values, increased dose proportionally with increasing AFM24 dose level, with dose proportionality ratios between 3.08 and 3.94 for the 3-fold increase from 8 to 24 mg/kg/week and between 2.43 and 2.95 for the 3.1-fold increase from 24 to 75 mg/kg/week.

A slight increase in the terminal half-life value as the dose level increased was observed in all studies and a dose-related change in the observed systemic clearance of AFM24. Volumes of distribution indicate that AFM24 is mainly located in the plasma volume.

1.3.3 Non-Clinical Toxicity

Several studies were performed to identify a relevant species for PK and toxicity *in vivo* studies of AFM24. It was demonstrated that the cynomolgus monkey is the only relevant species for AFM24, showing similar binding properties to cynomolgus and human EGFR and to cynomolgus CD16 and human CD16A. As a result, mice and dogs were excluded as relevant species for toxicity testing.

Two repeat dose toxicity studies were performed with AFM24 in cynomolgus monkeys, using identical treatment dose levels and schedules: a maximum tolerated dose (MTD) pilot toxicity study followed by a pivotal GLP toxicity study. The results of the 2 studies were very similar. The GLP toxicity study is described below. Further details are provided in the IB.

In the GLP toxicity study, monkeys were dosed weekly at 7, 24, and 75 mg/kg over 4 weeks (5 doses in total, every 7 days [q7d] × 5) by a 2-hour infusion followed by a 4-week recovery phase. Assessment of toxicity was based on clinical observations, body weights, body temperature, ophthalmic examinations, and clinical and anatomic pathology. Complete necropsies were performed on all animals, and macroscopic and microscopic examinations were conducted. Blood was collected for toxicokinetic, immunogenicity, and immunotoxicity evaluation of AFM24. Safety pharmacology endpoints comprised complete blood counts, clinical chemistries, electrocardiograms (ECGs), blood pressure, respiratory rate, and neurological behavior. Additionally, cytokine levels (IL-2, IL-6, IL-8, tumor necrosis factor-α, interferon-γ), and lymphocyte numbers and phenotypes were determined.

AFM24-related clinical findings were limited to emesis in 2 animals in the high dose group (75 mg/kg on Day 1 only). AFM24 caused non-dosedependent-, marked but transient increases in white blood cell counts, particularly neutrophil counts, at 4 hours after the completion of dosing on Day 1 of the dosing phase. Absolute neutrophil counts were approximately 3-fold higher compared with mean pre-dose values or vehicle treated control animals. These findings were reversible, returning to baseline 24 hours post-dose in the highest dose group (no sample was collected for other groups at this timepoint) and by Day 8 at the low and intermediate dose groups. A transient reduction in absolute NK cell counts (CD3-CD20-CD159a^{+}) at a dose ≥8 mg/kg, 4 hours after dosing on Day 1 ($P \leq 0.05$) in both males and females was observed. The reduction on Day 1 was for males and females -84%/-59% at 8 mg/kg and -57%/-67% at 24 mg/kg and -81%/-84% at 75 mg/kg when compared with data generated on Day 1 before dosing. All values returned to pre-dose levels by Day 8 in nearly all animals.

The first administration of AFM24 had a temporary effect on circulating IL-6 levels 2 hours after start of infusion of AFM24 dosing in all dose groups, which reached maximum levels of 602 pg/mL in the 24 mg/kg dose group and 416 pg/mL in the 75 mg/kg dose group. No clear dose response was observed. Four hours after start of infusion, IL-6 levels were strongly reduced in all animals and returned to normal within 24 hours. No clinical signs were associated with the increase of IL-6. As expected for the species, high heterogeneity was observed for IL-8 levels in all tested animals but no clear pattern of AFM24-mediated IL-8 release was apparent. All other cytokines assessed were below the limit of quantification.

No adverse effects were observed for standard parameters as clinical observations, body weights, body temperature, ophthalmic examinations, and clinical and anatomic pathology. No findings were reported during necropsies, macroscopic and microscopic examinations. No AFM24-related effects on safety pharmacology endpoints comprising ECGs, blood pressure, respiratory rate and neurological behavior were noted. Therefore, the no observed adverse

effect level (NOAEL) was 75 mg/kg under the conditions of the MTD pilot toxicity study and the pivotal GLP study.

Binding of AFM24 to normal human and cynomolgus monkey tissues was investigated in a full panel of human and cynomolgus monkey tissues in a GLP tissue cross reactivity study. In both species a congruent binding pattern was observed, further identifying human and cynomolgus monkeys as a relevant species. AFM24 produced membranous and/or cytoplasmic staining in various epithelia (eg, skin, cervix) and in mononuclear immune cells consistent with macrophages. The staining pattern and distribution were consistent with on-target binding of AFM24.

1.3.4 AFM24 Clinical Experience

This is a first in human (FIH) Phase 1/2a study. The preliminary safety and efficacy data from the AFM24-101 study is available in the current Investigator's Brochure.

1.4 Study Rationale

The introduction of TKI targeting the EGFR intracellular kinase domain and mAbs targeting the extracellular domain of EGFR have resulted in improvements in clinical outcomes for patients with NSCLC, CRC, and head and neck squamous cell carcinoma; however, treatment is associated with significant toxicities in organs where EGFR is expressed (mainly skin) which limits the therapeutic utility of these agents (Morgillo et al., 2007).

In contrast, the mode of action of AFM24 is primarily through ADCC and ADCP, and not through inhibition of signaling. Therefore, it is expected that AFM24 will potentially have less adverse effects on healthy tissues and result in a wider therapeutic window.

Additionally, there remains a high unmet medical need due to the limited efficacy of currently available SOC agents for patients with $EGFR^+$ cancers and to the occurrence of either intrinsic or acquired resistance to EGFR-targeted inhibitors in patients (Morgillo et al., 2007; Mirone et al., 2016). In addition, existing agents offer little to no benefit in other patient groups whose tumors express EGFR, such as gastric, pancreatic and biliary cancers, bladder and renal cancers, and glioblastoma multiforme.

Intrinsic resistance to EGFR-targeting therapies, such as the marketed anti-EGFR mAbs cetuximab and panitumumab, includes mutations in downstream signaling factors such as KRAS and BRAF, which are negative predictive biomarkers for clinical response to marketed anti-EGFR mAbs (Reddi, 2013). Cetuximab and panitumumab bind with high specificity to EGFR preventing ligand-induced homo- or heterodimerization of the receptors and subsequent EGFR activation; however, this mode of action is ineffective in tumors bearing KRAS mutations (Jorge et al., 2014; Pines et al., 2010; Reddi, 2013). For patients with EGFR mutated NSCLC, mechanisms of resistance to EGFR-targeted TKIs include secondary mutations (eg, T790M, C797S), activation of alternative signaling pathways (eg, c-MET, HGF, AXL, IGF-1R), mutations in downstream pathways (eg, BCL2-like 11 deletion polymorphism), and histological transformation (Morgillo et al., 2016). AFM24 binds to both $EGFR^+$ cancer cells and $CD16A^+$ NK cells and macrophages thereby creating an immunological synapse resulting in ADCC induced by NK cells and ADCP induced by macrophages as primary modes of action. These modes of action are independent of the blockade of the EGFR downstream signaling pathway. AFM24 can also down-modulate ligand-induced EGFR signaling, but only at high concentrations, and therefore this effect is not considered its primary mode of action. It is anticipated that the AFM24-induced ADCC and ADCP cannot be evaded by the presence of

existing or acquired mutations in the EGFR downstream signaling pathway. Therefore, all patients with tumors expressing EGFR could potentially benefit from AFM24 treatment regardless of the mutational status of the tumors.

1.5 Rationale for Starting Dose Selection in Phase 1

Selection of a safe clinical starting dose considers international guidance for starting dose selection for agents in cancer patients which include the:

- revised 2017 European Medicines Agency guideline on 'Strategies to identify and mitigate risks for first-in-human and early clinical trials with investigational medicinal products' (EMEA/CHMP/SWP/28367/07 Rev. 1).

- 2005 Food and Drug Administration (FDA) 'Guidance for Industry: Estimating the Maximum Safe Starting Dose in Initial Clinical Trials for Therapeutics in Adult Healthy Volunteers'.

- International Council for Harmonisation (ICH) Topic S9 – 'Nonclinical Evaluation for Anticancer Pharmaceuticals'

In the selection of starting dose for the FIH study, all available nonclinical data were considered. These include *in vivo* data from repeat dose toxicity and PK and toxicokinetic studies in cynomolgus monkeys, *in vivo* antitumoral efficacy data in humanized mice, and *in vitro* PD data of receptor binding and cellular interactions. The nonclinical data were used to extrapolate minimum anticipated biological effect levels (MABEL), pharmacologically active dose levels, lowest observed effect level (LOEL) and NOAEL and to define a pharmacologically active starting dose that is reasonably safe to use in patients with advanced cancer. Allometric scaling factors used to derive human equivalent dose levels (HED) were those defined in Section V of the 2005 FDA 'Guidance for Industry: Estimating the Maximum Safe Starting Dose in Initial Clinical Trials for Therapeutics in Adult Healthy Volunteers'. A listing of HEDs corresponding to benchmarks derived from *in vivo* and *in vitro* studies of AFM24 is provided in Table 1.

Based on the results of antitumoral efficacy studies in humanized mice and toxicity studies in cynomolgus monkeys, a human starting dose of 200 µg/kg is proposed for the planned FIH study in cancer patients. This dose level is:

- by a factor of 2.5 higher than the HED corresponding to the in vivo MABEL of a first trend of antitumoral activity against EGFR+ tumors in the mouse model (HED≈81 µg/kg).

- by a factor of approximately 4 lower than the HED corresponding to the murine dose level eliciting a statistically significant, antitumor effect against EGFR+ tumors (HED≈810 µg/kg).

- by a factor of approximately 4 lower than the HED corresponding to the adjusted LOEL for the onset of IL-6 release in cynomolgus monkeys (HED≈860 µg/kg).

- by a factor of approximately 40 lower than the HED corresponding to the adjusted NOAEL in cynomolgus monkeys (HED≈8060 µg/kg).

A clinical starting dose of 200 µg/kg is therefore deemed to be a good compromise between expected antitumoral efficacy and safety in cancer patients.

It is noteworthy that no toxicities were observed in the cynomolgus monkey GLP toxicity studies at doses ranging from 8 mg/kg q7d × 5 up to the maximum administered dose level of 75 mg/kg q7d × 5. The only clinical findings noted in these studies were transient elevations of IL-6 levels and neutrophil counts and transient decreases in NK cell counts. These effects may be regarded as part of the mode of action of AFM24 and were not considered as adverse effects. The IL-6 elevations were seen at all dose levels, and hence, the LOEL (IL-6 release) is defined as 8 mg/kg.

For purposes of benchmarking, the AFM24 dose levels administered to the cynomolgus monkey should be considered 3-fold lower than the actual doses administered due to the presence of an unanticipated cleaved form of AFM24 in the drug product used only in the GLP toxicity study and a correspondingly lower exposure to AFM24 in these animals (refer to IB for details). Including an allometric scaling factor (cynomolgus to human) of 3.1, the adjusted NOAEL corresponds to a HED of approximately 8 mg/kg, and the adjusted LOEL corresponds to a HED of approximately 0.8 mg/kg, approximately 40- and 4- fold higher, respectively, than the selected starting dose.

HED values extrapolated solely from *in vitro* data were too low for the estimation of a clinical starting dose in cancer patients. The lowest relevant benchmark in this context was the MABEL extrapolated from *in vitro* ADCC studies of human NK cells against glioblastoma -derived DK-MG target cells using an AUC model. This MABEL corresponds to a HED of 0.0192 µg/kg and would be by more than 5 orders of magnitude lower than the HED corresponding to the adjusted NOAEL determined in the GLP-toxicity study in cynomolgus monkeys (8060 µg/kg). Such a low starting dose would only be reasonable for high-risk protein therapeutics with agonistic properties.

In this context, the clinical experience with AFM13, a bispecific NK cell engager (CD30/CD16A) that contains CD16A binding domains that are identical to AFM24 (Rothe 2015), was also considered. AFM13 is currently in clinical development for patients with $CD30^{+}$ hematologic malignancies and has shown safety and tolerability in patients at doses up to 7 mg/kg weekly.

Results of serum PK and toxicokinetic studies of AFM24 in cynomolgus monkeys predict a serum half-life of 4 to 6 days in humans. Therefore, a weekly dosing schedule is anticipated to result in accumulation over the first 3 to 4 doses and achievement of a steady state thereafter. Based on preliminary data from the cynomolgus monkey PK studies of AFM24 a fixed dosing regimen appears to be associated with less inter-patient variability in exposure compared to body size-based dosing. Hence, a fixed dosing scheme was selected to be tested in the FIH Phase 1 study, and a fixed, weekly starting dose of 14 mg (0.2 mg/kg × 70 kg of average human) is proposed for the planned FIH Phase 1/2a study.

Table 1: Human-equivalent Doses Corresponding to Benchmarks Derived from *in vivo* and *in vitro* Studies of AFM24

Model	Benchmark	HED (µg/kg)
in vivo	NOAEL (cynomolgus, Pilot-TOX)	24190
	LOEL (cynomolgus, IL-6 release, Pilot-TOX)	2580
	adjusted* NOAEL (cynomolgus, GLP-TOX)	8060
	adjusted* LOEL (cynomolgus, IL-6 release, GLP-TOX)	860
	PAD (mouse, antitumoral)	810
	MABEL (mouse, antitumoral)	81
in vitro (AUC)	ADCC (NK vs. DK-MG; AUC)	0.0192
	NK activation (CD69; AUC)	2.22
	IL-6 release (PBMC; AUC)	6.662

ADCC = antibody-dependent cellular cytotoxicity; AUC = area under the concentration-time curve; CD69 = cluster of differentiation 69; GLP = Good Laboratory Practice; HED = human equivalent dose; IL-6 = interleukin-6; LOEL = lowest observed effect level; MABEL = minimum anticipated biological effect level; NK = natural killer; NOAEL = no observed adverse effect level; PAD = pharmacologically active dose level; PBMC = peripheral blood mononuclear cell; TOX = toxicology study.
Note: * adjusted LOEL and NOAEL refer to benchmarks determined in the GLP toxicity study and include an additional correction factor of 3 due to intrinsic properties of the applied bioanalytical assay in the GLP toxicity study (see discussion above).

1.6 Rationale for the Recommended Phase 2 Dose Selection

The selection of the recommended phase 2 dose (RP2D) was based on the review of the totality of available data including, but not limited to, the observed safety, tolerability and preliminary clinical activity of AFM24 as well as the available PK and pharmacodynamic (PD) data for AFM24. A brief summary of the data and the RP2D selection is provided below. Please refer to the Investigator's Brochure for more details.

As of a data cutoff date of 29 October 2021, 29 subjects were enrolled into 6 dose cohorts, with AFM24 doses ranging from 14 mg to 480 mg i.v. every 1 week (q1w). AFM24 was generally safe and well tolerated across dose levels, with infusion-related reactions (IRRs) (69%) being the most frequently reported treatment-emergent adverse events (TEAEs). There were no treatment-related deaths. No dose-limiting toxicities (DLTs) were observed in 6 subjects at the highest dose of 480 mg.

Best objective response (BOR) per Response Evaluation Criteria in Solid Tumors (RECIST) v1.1 was stable disease (SD) in 8 of 24 response-evaluable subjects.

At 480 mg, dose proportional PK was reached, suggesting a peripheral saturation of target (EGFR)-mediated elimination. The preliminary exposure-response curve with CD16a RO appeared to level off to approximately 30-40% RO at concentrations that were reached with 480 mg, indicating that higher exposures would not lead to higher CD16a RO. Moreover, estimated intra-tumoral AFM24 concentrations and CD16a RO were in the range associated with maximum tumor cell killing (SW-982 cells or A-431 cells) *in vitro* (Affimed Study No. AFM24_018).

Taken together, based on the review of the totality of available data, the Safety Review Committee (SRC) (Section 3.6) determined 480 mg i.v. q1w as an acceptable RP2D of AFM24. The Phase 1 part of the study was ongoing at the time of selection of this RP2D and Cohort 7 (720 mg q1w) had been opened for enrollment.

1.7 Safety Guidance Information for Investigators

Investigators should refer to the current edition of the IB for a full review of the potential risks associated with treatment with AFM24 and details of expected AEs.

1.8 Benefit-Risk Assessment

Information gathered to date is limited to nonclinical *in vitro* pharmacology, *in vivo* pharmacology in mice and cynomolgus repeat dose toxicity studies in cynomolgus monkeys, in conjunction with knowledge of the clinical profile of other EGFR targeting agents, and preliminary clinical data from this FIH study. Management of possible AFM24 related toxicities are described in Section 5.8.

AFM24 was well tolerated in cynomolgus monkeys, when administered weekly (q7d × 5) up to a maximum dose of 75 mg/kg. Findings of note were a temporary, non-dose-dependent reduction in absolute peripheral NK counts as well as an increase in neutrophil counts in all animals on Day 1. In addition, the first dose of AFM24 caused a transient elevation of circulating IL-6 levels 2 hours after administration which reverted to normal after 24 hours. These data are supported by *in vitro* cytokine release studies, where a dose-dependent release of IL-6 was detected in the presence of target cells and peripheral blood mononuclear cells as described in Section 1.3.1.2. Based on these observations, AFM24 has the potential to induce cytokine release in patients.

Cetuximab, a marketed EGFR-targeting monoclonal antibody, has been tested in cynomolgus monkeys, and has been found to induce significant toxicities directed to healthy tissues that express EGFR (EPAR, 2004). These toxicity findings were completely lacking in the AFM24 toxicity studies in cynomolgus monkeys, suggesting that AFM24 may have a more favorable safety profile in humans compared with cetuximab. However, it is possible that toxicities similar to those of the approved products that target the EGFR (mAbs or TKI small molecules) may occur with AFM24 treatment in humans. In addition, clinical experience with AFM13, another CD16A-targeted bispecific antibody in clinical studies, may be relevant to the safety profile of AFM24.

EGFR-targeting antibodies, such as cetuximab (EPAR 2019; US package insert 2019), panitumumab (US package insert 2015; EPAR 2018), or necitumumab (US package insert 2015; EPAR 2016) which block cellular signaling through EGFR as their primary mode of action, have been clinically validated and are now SOC for patients with advanced head and neck cancer and subgroups of patients with advanced colorectal and lung cancers. As the primary mode of action of AFM24 is likely not signal inhibition of the EGFR pathway, but redirecting NK cells and macrophages to EGFR-positive tumor cells and inducing ADCC and ADCP, respectively, the potential for AFM24 to manifest adverse reactions known to be associated with EGFR-targeting mAbs may be reduced. However, at high exposures, AFM24 also blocks EGFR-mediated cellular signaling, and there is a potential that adverse reactions seen with EGFR targeting mAbs will also manifest during AFM24 treatment. The most common adverse reactions seen in ≥20% of the patients in EGFR targeting monoclonal antibody clinical studies were cutaneous adverse reactions, headache, diarrhea, infection, nausea, vomiting, paronychia, and fatigue. The most common (≥5% of the patients) severe (Grade 3 and above) adverse reactions were dyspnea, skin disorders (erythema, rash, and acneiform dermatitis), thromboembolic events, diarrhea, fatigue, pain, nausea, vomiting, infections, dehydration, and confusion.

There is also potential overlap between the mechanism of action of AFM24 and that of small molecules that inhibit the kinase activity of mutated and wild-type EGFR. Such molecules include gefitinib (US package insert 2018; EPAR 2019), erlotinib (US package insert 2016; EPAR 2019), afatinib (EPAR 2018; US package insert 2018), dacomitinib (US package insert 2018; EPAR 2019), and osimertinib (EPAR 2018; US package insert 2018), which are SOC for the treatment of patients with NSCLC that harbor activating mutations of EGFR. These molecules block the intracellular kinase domain of EGFR and inhibit further downstream signaling. There is a potential for adverse reactions seen with EGFR kinase inhibitors to manifest during AFM24 treatment. The most common adverse reactions (seen in ≥20% of the patients treated) with EGFR-targeted kinase inhibitors in clinical studies were diarrhea, asthenia, rash, dry skin, pruritus, paronychia, stomatitis, cough, dyspnea, decreased weight, alopecia, nausea, vomiting, decreased appetite, and fatigue. The most common (≥5% of the patient) severe, (≥Grade 3) adverse reactions were rash, diarrhea, dyspnea, stomatitis, paronychia, and hypertension.

AFM13 is a CD30/CD16A bispecific (NK cell and macrophage) engager currently in development for the treatment of Hodgkin and T-cell lymphomas. Although the molecular structure is different, as AFM13 does not have an Fc portion, the mode of action is similar to AFM24 as AFM13 redirects CD16A-positive cells to CD30-positive tumor cells to induce ADCC and ADCP of the tumor target cells. There is a potential that AFM24 treatment is associated with similar adverse reactions as observed for AFM13. AFM13 is generally well tolerated; however, mild to moderate IRRs are common and often require premedication with acetaminophen and H1/H2 antagonists. Severe IRRs have also occurred, although infrequently (Ansell et al., 2019).

The Phase 1/2a study will evaluate AFM24 in subjects with advanced or metastatic solid malignancies that express the EGFR and therefore have the potential to respond to AFM24-induced tumor target cytotoxicity. The subject population selected have advanced or metastatic disease which has progressed during or after treatment with SOC therapies. In the dose escalation phase (Phase 1), subjects with a variety of advanced solid malignancies are eligible, whereas in the dose expansion phase (Phase 2a), subjects with advanced CRC, clear cell renal cell carcinoma (ccRCC), and NSCLC are eligible. Effective treatment options for subjects with these advanced cancers after disease progression are extremely limited and new therapies are urgently needed. The choice of subject population is further supported by nonclinical testing which has demonstrated significant antitumor activity in $EGFR^+$ tumor cell lines and *in vivo* models.

The primary objective of the Phase 1 dose escalation portion of this Phase 1/2a study is to determine the MTD and/or to select one or more recommended phase 2 doses (RP2Ds), and generally investigate safety and tolerability of AFM24. The nonclinical toxicity studies have not identified any risks that would preclude investigation of AFM24 in the advanced cancer setting, although the safety profile of AFM24 is difficult to predict. Based on the identified and potential risks associated with AFM24 treatment, this clinical study protocol incorporates mandatory and thorough safety monitoring procedures and additional guidance documents to assist with early diagnosis and rapid management of potential treatment related toxicities. The safety monitoring plan takes into consideration the results of AFM24 toxicity studies as well as the known safety profile of other EGFR targeting or NK-cell engager drugs.

The Phase 1 dose escalation portion of the study is designed to maximize safety while minimizing the number of subjects treated at subtherapeutic dose levels. The first 2 cohorts will enroll a minimum of 2 subjects, whereas subsequent cohorts will enroll a minimum of 3

and up to 6 subjects. Dose escalation will be guided by an adaptive Bayesian logistic regression model (BLRM) following the dose escalation with overdose control (EWOC) principle. This design uses all accumulating toxicity data to assign enrolling subjects to doses that have a higher chance of targeted toxicity (close to the MTD), while controlling the risk of excessive toxicity. To further ensure safety, the safety findings of each cohort will be carefully reviewed by the Safety Review Committee (SRC) prior to dose escalation decisions for the subsequent dose cohort.

During Phase 1, if a subject is tolerating AFM24 without significant evidence of disease progression or AFM24-related toxicity, the subject may, beginning with Cycle 3 or a subsequent cycle, have the dose increased to a dose that has already been established as tolerable by the SRC, and with the agreement of the SRC. This intra-subject dose escalation may allow subjects a greater possibility of benefit from treatment with AFM24 than might be achieved at the starting dose in his/her assigned dose cohort.

Risks of the tumor biopsy (mandatory for the subjects in the dose escalation phase [Phase 1]) include pain and tenderness at the tumor biopsy site and potential bleeding complications, which will be minimized by inclusion of subjects who have at least 1 site of tumor that is accessible to biopsy and that is considered by the Investigator to be low risk and of sufficient size to undergo a biopsy procedure, and monitoring per institutional practice.

No reproductive toxicity or carcinogenicity studies have been conducted with AFM24 to date. Both women and men should be fully informed of the lack of reproductive toxicity testing. Women of childbearing potential and men must agree to use adequate contraception from 14 days prior to the first dose of study drug up to 120 days after the last dose of study drug. Women must have a negative pregnancy test within 7 days prior to first dose of AFM24. It is unknown whether the drug is excreted in human milk, and women who are breast feeding are excluded from the study.

The study design for this FIH Phase 1/2a dose escalation/expansion study of AFM24 aims to minimize potential risks and offer the potential to benefit subjects with advanced or metastatic solid tumors. Although the potential benefits to subjects are unknown at this time, nonclinical data demonstrate evidence of potent antitumor efficacy, and the potential toxicities can be monitored and managed appropriately. The benefit/risk assessment for this study was based on the lack of effective alternative treatments, the limited life expectancy of the subject population, and the strength of the nonclinical data in support of potent antitumor activity. The preliminary safety, tolerability, and clinical activity data from the first cohorts of the Phase 1 part of study AFM24-101 are described in Section 1.6 of this protocol and in the Investigator's Brochure. The risk/benefit assessment remains unchanged.

2.0 STUDY OBJECTIVES AND ENDPOINTS

The study objectives and their respective endpoints for assessment are described in Table 2.

Table 2: Study Objectives and Endpoints

Objective	Endpoint(s)
Phase 1 (Dose Escalation)	
Primary Objective	**Primary Endpoint**
Determine the MTD, and/or to select one or more RP2Ds, and investigate the safety and tolerability of AFM24 in subjects with advanced or metastatic solid malignancies	The incidence of DLTs (during DLT observation period)
Secondary Objectives	**Secondary Endpoints**
Characterize the safety and tolerability of AFM24, including both acute and chronic toxicities	Incidence of subjects with TEAEs and SAEs
Characterize the PK of AFM24 administered i.v.	Serum PK parameters: AUC_{tau}, C_{max}, T_{max}, C_{min}
Characterize the immunogenicity of AFM24	Incidence of subjects who develop ADAs during treatment with AFM24 (by measurement of ADA before and throughout treatment with AFM24)
Assess the preliminary antitumor efficacy of AFM24	OR (CR + PR), DOR, and disease control (CR + PR + SD) assessed by: • Local RECIST v1.1
Exploratory Objectives	**Exploratory Endpoints**
Assess the preliminary antitumor efficacy of AFM24, using iRECIST tumor response criteria	OR (CR + PR), DOR, and disease control (CR + PR + SD) assessed by: • Local iRECIST; • Central RECIST v1.1; and • Central iRECIST. PFS measured by local and central assessments Overall survival
Assess AFM24 pharmacodynamics	
Phase 2a (Expansion)	
Primary Objective	**Primary Endpoint**
Assess the preliminary antitumor efficacy of AFM24, by local RECIST v1.1	Overall response (CR + PR) assessed by local RECIST v1.1.
Secondary Objectives	**Secondary Endpoints**
Characterize the safety and tolerability of AFM24, including both acute and chronic toxicities	Incidence of subjects with TEAEs and SAEs
Characterize the PK of AFM24 administered i.v.	AFM24 serum concentrations will be included in a population PK analysis
Characterize the immunogenicity of AFM24	Incidence of subjects who develop ADAs during treatment with AFM24 (by measurement of ADA before and throughout treatment with AFM24)
Assess the preliminary antitumor efficacy of AFM24	OR (CR + PR) assessed by • Central RECIST v1.1;

Objective	Endpoint(s)
	DOR, and disease control (CR + PR + SD) assessed by • Local RECIST v1.1; • Central RECIST v1.1; PFS measured by local and central assessments Overall Survival
Exploratory Objectives	**Exploratory Endpoints**
Assess the preliminary antitumor efficacy of AFM24, using iRECIST tumor response criteria	OR (CR + PR) assessed by • Local iRECIST • Central iRECIST DOR (CR + PR + SD) assessed by • Local iRECIST • Central iRECIST
Assess AFM24 pharmacodynamics	
Explore the predictive potential of biomarkers measured in blood and/or tumor tissue in response to AFM24	

ADA = antidrug antibody; AUC_{tau} = area under the concentration-time curve over the dose interval; C_{max} = maximum plasma concentration; C_{min} = minimum plasma concentration; CR = complete response; DLT = dose-limiting toxicity; DOR = duration of response; iRECIST = Response Evaluation Criteria in Solid Tumors for immunotherapy; i.v.= intravenously; MTD = maximum tolerated dose; OR = overall response; PFS = progression-free survival; PK = pharmacokinetics; PR = partial response; RP2D = recommended phase 2 dose; RECIST = Response Evaluation Criteria in Solid Tumors; SAE = serious adverse events; SD = stable disease; TEAE = treatment-emergent adverse events; T_{max} = time to C_{max}.

