NCT Number: NCT02984683

AMENDED CLINICAL TRIAL PROTOCOL NO. 01

COMPOUND: SAR566658

Open-label Phase 2 study evaluating efficacy and safety of SAR566658 treatment in patients with CA6 positive metastatic Triple Negative Breast Cancer

STUDY NUMBER: ACT14884

VERSION DATE / STATUS: Approval date (15-Dec-2016) / Approved

Protocol Amendment 01		Version number: 1 (electronic 1.0)	Date: 15-Dec-2016
Clinical Trial Protocol		Version number: 1 (electronic 1.0)	Date: 24-May-2016
Version Number:	1	EudraCT: IND Number(s): WHO universal trial number:	2016-001962-27 129987 U1111-1182-7044
Date:	15-Dec-2016	Total number of pages:	108

NAMES AND ADDRESSES OF

COORDINATING INVESTIGATOR	Name: Address: Tel: Fax: E-mail:	
MONITORING TEAM'S REPRESENTATIVE	Name: Address: Tel: Fax: E-mail:	
SPONSOR	Company: Address:	
OTHER EMERGENCY TELEPHONE NUMBERS		

CLINICAL TRIAL SUMMARY

COMPOUND: SAR566658	**STUDY No.: ACT14884**
TITLE	Open-label Phase 2 study evaluating efficacy and safety of SAR566658 treatment in patients with CA6 positive metastatic Triple Negative Breast Cancer
INVESTIGATOR/TRIAL LOCATION	International
PHASE OF DEVELOPMENT	Phase II
STUDY OBJECTIVE(S)	**Primary objective:** • To evaluate the tumor Objective Response Rate (ORR), according to the Response Evaluation Criteria in Solid Tumors (RECIST 1.1) (1) of SAR566658 in patients with CA6-positive metastatic triple negative breast cancer (TNBC). • **Part 1:** To select the SAR566658 dose based on ORR and safety of 2 dose levels of SAR566658 in patients with metastatic TNBC overexpressing CA6 (membrane intensity of 2+, 3+ in ≥30% of tumor cells). • Part 2: - ***Part 2a:*** To demonstrate the activity of SAR566658 based on ORR in patients with metastatic TNBC overexpressing CA6 (membrane intensity of 2+, 3+ in ≥30% of tumor cells) treated at the selected dose in an expanded cohort, in addition to the patients treated in Part 1, - ***Part 2b:*** To assess the efficacy of SAR566658 based on ORR in patients with metastatic TNBC and mild CA6 expression (with at least 1% positive tumor cells at intensity ≥1+ and <30% of tumor cells at intensity of 2+, 3+) treated at the selected dose in a "mild CA6 expression cohort". **Secondary objectives:** ***Part 1 and Part 2*** • To assess: - Disease Control Rate (DCR), Duration Of Response (DOR), Progression-Free Survival (PFS), and Time To Progression (TTP), - The impact of ocular primary prophylaxis on the incidence of keratopathies, - The pharmacokinetic (PK) profile of SAR566658, - The potential immunogenicity of SAR566658, - The relationship between CA6 expression level in the tumor, and circulating CA6 in blood at baseline, and efficacy outcomes. • To evaluate the global safety profile.

	Exploratory objectives: [redacted]
STUDY DESIGN	This is an open-label, multicenter, Phase II study evaluating the efficacy and safety of SAR566658 administered as a single agent by intravenous infusion in patients with CA6-positive metastatic TNBC after at least 1 prior chemotherapy regimen, but no more than 3 for advanced/metastatic disease. CA6 expression will be assessed by immunohistochemistry (IHC) at a central laboratory on the most recent available tumor sample (ie, archive tumor tissue at diagnosis, archive tumor tissue at surgery, or most recent metastatic biopsy). The prescreening phase will correspond to the timing for the patient's tumor sample collection to allow determination of CA6 expression by central IHC. Patient prescreening, screening and enrollment will be centralized by Interactive Voice/Web Response System (IVRS/IWRS). The study will be performed in 2 parts: **Part 1** A total of 28 patients with metastatic TNBC overexpressing CA6 (membrane intensity of 2+, 3+ in ≥30% of tumor cells) will be randomized either to the 90 mg/m^2 or to the 120 mg/m^2 cohort in a 1:1 ratio, both given at Day 1 and Day 8 of each 3-week cycle. Patients randomized but not treated will be replaced. Study treatment should be initiated no later than 3 days after randomization. During treatment, safety will be monitored and the risks for predefined safety criteria (see endpoints) during the first 2 cycles will be followed and assessed using a Bayesian binomial model. In particular, risks for overdosing and unacceptable toxicity will be assessed as soon as 4 patients treated at the dose level of 120 mg/m^2 become evaluable for the predefined safety criteria. The Bayesian model assessing the rate of predefined safety criteria will use dose as a parameter. The decision to stop 1 arm may be taken on the basis of risk of the assessed overdosing (ie, predefined safety criteria rate above 40%) and unacceptable toxicity (ie, predefined safety criteria rate above 60%). The model recommends stopping 1 arm when its overdosing risk or unacceptable toxicity risk will not be controlled at the levels of 25% and 5%, respectively. Randomization will be centralized by IVRS/IWRS, stratified on Eastern Cooperative Oncology Group (ECOG) performance status (PS) (0 versus 1). Randomization should be done when all eligibility criteria are checked and the patient deemed eligible. Randomization will be stopped at the end of Part 1 and the recruitment will be authorized in Part 2 only when the selected dose is chosen.

	The selection of the dose to be continued in Part 2 will be made at the end of Part 1. An interim futility and overwhelming efficacy analysis on ORR according to RECIST 1.1 will be done on the first 14 patients treated in each cohort; if at least 2 confirmed responses (partial response [PR] or complete response [CR]) in at least 1 arm are observed then the study can continue in Part 2, if the safety profile is acceptable. In addition to the efficacy criteria, safety criteria including the rate (%) of patients experiencing an eye disorder, or peripheral neuropathy, or a treatment-emergent adverse event (TEAE) leading to dose modification (reduction or omission) or drug discontinuation, will be considered. In case of the efficacy criteria (<2 PR or CR in 14 patients) not being reached for a given dose, then this dose is not selected. In case of neither dose reaching the efficacy criteria (<2 PR or CR in 14 patients), then the study will be stopped. In case of comparable ORR and safety profile between 90 mg/m^2 D1D8 q3w and 120 mg/m^2 D1D8 q3w, then the lower dose (90 mg/m^2 D1D8 q3w) will be chosen. In case of higher ORR in 120 mg/m^2 D1D8 q3w and a comparable safety profile to 90 mg/m^2, then 120 mg/m^2 D1D8 q3w will be chosen. In case of higher ORR in 120 mg/m^2 D1D8 q3w and a better safety profile with 90 mg/m^2, then the dose will be selected on the best risk/benefit assessment. If there are 6 objective responses or more in the first 14 patients treated at 1 dose, then the study could be stopped for overwhelming efficacy. **Part 2** ***Part 2a:*** The expansion/overexpressing CA6 cohort with an additional 15 metastatic TNBC patients with CA6 overexpression (membrane intensity of 2+, 3+ in ≥30% of tumor cells) will start at the selected dose using the same selection criteria as for Part 1. If at least 7 responders (PR or CR) are seen among the 29 patients, then the null hypothesis of 12% ORR can be rejected. This test has a 1-sided Type 1 error of 10% and 80% power for an alternative hypothesis of 30% response rate. ***Part 2b:*** An additional mild CA6 expression cohort of 20 metastatic TNBC patients with mild CA6 membrane intensity with at least 1% positive tumor cells at intensity ≥1+ and <30% of tumor cells at intensity of 2+, 3+, will be assessed at the selected dose.
STUDY POPULATION **Main selection criteria**	**Inclusion criteria:** I 01. Metastatic TNBC. I 02. Patient with measurable disease, as per RECIST 1.1 criteria (Appendix A). I 03. Histologically documented TNBC (either at primary diagnostic or at metastatic site) that is estrogen receptor (ER)-negative and progesterone receptor (PgR)-negative (<1% tumor staining by IHC), and human epidermal growth factor receptor 2 (HER2) nonoverexpressing by IHC (0, 1+) or in situ hybridization-negative based on single-probe average HER2 copy number

	<4.0 signals/cell or dual-probe HER2/CEP17 ratio <2 with an average HER2 copy number <4.0 signals/cell as per American Society of Clinical Oncology (ASCO) guidelines (2). I 04. Patients with CA6-positive disease defined as membrane intensity of 2+, 3+ in ≥30% of tumor cells (Part 1 and Part 2a) or with at least 1% positive tumor cells at intensity ≥1+ and <30% of tumor cells at intensity of 2+, 3+ (Part 2b). I 05. Patients received at least 1 prior chemotherapy regimen but no more than 3 for advanced/metastatic disease. a) Adjuvant/neo-adjuvant therapy will be counted as prior chemotherapy regimen if the patient had a progression/recurrence within 6 months after completion of the treatment, b) Prior hormonal, biologic (eg, bevacizumab) or immunotherapy, without a cytotoxic agent, are allowed and are not counted as line of therapy, c) A chemotherapy line in advanced/metastatic disease is an anticancer regimen that contains at least 1 cytotoxic chemotherapy agent and was discontinued due to progression. If a cytotoxic chemotherapy regimen was discontinued for a reason other than disease progression then this regimen does not count as a "prior line of chemotherapy" unless this regimen was discontinued after treatment response (CR, PR or stable disease [SD]) and disease progression occurring before another line of chemotherapy. I 06. Prior anticancer therapy must have contained anthracycline (eg, doxorubicin), if not contraindicated, and a taxane (eg, docetaxel, paclitaxel) in an adjuvant/neo-adjuvant or metastatic setting. I 07. Signed written informed consent. **Exclusion criteria:** <u>Related to methodology</u> E 01. ECOG PS ≥2 (Appendix B). E 02. Patient less than 18 years old. E 03. Any severe acute or chronic medical condition including uncontrolled diabetes mellitus, history of cardiovascular disease (congestive heart failure, severe or unstable angina pectoris, recent myocardial infraction within last 6 months, history of clinically significant active chronic obstructive pulmonary disease [COPD], or other moderate-to-severe chronic respiratory illnesses present within last 6 months) which, in the Investigator's opinion, may impair the ability of the patient to participate in the study, or interfere with interpretation of study results, or make the patient unable to comply with the study procedures. E 04. Pregnant or breast-feeding women. E 05. Patients with reproductive potential who do not agree to use accepted and effective method of contraception during the study treatment period and for 6 months following discontinuation of study drug. The definition of "effective method of contraception" described hereafter: oral contraceptives, combined hormonal intravaginal, transdermal, intrauterine device or condoms will be based on country-specific regulatory requirements, and documented in the Informed Consent Form (Appendix C).

	E 06. Adverse events (AEs) (excluding alopecia and those listed in the specific exclusion criteria) from any prior anticancer therapy of Grade >1 (National Cancer Institute Common Terminology Criteria for Adverse Events [NCI CTCAE] v4.03; see Appendix D) at the time of randomization. E 07. Wash out period of less than 3 weeks or 5 half-lives from previous antitumor chemotherapy, immunotherapy, or any investigational treatment. E 08. Patient has received wide field radiotherapy ≤4 weeks prior to starting study treatment, or limited field radiation for palliation ≤2 weeks prior to starting study treatment, or has not recovered from the side effects of such therapy. E 09. Patient has undergone major surgery ≤3 weeks prior to starting study treatment, or has not recovered from the side effects of major surgery. E 10. History of brain metastasis (other than totally resected or previously irradiated and nonprogressive/relapsed), spinal cord compression or carcinomatous meningitis, or new evidence of brain leptomeningeal disease. E 11. Prior malignancy. Adequately treated basal cell or squamous cell skin or superficial (pTis, pTa, and pT1) and bladder cancer are allowed, as well as any other cancer for which treatment has been completed ≥3 years ago and from which the patient has been disease-free for ≥3 years. E 12. Participation in another clinical trial and any concurrent treatment with any investigational drug within 30 days prior to randomization. E 13. Prior treatment with eribulin as last therapy prior to enrollment, or prior maytansinoid treatments (DM1 or DM4 antibody-drug conjugates [ADCs]). Related to study treatment E 14. Acquired immunodeficiency syndrome (AIDS-related illnesses) or known HIV disease requiring antiretroviral treatment. E 15. Known active hepatitis A, B, or C infection that requires treatment. E 16. Known intolerance to infused protein products including other monoclonal antibodies and ADCs. E 17. Poor bone marrow reserve as defined by absolute neutrophil count <1.5 x 10^9/L or platelets <100 x 10^9/L or hemoglobin <9 g/dL. E 18. Poor organ function as defined by 1 of the following: a) Total bilirubin >1.5 x upper limit of normal (ULN) (except patients with Gilbert's syndrome: total bilirubin ≤3.0 x ULN, with direct bilirubin ≤1.5 x ULN), b) Aspartate aminotransferase, alanine aminotransferase, or alkaline phosphatase >2.5 x ULN; except >5 x ULN in case of documented liver metastasis or alkaline phosphatase >5 x ULN in case of documented bone metastasis, c) Serum creatinine >1.5 x ULN, except if calculated creatinine clearance ≥60 mL/min (as per Cockcroft-Gault formula, see Appendix E). E 19. Symptomatic peripheral neuropathy Grade ≥2 (NCI CTCAE v4.03).

	E 20. Previous history of chronic corneal diseases (even if asymptomatic) or unresolved acute nonrecurrent corneal conditions. E 21. Patients wearing contact lenses who are not willing to stop wearing them for the duration of the study. E 22. Medical conditions requiring concomitant administration of strong CYP3A4 inhibitors (see Appendix F), unless it can be discontinued at least 2 weeks before 1st administration of SAR566658. E 23. Contraindications to the use of ophthalmic vasoconstrictor and/or corticosteroid as per package insert of each drug, including the following: increased intraocular pressure, prior or current glaucoma, narrow-angle glaucoma, ongoing eye infection, uncontrolled hypertension, known/suspected allergy to constituents of the preparation (such as sodium bisulfite).
Total expected number of patients **Expected number of sites:**	A total of approximately 63 patients will be enrolled into this study (Part 1: 28 patients [14 in each cohort]; Part 2: 35 patients at the selected dose [Part 2a: 15 patients and Part 2b: 20 patients]). The actual sample size will vary depending on safety assessment and whether futility and overwhelming criteria are met in Part 1. Approximately 30 sites internationally.
STUDY TREATMENT(S) **Investigational medicinal product(s)** **Formulation:** **Route(s) of administration:** **Dose regimen:**	SAR566658 SAR566658 is supplied as a 25 mL, extractable, colorless to slightly yellow concentrate for solution for infusion of 125 mg in a 30 mL Type I glass vial. SAR566658 will be administered by intravenous (IV) infusion at a rate of 2.5 mg/min for 30 minutes and then increased to a maximal rate of 5 mg/min in the absence of hypersensitivity reactions. SAR566658 will be administered on Day 1 and Day 8 of every 21-day cycle. Dose modification (reduction or omission), treatment delay, and/or treatment discontinuation are planned in case of severe toxicity. **Part 1:** Patients will be randomly allocated to receive 1 of the 2 following doses: • Cohort 1: 90 mg/m^2 of SAR566658 on D1 and D8 repeated every 21 days. This will constitute 1 cycle of treatment. • Cohort 2: 120 mg/m^2 of SAR566658 on D1 and D8 repeated every 21 days. This will constitute 1 cycle of treatment. **Part 2:** **Expansion/overexpressing CA6 and mild CA6 expression cohorts** SAR566658 will be administered at the dose of 90 mg/m^2 or 120 mg/m^2 on D1 and D8 of every 21-day cycle depending on dose level selected from Part 1. **Ocular primary prophylaxis (Part 1 and Part 2):** All patients (Part 1 and Part 2) will receive ocular primary prophylaxis in each eye in order to prevent the occurrence of keratopathies at the

	time of each infusion (vasoconstrictor, ophthalmic topical steroid, and cold mask on eyes) and steroid eye drops for an additional 2 days following SAR566658 administration (a total of 3 days steroid ophthalmic therapy including Day 1 for each cycle). Topical artificial tears are recommended to be instilled in each eye up to 6 times per day during the whole study treatment period. **Premedication** Premedication with histamine H1 antagonist (diphenhydramine 50 mg or equivalent given orally approximately 1 hour before SAR566658 administration) is required for all patients.
ENDPOINT(S)	**Primary endpoints:** ***Part 1*** **Safety endpoint** Incidence of investigational medicinal product (IMP)-related predefined safety criteria during Cycle 1 and Cycle 2. Predefined safety criteria are defined as the occurrence of any following related TEAE using NCI CTCAE v4.03: • Grade ≥3 TEAE from the System Organ Class of eye disorders. • Grade ≥3 peripheral neuropathy (Preferred Term). • Grade ≥4 TEAE. **Efficacy endpoint** Objective Response Rate, defined as the proportion of CR and PR as best response according to RECIST 1.1. Confirmation of objective responses will be performed by repeat tumor imaging (Computerized Tomography [CT] scan, Magnetic Resonance Imaging [MRI]) at least 4 weeks after the first radiological documentation of response. ***Part 2*** **Part 2a (expansion/overexpressing CA6 cohort)** Objective Response Rate (see Part 1). A total of 15 additional patients will be treated and the analyses performed on the whole population treated at the selected dose (Part 1 and Part 2a). **Part 2b (mild CA6 expression cohort)** Objective Response Rate (see Part 1). A total of 20 patients with a mild CA6-positive membrane intensity, with at least 1% positive tumor cells at intensity $\geq$1+ and <30% of tumor cells at intensity of 2+, 3+, will be treated and the analyses performed. **Secondary endpoints (Part 1 and Part 2):** • Disease control rate (DCR): number of patients with CR, PR and stable disease (SD) with a duration of at least 3 months. • Duration of Response (DOR): defined as the time from the first documentation of objective tumor response (CR or PR) to the first radiological documentation of tumor progression or death (due to any cause), whichever comes first. • Progression-free survival (PFS): defined as the time interval between the date of first study treatment administration and

	the date of documented tumor progression or death (due to any cause), whichever comes first. • Time to progression (TTP): defined as the time interval between the date of first study treatment administration and the date of the first radiologically documented tumor progression. • Safety profile of the study treatment in terms of AEs/Serious Adverse Events (SAEs) and laboratory parameters: - Type, frequency, severity, seriousness, and relatedness of study TEAEs will be assessed according to NCI CTCAE v4.03, - Laboratory abnormalities will be assessed according to NCI CTCAE v4.03. • Evaluation of keratopathies using ocular primary prophylaxis. • PK parameters assessed for SAR566658, naked huDS6 (SAR404461), and unconjugated maytansinoids (DM4 and Me-DM4). • Immunogenicity evaluation: anti-SAR566658 antibodies (antitherapeutic antibodies [ATA]). • CA6 expression in tumors by IHC at baseline. • Circulating CA6 at baseline. **Other endpoints:** [redacted]
ASSESSMENT SCHEDULE	Clinical examinations (including height at baseline only, weight, ECOG PS, and vital signs), laboratory tests (including complete blood counts, serum chemistry and coagulation), 12-lead ECG, concomitant medications, and AEs (NCI CTCAE v.4.03) will be obtained prior to drug administration, every cycle before treatment administration and up to 30 days after the last study treatment administration. Laboratory tests (including complete blood counts, and serum chemistry) will be also obtained at D8 and D15 for the first 2 cycles and complete blood counts only at D8 for the subsequent cycles, before treatment administration where applicable. An ECG will be obtained within 7 days prior to first drug administration and at the end of treatment. **Efficacy evaluation:** Tumor assessments (CT-scan or MRI and any other exams as clinically indicated) will be performed at baseline and every 6 weeks during the study treatment period from baseline to disease progression even if the patient discontinued study treatment before progressive disease or study cut-off whichever comes first. Confirmatory radiological evaluation will be performed at least 4 weeks after initial documentation of response.

	PK evaluation/immunogenicity: Assessments will be performed using blood-samples collected at baseline, at specific time points of each cycle, and at the end of treatment and follow-up visits as specified in the PK/immunogenicity flow chart (Section 1.4). **Biomarker analyses:** CA6 expression will be assessed by IHC at a central laboratory on the most recent available tumor sample (ie, archive tumor tissue at diagnosis, archive tumor tissue at surgery, or most recent metastatic biopsy). Blood samples for circulating CA6 and [redacted] will be collected as specified in the flow chart (Section 1.2). [redacted] (Section 1.2). [redacted] (Section 1.2). After study treatment discontinuation, patients will be followed every 6 weeks until death, study cut-off date or withdrawal of patient's consent.
STATISTICAL CONSIDERATIONS	**Randomization:** In Part 1, treatment assignment will be done centrally via an IVRS/IWRS using a permuted–block randomization stratified according to ECOG PS (0 versus 1). All eligible patients will be randomly assigned to either the dose 90 mg/m^2 D1D8 q3w or to the dose 120 mg/m^2 D1D8 q3w in a 1:1 proportion. **Sample size determination:** It is anticipated that approximately 63 patients will be enrolled into this study. This study is separated into 2 parts: **Part 1:** 14 patients overexpressing CA6 will be treated in parallel at each dose level: 90 mg/m^2 D1D8 q3w and 120 mg/m^2 D1D8 q3w. Based on efficacy and safety (including predefined safety criteria), supported by PK data, 1 dose will be selected if the futility criteria on ORR is not met (see study design). **Part 2:** ***Part 2a:*** 15 additional patients overexpressing CA6 will be treated in the expansion cohort at the selected dose. ***Part 2b:*** In parallel, 20 additional patients in a mild CA6 expression cohort will be treated at the selected dose. • Sample size determination for Part 1 and Part 2a (expansion/overexpressing CA6 cohort) The sample size calculation is based on efficacy criteria (ORR). A 2-stage design will be used for the selected dose. It is expected that a beneficial ORR under SAR566658 is of at least 30% (H_1). An ORR of 12% (or less) will be considered as clinically nonrelevant (H_0). On the basis of these assumptions, 29 treated patients at the selected dose at the end of Part 2a would be necessary to reject null response rate of 12% with a global power of 80% and a 1-sided

	alpha level of 10%. An interim analysis is planned in Part 1 after 14 patients have been treated at each dose. ***Part 1*** An interim analysis will be performed to assess futility (to reject early the hypothesis that the response rate is 30%). If there is 0 or 1 response (CR or PR) in the first 14 patients treated at each dose, the critical boundary 7.1% is not met and the alternative hypothesis of at least 30% will be rejected. If the critical boundary of 7.1% is reached (2 responses or more), the study will continue in Part 2 at the selected dose. At the same interim analysis, overwhelming efficacy will be assessed (to reject early that the response rate is less or equal to 12%). If there are 6 responses or more in the first 14 patients treated at 1 dose, the critical boundary of 42.9% is reached and the null hypothesis of 12% will be rejected. Overall, this procedure has 80% statistical power (1-sided alpha level of 10%) to reject the null hypothesis, using a gamma (-2) beta spending function for futility analysis and a Lan-DeMets (OF) alpha spending function in a 1 sample test for a binomial proportion (East version 6.3 using exact computations, Cytel Software, Cambridge, MA). The dose selection will be done at the end of Part 1, following decision criteria explained in the study design section. ***Part 2a*** A total of 7 confirmed responses (CR or PR) or more out of 29 patients (patients from Part 1 and Part 2a at the selected dose) will be necessary to reject the null hypothesis at the end of the Part 2a expansion/overexpressing CA6 cohort. • Sample size determination for the Part 2b (mild CA6 expression cohort) At the selected dose, the relationship between CA6 expression level and efficacy outcomes will be assessed by adding a cohort of 20 patients with mild CA6 membrane staining (with at least 1% positive tumor cells at intensity ≥1+ and <30% of tumor cells at intensity of 2+, 3+). With a sample size of 20 patients, a true response rate above 15% can be rejected with 83% confidence if we observe 0 or 1 response. Moreover, if we observe 7 responses in the 29 patients in the CA6 overexpression cohort (≥30%, 2+/3+) and ≤1 response in the mild CA6 expression cohort (CA6 IHC = (<30% 2+, 3+ and at least 1% positive cells at intensity ≥1+), the 1-sided p-value (according to Fisher's exact test) will be around 7% suggesting an association between biomarker status and ORR. **Analysis population:** Safety population: The all treated population consisting of patients who will actually receive at least 1 dose (or any partial) of SAR566658. This population is the primary population for the analyses of efficacy and safety parameters.

