CLINICAL STUDY PROTOCOL
Protocol CDI-CS-003

Version 7.0
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BAL101553

An open-label Phase 1/2a study of BAL101553 administered as intravenous 48-hour infusions in adult patients with advanced solid tumors or recurrent glioblastoma

PROTOCOL APPROVAL	
Protocol Number/Version:	CDI-CS-003 (SAKK number: SAKK 67/15) / 7.0
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Function:	**Name:**
Project Physician	[redacted]
Coordinating Investigator	[redacted]
Clinical Pharmacologist	[redacted]
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Sponsor:	Basilea Pharmaceutica International Ltd Grenzacherstrasse 487 CH-4058 Basel/Switzerland; Tel + 41 61 606 1111

SIGNATURE PAGE

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Compound:	BAL101553	
Phase of development:	Phase 1/2a	
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Project Physician	[redacted]	[redacted]
Coordinating Investigator	[redacted]	[redacted] 05/10/18
Clinical Pharmacologist	[redacted]	09-OCT-2018 [redacted]
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PROTOCOL SYNOPSIS

TITLE

An open-label Phase 1/2a study of BAL101553 administered as intravenous 48-hour infusions in adult patients with advanced solid tumors or recurrent glioblastoma

SPONSOR

Basilea Pharmaceutica International Ltd, Switzerland

STUDY PHASE

Phase 1/2a

OBJECTIVES

The primary objectives of this study are to determine the maximum tolerated dose (MTD) and to characterize dose-limiting toxicities (DLTs) of BAL101553, administered as an intravenous (IV) infusion over 48 hours on study Days 1, 8 and 15 of a 28-day treatment cycle, to adults with advanced or recurrent solid tumors who have failed standard therapy or for whom no effective standard therapy is available.

Secondary objectives:

- To evaluate the safety and tolerability of BAL101553 administered as a 48-hour continuous IV infusion.
- To assess the antitumor activity of BAL101553 administered as a 48-hour continuous IV infusion.
- To assess the pharmacokinetics (PK) of BAL101553 and BAL27862 after 48-hour IV infusion; and after daily oral administration on study Days 15–21 of Cycle 2 (Phase 1 only).

Exploratory objectives:

- To assess the use of biomarkers to characterize the pharmacodynamic (PD) effects of BAL101553, administered as a 48-hour continuous IV infusion.
- To explore the potential utility of biomarkers in blood and/or tumor tissue as predictive biomarkers.

STUDY DESIGN

Single-agent, open-label, multi-center, Phase 1/2a study in two parts:

1. a Phase 1 dose-escalation portion using a 3+3 titration design to determine the MTD in solid-tumor patients; and
2. a Phase 2a expansion portion to further characterize safety and tolerability of BAL101553 at the MTD (70 mg/m^2) and obtain efficacy data in patients with platinum-resistant/refractory ovarian cancer or recurrent glioblastoma (GBM).

PLANNED NUMBER OF PATIENTS

- Dose-escalation portion: planned up to 42 evaluable patients, completed with 16 patients evaluable for MTD assessment (20 patients dosed).
- Expansion portion: up to 40 evaluable patients.

NUMBER OF CENTERS/LOCATIONS

- Dose-escalation portion: three study centers
- Expansion portion: approximately ten study centers

INCLUSION CRITERIA

Patients meeting all of the following inclusion criteria at screening will be eligible for enrollment in the study. Informed consent must be obtained within the 28 days prior to the start of treatment. Screening evaluations will be performed within the 15 days prior to the start of treatment (within 21 to 28 days for radiology assessments).

Patients meeting **all** of the following:

1. Age 18 years or older.
2. Patients who have:
   a. Phase 1: Histologically- or cytologically-confirmed advanced or recurrent solid tumor, who failed standard therapy or for whom no effective standard therapy is available.
      - Patients with brain metastases must have undergone definitive treatment (surgery and/or radiation) at least 3 months prior to starting study drug and be documented as having stable disease by imaging.

   b. Phase 2a:
      i. Histologically-confirmed ovarian, fallopian tube or primary peritoneal cancer (collectively referred to herein as 'ovarian cancer') that is either platinum-resistant (disease progression within 6 months of the last receipt of platinum-based chemotherapy) or refractory (lack of response or disease progression while receiving the most recent platinum-based therapy).
         - Patients may have received up to four lines of prior cytotoxic chemotherapy, but none of them in the platinum-resistant/refractory setting. Confirmed high-grade serous, endometrioid, or carcinosarcoma histotypes are permitted.
         - An archived fixed-frozen paraffin-embedded tumor tissue block, or a minimum of 15 slides from such a block, must be available, otherwise a new tumor biopsy should be obtained in accordance with local institutional practices.
         - Patients must have at least one site of measurable disease as defined by RECIST criteria, and no clinical or radiological evidence of bowel obstruction.
         - Patients with brain metastases must have undergone definitive treatment (surgery and/or radiation) at least 3 months prior to starting study drug and be documented as having stable disease by imaging.

      ii. Histologically-confirmed glioblastoma (GBM) in first relapse, defined as: progression following initial therapy, i.e., radiation, chemotherapy, or radiation + chemotherapy, with or without prior surgery.
         - Patients being treated with steroids must be on a stable or decreasing dose.

3. Patients with advanced solid tumors (excluding GBM) must have measurable disease (according to Response Evaluation Criteria in Solid Tumors [RECIST] v1.1), documented within the 28 days prior to study-drug administration.
   Patients with GBM must have measurable disease, defined by contrast-enhancing magnetic resonance imaging (MRI), performed within 21 days prior to study-drug administration.
4. Life expectancy of ≥ 12 weeks.
5. Acceptable organ and marrow function documented within 15 days prior to starting study drug, defined as follows:
   - Absolute neutrophil count ≥ 1.5×10^9/L.
   - Platelets ≥ 100×10^9/L.
   - Hemoglobin ≥ 9 g/dL.
   - Total bilirubin ≤ 1.5 × institutional upper limit of normal (ULN), unless the patient has known Gilbert's syndrome.
   - Aspartate amino transferase (AST) and alanine amino transferase (ALT) ≤ 2.5 × institutional ULN or ≤ 5 × ULN in presence of liver metastasis.
   - Serum creatinine ≤ 1.5 × institutional ULN, or creatinine clearance ≥ 60 mL/min by Cockcroft-Gault formula.
   - Serum sodium ≥ the institutional lower limit of normal (LLN).

6. Patients (excluding those with GBM) must have an Eastern Cooperative Oncology Group (ECOG) performance status ≤ 1, and those with GBM must have an ECOG performance status ≤ 2.
7. Female patients who are not pregnant or breast-feeding and meet one of the following conditions:
   - Postmenopausal for at least 1 year.
   - Post-hysterectomy and/or post-bilateral ovariectomy.
   - Women of childbearing potential must have a negative serum human chorionic gonadotropin (hCG) pregnancy test result and must use highly effective contraceptive methods for the duration of the study and for an additional 90 days after the last dose of study drug. Highly effective contraceptive methods include male or female sterilization (bilateral tubal occlusion or vasectomy); intrauterine device (IUD); or combined (estrogen and progesterone containing) hormonal contraception (oral, vaginal ring or transdermal patch) with an ethinylestradiol dose of at least 30 µg, plus use of male condoms (preferably with spermicides), female condoms, a female diaphragm or a cervical cap.
8. Male patients must agree not to donate sperm from the first dose of study drug until 90 days after the last dose of study drug. Male patients, without a vasectomy and with a partner of childbearing potential, must agree to use condoms during the study and for at least 90 days after the last dose of study drug. The patient should be instructed that their female partner should use another form of contraception for the duration of the study and continue this use for at least 90 days after the last dose of study drug.
9. Signed, written informed consent must be obtained and documented according to the International Conference on Harmonization's Guideline for Good Clinical Practice E6 (ICH-GCP) [1], the local regulatory requirements, and the permission to use private health information in accordance with the Health Insurance Portability and Accountability Act (HIPAA), where required, before performing any study-specific screening procedures.
10. Patients must have an implantable venous access system ('PORT') at the time of screening or must be willing to have a venous access system implanted for the purpose of the study. Patients with an existing PORT will be eligible for the study if the PORT chamber is made of titanium and the cathether is made of either silicon or polyurethane. If a patient has an exisiting PORT made of any other material, their eligibility may be approved by the Sponsor, based on the availability of compatibility data.

EXCLUSION CRITERIA

Patients meeting any of the following exclusion criteria at screening must not be enrolled in the study:

1. Patients with advanced or recurrent solid tumors (excluding GBM) who:
   - Have received chemotherapy, radiotherapy, immunotherapy, or investigational agents within the 4 weeks (2 weeks for single fraction of palliative radiotherapy, 6 weeks for nitrosoureas or mitomycin C) prior to starting study drug; or
   - Have not recovered to ≤ Common Terminology Criteria for Adverse Events version 4.03 (CTCAE) grade 1 from all side effects of prior therapies, except for residual toxicities such as alopecia, which do not pose an ongoing medical risk.

   Patients with prostate cancer must have discontinued anti-androgens (e.g., bicalutamide, nilutamide) for at least 6 weeks prior to starting study drug; chemical castration with luteinizing hormone-releasing hormone analogues can be continued.

   Patients with GBM who:
   - Have received radiotherapy within 12 weeks prior to starting study drug, unless there is a new area of enhancement consistent with recurrent disease outside of the radiation field, or there is histological confirmation of unequivocal tumor progression; or
   - Have received administration of prior antitumor chemotherapy within the 4 weeks prior to starting study drug, or within the 6 weeks prior to starting study drug in the case of nitrosoureas; or
   - Have undergone surgical resection within 4 weeks prior to starting study drug, or a stereotactic biopsy/core biopsy within 1 week prior to starting study drug; or
   - Have been treated previously with bevacizumab.
2. Patients who have had prior exposure to BAL101553.
3. Inability to swallow oral medication (Phase 1).

4. Patients with gastrointestinal disease or those who have had a procedure that is expected to interfere with the oral absorption or tolerance of BAL101553 (e.g., functionally relevant gastrointestinal obstruction, or frequent vomiting) (Phase 1).
5. Symptomatic brain metastases or metastatic leptomeningeal disease, indicative of active disease
6. Peripheral neuropathy ≥ CTCAE grade 2.
7. Known human immunodeficiency virus (HIV) infection.
8. Known acute or chronic hepatitis B or hepatitis C infection.
9. Average triple systolic blood pressure (SBP) ≥ 140 mmHg or average triple diastolic blood pressure (DBP) ≥ 90 mmHg at the Screening visit. Patients with an initial BP ≥ 140/90 mmHg may be included if SBP < 140 mmHg and DBP < 90 mmHg is confirmed in two subsequent BP measurements on the same day.
10. Blood pressure (BP) combination treatment with more than two antihypertensive medications.
11. Any history of cerebral hemorrhage, cerebral aneurysm, or ischemic stroke; or a history of transient ischemic attack within 24 months prior to screening.

    Acute or subacute intratumoral hemorrhage in patients with GBM, considered by the Investigator to be clinically significant.
    - Patients with MRI or computed tomography (CT) demonstrating old hemorrhage, or a subacute bleed after a neurosurgical procedure (biopsy or resection), will be eligible.
12. Significant cardiac disease or abnormality, including any one of the following:
    - Left ventricular ejection fraction < 50% at screening (assessed by echocardiography).
    - QTcF > 470 ms on screening electrocardiogram (ECG) or a clinically relevant ECG abnormality.
    - Congenital long QT syndrome.
    - History of sustained ventricular tachycardia, ventricular fibrillation or torsades de pointes.
    - Presence of atrial fibrillation with tachyarrhythmia (ventricular response rate > 100 bpm).
    - Bradycardia (heart rate < 50 bpm).
    - Complete left bundle branch block.
    - Bifascicular block (complete right bundle branch block and anterior or posterior left hemiblock).
    - Myocardial infarction, acute coronary syndrome (including unstable angina), coronary revascularization procedures, or coronary arterial bypass grafting within 6 months prior to starting study drug.
    - Cardiac troponin (either troponin T or troponin I) above the institutional ULN.
    - Congestive heart failure of New York Heart Association class III or IV.
13. Uncontrolled intercurrent illness that would unduly increase the risk of toxicity or limit compliance with study requirements in the opinion of the Investigator; including but not limited to: ongoing or active symptomatic infection, uncontrolled diabetes mellitus, unstable or uncompensated cardiac, hepatic, renal, respiratory, or psychiatric illness.
14. Current anticoagulation with warfarin potassium or other coumarin derivates. Heparin/low-molecular weight heparin (at prophylaxis or treatment doses), aspirin or other oral platelet inhibitors are permitted.
15. Women who are pregnant or breast-feeding. Men or women of reproductive potential who are not willing to apply effective birth control during the study and for at least 90 days after the last dose of study drug in both sexes.

INVESTIGATIONAL PRODUCT

BAL101553 as a powder for concentrate for solution for infusion.
BAL101553 hard capsules for daily oral administration.

DOSE / ROUTE / REGIMEN

BAL101553 will be given as a 48-hour continuous infusion using a Baxter elastomeric pump (pump models 2C4711K or 2C1009KP/2C4009K) that will be connected to an implantable venous access system ('PORT') on study Days 1, 8 and 15 of each 28-day treatment cycle until disease progression, unacceptable toxicity, or another reason for withdrawal from study drug occurs (see Section 4.4). In Phase 1, during Cycle 2 only, the Day 15 IV dose will be replaced by 7 days of oral BAL101553 capsules. There will be no oral dosing in Phase 2a.

Administration

Intravenous infusion on study Days 1, 8 and 15 of each 28-day treatment cycle, with the exception of study Days 15–21 of Cycle 2, during which time patients will be administered daily oral BAL101553 (Phase 1 only).

Starting dose

In Cohort 1, the starting dose for IV BAL101553, administered as a 48-hour continuous infusion on study Days 1, 8 and 15 of each 28-day treatment cycle, is 30 mg/m^2; the starting dose for oral BAL101553, administered as daily capsules on study Days 15–21 of Cycle 2, is 8 mg per day. The cumulative weekly-oral dose for subsequent dose levels will be calculated based on PK modeling to approximate the weekly-IV dose or exposure.

Dose-escalation portion (Phase 1) of the study:

Dose escalation will be performed using a 3+3 titration design (see Table 1 and Section 3.1.2). The starting doses of 30 mg/m^2 IV and 8 mg/day oral BAL101553 are based on the clinical experience and safety data from study CDI-CS-001 in patients with advanced solid tumors administered BAL101553 via a 2-hour infusion and from study CDI-CS-002 in patients with advanced solid tumors administered BAL101553 as daily oral capsules.

Dose cohorts will comprise three patients. If a DLT is observed in any of these patients, the dose level will be expanded to include a second cohort of [up to] three patients. Dose increments between dose levels, ranging from approximately 33–50%, will be based on the extent and severity of observed drug toxicity.

On study Days 15–21 of Cycle 2, patients will receive oral BAL101553 capsules in place of the Day 15 infusion to assess the bioavailability of daily oral BAL101553.

DLT will be defined as any one of the following events, assessed by the Investigator as being BAL101553 study-treatment-related and graded according to CTCAE, during the first 28-day treatment cycle:

- Grade 4 neutropenia (absolute neutrophil count [ANC] < 0.5 × 10^9/L) lasting for ≥ 5 consecutive days.
- Febrile neutropenia (ANC < 1.0 × 10^9/L and single temperature of > 38.3°C, or a sustained temperature of ≥ 38.0°C for > 1 h).
- Grade 4 thrombocytopenia (platelet count < 25 × 10^9/L), or grade 3 thrombocytopenia (platelet count < 50 × 10^9/L) with bleeding.
- Any other ≥ grade 4 hematological AE.
- ≥ Grade 3 nausea, vomiting, or diarrhea despite appropriate pre-medication and/or management.
- Grade 3 AST or ALT elevations (> 5–20 × ULN) for > 7 days, or grade 4 (> 20 × ULN) for any duration.
- Grade 3 QTc interval prolongation (QTcF > 500 ms or > 60 ms change from baseline).
- Hypertension-related DLT:
  - Grade 4 hypertension (CTCAE).
  - Any recording of SBP > 220 mmHg or DBP > 110 mmHg.
  - At least one observation of SBP ≥ 160 mmHg or DBP ≥ 100 mmHg that does not resolve to SBP < 160 mmHg and DBP < 100 mmHg within 24 hours, despite antihypertensive treatment.

  Note: The need for administration of new antihypertensive medication or modification to more intensive antihypertensive medication will not be considered a DLT.
- Any study-treatment-related AE which leads to missing both the Day 8 and Day 15 doses in Cycle 1, or that causes a delay in the start of Cycle 2 by more than 14 days.
- Any other study-treatment-related AEs which, in the view of the Investigator and/or Sponsor, represent a clinically significant hazard to the patient.
- Any other ≥ grade 3 non-hematological study-treatment-related AE.

Note: The following study-treatment-related AEs will not be considered DLT unless considered to present a clinically significant hazard to the patient:

- Grade 3 fatigue.
- Grade 3 or 4 elevations in alkaline phosphatase.
- Grade 3 or 4 hypophosphatemia.
- Grade 4 lymphopenia.

There will be a minimum period of observation of 28 days between the first dose of the last patient treated at that dose level, to the first dose of the first patient treated at the next dose level. Additionally, a delay of at least 7 days must be implemented between the first dose of the first and second patients at the same dose level. No delay is required between the second patient and any subsequent patient enrolled at the same dose level. As a delay in the start of the second cycle by more than 14 days due to a drug-related AE is considered a DLT, no patient will be permitted to be enrolled at a new dose level until all patients in the current dose group have initiated treatment Cycle 2, or have discontinued the study for reasons other than drug-related toxicity.

Decisions to escalate dose levels and determination of the MTD will be made by a Dose-Cohort Escalation Committee, as summarized below:

- If no DLTs are observed during Cycle 1 at a given dose level, escalation to the next dose level will proceed. If one DLT is observed during Cycle 1 at a given dose level, that dose level will be expanded to include a second cohort of [up to] three patients; escalation to the next dose level will proceed only if DLTs are observed in < 33% of patients (i.e., one of six patients). If DLTs are observed in ≥ 33% of patients (i.e., ≥ two patients) at a given dose level, that dose will be defined as the maximum administered dose (MAD) and dose escalation will be stopped. Additional, intermediate dose levels between the MAD and the next lower dose level may be explored, at the discretion of the Dose-Cohort Escalation Committee (see Section 3.2.1).
- The MTD is defined as the highest dose level below the MAD with an acceptable tolerability profile. Dose escalation and MTD determination will be primarily based on the occurrence of DLTs during Cycle 1, however, will also include a clinical review of all relevant available data from the current and previous dose levels. At least six patients must be treated at the MTD dose level in the dose-escalation portion of this study.
- Dosing of any new patient may only be started after approval by the Sponsor. All study centers must notify the Sponsor when a patient is screened, is scheduled for dosing and after administration of the first dose.

Recommendations for dose delays or dose modifications in patients experiencing BAL101553 related toxicities are summarized below:

- In patients who experience a DLT, dosing may only be resumed after recovery to ≤ CTCAE grade 1, or baseline, and subsequent doses of BAL101553 will be reduced by one dose level, or by half if this occurs at the starting dose level (i.e. to 15 mg/m^2). A maximum of two dose reductions per patient will be allowed and the dose may not be re-escalated. Non-DLT events may also require dose delay or dose reduction (see Section 3.2.3 and Table 4).
- Patients who experience a drug-related AE which leads to missing both the Day 8 and 15 doses within any 28-day cycle, or which delays the start of the subsequent cycle by more than 14 days, should be discontinued from the study. Such events will be considered a DLT if they occur during Cycle 1.