3.0 INVESTIGATIONAL PLAN

3.1 Overall Study Design

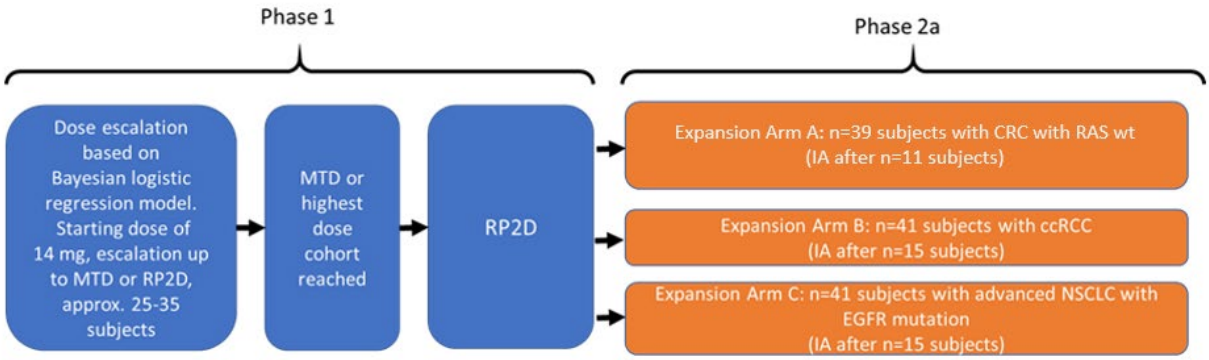
AFM24-101 is a FIH Phase 1/2a open-label, non-randomized, multicenter, multiple ascending dose escalation/expansion study evaluating AFM24 as monotherapy in subjects with advanced or metastatic solid malignancies whose disease has progressed after treatment with previous anticancer therapies.

An overview of overall study design is provided in Figure 2.

There will be 2 parts to this study: a dose escalation phase (Phase 1) and a dose expansion phase (Phase 2a). The aim of the dose escalation phase (Phase 1) is to determine the MTD and/or establish at least one RP2D. An adaptive 2-parameter BLRM guided by the EWOC principle will be used in the escalation phase to guide determination of the MTD and/or RP2D in subjects with advanced or metastatic solid malignancies (Section 9.3.4.1).

The dose escalation phase (Phase 1) will be followed by the dose expansion phase (Phase 2a) once the MTD and/or one or more RP2Ds of AFM24 monotherapy has been determined. The dose expansion phase (Phase 2a) of the study is intended to collect preliminary evidence of efficacy and to further confirm the safety of AFM24 as a monotherapy in distinct patient populations. The expansion phase will have 3 cohorts based on tumor type, as described in Figure 2. The expansion cohorts may be opened in parallel or subsequently.

Figure 2: Overall Study Design



approx. = approximately; CRC = metastatic colorectal cancer; ccRCC = clear cell renal cell carcinoma; EGFR = epidermal growth factor receptor; MTD = maximum tolerated dose; NSCLC = non-small cell lung cancer; RAS = rat sarcoma gene; RP2D = recommended phase 2 dose; wt = wild type.

The study scheme, including pre-screening/screening, treatment, and follow-up, for each subject receiving study drug as weekly dosing regimen is described in Figure 5.

Based on the findings in the dose escalation phase (Phase 1) part of the study, additional treatment schedules (i.e., every 2 weeks [q2w] dosing) may be explored in the dose expansion phase cohorts (Phase 2a). The study scheme, including pre-screening/screening, treatment, and follow-up, for each subject receiving study drug as q2w dosing regimen is described in Figure 6.

3.2 Pre-screening and Screening

Pre-screening:

Pre-screening is required for subjects in Phase 2a only. EGFR expression is to be assessed as per inclusion criterion #1) before the subject enters the screening phase. Archived paraffin embedded tumor tissue is acceptable for EGFR determination; otherwise, a fresh tumor biopsy must be performed. Local EGFR assessment is acceptable.

Subjects will sign a pre-screening informed consent form (ICF) allowing the testing of EGFR expression to determine whether eligibility criteria for EGFR expression have been met prior to entering the screening phase (**Note:** if a positive EGFR test has been performed from a subject's tumor tissue, and the EGFR laboratory report is available, the subject does not have to sign the pre-screening ICF and perform the pre-screening assessment and can directly proceed to signing the Main ICF and the screening activities).

For patients in Phase 2a, the screening phase starts only after the subject has met the eligibility criterion for EGFR expression and has signed the Main ICF.

Screening:

For each subject in the escalation phase (Phase 1), the study starts with a screening phase. The screening phase lasting up to 21 days begins for all subjects (in Phase 1 and 2a) when the (Main) ICF is signed and ends on the day before the first dose of study drug. Before entering the (main) study, all study procedures and possible risks will be explained to each subject who is asked to participate in the study. After provision of written informed consent for the study, screening assessments will include a careful review of the subject's medical history, assessment of Eastern Cooperative Oncology Group (ECOG) performance score (PS), physical examination, ECGs, laboratory assessments, and tumor assessments by computed tomography (CT) or magnetic resonance imaging (MRI), and tumor histopathology. Eligible subjects in dose escalation must have a tumor site that is accessible to biopsy and be willing to undergo at least 2 biopsy procedures (ie, 1 prior to and at least 1 during treatment with AFM24); see Section 4.1, inclusion criterion #9). Screening assessments are to be performed within 21 days of the first study drug dose, except for CT/MRI studies and tumor biopsies which may be performed within 28 days of the first study drug dose. Subjects who do not meet 1 or more eligibility criteria may be re-screened. The assessments for hepatitis C, hepatitis B, and human immunodeficiency virus (HIV) do not need to be repeated for re-screened subjects if it was done within 3 months before first dose of AFM24.

3.3 Treatment Assignment

Subjects will be enrolled in the study based on their eligibility criteria confirmed by the Sponsor's medical monitor.

3.4 Dose Escalation Phase (Phase 1)

Phase 1 will employ an adaptive BLRM with 2 parameters guided by the EWOC principle to make dose recommendations and estimate the MTD (Section 9.3.4.1). It is estimated that approximately 25 to 41 subjects will be enrolled into Phase 1 of the study. The number of subjects is dependent on the tested dose cohorts and safety profile of AFM24. As multiple centers will contribute to the enrollment a communication plan will be established to ensure distribution of safety data and study progress amongst the participating centers.

Dose-limiting toxicities (DLTs) will be assessed in the first treatment cycle (ie, the first 4 weeks of treatment for each subject), referred to as the DLT observation period.

The starting dose of AFM24 in the first dose cohort is 14.0 mg administered as an i.v. infusion on a once weekly dosing schedule divided into 4-week cycles.

Dose Cohorts 1 and 2:

To minimize the number of subjects treated at potentially subtherapeutic dose levels in the dose escalation phase (Phase 1), the first 2 dose cohorts will enroll a minimum of 2 subjects. The first 2 subjects of each dose cohort will begin treatment in a staggered approach with at least 7 days between first dosing of these 2 subjects. After the first subject in each cohort has begun treatment and been observed for at least 7 days, additional subjects within the cohort may begin treatment concurrently. All subjects who start treatment need to complete the 28-day DLT observation period or experience a DLT before the SRC meeting and dose escalation decision. A minimum of 2 subjects needs to be evaluable for DLT assessment (Section 3.4.2) to allow for a dose escalation decision by the SRC. If none or only 1 of the subjects is evaluable for DLT assessment, replacement subject(s) will be enrolled. The dose cohorts might be extended to up to 6 subjects based on the SRC decision.

Dose Cohort 3 and any Subsequent Cohorts:

Dose Cohort 3 and any subsequent cohorts will enroll at least 3 subjects. A fourth subject may be enrolled if treatment of the fourth subject is anticipated to begin within 14 days of treatment initiation of the third subject in the cohort. The first 2 subjects of each dose cohort will begin treatment in a staggered approach with at least 7 days between first dosing of these 2 subjects. Subsequent subjects may be enrolled concurrently. All subjects who start treatment need to complete the 28-day DLT observation period or experience a DLT before the SRC meeting and dose escalation decision. A minimum of 3 subjects need to be evaluable for DLT assessment (Section 3.4.2) to allow for a dose escalation decision by the SRC. If less than 3 subjects are evaluable for DLT assessment, replacement subject(s) will be enrolled. The dose cohorts might be extended to up to 6 subjects based on the SRC decision.

The BLRM will be assessed for those subjects who are evaluable for DLT assessment in the dose-determining set (DDS) consisting of all subjects who received at least 1 dose of AFM24, and either experienced a DLT at any time during Cycle 1 or met the minimum treatment and safety evaluation requirements without experiencing a DLT within Cycle 1. After completion of a given dose cohort, or at any time the BLRM is updated, the decision to dose escalate and the actual dose chosen will be based on the recommendation of the BLRM regarding the highest admissible dose according to the EWOC principle (Section 9.3.4.1) and the medical review of all available clinical, laboratory, and PK data. The outcome of these analyses and the respective datasets will be reviewed by the SRC consisting of the Principal Investigators at each study center and the Sponsor's Medical representative(s), and additional clinical experts, as needed. The SRC will confirm the dose level selection of the next dose cohort prior to enrollment. Dose escalation will continue until the MTD and/or at least one RP2D is determined.

In the event of a Common Terminology Criteria for Adverse Events (CTCAE) Grade 5 adverse event (AE) or a second CTCAE Grade 4 AE at least possibly related to AFM24 at any time during Phase 1, the Sponsor will suspend further accrual and will perform a safety analysis that will be reviewed by an ad-hoc SRC meeting to decide on further progression of the study.

3.4.1 Definition of Maximum Tolerated Dose

The MTD is defined as the highest dose of AFM24 if both of the following criteria are fulfilled:

- The posterior probability of the true DLT rate being in the target interval (≥16% to <33%) is >50% with less than 25% risk of the true DLT rate being above 33%; and
- At least 6 subjects have been treated at that cohort in the first cycle of AFM24 treatment under that dosing schedule.

As described in Section 3.4.3, an RP2D can be declared if:

- The MTD criteria are not met on any dose level and/or clinical and laboratory data indicate an optimal biologically active dose has been reached (with less than 25% risk of the true DLT rate being above 33%).

  AND

- At least 6 subjects have been treated at that dose level.

3.4.2 Definition of Dose-Limiting Toxicity (DLT)

Dose-limiting toxicity is defined as an AE or abnormal laboratory value assessed as unrelated to underlying disease, disease progression, inter-current illness, or concomitant medications, that occurs ≤28 days following the first dose of AFM24 (Cycle 1) and that meets any of the following criteria shown in Table 3. Clinically relevant toxicities will be evaluated according to the National Cancer Institute (NCI)/National Institutes of Health CTCAE v5.0. Subjects who experience a DLT during Cycle 1 must permanently discontinue AFM24.

Subjects must receive ≥80% of their assigned AFM24 dose in Cycle 1 and complete the 28-day DLT observation period or have had a DLT within the first cycle of treatment to be considered evaluable for DLT.

For dose-escalation decisions, only DLTs occurring during Cycle 1 of treatment will be considered in the 2-parameter BLRM.

Table 3: Definition of Dose Limiting Toxicity

Toxicity	Any of the following criteria
Hematological[a]	≥CTCAE Grade 4 neutropenia (ANC <0.5×10^9/L) lasting for longer than 4 consecutive days
	Febrile neutropenia (ANC<1.0×10^9/L of any duration accompanied by fever ≥38.5°C or systemic infection)
	CTCAE Grade 3 thrombocytopenia (platelets 25 to <50×10^9/L) associated with bleeding
	CTCAE Grade 4 thrombocytopenia (platelets <25×10^9/L)
	≥CTCAE Grade 4 anemia that is considered to be treatment related
Non-hematological	Any ≥CTCAE Grade 3 AE including, but not limited to: • CTCAE Grade 3 infusion-related reaction/cytokine release syndrome not responsive to symptomatic treatment within 6 hours (ie, no improvement to Grade 2 or better within 6 hours with optimal medical management) • CTCAE Grade 4 infusion-related reaction/cytokine release syndrome • QTcF prolongation (>500 msec)

Toxicity	Any of the following criteria
	• CTCAE Grade 3 hypertension for >14 consecutive days despite optimal anti-hypertension therapy • CTCAE Grade 4 hypertension • ≥CTCAE Grade 3 total bilirubin (>3×ULN) • ≥CTCAE Grade 3 ALT, AST, or ALP (>5×ULN) • Subjects without hepatic metastasis: subjects fulfilling Hy's law criteria or 1.5 times increase from baseline value of total bilirubin for >2 weeks[b]; • Subjects with hepatic metastasis: 1.5 times increase from baseline value of total bilirubin for >2 weeks[b]; • ≥CTCAE Grade 3 vomiting or nausea for ≥72 hours despite optimal anti-emetic therapy; and/or • ≥CTCAE Grade 3 diarrhea for ≥72 hours despite optimal anti-diarrhea treatment
	Any other ≥CTCAE Grade 3 AE not listed above, except for the exclusions noted below
	Inability to receive at least 3 of the scheduled doses of AFM24 in Cycle 1 due to treatment-related toxicity
	Any other toxicity (irrespective of grade) that: • Is greater than that at baseline and clinically significant and/or unacceptable and/or does not respond to supportive care and judged to be a DLT by the SRC; or • Results in a disruption of AFM24 dosing for more than 2 weeks
Exceptions to DLT criteria[c]	Isolated laboratory changes of any grade without clinical sequelae or clinical significance with the exception of those laboratory changes outlined above
	CTCAE Grade 3 fever (in the absence of neutropenia) or fatigue that resolves to <Grade 3 within 72 hours
	CTCAE Grade 3 hypertension for ≤14 consecutive days
	CTCAE Grade 3 nausea, vomiting, diarrhea, or dehydration that resolves to <Grade 3 within 72 hours of initiating optimal supportive care treatment
	CTCAE Grade 3 infusion-related reaction/cytokine release syndrome responsive to symptomatic treatment within 6 hours (ie, improvement to Grade 2 or better within 6 hours with optimal medical management)

AE = adverse event; ALT = alanine aminotransferase; ALP = alkaline phosphatase; ANC = absolute neutrophil count; AST = aspartate aminotransferase; CTCAE = Common Terminology Criteria for Adverse Events; DLT = dose-limiting toxicity; NCI = National Cancer Institute; QTcF = corrected QT interval by Fridericia; SRC = Safety Review Committee; ULN = upper limit of normal.

a. Subjects may receive supportive care (eg, use of granulocyte-colony stimulating factor, packed red blood cells, and platelets) as per local institutional guidelines. However, during the DLT observation period, it is not allowed to administer these supportive measures without clinical indication.
b. Subjects fulfilling potential Hy's law criteria need to have a repeat blood draw immediately and study drug withheld while the case is reviewed and follow-up assessments are performed. The Investigator will review all previous laboratory data to determine whether potential Hy's Law criteria were met at any study visit prior to or after starting study drug and will review the case with the Medical Monitor and agree on the approach for the subjects' follow-up assessments.
   Investigators should use their best judgment based on clinical and radiological criteria to exclude progressive disease as the cause of increased hepatic dysfunction.
c. The SRC will closely monitor and review all Aes including the incidences of the Aes listed under the "Exceptions to DLT criteria" during the scheduled and any ad-hoc SRC meetings.

Note: NCI CTCAE v5.0 will be used for all grading.

3.4.3 Estimation of MTD/RP2D

A 2-parameter BLRM employing the escalation with EWOC principle will be used during the escalation phase for selection of doses to investigate and for estimation of the MTD (Section 9.3.4.1). The general plan is that cohorts of subjects will receive escalating doses of AFM24 until the MTD is reached. Each cohort will consist of newly enrolled subjects.

Estimation of the MTD during the escalation phase of the study will be based upon the estimation of the probability of DLT in Cycle 1 in subjects who are evaluable for DLT assessment. If the MTD cannot be reached in the dose escalation phase (Phase 1), one or more RP2Ds will be determined as the dose resulting in the best therapeutic window for AFM24 based on the review of DLTs, AEs, serious AEs (SAEs), and laboratory, PK, and PD data. MTD and/or at least one RP2D (as defined in Section 3.4.3) might be determined based on dosing schedules and cancer indications.

At all decision time points, the adaptive BLRM permits alterations in the dose increments based on the observed toxicities. It will be possible for additional, intermediate dose levels to be added during the study.

Dose escalation will not exceed a 200% increase from the current dose being studied. Cohorts may be expanded at any dose level below the highest dose deemed unacceptable in order to better understand safety, tolerability, PK, or PD.

Provisional dose escalation levels are provided in Table 4; however, dose decisions during escalation are not limited to the values provided. Based on the recommendation of the BLRM regarding the highest dose that may not be exceeded at any decision point during escalation and the maximum increase in dose allowed by the protocol, intermediate doses may be administered to subsequent new cohorts of subjects. This includes doses lower than the starting dose or intermediate doses between the current and next (lower or higher) provisional doses. To further characterize the safety, PK, and/or PD, for a dose of AFM24 that is considered acceptably safe, i.e., lower than the MTD, the associated cohort may be expanded. In addition, dose escalation may be terminated at any time without establishing the MTD based on emerging safety concerns or based on clinical and laboratory data that indicate an optimal biologically active dose has been reached.

Table 4: Provisional Dose-Escalation Levels

Dose Level	Proposed Dose[a] (mg)	Increment from previous dose
-1[b]	7	50% decrease
1	14	Starting dose
2	40	200%
3	120	200%
4	360	200%
5	1000	200%

a. It is possible for additional, intermediate dose levels to be added during the course of the study.
b. Dose level -1 represents a dose that may be evaluated if dose level 1 is poorly tolerated. No dose de-escalation below this level is planned for this study. If dose level -1 is poorly tolerated the study will be terminated.

3.4.4 Replacement of Subjects

In the first 2 cohorts of the dose escalation phase (Phase 1) a subject will be replaced (ie, an additional subject will be added to the cohort) if only 1 or none of the treated subjects is evaluable for DLT assessment.

In the subsequent cohorts a subject will be replaced (ie, an additional subject will be added to the cohort) if less than 3 subjects are evaluable for DLT assessment.

In the dose expansion phase (Phase 2a) all patients in the **safety set** will not be replaced, independent of the availability of their post-baseline disease assessments.

3.5 Dose and Schedule Modifications

The BLRM will be updated with the newly accumulated data. The overdose risk will then be calculated for each dose, and escalation will be permitted to all doses, which fulfill the EWOC criterion (Section 9.3.4.1).

If DLTs are observed in the first 2 consecutive subjects receiving a dose level that has not been cleared for safety, subsequent enrollment to that cohort will be stopped. The BLRM will be re-run to confirm that the dose-level still fulfills the EWOC criterion. Based on this information, the SRC will evaluate whether the next subjects will be enrolled on the same dose level, or if they will be enrolled to a lower dose level.

Dose decisions for dose escalation cohorts (Phase 1) and additional dosing schedules to be explored in the expansion cohorts (Phase 2a) will be based on all relevant data available including safety information, DLTs, all ≥CTCAE Grade 2 toxicity data during Cycle 1 and PD and PK data, as available, from evaluable subjects in any cohort.

3.6 Safety Review Committee

The SRC will consist of the Sponsor's medical representative and the Principal Investigator or delegate from each active study center. The SRC will be co-chaired by 1 of the participating Principal Investigators and the Sponsor's medical representative. The study statistician will participate in the SRC. *Ad hoc* participants such as the clinical pharmacology scientist and clinical operations leader may be invited as appropriate. Additional experts may be consulted by the SRC as needed. Appropriate representatives of the coordinating contract research organization will also attend and minute the meeting.

The SRC has the responsibility for monitoring the clinical study's progress and the safety of the participating subjects. After there are 2 evaluable subjects for the first 2 cohorts and at least 3 evaluable subjects for subsequent cohorts at each dose level during Phase 1 of the study, the SRC will review and assess all available safety data from the cohort together with available PK data and recommendations from the BLRM to make a decision on the dose for the next cohort of subjects. The decision may be to:

- Proceed with dose escalation;
- Expand the cohort to a maximum of 6 evaluable subjects;
- De-escalate the dose to a lower dose level or to an intermediate lower dose level; or
- Stop the dose escalation.

The decisions and decision-making of the SRC will be documented and will be provided to the Investigators before dosing any new subjects on the next dose level.

During the dose expansion phase (Phase 2a) of the study, an Independent Data Monitoring Committee (IDMC) will periodically review all safety data generated throughout the dose expansion phase (Phase 2a) part of the study on a regular basis (Section 3.7).

All details regarding the SRC composition, meetings, reviewed data and the decision-making process will be documented in the study-specific SRC Charter.

3.7 Independent Data Monitoring Committee

Prior to initiation of dose expansion phase (Phase 2a), an Independent Data Monitoring Committee (IDMC) will be established consisting of clinical experts who are not directly involved in this clinical study. The IDMC will review all safety data generated throughout the dose expansion phase (Phase 2a) part of the study on a regular basis. Based on the outcome of their review, the IDMC will provide recommendations to the Sponsor with regard to study conduct or study procedures. The set-up and operational process for this IDMC will be described in a separate IDMC charter.

3.8 Dose Expansion Phase (Phase 2a)

Once at least one RP2D dose has been determined, then enrollment into 1 or more expansion cohorts for selected cancer indication in the dose expansion phase (Phase 2a) will begin. Other expansion cohorts may follow with the same or a different RP2D dose level. An optimum Simons two-stage design will be applied for the preliminary efficacy analyses for the following expansion cohorts (Figure 2):

- Expansion Cohort A will enroll up to a total of 39 subjects with microsatellite stable CRC with rat sarcoma gene (RAS) wild-type tumor, the interim analysis (IA) will be conducted after 11 subjects.

- According to Simons two-stage design it was planned that Expansion Cohort B will enroll up to a total of 41 subjects with ccRCC, and the IA will be conducted after 15 subjects. After conducting the interim analysis for Cohort A and C and stopping these cohorts for futility, it was considered unlikely that the continuation criteria can be met in Cohort B. Hence it was decided to prematurely stop enrollment after 8 patients in Cohort B.

- Expansion Cohort C will enroll up to a total of 41 subjects with advanced or metastatic NSCLC with an EGFR mutation, the IA will be conducted after 15 subjects.

3.9 Period of Observation

After completion of study drug, subjects will enter follow-up and will be contacted regularly by the Investigator or study personnel to collect information about subsequent therapies, disease status, and survival. Subjects will be followed for safety, duration of response (DOR), progression f-ree survival (PFS), and overall survival (OS) until the end of the study, (see below).

Observation Visits:

- End of Treatment visit: Visit to be performed 14 days (±2 days) from last drug intake or before start of any new anti-cancer treatment whichever is sooner. For subjects who discontinue prematurely before disease progression it must be performed as the last visit.
- Safety Follow Up visit: All subjects will undergo one Safety Follow-up visit 30 days (±5 days) after the last AFM24 infusion or before start of any new anti-cancer treatment whichever is sooner.
- Long-term Follow Up: Additional follow-up (phone contact) will take place at 3-month intervals (±2 weeks) after end of treatment visit until death, lost to follow-up- or mutual decision between PI and sponsor to discontinue Long-term Follow Up of the patient, whichever is sooner.
- End of Study: The study will be terminated as soon as all subjects have completed the first Long-term Follow-Up interval, withdrawn, or died, whichever occurs first.

The study will be analyzed and reported once the last subject of the study has experienced at least one of the following:

- Has been treated till at least 4 weeks after the 1st post-baseline tumor assessment
- Disease progression
- Withdrawal from treatment due to a drug related AE
- Fatal event
- Lost to Long-term Follow-Up
- Withdrawal of consent
- Start of other anti-cancer treatment

In case subjects are still being treated with study medication at the primary analysis cut-off date for this study, such subjects will be kept on treatment in the study and data collected will then be reported in an addendum to the final clinical study report (CSR). It will be noted in the final CSR that such a revised report may be provided.

3.10 Number of Subjects

The study will enroll subjects with advanced or metastatic solid malignancies whose disease has progressed after treatment with previous anticancer therapies.

It is estimated that approximately 25 to 41 subjects will be enrolled into Phase 1 (dose escalation) of the study. The number of subjects is dependent on the tested dose cohorts and safety profile of AFM24.

Additionally, 3 expansion cohorts (in Phase 2a [Expansion Phase]), with up to a total of 39, 41, and 41 subjects in Cohorts A, B, and C, respectively, for a maximum of 121 subjects, will be enrolled to assess the preliminary efficacy of AFM24 in 3 different subject populations. Depending on the preliminary efficacy observed in the dose escalation phase (Phase 1) of the study, additional expansion cohorts may be added by a protocol amendment.

3.11 Study Initiation and Completion

The start of this clinical study is defined as the first act of screening (signing of the Main ICF) for a potential subject.

The end of the study is defined as when all subjects have completed the first Long-term Follow-Up interval, withdrawn, or died, whichever occurs first.

4.0 SELECTION AND WITHDRAWAL OF SUBJECTS

Subjects will be considered eligible to be enrolled in the study if ALL the inclusion criteria and NONE of the exclusion criteria are met as defined below.

Prospective approval of protocol deviations to recruitment and enrollment criteria, also known as protocol waivers or exemptions, is not permitted. Please note that based on various guidelines (eg, *NCCN Guidelines: Cancer and COVID-19 Vaccination* [NCCN 2021] and *MHRA Guidance on Coronavirus [COVID-19]* [MHRA 2021]), COVID-19 vaccination should be prioritized for subjects with cancer with the understanding that there are limited safety and efficacy data in this subject group. These guidelines also state:

- "Delay of vaccination until immunosuppressive therapy is reduced and/or based on immunophenotyping of T cell and B cell immunity can be considered."
- "Systemic corticosteroids and targeted agents are expected to blunt immune responses to vaccination."