	Response evaluable population: Sensitivity analyses of the primary efficacy endpoint will be performed on the response evaluable population, defined as patients with measurable disease at study entry, with CA6 positivity according to the threshold defined in the relevant study part (Part 1 and Part 2a or Part 2b), and who had an evaluable response assessment during the treatment period (see Section 11.3.3 and Section 11.4.5.1). Treated patients who could not have a postbaseline tumor assessment because of early disease progression or early death due to progressive disease are also included in the response evaluable population. Evaluable for predefined selection criteria population: Only for Part 1, predefined safety criteria evaluation will be performed on patients treated in the study who have completed 2 cycles, or who experienced predefined safety criteria (whatever the dose received). Other populations for secondary endpoints analysis (eg, PK populations, and population evaluable for ATA) will be defined in the body of the protocol. **Primary analysis of the primary endpoints:** **Safety endpoint (Part 1)** Predefined safety criteria occurring at Cycle 1 and 2 and AEs meeting predefined safety criteria occurring at any additional cycle will be assessed and analyzed on the all treated population. **Efficacy endpoint (Part 1 and Part 2)** The ORR will be estimated on the all treated population and provided with its exact 80% confidence interval. **Analysis of secondary endpoints:** The DCR will be estimated on the all treated population and provided with its exact 95% confidence interval. Duration of response will be provided for responding patients. Time to progression as well as PFS will be estimated on the all treated population using the Kaplan-Meier method. Kaplan-Meier curves for TTP and PFS will be provided. Type (according to current version of Medical Dictionary for Regulatory Activities [MedDRA]), frequency, seriousness, severity (according to NCI CTCAE v4.03) and relationship of TEAEs, including predefined safety criteria, will be assessed and analyzed for all treated patients. Occurrence, time to occurrence, and severity of keratopathy will also be evaluated for patients with primary prophylaxis. Pharmacokinetics and immunogenicity parameters will be summarized with descriptive statistics. Analyses will be performed in order to assess the correlation between clinical outcomes and CA6 tumor expression and circulating CA6. **PK evaluation** Pharmacokinetic samples will be collected in all patients in order to perform population PK analysis using a nonlinear mixed-effects modelling approach. This analysis will involve an estimation of interpatient PK variability, the population PK parameter estimates, and the assessments of demographic and patho-physiologic covariate effects on clearance, and possibly on volume if warranted. Empirical Bayesian estimation of individual PK model parameters and of individual exposure parameters of interest (such as maximum

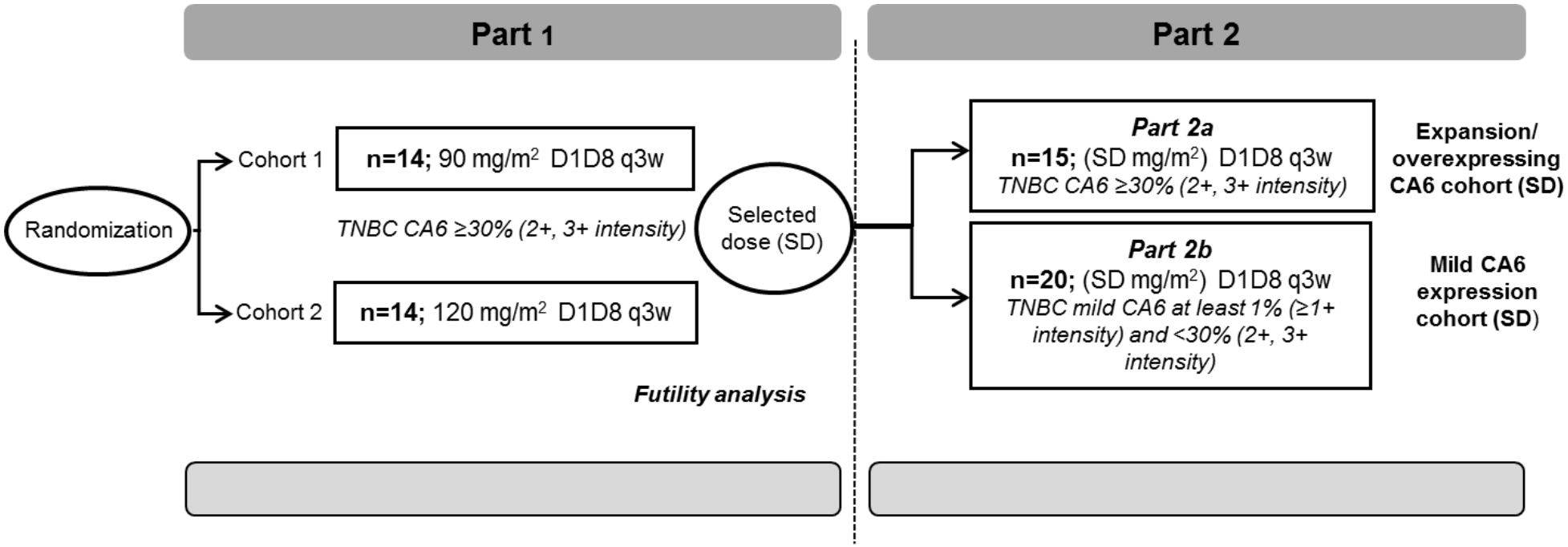
	concentration [C_{max}] and area under the plasma concentration-time curve [AUC]) will also be performed. Those estimates will then be investigated as prognostic factors for clinical outcome including safety and efficacy endpoints, if possible. [redacted]
DURATION OF STUDY PERIOD (per patient)	The duration of the study for 1 patient will include a screening period of up to 21 days prior to first study drug administration, 3-week treatment cycle(s) (until 30 days after last SAR566658 administration), and a follow-up period. Each patient will be treated until radiological disease progression, unacceptable toxicity, or patient's refusal of further study treatment. After the completion of the study treatment, each patient will be followed every 6 weeks until radiological disease progression, death, study cut-off, or withdrawal of patient's consent, whichever comes first. For patients who discontinue study treatment prior to documentation of disease progression, date of disease progression and further anticancer treatment will be collected at the follow-up visit. The first cut-off date for the selection of the selected dose corresponds to the date on which all patients treated in Part 1, whatever the dose, have had at least 4 postbaseline tumor assessments, experienced confirmed objective response, or have discontinued the study for any reason. However, if the futility criteria of 2 responders is either met or not met with certainty for both arms when all patients have had 2 postbaseline tumor assessments, experienced confirmed objective response, or discontinued the study for any reason, the first cut-off date may be done at that time instead. The recruitment will be put on hold at the time of the interim analysis until the decision regarding dose selection and the start of Part 2 has been made. The second cut-off date for primary ORR analysis corresponds to the date on which all patients treated in Part 2a and Part 2b have had at least 4 postbaseline tumor assessments, experienced confirmed objective response, or have discontinued the study for any reason. However, if the primary criteria of 7 responders is either met or not met with certainty at the end of the Part 2a in the selected dose when all patients have had 2 postbaseline tumor assessments, experienced confirmed objective response, or discontinued the study for any reason and when all the patients of the Part 2b have had 2 postbaseline tumor assessments, experienced confirmed objective response, or discontinued the study for any reason, the second cut-off date may be done at that time instead. After the second cut-off date for primary ORR analysis, patients who are still receiving study treatment can continue study treatment, if clinical benefit is observed, until progressive disease, unacceptable toxicity, or patient's refusal, and will continue to undergo all assessments as per the study flow chart. For patients in follow-up and still alive at the cut-off date, an update for survival status at 6 months after this date will be collected. Patients without documented disease progression but not on treatment at the second cut-off date will be followed for any ongoing AEs. In addition, imaging to document disease progression and survival status will be collected (every 6 weeks) for 6 months after the cut-off date.

STUDY COMMITTEE	A Steering Committee will be responsible for monitoring and supervising the progress of the study. This committee will include the study chairman, 2 main Investigators, Sponsor representatives and any ad hoc ophthalmologist external expert, as needed. The Steering Committee procedures will be detailed in a Steering Committee charter and approved by the Steering Committee members.

1 FLOW CHARTS

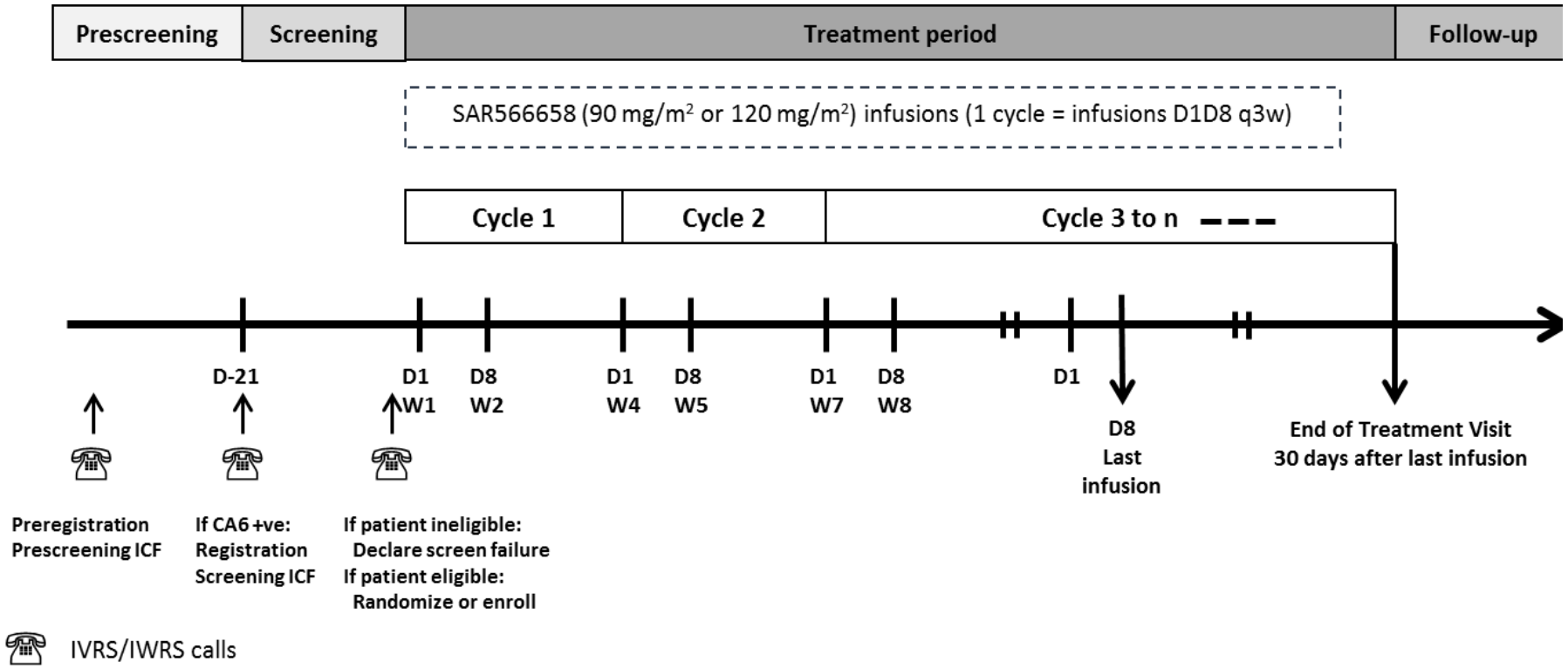
1.1 GRAPHICAL STUDY DESIGN

1.1.1 Overall study design



Abbreviations: D: day; q3w: every 3 weeks; SD: selected dose; TNBC: triple negative breast cancer.

1.1.2 Schematic study schedule (Part 1 and Part 2)



Abbreviations: +ve: positive; D: day; ICF: informed consent form; IVRS/IWRS: Interactive Voice/Web Response System; q3w: every 3 weeks; W: week.

1.2 STUDY FLOW CHART

	Prescreening[a]	Screening (prior to first infusion)[b]		RANDOMIZATION[c]	Treatment Cycle 1					Treatment Cycle 2				Subsequent cycles			End of treatment (Day 30 after last infusion)	Follow-up period[t]
Day		**-21 to 1**	**-7 to 1**		**-1**	**1[d]**	**8[d]**	**15**	**21**	**1[d]**	**8[d]**	**15**	**21**	**1[d]**	**8[d]**	**21**		
CA6 expression status (archival tumor tissue) – central IHC/ prescreening Informed consent	X																	
Inclusion/exclusion criteria/ Informed Consent		X																
Demography and medical/disease history		X																
Physical examination[e]/ signs and symptoms			X				X	X	X		X	X	X		X	X	X	X
Hematology[f]			X				X	X	X		X	X	X		X	X	X	
Coagulation[g]			X						X				X			X	X	
Blood chemistry[h]			X				X	X	X		X	X	X			X	X	
Serum pregnancy test[i]			X							X				X			X	
12-lead ECG[j]			X														X	
SAR566658 administration[k]						X	X			X	X			X	X			
Primary prophylaxis for ocular event[l]						X	X			X	X			X	X			
Hospitalization[m]					X	X												
AE assessment[n]		Continuously throughout the study period																
Concomitant medication[o]		Continuously throughout the study period																
PK/immunogenicity assessment[p]		See PK/immunogenicity flow chart																
Specific ocular tests[q]		X																
Tumor assessment[r]		X											X				X	X

	Prescreening[a]	Screening (prior to first infusion)[b]		Treatment Cycle 1					Treatment Cycle 2				Subsequent cycles			End of treatment (Day 30 after last infusion)	Follow-up period[t]
Day		**-21 to 1**	**-7 to 1**	**-1**	**1[d]**	**8[d]**	**15**	**21**	**1[d]**	**8[d]**	**15**	**21**	**1[d]**	**8[d]**	**21**		
Circulating CA6[s]					X												
[redacted]					X				X				X			X	X
[redacted]					X											X	
[redacted]					X												
Further anticancer therapy																	X
Survival status[u]																	X

1.3 FOOTNOTES FOR STUDY FLOW CHART

a **Prescreening:** the preselection test on CA6 positivity will be determined by centralized IHC on FFPE slides collected from the most recent available tumor samples (6 FFPE slides). Extra slides, if available, will be preserved and used to support the development of a potential in vitro diagnostic assay for a registration trial. The CA6 IHC staining will be performed at a centralized laboratory; a prescreening Informed Consent will be signed by the patient for this purpose. The positivity of CA6 is defined by IHC with membrane staining of ≥30% (2+, 3+) of tumor cells for Part 1 and Part 2a, and membrane staining of at least 1% positive tumor cells at intensity ≥1+ and <30% of tumor cells at intensity 2+, 3+ for Part 2b. Both CA6 cytosolic and membrane percent staining at intensity 1+, 2+, and 3+ will be recorded.

b **Screening** assessments must be performed prior to first IMP administration: patients must have confirmed CA6 expression as assessed centrally. Baseline evaluation should be completed within 1 week prior to initiation of therapy, except for tumor assessment and ocular tests that may be performed within 3 weeks prior to the first IMP administration. Results of these tests should be reviewed by the Investigator prior to randomization. If any laboratory tests are abnormal, these must be repeated within 2 days before the first IMP administration.

c Only for Part 1: all eligible patients will be randomly assigned to one of the 2 dose level treatment cohorts using an IVRSIWRS. Study treatment should be started within 3 calendar days from randomization.

d D1 and D8: Cycle 1 D1D8 refers to the days the patient receives the initial dose of IMP. D1 of Cycle 2 and of each subsequent cycle corresponds to D22 of the previous cycle. Before Cycle 1, evaluations such as ECOG PS, body weight, signs and symptoms, physical examination, hematology, and blood chemistry should be performed less than 7 days before IMP administration and should be repeated within 2 days before IMP administration if abnormal. For further cycles, assessment can be done on the day of infusion (before infusion) or the day before.

e **Physical examination** will include: examination of major body systems, height (at baseline only), body weight, ECOG PS, and vital signs (temperature, blood pressure). At the follow-up visit, only ECOG PS and weight will be collected. Signs and symptoms will be reported in the eCRF as AEs only if they are still present at the time of first IMP administration.

f **Hematology:** hemoglobin, WBC with differential, platelet counts. These tests will be done weekly for Cycles 1 and 2. If Grade 4 neutropenia occurs, assess ANC every 2-3 days until ANC ≥0.5 x 10^9/L.

g **Coagulation:** INR.

h **Blood chemistry:** liver function tests: AST, ALT, total bilirubin, conjugated bilirubin, AP, electrolytes: sodium, potassium, calcium, phosphate, and chloride. Renal function tests: creatinine and BUN or urea. Others: glucose, LDH, albumin, and total proteins. These tests will be done weekly during the 2 first cycles then every 3 weeks for subsequent cycles, except for BUN and chloride that will be done weekly only during the first cycle. Additional tests will be performed when clinically appropriate. In case of Grade ≥3 liver function abnormal tests, additional tests will be done every 2 to 3 days until recovery to baseline value.

i **Serum pregnancy test:** women of child-bearing potential must have a negative serum pregnancy test result within 7 days prior to the initial dose of IMP and at the end of treatment evaluation (between D22 and D30 after the last IMP administration). The serum pregnancy test will also be performed before each cycle, only in countries where it is a regulatory requirement.

j **12-lead ECG** is required at baseline and at end of treatment. To be repeated as clinically indicated.

k **SAR566658 administration:** on Day 1 and Day 8 of each treatment cycle, the patient's BSA will be determined using the current weight and baseline height. For patients with a BSA >2.0 m^2, the dose will be calculated on the basis of 2.0 m^2 BSA. Premedication with histamine H1 antagonist is required: diphenhydramine 50 mg given orally approximately 1 hour before SAR566658 administration.

l **Primary prophylaxis for eye disorders** is required in each eye (vasoconstrictor and steroid eye drops, cold mask) at the time of infusion and for 2 additional days after infusion for steroid eye drops only (making a total of 3 days of ophthalmic topical steroid including Day 1 of each cycle). Topical artificial tears are recommended to be instilled in each eye up to 6 times per day during the whole study treatment period.

m **Hospitalization** for the first IMP administration is recommended for safety monitoring, until at least 6 hours after the end of IMP administration. Ambulatory hospitalization can be considered at the Investigator's discretion.

n **Adverse event/serious adverse event assessment:** the period of safety observation extends from the date the study informed consent is signed, until at least D30 after the last IMP administration. Concomitant medication will be recorded in the eCRF. Adverse events will be recorded according to NCI CTCAE version 4.03 (Appendix D).

o **Concomitant medication** will be recorded in the eCRF from 21 days prior to the first study treatment administration, before every cycle during the study treatment period, and for up to 30 days after the final dose of study drug. Once the patient has withdrawn from study treatment, concomitant medication should only be recorded if used to treat new or unresolved study treatment-related adverse events.

p **PK/immunogenicity:** see detailed flow chart (Section 1.4).

q **Specific complete ocular examination** at baseline will include: assessment of ocular/visual symptoms, visual acuity, full ocular tests including slit lamp with fluorescein under dilatation, and Schirmer's test preferably with anesthetics. In patients with any ocular/visual symptom(s) (eg, blurred vision, photophobia) the complete ocular tests will be repeated at the time of the occurrence of the ocular toxicity. Then, visual acuity, slit lamp examination under dilatation, and Schirmer's test will be repeated once weekly until resolution to Grade 1. In case of recurrent ocular toxicity observed in subsequent cycles, visual acuity and slit lamp examination with fluorescein under dilatation, and Schirmer's test preferably with anesthetics will be performed at the time of the event onset, then weekly until resolution to Grade 1. Moreover, tonometry will be performed at screening, at the end of Cycle 6 (with a time window of 4 days preceding the following cycle administration), whenever clinically indicated, and at End of Treatment, to assess and monitor intraocular pressure. At screening, tonometry will be performed with and without dilation, and only without dilation at the subsequent time points.

r **Tumor assessment** as per RECIST1.1: CT-scan or MRI and any other examinations as clinically indicated will be performed to assess disease status at baseline, every 6 weeks during the study treatment period until radiological disease progression or study cut-off, whichever comes first, and at the end of study treatment, except if already done at last cycle. Confirmatory radiological evaluation will be performed at least 4 weeks after initial documentation of response.

s [redacted].

t **Follow-up period (every 6 weeks):** during the follow-up period, SAEs (regardless of relationship with study treatment) and IMP-related AEs ongoing at the end of study treatment, and any new IMP-related AE/SAE will be followed until resolution or stabilization (stabilization is defined as an event ongoing without any change for at least 3 months). Patients achieving stable disease, complete or partial response should be followed until radiological disease progression, death, study cut-off, or withdrawal of patient's consent, whichever comes first. For patients who discontinue study treatment prior to radiological documentation of disease progression, a tumor assessment will be performed every 6 weeks. Date of disease progression and further anticancer treatment will be collected at the follow-up visit.

u **Survival status:** During the follow-up period, patients without documented disease progression but not on treatment at the second cut-off date will be followed every 6 weeks to collect survival status for a further 6 months or until documented disease progression, death, or withdrawal of consent, whichever comes first.

Abbreviations: AE: adverse event; ALT: alanine aminotransferase; ANC: absolute neutrophil count; AP: alkaline phosphatase; AST: aspartate aminotransferase; BSA: Body Surface Area; BUN: Blood Urea Nitrogen; [redacted]; CT: Computed Tomography; D: Day; ECOG: Eastern Cooperative Oncology Group; eCRF: electronic Case Report Form; FFPE: formalin-fixed paraffin-embedded; IHC: immunohistochemistry; IMP: investigational medicinal product; INR: International Normalized Ratio; IVRS/IWRS: Interactive Voice/Web Response System; LDH: lactate dehydrogenase; MRI: Magnetic Resonance Imaging; NCI CTCAE: National Cancer Institute Common Terminology Criteria for Adverse Events; PS: performance status; RECIST: Response Evaluation Criteria in Solid Tumors; SAE: serious adverse event; TNBC: triple negative breast cancer; WBC: white blood cell.

1.4 PHARMACOKINETICS/IMMUNOGENICITY FLOW CHART

Cycle	**Cycle 1 and Cycle 2**								**Subsequent Cycles**		**EOT**	**FU**
Week within Cycle	**W1**				**W2**			**W3**	**W1**			
Day within Cycle	D1			D4 or D5	D8			D15	D1		D30[f]	6 weeks after EOT
Time[a] - SAR566658	0h[b]	EOI[c]	EOI + 6h	72h or 96h	0h[b]	EOI[c]	EOI + 6h	168h	0h[b]	EOI[c,d]		
Indicative clock time	8am	9am	3pm	8am	8am	9am	3pm	8am	8am	9am		
IMP administration (IV infusion)												
SAR566658	<---------->				<---------->				<---------->			
PK samples												
SAR566658	P00[b]	P01[c]	P02	P03	P04[b]	P05[c]	P06	P07	P00[b]	P01[c,d]	PF00	
DM4 and Me-DM4	P00[b]	P01[c]	P02	P03	P04[b]	P05[c]	P06	P07	P00[b,d]	P01[c,d]		
Naked hu-DS6	P00[b]	P01[c]	P02	P03	P04[b]	P05[c]	P06	P07	P00[b]	P01[c,d]	PF00	
Immunogenicity												
ATA	AB00[b]								AB00[b]		ABF00	ABF01[e]

a Time relative to the start of last infusion.

b Samples collected before start of infusion.

c Samples collected just before the end of infusion.

d Until Cycle 6 only.

e In case of a positive result for the ATA sample at FU1, additional ATA samples will be collected at subsequent 6-weekly follow-up visits (and thereafter every 3 months until a negative result is obtained).

f The reference date of D30 is the date of last study treatment infusion.

Abbreviations: AB: antibody; ATA: antitherapeutic antibodies; D: day; EOI: end of infusion; EOT: end-of-treatment; FU: follow-up; IMP: investigational medicinal product; IV: intravenous; P: plasma; PK: pharmacokinetics; W: week.

Note: For the comfort of patients, some PK and/or ATA samplings may be deleted during the course of the study if they are no longer deemed necessary by the Sanofi PK team.