Intra-patient dose escalation, including multiple subsequent increases of dose levels, may be allowed in patients who have stable disease or response and did not experience drug-related AEs ≥ CTCAE grade 2 during their most recent treatment cycle; if all patients in the next-higher dose level have completed their first treatment cycle with acceptable tolerability; and if a decision has been taken to start dosing at the subsequent higher dose level. Dose increases will be at the discretion of the Investigator, after discussion with the Sponsor and review of available safety data for all patients. Dose increases will only occur at the start of a subsequent cycle (i.e., Day 1 of the next treatment cycle) for an eligible patient. Any DLTs experienced by patients after intra-patient dose escalation will not count in the calculation of DLT incidence for the corresponding dose level.

Expansion portion (Phase 2a) of the study:

In December 2017, the MTD was defined as 70 mg/m^2; up to 40 additional evaluable patients will be enrolled at this dose to further evaluate the safety and tolerability, pharmacodynamic effects and antitumor activity of BAL101553. There will be two separate target populations, each with up to 20 evaluable patients: the first will comprise ovarian cancer patients; and the second will comprise GBM patients. For each target population, a separate cumulative safety evaluation will be performed after six patients have completed their first 28-day cycle or have discontinued treatment, and after completion of the first cycle, or discontinuation, by each subsequent group of six patients.

DURATION OF PATIENT PARTICIPATION

Patients with an objective response or stable disease may continue to receive BAL101553 until disease progression, unacceptable toxicity, or another discontinuation criterion is met.

Discontinuation of treatment will be recorded and reasons may include:

- Disease progression.
- Adverse event (AE).
- Abnormal laboratory value.
- Abnormal test procedure result.
- Missing both the Day 8 and Day 15 doses within any 28-day cycle, or causing a delay of more than 14 days in the start of a subsequent cycle, due to toxicity.
- Requirement for more than two dose level reductions in a patient due to AEs.
- Intercurrent illness that prevents further administration of treatment.
- Withdrawal of consent.
- Withdrawn from the study at Investigator discretion.
- Protocol violation
- Protocol non-compliance.
- Lost to follow-up.
- New cancer treatment/therapy.
- Administrative reasons.
- Death

ASSESSMENTS

A detailed study visit and assessment schedule is provided in Table 5 (Phase 1) and Table 6 (Phase 2a) (Section 5.1).

Patients who provide informed consent will undergo screening evaluations to determine eligibility. Informed consent must be obtained within the 28 days prior to the first administration of study drug. Screening assessments will be initiated and completed within the 15 days prior to the first dose of study drug (except for radiology assessments, which may be obtained within 28 days [excluding GBM patients] or 21 days [GBM patients] prior to the first dose of study-drug administration).

Safety / tolerability

The severity of AEs will be described using the CTCAE criteria. Safety evaluations will include analysis of AEs, laboratory assessments (hematology, biochemistry, cardiac troponin, coagulation, urinalysis), pregnancy testing in women of childbearing potential, ECG, transthoracic echocardiography, chest X-ray/CT/MRI, vital signs, ECOG performance status, physical examination, and evaluation of concomitant medications.

Pharmacokinetics

Phase 1: PK variables calculated from rich plasma concentration data using noncompartmental analysis for BAL101553 (if applicable) and for BAL27862 will comprise: C_{max}, T_{max}, $AUC_{0-\tau}$, AUC_{0-last}, $AUC_{0-\infty}$, $t_{½}$, systemic clearance and volume of distribution.

Phase 2a: Plasma concentrations will be presented as tabulated lists according to the PK schedule.

Efficacy

In patients with advanced or recurrent solid tumors (excluding GBM), evaluation of disease progression and response in patients with measurable disease will be assessed clinically and/or by RECIST v1.1 criteria. For GBM patients, evaluation of disease progression and response will be assessed based on the Response Assessment in Neuro-Oncology (RANO) criteria.

Biomarker analysis

- Filter cards for dried-blood-spot analysis of single nucleotide polymorphisms, genes involved in drug transport or drug metabolism, and/or potential biomarkers.
- Archival tumor blocks (collected from all patients when available).
- Tumor biopsies (if patient is willing to undergo biopsy; excluding GBM patients).

- Circulating tumor cells [CTCs] from blood.
  - Collection of CTCs will be performed in at least two study centers with a goal to obtain samples from at least 50% of patients in Phase 1 and 50% of ovarian-cancer patients in Phase 2a.
- Malignant pleurocentesis or paracentesis fluid (when available during routine clinical course) will be analyzed.

STATISTICAL ANALYSIS

Analysis populations

- The full analysis population (FAP) will include patients who receive at least one partial or complete dose of BAL101553.
- Safety population: FAP with at least one post-baseline safety assessment.
- PK population: FAP with at least one post-baseline PK assessment.
- The MTD-determining population will consist of Phase 1 patients who have: received at least one partial or complete dose of BAL101553 and experienced a DLT; or received all scheduled doses of BAL101553 on study Days 1, 8 and 15 in Cycle 1 without a DLT, have been observed for ≥ 28 days following the first dose, and have been evaluated for safety.
- The efficacy-evaluable populations (EEPs) will include all Phase 2a patients:
  - With progressive disease who complete at least Cycle 1 dosing (i.e. received study drug on Days 1, 8 and 15) and who undergo at least one on-study clinical tumor assessment, or radiological assessment by RECIST v1.1 guidelines, or RANO criteria.
  - With stable disease, partial response, or complete response, based on a radiological assessment by RECIST v1.1 guidelines or RANO criteria at the end of Cycle 2, who receive at least four doses of study drug in the first two cycles.

For the Phase 2a portion of the study, separate analyses will be performed for the ovarian-cancer and GBM target populations.

DLT, MAD, and MTD recommendation

The number of patients experiencing DLT and the types of DLTs will be listed by dose level. The MAD is defined as the dose level at which DLTs are observed in ≥ two of [up to] six evaluable patients during treatment Cycle 1 (i.e., in a regular or expanded dose level). The MTD is defined as the highest dose level below the MAD with an acceptable tolerability profile.

Adverse events

Adverse events (AEs) and serious adverse events (SAEs) will be described by body system, in individual listings and frequency tables, for each dose level and cycle as appropriate.

Laboratory evaluations

The frequency of laboratory abnormalities will be displayed by worst CTCAE grade and by dose level and cycle as appropriate. Newly-occurring laboratory abnormalities will be displayed in a separate listing. Shift tables will be provided for laboratory parameters classified according to worst CTCAE grade.

Efficacy analysis

The objective response rate and disease control rate will be presented by dose level and by disease subgroups, as appropriate. Progression-free survival (until end of study and at 6 months after first study-drug administration) will be listed by dose level.

Pharmacokinetic analysis

Listings and descriptive analysis of PK variables will be presented by dose level, including arithmetic and geometric means, coefficient of variations, standard deviations, minimum, maximum, and median. Bioavailability will be determined as the ratio of the AUCs after oral and IV administration.

Biomarker analysis

Listings and descriptive analysis of biomarkers will be presented by dose level, scheduled time point/cycle, and by disease subgroup, as appropriate. Analyses of biomarkers and their association to clinical response or PK will be exploratory.

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LIST OF ABBREVIATIONS

ADR	Adverse drug reaction
AE	Adverse event
ALT	Alanine amino transferase
ANC	Absolute neutrophil count
AST	Aspartate amino transferase
$AUC_{0-\infty}$	Area under the concentration-time curve from time zero to infinity; calculated as $AUC_{0-last} + C_{last}/\lambda z$
AUC_{0-last}	Area under the concentration-time curve from time zero to the last quantifiable concentration
$AUC_{0-\tau}$	Area under the concentration-time curve from time zero to time (τ); where tau is the length of the dosing interval
BP	Blood pressure
BRCA1/2	Breast cancer susceptibility gene 1/2
BSA	Body surface area
CA-125	Cancer antigen 125
CDI	Cell death inducer
CEC(s)	Circulating endothelial cell(s)
CEP(s)	Circulating endothelial progenitor cell(s)
C_{max}	Maximum observed plasma concentration
CRA	Clinical research associate
CRF	Case report form
CT	Computed tomography
CTC(s)	Circulating tumor cell(s)
CTCAE	Common Terminology Criteria for Adverse Events version 4.03
CYP	Cytochrome P450
D	Day (of a treatment cycle)
DBP	Diastolic blood pressure
DCEC	Dose-Escalation Cohort Committee
DLT	Dose-limiting toxicity
DNA	Deoxyribonucleaic acid
ECG	Electrocardiogram
ECOG	Eastern Cooperative Oncology Group
eCRF	Electronic case repot form
EEP	Efficacy-evaluable population
FAP	Full analysis population
GBM	Glioblastoma
GCP	Good Clinical Practice

GLP	Good Laboratory Practice
hCG	Human chorionic gonadotropin
HIPAA	Health Insurance Portability and Accountability Act
HIV	Human Immunodeficiency Virus
ICH	International Conference on Harmonisation
IDH	Isocitrate dehydrogenase gene
IEC/IRB	Independent Ethics Committee / Institutional Review Board
ISF	Investigator site file
IUD	Intrauterine device
IV	Intravenous
LLN	Lower limit of normal
MAD	Maximum administered dose
MGMT	O6-methylguanin-DNA-methyltransferase gene
MRI	Magnetic resonance imaging
MTA	Microtubule targeting agent
MTD	Maximum tolerated dose
N	Number
PD	Pharmacodynamic(s)
PET	Positron emission tomography
Pgp	P-glycoprotein
PK	Pharmacokinetic(s)
QTcF	QT interval corrected for heart rate (Fridericia correction)
RANO	Response Assessment in Neuro-Oncology
RECIST v1.1	Response Evaluation Criteria in Solid Tumors Version 1.1
RNA	Ribonucleic acid
RP2D	Recommended Phase 2 dose
RT	Radiotherapy
SAE	Serious adverse event
SBP	Systolic blood pressure
SUSAR	Suspected unexpected serious adverse reaction
$t_{½}$	Terminal elimination half-life
T_{max}	Time to maximum plasma concentration
TB	Total bilirubin
TMZ	Temozolomide
ULN	Upper limit of normal
URL	Uniform resource locator

1. BACKGROUND AND RATIONALE

1.1 Microtubule targeting agents in cancer chemotherapy

Microtubule targeting agents (MTAs) are among the most active cytotoxic anticancer drugs currently in use, and have a broad spectrum of activity. Microtubule destabilizers (e.g., Vinca alkaloids) are used in the treatment of several types of hematologic malignancies, and solid tumors such as lung cancer; microtubule stabilizers (e.g., taxanes) are used in the treatment of a variety of solid tumors.

Despite a high initial sensitivity of many malignancies to MTAs, resistance can arise through several potential mechanisms, including tumor overexpression of P-glycoprotein (Pgp), elevated levels of β-tubulin subtype III, reduced levels of the cancer susceptibility gene BRCA1, elevated levels of the cell cycle inhibitory protein p21, and acquired mutations in β-tubulin. Accordingly, it is important to identify improved tubulin-inhibiting agents that may overcome these resistance factors and improve the effectiveness of treatment.

1.2 BAL101553 as a microtubule targeting agent

BAL101553 is a water-soluble, lysine pro-drug of the synthetic small molecule BAL27862. The active drug BAL27862 (a furazano-benzimidazole derivative), reversibly binds tubulin heterodimers at the colchicine site, inhibiting microtubule formation and disrupting microtubule organization [2].

The active compound BAL27862 (molecular weight = 387.4 g/mol) is lipophilic (LogD = 2.49 at pH 7.4), highly permeable (permeability = 135×10^{-6} cm/s in a Caco-2 model), and demonstrated excellent drug penetration into tissues including the brain, in mice [3].

BAL27862 displays a novel microtubule fragmentation activity, generating mobile, short microtubule fragments in interphase cells. BAL27862 destabilizes the mitotic spindle leading to the formation of tiny microtubule asters. The microtubule phenotype associated with BAL27862 treatment is distinct from that observed with conventional MTAs, including taxanes and Vinca alkaloids.

1.3 Nonclinical studies with BAL101553

1.3.1 Nonclinical pharmacodynamics and activity

BAL27862 induces apoptosis, and shows marked antiproliferative activity against cancer cell lines and patient-derived tumor cells from several solid-tumor histotypes. Antiproliferative activity is retained in tumor cells that over-express the drug efflux pump Pgp, as well as diverse tumor models that are refractory to Vinca alkaloids, taxanes, and epothilone B through non-Pgp-related resistance mechanisms. BAL27862 is also active against temozolomide-sensitive and -resistant glioblastoma (GBM) cell lines and paclitaxel-resistant ovarian cell lines. Importantly, patient-derived tumor cells exhibiting intrinsic resistance to paclitaxel have been demonstrated to be sensitive to BAL27862 using clonogenic assays. Normal human stem cells and peripheral blood mononucleocytes are relatively insensitive to BAL27862.

BAL27862 and BAL101553 exhibit antitumor activity with intravenous (IV) administration in human xenograft mouse models derived from several chemo-sensitive tumor histotypes, where activity is comparable to standard antineoplastic drugs.

Immunohistochemical examination of treated tumors indicates profound effects on tumor cell proliferation and viability, together with a potent disruption of the tumor vasculature; supporting *in vitro* analyses indicating a dual mechanism of action on refractory tumor cells and vascular cells. Moreover, a single BAL101553 administration has dose-dependent effects on tumor vascularization, with more profound antivascular effects at higher drug doses resulting in less efficient drug distribution to tumor. Hence, higher doses may not necessarily result in proportionally higher tumor drug levels. Fractionation of the IV dose does not decrease antitumor activity, indicating that AUC rather than C_{max} is the main factor in antitumor response. BAL27862 and BAL101553 also exhibit antitumor activity after oral administration in a number of xenograft models, with equivalent antitumor responses observed with both daily and weekly oral BAL101553 dosing in a Pgp-overexpressing colorectal cancer model.

Significant antitumor activity has also been observed with both BAL27862 (oral and IV) and BAL101553 (IV) in a Pgp-overexpressing mammary tumor xenograft model. These Pgp models are known to be refractory to standard MTAs, such as paclitaxel and vincristine.

Moreover, BAL101553 (IV) exhibits antitumor activity in an epothilone- and taxane-resistant non-small cell lung cancer xenograft model associated with mutation of class I β-tubulin and in a serous ovarian xenograft model that is partially refractory to cisplatin. In mice bearing orthotopic GBM tumors, daily-oral administration of BAL101553 as a single agent led to survival advantages in both MGMT-methylated (e.g. GBM39) and -unmethylated (e.g. GBM26) models.

Co-administration of capecitabine or cisplatin results in a trend towards increased antitumor activity, suggesting a potential for combination with cytotoxic agents. More profound antitumor effects have also been shown in combination with ionizing radiation and trastuzumab as compared to single agent treatment.

In GBM models, BAL101553 has shown anticancer activity as a single agent, as well as in combination with radiotherapy (RT) and with radiochemotherapy. In an orthotopic GBM model (GBM6) with reduced sensitivity to temozolomide (TMZ) and RT, more profound survival effects were observed when oral BAL101553 was combined with RT or RT/TMZ as compared to the single agents or RT and TMZ combined. These results indicate a potential to combine BAL101553 with radiotherapy, other chemotherapies and therapeutic antibodies.

Correlative studies suggest that high expression of stathmin, MAP4, phospho-AKT (Serine 473) and detyrosinated-(Glu-) and acetylated-tubulin may be associated with resistance to BAL27862. Moreover, reduced expression of the mitotic spindle checkpoint kinase BubR1 confers resistance on sensitive tumor cell lines. Monitoring of tumor p21 expression levels, as well as proliferation, viability and vascularization, may also be useful to show treatment-related pharmacodynamic (PD) effects. Validated tumor immunohistochemical assays are available for all the selected biomarkers and initial tumor epidemiology studies have been performed in a bank of human non-small-cell lung cancer, small-cell lung cancer, GBM and breast, colorectal, prostate, ovarian, pancreatic, hepatobiliary and gastric cancer specimens.

1.3.2 Nonclinical pharmacokinetics

The pro-drug BAL101553 is converted *in vitro* and *in vivo* to the active drug BAL27862 in blood, but to a much lesser extent in plasma, suggesting the involvement of a membrane-bound enzyme for the cleavage of the lysine pro-moiety. Metabolism (oxidation, side chain cleavage and conjugation) is complex, but several Cytochrome P450 (CYP) isoenzymes are involved. Metabolite patterns *in vitro* and *in vivo* qualify rat, rabbit and dog as suitable toxicological species. The main *in vivo* metabolites (> 10% of the administered dose) have no anticancer activity. The potential for drug-drug interactions with BAL27862 is low, with the exception of a potential CYP2C9-mediated interaction. Plasma protein binding is species independent and amounted to ~97%.

Caco-2 cells grown in monolayer are highly permeable to the active drug BAL27862, and the drug is not a substrate of Pgp. The pro-drug is cleaved on the brush border and intracellularly, and the remaining intact pro-drug is moderately permeable through Caco-2 cell monolayers. *In vivo* this translates to good oral bioavailability of the drug administered either as drug or pro-drug.

1.3.2.1 *Intravenous pharmacokinetics*

After IV administration of the pro-drug, the conversion into the active BAL27862 amounts to between 35% and 61% in mice, rats, and dogs. Conversion of pro-drug is rapid, with a half-life ranging from 0.1–2 h. In animals BAL27862 has a large volume of distribution, a moderate-to-high metabolic clearance, and half-lives ranging from 2.0–5.3 h in animals. Administration of pro-drug or drug leads to distribution into all tissues, notably tumor and brain; tumor retention is observed to be longer after administration of the pro-drug. In contrast to the increase in systemic exposure observed upon administration of increasing drug doses in mouse xenograft models, tumor exposure does not change, which is most likely due to the additional antivascular effects of the drug at higher doses. The mass-balance of both IV BAL27862 and BAL101553 is complete, with predominant elimination in the feces. Urinary excretion of both drug and pro-drug as unchanged drug is < 1%.

After repeated IV administration of BAL27862 or BAL101553 to mice, rats and dogs, the exposure is almost dose proportional, without indication of a gender effect, accumulation or induction.

1.3.2.2 *Oral pharmacokinetics*

After repeated oral administration of BAL27862 or BAL101553 to rats and dogs, the exposure is almost dose proportional, without indication of accumulation or induction; female rats tend to be more exposed than male rats, however, this gender difference is not observed in dogs. Comparison of the exposures after oral administration of the pro-drug as a solution, with those observed after IV administration of the drug, suggests an oral bioavailability ranging from 30–50% in the rat and 50–100% in the dog. Importantly, the oral bioavailability of BAL27862 in the rat is similar after administration of either the drug or the pro-drug. After oral administration only traces of the pro-drug are detected in plasma, suggesting a pre-systemic cleavage. These findings are in agreement with experiments in Caco-2 cells which showed that cleavage of BAL101553 to BAL27862 occurs both in the incubation medium and intracellularly, and that BAL27862 is highly

permeable. A dedicated pharmacokinetic (PK) study performed in dogs, using the capsule formulation intended for clinical use, confirmed the excellent oral bioavailability of BAL101553.