This study utilizes a mandatory premedication regimen that contains corticosteroids for at least the duration of the first cycle (ie, Cycle 1). **Therefore, for any new subjects to be enrolled in the study**, every effort should be made to vaccinate subjects prior to being considered for this study based on the Investigator's risk/benefit analysis for each subject. Any COVID-19 vaccination should be at least 2 weeks prior to C1D1; live attenuated vaccines at least 4 weeks prior to C1D1. **For subjects whose opportunity for COVID-19 vaccination arrives during the conduct of the study (ie, ongoing subjects in the study),** see instructions for COVID-19 vaccination provided in Section 5.6.1.1.

4.1 Subject Inclusion Criteria

The study will enroll subjects with advanced or metastatic solid malignancies whose disease has progressed after treatment with previous anticancer therapies.

Subjects are eligible only if all the following criteria are met:

1) For the dose escalation phase (Phase 1): histologically or cytologically confirmed advanced or metastatic solid malignancies that are known to express EGFR.

   For the dose expansion phase (Phase 2a): histologically or cytologically confirmed advanced or metastatic EGFR+ malignancies. EGFR expression is defined as positive staining for EGFR in ≥1% of tumor cells determined by a validated immunohistochemistry assay. Archived paraffin embedded tumor tissue is acceptable for EGFR determination – otherwise a fresh tumor biopsy must be performed. Local laboratory EGFR assessment is acceptable.

2) For dose escalation phase (Phase 1): Subjects must have been previously treated with 1 or more lines of anticancer therapy and have documented disease progression during or after their most recent line of anticancer therapy. In addition, either there is no further SOC therapy for the subject or the remaining SOC therapies are deemed not appropriate for the subject by the Investigator.
3) Subjects must have documented radiological progression during or after their latest therapy for all phases.
4) Voluntary provision and understanding of signed and dated, written informed consent prior to any mandatory study-specific procedures, sampling, or analysis.
5) Male or female aged ≥18 years on the day of signing informed consent (or of an acceptable age according to local regulations, whichever is older).
6) Eastern Cooperative Oncology Group (ECOG) Performance Score (PS) 0 or 1.
7) Adequate organ function, assessed within 14 and within 7 days before first AFM24 infusion, defined as follows:

   Note: Transfusions and hematopoietic growth factors to help meet eligibility are not allowed.

   - Bone marrow: Absolute neutrophil count ≥1.5×10^9/L, platelet count ≥100×10^9/L, and hemoglobin ≥8 g/dL;
   - Hepatic: total bilirubin ≤1.5×upper limit of normal (ULN) (or ≤3×ULN in participants with Gilbert's syndrome), alanine aminotransferase and aspartate aminotransferase ≤2.5×ULN for subjects without liver metastasis and alanine aminotransferase and aspartate aminotransferase ≤5×ULN for subjects with liver metastasis;
   - Renal: If serum creatinine concentration ≥1.5×ULN, then estimated creatinine clearance must be ≥50 mL/min (Cockcroft-Gault formula).

8) Serum potassium, calcium, magnesium, and phosphate within normal limits or not worse than CTCAE v5.0 Grade 1 and asymptomatic. If values are low on the initial screening assessment, supplements may be given, if clinically appropriate, and values repeated to confirm within CTCAE v5.0 Grade 1 limits.
9) For dose escalation phase (Phase 1): Subjects must have (mandatory) at least 1 tumor site that is accessible to biopsy and that is considered by the Investigator to be low risk and of sufficient size to undergo a core biopsy procedure on at least 2 separate occasions.
10) For the dose expansion phase (Phase 2a) only: Subjects must have measurable disease per Response Evaluation Criteria in Solid Tumors (RECIST) v1.1 (ie, at least 1 measurable lesion ≥10 mm by CT scan or MRI or ≥20 mm by chest X-ray, malignant lymph nodes are considered measurable if short axis is ≥15 mm assessed by CT scan), with the last imaging performed within 28 days before Cycle 1 Day 1 (C1D1).
11) Subjects in dose expansion phase (Phase 2a) must have histologically confirmed advanced or metastatic EGFR-positive malignancy for each expansion cohort as listed below:

    - Cohort A: Subjects with RAS wild type, microsatellite stable CRC whose disease has progressed after having received ≥2 prior lines of therapy, which

must have included oxaliplatin, irinotecan, and fluoropyrimidine. If available, prior therapy must also have included an anti-vascular endothelial growth factor (anti-VEGF) or anti-vascular endothelial growth factor and its receptor (anti-VEGFR) therapy (eg, bevacizumab, aflibercept, or ramucirumab), and an anti-EGFR therapy (eg, cetuximab or panitumumab).

- Cohort B: Subjects with ccRCC whose disease has progressed after having received ≥1 prior line(s) of therapy, which must have included a TKI (eg, sunitinib, pazopanib) and a checkpoint inhibitor (eg, pembrolizumab, avelumab, nivolumab).
- Cohort C: Subjects with advanced or metastatic NSCLC harboring a targetable EGFR kinase domain mutation and whose disease has progressed on or after having received ≥1 prior lines of therapy for advanced disease including ≥1 prior TKI approved for EGFR mutated NSCLC, such as gefitinib, erlotinib, afatinib, dacomitinib, or osimertinib. Subjects who were treated with a 1st or 2nd generation TKI in 1st line and developed a documented T790M mutation must have received a TKI targeting this mutation such as osimertinib or lazertinib to be eligible. Subjects must have documentation of EGFR mutated NSCLC as assessed by an approved test using genomic sequencing of tumor or circulating free tumor DNA.

12) Female subjects must have a negative urine or serum pregnancy test within 7 days prior to first dose of AFM24 if of childbearing potential or be of non-childbearing potential. If the urine pregnancy test is positive or cannot be confirmed as negative, a serum pregnancy test will be required. The serum pregnancy test must be negative for the subject to be eligible. Non-childbearing potential is defined as:
    - Postmenopausal, 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 post-menopausal state in women not using hormonal contraception or hormonal replacement therapy. However, in the absence of 12 months of amenorrhea, a single FSH measurement is insufficient.
    - Surgically sterile. Surgical sterilization methods include hysterectomy, bilateral salpingectomy, and bilateral oophorectomy.
13) Females of childbearing potential must agree to sexual abstinence (defined below) or be willing to use a highly effective method of contraception for the course of the study from 14 days prior to the first dose of study drug through 120 days after the last dose of study drug. Acceptable highly effective birth control methods include:
    - Oral, intravaginal, or transdermal combined (estrogen and progestogen containing) hormonal contraception associated with inhibition of ovulation;
    - Oral, injectable, or implantable progestogen-only hormonal contraception associated with inhibition of ovulation;
    - Intrauterine device;
    - Intrauterine hormone-releasing system;
    - Bilateral tubal occlusion;

- Vasectomized partner (provided that partner is the sole sexual partner of the female of reproductive potential and that the vasectomized partner has received medical assessment of the surgical success); and
- Sexual abstinence. In the context of this study, sexual abstinence is considered a highly effective method only if defined as refraining from heterosexual intercourse from 14 days prior to the first dose of study drug up to 120 days after the last dose of study drug. The reliability of sexual abstinence needs to be evaluated in relation to the duration of the clinical study and the preferred and usual lifestyle of the subject.

14) Males who have female partners of childbearing potential must agree to use a highly effective method of contraception as described in inclusion criterion 13, starting with the first dose of study drug through 120 days after the last dose of study drug.

4.2 Subject Exclusion Criteria

Subjects are eligible only if none of the following criteria are met:

1) Currently participating in a study and receiving study therapy or participated in a study of an investigational agent and received study therapy or used an investigational device within 4 weeks of the first dose of study drug.
2) Treatment with systemic anticancer therapy within 4 weeks (6 weeks if therapy was mitomycin C and/or nitrosoureas), or within 5 half-lives of the agent if half-life is known and it is shorter, before first dose of study drug. Anticancer therapies include cytotoxic chemotherapy, targeted inhibitors, and immunotherapies, but do not include hormonal therapy or radiotherapy.
3) Radiation therapy within 2 weeks before first dose of study drug or unresolved (NCI CTCAE v5.0 >Grade 1) toxicity from previous radiotherapy (e.g., radiation dermatitis).

   Note: Palliative (limited field) radiotherapy for managing pain associated with bone metastases present at baseline is permitted during the study.
4) Major surgical procedure, open biopsy, or significant traumatic injury within 4 weeks before first dose of study drug or anticipation of need of a major surgical procedure during the course of study. Note: Procedures that are considered to be minimally invasive (e.g., peripherally inserted central catheters lines and/or port placements) will be exceptions.
5) Subjects with toxicities (as a result of prior anticancer therapy) which have not recovered to baseline or CTCAE v5.0 ≤Grade 2, except for AEs not considered a likely safety risk (e.g., alopecia, specific laboratory abnormalities).
6) History of any other invasive malignancy, unless previously treated with curative intent and the subject has been disease free for 3 years or longer. Examples for acceptable previous malignancies include: completely removed in situ cervical intra-epithelial neoplasia, non-melanoma skin cancer, ductal carcinoma in situ, and early-stage prostate cancer that has been adequately treated.
7) One or more of the following cardiac criteria:
   - Unstable angina;
   - Myocardial infarction within 6 months prior to screening;
   - New York Heart Association Class III to IV heart failure;

- Corrected QT interval >470 msec obtained as the mean from 3 consecutive resting ECGs using the Fridericia's formula;
- Clinically important abnormalities in rhythm, conduction, or morphology of resting ECG (e.g., complete left bundle branch block or third-degree heart block);
- Congenital long QT syndrome;
- Uncontrolled hypertension (≥150/100 mmHg based on accurate measurement and average of ≥2 readings which are ≥5 minutes apart on ≥2 occasions) despite maximum antihypertensive therapy.

  Note: Patients who initially fail screening due to uncontrolled hypertension as defined above, but who then attain controlled hypertension with intensified antihypertensive therapy are allowed to undergo rescreening.

8) Stroke or transient ischemic attack within 6 months prior to screening.
9) History of leptomeningeal disease or spinal cord compression.
10) Known brain metastases unless asymptomatic and not requiring steroids for at least 4 weeks prior to start of study drug.
11) Subjects with primary brain tumor who require high dose steroids (defined as ≥30 mg prednisolone or equivalent per day) or who received high dose steroids within 4 weeks prior to first dose of study drug.
12) Diagnosis of immunodeficiency or active infection including known hepatitis B, hepatitis C, or HIV. A negative confirmatory test within 3 months of treatment start does not have to be repeated during the screening period.
13) Active autoimmune disease that requires systemic treatment with steroids or other immunosuppressive agents, or subjects who have received such agents within 4 weeks prior to first dose of study drug:

    Exceptions:

    - Topical (≤20% of the skin surface area), ocular, intra-articular, intranasal, or inhalation corticosteroids with minimal systemic absorption
    - A short course (≤7 days) of corticosteroids prescribed prophylactically (e.g., for contrast dye allergy or antiemetic therapy) or for treatment of non-autoimmune causes (e.g., delayed hypersensitivity reaction caused by contact allergen)
    - Physiological replacement doses of corticosteroids for adrenal or pituitary insufficiency

14) Has received a live vaccine administered within 28 days of planned treatment start (C1D1) or while participating in the study. Seasonal vaccines for influenza are generally inactivated vaccines and are allowed. Intranasal vaccines are live vaccines and are not allowed.
15) Subjects who require systemic steroid treatment or any other immunosuppressive therapy, or subjects who received such therapy within 4 weeks prior to the first dose of study drug, with the exceptions as outlined under exclusion criterion #13).
16) Pregnant, breastfeeding, or expecting to conceive or father children within the projected duration of the study, starting with the Screening visit (females) or first dose of study drug (males) through 120 days after the last dose of study drug.

17) Subject's unwillingness to comply with the protocol or inability to appreciate the nature, meaning, and consequences of the study and to formulate his/her own wishes correspondingly.

18) Any medical, psychological, or social condition that would interfere with the subject's participation in the study.

4.3 Subject Withdrawal from Study

Throughout the study, treatment with AFM24 may continue until the occurrence of 1 of the following events, whichever comes first:

- Subject withdrawal of consent;
- Disease progression (if initial radiological progressive disease is observed, while the clinical condition of the subject is stable, treatment continuation is allowed at the discretion of the Investigator. If treatment is continued after initial progressive disease, a confirmatory scan should be acquired within 4 to 6 weeks);
- Occurrence of intolerable toxicity;
- DLT during Cycle 1 in the Phase 1 part;
- Subject non-compliance and the need for withdrawal for this reason as assessed by the Investigator; or
- Investigator decision that it is in the subject's best interest to withdraw from the study.

Upon withdrawal from study drug, the reason for withdrawal should be sought and recorded in the subject file and the withdrawal will be captured in the electronic case report form (eCRF). Every effort will be made to complete the End of Treatment visit, the Safety Follow-up visit and for the subject to be followed up every 3 months thereafter. Where a subject withdraws his/her consent to participate in the study, such follow-up assessments cannot be conducted. The management and holding of data around subject withdrawal will be described in the subject ICF.

4.4 Subject Compliance

Subjects will be considered lost to follow-up if they repeatedly fail to return for scheduled visits and are unable to be contacted by the study site. The following actions must be taken if a subject fails to return to the clinic for a required study visit:

- The site must attempt to contact the subject and reschedule the missed visit as soon as possible and counsel the subject on the importance of maintaining the assigned visit schedule and ascertain whether or not the subject wishes to and/or should continue in the study;
- Before a subject is deemed lost to follow up, the Investigator or designee must make every effort to regain contact with the subject (where possible, 3 telephone calls and, if necessary, a registered letter to the subject's last known mailing address or local equivalent methods). These contact attempts should be documented in the subject's medical record; and
- Should the subject continue to be unreachable, he/she will be considered to have withdrawn from the study.

Situations of non-compliance will be reviewed on a case-by-case basis with the Sponsor and the site will be provided guidance on subject withdrawal from treatment and/or the study, where appropriate.

5.0 TREATMENT OF SUBJECTS

5.1 Description of Study Drug

AFM24 is a member of a new class of antibody drugs that recruits NK cells to eliminate cancer cells. AFM24 is a tetravalent, bispecific Fc-containing antibody that is bivalent for CD16A on NK cells and macrophages, and bivalent for EGFR on $EGFR^+$ tumor cells. The antigen binding domains are fused to a human Fc portion to facilitate FcRn binding and to achieve a serum half-life comparable to classical IgG antibodies. The Fc portion was engineered to eliminate binding to all Fcγ receptors but allows fixing of complement and CDC on $EGFR^+$ cells. AFM24 mediates specific, potent, and efficient lysis of human tumor cell lines that express EGFR solely by binding to $CD16A^+$ on NK cells or macrophages (ADCC and ADCP).

AFM24, constructed by means of recombinant technology, is expressed from 2 different genes (codon optimized for expression in Chinese hamster ovary cells) encoding 2 polypeptide chains (heavy chain 75 kDa and light chain 23 kDa) that subsequently form an IgG-like molecule consisting of 2 identical heavy and light chains at the size of about 196 kDa.

Please refer to the current version of the IB for additional information on the physical, chemical, and pharmaceutical properties of AFM24.

5.2 Study Drug Administration

All doses of AFM24 will be administered as an i.v. infusion. During the dose escalation phase (Phase 1), subjects will receive AFM24 as a weekly infusion. As mentioned in Section 3.1, additional dosing regimen (i.e., q2w) may be explored in the dose expansion phase (Phase 2a) **only.**

<u>For dose escalation phase (Phase 1) and dose expansion phase (Phase 2a)</u>

- Weekly dosing regimen (q1w): i.e., on Day 1, Day 8, Day 15, and Day 22 of a 28-day cycle (see APPENDIX A [Section 14.1]).

<u>For dose expansion phase (Phase 2a) **only**</u>

In addition to the weekly dosing regimen mentioned above, the following dosing regimen may be used:

- Every-2-weeks dosing regimen (q2w): i.e., on Day 1 and Day 15 of a 28-day cycle (see APPENDIX B [Section 14.2]). If the drug is given on a q2w schedule, the daily dose will not be higher than the highest daily dose that was tested in Phase 1 part of the study and was considered safe.

The baseline infusion time should not take less than approximately 4 hours for at least the first 2 AFM24 infusions (**Note:** infusion time is approximately 4 hours, any infusion time ≥3 hour 50 minutes will not be a deviation). It should also be noted that as the dose escalation continues into the higher dosing cohorts, the baseline infusion time may increase to >4 hours and as long as over 2 days (ie, split day dosing) based on a given subject's tolerability as detailed in the Pharmacy Manual for each cohort. For infusion times that span over 2 days (i.e., split day dosing), timepoints for different assessment may be affected and the Schedule of Assessment (SoA) tables should be referenced for details (See Section 14.1 and Section 14.2 for SoA tables

for weekly and q2w dosing schedules, respectively). If the first 2 consecutive AFM24 infusions are well tolerated (defined as no IRR/cytokine release syndrome (CRS) Grade >1), then the infusion time may be decreased to <4 hours to a minimum of 1 hour starting with the third subsequent infusion (ie, C1D15 for weekly dosing regimen and C2D1 for q2w dosing regimen) at the discretion of the Investigator along with a potential reduction of post infusion- observation period (with regular checks of vital signs, please refer to Table 5 for detailed description) from 4 hours to a minimum of 2 hours and a taper of corticosteroid premedication. Investigators should only make 1 modification per infusion at 1 time.

See APPENDIX F (Section 14.6) for details regarding treatment management for symptoms of IRR/CRS due to study drug). Refer to the Pharmacy Manual for full details regarding study drug administration.

Subjects may receive AFM24 as long as they continue to show clinical benefit, as judged by the Investigator, or until disease progression, other treatment discontinuation criteria are met, or withdrawal of consent (Section 4.3).

5.3 Premedication Regimen and Post-Dose Observation

Subjects are required to receive premedication with the following medications approximately 1 hour before each dose of AFM24:

- i.v dexamethasone 20 mg (or equivalent long-lasting steroid dose)
- i.v. H1 antagonist (e.g., diphenhydramine 50 mg or similar medication as used per local institutional practice) with or without an H2 antagonist (e.g., famotidine or similar medication as used per local institutional practice), and
- acetaminophen dosage as per local institutional practice (e.g., 650 mg to 1000 mg or equivalent).

Note: For infusion times that span over 2 days (i.e., split day dosing), subjects must receive premedication on Day 1 and as well on Day 2. This includes the H1 antagonist (with or without an H2 antagonist), acetaminophen, and dexamethasone. For Day 2, dexamethasone dose can be reduced to a minimum of 8 mg, according to local standards at the discretion of the Investigator/treating physician.

Subjects may also be administered prophylactic antiemetic medications as indicated. Additional oral premedication will be allowed on the day before each dose of AFM24 at the discretion of the Investigator, in particular for those subjects who may experience persistent IRR.

If the first 2 subsequent infusions are well tolerated (defined as no Grade >1 IRR/CRS), then the medication(s) within the premedication regimen can be tapered/decreased.

Clinicians should be prepared for an IRR or CRS to occur during or shortly after each AFM24 drug administration, with frequent monitoring of vital signs and medical equipment and supplies readily available and standing orders in place for immediate intervention. Please see APPENDIX F (Section 14.6) for details regarding treatment management for symptoms of IRR/CRS due to study drug.

After the first 2 subsequent doses of AFM24 subjects must be observed for at least 4 hours after the end of infusion (EOI), with regular checks of vital signs as described in Section 7.2.4.

In case of a split day dosing (over 2 days) subjects must be observed for at least 4 hours after the end of AFM24 infusion on each day. In this scenario, the split day dosing AFM24 infusion is considered 1 dose. If no signs or symptoms of CRS or an IRR (no Grade >1) are observed during or after the first 2 subsequent doses of AFM24 then the observation period following each AFM24 dose may be reduced from 4 hours to at least 2 hours after the end of infusion.

5.4 Dose Interruptions or Delays

AFM24 dosing delays may be permitted in the case of medical/surgical events or logistical reasons not related to study therapy (e.g., elective surgery, unrelated medical events, subject vacation and/or holidays). Subjects should re-commence study therapy within 3 weeks of the interruption, unless otherwise discussed and agreed with the Sponsor. Every effort should be made to avoid dose delays during the DLT observation period (Cycle 1 of the dose escalation phase).

Dose delays of up to 3 weeks (≤21 days between 2 consecutive doses) are allowed for subjects to recover from any AE and return to baseline or Grade ≤1 (except for fatigue or anorexia).

Subjects who do not recover from any AE and return to baseline or Grade ≤1 (except for fatigue or anorexia) within 3 weeks (≤21 days between 2 consecutive doses) must discontinue AFM24 permanently.

Please refer to APPENDIX A (Section 14.1) and APPENDIX B (Section 14.2) for more details of weekly and q2w AFM24 dosing schedules, respectively.

Weekly dosing schedule:

If the subject recovers from an AE and is able to continue study drug within 72 hours of the originally scheduled dosing day, then the subject should receive the delayed dose and continue treatment as per the original schedule, by not shifting any later doses. There should be at least 4 days without treatment before the subject receives the next dose. An example: if the subject has an AE on C1D15 and recovers in time and can receive the missed dose on C1D18, then the next dose for the subject is on C1D22.

If the subject does not recover from an AE within 72 hours, the missed dose(s) should be skipped and the subject should receive the next dose as per original schedule. An example: a missed dose on C2D1 and the subject recovered on C2D9, the next dose for this subject is on C2D15.

Every-2-weeks dosing schedule:

If the subject recovers from an AE and is able to continue study drug within 1 week from the original scheduled dosing day then the subject should receive the delayed dose and continue treatment as per the original schedule, by not shifting any later doses. There should be at least 7 days without treatment before the subject receives the next dose. An example: if the subject has an AE on C1D1 and recovers in time and can receive the missed dose latest on C1D8, then the next dose for the subject is on C1D15.

Further dose delays or skipping is not allowed for subjects to recover from any AE.

Further note, if an AE happens during the infusion, and the dose is interrupted, the subject can restart upon recovery to baseline or CTCAE v5.0 ≤Grade 1 within the same day of the event while keeping in mind the stability data of the AFM24 dose in the infusion bag (please refer to

the Pharmacy Manual for details as a new dose may have to be prepared depending on when the infusion was interrupted). If the subject already received ≥80% of the prescribed dose of that day at the time of the interruption or cannot recover within the same day of the event, the rest of the dose should be omitted.

5.5 Dose Modification

During Phase 1, if a subject is tolerating AFM24 well (ie, no drug-related Grade ≥2 toxicity) without evidence of disease progression following 2 cycles, the subject may, beginning with Cycle 3 or a subsequent Cycle, have the dose increased to a dose that has already been established as tolerable by the SRC, and with the agreement of the SRC.

Subjects who experience a DLT during Cycle 1 must permanently discontinue AFM24.

Dose reductions are not allowed.

5.6 Permitted and Restricted Concomitant Medications

5.6.1 Acceptable Concomitant Medications

All treatments and supportive care that the Investigator considers necessary for a subject's welfare may be administered at the discretion of the Investigator in keeping with the standards of medical care of the study site except for the prohibited concomitant medications listed in Section 5.6.2. All concomitant medication will be recorded in the subject's medical records and in the eCRF including all prescription, over-the-counter, herbal supplements, and i.v. medications and fluids. If changes occur during the study period, documentation of drug dosage, frequency, route, and date needs to also be included in the eCRF.

All concomitant medications received from Screening to the Safety Follow-up visit should be recorded as mentioned in the SoA tables (see APPENDIX A [Section 14.1] and APPENDIX B [Section 14.2]). Concomitant medications administered after the Safety Follow-up visit should be recorded for SAEs which are considered related to study drug (Section 8.1).

5.6.1.1 COVID-19 Vaccination

Various guidelines (eg, NCCN Guidelines: Cancer and COVID-19 Vaccination [NCCN 2021] and MHRA Guidance on Coronavirus [COVID-19] [MHRA 2021]) have noted that COVID-19 vaccination should be prioritized for subjects with cancer with the understanding that there are limited safety and efficacy data in this subject group. These guidelines also state:

- "Delay of vaccination until immunosuppressive therapy is reduced and/or based on immunophenotyping of T cell and B cell immunity can be considered."
- "Systemic corticosteroids and targeted agents are expected to blunt immune responses to vaccination."

This study utilizes a mandatory premedication regimen that contains corticosteroids (ie, 20 mg of i.v. dexamethasone) for at least the duration of the first cycle (ie, Cycle 1). Therefore, **for new subjects to be enrolled in the study,** every effort should be made to vaccinate subjects prior to being considered for this study based on the Investigator's risk/benefit analysis for each subject. Any COVID-19 vaccination should be at least 2 weeks prior to C1D1; live attenuated vaccines at least 4 weeks prior to C1D1.

For subjects whose opportunity for COVID-19 vaccination arrives during the conduct of the study (ie, ongoing subjects in the study), the following should be noted:

- COVID-19 vaccination should be avoided during the DLT period or Cycle 1 of the study period.
- As stated in Section 5.3, Investigators may taper premedication with corticosteroids for those subjects who do not experience IRR/CRS symptoms Grade >1 during the previous infusion starting with the third subsequent infusion (C1D15 for weekly dosing schedule and C2D1 for q2w schedule).
- If the vaccination opportunity falls within the mandatory corticosteroid premedication period, there should be a consideration by the Investigator for holding or tapering the corticosteroid to prioritize vaccination on a case-by-case basis based on the risk/benefit analysis by the Investigator/treating MD.
- COVID-19 vaccination is not permitted on AFM24 dosing days. Vaccination should be administered at least 3 days before or 3 days after the AFM24 treatment administration day.
- It should be noted that no planned dose delays for study drugs are allowed during the DLT period (ie, Cycle 1).

5.6.2 Prohibited Concomitant Medications

Medications specifically prohibited in the exclusion criteria are not allowed during the ongoing study. If there is a clinical indication for any medication specifically prohibited during the study, discontinuation from study drug may be required. The Investigator should discuss any questions regarding this with the Sponsor. The final decision on any supportive therapy rests with the Investigator and/or the subject's primary physician. However, in such cases, the decision to continue the subject on AFM24 study drug requires the mutual agreement of the Investigator, Sponsor, and subject.