2 TABLE OF CONTENTS

2.1 LIST OF TABLES

2.2 LIST OF FIGURES

3 LIST OF ABBREVIATIONS

ADC:	antibody-drug conjugate
AE:	adverse event
AESI:	adverse event of special interest
ALT:	alanine aminotransferase
ANC:	absolute neutrophil count
AST:	aspartate aminotransferase
ATC:	anatomical therapeutic chemical
AUC:	area under the plasma concentration-time curve
BOR:	best overall response
BSA:	body surface area
[redacted]	[redacted]
CI:	confidence interval
C_{max}:	maximum concentration
CR:	complete response
CT:	computed tomography
DCR:	disease control rate
DEHP:	di-(2-ethylhexyl) phthalate
DOR:	duration of response
ECG:	electrocardiogram
ECOG:	Eastern Cooperative Oncology Group
eCRF:	electronic case report form
ELISA:	enzyme-linked immunosorbent assay
ER:	estrogen receptor
FFPE:	formalin-fixed paraffin embedded
FIH:	first in human
GCP:	good clinical practice
HLGT:	high level group term
HLT:	high level term
IEC:	independent ethics committee
IHC:	immunohistochemistry
INR:	International Normalized Ratio
IRB:	institutional review board
IV:	intravenous(ly)
IVRS/IWRS:	interactive voice/web response system
LDH:	lactate dehydrogenase
mBC:	metastatic breast cancer
MedDRA:	Medical Dictionary for Regulatory Activities
Me-DM4:	methyl-DM4
NCI CTCAE:	National Cancer Institute Common Terminology Criteria for Adverse Events
NIMP:	noninvestigational medicinal product
ORR:	objective response rate

PFS:	progression-free survival
PgR:	progesterone receptor
PK:	pharmacokinetic(s)
PR:	partial response
PS:	performance status
PT:	preferred term
PVC:	polyvinyl chloride
q2w:	every 2 weeks
q3w:	every 3 weeks
RD:	recommended dose
RECIST:	response evaluation criteria in solid tumors
SAE:	serious adverse event
SAP:	statistical analysis plan
SD:	stable disease
SOC:	system organ class
TEAE:	treatment-emergent adverse event
TNBC:	triple negative breast cancer
TTP:	time to progression
ULN:	upper limit of normal
WBC:	white blood cells
WHO-DD:	World Health Organization Drug Dictionary

4 INTRODUCTION AND RATIONALE

4.1 INTRODUCTION

SAR566658 combines a humanized monoclonal antibody targeting CA6 (huDS6) with a maytansinoid chemotherapy DM4 attached through an optimized cleavable linker (SPDB). The huDS6 antibody is a humanized version of a murine monoclonal antibody, muDS6, which recognizes/binds the CA6 antigen, a tumor-associated sialoglycotope on the extracellular domain of the human MUC1 glycoprotein (cancer-induced aberrant glycosylation). Maytansinoids are anti-mitotic agents that inhibit tubulin polymerization and microtubule assembly through binding on the vinca alkaloid site.

After binding to the CA6 antigen, SAR566658 is internalized by the target cancer cells via antigen-mediated endocytosis, delivered to lysosomes and degraded into a lysine-linked derivative. Lysine-SBDP-DM4 and metabolites (DM4 and methyl-DM4 [Me-DM4]) bind to the intracellular target, tubulin, and cause cytotoxicity by inhibition of microtubule polymerization. Metabolites can exit and re-enter target cells or enter neighboring (bystander) cells. The bystander effect could be a clear advantage for solid tumors with heterogeneous antigen distribution.

The CA6 epitope is highly expressed in multiple human tumors with high prevalence (CA6 positivity in >1% tumor cells by IHC) in pancreatic cancer (83%), ovarian cancer (89%), breast cancer (78% to 86%), bladder cancer (90%), head and neck carcinoma (65%), and non-small cell lung cancer (84%). When considering the CA6 positivity in ≥30% tumor cells 2+/3+ (by immunohistochemistry [IHC]), the prevalence becomes 59%, 70%, 29% to 35%, 59%, 17%, and 56%, respectively. The CA6 glycotope has limited distribution in normal adult tissues making huDS6 a promising candidate for selective delivery of cytotoxic agents into CA6-positive tumor cells.

4.1.1 Preclinical data

In vivo, dose-dependent activity with SAR566658, as single agent administration has been observed against several CA6-positive human tumor xenografts. Complete response (CR) and cures can be achieved with single administration of SAR566658 conjugate, at doses ranging from 3.9 to 43 mg/kg, depending on the model. Treatment with equivalent dose of the nonconjugated huDS6 antibody and free DM4 showed no antitumor activity, demonstrating the added value of immune-conjugation. Dependence of SAR566658 activity on binding to target antigen has been demonstrated in the human ovarian OVCAR5 model where the antitumor activity of SAR566658 is inhibited by pretreatment (2 hours) of mice with excess huDS6 antibody. SAR566658 is also active in mice bearing advanced tumors of the human breast tumor cell line UISO BCA-1, a model refractory to standard chemotherapeutic agents including docetaxel and doxorubicin. SAR566658 is not only able to elicit CR and tumor-free survivors in mice with advanced tumors (100 to 200 mg at the start of treatment), but also in mice with bulky tumors (approximately 500 mg) arising from recurrent disease.

The Investigator's Brochure provides comprehensive information on SAR566658.

4.1.2 Phase I clinical data

A first in human (FIH) study (TED10499) was conducted to assess the safety, dose limiting toxicities/recommended dose (RD), and pharmacokinetics (PK), following SAR566658 intravenous (IV) administration given every 3 weeks (q3w)(10 to 240 mg/m^2), every 2 weeks (q2w)(120 mg/m^2) and D1D8 q3w (90 mg/m^2). Prescreening on CA6 expression was performed on 1067 patients, 60% were CA6 positive (≥1%) and 24% were CA6 positive (≥30% tumor cells with intensity 2+/3+). CA6 antigen expression was assessed by IHC on paraffin embedded archival tumor tissue. The IHC assay using SAR566658 has been developed and qualified by Sanofi and validated at Ventana.

One hundred and fourteen (114) patients with heavily pretreated solid tumors expressing CA6 (in ≥30% tumor cells with intensity 2+/3+ by IHC in almost all patients) were enrolled.

In the dose escalation phase, 34 heavily pretreated patients were enrolled, with CA6 positive solid tumors including ovary, pancreas, and breast. Dose limiting toxicities were observed in 2 patients out of 8 treated at the highest dose of 240 mg/m^2 q3w (Grade 3 diarrhea [Cycle 1] and Grade 3 keratitis [Cycle 2]). Overall, SAR566658 was well tolerated with late occurrence of reversible corneal adverse events (AE) (known with previous maytansine antibody-drug conjugates [ADCs]), a few hematological events, and some peripheral neuropathies, observed from the dose of 150 mg/m^2 q3w.

The initial RD of 190 mg/m^2 q3w was used in an expansion phase (breast, ovary, and pancreas); however, a high incidence of keratopathy was observed mainly at Cycle 2. The decision was taken to decrease the dose to 150 mg/m^2 q3w; the corneal toxicity decreased but the activity was impacted. Based on PK/safety simulations, 2 alternative schedules were proposed to preserve drug exposure (area under the plasma concentration-time curve [AUC]) and limiting keratopathy incidence by decreasing maximum concentration (C_{max}): 90 mg/m^2 D1D8 q3w and 120 mg/m^2 q2w. Go/no-go criteria based on efficacy and safety parameters were defined for the selection of the RD: ≥15% objective response rate (ORR) or probability of nonprogression at 12 weeks in ≥50% patients and ≤25% of ocular events leading to dose modification (delay and/or dose reduction/discontinuation).

A total of 89 patients treated at the selected doses of interest (150 mg/m^2 q3w, 190 mg/m^2 q3w, 90 mg/m^2 D1D8 q3w, and 120 mg/m^2 q2w) were assessed. Of the 89 patients, 33 patients were included in the 2 alternative schedules (17 and 16 patients, in 90 mg/m^2 D1D8 q3w and 120 mg/m^2 q2w, respectively). A primary prophylaxis to prevent corneal toxicity was implemented in the last 10 patients receiving alternative schedules. The most common AE was reversible Grade 2/3 keratopathy in 55/89 (62%) (Grade 3 in 6 patients). Among these 55 patients, 15/23 (65%) received 190 mg/m^2 q3w, 12/33 (36%) 150 mg/m^2 q3w, 6/17 (35%) 90 mg/m^2 D1D8 q3w, and 2/16 (13%) 120 mg/m^2 q2w. Eye disorders leading to dose modification occurred in 14/23 (61%) patients at 190 mg/m^2 q3w, 8/33 (24%) at 150 mg/m^2 q3w, 5/17 (29%) at 90 mg/m^2 D1D8 q3w, and 2/16 (13%) at 120 mg/m² q2w.

A total of 10 patients (6 in 90 mg/m^2 D1D8 q3w schedule and 4 in 120 mg/m^2 Q2W) received primary ocular prophylaxis and no eye disorders leading to dose modification were observed; only 1 patient presented with keratitis at 90 mg/m^2 D1D8 q3w. In this latter alternative schedule, the incidence of ocular corneal events (mainly keratitis) being the main AEs, was similar to 150 mg/m^2 q3w and lower than 190 mg/m^2 q3w. Other AEs were fatigue (36%), peripheral neuropathy (32%) with a higher rate at 190 mg/m^2 q3w, GI disorders (nausea [26%], abdominal pain [28%], and diarrhea [25%]). Low grade hematological, liver, and renal abnormalities were noted.

Considering the 89 patients treated at the selected doses of interest, 7/89 (8%) had ORR (1 complete response [ovary], 6 partial responses [(PR; 3 breast, 1 ovary, 1 cervix, and 1 bladder]) and 46/89 (52%) patients with stable disease (SD) were observed. Highest ORR was observed in 12.5% (2/16) at 90 mg/m^2 D1D8 q3w and 13% (3/23) at 190 mg/m^2 q3w.

Multivariate analysis on the best relative change from baseline in the sum of the target lesions was performed including, as covariates, demographic characteristics (age, Eastern Cooperative Oncology Group [ECOG] performance status [PS] at baseline, sex, body surface area [BSA], weight, tumor type, number of previous lines), exposure (dose intensity in mg/m^2/week, AUCs, C_{max}, C_{trough}, clearance), and CA6 biomarker expression. The results showed that best relative change from baseline in the sum of the target lesions improves when ECOG PS decreases (p=0.014), AUC_{07d} increases (p=0.039), and percentage of cells staining at intensity 2+/3+ increases (p=0.037). This correlation between efficacy and CA6 expression level is not robust to extreme values (excluding one influential patient) and needs to be further confirmed.

Finally, the go/no-go criteria to fix the RD based on efficacy and safety were in favor of SAR566658 90 mg/m^2 D1D8 q3w with an ORR of 12.5%, a probability of nonprogression at 12 weeks in 63.0% patients, and ocular toxicity leading to dose modification of 29.4%.

In conclusion, SAR566658 is an active drug with responses seen in breast, lung, bladder, and ovarian cancers. Both alternative schedules lead to an acceptable safety profile for eye disorders (as expected from simulation). Similar ORR at 90 mg/m^2 D1D8 q3w compared to 190 mg/m^2 q3w is observed. Primary prophylaxis of eye disorders might be beneficial and would lead to improvement of the ocular safety profile of SAR566658.

4.2 RATIONALE

The aim of this study is to assess the efficacy and safety of SAR566658 in a metastatic triple negative breast cancer (TNBC) population. TNBC accounts for approximately 20% of breast cancers diagnosed worldwide, which amounts to almost 200 000 cases each year (3). TNBC is more commonly diagnosed in women aged less than 40 years compared with hormone-positive breast cancer. In 1 study, there was a 2-fold higher attributable risk of TNBC in women under 40 years compared with women over 50 years (odds ratio 2.13, 95% confidence interval [CI] 1.34-3.39). TNBC appears to be more common among black women, compared with white women (odds ratio 2.41, 95% CI 1.81-3.21) (4).

From the TED10499 FIH study, analyses of patients presenting with metastatic breast cancers showed promising responses. A total of 19 patients treated at 150 mg/m^2 q3w, 120 mg/m^2 q2w, 190 mg/m^2 q3w, and 90 mg/m^2 D1D8 q3w were assessed for efficacy. Among these 19 patients, 2 were TNBC, 14 HER2- (estrogen receptor [ER]+ or progesterone receptor [PgR]+), and 3 HER2+. Three patients had a confirmed PR including 1 patient with TNBC who had progressed with liver metastasis and 2 additional patients had an unconfirmed PR assessment. An ORR of 15.8% (3 PR/19) was observed in these heavily pretreated metastatic breast cancer (mBC) patients with a disease control rate (DCR)(CR+PR+SD lasting at least 3 months) in 36.8% of patients. Stable disease was observed in 12/19 (63.2%) of the patients and a tumor shrinkage was seen in 42.1% of patients.

The CA6 expression in breast cancer was evaluated in 2 independent epidemiology studies, no difference in terms of expression level was seen between the TNBC and non-TNBC populations. It was noted that 78% to 86% of the mBC express CA6 (≥1% of tumor cells) and 29% to 35% express CA6 in ≥30% of tumor cells at intensity of 2+ and/or 3+.

The RD from the FIH study was proposed at 90 mg/m^2 D1D8 q3w with an acceptable safety profile, 2 PR of 16 and 63% of patients with no progression at 12 weeks. The implementation of corneal primary prophylaxis provided encouraging results with a low incidence of keratitis, however, this needs to be confirmed in more patients. Based on the prophylaxis first results, it is proposed to assess in the first part of this study a higher dose of 120 mg/m^2 D1D8 q3w in parallel to the 90 mg/m^2 D1D8 q3w. In the dose escalation of the FIH study, 240 mg/m^2 q3w was administered to patients and was considered as the maximum administered dose with 2 dose limiting toxicities including one Grade 3 keratitis occurring at Cycle 2. According to PK simulation, the schedule of administration of 120 mg/m^2 D1D8 q3w would induce a 30% decrease in SAR566658 C_{max} compared to the 240 mg/m^2 q3w schedule, while maintaining the exposure. This would lead to a reduction in keratitis occurrence as shown for the alternative schedules in the FIH study, and might be beneficial to the patient.

The threshold of 30% CA6 2+3+ membrane staining was set up based on the assumption that penetration of the payload needs a significant level of expression of CA6. This threshold was used in the FIH study and was also planned to be used in the current Phase II study. However, it would be of interest to include patients with a lower expression of CA6 in order to establish a potential correlation between efficacy (tumor shrinkage/ORR) and CA6 expression levels. For this reason, a “mild CA6 expression cohort” of patients with a lower level of CA6 membrane staining (at least 1% positive tumor cells at intensity ≥1+ and <30% of tumor cells at intensity of 2+, 3+) is proposed in the second part of the study.

5 STUDY OBJECTIVES

5.1 PRIMARY

- To evaluate the tumor ORR, according to the Response Evaluation Criteria in Solid Tumors (RECIST) 1.1 (1) of SAR566658 in patients with CA6-positive metastatic TNBC:
  - **Part 1:** To select the SAR566658 dose based on ORR and safety of 2 dose levels of SAR566658 in patients with metastatic TNBC overexpressing CA6 (membrane intensity of 2+, 3+ in ≥30% of tumor cells),
  - **Part 2**:
    - ***Part 2a:*** To demonstrate the activity of SAR566658 based on ORR in patients with metastatic TNBC overexpressing CA6 (membrane intensity of 2+, 3+ in ≥30% of tumor cells) treated at the selected dose in an expanded cohort, in addition to the patients treated in Part 1,
    - ***Part 2b:*** To assess the efficacy of SAR566658 based on ORR in patients with metastatic TNBC and mild CA6 expression (with at least 1% positive tumor cells at intensity ≥1+ and <30% of tumor cells at intensity of 2+, 3+) treated at the selected dose in a "mild CA6 expression cohort".

5.2 SECONDARY

Part 1 and Part 2:

- To assess:
  - DCR, Duration Of Response (DOR), Progression-Free Survival (PFS), Time To Progression (TTP),
  - The impact of ocular primary prophylaxis on the incidence of keratopathies,
  - The PK profile of SAR566658,
  - The potential immunogenicity of SAR566658,
  - The relationship between CA6 expression level in the tumor, and circulating CA6 in blood at baseline, and efficacy outcomes.
- To evaluate the global safety profile.

5.3 EXPLORATORY

[redacted]

6 STUDY DESIGN

6.1 DESCRIPTION OF THE STUDY

This is an open-label, multicenter, Phase II study evaluating the efficacy and safety of SAR566658 administered as a single agent via intravenous infusion in patients with CA6-positive metastatic TNBC tumors after at least 1 prior chemotherapy regimen, but no more than 3 for advanced/metastatic disease.

CA6 expression will be assessed by IHC at a central laboratory on the most recent available tumor sample (ie, archive tumor tissue at diagnosis, archive tumor tissue at surgery, or most recent metastatic biopsy).

Prescreening, screening, and randomization of patients will be performed centrally by Interactive Voice/Web Response System (IVRS/IWRS).

The prescreening phase will correspond to the timing for the patient's tumor sample collection to allow determination of CA6 expression by central IHC.

Prior to the start of prescreening procedures in order to determine CA6 positivity, the specific prescreening informed consent must be signed by the patient and the first call to IVRS/IWRS performed. For each patient, 6 formalin-fixed paraffin embedded (FFPE) slides will be requested and collected from the most recent available tumor samples. See Section 9.3.3.1 for further details.

Patients with CA6 positivity as required by the inclusion criteria (for the relevant part of the study) must sign the specific screening informed consent. Thereafter, the screening study procedures will be started and the second call to IVRS/IWRS performed to obtain the patient registration number.

After the patient has completed the necessary baseline study procedures, a third call to IVRS/IWRS will occur to randomize or enroll eligible patients (Part 1 and Part 2), or declare a screen failure for ineligible patients.

Initiation of study treatment must be within 3 calendar days after randomization/enrollment to treatment.

The study will be performed in 2 parts.

6.1.1 Part 1

Patients with metastatic TNBC overexpressing CA6 (membrane intensity of 2+, 3+ in ≥30% of tumor cells) will be randomized to either the 90 mg/m^2 or the 120 mg/m^2 cohort, both given at Day 1 and Day 8 of each 3-week cycle. Patients randomized but not treated will be replaced. Study treatment should be initiated no later than 3 calendar days after randomization.

During treatment, safety will be monitored and the risks for predefined safety criteria (see Section 9.1.1) during the first 2 cycles will be followed and assessed using a Bayesian binomial model. In particular, risks for overdosing and unacceptable toxicity will be assessed as soon as 4 patients treated at the dose level of 120 mg/m^2 become evaluable for the predefined safety criteria.

The Bayesian model assessing the rate of predefined safety criteria will use dose as a parameter. The elicitation of the prior distribution is derived from the data collected in the FIH study (TED10499) at various dose levels and schedules of administration (190 mg/m^2 q3w, 240 mg/m^2 q3w, 90 mg/m^2 D1D8 q3w, and 120 mg/m^2 q2w).

The decision to stop 1 arm may be taken on the basis of risk of the assessed overdosing (ie, predefined safety criteria rate above 40%) and unacceptable toxicity (ie, predefined safety criteria rate above 60%). The model recommends stopping 1 arm when its overdosing risk or unacceptable toxicity risk will not be controlled at the levels of 25% and 5%, respectively.

Randomization will be centralized by IVRS/IWRS, stratified on ECOG PS (0 versus 1). Randomization will be performed when all eligibility criteria are checked and the patient is deemed eligible. Randomization will be stopped at the end of Part 1 and the recruitment will be authorized in Part 2 only when the selected dose is chosen.

The selection of the dose to be continued in Part 2 will be made at the end of Part 1 following the criteria described in Section 6.3.

6.1.2 Part 2

6.1.2.1 Part 2a

The expansion/overexpressing CA6 cohort with an additional 15 metastatic TNBC patients with CA6 overexpression (membrane intensity of 2+, 3+ in ≥30% of tumor cells) will start at the selected dose using the same selection criteria as for Part 1. If at least 7 confirmed responses (PR or CR) are seen among the 29 patients, then the null hypothesis of 12% ORR can be rejected. This test has a 1-sided type 1 error of 10% and 80% power for an alternative hypothesis of 30% response rate.

6.1.2.2 Part 2b

An additional “mild CA6 expression” cohort of 20 patients with metastatic TNBC with at least 1% positive tumor cells at CA6 membrane intensity ≥1+ and <30% of tumor cells at intensity of 2+, 3+, will be assessed at the selected dose.

6.2 DURATION OF STUDY PARTICIPATION

6.2.1 Duration of study participation for each patient

The duration of the study for each patient will include a prescreening period, a screening period of up to 21 days prior to first study drug administration, 3-week treatment cycle(s) (until 30 days after last SAR56658 administration), and a follow-up period. Each patient will be treated until radiological disease progression, unacceptable toxicity, or patient's refusal of further study treatment.

After the completion of study treatment, each patient will be followed every 6 weeks until death, study cut-off, or withdrawal of patient's consent, whichever comes first. For patients who discontinue study treatment prior to documented disease progression, date of disease progression and further anticancer treatment will be collected at the follow-up visit.

Imaging to document disease progression will take place every 6 weeks and will continue to be performed during follow-up in case of treatment discontinuation prior to documented progression.

During the follow-up period, SAEs (regardless of relationship to study treatment) and related AEs ongoing at end of treatment, as well as new AEs/SAEs related to study treatment, will be collected and followed until resolution or stabilization, where stabilization is defined as an event ongoing without any change for at least 3 months.

6.2.2 Determination of end of clinical trial (all patients)

The first cut-off date for the selection of the selected dose corresponds to the date on which all patients treated in Part 1 (whatever the dose) have had at least 4 postbaseline tumor assessments, experienced confirmed objective response, or have discontinued the study for any reason. However, if the futility criteria of 2 responders is either met or not met with certainty for both arms when all patients have had 2 postbaseline tumor assessments, experienced confirmed objective response, or discontinued the study for any reason, the first cut-off date may be done at that time instead. The recruitment will be put on hold at the time of the interim analysis until the decision regarding dose selection and the start of Part 2 has been made. The recruitment will be authorized in Part 2 only when the selected dose is chosen.

The second cut-off date for primary ORR analysis corresponds to the date on which all patients treated in Part 2a and Part 2b have had at least 4 postbaseline tumor assessments, experienced confirmed objective response, or have discontinued the study for any reason. However, if the primary criteria of 7 responders is either met or not met with certainty at the end of the Part 2a in the selected dose when all patients have had 2 postbaseline tumor assessments, experienced confirmed objective response, or discontinued the study for any reason and when all the patients of the Part 2b have had 2 postbaseline tumor assessments, experienced confirmed objective response, or discontinued the study for any reason, the second cut-off date may be done at that time instead.

If a patient continues to benefit from the treatment after the second study cut-off, the patient can continue study treatment until disease progression, unacceptable toxicity, or patient's refusal of further study treatment, and will continue to undergo all assessments as per the study flow chart.

Patients without documented disease progression but not on treatment at the second cut-off date will be followed for any ongoing AEs. In addition, imaging to document disease progression and survival status will be collected (every 6 weeks) for 6 months after the cut-off date.

6.3 INTERIM ANALYSIS

Interim analyses of efficacy, safety, and other data will be performed after 14 patients are treated at each dose level at the end of the Part 1. Further statistical details are provided in Section 11.5.

A preliminary statistical evaluation of antitumor activity by RECIST 1.1 will be done on the first 14 patients treated in each cohort; if at least 2 confirmed responses (PR or CR) in at least 1 cohort are observed then the study can continue in Part 2, if the safety profile is acceptable.

In addition to the efficacy criteria, safety criteria including the number (%) of patients experiencing an eye disorder leading to dose modification or drug discontinuation, or peripheral neuropathy, or a treatment-emergent adverse event (TEAE) leading to dose reduction or drug discontinuation, will be considered.

In case of the efficacy criteria (<2 PR or CR in 14 patients) not being reached for a given dose, then this dose will not be selected.

In case of neither dose reaching the efficacy criteria (<2 PR or CR in 14 patients), then the study will be stopped.

In case of comparable ORR and safety profiles between 90 mg/m^2 D1D8 q3w and 120 mg/m^2 D1D8 q3w, then the lower dose (90 mg/m^2 D1D8 q3w) will be chosen.

In case of a higher ORR in 120 mg/m^2 D1D8 q3w and a comparable safety profile to 90 mg/m^2 D1D8 q3w, then 120 mg/m^2 D1D8 q3w will be chosen.

In case of a higher ORR in 120 mg/m^2 D1D8 q3w and a better safety profile with 90 mg/m^2 D1D8 q3w, then the dose will be selected on the best risk/benefit.

If there are 6 responses or more in the first 14 patients treated at 1 dose, then the study could be stopped for overwhelming efficacy.