1.3.3 Nonclinical toxicology

BAL101553 was investigated in 4-week oral toxicity studies in rats and dogs, with once daily administration. The patterns of clinical, functional, laboratory and post-mortem findings were consistent with the expected adverse events (AEs) of anticancer drugs, and was comparable to previous studies with once-weekly IV administration. The main targets of toxicity were the gastrointestinal tract, blood, immune and lymphatic systems, and the testes. With the exception of testicular degeneration, changes were generally reversible after a 4-week recovery period. Considering weekly exposure (AUC), daily oral administration was better tolerated than weekly IV administration. The no-adverse-effect-level after once-daily oral dosing was < 2.5 mg/kg/day in rats and 0.5 mg/kg/day in dogs; the maximum tolerated dose (MTD) was 10 and 5 mg/kg/day in male and female rats, respectively, and 2 mg/kg/day in dogs.

There were no indications of central nervous system or peripheral neurotoxicity, or drug-related effects on the QTc-interval, in IV- or oral-administration animal studies.

1.3.4 Correlative studies

Several possible prognostic factors or surrogate markers for BAL101553 activity have been proposed. These include the number of circulating tumor cells (CTCs), circulating endothelial cells (CECs), circulating endothelial progenitor cells (CEPs), and expression of specific proteins detectable in blood or in tumor tissue including stathmin, MAP4, BubR1, phospho-AKT (Serine 473), detyrosinated-(Glu)- and acetylated-tubulin. BAL101553 activity does not appear to be associated with β-tubulin variant III expression levels, a biomarker heavily implicated in resistance to standard MTAs. However, based on the prognostic importance of this marker, analysis of β-tubulin variant III is proposed. Antitumor activity may also be correlated to the basal proliferation index (as measured by expression of Ki67), apoptosis levels (as measured by caspase activation), vascular density (as measured by a vascular marker such as CD34), and expression of cell cycle regulators (such as $p21^{CIP1}$). These biomarkers also provide value as PD markers of tumor response, providing important information to aid dose evaluation during the study. It is therefore appropriate to investigate these potential biomarkers of BAL101553 activity. Early evaluation of the practicality of the assays for use in enrollment criteria, patient stratification, or for monitoring efficacy, will provide a basis for future clinical studies.

Accordingly, blood samples, and tumor biopsies obtained where possible, obtained from patients before, during, and after treatment will be analyzed to identify possible biomarkers of therapeutic response or resistance. Additional protein expression or genetic and epigenetic analyses (e.g., gene expression and mutation, DNA methylation, microRNA analysis) may be performed on remaining blood and tumor biopsy samples to further explore potential relevant biomarkers of disease and/or drug response. Filter cards for dried-blood-spot analysis will be used for exploratory analysis. This may include the

correlation of PK exposure variables of BAL101553/BAL27862 with genetic variations/haplotypes of CYP450, other drug-metabolizing enzymes, or drug transporters.

1.4 Clinical studies with BAL101553

1.4.1 CDI-CS-001: Multiple-ascending-dose study of intravenous BAL101553 administered as a 2-hour infusion in adult patients with advanced solid tumors

Study CDI-CS-001 was a single-agent, open-label first-in-human Phase 1/2a IV study carried out in patients with solid tumors who have failed standard anticancer therapy, or for whom no effective standard therapy is available. The Phase 1 dose-escalation portion of the study used a modified titration design to determine the MTD. The Phase 2a expansion portion of the study further characterized the safety and tolerability of BAL101553 at MTD and sub-MTD doses and aimed to obtain efficacy data in patients with advanced solid tumors. The study was completed in April 2016.

The primary objective of the Phase 1 portion of this study was to determine the MTD of BAL101553 when given as 2-h infusions on Days 1, 8, and 15 of each 28-day cycle. The MTD was defined as the highest dose administered in Cycle 1 without the occurrence of Dose-limiting toxicity (DLT) in two or more patients, in a dose cohort of at least six patients, and was determined to be 60 mg/m^2. Dose escalation was performed using a modified titration design [4, 5]. The starting weekly dose of BAL101553 was 15 mg/m^2, based on Good Laboratory Practice (GLP) toxicology studies.

A total of 24 patients received BAL101553 at the following dose levels: 15 mg/m^2 (n=1), 30 mg/m^2 (n=3), 45 mg/m^2 (n=3), 60 mg/m^2 (n=10), and 80 mg/m^2 (n=7). Two patients were replaced in the 60 mg/m^2 cohort, as they were considered to be non-evaluable for safety/MTD.

The objective of the Phase 2a portion of the study was to obtain further information related to the efficacy, safety, PK and pharmakodynamics of BAL101553. At the onset of this part of the study, patients were randomized to receive BAL101553 at 60 mg/m^2 or at a lower dose level of 30 mg/m^2, to define whether the MTD or a sub-MTD dose is more appropriate for further clinical development. After dosing of 23 patients (12 patients at 30 mg/m^2 and 11 patients at 60 mg/m^2), the 60 mg/m^2 dose level was discontinued due to safety concerns following observation of myocardial injury (troponin release and electrocardiogram [ECG] changes) in two patients. Patients were then randomized to dose levels of 45 mg/m^2 or 30 mg/m^2. Subsequently, one patient at the 45 mg/m^2 dose level experienced a small, asymptomatic myocardial infarction. In response to this, 30 mg/m^2 was declared to be the highest dose to be administered in the Phase 2a portion of the trial; this is now considered to be the highest-tested safe dose of IV BAL101553, administered as a 2-hour infusion on study Days 1, 8 and 15 of each 28-day cycle. A total of 49 patients were administered BAL101553 during this phase of the study, 40 of whom were evaluable for efficacy.

1.4.1.1 *Pharmacokinetic results*

In the CDI-CS-001 study, serial blood samples were obtained from patients for analysis of drug concentrations and PK profiles on Day 1 of Cycles 1 and 2. On Days 8 and 15 of Cycles 1 and 2, blood samples for PK assessment were obtained at the end of drug infusion.

The pro-drug BAL101553 was converted to active drug BAL27862 in all patients and at all doses. The mean elimination half-life of the pro-drug (BAL101553, ~2 h) was almost ten-fold shorter than that of the drug (BAL27862, ~15 h), both of which were independent of dose level. The mean volume of distribution of BAL27862 (185 L/m^2 corresponding to ~321 L) was much greater than total body water, in agreement with preclinical observations. No accumulation was observed after multiple weekly infusions at any dose.

Exposures to both BAL27862 and BAL101553 increased with dose and intra-patient variability in exposure was low (< 30%) within the same dose level; the inter-patient variability at the same dose level was moderate-to-high.

1.4.1.2 *Safety results*

The Phase 1 MTD for BAL101553, when administered as a 2-h infusion on Days 1, 8 and 15 of each 28-day treatment cycle, was determined to be 60 mg/m^2. In the Phase 1 dose-escalation portion of the study, BAL101553 did not lead to clinically-relevant myelosuppression and no relevant hepatic, renal, or pulmonary toxicities were observed at dose levels up to 80 mg/m^2. No consistent age ($< 65 / \geq 65$ years) or gender differences in exposure to either BAL27862 or BAL101553 were apparent.

In the Phase 2a portion of the study, two patients at 60 mg/m^2 and one patient at 45 mg/m^2 experienced troponin elevations and ECG changes that were considered to be due to microvascular myocardial injury. As a consequence, the highest dose to be administered in the Phase 2a portion of the study was lowered to 30 mg/m^2, which is considered the recommended Phase 2 dose (RP2D) for 2-hour IV infusion. These events are thought to have been a consequence of the vascular disrupting effect of BAL101553. Based on the time course of observed BP elevations, with peak BPs consistently being observed at the BAL101553 T_{max}, the vascular-disrupting effect of the drug is considered to be C_{max} related. Dosing strategies that minimize C_{max}, such as a continuous infusion regimen, are therefore expected to reduce BAL101553-related toxicity.

Based on the safety experience from 73 patients treated at dose levels from 15–80 mg/m^2 in the Phase 1 and Phase 2a portions of study CDI-CS-001, dose-related patterns were reported for systemic adverse drug reactions (ADRs) of nausea/vomiting, transient arterial hypertension, reversible or partially reversible peripheral sensory neuropathy, reversible gait disturbance, myocardial injury and potentially of pain at tumor site.

Dose-related blood pressure (BP) increases > 170 mmHg (systolic) were observed at dose levels ≥ 45 mg/m^2, consistent with the vascular-disrupting effect observed in animal models. The maximum BP elevations occurred ~1 h after conclusion of the BAL101553 infusion, coinciding with the T_{max} of the active drug BAL27862 and were generally resolved within 24 h following the IV dose.

At dose levels of 60 mg/m^2 and 80 mg/m^2, some patients presented with reproducible transient grade 2–3 abdominal pain, possibly reflecting tumor pain, which occurred during dosing and disappeared within a few hours of the end of study-drug administration.

Injection-site reactions were observed at low doses (15–30 mg/m^2) of BAL101553, but were mitigated by the use of Ringer's Lactate as the carrier solution. This change was implemented based on a dedicated non-clinical study (CDI-TOX-018), performed in rats, to assess venous tolerability using BAL101553 at different pH values, concentrations, and infusion rates. This study showed pH to be the most important determinant of venous tolerability to BAL101553 and also demonstrated the tolerability of BAL101553 with central-venous administration.

Additional systemic side effects considered to be characteristic for BAL101553, but which did not show a clear dose relationship, included anorexia, diarrhea, fatigue and pyrexia.

1.4.1.3 *Efficacy results*

Of the 73 patients dosed in study CDI-CS-001, 59 were evaluable for efficacy.

One partial response was observed in a [redacted]

An additional 14 patients had stable disease as best response in the Phase 1 (n=5) and Phase 2a (n=9) portions of the study (N=73 total), with six patients presenting with stable disease for four or more treatment cycles.

The remaining patients had progressive disease prior to, or at the end of, treatment Cycle 2.

Pharmacodynamic assessments using paired pre-and post-dose tumor biopsies showed vascular disrupting effects in the majority of patients and antiproliferative effects in some patients. Robust pre- and post-dose biopsy data were obtained for patients dosed at 60 mg/m^2, however, the small number of samples at 30 mg/m^2 did not allow for firm conclusions to be made for this dose. A difference in vascular effects between the 30 mg/m^2 and 60 mg/m^2 dose levels was suggested when assessing the changes in CEC and CEP numbers from baseline; higher mobilization of CECs and CEPs was observed at 30 mg/m^2 than at 60 mg/m^2.

1.4.2 CDI-CS-002: Multiple-ascending-dose study of daily oral BAL101553 in adult patients with advanced solid tumors

Study CDI-CS-002 is an ongoing, single-agent, open-label, first-in-human, oral-administration Phase 1/2a study being carried out in patients with solid tumors who have failed standard anticancer therapy, or for whom no effective standard therapy is available, and those with recurrent or progressive GBM/high-grade glioma; patients from these two groups are enrolled into separate dose cohorts.

The Phase 1 multiple-dose-escalation portion of the study, using a 3+3 titration design to determine the MTD, is to be carried out in up to 42 evaluable solid-tumor patients and up to 24 GBM/high-grade glioma patients. The Phase 2a expansion portion of the study, is a single-agent, open-label, non-comparative, multi-center, fixed-MTD dose study to be carried out in approximately 40 evaluable solid-tumor patients and six evaluable patients with recurrent or progressive GBM who will undergo surgery.

The Phase 1 part of the study was initiated in May 2015 and recruitment is ongoing. The solid-tumor arm completed enrollment in September 2017, with 26 patients treated at doses ranging from 8 mg/day to 30 mg/day, 23 of whom were evaluable for MTD determination. The GBM/high-grade glioma arm is ongoing with 12 patients treated to date at doses ranging from 8 mg/day to 20 mg/day.

1.4.2.1 *Pharmacokinetic results*

To date in study CDI-CS-002, BAL101553 was essentially not measurable systemically after oral administration. BAL27862 exposure appeared to be highly variable between subjects; this was particularly noted at the 20 mg/day dose. The accumulation ratio was around 1.6, in agreement with the estimated half-life of around 16 h; however, the accumulation did not always correlate to the half-life, possibly indicating intra-individual variability. The exposure was dose-related and almost dose-proportional.

1.4.2.2 *Safety results*

1.4.2.1.1 Solid-tumor arm

BAL101553 was well tolerated up to and including the dose level of 16 mg/day, with no observations of DLTs or severe drug-related AEs. There were no signals with respect to blood-pressure elevations or vascular toxicity. Dose levels of 8 mg/day (N=3, Cohort 3) and 16 mg/day (N=7, Cohorts 4 and 6) were shown to be safe and well tolerated. Drug-related side effects at these dose levels included Grade 1/Grade 2 anorexia, constipation, diarrhea, fatigue/lethargy, nausea, oral mucosa dryness, rhinorrhea, xeroderma, maculopapular rash and stomatitis. One patient developed a systolic blood pressure elevation > 160 mmHg, however this patient had variable pre-dose blood pressure levels and there was no clear impact on the overall blood pressure profile in this patient or in other patients treated at doses between 2 mg/day and 16 mg/day.

In Cohort 5, at 30 mg/day oral BAL101553, DLTs were observed in two of the three patients treated and included Grade 3 hyponatremia and hypokalemia and reversible Grade 2 hallucinations. Based on these observations, the dose level of 30 mg/day was defined as the maximum administered dose (MAD) for oral BAL101553. There was no impact on blood pressure at 30 mg/day.

In Cohort 7, the dose level of 20 mg/day oral BAL101553 was not sufficiently tolerable based on observations of drug-related symptomatic Grade 4 hyponatremia in two of the six MTD-evaluable patients. The MTD for daily oral BAL101553 in solid tumor patients was therefore defined as 16 mg/day.

1.4.2.1.2 GBM arm

BAL101553 was well tolerated up to and including the dose level of 15 mg/day, with no observations of DLTs or severe drug-related AEs. There were no signals with respect to blood-pressure elevations or vascular toxicity.

In Cohort 3, at 20 mg/day oral BAL101553, DLTs of Grade 2 depression and fatigue were observed in one of three MTD-evaluable patients. The dose level was therefore expanded to include an additional three patients. One of these additional three patients had been enrolled, completed the MTD assessment period without DLT, and was ongoing in the study.

1.4.2.3 ***Efficacy results***

To date no pharmacodynamic analyses have been completed for patients enrolled in CDI-CS-002.

Of the 19 solid-tumor patients evaluable for efficacy, seven had stable disease at best response, one of whom was treated for 10 months, one for 8 months, one for 6 months and three for 4 months. One patient is ongoing in Cycle 8 of the study. Of the eight patients evaluable for efficacy in the GBM arm of the study, three had stable disease at best response, one was treated for 3 months, and two for 4 months.

1.4.3 CDI-CS-003: Study of BAL101553 administered as an intravenous 48-hour infusion

1.4.3.1 ***Safety and efficacy results***

Enrollment in the Phase 1 dose escalation of this study has been completed with 20 patients dosed (four patients at 30 mg/m^2, three patients at 45 mg/m^2, nine patients at 70 mg/m^2 and four patients at 90 mg/m^2), 16 of whom were evaluable for MTD assessment.

There were no observations of DLTs or severe drug-related AEs at the 30 mg/m^2 and 45 mg/m^2 dose levels. One patient at 70 mg/m^2 experienced a DLT of Grade 3 hypotension. A second patient experienced Grade 3 peripheral neuropathy during Cycle 2, leading to study-drug discontinuation; this event was fully reversible within a timeframe of 24 days. At the dose level of 90 mg/m^2, one patient expeirenceed a DLT of reversible Grade 3 hyponatremia and another patient experienced DLTs of reversible Grade 2 hallucinations, Grade 2 ataxia and Grade 3 neutropenia. The dose level of 90 mg/m^2 was therefore declared as the MAD (two patients with DLTs out of four evaluable patients) and the dose level of 70 mg/m^2 was declared as the MTD (one patient with a DLT out of six evaluable patients).

[redacted]

1.4.3.2 *Pharmacokinetics*

BAL101553 was converted to active BAL27862 in all patients. Both compounds showed dose-related exposure with limited inter-individual variability. Comparison of exposure in the same subject across cycles indicates there may be some intra-individual variability. BAL101553 rapidly reached steady-state with relatively low C_{max}, whilst BAL27862 concentrations increase steadily over time during the first 24 h.

The PK data collected from patients after oral administration indicate that relative oral bioavailability of BAL27862 was high (>80%).

1.5 Rationale for study CDI-CS-003

1.5.1 Summary of study design

CDI-CS-003 is a single-agent, open-label, Phase 1/2a study of intravenous BAL101553, administered as a 48-h infusion, to be performed in two parts:

- a Phase 1 dose-escalation portion, using a 3+3 titration design to determine the MTD in patients with advanced/recurrent solid tumors; and
- a Phase 2a expansion portion, to further characterize safety and tolerability of BAL101553 at the MTD (70 mg/m^2) in patients with platinum-resistant/refractory ovarian cancer or recurrent GBM.

1.5.2 Purpose of the study and design rationale

In study CDI-CS-001, dose-limiting toxicities with BAL101553 were determined by the vascular-disrupting effect of the drug. The fast-onset and quickly-reversible gait disturbance with peripheral sensory neuropathy suggests microvascular damage at the large peripheral nerve fibers as a possible mechanism of action. Other toxicities observed in the Phase 2a portion of study CDI-CS-001, including tumor pain, transient BP elevations and microvascular myocardial injury, are also considered to be a result of the vascular-disrupting effect of BAL101553.

The time of occurrence of BP elevations and other vascular side effects observed in study CDI-CS-001, where BAL101553 was administered as a 2-hour infusion, correlated to the maximum plasma concentration. Peak transient BP elevations consistently coincided with the T_{max} (i.e., approximately 1 hour after the end of study-drug infusion).

While observed toxicities appeared to be primarily related to the C_{max}, the available preclinical data suggest that anti-proliferative effects of BAL101553 are AUC-driven.

Given this, dosing strategies to limit C_{max}-related toxicities provide the potential to administer higher dose levels of BAL101553, with less vascular toxicity and possibly enhanced antiproliferative effects. Such dosing strategies include the administration of daily oral BAL101553 and the extension of the infusion time when BAL101553 is administered IV. A study with daily oral dosing of BAL101553 capsules is ongoing (study CDI-CS-002). The protocol CDI-CS-003, described here, will explore the effects of an extended infusion duration on safety, PK, PD and antitumor activity of IV BAL101553. In addition, the Phase 1 portion of this study will determine the bioavailability of daily oral BAL101553 by means of administration of oral BAL101553

capsules on study Days 15–21 of Cycle 2, i.e. after completion of the MTD-relevant safety assessments in Cycle 1.

A 48-hour infusion was chosen for this study, as PK modelling has suggested that administration of BAL101553 over this timeframe would result in C_{max} levels which are 25% of those observed when the drug is given as a 2-hour infusion.

Dose level sizes of three patients (without DLT) and six patients (if DLT is observed) have been utilized in numerous dose-escalation studies of anticancer drugs, and can be considered as a standard approach [6, 7]. The proposed study design is intended to limit patient exposure to low and likely inefficacious dose levels, while allowing identification of adequately tolerated doses with the greatest likelihood of efficacy.

A minimum period of observation of 28 days, between the administration of the first dose to the last patient at the current dose level and the administration of the first dose to the first patient at the next higher dose level, was chosen as it provides a reasonable time window for the assessment of safety findings prior to the treatment of new patients. This observation period is also practical to maintain a consistent 28-day schedule for patient clinic visits. The 7-day delay in the initiation of treatment between the first and second patient in a dose level is intended to allow for further identification of untoward toxicity when starting a new dose level.

The continuation of therapy for patients who may benefit from treatment is also in line with current standards in anticancer studies. The provision to permit intra-patient dose increases as higher doses are tested and found to be well tolerated provides patients entered in the study an opportunity to be treated at a potentially therapeutic dose.