Apart from the exceptions listed in the inclusion/exclusion criteria, subjects are prohibited from receiving the following therapies during the Screening (see Exclusion Criteria Section 4.2) and Treatment periods of this study, with exception of the treatment of AEs occurring during the study:

- Antineoplastic systemic chemotherapy or biological therapy;

  Exceptions: LHRH agonists/antagonists, bisphosphonates, and RANK ligand inhibitors will only be allowed during the study provided that the treatment was started prior to the study and the subject has been on a stable dose for at least 3 months (i.e., ≥3 months) from first day of study drug. Additionally, LHRH agonists should not be discontinued during the study.
- Immunotherapy not specified in this protocol;
- Investigational agents other than AFM24;
- Radiation therapy;
- Immunosuppressant drugs such as systemic glucocorticoids (high-dose steroids defined as ≥10 mg prednisone or equivalent per day, exceptions see below), Janus kinase inhibitors (e.g., tofacitinib), calcineurin inhibitors (e.g., cyclosporine), mTOR inhibitors (e.g., sirolimus), IMDH inhibitors (e.g., azathioprine), biologics (e.g.,

etanercept), monoclonal antibodies (e.g., infliximab);

- Systemic glucocorticoids for any purpose other than to prevent IRR/CRS and/or to modulate symptoms from an AE of suspected immunological etiology.

  Exceptions:
  - Topical (≤20% of the skin surface area), ocular, intra-articular, intranasal, or inhalation corticosteroids with minimal systemic absorption
  - A short course (≤7 days) of corticosteroids prescribed prophylactically (e.g., for contrast dye allergy or antiemetic therapy) or for treatment of non-autoimmune causes (e.g., delayed hypersensitivity reaction caused by contact allergen)
  - Physiological replacement doses of corticosteroids for adrenal or pituitary insufficiency
  - Corticosteroid use for the management of symptoms of IRR/CRS is permitted

Subjects who, in the assessment by the Investigator, require the use of any of the aforementioned treatments for clinical management should be removed from the study. Subjects may receive other medications that the Investigator deems to be medically necessary.

5.7 Blinding and Procedures for Unblinding the Study

This is an open-label study, and there are no procedures for blinding and unblinding.

5.8 Management of AFM24-Related Toxicities

Any DLT during Cycle 1 in the Phase 1 part: Permanently discontinue AFM24.

Please see APPENDIX F (Section 14.6) for a summary of management of IRR/CRS, and other AFM24-related AEs.

Fever: Subjects who develop fever during AFM24 treatment should be supported with antipyretic medications such as paracetamol or metamizole-sodium. If the subject develops high fever (above 40°C body temperature) physical cooling of the body, e.g., with cold packs should be considered. AFM24 treatment is recommended to be held for subjects who have body temperature ≥38°C until temperature normalizes below 38°C.

Cytokine release syndrome: See APPENDIX F (Section 14.6; grading and management of IRRs, CRS, and other AFM24-related AE) for detailed grading criteria and detailed guidance on management.

Dermatological toxicities: Investigators are asked to pay special attention to ALL dermatological toxicities and consult with a dermatologist if needed. In cases of ≥Grade 3 skin toxicity, AFM24 treatment should be interrupted or postponed until the reaction resolves to ≤Grade 1 or baseline. Subjects should be asked to limit direct sunlight exposure and apply protective sun cream during treatment with AFM24. A rechallenge should be considered at the discretion of the Investigator but AFM24 should be permanently discontinued with a recurrence of Grade 3 skin toxicity.

IRRs: See APPENDIX F (Section 14.6; grading and management of IRs, CRS, and other AFM24-related AEs) for detailed grading criteria and detailed guidance on management.

Electrolyte abnormalities: Consider withholding AFM24 for ≥Grade 2 electrolyte abnormalities and resume when resolved. Replenish electrolytes as medically appropriate.

Pulmonary symptoms: In the event of acute onset or worsening of pulmonary symptoms, interrupt AFM24 therapy. Discontinue AFM24 therapy if interstitial lung disease is confirmed.

Hepatotoxicity: If severe (CTCAE Grade ≥3) hepatic impairment develops for subject with/without liver metastasis, AFM24 should be discontinued permanently.

Gastrointestinal Perforation: Permanently discontinue AFM24 in subjects who develop gastrointestinal perforation.

Other: For all CTCAE Grade 3 toxicities other than those that meet the definition of a DLT during Cycle 1 of the dose escalation (i.e., Phase 1) phase, and other than those described above, interrupt treatment with AFM24 until resolved to Grade ≤1 or baseline. If CTCAE Grade 3 toxicity recurs upon rechallenge or in case of CTCAE Grade 4 toxicity, permanently discontinue treatment.

6.0 STUDY DRUG MATERIALS AND MANAGEMENT

6.1 Provision and Replacement of AFM24

Sufficient doses of AFM24 study drug will be supplied. Where study drug supplies (or packaging) are apparently damaged on receipt or considered unfit for use by the study site, the Sponsor (or their delegate) must be notified immediately. Where required, clinical study supplies will be replaced. Further details on the handling of AFM24 study drug at site will be described in the Pharmacy Manual.

6.2 Labeling of AFM24

AFM24 clinical study supplies will be labeled in compliance with Good Manufacturing Practice Annex 13 requirements, United States (US) FDA requirements, and any other applicable local regulatory guidelines.

6.3 Storage of AFM24

AFM24 study drug will be shipped to the site and must be stored at the site in a secure location under controlled conditions and in the required temperature range. Please see the Pharmacy Manual for further details.

6.4 Drug Accountability

The Investigator is obliged to keep sufficient documentation of the delivery, use, and destruction or return of unused, used, or partially used AFM24 study drug. The documentation must include dates, quantities, subject numbers, batch numbers, or other identification number. The Investigator may assign some or all the Investigator's duties for drug accountability to an appropriate pharmacist. Roles and responsibilities of site staff will be recorded in the Investigator Site File.

The Investigator should maintain records that document adequately that the subjects were administered the doses specified in the protocol and reconcile all AFM24 study drug received for the study. The local clinical research associate (CRA) will be responsible for checking the drug accountability records maintained by the site during study monitoring visits.

AFM24 provided for this study is for use only as directed in the protocol. It is the Investigator and their institution's responsibility to establish a system for handling study drug to ensure that:

- Deliveries of AFM24 are correctly received by a responsible person;
- Such deliveries are recorded;
- Study drug is handled and stored safely and properly as stated on the label;
- Study drug is only dispensed to study subjects in accordance with the protocol; and
- Any unused study drug is destroyed locally or returned for destruction in liaison with the CRA after written approval by the Sponsor.

Certificates of delivery and return must be signed by the responsible pharmacist and copies retained in the Pharmacy File. Throughout the study, it must be possible to reconcile delivery records with records of usage and any destroyed/returned stock of AFM24. To help with compliance checks, records of usage should include an appropriate form of identification of the subject to whom the study drug was dispensed (using an indirect form to allow cross reference to the subjects' identity), plus the quantity and date of dispensing.

The return or destruction of unused drug will be conducted after written approval by the Sponsor, with appropriate documentation and drug accountability procedures completed following destruction.

7.0 STUDY PROCEDURES

The schedule of assessments to be followed for weekly and q2w dosing regimens are provided in APPENDIX A [Table 11 through Table 15] and APPENDIX B [Table 16 through Table 18], respectively.

Safety will be assessed by periodic vital signs, physical examinations, ECOG PS, 12-lead ECGs, clinical laboratory assessments, and monitoring of AEs. AEs will be graded using the NCI CTCAE, v5.0 (NCI 2017).

All AEs and SAEs that are related to study procedures occurring during pre-screening as well as all AEs and SAEs occurring from the time the subject signs the main ICF up to and including the Safety Follow-up visit (30 days [±5 days] after the last administration of AFM24) or until the start of a new anti-cancer treatment, whichever is sooner, will be collected. Adverse events occurring after signing of the Main ICF but prior to the first dose of study drug shall be recorded on the Medical History eCRF page (**Note:** any SAEs which are related to study procedures and occur during pre-screening and any SAEs that occur after the subject signs the Main ICF and prior to the first dose of study drug will still be reported using the SAE form).

7.1 Volume of Blood Sampling

Total blood volumes required during study participation will be provided in the ICF provided to each subject. Efforts will be made to limit blood sampling to avoid any redundancy. The requirements for blood sampling will be described and maintained in the Lab Manual.

7.2 Description of Study Interventions and Assessments

Details of the procedures to be followed for specified study assessments for weekly and q2w dosing regimens are provided in APPENDIX A (Section 14.1) and APPENDIX B

(Section 14.2), respectively. During the study, additional assessments may be carried out as clinically indicated.

7.2.1 Informed Consent, Medical History, and Demographics

Before starting the pre-screening process (for subjects in Phase 2a) or screening process, written informed consent will be obtained. Demographic information will be collected during the Screening visit. There will be a baseline assessment of relevant medical history and cancer history conducted at Screening to confirm eligibility and to record significant medical history and concurrent illnesses. Concurrent illnesses recorded at Screening (excluding the primary disease under evaluation) that worsen in severity or frequency from this baseline assessment during the study should be reported as AEs (see Section 8.1).

7.2.2 Pregnancy and FSH tests

Female subjects of reproductive potential will have a pregnancy test carried out at Screening and at time points specified in the SoA tables (APPENDIX A [Section 14.1] and APPENDIX B [Section 14.2] for weekly and q2w, dosing regimens, respectively). This test must be carried out within 7 days prior to first AFM24 administration. A urine test is acceptable; however, where a urine test is equivocal, a blood test must be performed to confirm the result. Subjects confirmed as pregnant will be excluded from participation in the clinical study.

Female subjects of reproductive potential with a negative pregnancy test at screening will continue to have pregnancy tests conducted at least every 4 weeks during the study and at the End of Treatment visit.

Female subjects who require documented confirmation of post-menopausal status will have their FSH levels assessed at Screening. Where post-menopausal status is not confirmed, subjects will be required to undergo pregnancy testing per protocol to confirm suitability to proceed.

7.2.3 ECOG Performance Score

ECOG PS will be assessed at Screening and Day 1 of each treatment cycle. Details of the ECOG PS categories are presented in APPENDIX C (Section 14.3). Subjects must be confirmed as ECOG PS 0 or 1 to be eligible for study participation and then reconfirmed at Day 1 of each cycle.

7.2.4 Vital Signs

Frequent monitoring of the subject's vital signs during and after AFM24 infusion is implemented as a precautionary measure in this protocol.

Vital sign parameters will be taken at Screening and at timepoints specified in the Schedule of Assessments Tables (APPENDIX A [Section 14.1] for weekly dosing schedule; APPENDIX B [Section 14.2] for q2w dosing schedule). The date and time of collection will be recorded in the source document and in the eCRF.

Vital sign parameters will consist of measurements of temperature, resting heart rate, seated blood pressure (systolic/diastolic) after 5 minutes resting, oxygen saturation, and respiratory rate (Table 5).

If no signs or symptoms of CRS or IRR (no >Grade 1) are observed during or after the first 2 infusions of AFM24, beginning from the third subsequent infusion (i.e., C1D15 for weekly

schedule and C2D1 for every-2-weekly schedule) the observation period after the end of infusion may be reduced from 4 hours to a minimum of 2 hours post infusion. The recording schedule of vital signs parameters is described in Table 5.

Table 5: Recording Schedule of Vital Sign Parameters

	Vital sign timepoints for first 2 consecutive AFM24 dosing days (i.e., Cycle 1 Day 1 and Day 8)	**Vital sign timepoints for subsequent AFM24 dosing days (i.e., Cycle 1 Day 15 and beyond) [a,b]**
Before infusion	Baseline (within 1 hour before start of the infusion)	Baseline (within 1 hour before start of the infusion)
During infusion	30 (±10) minutes after start of infusion Every 30 (±10 minutes) thereafter until EOI At the EOI (±10 minutes)	30 (±10) minutes after start of infusion [b] As clinically indicated [b]
After infusion	+60 (±10) minutes post EOI Every 60 (±10) minutes thereafter until the end of the observation period	As clinically indicated [b]

CRS = cytokine release syndrome; EOI = end of infusion; IRR = infusion related reaction.
Note: in addition to the above listed time points, subjects should be additionally monitored in accordance with the institutional guidelines/clinical practice and as clinically indicated.
In case of split dosing, vital signs assessments at similar timepoints need to be done on both days.
[a] If no CRS or IRR (no Grade >1) events are observed during or after the first 2 consecutive AFM24 dosing days, then a reduced schedule of vital signs assessments may be followed as indicated for Cycle 1 Day 15 and beyond.
[b] In case of the occurrence of Grade >1 events of CRS or IRR at a later infusion (ie, on Cycle 1 Day 15 or beyond), then the same schedule for increased vital signs assessments should be performed as done for Cycle 1 Day 1 and Cycle 1 Day 8. If, after two consecutive infusions, the patient does not have an IRR event Grade > 1, then a reduced schedule of vital signs assessments may be followed.

7.2.5 Physical Examinations

A physical examination will be performed at screening and at timepoints specified in the SoA tables (APPENDIX A [Section 14.1] for the weekly dosing regimen; APPENDIX B [Section 14.2] for q2w dosing regimen). A full physical examination will include assessment of the following categories: head, eyes, ears, nose, throat, heart, lungs, abdomen, skin, musculoskeletal, extremities, neurological, lymph nodes, and 'other'. After the screening assessment, the physical examination may be reduced to a symptom-directed assessment.

Height and weight will be measured at screening and at timepoints specified in the SoA tables (APPENDIX A [Section 14.1]; APPENDIX B [Section 14.2]). Weight will be measured within 24 hours of administration of AFM24 on Day 1 of each cycle. Height and body weight will be obtained while the subject is wearing light clothing (without shoes).

If any clinically significant findings are identified during the study, the Investigator will record these as an AE, where the finding represents a change from baseline.

7.2.6 Clinical Chemistry, Hematology, Urinalysis, Coagulation

Blood and urine samples for determination of clinical chemistry, hematology, urinalysis, and coagulation parameters will be taken as described in the SoA tables (APPENDIX A [Section 14.1] for weekly dosing schedule and APPENDIX B [Section 14.2] for q2w dosing schedule). Subjects must demonstrate adequate organ function when assessed within 14 and 7 days before first AFM24 infusion to remain eligible as outlined in the inclusion criteria (Section 4.1). Clinical chemistry, hematology, urinalysis, and coagulation samples must be

taken within 24 hours of AFM24 infusion start on days when AFM24 is administered. In case a subject receives AFM24 as a split dose then the time period 'within 24 hours' refers to the first day of infusion onset (ie, if infusion is given as split dose on both Day 1 and Day 2 [in weekly dosing regimen], then these samples need to be collected within 24 hours of AFM24 infusion start on Day 1).

Hepatitis B, hepatitis C, and HIV serology testing will be performed at Screening.

The laboratory variables to be measured are described in APPENDIX D [Section 14.4].

Copies of laboratory accreditation certificates and reference ranges will be obtained from each study site prior to analysis of their first subject sample and maintained over the course of the study.

If a clinically significant clinical chemistry, hematology, urinalysis, or coagulation finding is identified during the study, the Investigator will assess whether this finding is also considered an AE.

7.2.7 Electrocardiogram

A resting 12-lead ECG will be performed at timepoints specified in the SoA tables (APPENDIX A [Section 14.1] for weekly dosing schedule and APPENDIX B [Section 14.2] for q2w dosing schedule). **For Phase 1 only**, triplicate

ECGs should be taken at least 5 minutes apart before infusion and within approximately 15 minutes after the end of infusion (note plus only). **For Phase 2a**, ECGs will be performed in triplicate at least 5 minutes apart at the Screening visit only; all subsequent ECGs will be performed as single ECGs.

For those occasions when both an ECG and peripheral blood sample (PK and PD [cytokines]) collection are required at the EOI of AFM24 (ie, Cycle 1 Day 1 and Day 22), the blood draw must be completed first, as close to the EOI as possible, followed by the ECG. Both procedures should be completed within approximately 15 minutes after the EOI (note plus only).

All 12-lead ECGs should be recorded while the subject is in supine position. ECGs will be recorded at 25 mm/sec. All efforts should be made to ensure that an identical ECG machine is used to collect traces for individual subjects. The Investigator or designated physician will review the ECG results. If any clinically significant findings are identified during the study, the Investigator will record these as an AE where the finding represents a change from baseline. In addition, an unscheduled ECG might be performed at any time if clinically indicated.

7.2.8 Pharmacokinetic Assessments

The PK profile will be assessed by determining serum levels of AFM24 at intervals throughout the study, as described in the Schedules of Pharmacokinetic, Pharmacodynamic, Immunogenicity, and Translational Assessments (APPENDIX A, Section 14.1 [Table 12 through Table 15] for weekly dosing regimen schedule and APPENDIX B, Section 14.2 [Table 17 and Table 18] for q2w dosing schedule).

The nominal PK blood sampling times requested should be adhered to as closely as possible. It is essential that the actual date and time of collection of each blood sample is recorded in the subject's records and the eCRF.

The pre-dose PK sample collected on C1D1 may also be used for the determination of soluble EGFR; high soluble EGFR levels at baseline might lead to faster AFM24 clearance.

Full details of the PK blood sample collection, processing, and handling for PK samples will be described in the Lab Manual for the study.

7.2.9 Pharmacodynamic Assessments

Serum and peripheral blood mononuclear cells will be collected as described in the Schedule of Pharmacokinetic, Pharmacodynamic, Immunogenicity, and Translational Assessments (APPENDIX A, Section 14.1 [Table 12 through Table 15] for weekly dosing schedule; APPENDIX B, Section 14.2 [Table 17 and Table 18] for q2w dosing schedule). PD assessments will be performed by measuring cytokine levels (see Section 7.2.13) and various lymphocyte subsets including NK cells, activated NK cells, and macrophages.

Blood PD markers will be assessed as described in the Schedule of Pharmacokinetic, Pharmacodynamic, Immunogenicity, and Translational Assessments (APPENDIX A [Section 14.1] for weekly dosing schedule and APPENDIX B [Section 14.2] for q2w dosing schedule). Please see the Lab Manual for full details of sample collection and handling.

7.2.10 CD16A Receptor Occupancy

CD16A receptor occupancy by AFM24 on NK cells in the peripheral blood will be measured in Phase 1 subjects only as described in the Schedule of Pharmacokinetic, Pharmacodynamic, Immunogenicity, and Translational Assessments (APPENDIX A [Section 14.1] for weekly dosing schedule and APPENDIX B [Section 14.2] for q2w dosing schedule).

7.2.11 Disease Response Assessment

Disease response will be assessed by the Investigator, using local RECIST v1.1 (Eisenhauer et al., 2009; Schwartz et al., 2016) and Response Evaluation Criteria in Solid Tumors for immunotherapy (iRECIST) (Seymour et al., 2017). In Phase 1 and 2a, imaging results will also be sent for independent central review. Tumor assessment with CT and/or MRI will occur at Screening as well as at timepoints specified in the SoA tables (APPENDIX A [Section 14.1] for weekly dosing schedule and APPENDIX B [Section 14.2] for q2w dosing schedule). Partial or complete response needs to be confirmed with repeated assessment at least 4 weeks after the initial assessment.

If initial radiological progressive disease is observed, while the clinical condition of the subject is stable, treatment continuation is allowed at the discretion of the Investigator. If treatment is continued after initial progressive disease, a confirmatory scan should be acquired within 4 to 6 weeks. However, the first successive scheduled timepoint after the confirmatory scan may be skipped if the window is considered not clinically relevant (up to the discretion of the Investigator).

7.2.12 Tumor Genomics and Tumor Biopsy

Blood samples for the assessment of tumor genomics from circulating tumor DNA will be taken as described in the Schedule of Pharmacokinetic, Pharmacodynamic, Immunogenicity,

and Translational Assessments (see APPENDIX A [Section 14.1] for weekly dosing schedule and APPENDIX B [Section 14.2] for q2w dosing schedule). Analysis will measure quantitatively the amount of circulating tumor DNA and a search will be done for known targetable tumor mutations (such as but not limited to known mutations in EGFR, anaplastic lymphoma kinase, BRAF genes). Full details of sample collection and handling of the sample will be described in the Lab Manual for the study.

For Phase 1 only: An initial tumor biopsy will be performed at Screening and 1 tumor biopsy will be performed during treatment with AFM24 on Day 24 of Cycle 1 (see SoA tables APPENDIX A [Section 14.1] for weekly dosing schedule and APPENDIX B [Section 14.2] for q2w dosing schedule). Tumor biopsies are mandatory for subjects in escalation phase (Phase 1). Tumor samples will be evaluated centrally to assess EGFR positivity of cancer cells, infiltrating NK cells and macrophages and their subpopulations, and additional markers.

For Phase 2a only: for diagnostic purposes, a tumor biopsy at pre-screening is needed for EGFR assessment if there is no archived tumor tissue available. Tumor biopsies for central lab analysis are not collected in the expansion phase.

Samples will be used only for purposes related to this research. Unused samples of subjects who separately consented to long-term storage will be stored up to maximum of 15 years or until the Sponsor has determined that specimens are no longer needed, and the decision has been made that none of the samples needs to be reanalyzed, whichever is sooner. In addition, samples can be destroyed at any time at the request of the subject.

7.2.13 Cytokines

All subjects will have blood samples taken to assess cytokine levels as part of the PD assessment at the time points described in the Schedule of Pharmacokinetic, Pharmacodynamic, Immunogenicity, and Translational Assessments (APPENDIX A [Section 14.1], for weekly dosing schedule and APPENDIX B [Section 14.2] for q2w dosing schedule). Samples collected for cytokine analysis may also be used for measurement of chemokines and/ or soluble receptors.

In case of suspected CRS or IRR or any anaphylactic reaction during or close to AFM24 infusion, a sample for central laboratory testing should be drawn. Sampling should occur at the first sign of the AE and 1 hour later to assess cytokine changes. In addition, local cytokine testing is recommended as clinically indicated and in accordance with institutional treatment guidelines.

Full details of sample collection and handling of cytokine samples will be described in Lab Manual for the study.

7.2.14 Antidrug Antibodies

All subjects will have blood samples drawn to assess for antidrug antibodies as described in Schedule of Pharmacokinetic, Pharmacodynamic, Immunogenicity, and Translational Assessments (APPENDIX A [Section 14.1] for weekly dosing schedule and APPENDIX B [Section 14.2] for q2w dosing schedule). Antidrug antibody samples should be taken just before administration of AFM24.

Full details of sample collection and handling of antidrug antibody samples will be described in the Lab Manual.

8.0 ASSESSMENT OF SAFETY

All subjects who receive treatment with AFM24 will be considered evaluable for safety. All AEs and SAEs that are related to study procedures occurring during pre-screening as well as all AEs and SAEs occurring from the time the subjects sign the Main ICF up to and including the Safety Follow-up visit (30 days [±5 days] after the last administration of AFM24 or before start of any new anti-cancer treatment whichever is sooner) will be collected. Detailed instructions on how to record/report AEs are provided in Section 8.1.3.

8.1 Adverse and Serious Adverse Events

8.1.1 Definition of Adverse Events

An AE is defined as any new untoward medical occurrence or worsening of a pre-existing medical condition in a subject or clinical investigation subject administered a medicinal product and which does not necessarily have a causal relationship with this treatment. An AE can therefore be any unfavorable and unintended sign (including a clinically significant abnormal laboratory finding, for example), symptom, or disease temporally associated with the use of a medicinal (investigational) product, whether considered related or unrelated to AFM24.

During clinical studies, AEs can be spontaneously reported or elicited during open-ended questioning, examination, or evaluation of a subject. To prevent reporting bias, subjects should not be questioned regarding the specific occurrence of 1 or more AEs. Adverse events include:

- Worsening (change in nature, severity, or frequency) of conditions present at the start of the study;
- Intercurrent illness;
- Drug interactions;
- Experiences related or possibly related to concomitant medications;
- Clinically significant abnormal laboratory values or shifts from baseline;
- Clinically significant abnormalities in physical examination, vital signs, weight, or ECG; and
- An accident or injury.
- Adverse events which are related to study procedures (for example a biopsy)

Adverse Events Expected Due to Disease Progression

The term “disease progression” alone should not be used when reporting AEs or SAEs, due to its lack of specificity. Rather, symptoms of disease progression should be reported. If death occurs as consequence of disease progression, this would be considered an outcome, and NOT an AE.

> *Example, a subject died due to a pulmonary hemorrhage secondary to tumor progression; an SAE report should be submitted with the event pulmonary hemorrhage notified as a Grade 5 (fatal) event.*

Surgical procedures or other therapeutic interventions themselves are not AEs, but the condition for which the surgery/intervention is required is an AE and should be documented accordingly.

Planned surgical measures and the condition(s) leading to these measures are not AEs if the condition(s) was (were) known before the period of observation and did not worsen during study. In the latter case, the condition should be reported as medical history.

8.1.2 Importance of Adverse Event Reporting

Timely and complete reporting of safety information is very important to assist in the identification of any untoward medical occurrence, thereby ensuring:

- The safety of study subjects;
- A greater understanding of the overall safety profile of the investigational drug;
- Recognition of any dose-related investigational drug toxicity;
- Appropriate modification of study protocols;
- Improvements in study design or procedures as required; and
- Adherence to required ethical and regulatory requirements for clinical study conduct.

8.1.3 Evaluating Adverse Events

During pre-screening, only AEs which are related to study procedures (e.g., a biopsy) should be collected. The AEs must be recorded and described on the appropriate AE page of the eCRF

Following the subject's written Main consent to participate in the study and up to the 30-day Safety Follow-up Visit, all AEs should be collected.

Adverse events that occur following signing of the Main ICF but prior to the first dose of study drug shall be recorded on the Medical History page of the eCRF.

Adverse events occurring after the subject signs the Main ICF and at/after the first dose of study drug and up to the 30-day Safety Follow-up Visit must be recorded and described on the appropriate AE page of the eCRF. (**Note:** any SAEs that are related to study procedures and occur during pre-screening and any SAEs that occur following signing the Main ICF and prior to the first dose of study drug will still be reported using the SAE form). Where known, the diagnosis of the underlying illness or disorder shall be recorded, rather than listing individual symptoms.

Please refer to Table 6, which describes the timelines of AE/SAE reporting and documentation in the eCRF.

The following information shall be captured for all AEs: date of onset and resolution, seriousness and seriousness criteria, severity of the event, causality assessment, treatment required for the AE, action taken with study drug, and information regarding resolution/outcome.

Table 6: Reporting of Adverse Events

	… between Pre-Screening ICF and Main ICF	… between Main ICF and first infusion	… at/after first infusion
AE unrelated to Study Procedure occurs …	no documentation needed	**document in medical history**	**document as AE**
AE related to Study Procedure occurs …	**document as AE**	**document in medical history**	**document as AE**
SAE unrelated to Study Procedure occurs …	no documentation needed	**document as SAE**	**document as SAE**
SAE related to Study Procedure occurs …	**document as SAE**	**document as SAE**	**document as SAE**

Abbreviations: AE = adverse event; ICF = informed consent form; SAE = serious adverse event

8.1.4 Definition of Serious Adverse Events

An SAE is defined as any untoward medical occurrence that at any dose causes or qualifies as the following:

- Results in death;
- Is life-threatening;
    - "Life-threatening" means that the subject was at immediate risk of death at the time of the SAE; it does not refer to an SAE that hypothetically might have caused death if it were more severe.
- Requires hospitalization or prolongation of existing hospitalization;
    - This means that hospital inpatient admission or prolongation of hospital stay were required for the treatment of the SAE or that they occurred as a consequence of the event.
    - Visits to a hospital by ambulance or to the emergency room without admission will not be regarded as hospitalization unless the event fulfills any other of the serious criteria.
- Results in persistent or significant disability or incapacity;
    - "Persistent or significant disability or incapacity" means a permanent or significant and substantial disruption of a person's ability to carry out normal life functions.
- Is a congenital anomaly or birth defect; and/or
- Is an important medical event.
    - Medical and scientific judgment should be exercised in deciding whether expedited reporting is appropriate in situations where none of the outcomes listed above occurred. Important medical events that may not be immediately life-threatening or result in death or hospitalization but may jeopardize the subject or may require intervention to prevent 1 of the other outcomes listed in the definition above should also usually be considered serious. Examples of such events include allergic bronchospasm requiring intensive treatment in an

emergency room or at home, blood dyscrasias, convulsions that do not result in inpatient hospitalization, or repeated IRRs.