6.4 STUDY COMMITTEES

A Steering Committee including the Study Chairman, 2 main Investigators, Sponsor representatives and an ad hoc ophthalmologist expert, as needed, will be responsible for:

- Supervising the progress of the trial towards its overall objectives,
- Reviewing at regular intervals relevant information that may affect the study conduct, and,
- Reviewing the safety and efficacy including the interim analysis for ORR.

7 SELECTION OF PATIENTS

7.1 INCLUSION CRITERIA

I 01. Metastatic TNBC

I 02. Patient with measurable disease, as per RECIST 1.1 criteria (Appendix A).

I 03. Histologically documented TNBC (either at primary diagnostic or at metastatic site) that is ER-negative and PgR-negative (<1% tumor staining by IHC), and HER2 nonoverexpressing by IHC (0, 1+) or in situ hybridization-negative based on single-probe average HER2 copy number <4.0 signals/cell or dual-probe HER2/CEP17 ratio <2 with an average HER2 copy number <4.0 signals/cell as per ASCO guidelines (2).

I 04. Patients with CA6-positive disease defined as membrane intensity of 2+, 3+ in ≥30% of tumor cells (**Part 1 and Part 2a**) or with at least 1% positive tumor cells at intensity ≥1+ and <30% of tumor cells at intensity of 2+, 3+ (**Part 2b**).

I 05. Patients received at least 1 prior chemotherapy regimen but no more than 3 for advanced/metastatic disease:

a) Adjuvant/neo-adjuvant chemotherapy will be counted as a prior chemotherapy for metastatic/recurrent disease if the patient had a progression/recurrence within 6 months after completion of the treatment,

b) Prior hormonal, biologic (eg, bevacizumab) or immunotherapy, without a cytotoxic agent, are allowed and are not counted as a line of therapy,

c) A chemotherapy line in advanced/metastatic disease is an anticancer regimen that contains at least 1 cytotoxic chemotherapy agent and was discontinued due to progression. If a cytotoxic chemotherapy regimen was discontinued for a reason other than disease progression then this regimen does not count as a "prior line of chemotherapy" unless this regimen was discontinued after treatment response (CR, PR or SD) and disease progression occurred before another line of chemotherapy.

I 06. Prior anticancer therapy must have contained anthracycline (eg, doxorubicin), if not contraindicated, and a taxane (eg, docetaxel, paclitaxel) in an adjuvant/neo-adjuvant or metastatic setting.

I 07. Signed written informed consent.

7.2 EXCLUSION CRITERIA

Patients who have met all the above inclusion criteria listed in Section 7.1 will be screened for the following exclusion criteria which are sorted and numbered in the following 2 subsections:

7.2.1 Exclusion criteria related to study methodology

E 01. ECOG performance status ≥2 (Appendix B).

E 02. Patient less than 18 years old.

E 03. Any severe acute or chronic medical condition including uncontrolled diabetes mellitus, history of cardiovascular disease (congestive heart failure, severe or unstable angina pectoris, recent myocardial infraction within last 6 months, history of clinically significant active chronic obstructive pulmonary disease [COPD], or other moderate-to-severe chronic respiratory illnesses present within last 6 months), which in the Investigator's opinion, may impair the ability of the patient to participate in the study, or interfere with interpretation of study results, or make the patient unable to comply with the study procedures.

E 04. Pregnant or breast-feeding women.

E 05. Patients with reproductive potential who do not agree to use accepted and effective method of contraception during the study treatment period and for 6 months following discontinuation of study drug. The definition of "effective method of contraception" described hereafter: oral contraceptives, combined hormonal intravaginal, transdermal, intrauterine device or condoms will be based on country-specific regulatory requirements, and documented in the Informed Consent Form (Appendix C).

E 06. Adverse events (excluding alopecia and those listed in the specific exclusion criteria) from any prior anticancer therapy of Grade >1 (National Cancer Institute Common Terminology Criteria for Adverse Events [NCI CTCAE] v4.03; see Appendix D) at the time of randomization.

E 07. Wash out period of less than 3 weeks or 5 half-lives from previous antitumor chemotherapy, immunotherapy or any investigational treatment.

E 08. Patient has received wide field radiotherapy ≤4 weeks prior to starting study treatment, or limited field radiation for palliation ≤2 weeks prior to starting study treatment, or has not recovered from the side effects of such therapy.

E 09. Patient has undergone major surgery ≤3 weeks prior to starting study treatment or has not recovered from the side effects of major surgery.

E 10. History of brain metastasis (other than totally resected or previously irradiated and nonprogressive/relapsed), spinal cord compression, or carcinomatous meningitis, or new evidence of brain leptomeningeal disease.

E 11. Prior malignancy. Adequately treated basal cell or squamous cell skin or superficial (pTis, pTa, and pT1) and bladder cancer are allowed, as well as any other cancer for which treatment has been completed ≥3 years ago and from which the patient has been disease-free for ≥3 years.

E 12. Participation in another clinical trial and any concurrent treatment with any investigational drug within 30 days prior to randomization.

E 13. Prior treatment with eribulin as last therapy prior to enrollment, or prior maytansinoid treatments (DM1 or DM4 ADCs).

7.2.2 Exclusion criteria related to the current knowledge of Sanofi compound

E 14. Acquired immunodeficiency syndrome (AIDS-related illnesses) or known HIV disease requiring antiretroviral treatment.

E 15. Known active hepatitis A, B, or C infection that requires treatment.

E 16. Known intolerance to infused protein products including other monoclonal antibodies and ADCs.

E 17. Poor bone marrow reserve as defined by absolute neutrophil count (ANC) $<1.5 \times 10^9$/L or platelets $<100 \times 10^9$/L or hemoglobin <9 g/dL.

E 18. Poor organ function as defined by 1 of the following:

a) Total bilirubin >1.5 x upper limit of normal (ULN) (except patients with Gilbert's syndrome: total bilirubin ≤3.0 x ULN, with direct bilirubin ≤1.5 x ULN),

b) Aspartate aminotransferase (AST), alanine aminotransferase (ALT), or alkaline phosphatase >2.5 x ULN; except >5 x ULN in case of documented liver metastasis or alkaline phosphatase >5 x ULN in case of documented bone metastasis,

c) Serum creatinine >1.5 x ULN, except if calculated creatinine clearance ≥60 mL/min (as per Cockcroft-Gault formula; see Appendix E).

E 19. Symptomatic peripheral neuropathy Grade ≥2 (NCI CTCAE v.4.03).

E 20. Previous history of chronic corneal diseases (even if asymptomatic) or unresolved acute nonrecurrent corneal conditions.

E 21. Patients wearing contact lenses who are not willing to stop wearing them for the duration of the study.

E 22. Medical conditions requiring concomitant administration of strong CYP3A4 inhibitors, unless it can be discontinued at least 2 weeks before 1st administration of SAR566658 (see Appendix F).

E 23. Contraindications to the use of ophthalmic vasoconstrictor and/or corticosteroid as per package insert of each drug, including the following: increased intraocular pressure, prior or current glaucoma, narrow-angle glaucoma, ongoing eye infection, uncontrolled hypertension, known/suspected allergy to constituents of the preparation (such as sodium bisulfite).

8 STUDY TREATMENTS

8.1 INVESTIGATIONAL MEDICINAL PRODUCT(S)

SAR566658 is the only IMP in this study.

Table 1 - SAR566658 product characteristics

Items	Specification
Route of administration (ie, IV - infusion or bolus, SC, other)	IV
Dosage form (ie, solution, concentrate for solution for infusion, lyophilizate, suspension, emulsion, other)	Concentrate for solution for infusion
Concentration (mg/mL)	5
Dose/vial (mg)	125 mg/25 mL
Single or multi-dose use	Single use
Primary packaging (ie, vial, syringe, other)	Vial
Container definition	30 mL USP type I clear glass vials
Closure definition	ETFE (copolymer of ethylene and tetrafluoroethylene)-coated stoppers and seals with flip-off cap
Device (yes/no), description if any	No
Storage conditions	+ 2°C-8°C; protect from light

Abbreviations: IV: intravenous; SC: subcutaneous; USP: United States Pharmacopeia.

8.1.1 Pharmaceutical form

SAR566658 is supplied as a colorless to slightly yellow, 25 mL, extractable concentrate for solution for infusion of 125 mg in a 30 mL Type I glass vial.

8.1.2 Dilution and infusion method

Details for infusion rate and dilution/dose preparation depending on the patient dose and BSA are provided in the Pharmacy Manual.

8.1.3 Stability under light

In the conditions tested during the in-use stability study (infusion to patients at the latest 16 hours after infusion bag is prepared), SAR566658 was stable under light exposure at room temperature.

8.1.4 Compatible material for administration

The SAR566658 concentrate for solution for infusion has been shown to be compatible with prefilled infusion bags made of polyolefine or polyvinyl chloride (PVC; with di-(2-ethylhexyl) phthalate [DEHP]) and any peristaltic infusion pump that uses infusion tubing made of polyethylene or PVC DEHP-free, and an in-line filter of polyethersulfone.

Before allowing the use of any other plastic material for infusion bags and/or tubing, compatibility must be ensured.

8.2 DOSAGE AND SCHEDULE

Administration of IMP must be initiated no later than 3 days after randomization.

SAR566658 will be administered by IV infusion at a rate of 2.5 mg/min for 30 minutes and then increased to a maximal rate of 5 mg/min, in the absence of hypersensitivity reactions.

The exact dose and time of IMP administration (day/month/year, hour:minute) will be documented in the electronic case report form (eCRF).

There is no limitation in the number of cycles to be administered in the absence of major toxicity, disease progression, or any other discontinuation criteria as defined in Section 10.3.2.

The patient's BSA will be calculated using their height and actual body weight to allow calculation of the dose. For patients with a BSA >2.0 m^2, the dose will be calculated on the basis of 2.0 m^2 BSA.

The preferred Dubois and Dubois equation is: BSA in units of m^2 = (weight in kg)$^{0.425}$ x (height in cm)$^{0.725}$ x 0.007184.

Dose adjustment will be permitted for subsequent treatment cycles based on individual patient tolerance (see Section 8.2.3). Treatment will continue unless any of the withdrawal criteria are met, as described in Section 10.3.2.

8.2.1 Dose of IMP per administration

Part 1 (overexpressing CA6)

Patients will be randomly allocated to receive 1 of the following 2 doses in a 1:1 ratio:

- Cohort 1: 90 mg/m^2 of SAR566658 on D1 and D8 repeated every 21 days. This will constitute 1 cycle of treatment.
- Cohort 2: 120 mg/m^2 of SAR566658 on D1 and D8 repeated every 21 days. This will constitute 1 cycle of treatment.

Part 2 (expansion/overexpressing CA6 and mild CA6 expression cohorts)

SAR566658 will be administered at the dose of 90 or 120 mg/m^2 on D1 and D8 repeated every 21 days, depending on the dose selected from Part 1.

8.2.2 Premedication

Premedication with histamine H1 antagonist (diphenhydramine 50 mg or equivalent given orally approximately 1 hour before SAR566658 administration) is required for all patients.

Ocular prophylaxis

Eye drops (ie, topical artificial tears and/or hyaluronic ophthalmic gel) are strongly recommended to be instilled in each eye up to 6 times a day during the study treatment period in all patients. These eye drops should not be applied within 15 minutes (before or after) of preventive corneal toxicity drop instillation.

The potential ocular/visual toxicity could include, but is not limited to, blurred vision, dry eye, and photophobia. Curative treatment may be used as recommended by an ophthalmologist.

All patients in Part 1 and Part 2 of this study will receive corneal toxicity (keratopathy/keratitis) prophylaxis around the time of each infusion, to include:

- Vasoconstrictor (phenylephrine 2.5% ophthalmic solution or equivalent) will be administered to each eye with 1 drop prior to the start of infusion and then 1 drop every 20 minutes, with a total of 3 drops.
- Corticosteroid ophthalmic solution, ointment, or gel (such as dexamethasone 0.16% or equivalent) administered to each eye 3 times a day (morning, midday, and night), starting on the day of the infusion and for 2 days after infusion, for a total of 3 days of steroid ophthalmic therapy including Day 1 of each cycle.
- Use of cold eye mask/pad (unless patient cannot tolerate it), from start until end of infusion.

Before implementation of the preventive measures, it should be ensured that the patient has no contraindication as per labeling of the topical treatment used. Patients should be informed that they will experience blurred vision that may last up to 1 to 2 hours after application of the ocular preparations.

8.2.3 Dose modification and dose delay

Dose modification (reduction or omission) or cycle delay is planned in case of AEs. Dose modification will be made according to the worst grade toxicity observed within a cycle. Adverse events will be graded according to NCI CTCAE v4.03.

Dose may be reduced depending on the severity of the AE.

If a patient experiences several AEs and there are conflicting recommendations, the most conservative recommended dose adjustment (dose reduction/omission/delay appropriate to the most severe AE) should be followed.

8.2.3.1 Dose modification

Dose can be reduced for SAR566658 when necessary, as described in the following sections. The dose, which has been reduced due to an AE, must not be re-escalated. Up to a maximum of 2 dose

reductions will be allowed per patient. If a third dose reduction is required per the modifications below, the patient should discontinue study treatment. Dose levels for each arm in case of dose reduction are described in Table 2 below.

The patient may have the Day 8 dose omitted if an AE occurs and they have not recovered on the theoretical day of infusion. The patient will receive the next cycle after recovery from the AE, as described.

Table 2 - Dose reduction levels

	Initial dose (mg/m^2)		Dose reduction 1 (mg/m^2)		Dose reduction 2 (mg/m^2)
SAR566658	90	→	75	→	60
SAR566658	120	→	90	→	75

8.2.3.2 Treatment delay

At Day 22, a treatment delay ≥4 days should be justified (ie, to be reported in the eCRF). Study treatment may be delayed up to 2 weeks to allow recovery from acute toxicity. In case of a delay due to IMP-related AEs ≥2 weeks (except for alopecia), the patient will be withdrawn from the treatment.

The dose of SAR566658 will be modified in case of AEs. Dose modifications are summarized in Table 3.

Table 3 - Dose modifications for SAR566658

Adverse event	Grade 2	Grade 3	Grade 4
Diarrhea	Delay[a] next infusion until recovery (Grade ≤1). No dose reduction required.	On Day 8, omit the dose. On Day 22, delay[a] next infusion until recovery (Grade ≤1): - 1st episode: reduce dose by 1 dose level, - 2nd episode: reduce dose by 1 more dose level, - 3rd episode: withdraw from study treatment.	
Creatinine increase	No delay, in case of creatinine >1.5 x ULN to calculate creatinine clearance (CLcr)[b] on D21: - If ≥50 mL/min, no dose modification, - If clearance ≥30 mL/min and < 50 mL/min, reduce dose by 1 dose level, - If clearance <30 mL/min, withdraw from study treatment.		
Peripheral neuropathy	No delay. Reduce by 1 dose level.	Delay[a] next infusion until recovery (Grade ≤1): - 1st episode: reduce dose by 1 dose level, - 2nd episode: reduce dose by 1 more dose level, - 3rd episode: withdraw from study treatment.	Withdraw from study treatment.
Total bilirubin elevation	In case of bilirubin >1.5 x ULN: On Day 8, omit the dose. On Day 22, delay[a] until recovery to bilirubin ≤1.5 x ULN and then reduce by 1 dose level. If no recovery after 2 dose reductions, withdraw from study treatment.		
Transaminases elevation	On Day 8, omit the dose. On Day 22, delay[a] until recovery to AST/ALT Grade ≤1. No dose adjustment.	On Day 8, omit the dose. On Day 22, delay[a] until recovery to AST/ALT Grade ≤1: - 1st episode: reduce dose by 1 dose level, - 2nd episode: reduce dose by 1 more dose level, - 3rd episode: withdraw from study treatment.	Withdraw from study treatment.

Dose reduction levels provided in Table 2.

a A maximum of 2 weeks delay at D22, otherwise the patient will be withdrawn from study treatment.

b As per Cockcroft-Gault formula; see Appendix E.

Abbreviations: ALT: Alanine aminotransferase; AST: Aspartate aminotransferase; D: day; ULN: upper limit of normal.

8.2.3.3 Specific recommendations

8.2.3.3.1 Hypersensitivity reactions

Premedication with histamine H1 antagonist (diphenhydramine 50 mg given orally approximately 1 hour before SAR566658 administration) is required for all patients.

Infusion-related hypersensitivity reactions (NCI CTCAE v4.03 term 'allergic reaction/cytokine release syndrome/anaphylaxis' [Appendix D]) are defined as events occurring on the day of IMP infusion.

Management plans for infusion-related hypersensitivity reactions are described in Table 4.

Table 4 - Infusion-related hypersensitivity reactions and recommendations

Symptom severity (NCI CTCAE v4.03)	Intervention recommendation
Mild Grade 1 (eg, localized cutaneous reaction, pruritus, flushing, rash)	Continue SAR566658 infusion Give diphenhydramine 50 mg IV (or equivalent) and/or dexamethasone 10 mg IV
Moderate eg, Grade ≤2 nausea, headache, tachycardia, hypotension, rash, shortness of breath	Stop SAR566658 infusion Give diphenhydramine 50 mg IV (or equivalent) and/or dexamethasone 10 mg IV SAR566658 may be resumed[a] only after patient recovery (all signs and/or symptoms of infusion-related reaction disappear or return to Grade ≥1); infusion should be resumed, at half the previous infusion rate
Severe and life-threatening eg, Grade ≥3 symptomatic bronchospasm, urticaria lesions covering >30% BSA, hypotension, angioedema	Stop SAR566658 infusion Give diphenhydramine 50 mg IV (or equivalent) and/or dexamethasone 10 mg IV and/or epinephrine as needed Definitive treatment discontinuation

a SAR566658 is stable for a maximum of 16 hours in the infusion bag at room temperature. If necessary, a new infusion should be prepared with the remaining dose to be administered.

Abbreviations: BSA: body surface area; IV: intravenously; NCI CTCAE: National Cancer Institute Common Terminology Criteria for Adverse Events.

8.2.3.3.2 Corneal toxicity

The potential corneal toxicity could include, but is not limited to, blurred vision, dry eye, and photophobia. Treatment with topical steroids or other medications (such as hyaluronic acid gel) may be used as recommended by an ophthalmologist. Recent findings from ocular examinations performed to assess and follow-up patients experiencing corneal toxicity (commonly reported as "keratitis") from other DM4 immuno-conjugate drugs indicate that the primary corneal lesion induced is rather reversible, centripetal (moving from periphery towards the center upon resolution) corneal microcysts and/or deposits, and is noninflammatory in nature (5). Similar findings were observed in the SAR566658 FIH study (TED10499). Therefore, it is thought that corneal toxicity would be better described by distinguishing between keratitis and keratopathy.

Keratitis would not be limited to corneal inflammation but can be keratopathy as well. Corneal toxicity management will be applicable to both keratitis and keratopathy. The current CTCAE v4.03 is not fully adapted to eye toxicity reporting and does not include a grading tailored to keratopathy nor to asymptomatic corneal findings. The grading currently applied to keratitis is extended to keratopathy with the option to use G1 as severity grading (eg, asymptomatic corneal findings only observed on ocular examinations) to properly document corneal findings evolution up to complete recovery.

Corneal toxicity management

In case of occurrence of a corneal toxicity, the management of the keratopathy/keratitis is described below in Table 5.

Table 5 - Corneal toxicity (keratopathy/keratitis) management recommendation

Symptom severity (NCI CTCAE v4.03)[a]	Intervention recommendation
Asymptomatic keratitis (Grade 1)[a] Corneal lesions only observed on routine ocular examination and not requiring topical treatment	• Next infusion at the same dose, with or without dose delay, depending on the recommendation from the ophthalmologist (nature and extent of the lesion). • Perform the complete ocular examination, including assessment of ocular/visual symptoms, visual acuity, full ocular tests including slit lamp with fluorescein under dilatation, and Schirmer's test preferably with anesthetics, and then repeat every cycle.
Grade 2 keratitis[b] Symptomatic or requiring topical treatment (curative) or limiting instrumental activity of daily life	• Perform the complete ocular examination, including assessment of ocular/visual symptoms, visual acuity, full ocular tests including slit lamp with fluorescein under dilatation, and Schirmer's test preferably with anesthetics. Repeat the complete ocular examination on a weekly basis until resolution (asymptomatic), and then every cycle. • Start curative treatment per ophthalmologist recommendation (eg, topical steroids). • Dose delay until resolution (asymptomatic). • Continue ocular primary prophylaxis before infusion and dose reduction at the next cycle[c] • Management of study drug upon recurrence to be discussed according to grade of the event at recurrence, clinical benefit from study drug, and recommendation from the ophthalmologist.
Grade 3 keratitis[b] Decline in vision (worse than 20/40 but better than 20/200) or limiting self-care activity of daily life	• Perform the complete ocular examination, including assessment of ocular/visual symptoms, visual acuity, full ocular tests including slit lamp with fluorescein under dilatation, and Schirmer's test preferably with anesthetics. Repeat the complete ocular examination on a weekly basis until resolution (asymptomatic), and then every cycle. • Start curative treatment per ophthalmologist recommendation (eg, topical steroids. • Dose delay until resolution (asymptomatic). • Continue ocular primary prophylaxis before infusion and dose reduction at the next cycle[c] • Permanently discontinue SAR566658 upon recurrence.
Grade 4 keratitis Perforation or blindness (20/200 or worse)	• Complete ocular examination on a weekly basis until resolution (asymptomatic)[b] . • Start curative treatment per ophthalmologist recommendation. • Permanently discontinue SAR566658.

a Grading of keratitis starts at Grade 2 in NCI CTCAE v4.03. The option is to use Grade 1 as severity grading (eg, asymptomatic corneal findings only observed on ocular examinations) to properly document corneal findings evolution up to complete recovery. The same NCI CTCAE v4.03 grading is applied to keratopathy.

b When possible at the site, photographs should be taken when findings are first documented and to follow progression when relevant. Any additional relevant ocular examination can be done if indicated.

c Measure intraocular pressure by tonometry whenever clinically indicated and at end of treatment.

8.2.3.3.3 Other toxicities

If a patient experiences any other AE Grade ≥3, except fatigue, local reaction, anemia, and other toxicities that are uncomfortable but do not cause serious morbidity, dosing should be delayed until recovery to Grade ≥1, then resumed at the same or a reduced dose at the discretion of the Investigator. Up to 2 dose reductions are allowed for AEs.

8.3 BLINDING PROCEDURES

Not applicable. This is an open-label study.

8.4 METHOD OF ASSIGNING PATIENTS TO TREATMENT GROUP

The randomized treatment kit number list is generated centrally by Sanofi. The IMP is packaged in accordance with this list.

The IVRS/IWRS generates the patient randomization list and allocates the dose level in Part 1.

During the screening phase, patients with tumor CA6 positivity level as required by the inclusion criteria (as relevant for the part of the study) will be asked to sign the specific screening informed consent. Once this is done, the protocol study procedures can be started and the IVRS/IWRS called to obtain the registration number.

After the patient has completed the necessary baseline study procedures and is deemed eligible, a call to IVRS/IWRS will occur to randomize the patient to either cohort to receive 90 mg/m^2 or 120 mg/m^2 SAR566658 in a 1:1 ratio in Part 1, or to enroll the patient (Part 2). Randomization will be stratified by ECOG PS (0 versus 1) in Part 1.

The randomization will be stopped at the end of Part 1 and the recruitment will be authorized in Part 2 only when the selected dose is chosen. Randomization will not be required in Part 2.

Patients randomized or enrolled but not treated will be replaced.

8.5 PACKAGING AND LABELING

Packaging is in accordance with the administration schedule. The content of the labeling is in accordance with the local regulatory specifications and requirements.

8.6 STORAGE CONDITIONS AND SHELF LIFE

Investigators or other authorized persons (eg, pharmacists) are responsible for storing the IMP in a secure and safe place in accordance with local regulations, labeling specifications, policies, and procedures.

Control of IMP storage conditions, especially control of temperature (eg, refrigerated storage) and information on in-use stability and instructions for handling the Sanofi compound should be managed according to the rules provided by the Sponsor.

The IMP is to be stored at +2°C to +8°C (36°F to 46°F). All vials must be kept in their box until use so that vials are protected from light.

No protection from light is required for storage in the infusion bags.

Details of the storage conditions for the diluted solution are provided in the Pharmacy Manual.

8.7 RESPONSIBILITIES

The Investigator, the hospital pharmacist, or other personnel allowed to store and dispense the IMP will be responsible for ensuring that the IMP used in the clinical trial is securely maintained as specified by the Sponsor and in accordance with applicable regulatory requirements.