The Phase 2a expansion portion of the study is intended to confirm the tolerability of BAL101553 at the MTD (70 mg/m^2), and to provide additional information about its safety and tolerability profile, PK, PD and antitumor efficacy in patients with platinum-resistant/refractory ovarian cancer and in patients with recurrent GBM.

An expansion in the target population of patients with platinum-resistant/refractory ovarian cancer is justified by a clinical signal, with a response seen in one patient dosed at 70 mg/m^2, supported by: non-clinical data in a serous-ovarian xenograft model partially refractory to cisplatin; other taxane-resistant cellular models in which BAL101553 has demonstrated activity; and based on the utility of other microtubule-targeting drugs (e.g. taxanes) in the indication of ovarian cancer.

An expansion in the target population of patients with recurrent GBM is justified by extensive non-clinical data using BAL101553 as a single agent, as well as in combination with radiotherapy (RT) and radiochemotherapy, and considering the excellent brain penetration of BAL27862 (a small, lipophilic molecule), which was demonstrated in a mouse model.

Treatment in both study phases (Phase 1 dose-escalation and Phase 2a expansion) will be extended for patients who may benefit from therapy.

1.5.3 Starting-dose rationale

1.5.3.1 *Intravenous BAL101553*

The starting dose of 30 mg/m^2 of IV BAL101553 was chosen based on the clinical experience in study CDI-CS-001, where IV BAL101553 was given as a 2-hour infusion. The dose level of 30 mg/m^2 was shown to be safe and well tolerated in 36 patients for whom this was the starting dose, and in an additional nine patients who were either dose escalated or dose reduced to this level.

Drug-related AEs characteristic of the 30 mg/m^2 dose administered in study CDI-CS-001, included Grade 1–2 nausea/vomiting, peripheral neuropathy, pyrexia, anorexia, fatigue and generally low-grade, transient BP increases (not considered to be clinically significant). The events observed at this dose level did not require intensified clinical monitoring or therapeutic interventions [8].

The local side effect of injection-site reaction was initially observed when physiological saline was used as the carrier solution; however, this was mitigated with the use of Ringer's Lactate, which maintains in an infusion-solution pH of 5.0 to 6.5 [5].

The BAL27862 C_{max} is considered to be the main PK driver of (vascular) toxicity and dosing regimens aimed at reducing the C_{max} are thus expected to reduce such adverse effects. The weekly exposure ($AUC_{\infty} \times 7$) to BAL27862 observed with daily-oral administration at 8 mg/day in study CDI-CS-002 was 2530 ng.h/mL (N=7), which is within the range of that achieved after once-weekly-IV administration at 30 mg/m^2 (3620 ng.h/mL [N=36]) in study CDI-CS-001. As expected, the average C_{max} with daily dosing at 8 mg/day (49.2 ng/mL [N=7]) was significantly lower than that observed with the 2-hour infusion at 30 mg/m^2 (271 ng/mL [N=36]). Extending the duration of the infusion from 2 hours to 48 hours successfully reduced the C_{max} by approximately 75%, whilst maintaining the same AUC.

As both the 30 mg/m^2 2-hour IV-dosing regimen and the 8 mg/day oral-dosing regimen were shown to be safe and well tolerated, a 48-hour continuous-infusion regimen providing similar AUC levels and C_{max} levels intermediate of those two dosing regimens, is also considered to be safe. A starting-dose level of 30 mg/m^2, given as 48-hour infusion, has therefore been selected for this study as it is expected to provide a potentially clinically-active exposure (AUC, one patient with a partial response using a 2-hour infusion regimen at 30 mg/m^2), is considered to be safe, and is not expected to result in a C_{max} or AUC exposures that would cause clinically-relevant toxicities.

Dose increments of approximately 50% are planned from 30 mg/m^2 onwards. Once a DLT is observed in any patient, the dose increment to the next higher dose level will be approximately one-third.

1.5.3.2 *Oral BAL101553*

In Phase 1, the cumulative weekly-oral starting dose, to be administered on study Days 15–21 of Cycle 2, has been selected to match the weekly IV dose of 30 mg/m^2. Based on observed PK from the three completed dose cohorts in study CDI-CS-002 (daily-oral BAL101553), the expected AUC at an IV dose of 30 mg/m^2 administered over 48 hours corresponds to an oral dose of approximately 8 mg/day.

Subsequent oral dose levels will be calculated to approximate the weekly IV dose or exposure. The oral-dose calculation may be modified based on observed PK during the study.

There will be no oral dosing in Phase 2a.

2. OBJECTIVES OF THE STUDY

2.1 Primary objectives

Dosing strategies which limit C_{max}-related BAL101553 toxicities provide the potential to administer higher dose levels of the drug in order to enhance its antiproliferative effects.

The primary objectives of this study are to determine the MTD and to characterize dose-limiting toxicities (DLTs) of BAL101553, administered as an IV infusion over 48 hours on study Days 1, 8 and 15 of a 28-day treatment cycle, to adults with advanced or recurrent solid tumors who have failed standard therapy, or for whom no effective standard therapy is available.

2.2 Secondary objectives

The secondary objectives are:

- To evaluate the safety and tolerability of BAL101553 administered as a 48-hour continuous IV infusion.
- To assess the antitumor activity of BAL101553 administered as a 48-hour continuous IV infusion.
- To assess the PK of BAL101553 and BAL27862 after 48-hour IV infusion; and after daily oral administration on study Days 15–21 of Cycle 2 (Phase 1 only).

2.3 Exploratory objectives

- To assess the use of biomarkers to characterize the PD effects of BAL101553, administered as a 48-hour continuous IV infusion.
- To explore the potential utility of biomarkers in blood and/or tumor tissue as predictive biomarkers.

3. STUDY DESIGN

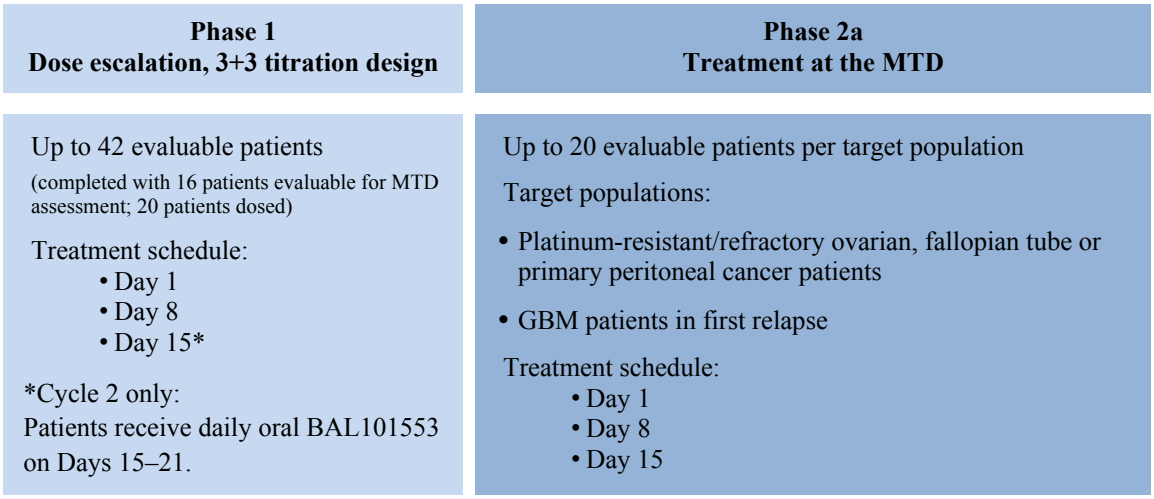
3.1 Overview of study design and dosing regimen

This is a single-agent, open-label, multi-center, Phase 1/2a study of BAL101553, administered IV over 48 hours on study Days 1, 8 and 15 of a 28-day treatment cycle. Additionally, the Phase 1 part of this study aims to determine the bioavailability of oral BAL101553 by means of daily administration of BAL101553 capsules on study Days 15–21 of Cycle 2, i.e., after completion of the MTD-relevant safety assessments in Cycle 1.

The study will be conducted in two parts: a Phase 1 multiple-ascending-dose-escalation portion using a 3+3 titration design to determine the MTD, to be carried out in up to 42 evaluable patients (completed with 16 patients evaluable); and a Phase 2a expansion portion to further characterize safety and tolerability of BAL101553 at the MTD (70 mg/m^2) and to obtain efficacy data. The Phase 2a part of the trial will include two target

populations, each with up to 20 evaluable patients: the first will comprise platinum-resistant/refractory ovarian, fallopian tube or primary peritoneal cancer (collectively referred to herein as 'ovarian cancer') patients; and the second will comprise GBM patients in first relapse. For each target population, a separate cumulative safety evaluation will be performed after six patients have completed their first 28-day cycle or have discontinued treatment (see Section 3.2.2.1), and after completion of the first cycle, or discontinuation, by each subsequent group of six patients. An overview of the study protocol design is presented in Figure 1.

Figure 1 Schematic overview of study design



3.1.1 Treatment cycles

For the Phase 1 part of this study, each treatment cycle will comprise 28 days, during which IV BAL101553 will be given as a 48-hour IV infusion on study Days 1, 8 and 15, using an elastomeric Baxter pump (pump models 2C4711K or 2C1009KP/2C4009K). On study Days 15–21 of Cycle 2, oral BAL101553 capsules will be given daily, instead of the Day 15 IV infusion (see Section 3.1.2.2). In this phase of the study, patients will be replaced if the minimum safety evaluation requirements for assessment of the MTD in Cycle 1 have not been met (see Sections 4.5 and 6.6.1.1).

For the Phase 2a part of the study, each treatment cycle will comprise 28 days, during which IV BAL101553 will be given as a 48-hour IV infusion starting on study Days 1, 8 and 15. In this phase of the study, patients will be replaced if they could not complete Cycle 1 and Cycle 2, for reasons other than progressive tumor disease (see Sections 3.1.3, 4.5 and 6.6.1.2).

Section 3.2.4 describes the planned treatment duration. Patients will be allowed to receive repeated 28-day treatment cycles until the occurrence of progressive disease, or unacceptable toxicity.

3.1.2 Dose escalation (Phase 1)

Patients will be enrolled in sequential (escalating) dose levels comprising three to six patients, using a body surface area (BSA)-adjusted dosing approach. For each dose level, new patients will be recruited and evaluated for safety, PK, PD effects, and for antitumor activity (see Section 3.2.1).

Cohorts will comprise three patients; the dose level will be expanded if patients experience specific Common Terminology Criteria for Adverse Events version 4.03 (CTCAE)-graded toxicity (see Section 3.2). Each dose level will utilize a 3+3 dose-escalation design and will be based upon the occurrence of BAL101553-related toxicities (DLTs) during Cycle 1 of treatment.

3.1.2.1 *Planned dose-escalation levels*

The IV BAL101553 starting-dose level will be 30 mg/m^2 (see Section 1.5.3.1). The oral BAL101553 starting-dose level will be 8 mg/day (see Section 1.5.3.2). Oral dose-escalation will mirror that of the IV dose escalation (see Section 3.2.3.2).

Dose increments of approximately 50% are planned from 30 mg/m^2 onwards, until DLT is observed. Once a DLT is observed in any patient, the dose increment for all subsequent dose levels will be approximately 33% (see Section 3.2.1, Table 1). If a DLT is observed in one patient at the starting dose level (30 mg/m^2), this dose level will be expanded [up] to six patients. If two or more of these [up to] six patients experience a DLT, the dose for the subsequent dose level will be decreased to 15 mg/m^2 and all subsequent dose levels will be increased by approximately 33%.

3.1.2.2 *Evaluable patient population for MTD-determination (Phase 1)*

Up to 42 evaluable patients (see Section 4.5.1) are planned to be enrolled in the Phase 1 part of the study, with the actual enrollment determined by the number of cohorts and the degree of cohort expansion required (see Section 3.3). At least six evaluable patients must be treated at the MTD dose level in the dose-escalation phase of the study.

BAL101553 treatment will be continued in patients enrolled in the dose-escalation phase until disease progression, occurrence of unacceptable toxicity, patient withdrawal, or discontinuation of the patient at the Investigator's discretion (see criteria for discontinuation of treatment in Section 4.4). Efficacy assessments to assess objective response to treatment must be scheduled at the end of at least each even-numbered treatment cycle (see Table 5 and Section 5.4.3) and subsequent treatment cycles may not be initiated if disease progression is observed. From Cycle 6 onwards, the interval between computed tomography (CT)/magnetic resonance imaging (MRI) scans may be extended from 8 weeks to 12 weeks.

Intra-patient dose escalation is permitted in patients who have completed at least two 28-day treatment cycles with BAL101553 and have not experienced any drug-related AEs ≥ CTCAE grade 2 in their most recent treatment cycle (see Section 3.2.3.1). Intra-patient dose escalation should begin as the first dose of a subsequent cycle.

3.1.3 Expansion portion (Phase 2a)

In December 2017, the MTD was defined as 70 mg/m^2; up to 40 additional evaluable patients (see Section 4.5.2) will be treated at this dose and evaluated for safety, PK, PD effects, and for antitumor activity (see Table 6).

The Phase 2a part of the study will include two separate target populations, each with up to 20 evaluable patients: the first will comprise platinum-resistant/refractory-ovarian cancer patients; and the second will comprise GBM patients in first relapse.

For each target population, a separate cumulative safety evaluation will be performed after six patients have completed their first 28-day cycle or have discontinued treatment (see Section 3.2.2.1), and after completion of the first cycle, or discontinuation, by each subsequent group of six patients.

BAL101553 treatment will be continued in patients enrolled in the dose-expansion portion until disease progression, occurrence of unacceptable toxicity, or until the patient withdraws from the study (see Section 4.4). Efficacy assessments to assess objective response to treatment must be scheduled at the end of at least each even-numbered treatment cycle (e.g., end of Cycle 2, 4, 6, etc.) and subsequent treatment cycles may not be initiated if disease progression is observed. Section 5.4.3 provides criteria for assessing response, stable disease, and disease progression.

3.1.4 End of study

The end of the study is defined as the completion of the last study-related contact with any patient.

3.2 Treatment plan

3.2.1 Phase 1 - intravenous dose-escalation scheme

The planned IV dose-escalation scheme to determine the maximum administered dose (MAD) and MTD of IV BAL101553, including the percent increases between the planned IV doses and the planned number of patients to be enrolled at each dose level, is presented in Table 1.

Each dose level will utilize a 3+3 dose-escalation design. The number of patients required to evaluate a dose level refers to patients who are considered evaluable for MTD assessment (see definition in Section 4.5). Cohorts of patients will receive increasing dose levels of BAL101553 until the MAD is reached. For each cohort, new patients will be recruited. The MAD will be defined as the dose level at which DLTs are observed during treatment Cycle 1 in two or more of [up to] six patients (i.e., > 33%). The MTD will be defined as the highest tested dose below the MAD with an acceptable tolerability profile. A minimum of six patients must be treated at a dose level for it to be declared the MTD.

After the planned number of patients have completed at least one cycle of BAL101553 at a given dose level and have been evaluated for safety, the members of the Dose-Cohort Escalation Committee (DCEC) will decide whether to proceed to the next higher dose level (see Section 3.2.1.2). Dose escalation will be primarily based on whether DLTs are observed during Cycle 1 at each dose level. However, the dose-escalation decisions must also include a clinical review of all relevant available data (including unmonitored data)

from the current and previous dose cohorts, and will not be solely based on Cycle 1 DLT information. The process for dose-escalation decisions is described in Section 3.2.1.2; a summary of the rules governing escalation decisions is presented in Table 3.

Dose increments of approximately 50% are planned from 30 mg/m^2 onwards, until observation of a DLT. Once a BAL101553-related DLT is observed, the dose level at which the toxicity occurred will be expanded [up] to six patients. If no other patients (i.e., only one of the six patients) experience a DLT at this level, three patients will be enrolled at the next dose level, the increment of which will be approximately 33% (see Table 1). If any further patients (i.e., ≥ two of the [up to] six patients) experience a DLT, dose escalation must be stopped and this dose will be declared the MAD. Furthermore, at least three additional patients must be enrolled at the next lowest dose level, if only three patients were previously treated at that dose. Lower and intermediate dose levels may be explored to determine the MTD.

If a DLT is observed in any patient in Cohort 1 (i.e., at a dose of 30 mg/m^2), that dose level will be expanded [up] to six patients. If ≥ two of these [up to] six patients experience a DLT, the dose for the subsequent cohort will be decreased to 15 mg/m^2 and all subsequent dose levels will be increased by approximately 33%.

There will be a minimum period of observation of 28 days from the first dose of the last patient treated at that dose level, to the first dose of the first patient treated at the next dose level. There will be a minimum period of observation of 7 days between the first doses given to the first and second patients in the cohort. No delay is required between the second patient and any subsequent patient enrolled at the same dose level. A delay in the start of the second cycle by more than 14 days due to a drug-related AE is considered a DLT. Therefore, no patients will be permitted to enroll at a new dose level until all patients in the current dose cohort have started treatment in Cycle 2, or have discontinued the study for reasons other than drug-related toxicity.

Recommendations for dose delays or dose modifications in patients experiencing BAL101553-related toxicities, are described in Section 3.2.3.2.

The IV dose levels listed in Table 1 are to be considered provisional. Possible changes include:

- administration of dose levels below the planned starting dose for the study
- expansion of the current dose group
- termination of further dose escalation
- administration of intermediate dose levels (e.g., between the current and previous dose levels, or between the current and the next planned dose level)

Table 1 Cohorts 1–4: Planned intravenous dose-escalation levels

Dose level 1	**Starting dose: 30 mg/m^2**											
	NRT							1×DLT*			>1×DLT	
Dose level 2	**45 mg/m^2 (50% increase)**						>1×DLT	**40 mg/m^2 (33% increase)**				**MAD**
	NRT			1×DLT				NRT	1×DLT	>1×DLT		
Dose level 3[#]	**70 mg/m^2 (~50% increase)**			**60 mg/m^2 (~33% increase)**			**MAD**	**53 mg/m^2 (~33% increase)**			**MAD**	
	NRT	1×DLT	>1×DLT	NRT	1×DLT	>1×DLT		NRT	1×DLT	>1×DLT		
Dose level 4	**100 mg/m^2 (~50% increase)**	**90 mg/m^2 (~33% increase)**	**MAD**	**80 mg/m^2 (~33% increase)**		**MAD**		**70 mg/m^2 (~33% increase)**		**MAD**		

NRT = no relevant toxicity; DLT = dose-limiting toxicity; MAD = maximum administered dose.
*Observation of a DLT in any patient will trigger an expansion of the dose level to [up to] six patients.
[#] The change from dose level 2 (45 mg/m^2) to dose level 3 (70 mg/m^2) corresponds to a 55% increase.

3.2.1.1 *Dose-limiting toxicity*

Whenever possible, AEs will be graded according to the CTCAE. DLT will be defined as any one of the AEs shown in Table 2 which occur during Cycle 1 and if considered by the Investigator to be at least possibly related to BAL101553.