- A diagnosis of new cancer/ malignant tumor during a treatment should always be considered as medically important.
- For this study, any DLTs (as per Section 3.4.2) are considered as important medical events and should be reported as an SAE.

All SAEs will be followed until resolution, the condition stabilizes or is considered chronic, the event is otherwise explained, or the subject is lost to follow-up or withdraws consent.

8.1.5 Severity

All AEs (including SAEs) are to be accurately recorded on the AE page of the subject's eCRF. Each event will be graded for severity using the classifications of NCI CTCAE v5.0 (NCI 2017). For events not addressed in the NCI CTCAE v5.0 classifications, the following grading will apply:

- **Mild (Grade 1)** - Mild; asymptomatic or mild symptoms; clinical or diagnostic observations only; intervention not indicated.
- **Moderate (Grade 2)** - Moderate; minimal, local or noninvasive intervention indicated; limiting age-appropriate instrumental activity of daily living.
- **Severe (Grade 3)** - Severe or medically significant but not immediately life-threatening; hospitalization or prolongation of hospitalization indicated; disabling; limiting self-care activity of daily living.
- **Life-threatening (Grade 4)** - Life-threatening consequences; urgent intervention indicated.
- **Fatal (Grade 5)** - Related to AE.

During initial dosing and its respective post-observation period, any clinical finding despite its severity that represents a change from baseline (e.g., mild skin reaction, fatigue, myalgia, etc.) shall be recorded and followed until resolution. Likewise, any clinically significant finding identified during the remaining course of the study, which represents a change from baseline would be required to be recorded by the Investigator.

8.1.6 Unexpected Adverse Events

The Sponsor will assess all SAEs whether they are expected or unexpected. An unexpected AE is any adverse drug event, the outcome, specificity, or severity of which is not consistent with those noted in the Reference Safety Information section of the current IB.

8.1.7 Causality Assessments

All AEs (including SAEs) will be assessed by the Investigator and Sponsor for the causal relationship of the AE to the study drug using the following definitions described in Table 7.

For reporting and data analysis purposes, AEs reported with a causality assessment of "Definitely", "Probably", and "Possibly" are to be considered as "having a reasonable causal relationship" to study drug. In case of disagreement between the Investigator and the Sponsor, the more conservative assessment will determine the reportability of the case.

Table 7: Relationship to Study Drug

	Relationship	Description
1	Not related	This category applies to those AEs which, after careful consideration, are clearly and incontrovertibly due to extraneous causes (disease, environment, etc.).
2	Unlikely (must have 2)	In general, this category can be considered applicable to those AEs which, after careful medical consideration at the time when they are evaluated, are judged to be unrelated to the study drug. An AE may be considered unlikely if or when: 1. It does not follow a reasonable temporal sequence from administration of the test drug. 2. It could readily have been produced by the subject's clinical state, environmental or toxic factors, or other modes of therapy administered to the subject. 3. It does not follow a known pattern of response to the test drug. 4. It does not reappear or worsen when the drug is re-administered.
3	Possibly (must have 2)	This category applies to those AEs for which, after careful medical consideration at the time they are evaluated, a connection with the test drug administration appears unlikely but cannot be ruled out with certainty. An AE may be considered possibly related if or when: 1. It follows a reasonable temporal sequence from administration of the test drug. 2. It could not readily have been produced by the subject's clinical state, environmental or toxic factors, or other modes of therapy administered to the subject. 3. It follows a known pattern of response to the test drug.
4	Probably (must have 3)	This category applies to those AEs for which, after careful medical consideration at the time they are evaluated, are felt with a high degree of certainty to be related to the test drug. An AE may be considered probably related if or when: 1. It follows a reasonable temporal sequence from administration of the test drug. 2. It could not be reasonably explained by the known characteristics of the subject's clinical state, environmental or toxic factors, or other modes of therapy administered to the subject. 3. It disappears or decreases on cessation or reduction in dose. There are important exceptions when an AE does not disappear upon discontinuation of the drug, yet drug-relatedness clearly exists (eg, bone marrow depression, fixed drug eruptions, tardive dyskinesia). 4. It follows a known pattern of response to the test drug.
5	Definitely (must have all)	This category applies to those AEs which the Investigator feels are incontrovertibly related to test drug. An AE may be assigned an attribution of definitely related if or when: 1. It follows a reasonable temporal sequence from administration of the test drug. 2. It could not be reasonably explained by the known characteristics of the subject's clinical state, environmental or toxic factors, or other modes of therapy administered to the subject. 3. It disappears or decreases on cessation or reduction in dose with re-exposure to drug. (**Note:** this is not to be construed as requiring re-exposure of the subject, however, a category of definitely related can only be used when a recurrence is observed.)

	Relationship	Description
		4. It follows a known pattern of response to the test drug.

AE = adverse event.

8.2 Reporting Serious Adverse Events and Adverse Events of Special Interest

Investigators must report SAEs which are related to study procedures and occur during prescreening and SAEs/adverse events of special interest (AESIs) occurring from the time the subject signs the Main ICF up to 30 days after the last administration of AFM24 or until the start of a new anti-cancer treatment, whichever is sooner, to the Sponsor or delegate within 24 hours of becoming aware of the event, by entering all required information in to the Electronic Data Capture (EDC) system by completing an electronic Case Report Form (eCRF) in accordance with the eCRF completion guidelines. Upon completion of the eCRF and submission of the eCRF, an automated notification will be triggered and will be received by the safety service provider and Sponsor.

In the unlikely event of a malfunction of the eCRF, sites are provided with paper-based SAE/AESI reporting forms; forms will be completed by the study Investigator and e-mailed within 24 hours to Affimed-PhV@spm2-safety.com. The Investigator shall ensure that the information is entered in the eCRF as soon as the eCRF technical issues are resolved.

(**Note:** Any SAEs that are related to study procedures and occur during pre-screening and any SAEs that occur following signing the Main ICF and prior to the first dose of study drug will still be reported using the SAE form).

Other supporting documentation of the event may be requested by the Sponsor or delegate and should be provided as soon as possible in an anonymized manner. Follow-up information about a previously reported SAE/AESI must be reported within the same applicable timeframe of receiving it. All SAEs/AESIs will be followed up until resolution or stabilization at a level acceptable to the Investigator and/or the Sponsor.

The Investigator is not responsible for actively seeking new SAEs after the follow-up period; however, if the Investigator becomes aware of an SAE that is reasonably associated with study treatment after the study period including follow up, this must be reported to the Sponsor.

8.3 Other Important Events for Immediate Reporting

Adverse events meeting the following criteria, although not categorized as 'serious' per International Council for Harmonisation (ICH) definition, are reportable to the Sponsor in the same timeframe as SAEs to meet certain local requirements and the study needs:

- A new cancer (that is not a condition of the study);
- A reported pregnancy or lactation after receipt of study drug and for ≤60 days from last dose; and
- An overdose (defined as a dose of AFM24 which is ≥10% above the intended daily dose or a dose interval <4 days between 2 consecutive doses).

Such events must be reported within 24 hours to the Sponsor either by electronic report or paper.

8.3.1 Adverse Events of Special Interest

Infusion-Related Reactions

The occurrence of IRRs is within the anticipated safety profile of AFM24, considering experiences with other EGFR and CD16 targeting agents.

Infusion-related reactions can manifest with allergic or anaphylactic symptoms, including but not limited to chills, flushing, hypotension, fever, hypoxia, loss of consciousness, bronchospasm, and even cardiac arrest. Although the majority of such IRRs are mild to moderate, in some rare cases these can be life threatening or even fatal. Most of the IRRs are associated with the first infusion (during or shortly after the infusion); however, IRRs can happen during or after any infusion, despite the lack of previous signs or symptoms. In the nonclinical studies of AFM24, there were no signs of IRRs or anaphylactic symptoms.

In order to increase the understanding of IRRs, these events are considered to be AESIs. This means:

- Any of these events should be reported within 24 hours of occurrence.
- The SAE form should be used.
- All symptoms suggesting an IRR should be mentioned.

Of particular interest is information related to the timely development of symptoms relative to dose per time, actions taken as well as outcome of events.

The data will not be subject to reporting to Independent Ethics Committee (IEC)/Independent Review Board (IRB)/Regulatory Authorities unless such an event qualifies as SAE.

8.3.2 Exposure During Pregnancy or Lactation

Pregnancy and breastfeeding are considered exclusion criteria for this study (Section 4.2). Although pregnancy and lactation are not considered AEs, it is the responsibility of Investigators or their designees to report any pregnancy or lactation in a subject (spontaneously reported to them) or pregnancy in a subject's partner that occurs during the study. Immediately discontinue AFM24 treatment permanently in case of pregnancy.

Pregnancies and lactations that occur in subjects after the ICF is signed but before starting study drug must be reported by the Investigator if they cause the subject to be excluded from the study. Pregnancies and lactations that occur in a study subject or a pregnancy in a subject's partner from the time of first study drug through to 60 days following cessation of AFM24 study drug, must be reported by the Investigator. All reported pregnancies must be followed to the completion or termination of the pregnancy. If the pregnancy continues to term, the outcome ie, the health of the infant, will be requested by the Sponsor. Parental and neonatal outcomes must be recorded even if they are completely normal and without AEs. Offspring should be followed up for at least 8 weeks after delivery. Longer observation periods may be determined by the Sponsor if an adverse outcome of the pregnancy was observed.

Such events must be reported within 24 hours to the Sponsor via email, fax, or telephone. The reporting procedures can be found in the SAE completion guidelines located in the Study Operations Manual (or equivalent).

8.3.3 Misuse, Medication Error, and Overdose

Study drug misuse, medication error, or overdose should be reported in the same format and within the same timelines as an SAE, even if they may not result in an adverse outcome. In the event of overdose, the subject should be observed closely for signs of toxicity. Appropriate supportive treatment should be provided if clinically indicated.

Overdose is defined as: ≥10% above the intended AFM24 planned dose is given or a dose interval <4 days between 2 consecutive doses. If the pharmacy discovers that an overdose has or may have been administered, they should contact the Investigator and Sponsor (or their delegate) immediately.

Medication error is defined as: An unintended failure in the drug treatment process that leads to, or has the potential to lead to, harm to the subject.

Misuse is defined as: Situations where an investigational medicinal product is intentionally and inappropriately used not in accordance with the terms of the current protocol.

8.3.4 Investigational Product Complaints

Pharmaceutical technical complaints associated with the investigational product must be reported to the Sponsor immediately, following the guidance specified in the Pharmacy Manual. The same reporting timelines as for SAEs will apply.

8.4 Follow-Up Information on an SAE

Collection of complete information concerning SAEs is extremely important. Thus, follow-up information that becomes available as the SAE evolves, as well as supporting documentation (eg, hospital discharge summaries and autopsy reports), should be collected subsequently if not available at the time of the initial report and immediately sent using the same procedure as the initial SAE report. The Sponsor (or their delegate) will also review SAE reports for missing information and send queries to the site for resolution as appropriate.

Appropriate diagnostic tests should be performed and therapeutic measures, if indicated, should be instituted. Appropriate consultation and follow-up evaluations should be carried out by the Investigator (or designee). An SAE is followed until it is considered resolved, returns to baseline, is chronically ongoing, stabilized or is otherwise explained by the Investigator. Reporting of Serious Adverse Events to Regulatory Authorities

In accordance with the US Code of Federal Regulations (CFR), Title 21 CFR Part 312.32, the EU Clinical Trial Regulation 536/2014 (EU-CTR), and the ICH Guidelines for Clinical Safety Data Management Definitions and Standards for Expedited Reporting, the Sponsor must submit written documentation in the form of an Investigational New Drug Application (IND) safety report or suspected unexpected serious adverse reaction (SUSAR) reports, respectively. The Sponsor should submit to the regulatory authority all safety updates and periodic reports, as required by applicable regulatory requirements. IND safety reports/SUSARs are required to be reported within 7 calendar days for life-threatening events and those resulting in death or 15 calendar days for all others. These timeframes begin with the first notification of the IND safety reports/SUSARs to the Sponsor or their delegate from the Investigator.

The Sponsor (or their delegate) will determine whether expedited reporting is necessary for SAEs depending on the assessment of seriousness, expectedness, and relationship. In case of

disagreement between the Investigator and the Sponsor regarding causal relationship, the more conservative assessment will determine the reportability of the case.

The Investigator must ensure they are aware and comply with any additional local reporting requirements. For all SAEs regardless of expectedness and relationship, the Sponsor (or their delegate) will assign a case number to be used in all future correspondence regarding the event and can provide a MedWatch or Council for International Organizations of Medical Sciences form describing the event, for the Investigators to report to their IRB/IEC, or other committee. Other SAEs (eg, expected or unrelated SAEs) should be reported per the relevant institution's procedures.

Where required, submission of safety updates by the Investigator to Competent Authorities should be handled according to local regulations. Otherwise, periodic safety reports to the regulatory agencies will be handled by the Sponsor (or their delegate). These safety updates will also include SAEs that do not require expedited reporting to the authorities.

Periodically (at least annually), the IB will be updated to include new and relevant safety information. Until such time that an AE becomes identified in the IB (see Summary of Data and Guidance for the Investigator), it should be considered unexpected.

9.0 STATISTICS

9.1 Analysis Sets

The **safety set** will consist of all subjects who received at least 1 dose of AFM24. The safety set will be the primary population for all safety-related endpoints except determination of the dose-DLT relationship, and for all efficacy related endpoints.

The **DDS** will consist of all subjects in the safety set who have either (a) experienced a DLT at any time during Cycle 1, or (b) met the minimum treatment and safety evaluation requirements without experiencing DLT within Cycle 1 (DLT evaluation period).

At least 2 subjects will be treated in each of the first 2 dose cohorts of AFM24. For all other dose cohorts, at least 3 subjects per cohort will be treated. The DDS will be used for determination of the MTD. The minimum treatment and safety evaluation requirements will have been met if the subject received ≥80% of their assigned AFM24 dose in Cycle 1 and completed the 28-day DLT observation period or have had a DLT within the first cycle of treatment to be considered evaluable for DLT. For the first 2 dose cohorts, at least 2 subjects are required to be evaluable for DLT for dose escalation to occur. For subsequent cohorts, at least 3 subjects are required to be evaluable for dose escalation to occur.

The DDS will be used in the BLRM to estimate the dose-DLT relationship.

The **PK set** consists of all subjects who have received at least 1 adequately documented dose of study drug and have at least 1 adequately documented post-dose PK measurement.

Subjects who were screened and have signed the informed consent but did not receive any treatment will be listed including reason for screening failure and any SAE that is related to study procedure. These subjects will not be part of any summary table except for summarizing disposition.

9.2 Missing Data/Discontinuation

Due to the dose escalation design of Phase 1 and the exploratory design of Phase 2a of the study, no imputation of missing values will be done for any analysis (except the imputation for missing partial dates of AEs, response assessments and concomitant medications). Reasons for discontinuation from the study and the study drug will be listed and summarized.

Currently, no drop out during the treatment period is foreseen. However, in the first 2 cohorts of Phase 1 (dose escalation), subjects will be replaced (ie, additional subjects will be added to the cohort) if <2 subjects are evaluable for DLT assessment. In the subsequent cohorts subjects will be replaced if <3 subjects are evaluable for DLT assessment. In the dose expansion phase (Phase 2a). all patients in the **safety set** will not be replaced, independent of the availability of their post-baseline disease assessments.

9.3 Statistical Analyses

9.3.1 Characteristics Demographics, Medical History, Prior Medication, and Other Baseline

Demographic characteristics, prior anti-cancer therapies and surgeries, medical history, prior medication, and other baseline data will be listed and summarized using descriptive statistics for numerical data and contingency tables for categorical data. Medical history and prior medication will be listed. Prior anti-cancer therapies will be coded by World Health Organization Anatomical, Therapeutic and Chemical terms and summarized. Prior cancer surgeries will be summarized.

9.3.2 Study Drug

Exposure to AFM24 will be summarized with descriptive statistics for the total number of infusions received. The total amount of time on AFM24 (duration of dosing in weeks) will also be derived and summarized. The number of infusions with interruptions (regardless of reason) will be summarized by dose cohorts and total.

9.3.3 Concomitant Medication

Concomitant medication and significant non-drug therapies after the start of study drug will be listed and summarized by World Health Organization Anatomical, Therapeutic and Chemical term in contingency tables.

9.3.4 Primary Analysis

9.3.4.1 Phase 1 (Dose Escalation)

An adaptive BLRM guided by the EWOC principle will be used in the dose escalation. The use of Bayesian response adaptive models for Phase 1 studies has been advocated by the European Medicines Agency adopted guideline on small populations (EMA, 2006) and by (Rogatko et al., 2007) and is one of the key elements of the FDA's Critical Path Initiative.

A 2-parameter BLRM (Neuenschwander et al., 2008) will be used for dose escalation of the monotherapy. Standardized doses will be used such that 1 of the doses (d*) equals 1, eg, doses are rescaled as d/d*. Consequently, α is equal to the odds of the probability of toxicity at d*. All information currently available about the dose-DLT relationship of AFM24 is summarized in a prior distribution. For this study, this includes preclinical data about the starting dose and predicted MTD of AFM24 within different animal species. This prior distribution is then updated after each cohort of subjects with all the DLT data available in the DDS from the

current study. Once updated, the distribution summarizes the probability that the true rate of DLT for each dose lies in the following categories:

- 0% to <16%: under-dosing;
- ≥16% to <33%: targeted toxicity; and
- ≥33% to 100%: excessive toxicity.

The EWOC principle (Babb et al., 1998; Neuenschwander et al., 2008) mandates that any dose of AFM24 that has more than a 25% chance of being in the excessive toxicity category is not considered for the next dose cohort. A clinical synthesis of the available toxicity information (including AEs that are not DLTs), PK, PD, and efficacy information as well as the recommendations from the Bayesian model, and the SRC will be used to determine the dose regimen for the next cohort at a dose-escalation teleconference. In any case where there is a change in dose schedule, a new model will be defined using a Meta-Analytic-Predictive prior, based on the observed data.

The frequency of DLTs will be tabulated by dose for subjects in the dose escalation phase (Phase 1) (especially for Cycle 1 and subjects in the DDS as the primary endpoint tabulation) and information about all DLTs will be listed by dose.

Bayesian Logistic Regression Model for MTD/RP2D Determination

The objective of the design is to determine the MTD defined as the highest dose with less than 25% risk of the true DLT rate being above 33%. The escalation Phase 1 dose-finding will be guided by a Bayesian 2-parameter logistic regression model with overdose control. These designs have been shown to be superior regarding the precision of MTD determination compared with 3+3 designs.

The model is formulated as follows:

$\text{logit}(p(d)) = \log(\alpha) + \beta * \log(d/d^*)$,

where $\text{logit}(p) = \log(p/(1-p))$. $p(d)$ represents the probability of having a DLT in the first cycle at dose d, $d^* = 180$ mg is the reference dose, allowing for the interpretation of α as the odds of a DLT at dose d^*, and $\theta = (\log(\alpha), \log(\beta))$ with $\alpha, \beta > 0$ is the parameter vector of the model.

Since a Bayesian approach is applied, a prior distribution $\pi(\theta)$ for the unknown parameter vector θ needs to be specified. This prior distribution will be specified as a multivariate normal distribution, ie,

$\pi(\theta) = \text{MVN}(\mu, \Sigma)$

the multivariate normal distribution with mean vector μ and covariance matrix Σ, with

$$\Sigma_i = \begin{pmatrix} \sigma_{i,11}^2 & \sigma_{i,11}\sigma_{i,22}\rho_i \\ \sigma_{i,11}\sigma_{i,22}\rho_i & \sigma_{i,22}^2 \end{pmatrix}$$

Prior derivation

For the current study, data from the non-clinical animal studies were available. Therefore, the observed toxicity data from a study in animals is used to derive the prior.

Prior from nonclinical data:

The starting dose of AFM24 will be 14.0 mg (200 µg/kg × 70 kg body weight), which is presumed to be at the lower end of the pharmacologically active dose range. No critical toxicities were observed in the cynomolgus toxicity studies up to the maximum applied AFM24 dose level of 75 mg/kg and furthermore, the bispecific NK engagers (in contrast to bispecific T cell engagers) tested so far by Affimed in nonclinical and clinical studies, were all well tolerated up to high dose levels. It is therefore highly unlikely that a severe toxicity defined as DLT in this study would occur at this starting dose, leading to the prior assumption that the median DLT rate at 14 mg is 0.1%. On the other hand, assuming dose-proportionality in humans using a cautious approach, the median DLT rate at the highest planned dose = 1000 mg was therefore assumed 25%.

Table 8: Summary of Prior Distribution

Mean vector	STD vector	Correlation
-1.983 -0.217	2.000, 1.000	0

STD = standard deviation.

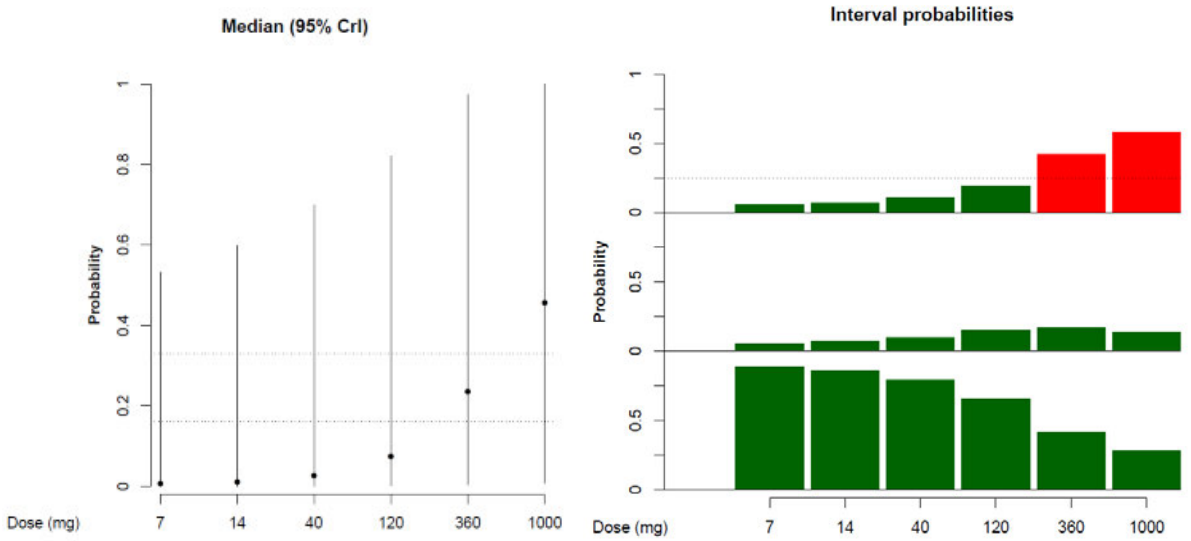
A summary of the prior probabilities of DLT at different doses, as well as the corresponding probability of under-, targeted, and overdosing, are shown in Table 9. Graphically, the prior medians with accompanying 95% credible intervals are shown in Figure 3. As can be seen from both Table 9 and Figure 3, the prior medians of the DLT probabilities are in line with the prior median derived from the non-clinical studies.

Table 9: Prior Probabilities of DLT at Selected Doses

Dose	Probability of true DLT rate in			Mean	STD	Quantiles		
	[0–0.16)	[0.16–0.33)	[0.33–1]			2.5%	50%	97.5%
7[a] mg	0.888	0.058	0.054	0.061	0.138	0.000	0.006	0.533
14 mg	0.859	0.072	0.069	0.075	0.153	0.000	0.011	0.597
40 mg	0.795	0.097	0.108	0.108	0.182	0.000	0.026	0.699
120 mg	0.655	0.148	0.196	0.178	0.227	0.001	0.074	0.821
360 mg	0.538	0.175	0.288	0.244	0.261	0.003	0.134	0.892
1000 mg	0.415	0.166	0.419	0.342	0.311	0.005	0.236	0.974

DLT = dose-limiting toxicity; STD = standard deviation.
Doses printed in bold type meet the overdose criterion, P(overdose) <0.25.
[a] Dose level -1 represents a dose that may be evaluated if dose level 1 is poorly tolerated. No dose de-escalation below this level is planned for this study. If dose-level -1 is poorly tolerated the study will be terminated.

Figure 3: Prior Medians and 95% Credible Intervals



CrL = credible interval; MTD = maximum tolerated dose; RP2D = recommended Phase 2 dose.

For MTD and/or RP2D definition, please refer to Section 3.4.3.

Statistical model assessment

The single agent model was assessed using 2 different metrics:

Hypothetical data scenarios: for various potential data constellations as they could occur in the actual study, the maximal next doses as allowed by the model and by the 200% escalation limit are investigated. Data scenarios thus provide a way to assess the "on-study" behavior of the model.

2. Simulated operating characteristics: these illustrate for different assumed true dose-toxicity relationships, how often a correct dose would be declared as MTD by the model. They are a way to assess the "long-run" behavior of the model.

In summary, the model showed very good behavior as assessed by these metrics. More details can be found in Appendix E (Section 14.5).

9.3.4.2 Phase 2a (Dose Expansion)

Once the MTD and/or at least one RP2D is determined, enrollment of subjects into 1 of several expansion cohorts for selected tumor indications may begin at the RP2D. The SRC may select an RP2D that is below the MTD, or if an MTD is not reached, an RP2D may be selected by the SRC after careful review of all available clinical and laboratory data from Phase 1. The RP2D will not exceed the MTD.

The primary objective of the expansion phase is to determine preliminary efficacy as objective response (OR) using a Simon's two-stage design. The primary endpoint is based on the objective response assessed by local Investigator according to RECIST v1.1 (Eisenhauer et al., 2009; Schwartz et al., 2016). The primary analysis will take place once all subjects per cohort had at least 1 confirmed response assessment (ie, ≥12 weeks post-baseline) or have been withdrawn from the study.

9.3.5 Secondary Analyses

9.3.5.1 Phase 1 (Dose Escalation) & Phase 2a (Dose Expansion)

9.3.5.1.1 Efficacy Analyses

All efficacy analyses will be done for Investigator assessed RECIST v1.1 (Eisenhauer et al., 2009; Schwartz et al., 2016), Investigator assessed iRECIST (Seymour et al., 2017), Central assessed RECIST v1.1 and Central assessed iRECIST. The local Investigator assessed RECIST is the primary endpoint for the Phase 2a.