All IMP will be dispensed in accordance with the Investigator's prescription and it is the Investigator's responsibility to ensure that an accurate record of IMP issued and returned is maintained.

Any quality issue noticed with the receipt or use of an IMP (deficiency in condition, appearance, pertaining documentation, labeling, expiration date, etc) should be promptly notified to the Sponsor. Some deficiencies may be recorded through a complaint procedure.

A potential defect in the quality of IMP may be subject to initiation of a recall procedure by the Sponsor. In this case, the Investigator will be responsible for promptly addressing any request made by the Sponsor, in order to recall the IMP and eliminate potential hazards.

Under no circumstances will the Investigator supply IMP to a third party, allow the IMP to be used other than as directed by this clinical trial protocol, or dispose of IMP in any other manner.

8.7.1 Treatment accountability and compliance

Administration of the IMP will be supervised by the Investigator or Subinvestigator.

The person responsible for drug dispensing is required to maintain adequate records of the IMP. These records (eg, drug movement form) include the date the IMP is received from the Sponsor, dispensed for patient, and destroyed or returned to the Sponsor. Both the packaging batch number and the treatment number on the vial must be recorded on the drug accountability form.

The person responsible for IMP administration to the patient will record precisely the date and the time of the IMP administration to the patient.

8.7.2 Return and/or destruction of treatments

All used and partially used IMP will be destroyed at the study site after an accurate accountability has been performed and signed by the Investigator (or the pharmacist).

All unused IMP may be destroyed at the site or retrieved by the Sponsor. The Investigator will not destroy the unused IMP unless the Sponsor provides written authorization.

A detailed treatment log form of the destroyed and/or returned IMP will be established with the Investigator (or the pharmacist) and countersigned by the Investigator and the Monitoring Team.

8.8 CONCOMITANT MEDICATION

A concomitant medication is any treatment received by the patient concomitantly to any IMP(s).

All treatments being taken by the patient within 21 days prior to first study treatment administration and at any time during the study, in addition to the IMP, are regarded as concomitant treatments and the type, dose, and route of administration must be documented on the appropriate screen of the eCRF.

Concomitant medications should be kept to a minimum during the study. However, if these are considered necessary for the patient's welfare and are unlikely to interfere with the IMP, they may be given at the discretion of the Investigator and recorded in the eCRF:

- Palliative radiotherapy may be given for control of pain for palliative intents. The Sponsor team should be notified to obtain agreement prior to treatment if palliative radiotherapy is being considered, and prior to resuming therapy on the study. The irradiated area should be as small as possible and should never involve more than 20% of the bone marrow in any given 3-week period. In all such cases, the possibility of tumor progression should be ruled out by physical and radiological assessments of the tumor. If the only evaluable lesions are to be irradiated, the patient will stop the study treatment. The irradiated area cannot be used as a parameter for response assessment.
- Supportive treatment as medically indicated for the patient’s well-being may be prescribed at the Investigator’s discretion. Every medication or treatment taken by the patient during the trial and the reason for its administration must be recorded on the eCRF.

The following concomitant treatments are not permitted during this study:

- Concurrent treatment with other investigational drugs.
- Concurrent treatment with any other anticancer therapy not specified in the protocol, including immunotherapy, hormonal therapy, targeted therapy, or biological therapies.
- The prophylactic use of granulocyte-colony stimulating factor (G-CSF) is not allowed during study treatment. Curative treatment is allowed (eg, febrile neutropenia, neutropenic infection).
- The use of erythropoietin during the first cycle.
- Concomitant use of strong CYP3A4 inhibitors (eg, ketoconazole, itraconazole, clarithromycin, atazanavir, indinavir, nefazodone, nelfinavir, ritonavir, saquinavir, telithromycin, and voriconazole) should be avoided from 2 weeks before SAR566658 administration up to the last SAR566658 administration or last PK sampling following SAR566658 administration, whichever is the latest (see Appendix F).

The use of contact lenses will not be permitted during the study treatment period.

9 ASSESSMENT OF INVESTIGATIONAL MEDICINAL PRODUCT

9.1 PRIMARY ENDPOINTS

9.1.1 Primary safety endpoint for Part 1

- Incidence of IMP-related predefined safety criteria during Cycle 1 and Cycle 2.

Predefined safety criteria are defined at the occurrence of any following related TEAE using NCI CTCAE v4.03:

- Grade ≥3 TEAE from the System Organ Class (SOC) Eyes disorders,
- Grade ≥3 peripheral neuropathy (Preferred Term [PT]),
- Grade ≥4 TEAE.

9.1.2 Primary efficacy endpoint for Part 1 and Part 2

The primary efficacy endpoint in Part 1 and Part 2 is ORR (proportion of patients with CR or PR as best overall response [BOR]) according to RECIST 1.1 (Appendix A), assessed by the Investigator. Confirmation of objective responses will be performed by repeat tumor imaging (Computed Tomography [CT] scan, MRI) at least 4 weeks after the first radiological documentation of response.

Tumor assessments will be performed until disease progression, even if the patient has discontinued study treatment before documented disease progression, or study cut-off date, whichever comes first.

The same imaging techniques should be used from baseline to disease progression to maintain consistency. If contrast agent is used at baseline, it must be used for all subsequent evaluations. Ultrasound is not permitted for evaluation of tumor progression.

Baseline imaging evaluations are to be performed within 21 days of the first study treatment administration. A chest and abdominal CT or MRI scan, or other relevant examinations as clinically indicated, are requested.

At each time point, evaluations must consist of a chest and abdominal CT or MRI scan and any other exams as clinically indicated.

Disease progression will be determined by at least a 20% increase in the sum of diameters of target lesions, taking as reference the smallest sum on study (this includes the baseline sum if that is the smallest on study). In addition to the relative increase of 20%, the sum must also demonstrate an absolute increase of at least 5 mm. The appearance of 1 or more new lesions or an unequivocal increase in the size of nontarget lesions is also considered as progression.

In the presence of evidence suggestive of progression, such as increasing liver enzymes, declining performance status, weight loss, or increasing pain, every reasonable effort should be made to document the nature of progressive disease by appropriate imaging studies. The Investigator may remove a patient from the study treatment either for clinical progression, when it is not possible to obtain an imaging study, or for any other reason determined as in the best interest of the patient to do so; however, the rationale for this decision must be recorded in the patient's medical chart and in the eCRF.

Clear evidence of response and of progression must be documented in the patient's medical record and this data will be recorded in the eCRF.

The Investigator at the site will be responsible for the assessment and collection of the radiographic information in compliance with the schedule of evaluations presented in this protocol.

A quick reference guide to RECIST 1.1 is included in Appendix A.

9.2 SECONDARY ENDPOINTS

9.2.1 Secondary efficacy endpoints

- DCR defined as the proportion of patients with CR, PR, or SD using RECIST 1.1 lasting more than 3 months as BOR.
- DOR defined as the time from the date of the first documentation of objective tumor response (CR or PR) to the date of first radiological documentation of tumor progression using RECIST 1.1, or death (due to any cause), whichever comes first.
- PFS defined as the time interval between the date of first study treatment administration and the date of the first radiologically documented tumor progression using RECIST 1.1, or death (due to any cause), whichever comes first.
- TTP defined as the time interval from the date of first study treatment administration and the date of the first radiologically documented tumor progression using RECIST 1.1.

9.2.2 Secondary safety endpoints

- Safety profile of the study treatment in terms of AEs/SAEs/deaths and laboratory parameters:
  - Type, frequency, severity, seriousness, and relatedness of study TEAEs will be assessed according to NCI CTCAE v4.03,
  - Laboratory abnormalities will be assessed according to NCI CTCAE v4.03.
- Evaluation of keratopathies using ocular primary prophylaxis.

9.2.2.1 Adverse events

Refer to Section 10.4 to Section 10.6 for details.

9.2.2.2 Laboratory safety variables

The clinical laboratory data consist of blood analysis (including hematology, clinical chemistry, and coagulation tests). These tests will be performed by local laboratories.

Clinical laboratory values will be analyzed after conversion into standard international units. International units will be used in all listings and tables.

Laboratory abnormalities will be assessed according to the NCI CTCAE v.4.03.

9.2.2.3 Evaluation of keratopathies using corneal toxicity primary prophylaxis

Standard specific ocular tests include:

- Assessment of ocular/visual symptoms, (eg, blurred vision, photophobia, dry eye).
- Visual acuity.
- Slit lamp with fluorescein under dilatation.
- Schirmer's test preferably with anesthetics.

The schedule for ocular tests is described in the study flow chart (Section 1.2), and in Section 10.1.

Standard specific ocular evaluations are planned at baseline. The outcome of the ocular assessment should be available before the first study treatment administration. In case of any ocular findings, complete ocular tests will be repeated once weekly until resolution to Grade 1.

Although increase in intraocular pressure is not anticipated with SAR566658, tonometry will also be done because of the potential adverse effect of ocular preventive therapy on intraocular pressure. Tonometry will be performed at screening (with and without dilation), at the end of Cycle 6, at end of treatment, and when clinically indicated (without dilation).

9.2.2.4 Vital signs

Assessment of vital signs will be performed at screening, Days 8, 15, and 21 in Cycles 1 and 2, and Days 1 and 21 in subsequent cycles. The final measurements will be performed at the end of treatment visit (see flow chart in Section 1.2).

Vital signs will include blood pressure and temperature.

9.2.2.5 12-lead electrocardiogram

A 12-lead electrocardiogram (ECG) will be performed at screening, at end of treatment, and when clinically indicated (see flow chart in Section 1.2).

Electrocardiogram data will be assessed by the Investigator based on the automatic device reading. The results of the ECG evaluation will be reported as normal or abnormal.

9.3 OTHER SECONDARY ENDPOINTS

- PK parameters assessed for SAR566658, naked huDS6 (SAR404461), and unconjugated maytansinoids (DM4 and Me-DM4).
- Immunogenicity evaluation: anti-SAR566658 antibodies (antitherapeutic antibodies [ATA]).
- Relationship between response and CA6 expression in tumors by IHC at baseline.
- Relationship between response and circulating CA6 in the plasma at baseline.

9.3.1 Pharmacokinetics

Plasma PK sample collection will be performed according to a sparse sampling strategy in all treated patients.

Plasma concentrations of SAR566658, naked huDS6 (SAR404461) and unconjugated maytansinoids (DM4 and Me-DM4) will be determined and used for population PK analysis using a nonlinear mixed-effects modelling approach. Additional details of the analysis plan will be provided in a separate document. This analysis will involve an estimation of interpatient PK variability, the population PK parameters estimates, and the assessments of patho-physiologic covariate effects on clearance and possibly on volume, if warranted. Empirical Bayesian estimation of individual PK model parameters and of individual exposure parameters of interest (such as C_{max} and AUC) will also be performed. Those estimates will then be investigated as prognostic factors for clinical outcome, including safety and efficacy endpoints, if possible.

9.3.1.1 Sampling time

It is of upmost importance to collect all blood samples at the specified times and according to the specifications. Samples missed or lost for any reason should be recorded.

Actual date and time of blood sample collection must be recorded in the eCRF. The date and time of start and end of infusion must also be precisely recorded.

The planned sampling times for blood collection can be found in the PK/immunogenicity flow chart (Section 1.4).

All collected samples will be used for population PK analysis.

9.3.1.2 Pharmacokinetics handling procedure

Detailed instructions for samples preparation and shipping will be provided to the study sites in a separate Laboratory Manual and are summarized in Table 6.

Table 6 - Pharmacokinetics handling for pharmacokinetic and antitherapeutic antibody samples

Sample type	SAR566658, naked huDS6, DM4, and Me-DM4	ATA
Matrix	Plasma	Plasma
Blood sample volume	5 mL	4 mL
Anticoagulant tube type	Vacutainer blood collection tubes with lithium heparinate	
Blood handling procedures	Keep blood on ice until plasma harvest (must be within 30 min of sampling time) by centrifugation at approx. 1500 g for approx. 10 min at 4°C	
Plasma aliquot split	4 aliquots: 3 aliquots of 0.5 mL (including1 pre-acidified aliquot for DM4 and Me-DM4) and the remaining plasma in a 4th aliquot	4 aliquots: 3 aliquots of 0.5 mL and the remaining plasma in a 4th aliquot
Storage conditions	Polypropylene tubes with screw caps and frozen promptly (within 1 hour after collection of blood) at -80°C or lower	Polypropylene tubes with screw caps and frozen promptly (within 1 hour after collection of blood) at -20°C
Shipment conditions	On dry ice	

ATA: antitherapeutic antibody.

9.3.1.3 Bioanalytical method

A summary of the bioanalytical methods are presented in Table 7.

Table 7 - Summary of bioanalytical methods

Sample type	SAR566658	DM4 and Me-DM4	Naked huDS6	ATA
Matrix	Plasma	Plasma (pre-acidified)	Plasma	Plasma
Analytical technique	ELISA	LC-MS/MS	EIA with pre-immunoprecipitation on magnetic beads	ELISA-bridge
Assay volume	50.0 µL	0.1 mL	50.0 µL	100 µL
Lower limit of quantitation	500 ng/mL	0.2 ng/mL	400 ng/mL	NA
Site of bioanalysis	Covance, Harrogate, UK	Covance, Harrogate, UK	Covance, Harrogate, UK	Sanofi R&D, (Alfortville, France)
Method reference	DOH1415	DOH1433	DOH1416	DOH1328

ATA: antitherapeutic antibody; EIA: enzyme immunoassay; ELISA: enzyme-linked immunosorbent assay; LC-MS: liquid chromatography-mass spectrometry; MS: mass spectrometry; NA: not applicable.

For DM4 and Me-DM4, incurred sample reproducibility analysis will be performed on selected samples in order to assess the reliability of all sample concentration data. These analyses will be reported in addition to the final concentration data.

9.3.1.4 Pharmacokinetics parameters

Collected PK samples could be used to perform descriptive statistics and population PK analysis by non-linear mixed effects modeling (see Section 11.4.6). Main PK parameters that will be provided should include C_{max}, AUC, total clearance, distribution volume, and half-life.

9.3.2 Immunogenicity

Plasma samples will be collected for determination of anti-SAR566658 antibodies on Day 1 of each treatment cycle, at end of treatment, and during follow-up. The planned sampling times for blood collection are detailed in the PK/immunogenicity flow chart (Section 1.4).

In case of a positive result for the ATA sample at the first follow-up visit, additional ATA samples will be collected at subsequent 6-weekly follow-up visits (and thereafter every 3 months) until a negative result is obtained.

For details of sample handling procedures and bioanalytical methods, see Section 9.3.1.

9.3.3 Evaluation of biomarkers

9.3.3.1 CA6 expression in tumor formalin-fixed paraffin embedded sample by IHC

At prescreening, determination of CA6 positivity in tumors will be performed by IHC on FFPE slides collected from the most recent available tumor samples. A total of 6 FFPE tumor 4-micron sections cut from the most recent available FFPE tumor block (ie, archive tumor tissue at diagnosis, archive tumor tissue at surgery, or most recent tumor sample) will be collected and sent to a centralized laboratory for CA6 staining by muDS6-IHC and for appropriate control. Staining will be analyzed by a dedicated pathologist. Stained and unstained slides will be kept for up to 5 years from the completion of the clinical study.

Both the membrane and cytoplasmic staining will be recorded for the percent of tumor cells positive at all intensities (1+, 2+, and 3+).

9.3.3.2 Circulating CA6 in plasma at baseline

For those patients who have already entered the trial, a blood sample will be collected at baseline prior to treatment and plasma will be extracted on site. Plasma will be stored in storage at -70°C or below and transferred on a planned schedule to a centralized laboratory until their authorized transfer to a testing laboratory, where circulating CA6 levels will be determined. Circulating CA6 will be determined by a semiquantitative sandwich enzyme-linked immunosorbent assay (ELISA).

9.4 EXPLORATORY BIOMARKERS ENDPOINTS

[redacted]

[redacted]

9.5 FUTURE USE OF SAMPLES

Not all of the samples collected during this study may be required for the tests planned in this clinical trial. For subjects who have consented, the samples that are unused or left over after testing may be used for other research purposes (excluding genetic analysis) related to SAR566658 efficacy, safety, or metabolism, related to TNBC or future development of a diagnostic test, other than those defined in the present protocol.

These other research analyses will help in the understanding of either disease subtypes or drug response, or to develop and/or validate a bioassay method, or to identify new drug targets or biomarkers.

These samples will remain labeled with the same identifiers as those used during the study (ie, subject ID). They will be transferred to a Sanofi site (or a subcontractor site) which may be located outside of the country where the study is conducted. The Sponsor has included safeguards for protecting subject confidentiality and personal data (see Section 14.3 and Section 14.5).

9.6 APPROPRIATENESS OF MEASUREMENTS

Each of the efficacy and safety assessments chosen for use in this study is considered well-established and relevant in an oncology setting. In addition, suitable steps have been built into each of these assessments to ensure their reliability and accuracy, and to minimize any risks to patient safety.

10 STUDY PROCEDURES

10.1 VISIT SCHEDULE

During the course of the study, all patients entering the study must be evaluated according to the schedule outlined in the flow charts (see Section 1.2 and Section 1.4) and described below. The results of the evaluations will be recorded in the eCRF until the patients are no longer followed.

10.1.1 Prescreening

Prescreening for CA6 positivity will be performed by IHC at a central laboratory on FFPE slides collected from the most recent available tumor sample (ie, archive tumor tissue at diagnosis, archive tumor tissue at surgery, or most recent tumor sample). See Section 9.3.3.1 for further details.

A prescreening written informed consent must be signed by the patient to consent to the prescreening assessment. Patients whose tumor samples have the required CA6 positivity by IHC will be deemed eligible to proceed to the screening period.

A first call must be made to IVRS/IWRS prior to sending the slides to central laboratory.

If it is documented that the patient is CA6 positive according to the protocol definition (as relevant to the part of the study), then the patient will have to go through all other screening assessments for the determination of full eligibility.

10.1.2 Screening

Each patient with a CA6 positive tumor will be examined before the start of the study to determine their eligibility for participation.

The screening written informed consent must be signed by the patient before any protocol specific procedures are performed and IVRS/IWRS called (second call) to obtain a patient registration number.

These tests are to be performed within 21 days prior to the first study treatment administration, with the exception of physical examination, biological tests, ECG and serum pregnancy test that must be performed no more than 7 days prior to first study treatment administration. If the time between biological baseline work-up and first administration of study treatment is more than 7 days, biological tests should be done again to check that eligibility criteria are still met. If any laboratory tests are abnormal, these must be repeated within 2 days before the first study treatment administration.

The following procedures will be performed:

- **Inclusion/exclusion criteria.**
- **Demographic characteristics.**

- **Medical, surgical, and oncological history** including significant prior and concurrent illnesses, primary diagnosis, and prior antitumor therapy.
- **Physical examination** (within 7 days prior to first study treatment administration) including major body systems examination, height and weight, ECOG PS, and vital signs (temperature and blood pressure).
- **Specific complete ocular tests**: assessment of ocular/visual symptoms, visual acuity, full ocular tests including slit lamp with fluorescein under dilatation, and Schirmer's test preferably with anesthetics.
- **Tonometry** (with and without dilatation) to measure intraocular pressure.
- **Prior and concomitant medications** will be recorded from 21 days prior to first study treatment administration.
- **Adverse events** (signs and symptoms will be reported in the eCRF as AEs only if they are still present at the time of first IMP administration).
- **12-lead ECG** within 7 days prior to first study treatment administration.
- **Hematology** within 7 days prior Day 1 Cycle 1 (time between hematological work-up and Day 1 Cycle 1 should not exceed 7 days; if time exceeds 7 days, hematological work-up should be repeated to check that eligibility criteria are still met): white blood cells (WBC) with differential count, hemoglobin, and platelet count.
- **Blood chemistry and coagulation tests** within 7 days prior Day 1 Cycle 1 (time between blood chemistry and coagulation work-up and Day 1 Cycle 1 should not exceed 7 days; if time exceeds 7 days, blood chemistry and coagulation work-up should be repeated to check that eligibility criteria are still met). Electrolytes: sodium, potassium, calcium, phosphate, and chloride. Renal function: creatinine, creatinine clearance if creatinine >1.5 x ULN, BUN or urea. Liver function: AST, ALT, total bilirubin, conjugated bilirubin, and alkaline phosphatase. Others: glucose, lactate dehydrogenase (LDH), albumin, and total protein. Coagulation test: International Normalized Ratio (INR).
- **Serum pregnancy test** for women of child-bearing potential within 7 days prior the first study treatment administration.
- **Tumor assessment** within 21 days prior to first study treatment administration: (abdominal/chest) CT scan or MRI, and all other examinations as clinically indicated (eg, brain CT scan or MRI in case of clinical suspicion of central nervous system involvement) to assess all TARGET or NON TARGET lesions (measurable and nonmeasurable). CT scan/MRI will be preferred to X-ray for the purposes of efficacy assessment. To ensure comparability, the imaging should be performed using identical techniques throughout the study period (ie, CT scan or MRI, scans performed immediately following bolus contrast administration using a standard volume of contrast, the identical contrast agent, and preferably the same scanner). When available, spiral CT acquisition should be done. Slice thickness should be adapted to the anatomical area and presumed size of the lesions. Slice thickness of 5 to 8 mm should be favored rather than 10 mm, especially during spiral acquisition.

  If limitations appear in volume acquisition, it is encouraged to choose a 1.5 pitch and thin slices, rather than a 1 pitch with thick slices. A centimeter scale should appear on films.

- **Other investigations** if clinically indicated.

10.1.3 Registration for initiation of treatment

Registration will take place once the consented patient has completed all the necessary screening procedures and is deemed eligible for study entry by the Investigator or designee.

The results of the screening examinations will be recorded in each registered patient's eCRF. Source documentation to support the baseline results must be maintained in the patient's medical record.

A third call to IVRS/IWRS must be made for all patients: eligible patients will be randomized or enrolled to receive treatment and ineligible patients will be declared as screen failures (see Section 8.4).

Study treatment should begin within 3 calendar days after registration.

10.1.4 During study treatment

At Cycle 1 Day 1, the inclusion/exclusion criteria and informed consent must be rechecked before any study-specific procedure is performed. All procedures should be performed prior to study treatment administration unless specified otherwise.

The following procedures will be performed:

- **Physical examination** (Cycles 1 and 2: Days 8, 15, and 21; subsequent cycles: Days 8 and 21) including major body systems examination, body weight, ECOG PS, and vital signs (temperature and blood pressure).
- **Concomitant medications** (to be assessed continuously throughout the on-treatment period and to be recorded at every cycle).
- **Adverse events** (to be assessed continuously throughout the on-treatment period and to be recorded at every cycle).
- **Tonometry** (without dilatation) to measure intraocular pressure at the end of Cycle 6 only.
- **Hematology** will be done before each study treatment administration (-3 day window is allowed) and in case of fever or infection: WBC with differential count, hemoglobin, platelet count.
  In addition, hematology will be performed every week (Day 8 and Day 15) during the first 2 cycles (±1 day window is allowed), then during subsequent cycles at Day 8 and in case of fever or infection.
- **Blood Chemistry** will be done before each study treatment administration (-3 days window is allowed): sodium, potassium, calcium, phosphate, chloride, creatinine, creatinine clearance if creatinine >1.5 x ULN, BUN or urea, AST, ALT, total bilirubin, conjugated bilirubin, alkaline phosphatase, glucose, LDH, albumin, and total protein.
  In addition, blood chemistry (sodium, potassium, calcium, phosphate, chloride, creatinine, creatinine clearance if creatinine >1.5 x ULN, BUN or urea, AST, ALT, total bilirubin, conjugated bilirubin, alkaline phosphatase, glucose, LDH, albumin, and total protein) will be performed every week (Day 8 and Day 15) during the 2 first cycles (±1 day window is

allowed), except for BUN and chloride that will be done weekly only during the first cycle.