Table 2 Overview of dose-limiting toxicities

Toxicity	CTCAE v4.03 criteria
Hematological	• Grade 4 Neutropenia (ANC < 0.5×10^9/L) lasting for ≥ 5 consecutive days. • Febrile neutropenia (ANC < 1.0×10^9/L and single temperature of > 38.3 °C, or a sustained temperature of ≥ 38.0 °C for > 1 h). • Grade 4 thrombocytopenia (platelet count < 25×10^9/L) or grade 3 thrombocytopenia (platelet count < 50×10^9/L) with bleeding. • Any other ≥ grade 4 hematological AE.
Gastrointestinal	• ≥ Grade 3 nausea, vomiting or diarrhea despite appropriate pre-medication and/or management.
Hepatic	• Grade 3 AST or ALT elevations (> 5–20 × ULN) for > 7 days, or grade 4 (> 20 × ULN) for any duration.
Cardiac	• Grade 3 QTc interval prolongation (QTcF > 500 ms or > 60 ms change from baseline). • Hypertension-related DLT: – Grade 4 hypertension. – Any recording of SBP > 220 mmHg or DBP > 110 mmHg. – At least one observation of SBP ≥ 160 mmHg or DBP ≥ 100 mmHg that does not resolve to SBP < 160 mmHg and DBP < 100 mmHg within 24 hours, despite antihypertensive treatment. Note: The need for administration of new antihypertensive medication or modification to more intensive antihypertensive medication will not be considered a DLT.
Other AEs	• Any study-treatment-related AE which leads to missing both the Day 8 and Day 15 doses in Cycle 1, or causes a delay in the start of Cycle 2 by > 14 days. • Any other study-treatment-related AE which, in the view of the Investigator and/or Sponsor, represents a clinically significant hazard to the patient. • Any other ≥ grade 3 non-hematological study-treatment-related AE.
Exceptions	• The following study-treatment-related AEs will not be considered DLT unless considered to present a clinically significant hazard to the patient: – Grade 3 fatigue. – Grade 3 or 4 elevations in alkaline phosphatase. – Grade 3 or 4 hypophosphatemia. – Grade 4 lymphopenia.

3.2.1.2 *Dose-escalation decisions and patient enrollment*

3.2.1.2.1 Responsibilities

Review of DLTs, as well as decisions to escalate the study-drug dose for each cohort, or to expand enrollment in cohorts, will be made by the DCEC, which will at minimum consist of:

- The Principal Investigator (or qualified delegate) from each investigational site.
- The Sponsor's Project Physician (or qualified delegate).

Further internal or external experts may be included in the DCEC as necessary. Detailed information regarding composition, processes, and dose-escalation decisions will be provided in the Dose-Escalation Charter.

3.2.1.2.2 Consultation

At scheduled intervals, and *ad hoc* as needed, DCEC will confer to review and discuss all safety information. In particular, a discussion will be held prior to each dose escalation. In this conference, safety information including DLT and all ≥ CTCAE grade 2 AEs during Cycle 1 from the current dose level, will be reviewed. Data collection for this review will be coordinated by the Sponsor. Safety information from patients in later cycles, updated safety data from ongoing/completed patients from previous levels (including intra-patient dose escalation), PK data and efficacy information must also be considered. DLT which occurred in Cycle 1 at the current dose level must be considered in the dose-escalation decision, however, the dose-escalation decisions will be based on a clinical review of all relevant available data from the current and previous dose cohorts. Minutes of the conference will be prepared by the Sponsor and approved by the entire DCEC.

After reaching consensus the DCEC will select the actual IV dose for the next cohort of patients, based on the planned dose-escalation levels (see Table 1) or intermediate levels as a guide. The corresponding cumulative-weekly oral dose will also be selected as described in Section 3.1.2.1.

3.2.1.2.3 Dose-escalation criteria

Dose-level expansion and escalation will mainly depend on the occurrence of DLTs (Table 2). The process and rules for dose-escalation decisions are presented in Table 3. Dose escalation and enrollment of a new cohort will require consultation and agreement within the DCEC, after all patients in the previous cohort have completed one cycle of dosing and observation, and after a review of all available safety and PK data. The magnitude of a dose increment will depend on the observation of drug-related grade 3 toxicities at the previous dose level (see Section 3.2.1). If toxicities occur that warrant inclusion of additional patients to assess the safety profile at a given dose level, the DCEC may decide to include a second cohort of [up to] three patients in the absence of a DLT. The DCEC may also decide to modify the dose-escalation plan, i.e. reduce the increment to the next dose level, in the absence of a DLT or grade 3 toxicity.

Dose escalation must not occur before completion of the first treatment cycle by all patients at the preceding dose level, where completion means either occurrence of DLT, or administration of the planned dose of BAL101553 on study Days 1, 8 and 15 in treatment Cycle 1 and observation for ≥ 28 days of the cycle with safety evaluation. Section 4.5 describes the replacement of patients who do not complete at least one treatment cycle for reasons other than occurrence of DLT.

Recommendations for dose delays or dose modifications in patients experiencing BAL101553-related toxicities, are described in Section 3.2.3.

Table 3 Dose-escalation criteria

Number of patients with DLT in the first 3 patients of a dose cohort [1]	Escalation decision
0 of 3 patients with DLT	Enroll 3 patients at the next dose level[2].
1 of 3 patients with DLT	• Enter 3 additional patients at this dose level. – If only 1 of the 6 patients experiences a DLT, enter 3 patients at the next-higher dose level[2]. – If ≥ 2 of the [up to] 6 patients experience DLT, then dose escalation is stopped; this dose is declared the MAD. If only 3 patients were treated at the previous dose level, at least 3 additional patients must be enrolled at that dose to determine the MTD[2].
≥ 2 of 3 patients with DLT	Dose escalation must be stopped. This dose level will be declared the MAD. If only 3 patients were treated at the previous dose level, at least 3 additional patients must be enrolled at that dose to determine the MTD[2].

Maximum administered dose (MAD):
The MAD is the dose level with a rate of DLT in ≥ 33% of patients during treatment Cycle 1, i.e.:
- ≥ 2 of [up to] 3 patients with DLT in the first 3 patients of a dose level.
- ≥ 2 of [up to] 6 patients with DLT in a dose level that was expanded to 6 patients.

Maximum tolerated dose (MTD):
The MTD is the highest dose level below the MAD with an acceptable tolerability profile, i.e.:
- Not more than 1 of 6 patients with DLT at the highest dose level below the MAD.

At least 6 patients must be treated at the MTD level during the dose-escalation phase.
Intermediate dose levels may be assessed, e.g., if one dose is well tolerated without DLT and the subsequent dose level is defined as the MAD.

The number of patients refers to patients evaluable for DLT assessment. DLT=dose-limiting toxicity.
[1] Treatment related means causal relationship of the event to BAL101553 is considered to be at least 'possible'.
[2] Refer to Table 1 for descriptions of provisional dose levels.

3.2.1.2.4 Enrollment

Following each consultation and dose-escalation decision, the Principal Investigators of all study centers must be notified by the Sponsor of both the IV dose (in mg/m^2) and the oral dose (in mg) to be given to patients in the new dose cohort. The dose levels will be documented in the dose-escalation meeting minutes. Investigators must not enroll patients at a new dose level until they have received notification of the consensus decision, the agreed new dose level and the start date for enrollment into the new cohort.

All study centers must notify the Sponsor when a patient is screened (within 24 hours of informed consent); when a patient is scheduled for their first dosing (at least 24 hours prior to the scheduled dosing), after administration of the first dose (within the 24 hours after dosing), and when a patient discontinues treatment (within the 24 hours after discontinuation, for any reason).

Dosing of any new patient may only be started after approval by the Sponsor. Approval of dosing for new patients must conform to planned dose-level size and the post-dose observation periods as described in Section 3.2.1.2.

The Sponsor must notify all centers when dosing for a new patient has been approved, and in addition, must provide a screening/enrollment log for the entire study which will

be accessible to all Investigators of participating study centers. This screening/enrollment log must be updated on an ongoing basis.

3.2.2 Phase 2a - fixed-dose treatment at the MTD

In December 2017, the MTD was defined as 70 mg/m^2; up to an additional 40 evaluable patients will be enrolled to the expansion portion of the study and treated at this dose (see Figure 1 and Section 3.1.3). Dose reductions in case of AEs are described in Section 3.2.3.2.

This part of the study will include two target populations, each with up to 20 patients evaluable for safety and efficacy assessment as described in Section 4.5.2. The first population will be comprised of platinum-resistant/refractory ovarian cancer patients and second will be comprised of GBM patients in first relapse. Dosing of any new patient may only be started after approval by the Sponsor.

3.2.2.1 *Safety Evaluations*

A separate cumulative safety evaluation will be performed for each target population after six patients have completed their first 28-day cycle or have discontinued treatment (see Section 3.2.2.1), and after completion of the first cycle, or discontinuation, by each subsequent group of six patients. These evaluations will be performed by a committee comprising a minimum of:

- The Principal Investigator (or qualified delegate) from each investigational site.
- The Sponsor's Project Physician (or qualified delegate).

Detailed information regarding composition, processes, and decisions will be provided in the Safety Evaluation Charter.

3.2.3 Dose modifications

3.2.3.1 *Dose increases*

In Phase 1, intra-patient dose increases, including multiple increases, will be allowed to higher dose-escalation levels if all of the following conditions apply:

- The patient has completed at least two treatment cycles without experiencing significant drug-related toxicities (i.e., no drug-related AE ≥ CTCAE grade 2) in their most recent cycle.
- The patient has completed the efficacy assessments scheduled at the end of at least each even-numbered cycle and disease progression has not been observed.
- All patients in the next-higher dose level have completed their first treatment cycle with acceptable tolerability and a decision has been taken to start dosing at the subsequent higher dose level. The final decision on intra-patient dose increases will be at the discretion of the Investigator after review of available safety data for all patients and discussion with the Sponsor.

Dose increases may only occur at the start of a subsequent cycle (i.e., Day 1 of the next treatment cycle) for an eligible patient.

Patients receiving increased doses are not considered to be part of the corresponding higher dose level for MTD determination, and DLT occurring after a dose increase will not be counted in the formal computation of DLT incidence for any dose level. However,

DLT reported after dose increases may be taken into account in dose-escalation decisions (Section 3.2.1.2).

3.2.3.2 *Dose reductions and dose delays due to adverse events*

When a patient experiences a DLT, treatment with BAL101553 must be interrupted until recovery to ≤ CTCAE grade 1 or baseline. If the patient continues treatment, subsequent doses of BAL101553 will be reduced by one dose level, or by half if this occurs at the starting dose level (i.e., to 15 mg/m^2). Non-DLT events may also require dose delays and/or dose reductions, or study discontinuation. Cycle 1 will be regarded as complete if all three scheduled doses of BAL101553 are administered, with recovery of toxicity to permit initiation of Cycle 2 with a maximum delay of 14 days.

Phase 1 patients in ≥ Cycle 2 and Phase 2a patients who experience a BAL101553-related AE that is equivalent to a DLT, must stop study medication, but may restart at a lower dose level if they recover to ≤ CTCAE grade 1 (or baseline severity) within 14 days and the patient is determined by the Investigator to be receiving clinical benefit from the investigational agent. Non-DLT events may also require dose reductions.

Table 4 provides criteria to guide dose interruption, dose modification and re-initiation when toxicities with BAL101553 treatment occur. These criteria are intended as general guidance and Investigators may deviate from these recommendations if the optimal medical management of the individual patient requires a different course of action. The Sponsor must be notified about any ≥ CTCAE grade 3 AEs and any dose modifications in a timely fashion.

Deviations from the visit schedule by ± 2 days are permitted for reasons other than toxicity, e.g., for administrative reasons or to accommodate travel logistics.

For each patient, a maximum of two dose reductions by one dose level each will be allowed. Once a dose level reduction has occurred, the dose level may not be re-escalated during subsequent treatment cycles with BAL101553. Patients who require more than two dose reductions must be discontinued from the study.

A patient must be discontinued from the study if the same toxicity recurs with the same or worse severity after treatment is resumed at a lower dose.

If, after interruption of treatment and resolution, treatment is re-initiated at the same dose level according to the criteria in Table 4 and the same toxicity reoccurs with the same severity, the next treatment re-initiation must resume at a lower dose, regardless of the duration of the toxicity.

Patients who discontinue the study due to AEs or a laboratory abnormality must be followed as described in Sections 5.4.2.8 and 7.3.2.1.

Table 4 General guidelines for treatment continuation criteria and recommendations for dose modification

Type of event (CTCAE grading)	Criteria to start a new treatment cycle	Criteria to withhold dose within a cycle	Criteria to reduce dose by one level	Criteria to resume treatment within a cycle	Criteria to withdraw a patient from the study
General aspects	Laboratory results consistent with enrollment criteria (Section 4.2)	See criteria below	Any DLT[1] or criterion below	Resolution of DLT[1] to ≤ CTCAE grade 1 (or baseline) and any criterion below	Any drug-related event which delays new cycle by > 14 days
Specific events					
Absolute neutrophil count (ANC)	≥ 1.5 per 10^9/L	< 1.0 per 10^9/L	< 1.0 per 10^9/L	≥ 1.0 per 10^9/L ≥ 1.5 per 10^9/L after DLT	(No specific criteria)
Febrile Neutropenia	None/fully resolved	Any occurrence	Any occurrence	Fully resolved	(No specific criteria)
Thrombocytopenia	≥ 100 per 10^9/L	< 50 per 10^9/L	< 50 per 10^9/L	≥ 75 per 10^9/L ≥ 100 per 10^9/L after DLT	(No specific criteria)
Hemoglobin	≥ 9 g/dL	< 6.5 g/dL	< 6.5 g/dL	≥ 8 g/dL	Grade 4 anemia
S-Creatinine (S-Cr)	≤ 1.5 × ULN	> 2.0 × ULN	> 2.5 × ULN	≤ 1.5 × ULN	≥ Grade 3 (S-Cr > 3.0 × ULN)
ALT/AST	≤ 2.5 (5.0)[2] × ULN	> 5.0 × ULN (any duration)	> 5.0 × ULN for > 7 days	≤ 3.0 (5.0)[2] × ULN	(No specific criteria)
Total bilirubin (TB)	≤ 1.5 (2.0)[2] × ULN	> 2.0 (2.5)[2] × ULN	> 2.0 (2.5)[2] × ULN	≤ 1.5 (2.0)[2] × ULN	Grade 4 (TB > 10 × ULN)
Neurotoxicity[3]	Grade 0 or 1	≥ Grade 2	≥ Grade 2	Grade 0 or 1	≥ Grade 3
Diarrhea[4]	Grade 0 or 1	≥ Grade 3	≥ Grade 3	Grade 0 or 1	Grade 4
QTcF	≤ 470 ms	> 500 ms or > 60 ms change vs baseline[4]	> 500 ms or > 60 ms change vs baseline[5]	≤ 470 ms	Recurrent QTcF > 500 ms or > 60 ms change vs baseline
Other toxicity[6,7]	≤ Grade 1 (or baseline)	≥ Grade 3	Grade 3	≤ Grade 1 (or baseline)	Grade 4

Abnormal laboratory values must be monitored at least twice per week until resolution to ≤ CTCAE grade 1, or stabilization.

[1] DLT during Cycle 1, or event of equivalent severity occurring in any subsequent cycle.

[2] Refers to patients with tumor involvement of the liver or liver metastases.

[3] Consider neurology consultation if neurotoxicity occurs.

[4] Despite appropriate medication/management.

[5] See Section 5.4.2.6: requires ECG monitoring, clinical assessment, blood sampling for PK assessment and increased ECG monitoring at next dosing.

[6] Grade 3 fatigue; grade 3/4 alkaline phosphatase elevations, asymptomatic hypophosphatemia, or lymphopenia; do not require dose delays/modifications unless considered clinically significant.SBP must be

[7] Blood Pressure: BP must be < 140 mmHg and DBP < 90 mmHg prior to dosing on Day 1 of Cycle 1 and Cycle 2. From Cycle 3 onwards SBP must be < 160 mmHg and DBP < 100 mmHg prior to dosing on Day 1. If a patient's systolic BP exceeded 180 mmHg or diastolic BP exceeded 110 mmHg on any dosing day, then systolic BP must be < 140 mmHg and diastolic BP must be < 90 mmHg prior to any subsequent dosing.

3.2.4 Duration of treatment

All patients will be scheduled to receive two 28-day treatment cycles.

BAL101553 treatment may be continued after the second 28-day cycle until disease progression, occurrence of unacceptable toxicity, or other criteria for discontinuation are met (see Section 4.4). To continue treatment beyond two 28-day treatment cycles, efficacy assessments scheduled at the end of at least each even-numbered cycle must be completed. Subsequent treatment cycles may not be initiated if disease progression is observed. In Phase 1, from Cycle 6 onwards, the interval between CT/MRI scans may be extended from 8 weeks to 12 weeks.

Unless treatment is stopped due to occurrence of DLT, patients in the dose-escalation portion of the study (Section 3.1.2) will be replaced if they could not complete at least one 28-day treatment cycle (see Sections 4.5.1 and 6.6.1.1), and patients in the expansion portion of the study (Section 3.1.3) will be replaced if they could not complete at least two 28-day treatment cycles (see Sections 4.5.2 and 6.6.1.2), for reasons other than progressive disease.

3.3 Number of patients

A total of up to 56 evaluable patients will be enrolled in the study.

The dose-escalation portion of the study to determine and characterize the MTD of BAL101553 administered as a 48-hour infusion has been completed with 20 patients dosed and 16 patients evaluable for MTD assessment. Up to 20 evaluable ovarian cancer and 20 evaluable GBM patients are expected to be treated in the expansion portion of the study, to further characterize the safety and tolerability profile of IV BAL101553 at the MTD (70 mg/m^2) and to obtain efficacy data in patients with these solid-tumor types.

Assuming approximately 25% drop-out rate, up to 70 patients may be enrolled in total.

3.4 Study centers

Up to three investigational centers will participate in the dose-escalation portion designed to characterize the MTD, and approximately ten investigational centers will participate in the expansion portion in patients treated at the MTD.

4. STUDY POPULATIONS

4.1 Target populations

4.1.1 Phase 1

Those eligible for enrollment into the study include consenting patients who meet the inclusion/exclusion criteria and have:

- A histologically- or cytologically-confirmed advanced or recurrent solid tumor, who have failed standard therapy, or for whom no effective standard therapy is available, and who meet the inclusion/exclusion criteria, will be eligible for enrollment into the study.

4.1.2 Phase 2a

Those eligible for enrollment into the study include consenting patients who meet the inclusion/exclusion criteria and have:

- A histologically-confirmed ovarian, fallopian-tube or primary-peritoneal cancer that is either platinum-resistant or refractory; or
- A histologically-confirmed GBM in first relapse.

4.2 Inclusion criteria

Patients meeting all of the following inclusion criteria at screening will be eligible for enrollment in the study. Informed consent must be obtained within the 28 days prior to the start of treatment. Screening evaluations will be performed within the 15 days prior to the start of treatment (within 21 to 28 days for radiology assessments).

Patients meeting **all** of the following:

1. Age 18 years or older.
2. Patients who have:
   a. Phase 1: Histologically- or cytologically-confirmed advanced or recurrent solid tumor, who failed standard therapy or for whom no effective standard therapy is available.
      - Patients with brain metastases must have undergone definitive treatment (surgery and/or radiation) at least 3 months prior to starting study drug and be documented as having stable disease by imaging.

   b. Phase 2a: either
      i. Histologically-confirmed ovarian, fallopian tube or primary peritoneal cancer (collectively referred to herein as 'ovarian cancer') that is either platinum-resistant (disease progression within 6 months of the last receipt of platinum-based chemotherapy) or refractory (lack of response or disease progression while receiving the most recent platinum-based therapy).
         - Patients may have received up to four lines of prior cytotoxic chemotherapy, but none of them in the platinum-resistant/refractory setting. Confirmed high-grade serous, endometrioid, or carcinosarcoma histotypes are permitted.