9.3.5.1.1.1 Overall Response Rate

Overall response as defined by achieving confirmed CR and/or PR assessed by RECIST v1.1 will be presented by percentage rates and where appropriate the 95% confidence intervals (CIs). Partial or complete response needs to be confirmed with repeated assessment at least 4 weeks after the initial assessment. For changes in solid tumor size waterfall plots will be presented. For all response assessments swimmer plots will be presented. All response assessments will be listed.

9.3.5.1.1.2 Disease Control Rate at Month 3, 6, and 9

Disease control at months 3, 6, and 9, as defined by achieving CR and/or PR and/or SD assessed by RECIST v1.1 will be presented by percentage rates and where appropriate the 95% CIs. Waterfall plots will be presented.

9.3.5.1.1.3 Duration of Response

The DOR defined as time from first assessment of PR or CR to follow-on first assessment of progressive disease will be summarized by descriptive statistics including median DOR and where appropriate the respective 95% CIs. DOR will also be listed.

9.3.5.1.1.4 Progression Free Survival and Overall Survival

Time from first treatment received until disease progression or OS will be summarized by Kaplan-Meier estimates, median PFS/OS and where appropriate the respective 95% CIs. Subjects with no event will be censored at the last available tumor assessment for PFS and at the last timepoint known alive for OS.

9.3.5.1.2 Pharmacokinetic Analyses

The PK analysis plan for the assessment of AFM24 will be described in a separate Data Analysis Plan. Where feasible, non-compartmental analysis will be conducted using concentration-time data of AFM24. Summary statistics of PK parameters such as area under the concentration-time curve over the dose interval, maximum plasma concentration, time to maximum plasma concentration, and minimum plasma concentration will be reported by dose group. Additional parameters or model-based analysis may be calculated depending on the available data.

In the expansion cohorts, owing to sparse data sampling population exploratory PK analysis may be conducted to provide more comprehensive PK parameters for these subjects. If a population PK analysis is conducted, all available AFM24 serum concentrations will be used.

9.3.5.1.3 Immunogenicity Analyses

Immunogenicity parameters will be summarized by descriptive statistics and listed.

9.3.6 Safety Analyses

9.3.6.1 Adverse Events

Adverse events, related AEs, SAEs and related SAEs, AEs with NCI CTCAE Grades ≥3, AEs leading to premature discontinuation, interruptions or discontinuation of study drug, and standard medical queries will be analyzed descriptively utilizing corresponding Medical Dictionary for Regulatory Activities System Organ Classes and Preferred Terms. NCI CTCAE v5.0 toxicity Grades will be utilized for classifying severity.

Deaths within 28 days after the last dose and the corresponding reasons will be summarized. Also, all deaths overall will be summarized.

9.3.6.2 Safety Laboratory

Safety laboratory results will be graded by NCI CTCAE v5.0 if no grading exists values will be classified into low/normal/high based on laboratory normal ranges. Each parameter will be presented by descriptive statistics at each visit including change from baseline (Screening). Shift tables for CTCAE grades and normal ranges will be presented. All laboratory values will be listed. A separate listing for abnormal lab values (Grade 3 and higher, and low/high values) will be presented.

9.3.6.3 Vital Signs

Vital signs will be summarized by descriptive statistics at each visit including change from baseline will be presented and a listing will be provided.

9.3.6.4 Electrocardiogram

Local-read ECG data will be listed overall and a separate listing for any clinically significant finding in ECG values will be provided. The frequency and percentage of subjects with notable ECGs and newly occurring qualitative ECG abnormalities will be tabulated by cohort.

9.3.7 Exploratory Analysis

Exploratory biomarker analyses will be described in a biomarker statistical analyses plan.

Exploratory PD and biomarker analyses are dependent upon the availability of appropriate assays and may be deferred or not performed if, during or at the end of the study, it becomes clear that the analysis will have no scientific value or if there are not enough samples or responders to allow for adequate biomarker evaluation. If the study is terminated early or shows poor clinical efficacy, completion of biomarker assessments will be based on justification and intended utility of the data.

9.3.8 Interim Analyses

9.3.8.1 Phase 1 (Dose Escalation)

An interim analysis (IA) will be conducted at each dose escalation step. The BLRM will be updated with the respective number of subjects treated and the number of DLTs observed in the last cohort. The updated model will then give a statistical recommendation for the next escalation step. In addition, a risk-benefit assessment that includes a comprehensive analysis of safety and available clinical information will be done to decide on the next escalation steps.

In the event of a CTCAE Grade 5 AE or a second CTCAE Grade 4 AE at least possibly related to AFM24 at any time during Phase 1, the Sponsor will suspend further enrollment and interim

analysis will be done. The interim safety analysis will be reviewed by an ad-hoc SRC meeting to decide on further progression of the study.

At least 1 IA (end of Phase 1) will be performed after all subjects treated in Phase 1 have completed their first post-baseline disease assessment and its confirmation (2nd post-baseline assessment, ie, ≥12 weeks post-baseline) or have withdrawn from the study. In case several RP2Ds will be determined, additional IAs might be performed after the respective dose level. No formal interim report will be written. All subjects still ongoing at this timepoint will continue until disease progression, intolerable toxicity, Investigator discretion, or subject's withdrawal of consent and all assessments will be included in final analysis at the end of study.

9.3.8.2 Phase 2a (Dose Expansion)

An IA will be performed for each cohort independently, once the defined number of subjects (11, 15, and 15 subjects for Cohorts A, B, and C, respectively, – see Table 10) in the respective cohort have completed their first post-baseline assessment and its confirmation (2nd post-baseline assessment, ie, ≥12 weeks post-baseline) to be categorized under the primary response endpoint or have withdrawn from the study. Each cohort will be then assessed for futility. The results from this IA will be non-binding, unless no signs of efficacy are observed. Safety criteria will also be evaluated to decide on the continuation of the cohorts. During the conduct of the study, after the interim analysis for Cohort A and C and stopping these cohorts for futility, it was considered unlikely that the continuation criteria can be met in Cohort B. Hence it was decided to prematurely stop enrollment after 8 patients in Cohort B.

9.4 Sample Size

9.4.1 Phase 1 (Dose Escalation)

During the study, for the first 2 dose cohorts of the monotherapy, at least 2 subjects need to be evaluable. For the remaining cohorts, a minimum of 3 subjects evaluable for the DDS will be treated per dose cohort until determination of the MTD and/or one or more RP2Ds. At least 2 evaluable subjects are planned for the first 2 cohorts and at least 3 evaluable subjects per any following dose cohort thereafter. It is estimated that up to 41 subjects will be enrolled taking dropouts and additional subjects enrolled for some of the dose groups into account. The actual number of subjects will depend on the number of dose levels/cohorts that are tested.

9.4.2 Phase 2a (Dose Expansion)

An optimum Simon's two-stage design will be used for the expansion phase (Simon 1989). The assumptions and sample size calculations for different cohorts are summarized in Table 10.

Table 10: Sample Size Consideration for Expansion Cohorts

Indication	Objective Response Rate		Interim Analysis		Final Analysis		One-sided test	
	Alternative hypothesis	Null hypothesis	Number of subjects	OR, that may lead to stop	Number of subjects*	OR (rejection of the null hypothesis)	Power	Type I error rate (α)

RAS wt, microsatellite stable CRC	25%	5%	11	≤1	39	≥4	80%	5%
ccRCC	30%	14%	15	≤2	41	≥10	81%	5%
NSCLC EGFRmut	30%	14%	15	≤2	41	≥10	81%	5%
Maximum number of subjects:				**121**				

ccRCC = clear cell renal cell carcinoma; CRC = colorectal cancer; EGFRmut = epidermal growth factor receptor mutant; NSCLC = non-small cell lung cancer; OR = objective response; RAS = rat sarcoma gene; wt = wild type.
*Up to a total of N~40 subjects per cohort according to the FDA guideline, 2018

In other words:

RAS wt, microsatellite stable CRC: The power that is computed at ORR=25% (alternative hypothesis) is 80%. If the treatment is actually not effective, there is a 0.05 (α) probability of concluding that it is. After testing the treatment on 11 subjects in the first stage, the study may be terminated if 1 or fewer responds. At final analysis (N=39) if the total number responding is less than or equal to 3, the treatment is rejected.

ccRCC: The power that is computed at ORR=30% (alternative hypothesis) is 81%. If the treatment is actually not effective, there is a 0.05 (α) probability of concluding that it is. After testing the treatment on 15 subjects in the first stage, the study may be terminated if 2 or fewer responds. At final analysis (N=41), if the total number responding is less than or equal to 9, the treatment is rejected.

NSCLC EGFRmut: The power that is computed at ORR=30% (alternative hypothesis) is 81%. If the treatment is actually not effective, there is a 0.05 (α) probability of concluding that it is. After testing the treatment on 15 subjects in the first stage, the study may be terminated if 2 or fewer responds. At final analysis (N=41), if the total number responding is less than or equal to 9, the treatment is rejected.

The sample size is based on the safety analysis set for all subjects.

10.0 QUALITY CONTROL AND QUALITY ASSURANCE

10.1 Data Recording, Monitoring of the Study, and Regulatory Compliance

The project manager, or their designee, will make an initiation site visit to each institution to review the protocol and its requirements with the Investigator(s), inspect the drug storage area, fully inform the Investigator of his/her responsibilities and the procedures for assuring adequate and correct documentation. During the initiation site visit, the eCRF and other pertinent study materials will be reviewed with the Investigator's research staff. During the study, the CRA will make regular site visits in order to review protocol compliance, examine CRFs and individual subject's medical records, and assure that the study is being conducted according to pertinent regulatory requirements including ICH-Good Clinical Practice (GCP). Sites should ensure that source documentation is available to enable verification of all eCRF data entries. The review of medical records will be done in a manner to ensure that subject confidentiality is maintained.

All eCRF data will be collected using an eCRF within a fully validated and CFR 21 Part 11-compliant electronic data capture system. All data will be entered into the eCRF by the site staff. These data will then be source-data verified and reviewed by the CRAs before data cleaning by Data Management is performed. All queries will be raised and resolved within the electronic data capture system. During entry, programmatic checking of the data will be performed and once saved into the database, more complex programmatic checks will also be performed. During the conduct of the study, all system users will have real-time access to the data. The level of access to the data and study privileges will be determined by their user role.

After all queries have been resolved, the Statistical Analysis Plan approved and signed, and any summary/analysis populations approved, the database will be locked, and the data released for summary and analysis. All summary and analysis of the data will be performed using appropriate versions of SAS® and WinNonLin Pro, or equivalent.

10.2 Study Monitoring

Clinical research associates will be responsible for the monitoring of the study. The CRA will review the progress of the study on a regular basis to ensure adequate and accurate data collections. Monitoring site visits to review the eCRF, subject case notes, administrative documentation including the Investigator Site File, and frequent telephone/e-mail communications with the site will be performed throughout the study.

At each study monitoring visit, the Investigator will make available all records pertaining to the study. To allow sufficient time to assemble documentation for the CRA, monitoring visits will be confirmed in advance of planned visits.

The process for study monitoring and source data verification requirements for the study will be specified in the Monitoring Plan (or equivalent).

10.3 Clinical Study Audit

The Sponsor, Sponsor representative, or external regulatory agency may at any time during or after completion of the study conduct a GCP audit. Prior notice will be given to each site selected for audit in advance of a planned audit.

10.4 Clinical Study Report

The results of the study will be presented in an integrated CSR according to ICH guidelines. The CSR will be written once all expansion cohorts reach the primary endpoint assessment (see Section 9.3.4.2).

In case subjects are still being treated with study medication at the primary analysis cut-off date for this study, such subjects will be kept on treatment in the study and data collected will then be reported in an addendum to the final CSR. It will be noted in the final CSR that such a revised report may be provided.

10.5 Data Availability

The Investigator is required to maintain copies of all essential study documentation, including the Site Study File, all eCRF data (including the full audit trail and all data queries), signed ICFs, and records for the receipt and disposition of study drug.

During the study, the Investigator must make study data accessible to the CRA, the Sponsor (or a third-party auditor assigned by the Sponsor), and relevant IRB/EC and regulatory agencies. A file (or appropriate records) for each subject must be maintained that includes the signed ICF and all source documentation related to that subject. The Investigator must ensure the availability of source documents from which the information in the eCRF was derived.

Please refer to Section 12.2 for details of required record retention for the study.

10.6 Curricula Vitae and Financial Disclosure of Investigators

All Principal Investigators will be required to provide a current signed and dated curriculum vitae, a completed FDA Form 1572 (or accepted equivalent) and a financial disclosure statement. All Sub-Investigators will be required to provide a current curriculum vitae and a financial disclosure statement.

10.7 Protocol Modifications

No modification of the protocol should be implemented without the prior written approval of the Sponsor. Any such changes which may affect a subject's treatment or informed consent, especially those increasing potential risks, must receive prior approval by the IRB/EC. The exception to this is where modifications are necessary to eliminate an immediate hazard to study subjects, or when the change involves only logistical or administrative aspects of the study (e.g., change in monitor, change in telephone number). Other administrative revisions which may impact the clinical portion of a study will be duly reported to the IRB/EC by the Principal Investigator.

10.8 Study or Site Termination

If the Sponsor or their representatives, Investigator, or Competent Authority discover conditions during the study that indicate that the study or site involvement should be terminated, this action may be taken after appropriate consultation with the Sponsor and the Investigator. Conditions that may warrant termination of the study or a study site include, but are not limited to:

- The discovery of an unexpected, serious, or unacceptable risk to subjects enrolled in the study;
- The decision on the part of the Sponsor to suspend or discontinue testing, evaluation, or development of the study drug;
- Failure of an Investigator(s) to comply with pertinent clinical study regulations;
- Submission of knowingly false information from the study site to the Sponsor, CRA, or Competent Authority; and
- Insufficient adherence to protocol requirements.
- Study termination and/or site close out will be performed in accordance with applicable local regulations.

11.0 ETHICAL CONSIDERATIONS

The Investigator will obtain written informed consent from each subject, or their authorized representative, participating in the study. The ICF must be signed, witnessed, and dated. The ICF will contain all the Essential Elements of Informed Consent set forth in 21 CFR, Part 50, the ICH Guideline for GCP, and the terms of the Declaration of Helsinki. Copies of the signed document should be given to the subject and filed in the Investigator's Study File, as well as the subject's medical record if in conformance with the institution's standard operating procedures.

The final study protocol and subject ICF will be approved by the appropriate IRB/EC for each investigational site. Approval will be received in writing before initiation of the study.

Changes to the protocol during the study will be documented as amendments. Depending on the contents of the amendment and local legal requirements, the amendment will be submitted for approval to the relevant IRB/EC and to the relevant competent authorities prior to implementation. Exceptions are cases of changes made to protect subject safety, which will be implemented immediately.

If an amendment substantially alters the study design, increases the potential risk to the subjects, affects the treatment of the subject, or might otherwise influence the willingness of the subject to participate in the study, then the ICF must be revised and submitted to the relevant IRB/EC and, where necessary, to the relevant competent authorities, for review and approval. When a subject is currently undergoing study procedures and is affected by the amendment, then the subject must be asked to consent again using the new ICF.

11.1 Ethical Conduct of the Study

The study will be conducted in accordance with ICH GCP, the Declaration of Helsinki, the European Union Clinical Trials Directive 2001/20/EC, the GCP Directive 2005/28/EC, the requirements of local IRB/EC, and the US Code of Federal Regulations, Title 21 CFR Part 50.

11.2 Informed Consent

The principles of informed consent in the Declaration of Helsinki and GCP guidelines will be implemented before any protocol-specific procedures or interventions are carried out.

All subjects will be informed that participation is voluntary and that they can cease participation at any time without necessarily giving a reason and without any penalty or loss of benefits to which they are entitled.

With the help of the ICF, the subject will be informed about the AFM24 study drug and anticipated effects and the reason, design, and implication of the study. The subject must give consent to participate prior to enrollment in the study. This consent must be given in writing. The Investigator who conducts the informed consent discussion must also sign the ICF. The Investigator may delegate this responsibility to a suitably qualified member of the study team (eg, Sub-Investigator) if permitted by local regulations. This delegation of responsibility must be recorded in the Study File. By giving signed consent, the subject will confirm that his or her participation is voluntary and that he or she will follow the instructions of the Investigator and answer the questions asked. Signatures must be personally dated.

The signed and dated consent form will be kept by the Investigator. Prior to participation in the study, the subject should receive a copy of the signed and dated written ICF.

The ICF must include all elements required by law, local regulations, GCP guidelines, and ICH guidelines, including consent to allow the Sponsor, Sponsor representative, or external regulatory auditor to review the subject's medical records. This gives permission to examine, analyze, verify, and reproduce any records and reports that are important to the evaluation of the study.

Any party with direct access must take all reasonable precautions within the constraints of the applicable regulatory requirement(s) to maintain the confidentiality of the subjects' identities and Sponsor's proprietary information. It is the CRA's responsibility to verify that each subject has consented, in writing, to direct access.

11.3 Subject Participation Card

A study participation card will be provided to subjects where required by local regulations or IRB/EC. The card will indicate that he or she is participating in a clinical study and give the name and contact details of the Sponsor and the Investigator/study site. The subject will be asked to retain this card while participating in the study and show it to any other medical practitioners consulted during this time. Subjects will be advised to contact the Investigator/study site if there are any questions. A sample subject participation card is shown in Figure 4.

Figure 4: Sample Subject Participation Card

Dear Subject, ***Please inform any physician you visit during the study that you are participating in a clinical study by presenting this contact card.*** ***Please always carry this card with you until the end of the study.*** **Subject Name:**..... is participating in an open-label study and is receiving an investigational product, AFM24, a novel, tetravalent bispecific chimeric (anti-human EGFR x anti-human CD16A) recombinant antibody construct. Subject Contact Card Version X/date		**Clinical Trial Contact Card** **Study AFM24-101: A Phase 1/2a Open label, Multicenter Study to Assess the Safety, Tolerability, Pharmacokinetics and Preliminary Efficacy of AFM24 in Subjects with Advanced Solid Cancers** **In the case that additional medications must be prescribed, you need more information about the clinical study, or the subject's condition has worsened, please contact the treating study physician:** Name: ..... Phone: ..... Address: .....

11.4 Insurance

Appropriate insurance for this study will be arranged by the Sponsor (or their delegate), as Sponsor of the clinical study, in accordance with the regulatory requirements of the countries involved. A copy of the country-specific insurance certificate will be held in the Trial Master File and in the Investigator Site File.

11.5 Institutional Review Board/Independent Ethics Committee

The study will not be initiated without approval of the IRB/EC and compliance with all administrative requirements of the governing body of the institution. This protocol, consent procedures, and any amendments must be approved by the IRB/EC in compliance with current regulations of the FDA and the European Union as applicable and in accordance with ICH GCPs. A letter of approval will be sent to the Sponsor prior to initiation of the study and when any subsequent modifications are made. The IRB/EC will be kept informed by the Investigator, contract research organization, or the Sponsor, as required by national regulations, as to the progress of the study as well as to any serious and unexpected AEs.

11.6 Subject Privacy

The Investigator must ensure that subject privacy is maintained. On the eCRF or other documents submitted to the Sponsor, subjects will be identified by a subject number only. Clinical study documents that are not submitted to the Sponsor (eg, signed ICF) should be kept in a confidential file by the Principal Investigator.

In accordance with local, national, or federal regulations, the Investigator will allow the Sponsor or their designee personnel access to all pertinent medical records to verify the data gathered on the CRFs and to audit the data collection process. Regulatory agencies such as the FDA may also request access to all study records, including source documentation for inspection. Clinical information will not be released without the written permission of the subject as outlined in the subject consent form.

12.0 DATA HANDLING AND RECORDKEEPING

12.1 Recording of Data

The Investigator will be responsible for the recording of all data on the CRFs provided, as certified by the Investigator's signature and date. Should any value be significantly different from normal, the Investigator will comment in the appropriate sections provided in the CRFs.

The Investigator will provide access to his/her original records to permit a representative from the Sponsor to verify the proper transcription of data.

12.2 Study Record Retention

All clinical study documents must be retained by the Investigator until at least 2 years or according to local laws, whichever is longer, after the last approval of a marketing application in an ICH region (ie, US, Europe, or Japan) and until there are no pending or planned marketing applications in an ICH region. If no application is filed or if the application is not approved for such indication, the Investigator must retain all clinical study documents until 2 years after the investigation is discontinued and regulatory authorities have been notified. Investigators may be required to retain documents longer if specified by regulatory requirements, or by local regulations.

Subjects' medical files should be retained in accordance with applicable legislation and with the maximum period permitted by the hospital, institution or private practice.

12.3 Data Confidentiality and Publication Policy

The original CRFs and all data generated during the clinical study are the property of the Sponsor. In addition, all information regarding AFM24 and the Sponsor's operations (e.g.,

patent applications, formulas, manufacturing processes, basic scientific data, or formulation information) supplied by the Sponsor to the Investigator and not previously published is considered confidential. This confidential information remains the sole property of the Sponsor and shall not be disclosed to others without the written consent of the Sponsor. The Investigator agrees to use this information only to perform this study and will not use it for other purposes, including publications and presentations, without the Sponsor's written consent.

The first publication of the study results shall be made by the Sponsor. Any proposed publication or presentation (including a manuscript, abstract, or poster) for submission to a journal or scientific meeting should be sent to the Sponsor for review prior to submission. Publication of the results will not include confidential information, including inventions, non-public intellectual property rights, and know-how, without the permission of the Sponsor. The full terms of confidentiality, intellectual property, and publication policy are described in the current Clinical Trial Agreement between the Sponsor and the site.

The Sponsor may announce quality assured summary data to comply with Financial Regulatory Authorities, while ensuring, so far as possible, that such announcements will not compromise the Investigators ability to publish the data in appropriate scientific forums.

13.0 LIST OF REFERENCES

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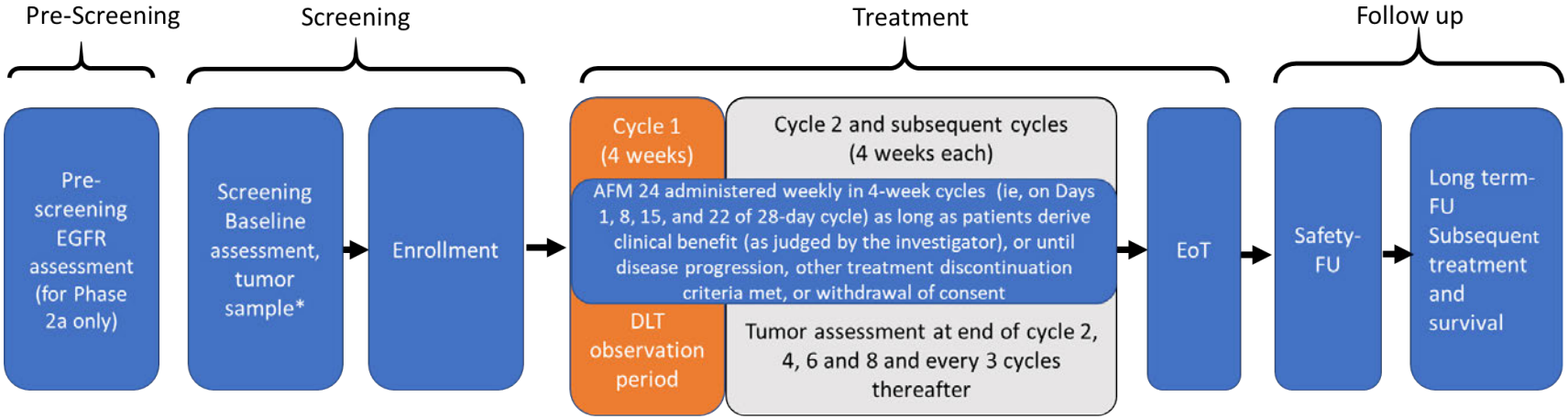
14.0 APPENDICES

14.1 APPENDIX A: Weekly Dosing Regimen (q1w) – Phase 1 and Phase 2a

Figure 5: Study Scheme for Each Subject in Weekly Dosing Regimen



DLT = dose-limiting toxicity; EOT = end of treatment; FU = follow-up
* Collection of tumor sample (for central analysis) and DLT observation period is applicable for the dose escalation phase (Phase 1) only.
Note: If a positive EGFR test has been performed from a subject's tumor tissue, and the EGFR laboratory report is available, the subject does not have to sign the pre-screening ICF and perform the pre-screening assessment and can directly proceed to signing the Main ICF and the screening activities.

Table 11: General Schedule of Assessment for Weekly AFM24 Dosing Regimen- For both Phase 1 and Phase 2a

Activity	Pre-SCR[#] *(Phase 2a only)*	SCR	Cycle 1											
Day			**D1**	**D2 (Split Dose)**	**D3**	**D7[a]**	**D8**	**D9 (Split Dose)**	**D15**	**D16 (Split Dose)**	**D22**	**D23 (Split Dose)**	**D24**	**D28[a]**
Informed consent	X	X												
Confirm I/E criteria[b]		X												
EGFR assessment	X[c]													
Demographics		X												
Medical & cancer history		X												
Physical examination		X	X[d]											
Weight[e]		X	X[d]											
Height[e]		X												
Pregnancy test/FSH test[f]		X	X[d]											
Hepatitis B and C and HIV serology		X												
ECOG PS[g]		X	X											
Vital signs[h]		X	X[h]	X[h]			X[h]	X[h]	X[h]	X[h]	X[h]	X[h]		
ECG[i]		X	X[j]								X[j]			
Hematology[k]		X	X[l,d]	X[m]	X *(Phase 2a only)*		X[d]		X[d]		X[l, d]	X[m]	X *(Phase 2a only)*	
Clinical chemistry[n]		X	X[d]				X[d]		X[d]		X[d]			
Urinalysis[o]		X	X[d]				X[d]		X[d]		X[d]			
Coagulation[k,p]		X	X[d]											
Tumor biopsy[q] *(Phase 1 only)*		X											X[r]	
Radiographic tumor assessment (CT/MRI)		X[s]												
AFM24 administration			X*	X*			X*	X*	X*	X*	X*	X*		
Adverse events[t]	X[t]													
Concomitant medication		Concomitant medications are recorded from signature of the Main ICF to 30-S-FU visit.												
PK sampling			See Table 12 through Table 15											
ADA														
PD (cytokines)														
PD (circulating lymphocytes)														
CD16a receptor occupancy														
Tumor genomics (ctDNA)														

Table 11: General Schedule of Assessment for Weekly AFM24 Dosing - For both Phase 1 and Phase 2a (Continued)

Activity	Subsequent Cycles										
Day	D1+1 day	D2+1 day (Split Dose)	D8±1 day	D9±1 day (Split Dose)	D15±1 day	D16±1 day (Split Dose)	D22±1 day	D23±1 day (Split Dose)	EOT±2 days[##]	S-FU ±5 days [###]	LT-FU [####]
Physical examination	X[d]								X		
Weight[e]	X[d]								X		
Pregnancy test/FSH test[f]	X[d]								X		
ECOG PS[g]	X										
Vital signs[h]	X[h]	X[h]	X[h]	X[h]	X[h]	X[h]	X[h]	X[h]			
ECG[i]									X		
Hematology[k]	X[d]		X[d]		X[d]		X[d]		X		
Clinical chemistry[n]	X[d]		X[d]		X[d]		X[d]		X		
Urinalysis[o]	X[d]		X[d]		X[d]		X[d]		X		
Coagulation[k,p]	X[d]								X		
Radiographic tumor assessment (CT/MRI)							X[s]				
AFM24 administration	X*	X*	X*	X*	X*	X*	X*	X*			
Subsequent treatments and survival											X
Adverse events[t]	X[t]										
Concomitant medication	Concomitant medications are recorded from signature of the Main ICF to 30-S-FU visit.										X[u]
PK sampling	See Table 12 through Table 15										
ADA											
PD (cytokines)											
PD (circulating lymphocytes)											
CD16a receptor occupancy											
Tumor genomics (ctDNA)											

General Notes:

[*] ---- (demarcated lines) between columns indicate split dosing days (ie, AFM24 infusion time can span over 2 consecutive days).