- **Coagulation tests** (Day 21 of each cycle): INR.
- **Serum pregnancy test** (Day 1 of each cycle from Cycle 2 onwards): for women of child-bearing potential, only in countries where it is a regulatory requirement.
- **Blood sample for circulating CA6** (Cycle 1 Day 1 only): 1 sample will be taken prior to study treatment administration.
- [redacted]
- [redacted]
- [redacted]
- **Blood sampling for PK**: as specified in PK/immunogenicity flow chart (see Section 1.4).
- **Blood sampling for ATA**: as specified in PK/immunogenicity flow chart (see Section 1.4).
- **Tumor assessment** every 6 weeks after first study treatment administration: (abdominal/chest) CT Scan or MRI, and all other exams as clinically indicated (eg, brain CT scan or MRI in case of clinical suspicion of central nervous system involvement) to assess all TARGET or NON TARGET lesions. To ensure comparability, the imaging should be performed using identical techniques throughout the study period (ie, scans performed immediately following bolus contrast administration using a standard volume of contrast, the identical contrast agent, and preferably the same scanner).

  Confirmation of objective responses will be performed by repeat tumor imaging (CT scan, MRI) at least 4 weeks after the first radiological documentation of response (see Section 9.1.2).
- **Other investigations** if clinically indicated.

10.1.5 End of treatment

All patients must continue to be observed for at least 30 days after the final dose of study treatment. The following procedures should be performed between 25 and 35 days after the last SAR566658 administration:

- **Physical examination** including major body systems examination, body weight, ECOG PS, and vital signs (temperature and blood pressure).
- **Concomitant medications.**
- **Adverse events.**
- **Tonometry** (without dilatation) to measure intraocular pressure.
- **Hematology**: WBC with differential count, hemoglobin, platelet count.

- **Blood Chemistry**: sodium, potassium, calcium, phosphate, chloride, creatinine, creatinine clearance if creatinine >1.5 x ULN, BUN or urea, AST, ALT, total bilirubin, conjugated bilirubin, alkaline phosphatase, glucose, LDH, albumin, and total protein.
- **Coagulation tests**: INR.
- **Serum pregnancy test** for women of child-bearing potential.
- **12-lead ECG.**
- [redacted]
- [redacted]
- **Blood sampling for PK**: as specified in PK/immunogenicity flow chart (see Section 1.4).
- **Blood sampling for ATA**: as specified in PK/immunogenicity flow chart (see Section 1.4).
- **Tumor assessment**: (abdominal/chest) CT scan or MRI, and all other exams as clinically indicated (eg, brain CT scan or MRI in case of clinical suspicion of central nervous system involvement) to assess all TARGET or NON TARGET lesions. To ensure comparability, the imaging should be performed using identical techniques throughout the study period (ie, scans performed immediately following bolus contrast administration using a standard volume of contrast, the identical contrast agent, and preferably the same scanner).

  Confirmation of objective responses will be performed by repeat tumor imaging (CT scan, MRI) at least 4 weeks after the first radiological documentation of response (see Section 9.1.2).
- **Other investigations** if clinically indicated.

10.1.6 Follow-up period

During the follow-up period, SAEs (regardless of relationship with study treatment) and IMP-related AEs ongoing at the end of study treatment, as well as new IMP-related AEs/SAEs, will be followed until resolution or stabilization, where stabilization is defined as an event ongoing without any change for at least 3 months. During the follow up period, patients will be followed up every 6 weeks (±1 week) until death, study cut-off, or withdrawal of patient's consent, whichever comes first. For patients who discontinue study treatment prior to documented disease progression, a tumor assessment will be performed every 6 weeks. Date of disease progression and further anticancer treatment will be collected at the follow-up visit.

The following procedures will be performed/assessed:

- **ECOG PS and body weight.**
- **Tumor assessment** (if applicable, ie, if disease progression has not yet been documented).
- **Post-study treatments**: if used to treat new or unresolved treatment-related AEs.
- **Adverse events**: any treatment-related AEs and all SAEs ongoing at the end of study treatment, and new treatment-related AEs or SAEs will be recorded until recovery, or until the event has been stabilized.
- **Further anticancer therapy**: in case a patient discontinues study treatment due to a reason other than progressive disease, further antitumor therapy will not be initiated before progression is documented.

- [redacted]
- **Blood sampling for ATA**: as specified in PK/immunogenicity flow chart (see Section 1.4).

10.1.7 Post study cut-off date

- Patients still on study treatment at the second cut-off date can continue study treatment, if clinical benefit is observed, until disease progression, unacceptable toxicity, or the patient refuses further study treatment, and will continue to undergo all assessments as per the study flow chart.
- Patients without documented disease progression but not on treatment at the second cut-off date will be followed for any ongoing AEs. In addition, imaging to document disease progression and survival status will be collected (every 6 weeks) for 6 months after the cut-off date.

10.2 DEFINITION OF SOURCE DATA

Source data includes all information in original records and certified copies of original records of clinical findings, observations, or other activities necessary for the reconstruction and evaluation of the trial. Source data are contained in source documents.

Source documents are original documents, data, and records (eg, hospital records, clinical and office charts, laboratory notes, memoranda, patient diaries or evaluation checklists, pharmacy dispensing records, recorded data from automated instruments, copies or transcripts certified after verification as being accurate and complete, microfiches, photographic negatives, microfilm or magnetic media, X-rays, patient files, and records kept at the pharmacy, at the laboratories, and at medical-technical departments) involved in the clinical study. Source documentation must be maintained to support information provided within an eCRF.

10.3 HANDLING OF PATIENT TEMPORARY OR PERMANENT TREATMENT DISCONTINUATION AND OF PATIENT STUDY DISCONTINUATION

The IMP should be continued whenever possible. In case the IMP is stopped, it should be determined whether the stop can be made temporarily; permanent IMP discontinuation should be a last resort. Any IMP discontinuation should be fully documented in the eCRF. In any case, the patient should remain in the study as long as possible.

10.3.1 Permanent treatment discontinuation with investigational medicinal product(s)

Permanent treatment discontinuation is any treatment discontinuation associated with the definitive decision from the Investigator or the patient not to re-expose the patient to the IMP at any time.

10.3.2 List of criteria for permanent treatment discontinuation

All efforts should be made to document the reason(s) for treatment discontinuation and this should be documented in the eCRF.

- The patients may withdraw from treatment if they decide to do so, at any time and irrespective of the reason, or this may be the Investigator's decision.
- IMP should be discontinued in any of the following cases:
  - Unacceptable AE not manageable by symptomatic therapy, dose delay, or dose modification (see Section 8.2.3),
  - Disease progression, as defined in Section 9.1.2,
  - Poor compliance to the study protocol,
  - Lost to follow-up,
  - Intercurrent illness that prevents further administration of study treatment.

In all cases, the reason and date of withdrawal must be recorded in the eCRF and in the patient's medical records. The patient must be followed up to establish whether the reason was an AE and, if so, this must be reported in accordance with the procedures in Section 10.4.

Any abnormal laboratory value or ECG parameter will be immediately rechecked for confirmation after 24 hours, before making a decision of permanent discontinuation of the IMP for the concerned patient.

10.3.3 Handling of patients after permanent treatment discontinuation

Patients will be followed-up according to the study procedures specified in this protocol up to the scheduled date of study completion, or up to recovery or stabilization of any AE to be followed-up as specified in this protocol, whichever comes last.

After study treatment is discontinued, an end of treatment visit should be performed and then the patient will be followed for disease progression (imaging every 6 weeks), if discontinuation occurred prior to documented progression, and for survival status (every 6 weeks) until study cut-off date.

After the permanent discontinuation of treatment, patients will be assessed using the procedure normally planned for the last dosing day with the IMP including PK and immunogenicity samples, if appropriate.

All cases of permanent treatment discontinuation should be recorded by the Investigator in the appropriate pages of the eCRF when considered as confirmed.

10.3.4 Procedure and consequence for patient withdrawal from study

The patients may withdraw from the study before study completion if they decide to do so, at any time and irrespective of the reason. Withdrawal of consent for treatment should be distinguished

from withdrawal of consent for follow-up visits and from withdrawal of consent for non-patient contact follow-up, eg, medical records check. Patients requesting withdrawal should be informed that withdrawal of consent for follow-up may jeopardize the public health value of the study.

If possible, the patients are assessed using the procedure normally planned for the end of treatment visit including PK and immunogenicity samples, if appropriate.

Patients who withdraw should be explicitly asked about the contribution of possible AEs to their decision to withdraw consent, and any AE information elicited should be documented. Preferably the patient should withdraw consent in writing and, if the patient or the patient's representative refuses or is physically unavailable, the site should document and sign the reason for the patient's failure to withdraw consent in writing.

All study withdrawals should be recorded by the Investigator in the appropriate screens of the eCRF and in the patient's medical records when considered as confirmed. In the medical record, at least the date of the withdrawal and the reason should be documented.

For patients who fail to return to the site, unless the patient withdraws consent for follow-up, the Investigator should make the best effort to recontact the patient (eg, contact patient's family or private physician, review available registries or health care databases), and to determine his/her health status, including at least his/her vital status. Attempts to contact such patients must be documented in the patient's records (eg, times and dates of attempted telephone contact, receipt for sending a registered letter).

The Statistical Analysis Plan (SAP) will specify how these patients lost to follow-up for their primary endpoints will be considered.

Patients who have withdrawn from the study cannot be rerandomized (treated) in the study. Their inclusion and treatment numbers must not be reused.

10.4 OBLIGATION OF THE INVESTIGATOR REGARDING SAFETY REPORTING

10.4.1 Definitions of adverse events

10.4.1.1 Adverse event

An **adverse event** (AE) is any untoward medical occurrence in a patient or clinical investigation patient administered a pharmaceutical product and which does not necessarily have to have a causal relationship with this treatment.

10.4.1.2 Serious adverse event

A **serious adverse event** (SAE) is any untoward medical occurrence that at any dose:

- Results in death, or,

- Is life-threatening, or,
  Note: The term "life-threatening" in the definition of "serious" refers to an event in which the patient was at risk of death at the time of the event; it does not refer to an event which hypothetically might have caused death if it were more severe.
- Requires inpatient hospitalization or prolongation of existing hospitalization, or,
- Results in persistent or significant disability/incapacity, or,
- Is a congenital anomaly/birth defect,
- Is a medically important event.
  Medical and scientific judgment should be exercised in deciding whether expedited reporting is appropriate in other situations, such as important medical events that may not be immediately life-threatening or result in death or hospitalization but may jeopardize the patient or may require medical or surgical intervention (ie, specific measures or corrective treatment) to prevent 1 of the other outcomes listed in the definition above.

Note: The following list of medically important events is intended to serve as a guideline for determining which condition has to be considered a medically important event. The list is not intended to be exhaustive:

- Intensive treatment in an emergency room or at home for:
  - Allergic bronchospasm,
  - Blood dyscrasias (ie, agranulocytosis, aplastic anemia, bone marrow aplasia, myelodysplasia, pancytopenia, etc),
  - Convulsions (seizures, epilepsy, epileptic fit, absence, etc).
- Development of drug dependence or drug abuse,
- ALT >3 x ULN + total bilirubin >2 x ULN or asymptomatic ALT increase >10 x ULN,
- Suicide attempt or any event suggestive of suicidality,
- Syncope, loss of consciousness (except if documented as a consequence of blood sampling),
- Bullous cutaneous eruptions,
- Cancers diagnosed during the study or aggravated during the study (only if judged unusual/significant by the Investigators).

10.4.1.3 Adverse event of special interest

An adverse event of special interest (AESI) is an AE (serious or nonserious) of scientific and medical concern specific to the Sponsor's product or program, for which ongoing monitoring and immediate notification by the Investigator to the Sponsor is required. Such events may require further investigation in order to characterize and understand them. Adverse events of special interest may be added, modified or removed during a study by protocol amendment.

- Pregnancy of a female subject entered in a study as well as pregnancy occurring in a female partner of a male subject entered in a study with IMP/noninvestigational medicinal product (NIMP):

Pregnancy occurring in a female patient entered in the clinical trial or in a female partner of a male patient entered in the clinical trial. It will be qualified as an SAE only if it fulfills 1 of the seriousness criteria (see Section 10.4.1.2).

- In the event of pregnancy in a female participant, IMP should be discontinued.
- Follow-up of the pregnancy in a female participant or in a female partner of a male participant is mandatory until the outcome has been determined (see Appendix C).

- Symptomatic overdose (serious or nonserious) with IMP/NIMP:
  - An overdose (accidental or intentional) with the IMP/NIMP is an event suspected by the Investigator or spontaneously notified by the patient and defined as at least twice the intended dose within the intended therapeutic interval, adjusted according to the tested drug,
  - Infusion: increase of at least 30% of the highest planned dose (eg, 120 mg/m^2) to be administered in the specified duration or if the dose is administered in less than half the recommended duration of administration,
  - Injectable administration: at least twice the dose during the planned intervals.

  Of note, asymptomatic overdose has to be reported as a standard AE.

10.4.2 General guidelines for reporting adverse events

- All AEs, regardless of seriousness or relationship to IMP/NIMP, spanning from the signature of the informed consent form until the end of the study as defined by the protocol for that patient, are to be recorded on the corresponding page(s) or screen(s) of the eCRF.
- Whenever possible, diagnosis or single syndrome should be reported instead of symptoms. The Investigator should specify the date of onset, intensity, action taken with respect to IMP, corrective treatment/therapy given, additional investigations performed, outcome, and his/her opinion as to whether there is a reasonable possibility that the AE was caused by the IMP or by the study procedure(s).
- The Investigator should take appropriate measures to follow all AEs until clinical recovery is complete and laboratory results have returned to normal, or until progression has been stabilized, or until death, in order to ensure the safety of the patients. This may imply that observations will continue beyond the last planned visit per protocol, and that additional investigations may be requested by the monitoring team up to as noticed by the Sponsor.
- When treatment is prematurely discontinued, the patient's observations will continue until the end of the study as defined by the protocol for that patient.
- Laboratory, vital signs or ECG abnormalities are to be recorded as AEs only if:
  - Leading to IMP discontinuation or modification of dosing, and/or,
  - Fulfilling a seriousness criterion, and/or,
  - Defined as an AESI.

Instructions for AE reporting are summarized in Table 8.

10.4.3 Instructions for reporting serious adverse events

In the case of occurrence of an SAE, the Investigator or any designees must immediately:

- ENTER (within 24 hours) the information related to the SAE in the appropriate screens of the eCRF; the system will automatically send a notification to the monitoring team after approval of the Investigator within the eCRF or after a standard delay.
- SEND (preferably by fax or e-mail) a photocopy of all examinations carried out and the dates on which these examinations were performed, to the representative of the monitoring team whose name, fax number, and email address appear on the clinical trial protocol. Care should be taken to ensure that the patient's identity is protected and the patient's identifiers in the clinical trial are properly mentioned on any copy of a source document provided to the Sponsor. For laboratory results, include the laboratory normal ranges.
- All further data updates should be recorded in the eCRF as appropriate, and further documentation as well as additional information (for laboratory data, concomitant medications, patient status, etc) should be sent (by fax or e-mail) to the monitoring team within 24 hours of knowledge of the SAE. In addition, every effort should be made to further document any SAE that is fatal or life-threatening within a week (7 days) of the initial notification.
- A back-up plan (using a paper CRF process) is available and should be used when the eCRF system does not work.

Any SAE brought to the attention of the Investigator at any time after the end of the study for the patient and considered by him/her to be caused by the IMP with a reasonable possibility, should be reported to the monitoring team.

10.4.4 Guidelines for reporting adverse events of special interest

For AESIs, the Sponsor must be informed immediately (ie, within 24 hours), as per SAE notification guidelines described in Section 10.4.3, even if not fulfilling a seriousness criterion, using the corresponding pages of the CRF (to be sent) or screens in the eCRF. Instructions for AE reporting are summarized in Table 8.

Table 8 - Summary of adverse event reporting instructions

Event category	Reporting timeframe	Specific events in this category	Case Report Form completion		
			AE form	Safety Complementary Form	Other specific forms
Adverse Event (non-SAE, non-AESI)	Routine	Any AE that is not SAE or AESI	Yes	No	No
Serious Adverse Event (non-AESI or AESI)	Expedited (within 24 hours)	Any AE meeting seriousness criterion per Section 10.4.1.2	Yes	Yes	No
Adverse Event of Special Interest	Expedited (within 24 hours)	Pregnancy	Yes	Yes	Yes
		Symptomatic overdose	Yes	Yes	No

10.5 OBLIGATIONS OF THE SPONSOR

During the course of the study, the Sponsor will report in an expedited manner:

- All SAEs that are both unexpected and at least reasonably related to the IMP (SUSAR), to the regulatory authorities, independent ethics committees (IECs)/institutional review boards (IRBs) as appropriate and to the Investigators.
- All SAEs that are expected and at least reasonably related to the IMPs to the regulatory authorities, according to local regulations.
- The following AESIs to those regulatory authorities who require such reporting: pregnancy, symptomatic overdose.

Adverse events that are considered expected will be specified by the reference safety information.

The Sponsor will report all safety observations made during the conduct of the trial in the clinical study report.

10.6 ADVERSE EVENTS MONITORING

All events will be managed and reported in compliance with all applicable regulations, and included in the final clinical study report.

11 STATISTICAL CONSIDERATIONS

The material of this section of the Clinical Trial Protocol is the basis for the SAP for the study which will provide accurate definitions and detailed specifications for the analyses to be performed on the data collected from this study.

11.1 DETERMINATION OF SAMPLE SIZE

It is anticipated that approximately 63 patients will be enrolled into this study.

This study is separated into 2 parts:

Part 1:

Each dose level 90 mg/m^2 D1D8 q3w and 120 mg/m^2 D1D8 q3w will include in parallel 14 patients overexpressing CA6.

Based on efficacy and safety (including predefined safety criteria), 1 dose will be selected during the interim analysis at the end of the Part 1 if the futility criteria on ORR is not met and will be continued in Part 2.

Part 2:

Part 2a: An additional 15 patients overexpressing CA6 will be treated in the expansion cohort at the selected dose.

Part 2b: In parallel, 20 patients will be treated at the selected dose in a mild CA6 expression cohort.

11.1.1 Sample size determination for Part 1 and Part 2a

The sample size calculation is based on efficacy criteria (ORR).

A 2-stage design will be used for the selected dose. It is expected that a beneficial ORR under SAR566658 is of at least 30% (H_1). An ORR of 12% (or less) will be considered as clinically non relevant (H_0). On the basis of these assumptions, 29 treated patients at the selected dose at the end of Part 2a would be necessary to reject the null response rate of 12% with a global power of 80% and a 1-sided alpha level of 10%. The calculation takes into account 1 interim analysis using a gamma (-2) beta spending function for futility analysis and a Lan-DeMets (OF) alpha spending function in a 1 sample test for a binomial proportion.

An interim analysis is planned in Part 1 after 14 patients are treated at each dose. If at least 2 responses over the first 14 patients are observed, then 15 other patients will be treated in Part 2a at the selected dose, if the safety profile is tolerable.

A total of 7 confirmed responses (CR or PR) or more out of 29 patients (14 patients from Part 1 and 15 patients from Part 2a at the selected dose) will be necessary to reject the null hypothesis at the end of the Part 2a expansion cohort.

11.1.2 Sample size determination for the mild CA6 expression cohort (Part 2b)

At the selected dose, the relationship between CA6 expression level and efficacy outcome will be assessed by adding a cohort of 20 patients with mild CA6 membrane staining (at least 1% positive tumor cells at intensity ≥1+ and <30% of tumor cells at intensity 2+, 3+).

With a sample size of 20 patients, a true response rate above 15% can be rejected with 83% confidence if we observe 0 or 1 response. Moreover, if we observe 7 responses over the 29 patients in the biomarker positive group (≥30%, 2+,3+) and ≤1 response in the mild CA6 biomarker positive group (CA6 IHC = <30% 2+,3+ and ≥1%, ≥1+), the 1-sided p-value (according to Fisher's exact test) will be around 7%, suggesting an association between biomarker status and ORR.

11.2 DISPOSITION OF PATIENTS

The number of registered patients (patients who signed the informed consent) as well as the number and percentage of patients included in the analysis populations defined in Section 11.3 will be provided.

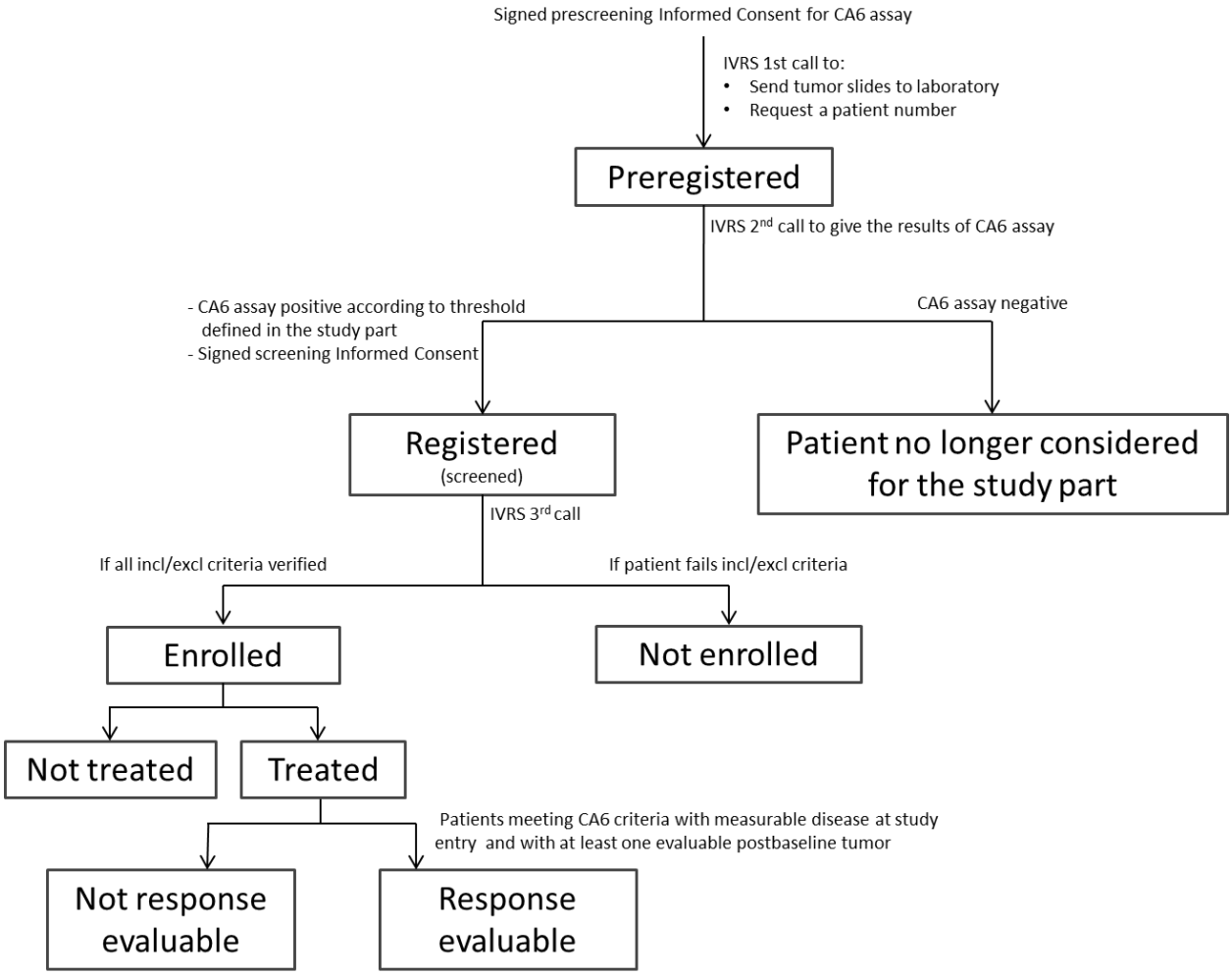
Reasons for treatment discontinuation will be summarized using the all treated/safety population.

11.3 ANALYSIS POPULATIONS

Different analysis populations are described. The main populations are described below.

An overview of the analysis populations is presented in Figure 1.

Figure 1 - Analysis population overview



11.3.1 Safety population

The all treated population consisting of patients who will actually receive at least 1 dose (or any partial) of SAR566658. This population is the primary population for the analyses of efficacy and safety parameters.

11.3.2 Evaluable for predefined selection criteria population (Part 1)

This population is only defined for Part 1.

Patients evaluable for predefined selection criteria will be defined as patients treated in the study who have completed 2 cycles or who experienced predefined safety criteria (whatever the dose received).

11.3.3 Response evaluable population

The response evaluable population will be defined as the patients of the all treated population, with measurable disease at study entry and with CA6 positivity according to the threshold defined in the relevant study part (Part 1 and Part 2a or Part 2b) and who had an evaluable response assessment during treatment (until 30 days after last SAR566658 administration). Treated patients who could not have a postbaseline tumor assessment because of early disease progression or early death due to progressive disease are also included in the response evaluable population.