- An archived fixed-frozen paraffin-embedded tumor tissue block, or a minimum of 15 slides from such a block, must be available, otherwise a new tumor biopsy should be obtained in accordance with local institutional practices.
- Patients must have at least one site of measurable disease as defined by RECIST criteria, and no clinical or radiological evidence of bowel obstruction.
- Patients with brain metastases must have undergone definitive treatment (surgery and/or radiation) at least 3 months prior to starting study drug and be documented as having stable disease by imaging; or

ii. Histologically-confirmed glioblastoma (GBM) in first relapse, defined as: progression following initial therapy, i.e., radiation, chemotherapy, or radiation + chemotherapy, with or without prior surgery.
- Patients being treated with steroids must be on a stable or decreasing dose.

3. Patients with advanced solid tumors (excluding GBM) must have measurable disease (according to RECIST v1.1), documented within the 28 days prior to study-drug administration.

   Patients with GBM must have measurable disease, defined by contrast-enhancing MRI, within the 21 days prior to study-drug administration.

4. Life expectancy of ≥ 12 weeks.

5. Acceptable organ and marrow function documented within 15 days prior to starting study drug, defined as follows:
   - Absolute neutrophil count ≥ 1.5×10^9/L.
   - Platelets ≥ 100×10^9/L.
   - Hemoglobin ≥ 9 g/dL.
   - Total bilirubin ≤ 1.5 × institutional upper limit of normal (ULN), unless the patient has known Gilbert's syndrome.
   - Aspartate amino transferase (AST) and alanine amino transferase (ALT) ≤ 2.5 × institutional ULN or ≤ 5 × ULN in presence of liver metastasis.
   - Serum creatinine ≤ 1.5 × institutional ULN, or creatinine clearance ≥ 60 mL/min by Cockcroft-Gault formula.
   - Serum sodium ≥ the institutional lower limit of normal (LLN).

6. Patients (excluding those with GBM) must have an Eastern Cooperative Oncology Group (ECOG) performance status ≤ 1, and and those with GBM must have an ECOG performance status ≤ 2.

7. Female patients who are not pregnant or breast-feeding and meet one of the following conditions:
   - Postmenopausal for at least 1 year.

- Post-hysterectomy and/or post-bilateral ovariectomy.
- Women of childbearing potential must have a negative serum human chorionic gonadotropin (hCG) pregnancy test result and must use highly effective contraceptive methods for the duration of the study and for an additional 90 days after the last dose of study drug. Highly effective contraceptive methods include male or female sterilization (bilateral tubal occlusion or vasectomy); intrauterine device (IUD); or combined (estrogen and progesterone containing) hormonal contraception (oral, vaginal ring or transdermal patch) with an ethinylestradiol dose of at least 30 µg, plus use of male condoms (preferably with spermicides), female condoms, a female diaphragm or a cervical cap.

8. Male patients must agree not to donate sperm from the first dose of study drug until 90 days after the last dose of study drug. Male patients, without a vasectomy and with a partner of childbearing potential, must agree to use condoms during the study and for at least 90 days after the last dose of study drug. The patient should be instructed that their female partner should use another form of contraception for the duration of the study and continue this use for at least 90 days after the last dose of study drug.
9. Signed, written informed consent must be obtained and documented according to the International Conference on Harmonization's Guideline for Good Clinical Practice E6 (ICH-GCP) [1], the local regulatory requirements, and the permission to use private health information in accordance with the Health Insurance Portability and Accountability Act (HIPAA), where required, before performing any study-specific screening procedures.
10. Patients must have an implantable venous access system ('PORT') at the time of screening or must be willing to have a venous access system implanted for the purpose of the study. Patients with an existing PORT will be eligible for the study if the PORT chamber is made of titanium and the cathether is made of either silicon or polyurethane. If a patient has an exisiting PORT made of any other material, their eligibility may be approved by the Sponsor, based on the availability of compatibility data.

4.3 Exclusion criteria

Patients meeting any of the following exclusion criteria at screening must not be enrolled in the study:

1. Patients with advanced or recurrent solid tumors (excluding GBM) who:
   - Have received chemotherapy, radiotherapy, immunotherapy, or investigational agents within the 4 weeks (2 weeks for single fraction of palliative radiotherapy, 6 weeks for nitrosoureas or mitomycin C) prior to starting study drug; or
   - Have not recovered to ≤ Common Terminology Criteria for Adverse Events version 4.03 (CTCAE) grade 1 from all side effects of prior therapies, except for residual toxicities such as alopecia, which do not pose an ongoing medical risk.

Patients with prostate cancer must have discontinued anti-androgens (e.g., bicalutamide, nilutamide) for at least 6 weeks prior to starting study drug; chemical castration with luteinizing hormone-releasing hormone analogues can be continued.

Patients with GBM who:

- Have received radiotherapy within the 12 weeks prior to starting study drug, unless there is a new area of enhancement consistent with recurrent disease outside of the radiation field, or there is histological confirmation of unequivocal tumor progression; or
- Have received administration of prior antitumor chemotherapy within the 4 weeks prior to starting study drug, or within the 6 weeks prior to starting study drug in the case of nitrosoureas; or
- Have undergone surgical resection within the 4 weeks prior to starting study drug, or a stereotactic biopsy/core biopsy within 1 week prior to starting study drug; or
- Have been treated previously with bevacizumab.

2. Patients who have had prior exposure to BAL101553.
3. Inability to swallow oral medication (Phase 1).
4. Patients with gastrointestinal disease or those who have had a procedure that is expected to interfere with the oral absorption or tolerance of BAL101553 (e.g., functionally relevant gastrointestinal obstruction, or frequent vomiting) (Phase 1).
5. Symptomatic brain metastases or metastatic leptomeningeal disease, indicative of active disease.
6. Peripheral neuropathy ≥ CTCAE grade 2.
7. Known human immunodeficiency virus (HIV) infection.
8. Known acute or chronic hepatitis B or hepatitis C infection.
9. Average triple systolic blood pressure (SBP) ≥ 140 mmHg or average triple diastolic blood pressure (DBP) ≥ 90 mmHg at the Screening visit. Patients with an initial BP ≥ 140/90 mmHg may be included if SBP < 140 mmHg and DBP < 90 mmHg is confirmed in two subsequent BP measurements on the same day.
10. Blood pressure (BP) combination treatment with more than two antihypertensive medications.
11. Any history of cerebral hemorrhage, cerebral aneurysm, or ischemic stroke; or a history of transient ischemic attack within 24 months prior to screening.

    Acute or subacute intratumoral hemorrhage in patients with GBM, considered by the Investigator to be clinically significant.

    - Patients with MRI/CT demonstrating old hemorrhage, or a subacute bleed after a neurosurgical procedure (biopsy or resection), will be eligible.

12. Significant cardiac disease or abnormality, including any one of the following:
    - Left ventricular ejection fraction < 50% at screening (assessed by echocardiography).
    - QTcF > 470 ms on screening ECG or a clinically relevant ECG abnormality.
    - Congenital long QT syndrome.
    - History of sustained ventricular tachycardia, ventricular fibrillation or torsades de pointes.
    - Presence of atrial fibrillation with tachyarrhythmia (ventricular response rate > 100 bpm).
    - Bradycardia (heart rate < 50 bpm).
    - Complete left bundle branch block.
    - Bifascicular block (complete right bundle branch block and anterior or posterior left hemiblock).
    - Myocardial infarction, acute coronary syndrome (including unstable angina), coronary revascularization procedures, or coronary arterial bypass grafting within 6 months prior to starting study drug.
    - Cardiac troponin (either troponin T or troponin I) above the institutional ULN.
    - Congestive heart failure of New York Heart Association class III or IV.
13. Uncontrolled intercurrent illness that would unduly increase the risk of toxicity or limit compliance with study requirements in the opinion of the Investigator; including but not limited to: ongoing or active symptomatic infection, uncontrolled diabetes mellitus, unstable or uncompensated cardiac, hepatic, renal, respiratory, or psychiatric illness.
14. Current anticoagulation with warfarin potassium or other coumarin derivates. Heparin/low-molecular weight heparin (at prophylaxis or treatment doses), aspirin or other oral platelet inhibitors are permitted.
15. Women who are pregnant or breast-feeding. Men or women of reproductive potential who are not willing to apply effective birth control during the study and for at least 90 days after the last dose of study drug in both sexes.

4.4 Criteria for discontinuation of treatment

Patients may continue to receive treatment until disease progression, unacceptable toxicity, or another discontinuation criterion is met.

Patients may voluntarily withdraw from the study at any time for any reason. The Investigator may also withdraw a patient from the study. If a patient who has received at least one partial or complete dose of study drug discontinues at any time, every effort must be made to complete the End-of-Study visit.

Reasons for discontinuation of treatment must be recorded and may include:

- Disease progression.
- Adverse event.
- Abnormal laboratory value.
- Abnormal test procedure result.
- Missing both the Day 8 and Day 15 IV doses within a cycle, or a delay of more than 14 days in the start of a subsequent cycle, due to toxicity.
- Requirement for more than two dose-level reductions in a patient due to AEs.
- Intercurrent illness that prevents further administration of treatment.
- Withdrawal of consent.
- Withdrawn from the study at Investigator discretion.
- Protocol violation.
- Protocol non-compliance.
- Lost to follow-up.
- New cancer treatment/therapy.
- Administrative reasons.
- Death.

For all patients who discontinue the study, AE monitoring must be continued for at least 28 days after the last dose of study drug (see Sections see Sections 7.3.2 and 7.4.2). Patients will also be contacted to record antineoplastic therapies received within 28 days after discontinuation of study drug (see Section 5.2.18).

For patients who fail to return for the End-of-Study visit, the Investigator must make every effort to contact the patient (by telephone or mail correspondence). The outcome of this contact must be documented by the Investigator and filed in the Investigator's study file. The reasons for discontinuation of treatment must be recorded in the case report form (CRF).

4.5 Evaluability and replacement of patients

4.5.1 Phase 1

Patients in the dose-escalation portion of the study (Section 3.1.2) must meet the following minimum evaluation requirements in Cycle 1 to be eligible for MTD determination:

- Received the correct dose as described in Sections 6.5 and 6.6.1.1.
- Received at least one partial or complete dose of BAL101553 and experienced a DLT.
- Received all three scheduled doses of BAL101553 (see Section 6.6.1.1) without experiencing a DLT (including the ability to initiate treatment Cycle 2), have been observed for ≥ 28 days following the first dose, and have been evaluated for safety.

Patients who do not meet these minimum requirements in the dose-escalation portion of the study will be replaced by recruitment of new patients.

4.5.2 Phase 2a

For patients to be considered eligible for efficacy analysis in the Phase 2a dose-expansion portion of the study (see Section 3.1.3):

- The correct dose must be given as described in Sections 6.5 and 6.6.1.2.
- Patients with progressive disease must have completed at least Cycle 1 dosing (i.e., received study drug on Days 1, 8 and 15), have undergone at least one on-study clinical tumor assessment or radiological assessment by RECIST v1.1 guidelines (ovarian cancer patients) or RANO criteria (GBM patients), and have been evaluated for safety.
- Patients with stable disease, partial response, or complete response, based on a radiological assessment by RECIST v1.1 guidelines (ovarian cancer patients) or RANO criteria (GBM patients) at the end of Cycle 2, must have received at least four doses of study drug in the first two cycles and have been evaluated for safety.

Patients who do not fulfill these requirements will be replaced by recruitment of new patients.

5. STUDY VISITS, ASSESSMENTS AND PROCEDURES

5.1 Schedule of assessments

A summary of the schedule of assessments to be performed from Screening through to the End-of-Study visit is presented in Table 5 for Phase 1 and in Table 6 for Phase 2a.

Table 5 Phase 1 - Schedule of assessments

	Screening	Cycle 1					Cycle 2					Cycle 3 and subsequent cycles					End of Study
Day (D) of cycle[1]	**−15 to −1**	**D1**	**D8**	**D15**	**D22**	**D28**	**D1**	**D8**	**D15**	**D21/22†**	**D28**	**D1**	**D8**	**D15**	**D22***	**D28**	
Informed consent[2]	X																
Inclusion/exclusion criteria	X																
Diagnosis and extent of cancer/prior anticancer therapy	X																
Demographics/medical history/baseline medical conditions and medications	X																
Physical examination/ECOG performance status[3]	X	X					X					X					X
Vital signs[4]	X	X	X	X	X		X	X	X	X		X	X	X	X		X
Blood pressure[5]	X	X	X	X	X		X	X	X	X		X	X	X	X		X
12-lead ECG[6]	X	X	X	X			X	X	X	X		X					X
Echocardiography[7]	X																X
Chest X-ray[8]	X																
Hematology[9]	X	X	X	X	X		X	X	X	X		X	X	X	X		X
Biochemistry[10]	X	X	X	X	X		X	X	X	X		X	X	X	X		X
Coagulation[11]	X	X					X					X					X
Urinalysis[11]	X	X					X					X					X
Cardiac troponin[12]	X	X	X	X			X	X	X								X
Pregnancy test[13]	X	X					X					X					X
Radiological assessment of tumor[8,14] (RECIST v1.1 criteria)	X										X					X(ENC)	X
Implantable venous access system (PORT system)[15]	X																
BAL101553 administration[16]		X	X	X			X	X	X	X		X	X	X			
Drug dispensing and accountability		X	X	X			X	X	X	X		X	X	X			
Adverse events/ Serious adverse events [17]		X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X
Concomitant medications/treatments	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X
Blood for pharmacokinetics[18]		X	X	X			X	X	X	X							X
Dried-blood-spot analysis (Centogene cards)[19]		X															
Blood for CTC analysis[20]		X		X	X					X							
Tumor biopsy[21]	X				X					X					X		
Archival tumor specimen collection (when available)	X																

ENC = even-numbered cycles (Note that from Cycle 6 onwards, the interval between CT/MRI scans may be extended from 8 weeks to 12 weeks).
†Note: Assessments normally scheduled for D22 visits should be performed on D21 of Cycle 2.
*Note: D22 visits are optional from Cycle 3 onwards

1. Deviations from the visit schedule by ± 2 days are permitted for reasons other than toxicity, e.g., for administrative reasons or to accommodate travel logistics. D28 assessments of a given cycle may be performed on D29 of that cycle, i.e., pre-dose on D1 of the subsequent cycle.
2. Informed consent must be obtained within the 28 days prior to D1 of Cycle 1. Screening assessments must be performed and completed within the 15 days prior to D1/Cycle 1, with the exception of radiology assessments, which if conducted within the 28 days prior to D1 of Cycle 1, do not need to be repeated during Screening.
3. For D1 of all cycles, the physical exam and ECOG status must be performed within the 3 days prior to dosing; if the Screening exam was performed ≤ 3 days prior to D1, these do not need to be repeated on D1/Cycle 1 (see Sections 5.4.2.3 and 5.4.2.1).
4. Complete vital signs (see Section 5.4.2.4) will be obtained at Screening, at any D22 in-clinic visit, at the End-of-Study visit, and:

   Cycle 1: On D1, pre-dose and 0.5 h, 1 h, 2 h, 3 h, 4 h, 6 h, 8 h, 24 h 30 h, 48 h, 52 h, 54 h and 72 h after the start of study-drug infusion.
   On D8 and D15, pre-dose, and 0.5 h and 1 h after the start of study-drug infusion, and at the end of the 48-hour study-drug infusion.

   Cycle 2: On D1, pre-dose, and 0.5 h, 1 h, 2 h, 3 h, 4 h, 6 h, 8 h, 24 h, 30 h, 48 h and 72 h after the start of study-drug infusion.
   On D8, pre-dose, and 0.5 h and 1 h after the start of study-drug infusion, and at the end of the 48-hour study-drug infusion.
   On D15, pre-dose, and 1 h, 2 h, 4 h and 6 h after the first intake of oral BAL101553.
   On D21, pre-dose, and 0.5 h, 1 h, 2 h, 4 h, 8 h, 24 h, 30 h and 48 h after the last intake of oral BAL101553.

   Cycle 3 onwards: Pre-dose, 1 h after the start of study-drug infusion and at the end of the 48-hour study-drug infusion, on all dosing days.

   The body weight measurement must be obtained within the 3 days prior to dosing on D1 of all cycles.
5. Triple BP measurements should be taken at Screening, pre-dose on all dosing days, at any D22 in-clinic visit, and at the End-of-Study visit. Single BP measurements will be obtained:

   Cycle 1: On D1, every 30 min after the start of the study-drug infusion, until 4 h after the start of the study-drug infusion; and then at 6 h, 8 h, 24 h, 30 h, 48 h, 52 h, 54 h, and 72 h after the start of study-drug infusion.
   On D8 and D15, 0.5 h and 1 h after the start of study-drug infusion; and at the end of the 48-hour study-drug infusion.

   Cycle 2: On D1, every 30 min after the start of the study-drug infusion, until 4 h after the start of the study-drug infusion; and then at 6 h, 8 h, 24 h, 30 h, 48 h and 72 h after the start of study-drug infusion.
   On D8, 0.5 h and 1 h after the start of study-drug infusion; and at the end of the 48-hour study-drug infusion.
   On D15, 1 h, 2 h, 4 h and 6 h after the first intake of oral BAL101553.
   On D21, 0.5 h, 1 h, 2 h, 4 h, 8h, 24 h, 30 h and 48 h after the last intake of oral BAL101553.

   Cycle 3 onwards: 1 h after the start of study-drug infusion and at the end of the 48-hour study-drug infusion, on all dosing days.

   SBP must be < 140 mmHg and DBP < 90 mmHg prior to dosing on D1 of Cycle 1 and Cycle 2. Pre-dose on D8 or D15 of Cycles 1 and 2, and on all dosing days from Cycle 3 onwards, a patient's SBP must be < 160 mmHg and DBP < 100 mmHg. If a patient's SBP is > 180 mmHg or DBP is > 110 mmHg on any dosing day, then their SBP must be < 140 mmHg and their DBP < 90 mmHg, prior to any subsequent dosing.

   If post-dose SBP ≥ 160 mmHg or DBP ≥100 mmHg occur, triple BP measurements will be taken every 10–15 min until return to SBP/DBP < 160/90 mmHg. Patients should only be discharged home once BP levels have stabilized to SBP levels < 160 mmHg and DBP levels < 100 mmHg (see Section 5.4.2.5).

6. Three sequential (i.e., triplicate) 12-lead ECG are to be obtained, each separated by ~1 min and all taken within a 5-min time window, at Screening to determine study eligibility of patients, at the End-of-Study visit and as follows (see Section 5.4.2.6):

   Cycle 1: On D1, pre-dose, and 1 h, 2 h, 4 h, 8 h, 24 h, 48 h and 72 h after start of study-drug infusion.
   On D8 and D15, pre-dose, 1 h after the start of study-drug infusion, and at the end of the 48-hour study-drug infusion.

   Cycle 2: On D1, pre-dose; and 1 h, 2 h, 4 h, 8 h, 24 h and 48 h after start of study-drug infusion.
   On D8, pre-dose, 1 h after the start of study-drug infusion, and at the end of the 48-hour study-drug infusion.
   On D15, pre-dose and 6 h after the first intake of oral BAL101553.
   On D21, pre-dose, and 1 h, 2 h, 4 h, 8h, 24 h and 48 h after the last intake of oral BAL101553.

   Cycle 3 onwards: Pre-dose on D1 only.

   In patients undergoing intra-patient dose escalation or dose reduction; on D1, D8 and D15 of the first two cycles at each new dose level: prior to and 1 h after the start of study-drug infusion, and at the end of the 48-hour study-drug infusion.

   Triplicate 12-lead ECG should also be obtained when patients experience SBP > 200 mmHg or DBP > 110 mmHg, or whenever clinical cardiovascular signs or symptoms occur.