[#] Pre-Screening Phase: applicable for Phase 2a only. **Note**: if a positive EGFR test has been performed from a subject's tumor tissue, and the EGFR laboratory report is available, the subject does not have to sign the pre-screening ICF and perform the pre-screening assessment and can directly proceed to signing the Main ICF and the screening activities.

[##] End of Treatment visit is scheduled 14 days (±2 days) after the last administration of AFM24 or before start of any new anti-cancer treatment whichever is sooner.

[###] Safety Follow-up visit is scheduled 30 days (±5 days) after the last administration of AFM24 or before start of any new anti-cancer treatment whichever is sooner.

[####] During Long-term Follow-Up interval, subjects are contacted every 3 months (±2 weeks) starting after EOT, to collect data on their subsequent therapies and disease status.

Study Assessment Notes

a. Only PK sampling is done on this visit, see Table 12 through Table 15.
b. Subjects must demonstrate adequate organ function when assessed within 7 days before first AFM24 infusion to remain eligible (Section 4.1).
c. For Phase 2a only: In case there is no archived tumor tissue, a local tumor biopsy for EGFR determination is required at pre-screening (see Inclusion criteria 1, Section 4.1). **Note**: if a positive EGFR test has been performed from a subject's tumor tissue, and the EGFR laboratory report is available, the subject does not have to sign the pre-screening ICF and perform the pre-screening assessment and can directly proceed to signing the Main ICF and the screening activities.
d. The following assessments could be completed within 24 hours prior to the AFM24 infusion at each visit noted in the above table: Pre-dose samples for hematology parameters, clinical chemistry parameters and urinalysis parameters, pregnancy test, weight, physical examination, and coagulation parameters.
e. Height and weight will be obtained while the subject is wearing light clothing (without shoes).
f. Female subjects who require documented confirmation of postmenopausal status will have their FSH levels assessed at Screening. Subjects who are not postmenopausal at screening will be required to undergo pregnancy testing per protocol to confirm suitability to proceed. Female subjects of reproductive potential will have a pregnancy test carried out at Screening. This test must be carried out within 7 days prior to first AFM24 administration.
g. Subjects must be confirmed as ECOG PS 0 or 1 to be eligible for study participation, and then assessed at Day 1 of each cycle.
h. Vital sign parameters will consist of measurements of temperature, resting heart rate, seated blood pressure (systolic/diastolic) after 5 minutes resting, oxygen saturation, and respiratory rate. For details, please refer to Table 5. In case of split dosing, vital signs assessments at similar timepoints need to be done on both days. **Note:** In addition to the above-listed time points, subjects should be additionally monitored in accordance with the institutional guidelines/clinical practice and as clinically indicated.
i. An unscheduled ECG might be performed any time if clinically indicated.
j. For the dose escalation phase (Phase 1), ECG is required on Cycle 1 Day 1 and Day 22, before infusion and within 15 minutes after the EOI (+15 minutes, note plus only). When both an ECG and peripheral blood sample collection (PK and PD [cytokines]) are required at the EOI of AFM24 (ie, Cycle 1 Day 1 and Day 22), the blood draw must be completed first as close to the EOI as possible, followed by the ECG. Both procedures should be completed within 15 minutes after the EOI (+ 15 minutes, note plus only). For Phase 2a, ECG is not required on Cycle 1 Day 1 and Day 22. ECG assessments are to be performed with the subject in the supine position. For the dose escalation phase (Phase 1) only, all ECGs should be performed in triplicate at least 5 minutes apart. For the dose expansion phase (Phase 2a), ECGs will be performed in triplicate at least 5 minutes apart at the Screening visit only. All subsequent ECGs will be performed as single ECGs.
k. Hematology (including coagulation) parameters include red cell count, mean corpuscular volume, hemoglobin, hematocrit, reticulocyte count, platelet count, white blood cells, leukocyte differential count (% and/or absolute), international normalized ratio or prothrombin time, and activated partial thromboplastin time (See APPENDIX D, Section 14.4).
l. Phase 1 without split day dosing: Additional blood sample for hematology on Cycle 1 Day 1 and Day 22 should be collected 1 hour after EOI (±15 minutes).
Phase 2a without split day dosing: Additional blood samples for hematology on Cycle 1 Day 1 and Day 22 should be collected after EOI (+15 minutes, note plus only) at sites that can perform the PBMC isolation according to the lab manual/Sponsor requirements.
m. Phase 1 and Phase 2a with split day dosing: Blood sample for hematology on Cycle 1 Day 2 and Day 23 should be collected after EOI (+15 minutes) at sites that can perform the PBMC isolation according to the lab manual/Sponsor requirements.
n. Clinical chemistry parameters include calcium, total protein, albumin, total bilirubin, alanine transaminase, aspartate transaminase, lactate dehydrogenase, alkaline phosphatase, glucose (random), sodium, potassium, bicarbonate, chloride, magnesium, urea (blood urea nitrogen), creatinine, phosphate, uric acid, amylase, lipase, and C-reactive protein (See APPENDIX D, Section 14.4).
o. Urinalysis parameters include glucose, protein, bilirubin, ketones, blood, pH, specific gravity (microscopic examination when indicated), FSH (to confirm post-menopausal status [Screening], and human chorionic gonadotropin (female pre-menopausal subjects [Screening] (See APPENDIX D, Section 14.4).
p. Coagulation may be assessed from the hematology sample.

q. Tumor biopsy for central analysis is required for subjects in the dose escalation phase (Phase 1) only.
r. +1 week: The second tumor biopsy will be performed on a non-dosing day during week 3 (+1 week).
s. CT or MRI will be done at Screening and during the last week of cycles 2, 4, 6, 8, and every 3 cycles thereafter.
t. During pre-screening, only AEs which are related to study procedures are to be recorded. AEs occurring after signing of the Main ICF but prior to the first dose of study drug should be recorded on the Medical History eCRF page (**Note:** any SAEs which are related to study procedures and occur during pre-screening and any SAEs that occur following signing the Main ICF and prior to the first dose of study drug will still be reported using the SAE form). Please also refer to Section 8.1.3 for detailed description.
u. Concomitant medications administered after the Safety Follow-up visit should be recorded for SAEs which are considered related to study drug.

ADA = anti-drug antibodies; C = cycle; CT = computed tomography; ctDNA = circulating tumor DNA; D = day; ECG = electrocardiogram; ECOG PS = Eastern Cooperative Oncology Group Performance Status; EGFR = epidermal growth factor receptor; EOI = end of infusion; EOT = End of Treatment visit; FSH = follicle-stimulating hormone; HIV = human immunodeficiency virus; I/E = inclusion/exclusion; ICF = informed consent form; LT-FU = long term follow-up; MRI = magnetic resonance imaging; PD = pharmacodynamics; PK = pharmacokinetics; SCR = screening; S-FU = Safety Follow-up visit.

Table 12: Schedule of Pharmacokinetic, Pharmacodynamic, Immunogenicity, and Translational Assessments for Weekly AFM24 Dosing Regimen (Without Split Dosing) - For Phase 1

		Cycle 1											
		D1			D3	D7	D8	D15	D22			D24	D28
Sample	SCR	Pre -2h max	EOI[a] +15 min	+1h EOI[a] ±15min	+48h EOI[a] ±2h	+144h EOI[a] ±12h	Pre -2h max	Pre -2h max	Pre -2h max	EOI[a] +15 min	+1h EOI[a] ±15 min	+48h EOI[a] ±2h	+144h EOI[a] ±12h
PK		X	X		X	X	X	X	X	X		X	X
ADA[b]		X					X	X	X				
CD16a RO	X				X				X			X	
PD (circulating lymphocytes)		X		X	X		X	X	X		X	X	
PD (cytokines)[c]		X	X		X		X	X	X	X		X	
Tumor genomics (ctDNA)	X							X					

	Cycle 2				Subsequent Cycles				EOT[d]
	D1+1	D8±1	D15±1	D22±1	D1+1	D8±1	D15±1	D22±1	
Sample	Pre -2h max	Pre -2h max	Pre -2h max	Pre -2h max	Pre -2h max	Pre -2h max	Pre -2h max	Pre -2h max	±2 days
PK	X	X	X	X	X				X
ADA[b]	X	X	X	X	X	X	X	X	X
CD16a RO	X								X
PD (circulating lymphocytes)	X								
PD (cytokines)[c]	X	In case of immune reaction only							
Tumor genomics (ctDNA)	X		X		X				X

a. The EOI samples refers to time since completion of AFM24 infusion (within 15 minutes of completion of AFM24 infusion).
b. On study drug administration days, ADA samples should be taken just before administration of AFM24.
c. In case of suspected CRS or IRR or any anaphylactic reaction during or close to AFM24 infusion a sample for central laboratory testing should be drawn. Sampling should occur at the first sign of the AE and 1 hour later to assess cytokine changes. In addition, local cytokine testing is recommended as clinically indicated and in accordance with institutional treatment guidelines.
d. End of Treatment visit is scheduled 14 days (±2 days) after the last administration of AFM24 or before start of any new anti-cancer treatment whichever is sooner.

ADA = anti-drug antibodies; AE = adverse event; CD16a RO = CD16a receptor occupancy testing; CRS = cytokine release syndrome; ctDNA = circulating tumor DNA; D = day; EOI = end of Infusion; EOT = End of Treatment visit; h = hour(s); IRR = infusion-related reaction; m = minutes; PD = pharmacodynamics; PK = pharmacokinetic; Pre = pre-dose; SCR = screening visit.

Table 13: Schedule of Pharmacokinetic, Pharmacodynamic, Immunogenicity, and Translational Assessments for Weekly AFM24 Dosing Regimen (Split Dosing) - For Phase 1

		Cycle 1								
		D1		D2		D3	D8	D9	D15	D16
		Pre	EOI[a]	Pre	EOI[a]	+24h EOI[a]	Pre	Pre	Pre	Pre
Sample	SCR	-2h max	+15min	-2h max	+15min	±2h	-2h max	-2h max	-2h max	-2h max
PK		X	X	X	X	X	X	X	X	X
ADA[b]		X					X		X	
CD16a RO	X					X				
PD (circulating lymphocytes)[c]		X			X	X	X		X	
PD (cytokines)[c]		X	X			X	X		X	
Tumor genomics (ctDNA)	X								X	

	Cycle 1 (continued)				
	D22		D23		D24
	Pre	EOI[a]	Pre	EOI[a]	+24h EOI[a]
Sample	-2h max	+15min	-2h max	+15min	±2h
PK	X	X	X	X	X
ADA[b]	X				
CD16a RO	X				X
PD (circulating lymphocytes)	X			X	X
PD (cytokines)[c]	X	X			X
Tumor genomics (ctDNA)					

	Cycle 2								Subsequent Cycles				EOT[d]
	D1+1	D2+1	D8±1	D9±1	D15±1	D16±1	D22±1	D23±1	D1+1	D8±1	D15±1	D22±1	
	Pre	Pre	Pre	Pre	Pre	Pre	Pre	Pre	Pre	Pre	Pre	Pre	
Sample	-2h max	-2h max	-2h max	-2h max	-2h max	-2h max	-2h max	-2h max	-2h max	-2h max	-2h max	-2h max	±2days
PK	X	X	X	X	X	X	X	X	X				X
ADA[b]	X		X		X		X		X	X	X	X	X
CD16a RO	X												X
PD (circulating lymphocytes)	X												
PD (cytokines)[c]	X	In case of IRR only											
Tumor genomics (ctDNA)	X				X				X				X

a. The EOI samples refers to time since completion of AFM24 infusion (within 15 minutes of completion of AFM24 infusion).
b. On study drug administration days, ADA samples should be taken just before administration of AFM24.

c. In case of suspected CRS or IRR or any anaphylactic reaction during or close to AFM24 infusion a sample for central laboratory testing should be drawn. Sampling should occur at the first sign of the AE and 1 hour later to assess cytokine changes. In addition, local cytokine testing is recommended as clinically indicated and in accordance with institutional treatment guidelines.
d. End of Treatment visit is scheduled 14 days (±2 days) after the last administration of AFM24 or before start of any new anti-cancer treatment whichever is sooner.

ADA = anti-drug antibodies; AE = adverse event; CD16a RO = CD16a receptor occupancy testing; CRS = cytokine release syndrome; ctDNA = circulating tumor DNA; D = day; EOI = end of infusion; h = hour(s); EOT = End of Treatment visit; IRR = infusion-related reaction; m = minutes; PD = pharmacodynamics; PK = pharmacokinetic; Pre = pre-dose; SCR = screening visit

Table 14: Schedule of Pharmacokinetic, Pharmacodynamic, Immunogenicity, and Translational Assessments for Weekly AFM24 Dosing Regimen (Without Split) - For Phase 2a

	Cycle 1											
	D1				D3	D8	D15	D22				D24
Sample	Pre -2h max	+2h SoI±15 min	+4h[a] SoI±15 min	EOI[b] +15 min	+48h EOI[b] ±2h	Pre -2h max	Pre -2h max	Pre -2h max	+2h SoI±15 min	+4h[a] SoI±15 min	EOI[b] +15 min	+48h EOI[b] ±2h
PK	X			X	X	X	X	X			X	X
ADA[c]	X					X	X	X				
PD (circulating lymphocytes)[d]	X			X	X	X	X	X			X	X
PD (cytokines)[e]	X	X	X	X	X	X	X	X	X	X	X	X
Tumor genomics (ctDNA)	X											

	Cycle 2				Subsequent Cycles		EOT[f]
	D1+1	D8± 1	D15±1	D22±1	D1+1	D15±1	
	Pre	Pre	Pre	Pre	Pre	Pre	±2 days
Sample	-2h max	-2h max	-2h max	-2h max	-2h max	-2h max	
PK	X	X	X	X	X[g]		X
ADA[c]	X		X		X[g]	X[g]	X
PD (circulating lymphocytes)[d]	X						
PD (cytokines)[e]	X				X[g]		
Tumor genomics (ctDNA)							X

a. If infusion lasts only for 4 h, please collect EOI sample only.
b. The EOI samples refers to time since completion of AFM24 infusion (within 15 minutes of completion of AFM24 infusion).
c. On study drug administration days, ADA samples should be taken just before administration of AFM24.
d. Blood for circulating lymphocytes will not be collected from subjects where the local laboratories of specific sites cannot perform the PBMC isolation according to the lab manual/Sponsor requirements.
e. In case of suspected CRS or IRR or any anaphylactic reaction during or close to AFM24 infusion a sample for central laboratory testing should be drawn. Sampling should occur at the first sign of the AE and 1 hour later to assess cytokine changes. In addition, local cytokine testing is recommended as clinically indicated and in accordance with institutional treatment guidelines.
f. End of Treatment visit is scheduled 14 days (±2 days) after the last administration of AFM24 or before start of any new anti-cancer treatment whichever is sooner.
g. PK, ADA and cytokines samples for subsequent cycles should be collected until C6 completion. All additional samples collected after this cycle can be used for analysis. However, the obligatory samples to be collected only until C6D22 completion. EOT samples are still to be drawn for PK, ADA and ctDNA.

ADA = anti-drug antibodies; ctDNA = circulating tumor DNA; D = day; EOI = end of infusion; h = hour(s); EOT = End of Treatment visit; min = minutes; max = maximum; PD = pharmacodynamics; PK = pharmacokinetic; Pre = pre-dose;

Table 15: Schedule of Pharmacokinetic, Pharmacodynamic, Immunogenicity, and Translational Assessments for Weekly AFM24 Dosing Regimen (Split Dosing) - For Phase 2a

Sample	Cycle 1										
	D1				D2		D3	D8	D9	D15	D16
	Pre -2h max	+2h SoI±15 min	+4h[a] SoI±15 min	EOI[b] +15m	Pre -2h max	EOI[b] +15m	+24h EOI ±2h	Pre -2h max	Pre -2h max	Pre -2h max	Pre -2h max
PK	X			X	X	X	X	X	X	X	X
ADA[c]	X							X		X	
PD (circulating lymphocytes)[d]	X					X	X	X		X	
PD (cytokines)[e]	X	X	X	X			X	X		X	
Tumor genomics (ctDNA)	X										

Sample	Cycle 1 (continued)						
	D22				D23		D24
	Pre -2h max	+2h SoI±15 min	+4h[a] SoI±15 min	EOI[b] +15m	Pre -2h max	EOI[b] +15m	+24h EOI[b] ±2h
PK	X			X	X	X	X
ADA[c]	X						
PD (circulating lymphocytes)[d]	X					X	X
PD (cytokines)[e]	X	X	X	X			X
Tumor genomics (ctDNA)							

Sample	Cycle 2								Subsequent Cycles		EOT[f]
	D1+1	D2+1	D8±1	D9±1	D15±1	D16±1	D22±1	D23±1	D1+1	D15±1	±2 days
	Pre -2h max	Pre -2h max	Pre -2h max	Pre -2h max	Pre -2h max	Pre -2h max	Pre -2h max	Pre -2h max	Pre -2h max	Pre -2h max	
PK	X	X	X	X	X	X	X	X	X[g]		X
ADA[c]	X				X				X[g]	X[g]	X
PD (circulating lymphocytes)[d]	X										
PD (cytokines)[e]	X								X[g]		
Tumor genomics (ctDNA)											X

a. If infusion lasts only for 4 h, please collect EOI sample only.
b. The EOI samples refers to time since completion of AFM24 infusion (within 15 minutes of completion of AFM24 infusion).
c. On study drug administration days, ADA samples should be taken just before administration of AFM24. ADA sample should be taken on first day of split dose.

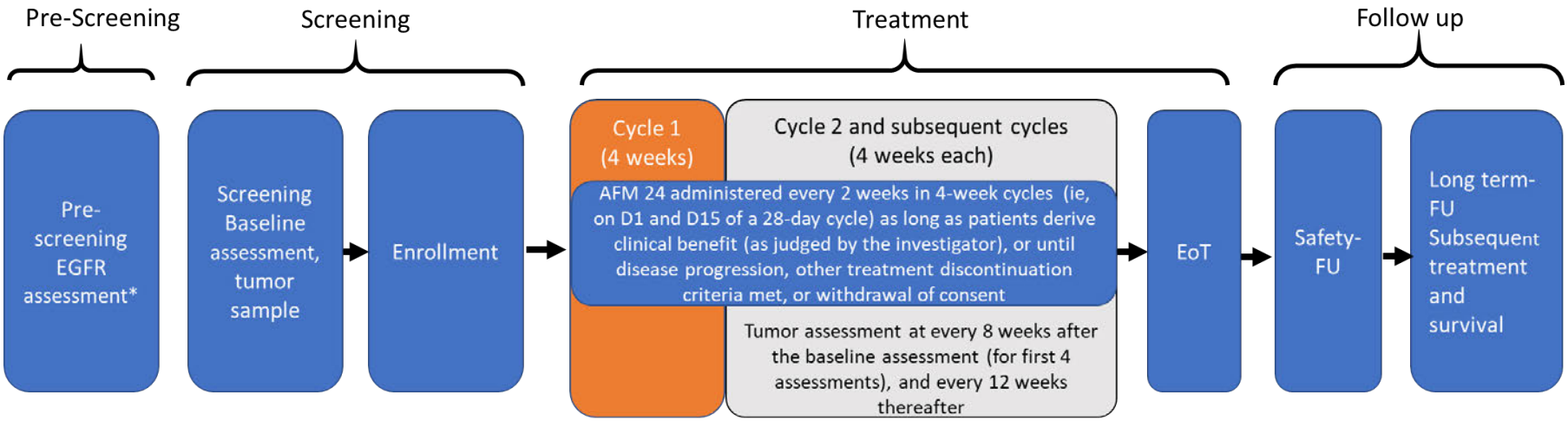
d. Blood for circulating lymphocytes will not be collected from subjects where the local laboratories of specific sites cannot perform the PBMC isolation according to the lab manual/Sponsor requirements.
e. In case of suspected CRS or IRR or any anaphylactic reaction during or close to AFM24 infusion a sample for central laboratory testing should be drawn. Sampling should occur at the first sign of the AE and 1 hour later to assess cytokine changes. In addition, local cytokine testing is recommended as clinically indicated and in accordance with institutional treatment guidelines.
f. End of Treatment visit is scheduled 14 days (±2 days) after the last administration of AFM24 or before start of any new anti-cancer treatment whichever is sooner.

g. PK, ADA and cytokines samples for subsequent cycles should be collected until C6 completion. All additional samples collected after this cycle can be used for analysis. However, the obligatory samples to be collected only until C6D22 completion. EOT samples are still to be drawn for PK, ADA and ctDNA.

ADA = anti-drug antibodies; AE = adverse event; CRS = cytokine release syndrome; ctDNA = circulating tumor DNA; D = day; EOI = end of infusion; h = hour(s); EOT= End of Treatment visit; IRR = infusion-related reaction; m = minutes; PD = pharmacodynamics; PK = pharmacokinetic; Pre = pre-dose; SoI = start of infusion

14.2 APPENDIX B: Every-2-Weeks Dosing Regimen (q2w) –Phase 2a Only

Figure 6: Study Scheme for Each Subject in Every-2-weeks Dosing Regimen



DLT = dose-limiting toxicity; EOT = end of treatment; FU = follow-up
* Local tumor biopsy for EGFR determination is required at pre-screening in case there is no archived tumor tissue.
Note: If a positive EGFR test has been performed from a subject's tumor tissue, and the EGFR laboratory report is available, the subject does not have to sign the pre-screening ICF and perform the pre-screening assessment and can directly proceed to signing the Main ICF and the screening activities.

Table 16: General Schedule of Assessments for Every-2-Weeks AFM24 Dosing- For Phase 2a only

Day	Pre-SCR[#]	SCR	Cycle 1						Subsequent Cycles						EOT ±2 days[##]	S-FU ±5 days[###]	LT-FU[####]
			D1	D2 (Split Dose)	D3	D7 or D8[a]	D15	D16 (Split Dose)	D1+1 day	D2+1 day (Split Dose)	D3+1 day	D15±1 day	D16±1 day (Split Dose)	D22±1 day			
Informed consent	X	X															
Confirm I/E criteria[b]		X															
EGFR assessment	X[c]																
Demographics		X															
Medical & cancer history		X															
Physical examination		X	X[d]						X						X		
Weight[e]		X	X[d]						X						X		
Height[e]		X															
Pregnancy test/FSH test[f]		X	X[d]						X						X		
Hepatitis B and C and HIV serology		X															
ECOG PS[g]		X	X						X								
Vital signs[h]		X	X[h]	X[h]			X[h]	X[h]	X[h]	X[h]		X[h]	X[h]				
ECG[i]		X													X		
Hematology[j]		X	X[k,d]	X[k]	X		X[d]		X[d,k]	X[k,q]	X[q]	X[d]			X		
Clinical chemistry[l]		X	X[d]				X[d]		X[d]			X[d]			X		
Urinalysis[m]		X	X[d]				X[d]		X[d]			X[d]			X		
Coagulation[j,n]		X	X[d]						X[d]						X		
Radiographic tumor assessment (CT/MRI)		X												X[o]			
AFM24 administration			X*	X*			X*	X*	X*	X*		X*	X*				
Subsequent treatments and survival																	X
Adverse events[r]	X[r]																
Concomitant medication		Concomitant medications are recorded from signature of the Main ICF to 30-S-FU visit.															X[p]
PK sampling			See Table 17 and Table 18														
ADA																	
PD (cytokines)																	
PD (circulating lymphocytes)																	

Day	Pre-SCR[#]	SCR	Cycle 1						Subsequent Cycles						EOT ±2 days[#] [#]	S-FU ±5 days [###]	LT-FU[##] [##]
			D1	D2 (Split Dose)	D3	D7 or D8[a]	D15	D16 (Split Dose)	D1+1 day	D2+1 day (Split Dose)	D3+1 day	D15±1 day	D16±1 day (Split Dose)	D22±1 day			
CD16a receptor occupancy			See Table 17 and Table 18														
Tumor genomics (ctDNA)																	

General Notes:

[*] ---- (demarcated lines) between columns indicate split dosing days (ie, AFM24 infusion time can span over 2 consecutive days).

[#] If a positive EGFR test has been performed from a subject's tumor tissue, and the EGFR laboratory report is available, the subject does not have to sign the pre-screening ICF and perform the pre-screening assessment and can directly proceed to signing the Main ICF and the screening activities.

[##] End of Treatment visit is scheduled 14 days (±2 days) after the last administration of AFM24 or before start of any new anti-cancer treatment whichever is sooner.

[###] Safety Follow-up visit is scheduled 30 days (±5 days) after the last administration of AFM24 or before start of any new anti-cancer treatment whichever is sooner.

[####] During Long-term Follow-Up interval, subjects are contacted every 3 months (±2 weeks) starting after EoT to collect data on their subsequent therapies and disease status.