Sensitivity analyses of the primary efficacy endpoint will be performed on the response evaluable population.

11.3.4 Preregistered population

The preregistered population is defined as the patients who signed the prescreening informed consent for CA6 assay assessment of their archival biopsy.

11.3.5 Registered population

The registered population is defined as the patients who concomitantly fulfill the following requirements:

- Signed screening informed consent for study participation.
- CA6 assay assessment of their archival tumor biopsy showing CA6 positivity according to the threshold defined in the relevant study part (Part 1 and Part 2a or Part 2b).

11.3.6 Enrolled population

The enrolled population includes registered patients who concomitantly have all inclusion/exclusion criteria verified. In addition, in Part 1, patients also need confirmation of a successful allocation of a randomization number through the IVRS/IWRS in order to be enrolled.

11.3.7 Pharmacokinetic population

The PK population will include all patients who received at least 1 dose of SAR566658, even if incomplete, and have data for at least 1 valid PK parameter available.

11.3.8 Evaluable population for immunogenicity

The evaluable population for immunogenicity will include all patients with at least 1 sample drawn postbaseline after study drug infusion (on-treatment period or follow-up) that is appropriate for ATA testing (patients with missing ATA at baseline will be considered evaluable).

11.4 STATISTICAL METHODS

A list of study endpoints and their definitions are provided in Section 9.

Data will be presented by dose level. Unless otherwise specified, analyses will be descriptive and performed based on the all treated population. The baseline for a given parameter is defined as the last assessment for this parameter before the first SAR566658 administration.

Continuous data will be summarized using number of available data, mean, standard deviation, median, minimum, and maximum for each dose level. Categorical and ordinal data will be summarized using number and percentage of patients in each dose level.

11.4.1 Analysis of demographic and baseline characteristics

Standard demographic and baseline characteristics, medical/surgical history, cancer history including primary tumor type and histopathology type, time from first diagnosis to first study treatment administration, prior antitumor therapy and tumor characteristics (lesions location, number and type of organs involved), assessment of CA6 expression at study entry, and laboratory parameters (including hematology, coagulation, and blood chemistry) at baseline will be described. Results of ECG evaluations will also be described.

Parameters will be summarized by dose level and overall using descriptive statistics.

11.4.2 Extent of study treatment exposure and compliance

The extent of IMP exposure and compliance will be assessed and summarized by dose level within the all treated population.

11.4.2.1 Extent of investigational medicinal product exposure

The following variables will be calculated and summarized with descriptive statistics to describe exposure to SAR566658:

- Number of cycles started and duration of exposure in weeks, defined as ([First day of last cycle – first day of first cycle + 21 days]/7).
- Cumulative dose (in mg/m^2), defined as the sum of all doses administered from first to last dose.
- Actual dose intensity, defined as the cumulative dose divided by the number of weeks on study.
- Relative dose intensity (in %), defined as the ratio of the actual dose intensity to the planned dose intensity. The relative dose intensity is an indicator of the feasibility of the chosen schedule of administration.
- Cycle delays: a dose at Day 22 (Day 1 of next cycle) is deemed to have been delayed if the study treatment is ≥4 days beyond the theoretical day of treatment.

- Dose reduction: for the second and subsequent infusions, a dose is deemed to have been reduced if the dose level a patient receives differs from the previous actual dose level. The first infusion will not be counted for a reduction.
- Infusion omission (Day 8): at a given infusion, dose omission will be considered if no drug is administered (dose=0 mg/m^2). Number of dose omissions within a cycle will be equal to the difference between expected number of infusions and number infusions actually received.
- Dose interruption: administration of SAR566658 infusion is temporarily stopped during the infusion.

Dose information variables will be assessed for each patient and summarized descriptively (N, mean, standard deviation, median, minimum, and maximum). Analyses will be performed based on the number of patients and on the number of cycles.

11.4.3 Prior/concomitant medication/therapy

The following parameters regarding prior anticancer therapy will be summarized:

- For surgery and radiotherapy: time from last procedure to first infusion.
- For chemotherapy, gene therapy, immunotherapy, hormonal therapy, targeted therapy: time from last administration to first infusion of the IMP.

Medications will be summarized by treatment group according to the World Health Organization Drug Dictionary (WHO-DD), considering the first digit of the Anatomical Therapeutic Chemical (ATC) class (anatomic category) and the first 3 digits of the ATC class (therapeutic category). All ATC codes corresponding to a medication will be summarized. Patients will be counted once in each ATC category (anatomic or therapeutic) linked to the medication.

Further treatment of interest for the analysis and given to the patient after withdrawal from IMP will be listed.

11.4.4 Analyses of efficacy endpoints

11.4.4.1 Analysis of primary efficacy endpoint(s)

The primary efficacy endpoint (refer to Section 9.1.2) is the ORR defined as the proportion of patients confirmed a CR or PR as BOR according to RECIST 1.1, relative to the total number of patients in the response evaluable population.

The ORR will be estimated and provided with its 80% CI using an exact method.

The primary efficacy analyses will be performed on the all treated population and sensitivity analyses on the response evaluable population.

11.4.4.2 Analyses of secondary efficacy endpoints

The DCR (refer to Section 9.2) will be summarized with descriptive statistics. Confidence intervals at 95% will be computed using an exact method.

The median DOR, PFS, and TTP (refer to Section 9.2) with 95% CI will be analyzed using Kaplan-Meier methods.

11.4.4.3 Analyses between CA6 expression level and efficacy endpoint

The relationship between circulating CA6 at baseline, CA6 tumor expression level by IHC at baseline (Hscore, % staining cells at intensity 2+/3+), and BOR parameters (responders versus non responders) or tumor shrinkage will be explored. Logistic regression or log-linear multivariate analyses (depending on the endpoints) might be performed.

11.4.4.4 Multiplicity considerations

No adjustment for multiplicity linked to the selection of dose will be done.

11.4.5 Analyses of safety data

All safety analyses will be performed on the all treated population.

The safety analysis will be based on the reported AEs and other safety information, such as clinical laboratory data, vital signs, and ECG (see Section 9.2.2).

11.4.5.1 Observation period

The observation period will be divided into 3 periods:

- The **screening** period is defined as the time from the signed informed consent date up to the first treatment administration.
- The **treatment** period is defined as the time from the first treatment administration to the last treatment administration +30 days.
- The **posttreatment** period is defined as the period of time starting the day after the end of the treatment period.

11.4.5.2 Predefined selection criteria

Predefined selection criteria will be summarized by dose level during the first 2 cycles, but also at subsequent cycles. Details will be provided (characteristics of predefined selection criteria) by patient (see Section 9.1.1).

11.4.5.3 Adverse events

Adverse events will be graded according to the NCI CTCAE v4.03 (and classified by SOC/PT) according to the latest available version of the Medical Dictionary for Regulatory Activities (MedDRA) dictionary.

Adverse event observation period

- Pretreatment AEs are defined as any AE reported during the screening period.
- TEAEs are AEs that developed or worsened or became serious during the treatment period.
- Posttreatment AEs are AEs that developed or worsened or became serious during the posttreatment period.

The grade will be taken into account in the summary. For patients with multiple occurrences of the same PT, the maximum grade will be used.

The primary focus of AE reporting will be the TEAEs. Posttreatment AEs will be described separately.

Treatment-emergent adverse events will be summarized with the number and percentage of patients with AEs, classified by MedDRA PT and intensity as graded by the NCI CTCAE v4.03.

Adverse event incidence tables will present the number (n) and percentage (%) of patients experiencing an AE by primary SOC, high level group term (HLGT), high level term (HLT), and PT, sorted by the SOC internationally agreed order. The other levels (HLGT, HLT, and PT) will be presented in alphabetic order.

The following TEAE summaries will be generated for the all treated population:

- Overview of TEAEs, summarizing number (%) of patients with any:
  - TEAE,
  - Grade ≥3 TEAE,
  - Grade 3 to 4 TEAE,
  - Grade 5 TEAE (any TEAE with a fatal outcome during the treatment period),
  - Serious TEAE,
  - TEAE leading to treatment discontinuation.
- In addition, an overview of Grade 5 AEs will be provided summarizing number (%) of patients with any:
  - Grade 5 AE (TEAE and posttreatment),
  - Fatal TEAE,
  - Grade 5 TEAE (TEAE with a fatal outcome during the treatment period),
  - Any grade TEAE with a fatal outcome during the posttreatment period,

- Posttreatment Grade 5 AE (excluding a TEAE that worsened to Grade 5 during the posttreatment period).

11.4.5.4 Deaths

The following summaries of deaths will be generated:

- Number (%) of patients who died by study period (screening, treatment, posttreatment) and reasons for death (disease progression, AE, or other reason).
- Deaths in nonenrolled patients or enrolled but not treated patients.
- All TEAEs leading to death by primary SOC and PT showing number (%) of patients.

11.4.5.5 Analyses of laboratory safety variables

Clinical laboratory values will be analyzed after conversion into standard international units. Clinical laboratory parameters will be graded according to the NCI CTCAE v4.03 scale, when applicable, and analyzed according to the out-of-normal laboratory range value, when the NCI CTCAE scale is not applicable.

The number of patients with abnormal laboratory tests at baseline (Grade ≥1) will be presented by grade. The frequency of patients in each grade of laboratory test during treatment will be summarized. For patients with multiple occurrences of the same laboratory variable during the on-treatment period, the maximum grade (worst) per patient will be used. The denominator used for the percentage calculation is the number of patients with at least 1 evaluation of the laboratory test during the considered observation period.

When the NCI CTCAE v4.03 scale is not applicable, the number of patients with a treatment-emergent out-of-normal laboratory range value will be displayed.

11.4.5.6 Analyses of vital signs variables

For blood pressure (systolic, diastolic), temperature, weight, and BSA, a descriptive table will be provided with the last and worst (highest and lowest) evaluations: raw data and changes from baseline.

For ECOG PS, a shift table reporting the last and worst evaluations respective to baseline will be provided.

11.4.5.7 Immunogenicity

Analyses will be performed on the evaluable population for immunogenicity.

The immunogenicity for SAR566658 will be assessed by summarizing the number and the percentage of patients with ATA positive or negative status at baseline. In addition, ATA titers will be summarized using descriptive statistics by dose level.

11.4.5.8 Analyses of other safety variables

Number (%) of patients with an ECG abnormality at baseline and/or at any postbaseline time points will be presented according to the baseline status.

11.4.6 Analyses of pharmacokinetic variables

Plasma concentrations of SAR566658, naked huDS6 (SAR404461) and unconjugated maytansinoids (DM4 and Me-DM4) will be summarized using arithmetic and geometric means, standard deviation, standard error of the mean, coefficient of variation, minimum, median, and maximum by theoretical sampling time (PXX). Allowed time windows will be specified in a separate document.

Plasma concentrations of SAR566658, naked huDS6 (SAR404461) and unconjugated maytansinoids (DM4 and Me-DM4) will be used for population PK analysis using a nonlinear mixed-effects modelling approach. Additional details of the analysis plan will be provided in a separate document. This analysis will involve an estimation of interpatient PK variability, population PK parameter estimates, and the assessments of patho-physiologic covariate effects on clearance and possibly on volume, if warranted. Empirical Bayesian estimation of individual PK model parameters and of individual exposure parameters of interest (such as C_{max} and AUC) will also be performed. Those estimates will then be investigated as prognostic factors for clinical outcome including safety and efficacy endpoints, if possible.

Previous PK data collected in other clinical studies such as TED10499, in which intensive blood sampling protocols were used, may be considered to help in model building.

Full details of the analyses of PK variables will be reported in a standalone population PK report.

11.4.7 Exploratory analyses on biomarkers

11.4.7.1 Predictive markers of response

[redacted] Analyses will be performed to explore the relationship between these markers and treatment efficacy (ORR, tumor shrinkage) in the all treated population.

Covariates as number of prior lines will be taken into consideration in interpreting the treatment efficacy observed in the all treated population.

Further analyses will be described in the SAP.

11.4.7.2 Pharmacodynamics biomarkers on posttreatment samples

[redacted]

Further analyses will be described in the SAP.

11.5 INTERIM ANALYSIS

Interim analyses of efficacy, safety, and other data will be performed after 14 patients are treated at each dose level at the end of Part 1. These interim analyses are planned to occur when all patients have completed at least 4 postbaseline tumor assessments, experienced confirmed objective response, or discontinued the study for any reason. However, if the futility criteria of 2 responders is either met or not met with certainty for both arms when all patients have completed 2 postbaseline tumor assessments, experienced confirmed objective response, or discontinued the study for any reason, the analyses may be conducted at that time instead. Enrollment will be interrupted after completion of enrollment in Part 1, until completion of the Part 1 interim analysis.

An interim analysis based on efficacy will be performed to assess futility (to reject early the hypothesis that the response rate is 30%). If there is 0 or 1 response (CR or PR) in the first 14 patients treated at each dose, the 7.1% critical boundary is not met and the alternative hypothesis of at least 30% will be rejected. If the critical boundary of 7.1% is reached (2 responses or more), the study can continue in Part 2 at the selected dose.

At the same interim analysis, overwhelming efficacy will be assessed (to reject early that the response rate is less than or equal to 12%). If there are 6 responses or more in the first 14 patients treated at 1 dose, the critical boundary of 42.9% (1-sided nominal significance level of 1.8%) is reached and the null hypothesis of 12% will be rejected.

Overall, this procedure has 80% statistical power (1-sided alpha level of 10%) to reject the null hypothesis, using a gamma (-2) beta spending function for futility analysis and a Lan-DeMets (OF) alpha spending function in a 1 sample test for a binomial proportion (East version 6.3 using exact computations, Cytel Software, Cambridge, MA).

12 ETHICAL AND REGULATORY CONSIDERATIONS

12.1 ETHICAL AND REGULATORY STANDARDS

This clinical trial will be conducted by the Sponsor, the Investigator, and delegated Investigator staff and Subinvestigator, in accordance with consensus ethics principles derived from international ethics guidelines, including the Declaration of Helsinki, and the ICH guidelines for good clinical practice (GCP), all applicable laws, rules and regulations.

This clinical trial will be recorded in a free, publicly accessible, internet-based registry, no later than 21 days after the first patient enrollment, in compliance with applicable regulatory requirements and with Sanofi public disclosure commitments.

12.2 INFORMED CONSENT

The Investigator (according to applicable regulatory requirements), or a person designated by the Investigator, and under the Investigator's responsibility, should fully inform the patient of all pertinent aspects of the clinical trial including the written information giving approval/favorable opinion by the ethics committee (IRB/IEC). All participants should be informed to the fullest extent possible about the study, in language and terms they are able to understand.

Prior to a patient's participation in the clinical trial, the written informed consent form should be signed, name filled in and personally dated by the patient or by the patient's legally acceptable representative, and by the person who conducted the informed consent discussion. A copy of the signed and dated written informed consent form will be provided to the patient.

The informed consent form used by the Investigator for obtaining the patient's informed consent must be reviewed and approved by the Sponsor prior to submission to the appropriate ethics committee (IRB/IEC) for approval/favorable opinion.

12.3 HEALTH AUTHORITIES AND INSTITUTIONAL REVIEW BOARD/INDEPENDENT ETHICS COMMITTEE (IRB/IEC)

As required by local regulation, the Investigator or the Sponsor must submit this clinical trial protocol to the health authorities (competent regulatory authority) and the appropriate IRB/IEC, and is required to forward to the respective other party a copy of the written and dated approval/favorable opinion signed by the chairman with IRB/IEC composition.

The clinical trial (study number, clinical trial protocol title, and version number), the documents reviewed (clinical trial protocol, informed consent form, Investigator's Brochure with any addenda or labeling documents [summary of product characteristics, package insert], Investigator's curriculum vitae, etc) and the date of the review should be clearly stated on the written (IRB/IEC) approval/favorable opinion.

The IMP will not be released at the study site and the Investigator will not start the study before the written and dated approval/favorable opinion is received by the Investigator and the Sponsor.

During the clinical trial, any amendment or modification to the clinical trial protocol should be submitted to the health authorities (competent regulatory authority), as required by local regulation, in addition to the IRB/IEC before implementation, unless the change is necessary to eliminate an immediate hazard to the patients, in which case the health authorities (competent regulatory authority) and the IRB/IEC should be informed as soon as possible. They should also be informed of any event likely to affect the safety of patients or the continued conduct of the clinical trial, in particular any change in safety. All updates to the Investigator's Brochure or labeling information, will be sent to the IRB/IEC and to health authorities (competent regulatory authority), as required by local regulation.

A progress report is sent to the IRB/IEC at least annually and a summary of the clinical trial's outcome at the end of the clinical trial.

13 STUDY MONITORING

13.1 RESPONSIBILITIES OF THE INVESTIGATOR(S)

The Investigator is required to ensure compliance with all procedures required by the clinical trial protocol and with all study procedures provided by the Sponsor (including security rules). The Investigator agrees to provide reliable data and all information requested by the clinical trial protocol (with the help of the eCRF, Discrepancy Resolution Form, or other appropriate instrument) in an accurate and legible manner according to the instructions provided and to ensure direct access to source documents by Sponsor representatives.

If any circuit includes transfer of data, particular attention should be paid to the confidentiality of the patient's data to be transferred.

The Investigator may appoint such other individuals as he/she may deem appropriate as Subinvestigators to assist in the conduct of the clinical trial in accordance with the clinical trial protocol. All Subinvestigators shall be appointed and listed in a timely manner. The Subinvestigators will be supervised by and work under the responsibility of the Investigator. The Investigator will provide them with a copy of the clinical trial protocol and all necessary information.

13.2 RESPONSIBILITIES OF THE SPONSOR

The Sponsor of this clinical trial is responsible to regulatory authorities for taking all reasonable steps to ensure the proper conduct of the clinical trial as regards ethics, clinical trial protocol compliance, and integrity and validity of the data recorded on the CRFs. Thus, the main duty of the monitoring team is to help the Investigator and the Sponsor maintain a high level of ethical, scientific, technical, and regulatory quality in all aspects of the clinical trial.

At regular intervals during the clinical trial, the site will be contacted, through monitoring visits, letters, or telephone calls, by a representative of the monitoring team to review study progress, Investigator and patient compliance with clinical trial protocol requirements, and any emergent problems. These monitoring visits will include, but not be limited to, review of the following aspects: patient informed consent, patient recruitment and follow-up, SAE documentation and reporting, AESI documentation and reporting, AE documentation, IMP allocation, patient compliance with the IMP regimen, IMP accountability, concomitant therapy use, and quality of data.

13.3 SOURCE DOCUMENT REQUIREMENTS

According to the ICH GCP, the monitoring team must check the eCRF entries against the source documents, except for the pre-identified source data directly recorded in the eCRF. The informed consent form will include a statement by which the patient allows the Sponsor's duly authorized personnel, the ethics committee (IRB/IEC), and the regulatory authorities to have direct access to original medical records which support the data on the CRFs (eg, patient's medical file, appointment books, original laboratory records, etc). These personnel, bound by professional secrecy, must maintain the confidentiality of all personal identity or personal medical information (according to confidentiality and personal data protection rules).

13.4 USE AND COMPLETION OF CASE REPORT FORMS (CRFS) AND ADDITIONAL REQUEST

It is the responsibility of the Investigator to maintain adequate and accurate CRFs (according to the technology used) designed by the Sponsor to record (according to Sponsor instructions) all observations and other data pertinent to the clinical investigation in a timely manner. All CRFs should be completed in their entirety in a neat, legible manner to ensure accurate interpretation of data.

Should a correction be made, the corrected information will be entered in the eCRF overwriting the initial information. An audit trail allows identifying the modification.

Data are available within the system to the Sponsor as soon as they are entered in the eCRF.

The computerized handling of the data by the Sponsor may generate additional requests (Discrepancy Resolution Form) to which the Investigator is obliged to respond by confirming or modifying the data questioned. The requests with their responses will be managed through the eCRF.

13.5 USE OF COMPUTERIZED SYSTEMS

The complete list of computerized systems used for the study is provided in a separate document which is maintained in the Sponsor and Investigator study files.

14 ADDITIONAL REQUIREMENTS

14.1 CURRICULUM VITAE

A current copy of the curriculum vitae describing the experience, qualification and training of each Investigator and Subinvestigator will be signed, dated and provided to the Sponsor prior to the beginning of the clinical trial.

14.2 RECORD RETENTION IN STUDY SITES

The Investigator must maintain confidential all study documentation, and take measures to prevent accidental or premature destruction of these documents.

The Investigator should retain the study documents for at least 15 years after the completion or discontinuation of the clinical trial.

However, applicable regulatory requirements should be taken into account in the event that a longer period is required.

The Investigator must notify the Sponsor prior to destroying any study essential documents following the clinical trial completion or discontinuation.

If the Investigator's personal situation is such that archiving can no longer be ensured by him/her, the Investigator shall inform the Sponsor and the relevant records shall be transferred to a mutually agreed upon designee.

14.3 CONFIDENTIALITY

All information disclosed or provided by the Sponsor (or any company/institution acting on their behalf), or produced during the clinical trial, including, but not limited to, the clinical trial protocol, personal data in relation to the patients, the CRFs, the Investigator's Brochure, and the results obtained during the course of the clinical trial, is confidential, prior to the publication of results. The Investigator and any person under his/her authority agree to undertake to keep confidentiality and not to disclose the information to any third party without the prior written approval of the Sponsor.

However, the submission of this clinical trial protocol and other necessary documentation to the ethics committee (IRB/IEC) is expressly permitted, the IRB/IEC members having the same obligation of confidentiality.

The Subinvestigators shall be bound by the same obligation as the Investigator. The Investigator shall inform the Subinvestigators of the confidential nature of the clinical trial.

The Investigator and the Subinvestigators shall use the information solely for the purposes of the clinical trial, to the exclusion of any use for their own or for a third party's account.

14.4 PROPERTY RIGHTS

All information, documents, and IMP provided by the Sponsor or its designee are and remain the sole property of the Sponsor.

The Investigator shall not, and shall cause the delegated Investigator staff /Subinvestigator not to, mention any information or the Product in any application for a patent or for any other intellectual property rights.

All the results, data, documents, and inventions, which arise directly or indirectly from the clinical trial in any form, shall be the immediate and exclusive property of the Sponsor.

The Sponsor may use or exploit all the results at its own discretion, without any limitation to its property right (territory, field, continuance). The Sponsor shall be under no obligation to patent, develop, market, or otherwise use the results of the clinical trial.

As the case may be, the Investigator and/or the Subinvestigators shall provide all assistance required by the Sponsor, at the Sponsor's expense, for obtaining and defending any patent, including signature of legal documents.

14.5 DATA PROTECTION

- The patient's personal data, which are included in the Sponsor database, shall be treated in compliance with all applicable laws and regulations.
- When archiving or processing personal data pertaining to the Investigator and/or to the patients, the Sponsor shall take all appropriate measures to safeguard and prevent access to this data by any unauthorized third party.
- The Sponsor also collects specific data regarding Investigators as well as personal data from any person involved in the study which may be included in the Sponsor's databases, and shall be treated by both the Sponsor and the Investigator in compliance with all applicable laws and regulations.

Subject race or ethnicity will be collected in this study for patients in the US only because these data are required by the FDA.

The data collected in this study will only be used for the purpose(s) of the study and to document the evaluation of the benefit/risk ratio, efficacy, and safety of the product(s). They may be further processed if they have been anonymized.

14.6 INSURANCE COMPENSATION

The Sponsor certifies that it has taken out a liability insurance policy covering all clinical trials under its sponsorship. This insurance policy is in accordance with local laws and requirements. The insurance of the Sponsor does not relieve the Investigator and the collaborators from any obligation to maintain their own liability insurance policy. An insurance certificate will be provided to the IECs/IRBs or regulatory authorities in countries requiring this document.

14.7 SPONSOR AUDITS AND INSPECTIONS BY REGULATORY AGENCIES

For the purpose of ensuring compliance with the clinical trial protocol, GCP, and applicable regulatory requirements, the Investigator should permit auditing by or on the behalf of the Sponsor and inspection by regulatory authorities.

The Investigator agrees to allow the auditors/inspectors to have direct access to his/her study records for review, being understood that these personnel are bound by professional secrecy, and as such will not disclose any personal identity or personal medical information.

The Investigator will make every effort to help with the performance of the audits and inspections, giving access to all necessary facilities, data, and documents.