   Any abnormal on-study ECG must be transmitted to a central ECG laboratory for evaluation (including QTc assessment).

7. A transthoracic echocardiography (M-Mode, 2D or 3D) must be performed at Screening and at the End-of-Study visit (see Section 5.4.2.7).

8. Chest X-ray to establish a baseline for safety assessments, to be repeated as clinically indicated. For tumor assessments where a chest CT scan is performed, a chest X-ray is not required. Radiology assessments conducted within the 28 days prior to D1 of Cycle 1 do not need to be repeated during Screening.

9. Hematology (see Section 5.4.2.8.1) must be performed at each study visit and reviewed:
   - Within the 3 days prior to first administration of BAL101553 on D1 of Cycle 1.
   - Within 1 day prior to administration of BAL101553 on any other dosing day.

10. Biochemistry (see Section 5.4.2.8.2) must be performed according to the same schedule as Hematology.

11. Coagulation and urinalysis (see Sections 5.4.2.8.4 and 5.4.2.8.5) must be performed and reviewed:
    - Within the 3 days prior to first administration of BAL101553 on D1 of Cycle 1.
    - Within 1 day prior to administration of BAL101553 on D1 of all subsequent cycles.

12. Cardiac troponin (see Section 5.4.2.8.3) must be performed and reviewed:
    - Within the 3 days prior to first administration of BAL101553 on D1 of Cycle 1.
    - At the end of the 48-hour study-drug infusion on D1 of Cycle 1.
    - Within 1 day prior to administration of BAL101553 on: Cycle 1 D8 and D15; and Cycle 2 D1, D8 and D15.

    The same test (cardiac troponin-I or troponin-T) must be used consistently for a given patient at Screening and throughout the study.

13. Women of child-bearing potential must have a negative serum pregnancy test (hCG) at Screening; and a negative serum or urine pregnancy test (hCG) prior to BAL101553 dosing on D1 of every cycle and at the End-of-Study visit. Screening labs performed ≤ 3 days prior to first dosing, and labs performed within 1 day prior to all other in-clinic dosing days, do not need to be repeated (see Section 5.4.2.8.6).

14. Tumor assessment by radiological exam (CT/MRI scans) will be performed at Screening (or within the 28 days prior to D1) and within the 7 days prior to completion of every even-numbered cycle, before administration of the next cycle of BAL101553. From Cycle 6 onwards, the interval between CT/MRI scans may be extended from 8 weeks to 12 weeks. The End-of-Study assessment does not need to be repeated if an assessment was done within the 28 days prior (see Section 5.4.3.1).

15. Patients who do not have an implantable venous access system (PORT) will undergo (ambulatory) surgery and will receive subsequent training by a qualified nursing team on the use and proper handling of the venous access system (see Section 5.4.1.4.6). Implantation of the PORT will be recorded in medical history (see Section 5.4.1.4).

16. On D1 of Cycle 1 and D21 of Cycle 2, patients will be hospitalized up to 3 days after the start of study-drug infusion or first oral-drug administration for serial PK sampling and safety monitoring. The pump should be inspected for functionality 1 h after the start of infusion, after the 30-h PK sample, and 2 h prior to the end of infusion. On all other IV dosing days, patients must stay in the study unit for at least 1 h after the start of the BAL101553 infusion, and must return to the unit at least 2 h before the end of the 48-hour infusion. Seven consecutive days of BAL101553 oral dosing (Cycle 2 D15–21) will replace the Cycle 2 D15 IV administration of the drug.

17. Non-serious changes in, or worsening of, a patient's condition that occur between informed consent and first study-drug administration will be collected as pre-dose medical history (see Section 5.4.1.1). If any such occurence is considered to be serious, it will additionally be reported following the procedures of an serious adverse event (SAE), to allow for an assessment of serious procedure-related events. All AEs occurring from the time of first study-drug administration to 28 days following the last dose of study drug will be collected following the procedures outlined in Section 7.3.2.1. AEs occurring between D1 and D28 of Cycle 1 will be assessed against the DLT definitions outlined in Table 2. DLTs will additionally be recorded on the End-of-Cycle 1 assessment page of the CRF.

18. Blood PK samples will be collected from all patients at the End-of-Study visit, when a patient reports a DLT (if possible) and as follows (see Section 5.4.4):

    Cycle 1: On D1, pre-dose, and 0.5 h, 1 h, 2 h, 4 h, 8 h, 24 h, 30 h, 48 h, 52 h, 54 h and 72 h after the start of study-drug infusion.
    On D8 and D15, pre-dose, and 1 h and 48 h after the start of study-drug infusion.

    Cycle 2: On D1, pre-dose, and 0.5 h, 1 h, 2 h, 4 h, 8 h, 24 h, 30 h, 48 h and 72h after the start of study-drug infusion.
    On D8, pre-dose, and 1 h and 48 h after the start of study-drug infusion.
    On D15, pre-dose.
    On D21, pre-dose, and 0.5 h, 1 h, 2 h, 4 h, 8 h, 24 h, 30 h and 48 h after oral administration of BAL101553.

    The sampling schedule may be amended based on observed PK in humans. In patients undergoing intra-patient dose escalation or dose reduction, blood PK samples will be collected during one cycle at each new dose level for a given patient, according to the schedule for Cycle 1 above.

19. One blood sample (approximately 4 mL) will be obtained in an EDTA-tube pre-dose on D1 of Cycle 1 and distributed onto Centogene filtercards for dried-blood-spot analysis of single nucleotide polymorphisms and/or genes involved in drug transport or drug metabolism or potential biomarkers (see Section 5.4.5.1.2).

20. Samples for CTCs will be taken at at least two study sites, with the goal to obtain samples from at least 50% of patients at each dose level. Samples will be obtained pre-dose on: D1 and D15 of Cycle 1; and D22 of Cycles 1 and 2. Samples for CTCs will also be obtained using the same schedule in patients undergoing intra-patient dose escalation or dose reduction, at each new dose level (see Section).

21. Where possible, a tumor biopsy will be obtained during Screening if it is agreed to by the patient, is easily accessible, and is deemed safe for the patient. Also, if possible, a post-treatment biopsy can be obtained on D22 of Cycle 1 and/or Cycle 2. Additional post-treatment biopsies may be obtained on D22 of one subsequent cycle after Cycle 2, or at progressive disease (see Section 5.4.5.2).

Table 6 Phase 2a - Schedule of assessments

	Screening	Cycle 1					Cycle 2					Cycle 3 and subsequent cycles					End of Study **
Day (D) of cycle[1]	**−15 to −1**	**D1**	**D8**	**D15**	**D22**	**D28**	**D1**	**D8**	**D15**	**D22**	**D28**	**D1**	**D8**	**D15**	**D22***	**D28**	
Informed consent[2]	X																
Inclusion/exclusion criteria	X																
Diagnosis and extent of cancer/prior anticancer therapy[3]	X																
Demographics/medical history/baseline medical conditions and medications	X																
Physical examination/ECOG performance status[4]	X	X					X					X					X
Vital signs[5]	X	X	X	X	X		X	X	X	X		X	X	X	X		X
Blood pressure[6]	X	X	X	X	X		X	X	X	X		X	X	X	X		X
12-lead ECG[7]	X	X	X	X			X	X	X			X					X
Echocardiography[8]	X																X
Chest X-ray[9]	X																
Hematology[10]	X	X	X	X	X		X	X	X	X		X	X	X	X		X
Biochemistry[11]	X	X	X	X	X		X	X	X	X		X	X	X	X		X
Coagulation[12]	X	X					X					X					X
Urinalysis[12]	X	X					X					X					X
Cardiac troponin[13]	X	X	X	X			X	X	X								X
Pregnancy test[14]	X	X					X					X					X
Radiological assessment of tumor[9,15] (RECIST v1.1/RANO criteria)	X										X					$X^{(ENC)}$	X
CA-125 monitoring (ovarian cancer patients only)	X										X					$X^{(ENC)}$	X
Implantable venous access system (PORT system)[16]	X																
BAL101553 administration[17]		X	X	X			X	X	X			X	X	X			
Drug dispensing and accountability		X	X	X			X	X	X			X	X	X			
Adverse events/ Serious adverse events [18]		X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X
Concomitant medications/treatments	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X
Blood for pharmacokinetics[19]		X	X				X	X									X
Dried-blood-spot analysis (Centogene cards)[20]		X															
Blood for CTC analysis (ovarian cancer patients only)[21]		X		X	X					X							
Tumor biopsy (ovarian cancer patients only)[22]	X				X					X					X		
Archival tumor specimen collection (when available)	X																

ENC = even-numbered cycles.
*Note: D22 visits are optional from Cycle 3 onwards

**Note: For patients in the Phase 2a portion of the study who did not have disease progression at the end of the 28-day safety follow-up period, the patient and/or their treating physicians will also be contacted at 4 months and 6 months after the date of their first study-drug administration for the purpose of assessing progression-free survival.

1. Deviations from the visit schedule by ± 2 days are permitted for reasons other than toxicity, e.g., for administrative reasons or to accommodate travel logistics. D28 assessments of a given cycle may be performed on D29 of that cycle, i.e., pre-dose on D1 of the subsequent cycle.
2. Informed consent must be obtained within the 28 days prior to D1 of Cycle 1. Screening assessments must be performed and completed within the 15 days prior to D1/Cycle 1, with the exception of radiology assessments, which if conducted within 21 days (GBM patients) or 28 days (ovarian cancer patients) prior to D1 of Cycle 1, do not need to be repeated during Screening.
3. This includes results available regarding BRCA1/BRCA2 mutation status in patients with ovarian cancer and IDH mutation status in GBM patients.
4. For D1 of all cycles, the physical exam and ECOG status must be performed within the 3 days prior to dosing; if the Screening exam was performed ≤ 3 days prior to D1, these do not need to be repeated on D1/Cycle 1 (see Sections 5.4.2.3 and 5.4.2.1).
5. Complete vital signs (see Section 5.4.2.4) will be obtained at Screening, at any D22 in-clinic visit, at the End-of-Study visit, and:

   Cycle 1: On D1, pre-dose; 0.5 h, 1 h, 2 h, 4 h and 24–30 h after the start of study-drug infusion; at the end of infusion; and 6 h and 24–48* h after the end of infusion.

   *Patients treated prior to the first Safety Evaluation only.

   All other dosing days: pre-dose, 1 h after the start of study-drug infusion, and at the end of infusion.

   The body weight measurement must be obtained within the 3 days prior to dosing on D1 of all cycles.
6. Triple BP measurements should be taken at Screening, pre-dose on all dosing days, at any D22 in-clinic visit, and at the End-of-Study visit. Single BP measurements will be obtained:

   Cycle 1: On D1, 0.5 h, 1 h, 2 h, 4 h and 24–30 h after the start of study-drug infusion; at the end of infusion; and 6 h and 24–48* h after the end of infusion.

   *Patients treated prior to the first Safety Evaluation only.

   All other dosing days: 1 h after the start of study-drug infusion, and at the end of infusion.

   SBP must be < 140 mmHg and DBP < 90 mmHg prior to dosing on D1 of Cycle 1 and Cycle 2. Pre-dose on D8 or D15 of Cycles 1 and 2, and on all dosing days from Cycle 3 onwards, a patient's SBP must be < 160 mmHg and DBP < 100 mmHg. If a patient's SBP is > 180 mmHg or DBP is > 110 mmHg on any dosing day, then their SBP must be < 140 mmHg and their DBP < 90 mmHg, prior to any subsequent dosing.

   If post-dose SBP ≥ 160 mmHg or DBP ≥100 mmHg occur, triple BP measurements will be taken every 10–15 min until return to SBP/DBP < 160/90 mmHg. Patients should only be discharged home once BP levels have stabilized to SBP levels < 160 mmHg and DBP levels < 100 mmHg (see Section 5.4.2.5).
7. Three sequential (i.e., triplicate) 12-lead ECG are to be obtained, each separated by ~1 min and all taken within a 10-min time window, at Screening to determine study eligibility of patients, at the End-of-Study visit and as follows (see Section 5.4.2.6):

   Cycle 1: On D1, pre-dose; 1 h, 2 h, 4 h and 24–30 h after the start of study-drug infusion; at the end of infusion; and 6 h and 24–48* h after the end of infusion.

   *Patients treated prior to the first Safety Evaluation only.

   All other dosing days in Cycles 1 and 2: pre-dose, 1 h after start of study-drug infusion, and at the end of infusion.

   Cycle 3 onwards: Pre-dose on D1 only.

   Triplicate 12-lead ECG should also be obtained when patients experience SBP > 200 mmHg or DBP > 110 mmHg, or whenever clinical cardiovascular signs or symptoms occur.

   Any abnormal on-study ECG must be transmitted to a central ECG laboratory for evaluation (including QTc assessment).

8. A transthoracic echocardiography (M-Mode, 2D or 3D) must be performed at Screening and at the End-of-Study visit (see Section 5.4.2.7).
9. Chest X-ray to establish a baseline for safety assessments, to be repeated as clinically indicated. For tumor assessments where a chest CT scan is performed, a chest X-ray is not required. Radiology assessments conducted within 21 days (GBM patients) or 28 days (ovarian cancer patients) prior to D1 of Cycle 1 do not need to be repeated during Screening.
10. Hematology (see Section 5.4.2.8.1) must be performed at each study visit and reviewed:
    - Within the 3 days prior to first administration of BAL101553 on D1 of Cycle 1.
    - Within 1 day prior to administration of BAL101553 on any other dosing day.
11. Biochemistry (see Section 5.4.2.8.2) must be performed according to the same schedule as Hematology.
12. Coagulation and urinalysis (see Sections 5.4.2.8.4 and 5.4.2.8.5) must be performed and reviewed:
    - At Screening and at the End-of-Study visit
    - Within the 3 days prior to first administration of BAL101553 on D1 of Cycle 1.
    - Within 1 day prior to administration of BAL101553 on D1 of all subsequent cycles.
13. Cardiac troponin (see Section 5.4.2.8.3) must be performed and reviewed:
    - At Screening and at the End-of-Study visit
    - Within the 3 days prior to first administration of BAL101553 on D1 of Cycle 1.
    - At the end of the 48-hour study-drug infusion on D1 of Cycle 1.
    - Within 1 day prior to administration of BAL101553 on: Cycle 1 D8 and D15; and Cycle 2 D1, D8 and D15.

    The same test (cardiac troponin-I or troponin-T) must be used consistently for a given patient at Screening and throughout the study.
14. Women of child-bearing potential must have a negative serum pregnancy test (hCG) at Screening; and a negative serum or urine pregnancy test (hCG) prior to BAL101553 dosing on D1 of every cycle and at the End-of-Study visit. Screening labs performed ≤ 3 days prior to first dosing, and labs performed within 1 day prior to all other in-clinic dosing days, do not need to be repeated (see Section 5.4.2.8.6).
15. Tumor assessment by radiological exam (CT/MRI scans) and CA-125 monitoring (only in ovarian cancer patients) will be performed at Screening, or within the 28 days prior to D1 (within the 21 days prior to D1 for GBM patients); and within the 7 days prior to completion of every even-numbered cycle, before administration of the next cycle of BAL101553. The End-of-Study assessment does not need to be repeated if an assessment was done within the 28 days prior (see Section 5.4.3.1).
16. Patients who do not have an implantable venous access system (PORT) will undergo (ambulatory) surgery and will receive subsequent training by a qualified nursing team on the use and proper handling of the venous access system (see Section 5.4.1.4.6). Implantation of the PORT will be recorded in medical history (see Section 5.4.1.4).
17. On D1 of Cycle 1, patients may be hospitalized up to 3 days after the start of study-drug infusion for serial PK sampling and safety monitoring (see Section 6.5). The pump should be inspected for functionality 1 h after the start of infusion, after the 24–30-h PK sample, and 2 h prior to the end of infusion. On all other IV dosing days, patients must stay in the study center for at least 1 h after the start of the BAL101553 infusion, and must return to the unit at least 2 h before the end of the 48-hour infusion.
18. Non-serious changes in, or worsening of, a patient's condition that occur between informed consent and first study-drug administration will be collected as pre-dose medical history (see Section 5.4.1.1). If any such occurence is considered to be serious, it will additionally be reported following the procedures of an serious adverse event (SAE), to allow for an assessment of serious procedure-related events. All AEs occurring from the time of first study-drug administration to 28 days following the last dose of study drug will be collected following the procedures outlined in Section 7.3.2.1.

19. Blood PK samples will be collected from all patients at the End-of-Study visit and as follows (see Section 5.4.4):

    Cycle 1: On D1, pre-dose; 1 h, 4 h and 24–30 h after the start of study-drug infusion; at the end of infusion; and 6 h and 24–48* h after the end of infusion.
    On D8, pre-dose and at the end of infusion.

    *Patients treated prior to the first Safety Evaluation only.

    Cycle 2: on D1 and D8, pre-dose and at the end of infusion.

    In patients undergoing intra-patient dose reduction: at each new dose level, D1 and D8 of the first cycle: pre-dose and at the end of infusion.

    The sampling schedule may be amended based on observed PK in humans.

20. One blood sample (approximately 4 mL) will be obtained in an EDTA-tube pre-dose on D1 of Cycle 1 and distributed onto Centogene filtercards for dried-blood-spot analysis of single nucleotide polymorphisms and/or genes involved in drug transport or drug metabolism or potential biomarkers (see Section 5.4.5.1.2).
21. Samples for CTCs will be taken at at least two study centers, with the goal to obtain samples from at least 50% of ovarian cancer patients. Samples will be obtained pre-dose on: D1 and D15 of Cycle 1; and D22 of Cycles 1 and 2 (see Section 5.4.5.1). Samples for CTC analysis will not be obtained from GBM patients.
22. Where possible, a tumor biopsy will be obtained from ovarian cancer patients during Screening if it is agreed to by the patient, is easily accessible, and is deemed safe for the patient. Also, if possible, a post-treatment biopsy can be obtained on D22 of Cycle 1 and/or Cycle 2. Additional post-treatment biopsies may be obtained on D22 of one subsequent cycle after Cycle 2, or at progressive disease (see Section 5.4.5.2). Tumor biopsies will not be obtained from GBM patients.

5.2 Study visits

Informed consent must be obtained within the 28 days prior to Cycle 1, Day 1. Patients must provide written informed consent before any study-specific screening assessments are performed. Study centers must maintain a log of all consenting patients, which must include date of consent.

AEs must be monitored on an ongoing basis and at each study visit. AE monitoring must be continued for at least 28 days following the last dose of study drug (see Section 5.2.17 and Section 7.3.2).

Deviations from the visit schedule by ± 2 days are permitted for reasons other than toxicity, e.g., for administrative reasons or to accommodate travel logistics. Day 28 assessments of a given cycle may be performed on Day 29 of that cycle, i.e., pre-dose on Day 1 of the subsequent cycle.

5.2.1 Screening visit

Patients will be assigned a subject number once they have provided consent. Patients are considered to be enrolled in the study once it is confirmed that they meet all of the eligibility criteria for the study, as confirmed by the Sponsor.

Screening assessments must be performed in accordance with Table 5 (Phase 1) and Table 6 (Phase 2a) and completed within the 15 days prior to Day 1 of Cycle 1, with the exception of radiology assessments (see below).