Study Assessment Notes

a. Only PK sampling is done on this visit, see Table 17 and Table 18.
b. Subjects must demonstrate adequate organ function when assessed within 7 days before first AFM24 infusion to remain eligible (Section 4.1).
c. In case there is no archived tumor tissue, a local tumor biopsy for EGFR determination is required at pre-screening (see Inclusion criteria 1, Section 4.1). **Note**: if a positive EGFR test has been performed from a subject's tumor tissue, and the EGFR laboratory report is available, the subject does not have to sign the pre-screening ICF and perform the pre-screening assessment and can directly proceed to signing the Main ICF and the screening activities.
d. The following assessments could be completed within 24 hours prior to the AFM24 infusion at each visit noted in the above table: Pre-dose samples for hematology parameters, clinical chemistry parameters and urinalysis parameters, pregnancy test, weight, physical examination, and coagulation parameters.
e. Height and weight will be obtained while the subject is wearing light clothing (without shoes).
f. Female subjects who require documented confirmation of post-menopausal status will have their FSH levels assessed at Screening. Subjects who are not post-menopausal will be required to undergo pregnancy testing per protocol to confirm suitability to proceed. Female subjects of reproductive potential will have a pregnancy test carried out at Screening. This test must be carried out within 7 days prior to first AFM24 administration.
g. Subjects must be confirmed as ECOG PS 0 or 1 to be eligible for study participation, and then assessed at Day 1 of each cycle.
h. Vital sign parameters will consist of measurements of temperature, resting heart rate, seated blood pressure (systolic/diastolic) after 5 minutes resting, oxygen saturation, and respiratory rate. For details, please refer to Table 5.
   Note: in addition to the above listed time points, subjects should be additionally monitored in accordance with the institutional guidelines/clinical practice and as clinically indicated.
i. An unscheduled ECG can be performed any time if clinically indicated. Electrocardiograms will be performed in triplicate at least 5 minutes apart at the Screening visit only. All subsequent ECGs will be performed as single ECGs.
j. Hematology (including coagulation) parameters include red cell count, mean corpuscular volume, hemoglobin, hematocrit, reticulocyte count, platelet count, white blood cells, leukocyte differential count (% and/or absolute), international normalized ratio or prothrombin time, and activated partial thromboplastin time (See APPENDIX D, Section 14.4).
k. Without split day dosing: Additional blood sample for hematology on Cycle 1 Day 1 and Cycle 2 Day 1 should be collected after EOI (+15 minutes).
   With split day dosing: Additional blood sample for hematology on Cycle 1 Day 2 and Cycle 2 Day 2 should be collected after EOI (+15 minutes) at sites that can perform the PBMC isolation according to the lab manual/Sponsor requirements.
l. Clinical chemistry parameters include calcium, total protein, albumin, total bilirubin, alanine transaminase, aspartate transaminase, lactate dehydrogenase, alkaline phosphatase, glucose (random), sodium, potassium, bicarbonate, chloride, magnesium, urea (blood urea nitrogen), creatinine, phosphate, uric acid, amylase, lipase, and C--reactive protein (See APPENDIX D, Section 14.4).

m. Urinalysis parameters include glucose, protein, bilirubin, ketones, blood, pH, specific gravity (microscopic examination when indicated), FSH (to confirm post-menopausal status [Screening], and human chorionic gonadotropin (female pre-menopausal subjects [Screening] (See APPENDIX D, Section 14.4).
n. Coagulation may be assessed from the hematology sample.
o. CT or MRI will be done every 8 weeks after baseline assessment for first 4 assessments, and every 12 weeks thereafter.
p. Concomitant medications administered after the Safety Follow-up visit should be recorded for SAEs which are considered related to study drug.
q. Only taken in Cycle 2 at sites that can perform the PBMC isolation according to the lab manual/Sponsor requirements.
r. During pre-screening, only AEs that are related to study procedures are to be recorded. AEs occurring after signing of the Main ICF but prior to the first dose of study drug should be recorded on the Medical History eCRF page (**Note:** any SAEs that are related to study procedures and occur during pre-screening and any SAEs that occur following signing the Main ICF and prior to the first dose of study drug will still be reported using the SAE form). Please also refer to Section 8.1.3 for detailed description.

ADA = anti-drug antibodies; C = cycle; CT = computed tomography; ctDNA = circulating tumor DNA; D = day; ECG = electrocardiogram; ECOG PS = Eastern Cooperative Oncology Group Performance Status; EGFR = epidermal growth factor receptor; EOI = end of infusion; EOT = End of Treatment visit; FSH = follicle-stimulating hormone; HIV = human immunodeficiency virus; I/E = inclusion/exclusion; ICF = informed consent form; LT-FU = long term follow-up; MRI = magnetic resonance imaging; PD = pharmacodynamics; PK = pharmacokinetics; SCR = screening visit; S-FU = Safety Follow-up visit.

Table 17: Schedule of Pharmacokinetic, Pharmacodynamic, Immunogenicity, and Translational Assessments for Every 2 Weeks AFM24 Dosing Regimen (Without Split) - Phase 2a Only

	Cycle 1							Cycle 2							Subsequent Cycles	EOT[f]
	D1				D3	D7 or D8	D15	D1+1				D3+1	D7 or D8	D15±1	D1+1	
Samples	Pre -2h max	+2h SoI ±15 min	+4h[a] SoI ±15 min	EOI[b] +15 min	+48 h EOI ±2h		Pre -2h max	Pre -2h max	+2h SoI±15 min	+4h[a] SoI±15 min	EOI[b] +15 min	+48h EOI ±2h		Pre -2h max	Pre -2h max	±2 days
PK	X			X	X	X	X	X			X	X	X	X	X[g]	X
ADA[c]	X						X	X						X	X[g]	X
PD (circulating lymphocytes)[d]	X			X	X		X	X			X	X		X		
PD (cytokines)[e]	X	X	X	X	X		X	X	X	X	X	X		X	X[g]	
Tumor genomics (ctDNA)	X															X

a. If infusion lasts only for 4h, please collect EOI sample only.
b. The EOI samples refers to time since completion of AFM24 infusion (within 15 minutes of completion of AFM24 infusion).
c. On study drug administration days, ADA samples should be taken just before administration of AFM24.
d. Blood for circulating lymphocytes will not be collected from subjects where the local laboratories of specific sites cannot perform the PBMC isolation according to the lab manual/Sponsor requirements.
e. In case of suspected CRS or IRR or any anaphylactic reaction during or close to AFM24 infusion a sample for central laboratory testing should be drawn. Sampling should occur at the first sign of the AE and 1 hour later to assess cytokine changes. In addition, local cytokine testing is recommended as clinically indicated and in accordance with institutional treatment guidelines.
f. End of Treatment visit is scheduled 14 days (±2 days) after the last administration of AFM24 or before start of any new anti-cancer treatment whichever is sooner.
g. PK, ADA and cytokines samples for subsequent cycles should be collected until C6 completion. All additional samples collected after this cycle can be used for analysis. However, the obligatory samples to be collected only until C6D22 completion. EOT samples are still to be drawn for PK, ADA and ctDNA.

ADA = anti-drug antibodies; AE = adverse event; CRS = cytokine release syndrome; ctDNA = circulating tumor DNA; D = day; EOI = End of Infusion; EOT = End of Treatment visit; h = hour(s); IRR = infusion-related reaction; m = minutes; max = maximum; PD = pharmacodynamics; PK = pharmacokinetic; Pre = pre-dose; q2w = every 2 weeks.

Table 18: Schedule of Pharmacokinetic, Pharmacodynamic, Immunogenicity, and Translational Assessments for Every 2 Weeks AFM24 Dosing (Split Dosing) - For Phase 2a Only

Samples	Cycle 1									
	D1				D2		D3		D15	D16
	Pre -2h max	+2h SoI ±15 min	+4h[a] SoI ±15 min	EOI[b] +15m	Pre -2h max	EOI[b] +15m	+24 h EOI ±2h	D7 or D8	Pre -2h max	Pre -2h max
PK	X			X	X	X	X	X	X	X
ADA[c]	X								X	
PD (circulating lymphocytes)[d]	X					X	X		X	
PD (cytokines)[e]	X	X	X	X			X		X	
Tumor genomics (ctDNA)	X									
Samples	**Cycle 2**									
	D1+1				D2+1		D3+1		D15±1	D16±1
	Pre -2h max	+2h SoI ±15 min	+4h[a] SoI ±15 min	EOI[b] +15m	Pre -2h max	EOI[b] +15m	+24 h EOI ±2h	D7 or D8	Pre -2h max	Pre -2h max
PK	X			X	X	X	X	X	X	X
ADA[c]	X								X	
PD (circulating lymphocytes)[d]	X					X	X		X	
PD (cytokines)[e]	X	X	X	X			X		X	
Tumor genomics (ctDNA)										
Samples	**Subsequent Cycles** D1+1 Pre -2h max						**EOT[f]** ±2 days			
PK	X[g]						X			
ADA[c]	X[g]						X			
PD (circulating lymphocytes)[d]										
PD (cytokines)[e]	X[g]									
Tumor genomics (ctDNA)							X			

a. If infusion lasts only for 4h, please collect EOI sample only.
b. The EOI samples refers to time since completion of AFM24 infusion (within 15 minutes of completion of AFM24 infusion).
c. On study drug administration days, ADA samples should be taken just before administration of AFM24. ADA sample should be taken on first day of split dose.
d. Blood for circulating lymphocytes will not be collected from subjects where the local laboratories of specific sites cannot perform the PBMC isolation according to the lab manual/Sponsor requirements.
e. In case of suspected CRS or IRR or any anaphylactic reaction during or close to AFM24 infusion a sample for central laboratory testing should be drawn. Sampling should occur at the first sign of the AE and one hour later to assess cytokine changes. In addition, local cytokine testing is recommended as clinically indicated and in accordance with institutional treatment guidelines.
f. End of Treatment visit is scheduled 14 days (±2 days) after the last administration of AFM24 or before start of any new anti-cancer treatment whichever is sooner.

g. PK, ADA and cytokines samples for subsequent cycles should be collected until C6 completion. All additional samples collected after this cycle can be used for analysis. However, the obligatory samples to be collected only until C6D22 completion. EOT samples are still to be drawn for PK, ADA and ctDNA.

ADA = anti-drug antibodies; AE = adverse event; CD16a RO = CD16a receptor occupancy testing; CRS = cytokine release syndrome; ctDNA = circulating tumor DNA; D = day; EOI = end of infusion; h = hour(s); IRR = infusion-related reaction; m = minutes; PD = pharmacodynamics; PK = pharmacokinetic; Pre = pre-dose; q2w= every 2 weeks.

14.3 APPENDIX C: Eastern Cooperative Oncology Group Performance Score

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

Source: Oken et al., 1982.

14.4 APPENDIX D: Local Laboratory Parameter

Clinical Chemistry	Hematology (Including Coagulation)
Calcium	Red cell count
Total protein	Mean corpuscular volume
Albumin	Hemoglobin
Total bilirubin	Hematocrit
Alanine aminotransferase	Reticulocyte count
Aspartate aminotransferase	Platelet count
Lactate dehydrogenase	White blood cells
Alkaline phosphatase	Leukocyte differential count (% and/or absolute)
Sodium	International normalized ratio or prothrombin time
Potassium	Activated partial thromboplastin time
Bicarbonate	**Urinalysis**
Chloride	Glucose
Magnesium	Protein
Urea (Blood urea nitrogen)	Bilirubin
Creatinine	Ketones
Phosphate	Blood
Uric acid	pH
C-reactive protein	Specific gravity (microscopic examination when indicated)
Amylase	Follicle-stimulating hormone (to confirm post-menopausal status, Screening)
Lipase	Human chorionic gonadotropin (female pre-menopausal subjects, Screening)
Glucose (random)	

Note: This is the full testing panel to be carried out locally by sites; any exceptions due to local testing restrictions must be reported immediately to Sponsor to ensure subject safety assessment is not jeopardized.

14.5 APPENDIX E: Statistical Appendix including Model Performance and Data Scenarios

14.5.1 Phase 1 (Escalation)

The model was assessed by 2 different metrics: hypothetical on-study data scenarios and long-run operating characteristics.

14.5.1.1 Hypothetical Data Scenarios

Hypothetical data scenarios are shown in Table 19. These scenarios reflect potential on-study data constellations and related escalation as allowed by the model and the 200% escalation limit. For each scenario, the probability of overdose for the current dose, as well as the next potential dose and related probabilities of under-dosing, target dose and over-dosing are shown.

For example, scenario 1 represents the case that no DLT is observed in the first subject at the starting dose of 14 mg. In this case, the next dose permitted by the model and by the 200% escalation rule is 40 mg. In scenario 5a, while no DLT was observed at dose 14 mg, 1 DLT is observed in the first 2 subjects at 40 mg and the model would then not allow to escalate and would require to stay at 40 mg and treat 4 more subjects at 40 mg before escalating to 120mg (scenario 5b). In scenario 9b, an intermediate dose escalation is show: While no subject experienced a DLT at dose levels 14 mg and 40 mg, 1 DLT was observed at 120 mg. The model would require that in total 6 subjects are treated at 120 mg and would thereafter only allow to escalate to 200 mg (and not to the maximum of the next level, which is 360 mg), to prevent potential overdosing. These cases illustrate the adaptive behavior of the model.

Table 19: Hypothetical Data Scenarios

Scenario	Dose	Data - #DLT	Data - #Sub	CD - P(OD)	Next Dose	ND - P(UD)	ND - P(TD)	ND - P(OD)
1	14	0	2	0.014	40	0.881	0.085	0.035
2	14	1	2	0.322	7	0.500	0.251	0.249
3	14	1	3	0.207	14	0.524	0.269	0.207
4	14	0	2	0.012	120	0.788	0.135	0.076
	40	0	2					
5a	14	0	2	0.209	40	0.506	0.285	0.209
	40	1	2					
5b	14	0	2	0.041	120	0.461	0.306	0.233
	40	1	6					
6	14	1	6	0.052	120	0.486	0.317	0.197
	40	0	3					
7	14	0	2	0.603	7	0.466	0.299	0.235
	40	2	2					

Scenario	Dose	Data - #DLT	Data - #Sub	CD - P(OD)	Next Dose	ND - P(UD)	ND - P(TD)	ND - P(OD)
	14	0	2	0.013	360	0.571	0.184	0.245
	40	0	2					
8	120	0	3					
	14	0	2	0.159	120	0.526	0.315	0.159
	40	0	2					
9a	120	1	3					
	14	0	2	0.043	200	0.471	0.312	0.217
	40	0	2					
9b	120	1	6					
	14	0	2	0.221	120	0.344	0.434	0.221
	40	0	2					
10	120	2	6					
	14	0	2	0.062	360	0.487	0.293	0.220
	40	0	2					
	120	1	6					
11	200	0	3					
	14	0	2	0.036	1000	0.585	0.190	0.225
	40	0	2					
	120	0	3					
12	360	0	3					
	14	0	2	0.280	200	0.685	0.251	0.063
	40	0	2					
	120	0	3					
13	360	1	3					

CD-P = current dose probability; DLT = dose-limiting toxicity; ND-P = current dose probability; OD = overdosing; #Sub = subject number; TD = target dosing; UD = underdosing.

14.5.1.2 Operating Characteristics

Operating characteristics are a way to assess the long-run behavior of a model. Under an assumed true dose-toxicity curve, metrics such as the probability of recommending a dose with true DLT rate in the target interval can be approximated via simulation Table 20 describes 3 assumed true dose-toxicity scenarios which were used to assess the operating characteristics of the model. These scenarios reflect a wide range of possible cases as follows:

Scenario 1 (P): aligned with prior means

Scenario 2 (H): high-toxicity scenario

Scenario 3 (LH): low-toxicity followed by high-toxicity

Table 20: Assumed True Dose-Toxicity Scenarios

Scenario		7 mg	14 mg	40 mg	120 mg	200 mg	360 mg	1000 mg
1 (P)	**P (DLT)**	0.061	0.075	0.108	**0.178**	**0.244**	0.342	0.486
2 (H)		0.150	**0.200**	**0.250**	0.350	0.400	0.450	0.500
3 (LH)		0.005	0.070	0.100	**0.300**	0.350	0.450	0.500

DLT = dose-limiting toxicity; H = high toxicity; LH = low-high toxicity; P = assumed true-dose toxicity.
Bold numbers indicate true DLT rates in the target interval [0.16-0.33).

For each of these scenarios, 500 studies were simulated. It was then assessed how often a dose was declared as MTD with true DLT rate in the under-, targeted or over-dose range. Furthermore, the average, minimum, and maximum number of subjects per study and the average number of DLTs per study are reported. Results are shown in Table 21.

Table 21: Hypothetical Data Scenarios

Scenario	% of studies declaring an MTD with true DLT rate in				# Subjects	# DLT
	Underdose	Target dose	Overdose	Stopped	Mean (Min-Max)	Mean (Min- Max)
1 (P)	29.0	51.2	18.0	1.8	18.57 (1-43)	3.26 (1-11)
2 (H)	1.4	58.6	17.4	22.6	13.90 (1-38)	3.55 (1-12)
3 (LH)	47.2	33.8	17.0	2.0	17.65 (1-42)	3.45 (1-10)

DLT = dose-limiting toxicity; H = high toxicity; LH = low toxicity; Max = maximum; Min = minimum; MTD = maximum tolerated dose; P = assumed true dose toxicity.

In Scenario 1, which reflects the case that the true dose-toxicity is aligned with prior means, 51.2% of the simulated studies declared a dose as MTD with true DLT rate in the targeted dose range. Since the dose of 1000 mg has a DLT probability of 48.6% it was identified quite rarely as MTD, namely in 4 case of the simulated cases.

In Scenario 2 (high-toxicity scenario), the starting dose has already 20% probability of observing at least 1 DLTs in the first cohort if 2 subjects enrolled. This contributes to the high percentage 22.6% of all simulated studies for which the study is stopped since none of the doses is considered tolerable anymore. This is an expected situation for a high-toxicity scenario.

In Scenario 3, 33.8% of the simulated studies declared a dose as MTD with true DLT rate in the targeted dose range.

The mean subject numbers range from 13.9 subjects (high scenario) to 18.57 subjects (true dose toxicity scenario) and the maximum number of subjects was 43. The low mean number of subjects in the high toxicity- scenario is explained by the frequent stopping of the study.

In summary, the considered data scenarios show a reasonable behavior of the model and the operating characteristics demonstrate a good precision of MTD determination.

14.6 APPENDIX F: Grading and Management of Infusion-related Reactions, including Anaphylaxis, Allergic Reaction, and Cytokine Release Syndrome

Investigators are asked to pay special attention to IRRs, which include hypersensitivity reactions and CRS. These reactions may be experienced by subjects during the infusion of investigational treatment (uniphasic reaction) and/or within hours of an infusion (biphasic/delayed reaction). The reaction may be caused by the therapeutic agent, diluent, or delivery vehicle. IRRs can have a broad variety of symptoms; from mild to moderate chills, flushing, itching, skin rashes, heart rate/blood pressure alterations, dyspnea, chest discomfort, back/abdominal pain, nausea, vomiting, diarrhea to severe and life threatening anaphylactic/anaphylactoid reactions; mostly appearing during or immediately after the investigational drug infusion. Special attention must be paid to CRS during investigational treatment which can manifest with fever, cardiac dysfunction, acute respiratory distress syndrome, neurologic toxicity, renal and/or hepatic failure, and disseminated intravascular coagulation. Skin rash, as well as gastrointestinal symptoms of nausea, vomiting or diarrhea may also occur. Fever is a hallmark for CRS, and many features of CRS can also mimic infection.

The aim of this appendix is to:

Provide guidance on monitoring for IRR/CRS

Provide guidance on the grading of IRR/CRS

Provide guidance on management of IRR/CRS.

In addition, pre-medication with steroids, antihistamines, and oral acetaminophen is advised to minimize the severity of IRR/CRS (see Section 5.3). Other premedication such as antiemetics (e.g., ondansetron, metoclopramide hydrochloride) may be administered at the discretion of the Investigator/ treating physician.

14.6.1 Monitoring for IRR/CRS

Frequent monitoring of the subject's vital signs during and after AFM24 infusion is implemented as a precautionary measure in this protocol. For the first 2 doses (ie, C1D1 and C1D8 in weekly schedule; C1D1 and C1D15 in q2w schedule) of AFM24 subjects must be observed for at least 4 hours after the end of infusion with regular checks of vital signs as described in Section 7.2.4. In case of a split day dosing (over 2 days) subjects must be observed for at least 4 hours after the end of AFM24 infusion on each day. In this scenario, the split day dosing AFM24 infusion is considered one dose. Starting from the third subsequent dose (ie, at any time point in the study starting from the third subsequent dose [C1D15 in weekly schedule, C2D1 in q2w schedule) for subjects who do not experience IRR/CRS symptoms >Grade 1 during the previous infusions, the infusion time for the next and/or subsequent infusions may be decreased to ≥1 hour (at least 1 hour), observation period may be reduced from 4 hours to a minimum of 2 hours, and steroids and other premedications could be tapered, all at the discretion of the Investigator. However, it should be kept in mind that only 1 modification should be made at a time per infusion day.

Any IRR/CRS occurring should be reported as AESIs using the SAE form within 24 hours (see Section 8.3.1).

14.6.2 Grading and Reporting of IRR/CRS

Any treatment-related IRRs are defined according to the NCI CTCAE v5.0 definition (Injury, poisoning and procedural complications). Symptoms occurring during or following infusion of investigational treatment may also be defined according to AE categories such as allergic reaction,

anaphylaxis, or cytokine release syndrome. If an allergic reaction, anaphylaxis or cytokine release syndrome is related to the infusion of AFM24, the term "infusion-related reaction" should be reported. In addition, Investigators are encouraged to use any additional terms to further describe the event (e.g., anaphylaxis, cytokine release syndrome, hypotension, bronchospasm, hypoxia).

The National Cancer Institute's Common Terminology Criteria for Adverse Events (CTCAE v5.0) contains a grading system for IRR and related events as provided in Table 22.

Table 22: Grading System for IRR and Related Events According to CTCAE v5.0

CTCAE Term	Grade 1	Grade 2	Grade 3	Grade 4	Grade 5
Infusion related reaction	Mild transient reaction; infusion interruption not indicated; intervention not indicated	Therapy or infusion interruption indicated but responds promptly to symptomatic treatment (e.g., antihistamines, NSAIDs, narcotics, i.v. fluids); prophylactic medications indicated for ≤24 hours	Prolonged (e.g., not rapidly responsive to symptomatic medication and/or brief interruption of infusion); recurrence of symptoms following initial improvement; hospitalization indicated for clinical sequelae	Life-threatening consequences; urgent intervention indicated	Death
Definition: A disorder characterized by an adverse reaction to the infusion of pharmacological or biological substances					
Navigational Note: Not applicable					
Allergic reaction	Systemic intervention not indicated	Oral intervention indicated	Bronchospasm; hospitalization indicated for clinical sequelae; intravenous intervention indicated	Life-threatening consequences; urgent intervention indicated	Death
Definition: A disorder characterized by an adverse local or general response from exposure to allergen.					
Navigational Note: If related to infusion, use Injury, poisoning, and procedural complication: Infusion related reaction. Do not report both					
Anaphylaxis	-	-	Symptomatic bronchospasm, with or without urticaria; parenteral intervention indicated; allergy related edema/angioedema; hypotension	Life-threatening consequences; urgent interventions indicated	Death
Definition: A disorder characterized by an acute inflammatory reaction resulting from the release of histamine and histamine-like substances from mast cells, causing a hypersensitivity immune response. Clinically, it presents with breathing difficulty, dizziness, hypotension, cyanosis and loss of consciousness, and may lead to death.					
Navigational Note: Not applicable.					
Cytokine release syndrome	Fever with or without constitutional symptoms	Hypotension responding to fluids; hypoxia responding to <40% oxygen	Hypotension managed with 1 pressor; hypoxia requiring ≥40% oxygen	Life-threatening consequences; urgent interventions indicated	Death
Definition: A disorder characterized by fever, tachypnea, headache, tachycardia, hypotension, rash, and/or hypoxia caused by the release of cytokines. **Navigational Note**: Also consider reporting other organ dysfunctions including neurological toxicities such as: Psychiatric disorders: Hallucinations or Confusions; Nervous system disorders: Seizure, Dysphasia, Tremor, or Headache					

CTCAE = Common Terminology Criteria for Adverse Events; i.v. = intravenous; NSAID = nonsteroidal anti-inflammatory drug.

14.6.3 IRR/CRS Management

The management of IRR and other related AEs is summarized in Table 23.

Table 23: Summary of Management of Infusion Related Reactions, including Anaphylaxis, Allergic Reactions, and Cytokine Release Syndrome*

CTCAE v5.0 Grade	Action to AFM24	Actions and medication to manage toxicity
Grade 1	Continue treatment without modification	Vigilant supportive care and treat in line with institutional practice including needed workup to rule out other differential diagnoses
Grade 2	Interrupt treatment and restart when symptoms resolve to ≤CTCAE Grade 1 or baseline Consider infusing the next AFM24 infusion with a >4-hour infusion time	Vigilant supportive care and treat in line with institutional practice including needed workup to rule out other differential diagnoses Consider symptomatic medication such as antihistamines, antipyretics, steroids, i.v. fluids, oxygen, as appropriate, and in line with institutional practice **In case subject of older age and/or with extensive co-morbidities and CRS**, consider: Administer tocilizumab 8 mg/kg (maximum 800 mg) i.v. over 60 min; may administer up to 3 additional doses of tocilizumab 8 mg/kg (maximum 800 mg) if no clinical improvement in signs/symptoms of CRS after first dose. Start corticosteroid treatment (e.g., methylprednisolone 2mg/kg/day)
Grade 3	**Interrupt treatment** **IRRs NOT responsive to symptomatic treatment** (i.e., no improvement of IRR-related symptoms to Grade 2 or better within 6 hours with optimal medical management): Discontinue AFM24 permanently **Any Grade 3 anaphylaxis:** Discontinue AFM24 permanently **IRRs other than anaphylaxis responsive to symptomatic treatment** (i.e., improvement to Grade 2 or better within 6 hours with optimal medical management)**:** Restart if symptoms resolve to ≤CTCAE Grade 1 or baseline only at the discretion of the Investigator based on the clinical status of the subject. If re-challenge is considered, administer the next AFM24 infusion with a >4-hour infusion time.	Vigilant supportive care and treat in line with institutional practice including needed workup to rule out other differential diagnoses Consider symptomatic medication such as antihistamines, antipyretics, steroids, i.v. fluids, oxygen, vasopressor, as appropriate, and in line with institutional practice Consider transfer to intensive care unit or have the subject under continuous surveillance. Monitor cardiac and other organ functions. **In case of CRS**: Administer tocilizumab 8 mg/kg (maximum 800 mg) i.v. over 60 min; may administer up to 3 additional doses of tocilizumab 8 mg/kg (maximum 800 mg) if no clinical improvement in signs/symptoms of CRS after first dose. Start corticosteroid treatment (e.g., methylprednisolone 2mg/kg/day)

CTCAE v5.0 Grade	Action to AFM24	Actions and medication to manage toxicity
Grade 4	**Discontinue permanently**	Vigilant supportive care and treat in line with institutional practice including needed workup to rule out other differential diagnoses Consider symptomatic medication such as antihistamines, antipyretics, steroids, i.v. fluids, oxygen, vasopressor, as appropriate, and in line with institutional practice Transfer to intensive care unit or have the subject under continuous surveillance. Monitor cardiac and other organ functions. **In case of CRS:** Administer tocilizumab 8 mg/kg (maximum 800 mg) i.v. over 60 min; may administer up to 3 additional doses of tocilizumab 8 mg/kg (maximum 800 mg) if no clinical improvement in signs/symptoms of CRS after first dose. Start corticosteroid treatment (e.g., methylprednisolone 2mg/kg/day)

CRS = cytokine release syndrome; CTCAE = Common Terminology Criteria for Adverse Events; IRR = infusion related reactions; i.v. = intravenous; NSAID = nonsteroidal anti-inflammatory drug.
*For further reference for management of CRS, please see: Lee DW et al, 2014. (Current concepts in the diagnosis and management of cytokine release syndrome. Blood 2014; 124(2):188-195) and Lee DW et al, 2019 (ASTCT Consensus Grading for Cytokine Release Syndrome and Neurologic Toxicity Associated with Immune Effector Cells. Biol Blood Marrow Transplant. 2019;25(4):625-638. doi:10.1016/j.bbmt.2018.12.758.)