As soon as the Investigator is notified of a planned inspection by the authorities, he will inform the Sponsor and authorize the Sponsor to participate in this inspection.

The confidentiality of the data verified and the protection of the patients should be respected during these inspections.

Any result and information arising from the inspections by the regulatory authorities will be immediately communicated by the Investigator to the Sponsor.

The Investigator shall take appropriate measures required by the Sponsor to take corrective actions for all problems found during the audit or inspections.

14.8 PREMATURE DISCONTINUATION OF THE STUDY OR PREMATURE CLOSE-OUT OF A SITE

14.8.1 By the Sponsor

The Sponsor has the right to terminate the participation of either an individual site or the study at any time, for any reason, including but not limited to the following:

- The information on the product leads to doubt as to the benefit/risk ratio.
- Patient enrollment is unsatisfactory.
- The Investigator has received from the Sponsor all IMP, means, and information necessary to perform the clinical trial and has not included any patient after a reasonable period of time mutually agreed upon.
- Noncompliance of the Investigator or Subinvestigator, delegated staff with any provision of the clinical trial protocol, and breach of the applicable laws and regulations or breach of the ICH GCP.
- The total number of patients are included earlier than expected.

In any case the Sponsor will notify the Investigator of its decision by written notice.

14.8.2 By the Investigator

The Investigator may terminate his/her participation upon thirty (30) days' prior written notice if the study site or the Investigator for any reason becomes unable to perform or complete the clinical trial.

In the event of premature discontinuation of the study or premature close-out of a site, for any reason whatsoever, the appropriate IRB/IEC and regulatory authorities should be informed according to applicable regulatory requirements.

14.9 CLINICAL TRIAL RESULTS

The Sponsor will be responsible for preparing a clinical study report and to provide a summary of study results to the Investigator.

14.10 PUBLICATIONS AND COMMUNICATIONS

The Investigator undertakes not to make any publication or release pertaining to the study and/or results of the study prior to the Sponsor's written consent, being understood that the Sponsor will not unreasonably withhold its approval.

As the study is being conducted at multiple sites, the Sponsor agrees that, consistent with scientific standards, a primary presentation or publication of the study results based on global study outcomes shall be sought. However, if no multicenter publication is submitted, underway, or planned within twelve (12) months of the completion of this study at all sites, the Investigator shall have the right to publish or present independently the results of this study in agreement with other Investigators and stakeholders. The Investigator shall provide the Sponsor with a copy of any such presentation or publication for review and comment at least 30 days in advance of any presentation or submission for publication. In addition, if requested by the Sponsor, any presentation or submission for publication shall be delayed for a limited time, not to exceed 90 days, to allow for filing of a patent application or such other justified measures as the Sponsor deems appropriate to establish and preserve its proprietary rights.

The Investigator shall not use the name(s) of the Sponsor and/or its employees in advertising or promotional material or publication without the prior written consent of the Sponsor. The Sponsor shall not use the name(s) of the Investigator and/or the collaborators in advertising or promotional material or publication without having received his/her and/or their prior written consent(s).

The Sponsor has the right at any time to publish the results of the study.

15 CLINICAL TRIAL PROTOCOL AMENDMENTS

All appendices attached hereto and referred to herein are made part of this clinical trial protocol.

The Investigator should not implement any deviation from, or changes to the clinical trial protocol without agreement by the Sponsor and prior review and documented approval/favorable opinion from the IRB/IEC and/or notification/approval of health authorities (competent regulatory authority) of an amendment, as required by local regulation, except where necessary to eliminate an immediate hazard(s) to clinical trial patients, or when the change(s) involves only logistical or administrative aspects of the trial. Any change agreed upon will be recorded in writing, the written amendment will be signed by the Investigator and by the Sponsor and the signed amendment will be filed with this clinical trial protocol.

Any amendment to the clinical trial protocol requires written approval/favorable opinion by the IRB/IEC prior to its implementation, unless there are overriding safety reasons.

In case of substantial amendment to the clinical trial protocol, approval from the health authorities (competent regulatory authority) will be sought before implementation.

In some instances, an amendment may require a change to the informed consent form. The Investigator must receive an IRB/IEC approval/favorable opinion concerning the revised informed consent form prior to implementation of the change and patient signature should be re-collected if necessary.

16 BIBLIOGRAPHIC REFERENCES

1. Eisenhauer EA, Therasse P, Bogaerts J, Schwartz LH, Sargent D, Ford R, et al. New response evaluation criteria in solid tumours: revised RECIST guideline (version 1.1). Eur J Cancer. 2009;45:228-47.

2. Wolff AC, Hammond ME, Hicks DG, Dowsett M, McShane LM, Allison KH, et al. Recommendations for human epidermal growth factor receptor 2 testing in breast cancer: American Society of Clinical Oncology/College of American Pathologists clinical practice guideline update. J Clin Oncol. 2013;31:3997-4013.

3. Swain SM. Triple-negative breast cancer: metastatic risk and role of platinum agents. Paper presented at: 44th Annual Meeting of the American Society of Clinical Oncology; May 30-June 3, 2008; Chicago, IL.

4. Trivers KF, Lund MJ, Porter PL, Liff JM, Flagg EW, Coates RJ, et al. The epidemiology of triple-negative breast cancer, including race. Cancer Causes Control. 2009;20:1071-82.

5. Eaton JS, Miller PE, Mannis MJ, Murphy CJ. Ocular adverse events associated with antibody-drug conjugates in human clinical trials. J Ocul Pharmacol Ther. 2015;31:589-604.

17 APPENDICES

Appendix A Modified Response Evaluation Criteria in Solid Tumors (RECIST 1.1)

Detailed information is provided in reference (1).

Definitions

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

Measurable:

- *Tumor lesions*: Must be accurately measured in at least 1 dimension (longest diameter in the plane of measurement is to be recorded) with a minimum size of:
  - 10 mm by CT scan (CT scan slice thickness no greater than 5 mm),
  - 10 mm caliper measurement by clinical exam (lesions which cannot be accurately measured with calipers should be recorded as non-measurable),
  - 20 mm by chest X-ray.
- *Malignant lymph nodes*: To be considered pathologically enlarged and measurable, a lymph node must be ≥15 mm in short axis when assessed by CT scan (CT scan slice thickness recommended to be no greater than 5 mm). At baseline and in follow-up, only the short axis will be measured and followed (see Special Issue 15). See also notes below on "Baseline documentation of target and non-target lesions" for information on lymph node measurement.

Non-measurable

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

Special considerations regarding lesion measurability

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

Bone lesions:

- Bone scan, PET scan, or plain films are not considered adequate imaging techniques to measure bone lesions. However, these techniques can be used to confirm the presence or disappearance of bone lesions.

- Lytic bone lesions or mixed lytic-blastic lesions, with identifiable soft tissue components, that can be evaluated by cross sectional imaging techniques such as CT or MRI can be considered as measurable lesions if the soft tissue component meets the definition of measurability described above.
- Blastic bone lesions are non-measurable.

Cystic lesions:

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

Lesions with prior local treatment:

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

Methods of measurement

- Measurement of lesions.

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

- Method of assessment.

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

  - Clinical lesions: Clinical lesions will only be considered measurable when they are superficial and 10 mm diameter as assessed using calipers (eg, skin nodules). For the case of skin lesions, documentation by color photography including a ruler to estimate the size of the lesion is suggested. As noted above, when lesions can be evaluated by both clinical exam and imaging, imaging evaluation should be undertaken since it is more objective and may also be reviewed at the end of the study,
  - Chest X-ray: Chest CT is preferred over chest X-ray, particularly when progression is an important endpoint, since CT is more sensitive than X-ray, particularly in identifying new lesions. However, lesions on chest X-ray may be considered measurable if they are clearly defined and surrounded by aerated lung,

- CT, MRI: CT is the best currently available and reproducible method to measure lesions selected for response assessment. This guideline has defined measurability of lesions on CT scan based on the assumption that CT slice thickness is 5 mm or less. When CT scans have slice thickness greater than 5 mm, the minimum size for a measurable lesion should be twice the slice thickness. MRI is also acceptable in certain situations (eg, for body scans),
- Ultrasound: Ultrasound is not useful in assessment of lesion size and should not be used as a method of measurement. Ultrasound examinations cannot be reproduced in their entirety for independent review at a later date and, because they are operator dependent, it cannot be guaranteed that the same technique and measurements will be taken from one assessment to the next. If new lesions are identified by ultrasound in the course of the study, confirmation by CT or MRI is advised. If there is concern about radiation exposure at CT, MRI may be used instead of CT in selected instances,
- Endoscopy, laparoscopy: The utilization of these techniques for objective tumor evaluation is not advised. However, they can be useful to confirm complete pathological response when biopsies are obtained or to determine relapse in trials where recurrence following complete response or surgical resection is an endpoint,
- Tumor markers: Tumor markers alone cannot be used to assess objective tumor response. If markers are initially above the upper normal limit, however, they must normalize for a patient to be considered in complete response. Specific guidelines for both CA-125 response (in recurrent ovarian cancer) and PSA response (in recurrent prostate cancer), have been published. In addition, the Gynecologic Cancer Intergroup has developed CA125 progression criteria which are to be integrated with objective tumor assessment for use in first-line trials in ovarian cancer,
- Cytology, histology: These techniques can be used to differentiate between PR and CR in rare cases if required by protocol (for example, residual lesions in tumor types such as germ cell tumors, where known residual benign tumors can remain). When effusions are known to be a potential adverse effect of treatment (eg, with certain taxane compounds or angiogenesis inhibitors), the cytological confirmation of the neoplastic origin of any effusion that appears or worsens during treatment can be considered if the measurable tumor has met criteria for response or SD in order to differentiate between response (or SD) and progressive disease,

Tumor response evaluation

To assess objective response or future progression, it is necessary to estimate the overall tumor burden at baseline and use this as a comparator for subsequent measurements. Only patients with measurable disease at baseline should be included in protocols where objective tumor response is the primary endpoint. Measurable disease is defined by the presence of at least 1 measurable lesion. In studies where the primary endpoint is tumor progression (either time to progression or proportion with progression at a fixed date), the protocol must specify if entry is restricted to those with measurable disease or whether patients having non-measurable disease only are also eligible.

For baseline documentation of target and non-target lesions in reference (1).

Response Criteria

For special notes on the assessment of target and non-target lesions in reference (1).

Table 1

Evaluation of target lesions	
Complete Response (CR):	Disappearance of all target lesions. Any pathological lymph nodes (whether target or non-target) must have reduction in short axis to <10 mm.
Partial Response (PR):	At least a 30% decrease in the sum of diameters of target lesions, taking as reference the baseline sum diameters.
Progressive Disease (PD):	At least a 20% increase in the sum of diameters of target lesions, taking as reference the smallest sum on study (this includes the baseline sum if that is the smallest on study). In addition to the relative increase of 20%, the sum must also demonstrate an absolute increase of at least 5 mm. (Note: the appearance of one or more new lesions is also considered progression).
Stable Disease (SD):	Neither sufficient shrinkage to qualify for PR nor sufficient increase to qualify for PD, taking as reference the smallest sum diameters while on study.

Table 2

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

Although a clear progression of “non target” lesions only is exceptional, in such circumstances, the opinion of the treating physician should prevail and the progression status should be confirmed later on by the review panel (or study chair).

New lesions: the appearance of new malignant lesions denotes disease progression in reference (1).

Evaluation of best overall response

See reference (1).

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

The BOR is determined once all the data for the patient is known.

Best response determination in trials where confirmation of CR or PR IS NOT required: Best response in these trials is defined as the best response across all time points (for example, a patient who has SD at first assessment, PR at second assessment, and PD on last assessment has a BOR of PR). When SD is believed to be best response, it must also meet the protocol specified minimum time from baseline. If the minimum time is not met when SD is otherwise the best time point response, the patient's best response depends on the subsequent assessments. For example, a patient who has SD at first assessment, PD at second and does not meet minimum duration for SD, will have a best response of PD. The same patient lost to follow-up after the first SD assessment would be considered inevaluable.

Best response determination in trials where confirmation of CR or PR IS required: CR or PR may be claimed only if the criteria for each are met at a subsequent time point as specified in the protocol (generally 4 weeks later). In this circumstance, the BOR can be interpreted as in Table 4.

Table 3

Target lesions	Non-target lesions	New lesions	Overall response
CR	CR	No	CR
CR	Non-CR/non-PD	No	PR
CR	Not evaluated	No	PR
PR	Non-PD or not all evaluated	No	PR
SD	Non-PD or not all evaluated	No	SD
Not all evaluated	Non PD	No	NE
PD	Any	Yes or No	PD
Any	PD	Yes or No	PD
Any	Any	Yes	PD

Table 4

Overall response First time point	Overall response Subsequent time point	Best overall response
CR	CR	CR
CR	PR	SD, PD or PR[a]
CR	SD	SD provided minimum criteria for SD duration met, otherwise, PD
CR	PD	SD provided minimum criteria for SD duration met, otherwise, PD
CR	NE	SD provided minimum criteria for SD duration met, otherwise NE
PR	CR	PR
PR	PR	PR
PR	SD	SD
PR	PD	SD provided minimum criteria for SD duration met, otherwise, PD
PR	NE	SD provided minimum criteria for SD duration met, otherwise NE
NE	NE	NE

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

Appendix B Eastern Cooperative Oncology Group Performance Status scale

ECOG Performance Status Scale

ECOG PS	0	Normal, fully functional
ECOG PS	1	Fatigue without significant decrease in daily activity
ECOG PS	2	Fatigue with significant impairment of daily activities or bed rest <50% of waking hours
ECOG PS	3	Bed rest/sitting >50% of waking hours
ECOG PS	4	Bedridden or unable to care for self

Appendix C Guidance on contraceptive methods and collection of pregnancy information

DEFINITIONS

Nonreproductive potential

1. Premenopausal female with 1 of the following:
   - Documented hysterectomy,
   - Documented bilateral salpingectomy,
   - Documented bilateral oophorectomy.
2. Postmenopausal
   - A postmenopausal state is defined as no menses for 12 months without an alternative medical cause. A high follicle stimulating hormone (FSH) level in the postmenopausal range may be used to confirm a postmenopausal state in women not using hormonal contraception or hormonal replacement therapy (HRT). However, in the absence of 12 months of amenorrhea, a single FSH measurement is insufficient.
   - Females on hormone replacement therapy (HRT) and whose menopausal status is in doubt will be required to use 1 of the highly effective contraception methods if they wish to continue their HRT during the study. Otherwise, they must discontinue HRT to allow confirmation of postmenopausal status before study enrolment.

Reproductive potential (WOCBP)

A woman is considered of reproductive potential (WOCBP), ie, fertile, following menarche and until becoming postmenopausal unless permanently sterile. Permanent sterilization methods include hysterectomy, bilateral salpingectomy and bilateral oophorectomy.

CONTRACEPTIVE GUIDANCE

Male subjects

- Male subjects with heterosexual partners of reproductive potential (WOCBP) are eligible to participate if they agree to use the following during the protocol defined timeline:
  - Refrain from donating sperm,

    and
  - At least 1 of the following conditions applies:
    - Are and agree to remain abstinent from penile-vaginal intercourse on a long term and persistent basis, when this is their preferred and usual lifestyle.

      or
    - Agree to use a male condom plus an additional contraceptive method with a failure rate of <1% per year (see table for female subjects).
- Men with a pregnant or breastfeeding partner must agree to remain abstinent from penile-vaginal intercourse or use a male condom for the time defined in the protocol

Highly Effective Contraceptive Methods That Are User Dependent

Failure rate of <1% per year when used consistently and correctly[a]

- Combined (estrogen- and progestogen-containing) hormonal contraception associated with inhibition of ovulation[b]
  - Oral,
  - Intravaginal,
  - Transdermal.

- Progestogen-only hormone contraception associated with inhibition of ovulation[b]
  - Oral,
  - Injectable.

Highly Effective Methods That Are User Independent

- Implantable progestogen-only hormone contraception associated with inhibition of ovulation[b] .

- Intrauterine device (IUD).

- Intrauterine hormone-releasing system (IUS).

- Bilateral tubal occlusion.

- Vasectomized partner.

  (Vasectomized partner is a highly effective contraceptive method provided that the partner is the sole sexual partner of the woman of childbearing potential and the absence of sperm has been confirmed. If not, an additional highly effective method(s) of contraception should be used. Spermatogenesis cycle is approximately 90 days.)

- Sexual abstinence.

  (Sexual abstinence is considered a highly effective method only if defined as refraining from heterosexual intercourse during the entire period of risk associated with the study drug. The reliability of sexual abstinence needs to be evaluated in relation to the duration of the study and the preferred and usual lifestyle of the subject.)

NOTES:

a) Typical use failure rates may differ from those when used consistently and correctly. Use should be consistent with local regulations regarding the use of contraceptive methods for subjects participating in clinical studies.

b) Hormonal contraception may be susceptible to interaction with the study drug, which may reduce the efficacy of the contraceptive method. In this case TWO highly effective methods of contraception should be used during the treatment period and for at least 6 months [corresponding to time needed to eliminate study treatment plus 30 days for study treatments with genotoxic potential] after the last dose of study treatment.

Female subjects:

Highly Effective Contraceptive Methods That Are User Dependent *Failure rate of <1% per year when used consistently and correctly*[a]
• Combined (estrogen- and progestogen-containing) hormonal contraception associated with inhibition of ovulation[b] – Oral, – Intravaginal, – Transdermal.
• Progestogen-only hormone contraception associated with inhibition of ovulation[b] – Oral, – Injectable.
Highly Effective Methods That Are User Independent
• Implantable progestogen-only hormone contraception associated with inhibition of ovulation[b].
• Intrauterine device (IUD).
• Intrauterine hormone-releasing system (IUS).
• Bilateral tubal occlusion.
• Vasectomized partner. *(Vasectomized partner is a highly effective contraceptive method provided that the partner is the sole sexual partner of the woman of childbearing potential and the absence of sperm has been confirmed. If not, an additional highly effective method(s) of contraception should be used. Spermatogenesis cycle is approximately 90 days.)*
• Sexual abstinence. *(Sexual abstinence is considered a highly effective method only if defined as refraining from heterosexual intercourse during the entire period of risk associated with the study drug. The reliability of sexual abstinence needs to be evaluated in relation to the duration of the study and the preferred and usual lifestyle of the subject.)*
NOTES: a) Typical use failure rates may differ from those when used consistently and correctly. Use should be consistent with local regulations regarding the use of contraceptive methods for subjects participating in clinical studies. b) Hormonal contraception may be susceptible to interaction with the study drug, which may reduce the efficacy of the contraceptive method. In this case TWO highly effective methods of contraception should be used during the treatment period and for at least 6 months [corresponding to time needed to eliminate study treatment plus 30 days for study treatments with genotoxic potential] after the last dose of study treatment.

COLLECTION OF PREGNANCY INFORMATION

Male subjects with partners of reproductive potential who become pregnant

- The Investigator will attempt to collect pregnancy information on any female partner of a male study subject who becomes pregnant while participating in this study. This applies only to subjects who receive study treatment.
- After obtaining the necessary signed informed consent from the pregnant female partner directly, the Investigator will record pregnancy information on the appropriate form and submit it to the Sponsor within 24 hours of learning of the partner's pregnancy.
- Partner will also be followed to determine the outcome of the pregnancy. Information on the status of the mother and child will be forwarded to the Sponsor.
- Generally, follow-up will be no longer than 6 to 8 weeks following the estimated delivery date. Any termination of the pregnancy will be reported regardless of fetal status (presence or absence of anomalies) or indication for procedure.

Female subjects who become pregnant

- The Investigator will collect pregnancy information on any female subject, who becomes pregnant while participating in this study.
- Information will be recorded on the appropriate form and submitted to the Sponsor within 24 hours of learning of a participant's pregnancy.
- Participant will be followed to determine the outcome of the pregnancy. The Investigator will collect follow-up information on participant and neonate, which will be forwarded to the Sponsor. Generally, follow-up will not be required for longer than 6 to 8 weeks beyond the estimated delivery date.
- Any termination of pregnancy will be reported, regardless of fetal status (presence or absence of anomalies) or indication for procedure.
- While pregnancy itself is not considered to be an AE or SAE, any pregnancy complication or elective termination of a pregnancy will be reported as an AE or SAE.
- A spontaneous abortion is always considered to be an SAE and will be reported as such.

Any SAE occurring as a result of a post-study pregnancy which is considered reasonably related to the study treatment by the Investigator, will be reported to the Sponsor as described in Section 10.4.3. While the Investigator is not obligated to actively seek this information in former study subjects, he or she may learn of an SAE through spontaneous reporting.

Appendix D National Cancer Institute Common Terminology Criteria for Adverse Events

Refer to NCI CTCAE v4.03 in the Study Reference Manual, or online at the following NCI website:

http://ctep.cancer.gov/reporting/ctc.html

1. Toxicity grade should reflect the most severe degree occurring during the evaluated period, not an average.

2. When 2 criteria are available for similar toxicities, the one resulting in the more severe grade should be used.

3. The evaluator must attempt to discriminate between disease/treatment and related signs/symptoms.

4. An accurate baseline prior to therapy is essential.

Appendix E Calculation of Cockcroft and Gault formula

$$\text{Creatinine clearance} = \frac{(140 - \text{age [years]} \times \text{body mass [kg]})}{\text{Plasma creatinine (mg/dL)} \times 72} \times \begin{matrix}\text{Gender correction factor} \\ \text{(male: 1.00; female: 0.85)}\end{matrix}$$

Appendix F List of strong CYP3A4 inhibitors

Any treatment known to strongly inhibit CYP3A4 activities is not allowed within 2 weeks before or during the treatment period.

List of CYP3A4 inhibitors	Precipitant therapeutic class	Victim[a] (oral, unless otherwise specified)	AUC ratio
Potent CYP3A4 inhibitors (yielding substrate AUC ratio >5)			
telaprevir[b]	Protease inhibitors	tacrolimus/midazolam	**77.98/9.0**
indinavir/RIT	Protease Inhibitors	alfentanil	**36.5**
tipranavir/RIT[c]	Protease Inhibitors	midazolam	**26.91**
ritonavir	Protease Inhibitors	midazolam	**26.41**
cobicistat (GS-9350)	None	midazolam	**19.03**
indinavir	Protease Inhibitors	vardenafil	**16.25**
ketoconazole	Antifungals	midazolam	**15.9**
troleandomycin	Antibiotics	midazolam	**14.8**
saquinavir/RIT	Protease Inhibitors	midazolam	**12.48**
itraconazole	Antifungals	midazolam	**10.8**
voriconazole	Antifungals	midazolam	**9.4**
mibefradil	Calcium Channel Blockers	midazolam	**8.86**
clarithromycin	Antibiotics	midazolam	**8.39**
lopinavir/RIT	Protease Inhibitors	aplaviroc	**7.71**
elvitegravir/RIT	Treatments of AIDS	midazolam IV	**6.8**
posaconazole	Antifungals	midazolam	**6.23**
nelfinavir	Protease Inhibitors	simvastatin	**6.07**
telithromycin	Antibiotics	midazolam	**6**
conivaptan	Diuretics	midazolam	**5.76**
nefazodone	Antidepressants	midazolam	**5.44**
boceprevir	Protease Inhibitors	midazolam	**5.3**
saquinavir	Protease Inhibitors	midazolam	**5.18**

a DDI studies with probe substrate midazolam were selected first. When no study with midazolam was available, the AUC ratio of another probe or sensitive substrate was chosen.

b Telaprevir is also an inhibitor of P-gp. Data for fold increase in tacrolimus AUC found on Washington Database and for fold increase in midazolam AUC found on Drugs.com.

c Tipranavir/ritonavir combination identified as potent CYP3A4 inhibitor in Washington Drug Interaction database www.druginteractioninfo.org but classified as weak inhibitor of CYP3A4 in vivo (AUC ratio ≥1.25 and <2).

Internal sanofi data – updated June 2013.

Abbreviations: AUC: area under the plasma concentration-time curve; DDI: drug-drug interaction; IV: intravenous; P-gp: P-glycoprotein; RIT: ritonavir

ACT14884 Amended Protocol 01

ELECTRONIC SIGNATURES

Signed by	Meaning of Signature	Server Date (dd-MMM-yyyy HH:mm)
[redacted]	Regulatory Approval	16-Dec-2016 16:40 GMT+0100
[redacted]	Clinical Approval	16-Dec-2016 17:50 GMT+0100
[redacted]	Clinical Approval	19-Dec-2016 19:12 GMT+0100