The following assessments and procedures are to be performed at the Screening visit:

- Patient demographics.
- Medical history, baseline medical conditions, and prior and concomitant current medications/treatments, as described in Section 5.4.1.
- Available results of BRCA1/BRCA2 mutation status in patients with ovarian cancer and IDH mutation status in GBM patients.
- Physical examination, as described in Section 5.4.2.3.
- Complete vital signs, as described in Section 5.4.2.4.
- BP measurements, as described in Section 5.4.2.5.
- Triplicate 12-lead ECGs, according to Section 5.4.2.6.
- Transthoracic echocardiography, as described in Section 5.4.2.7.
- A chest X-ray to establish a baseline for safety assessments, to be repeated as clinically indicated.
  - For tumor assessments where a chest CT scan is performed, a chest X-ray is not required.
  - Radiology assessments conducted within 28 days (excluding GBM patients) or 21 days (GBM patients) prior to Day 1 of Cycle 1 do not need to be repeated during Screening.
- Tumor assessment by radiological exam (CT/MRI scans), as described in Section 5.4.3.1.
- CA-125 in ovarian cancer patients.
- Laboratory safety tests (hematology, biochemistry, coagulation, cardiac troponin and urinalysis), as described in Section 5.4.2.8.

- Women of child-bearing potential must have a negative serum pregnancy test (hCG), as described in Section 5.4.2.8.6 (see also Section 7.3).
- ECOG performance status, as described in 5.4.2.1.
- PORT sytem implantation, as described in Section 5.4.1.4.6.
- Tumor biopsy, if easily accessible, agreed to by the patient, and deemed safe for the patient, as described in Sections 5.4.5 and 5.4.5.2 (excluding GBM patients).
- Collection of archival tumor specimen, as described in Section 5.4.5.3.

5.2.2 Day 1 of Cycle 1

Eligible patients enrolled in the study will return to clinic on study Day 1. Assessments must be performed in accordance with Table 5 (Phase 1) and Table 6 (Phase 2a). Screening labs, physical exams, and ECOG assessments performed within the 3 days prior to first dosing do not need to be repeated.

The following assessments and procedures are to be performed at the Cycle 1/Day 1 visit:

- Study-drug dispensing, administration and accountability.
- Concomitant medications/treatments, as described in Section 5.4.1.
- Physical examination, as described in Section 5.4.2.3.
- Complete vital signs, as described in Section 5.4.2.4:
  - Phase 1: pre-dose, and 0.5, 1, 2, 3, 4, 6, 8, 24, 30, 48, 52, 54 and 72 hours after the start of study-drug infusion.
  - Phase 2a: pre-dose; 0.5, 1, 2, 4 and 24–30 hours after the start of study-drug infusion; at the end of infusion; and 6 and 24–48* hours after the end of infusion.
- BP measurements as described in Section 5.4.2.5:
  - Phase 1: pre-dose, every 30 min, until 4 hours after the start of the study-drug infusion, and then at 6, 8, 24, 30, 48, 52, 54 and 72 hours after the start of study-drug infusion.
  - Phase 2a: pre-dose; 0.5, 1, 2, 4 and 24–30 hours after the start of study-drug infusion; at the end of infusion; and 6 and 24–48* hours after the end of infusion.
  - If post-dose SBP ≥ 160 mmHg or DBP ≥100 mmHg occur, BP should be monitored every 10–15 min until return to SBP/DBP < 160/90 mmHg.
- Triplicate 12-lead ECGs, according to Section 5.4.2.6:
  - Phase 1: pre-dose, and 1, 2, 4, 8, 24, 48 and 72 hours after the start of study-drug infusion.
  - Phase 2a: pre-dose; 1, 2, 4 and 24–30 hours after the start of study-drug infusion; at the end of infusion; and 6 and 24–48* hours after the end of infusion.
  - Triplicate 12-lead ECG should also be obtained when patients experience SBP > 200 mmHg or DBP > 110 mmHg, or whenever clinical cardiovascular signs or symptoms occur.
- Laboratory safety tests (hematology, biochemistry, coagulation, cardiac troponin and urinalysis), as described in Section 5.4.2.8:
  - Analyses must be performed and reviewed within the 3 days prior to BAL101553 administration.
  - One additional troponin assessment needs to be performed at the end of the study-drug infusion.

- Women of child-bearing potential must have a negative pregnancy test (hCG), prior to dosing, as described in Section 5.4.2.8.6 (see also Section 7.3):
  - Analyses must be performed and reviewed within the 3 days prior to BAL101553 administration.
- Blood samples for PK analysis, as described in Section 5.4.4:
  - Phase 1: Pre-dose, and 0.5, 1, 2, 4, 8, 24, 30, 48, 52, 54 and 72 hours after the start of study-drug infusion.
  - Phase 2a: Pre-dose; 1, 4 and 24–30 hours after the start of study-drug infusion; at the end of infusion; and 6 and 24–48* hours after the end of infusion.
- Blood sample collection for biomarker analysis, as described in Section 5.4.5.1:
  - Dried-blood-spot analysis: pre-dose.
  - CTC analysis: pre-dose (excluding GBM patients).
- ECOG performance status, as described in 5.4.2.1.
- Recording of changes in, or worsening of, a patient's condition and AE monitoring, as described in Section 7.3.2.

**Patients treated prior to the first Safety Evaluation only.*

5.2.3 Day 8 of Cycle 1

Assessments must be performed in accordance with Table 5 (Phase 1) and Table 6 (Phase 2a).

The following assessments and procedures are to be performed at the Cycle 1/Day 8 visit:

- Study-drug dispensing, administration and accountability.
- Concomitant medications/treatments, as described in Section 5.4.1.
- Complete vital signs, as described in Section 5.4.2.4:
  - Phase 1: pre-dose, 0.5 hours and 1 hour after the start of study-drug infusion, and at the end of the 48-hour study-drug infusion.
  - Phase 2a: pre-dose, 1 hour after the start of study-drug infusion, and at the end of infusion.
- BP measurements as described in Section 5.4.2.5:
  - Phase 1: pre-dose, 0.5 hours and 1 hour after the start of the study-drug infusion, and at the end of the 48-hour study-drug infusion.
  - Phase 2a: pre-dose, 1 hour after the start of study-drug infusion, and at the end of infusion.
  - If post-dose SBP ≥ 160 mmHg or DBP ≥100 mmHg occur, BP should be monitored every 10–15 min until return to SBP/DBP < 160/90 mmHg.
- Triplicate 12-lead ECGs, according to Section 5.4.2.6:
  - Pre-dose, 1 hour after the start of the study-drug infusion, and at the end of infusion (Phase 1 and Phase 2a).
  - Triplicate 12-lead ECG should also be obtained when patients experience SBP > 200 mmHg or DBP > 110 mmHg, or whenever clinical cardiovascular signs or symptoms occur.
- Laboratory safety tests (hematology, biochemistry and cardiac troponin), as described in Section 5.4.2.8:

- Analyses must be performed and reviewed within 1 day prior to BAL101553 administration.

- Blood samples for PK analysis, as described in Section 5.4.4:
  - Phase 1: pre-dose, 1 hour and 48 hours after the start of study-drug infusion.
  - Phase 2a: pre-dose and at the end of infusion.
- AE monitoring, as described in Section 7.3.2.

5.2.4 Day 15 of Cycle 1

Assessments must be performed in accordance with Table 5 (Phase 1) and Table 6 (Phase 2a).

The following assessments and procedures are to be performed at the Cycle 1/Day 15 visit:

- Study-drug dispensing, administration and accountability.
- Concomitant medications/treatments, as described in Section 5.4.1.
- Complete vital signs, as described in Section 5.4.2.4:
  - Phase 1: pre-dose, 0.5 hours and 1 hour after the start of study-drug infusion, and at the end of the 48-hour study-drug infusion.
  - Phase 2a: pre-dose, 1 hour after the start of study-drug infusion, and at the end of infusion.
- BP measurements as described in Section 5.4.2.5:
  - Phase 1: pre-dose, 0.5 hours and 1 hour after the start of the study-drug infusion, and at the end of the 48-hour study-drug infusion.
  - Phase 2a: pre-dose, 1 hour after the start of study-drug infusion, and at the end of infusion.
  - If post-dose SBP ≥ 160 mmHg or DBP ≥100 mmHg occur, BP should be monitored every 10–15 min until return to SBP/DBP < 160/90 mmHg.
- Triplicate 12-lead ECGs, according to Section 5.4.2.6:
  - Pre-dose, 1 hour after the start of the study-drug infusion, and at the end of infusion (Phase 1 and Phase 2a).
  - Triplicate 12-lead ECG should also be obtained when patients experience SBP > 200 mmHg or DBP > 110 mmHg, or whenever clinical cardiovascular signs or symptoms occur.
- Laboratory safety tests (hematology, biochemistry and cardiac troponin), as described in Section 5.4.2.8:
  - Analyses must be performed and reviewed within 1 day prior to BAL101553 administration.
- Blood samples for PK analysis, as described in Section 5.4.4 (Phase 1 only):
  - Pre-dose, 1 hour and 48 hours after the start of study-drug infusion.
- Blood sample collection for biomarker analysis, as described in Section 5.4.5.1:
  - CTC analysis: pre-dose (excluding GBM patients).
- AE monitoring, as described in Section 7.3.2.

5.2.5 Day 22 of Cycle 1

Assessments must be performed in accordance with Table 5 (Phase 1) and Table 6 (Phase 2a).

The following assessments and procedures are to be performed at the Cycle 1/Day 22 visit:

- Concomitant medications/treatments, as described in Section 5.4.1.
- Complete vital signs, as described in Section 5.4.2.4.
- BP measurements as described in Section 5.4.2.5.
- Laboratory safety tests (hematology and biochemistry), as described in Section 5.4.2.8.
- Blood sample collection for biomarker analysis, as described in Section 5.4.5.1:
  - CTC analysis (excluding GBM patients).
- Tumor biopsy, if easily accessible, agreed to by the patient, and deemed safe for the patient, as described in Section 5.4.5.2 (excluding GBM patients).
  - Note: the blood sample for biomarker analysis should be obtained prior to tumor biopsy.
- AE monitoring, as described in Section 7.3.2.

5.2.6 Day 28 of Cycle 1

Day 28 assessments of a given cycle may be performed on Day 29 of that cycle, i.e., pre-dose on Day 1 of the subsequent cycle.

Assessments must be performed in accordance with Table 5 (Phase 1) and Table 6 (Phase 2a).

The following assessments and procedures are to be performed at the Cycle 1/Day 28 visit:

- Concomitant medications/treatments, as described in Section 5.4.1.
- AE monitoring, as described in Section 7.3.2.

5.2.7 Day 1 of Cycle 2

Assessments must be performed in accordance with Table 5 (Phase 1) and Table 6 (Phase 2a).

The following assessments and procedures are to be performed at the Cycle 2/Day 1 visit:

- Study-drug dispensing, administration and accountability.
- Concomitant medications/treatments, as described in Section 5.4.1.
- Physical examination, as described in Section 5.4.2.3.
- Complete vital signs, as described in Section 5.4.2.4:
  - Phase 1: pre-dose, and 0.5, 1, 2, 3, 4, 6, 8, 24, 30, 48 and 72 hours after the start of study-drug infusion.
  - Phase 2a: pre-dose, 1 hour after the start of study-drug infusion, and at the end of infusion.
- BP measurements as described in Section 5.4.2.5:
  - Phase 1: pre-dose, every 30 min until 4 h after the start of the study-drug infusion, and then at 6, 8, 24, 30, 48 and 72 hours after the start of study-drug infusion.
  - Phase 2a: pre-dose, 1 hour after the start of study-drug infusion, and at the end of infusion.

  - If post-dose SBP ≥ 160 mmHg or DBP ≥100 mmHg occur, BP should be monitored every 10–15 min until return to SBP/DBP < 160/90 mmHg.
- Triplicate 12-lead ECGs, according to Section 5.4.2.6:
  - Phase 1: pre-dose, and 1, 2, 4, 8, 24 and 48 hours after the start of study-drug infusion.
  - Phase 2a: pre-dose, 1 hour after the start of the study-drug infusion, and at the end of infusion.
  - Triplicate 12-lead ECG should also be obtained when patients experience SBP > 200 mmHg or DBP > 110 mmHg, or whenever clinical cardiovascular signs or symptoms occur.
- Laboratory safety tests (hematology, biochemistry, coagulation, cardiac troponin and urinalysis), as described in Section 5.4.2.8:
  - Analyses must be performed and reviewed within 1 day prior to BAL101553 administration.
- Women of child-bearing potential must have a negative pregnancy test (hCG), prior to dosing, as described in Section 5.4.2.8.6 (see also Section 7.3):
  - Analyses must be performed and reviewed within 1 day prior to BAL101553 administration.
- Blood samples for PK analysis, as described in Section 5.4.4:
  - Phase 1: Pre-dose, and 0.5, 1, 2, 4, 8, 24, 30, 48 and 72 hours after the start of study-drug infusion.
  - Phase 2a: pre-dose and at the end of infusion.
- ECOG performance status, as described in 5.4.2.1.
- AE monitoring, as described in Section 7.3.2.

5.2.8 Day 8 of Cycle 2

Assessments must be performed in accordance with Table 5 (Phase 1) and Table 6 (Phase 2a).

The following assessments and procedures are to be performed at the Cycle 2/Day 8 visit:

- Study-drug dispensing, administration and accountability.
- Concomitant medications/treatments, as described in Section 5.4.1.
- Complete vital signs, as described in Section 5.4.2.4:
  - Phase 1: pre-dose, 0.5 hours and 1 hour after the start of study-drug infusion, and at the end of the 48-hour study-drug infusion.
  - Phase 2a: pre-dose, 1 hour after the start of study-drug infusion, and at the end of infusion.
- BP measurements as described in Section 5.4.2.5:
  - Phase 1: pre-dose, 0.5 hours and 1 hour after the start of the study-drug infusion, and at the end of the 48-hour study-drug infusion.
  - Phase 2a: pre-dose, 1 hour after the start of study-drug infusion, and at the end of infusion.
  - If post-dose SBP ≥ 160 mmHg or DBP ≥100 mmHg occur, BP should be monitored every 10–15 min until return to SBP/DBP < 160/90 mmHg.
- Triplicate 12-lead ECGs, according to Section 5.4.2.6:

- Pre-dose, 1 hour after the start of the study-drug infusion, and at the end of infusion (Phase 1 and Phase 2a).
- Triplicate 12-lead ECG should also be obtained when patients experience SBP > 200 mmHg or DBP > 110 mmHg, or whenever clinical cardiovascular signs or symptoms occur.

- Laboratory safety tests (hematology, biochemistry and cardiac troponin), as described in Section 5.4.2.8:
  - Analyses must be performed and reviewed within 1 day prior to BAL101553 administration.
- Blood samples for PK analysis, as described in Section 5.4.4:
  - Phase 1: Pre-dose, 1 hour and 48 hours after the start of study-drug infusion.
  - Phase 2a: pre-dose and at the end of infusion.
- AE monitoring, as described in Section 7.3.2.

5.2.9 Day 15 of Cycle 2

5.2.9.1 *Phase 1*

Note: BAL101553 is administered as oral capsules at this visit.

On the day of drug administration, all patients must have fasted for at least 4 hours (see Section 6.5 for more details).

Assessments must be performed in accordance with Table 5.

The following assessments and procedures are to be performed at the Cycle 2/Day 15 visit:

- Study-drug dispensing, administration and accountability.
- Concomitant medications/treatments, as described in Section 5.4.1.
- Complete vital signs, as described in Section 5.4.2.4:
  - Pre-dose, and 1, 2, 4 and 6 hours after the first oral study-drug administation.
- BP measurements as described in Section 5.4.2.5:
  - Pre-dose, and 1, 2, 4 and 6 hours after the first oral study-drug administation.
  - If post-dose SBP ≥ 160 mmHg or DBP ≥100 mmHg occur, BP should be monitored every 10–15 min until return to SBP/DBP < 160/90 mmHg.
- Triplicate 12-lead ECGs, according to Section 5.4.2.6:
  - Pre-dose and 6 hours after the first oral study-drug administration.
  - Note: the same schedule applies for patients undergoing intra-patient dose escalation (Phase 1 only).
  - Triplicate 12-lead ECG should also be obtained when patients experience SBP > 200 mmHg or DBP > 110 mmHg, or whenever clinical cardiovascular signs or symptoms occur.
- Laboratory safety tests (hematology, biochemistry and cardiac troponin), as described in Section 5.4.2.8:
  - Analyses must be performed and reviewed within 1 day prior to BAL101553 administration.
- Blood samples for PK analysis, as described in Section 5.4.4 (Phase 1 and Phase 2a):
  - Pre-dose.

- AE monitoring, as described in Section 7.3.2.

5.2.9.2 ***Phase 2a***

Assessments must be performed in accordance with Table 6.

The following assessments and procedures are to be performed at the Cycle 2/Day 15 visit:

- Study-drug dispensing, administration and accountability.
- Concomitant medications/treatments, as described in Section 5.4.1.
- Complete vital signs, as described in Section 5.4.2.4:
  - Pre-dose, 1 hour after the start of study-drug infusion, and at the end of infusion.
- BP measurements as described in Section 5.4.2.5:
  - Pre-dose, 1 hour after the start of study-drug infusion, and at the end of infusion.
  - If post-dose SBP ≥ 160 mmHg or DBP ≥100 mmHg occur, BP should be monitored every 10–15 min until return to SBP/DBP < 160/90 mmHg.
- Triplicate 12-lead ECGs, according to Section 5.4.2.6:
  - Pre-dose, 1 hour after the start of the study-drug infusion, and at the end of infusion.
  - Triplicate 12-lead ECG should also be obtained when patients experience SBP > 200 mmHg or DBP > 110 mmHg, or whenever clinical cardiovascular signs or symptoms occur.
- Laboratory safety tests (hematology, biochemistry and cardiac troponin), as described in Section 5.4.2.8:
  - Analyses must be performed and reviewed within 1 day prior to BAL101553 administration.
- AE monitoring, as described in Section 7.3.2.

5.2.10 Day 22 of Cycle 2

5.2.10.1 ***Phase 1***

In order to minimize the amount of time the patient must remain at the hospital, assessments that would normally be performed on Day 22 should be performed on Day 21 of this cycle.

Note: BAL101553 is administered as oral capsules at this visit.

Assessments must be performed in accordance with Table 5. On the day of drug administration, all patients must have fasted for at least 4 hours (see Section 6.5 for more details).

The following assessments and procedures are to be performed at the Cycle 2/Day 21 visit:

- Study-drug dispensing, administration and accountability.
- Complete vital signs, as described in Section 5.4.2.4:
  - Pre-dose, and 0.5, 1, 2, 4, 8, 24, 30 and 48 hours after the last oral study-drug administration.
- BP measurements as described in Section 5.4.2.5:

- Pre-dose, and 0.5, 1, 2, 4, 8, 24, 30 and 48 hours after the last oral study-drug administration.
- If post-dose SBP ≥ 160 mmHg or DBP ≥100 mmHg occur, BP should be monitored every 10–15 min until return to SBP/DBP < 160/90 mmHg.

- Triplicate 12-lead ECGs, according to Section 5.4.2.6:
  - Pre-dose, and 1, 2, 4, 8, 24 and 48 hours after the last oral study-drug administration.
  - Triplicate 12-lead ECG should also be obtained when patients experience SBP > 200 mmHg or DBP > 110 mmHg, or whenever clinical cardiovascular signs or symptoms occur.
- Laboratory safety tests (hematology and biochemistry as described in Section 5.4.2.8:
  - Analyses must be performed and reviewed within 1 day prior to BAL101553 administration.
- Blood samples for PK analysis, as described in Section 5.4.4:
  - Pre-dose, and 0.5, 1, 2, 4, 8, 24, 30 and 48 hours after the last oral study-drug administation.
- Blood sample collection for biomarker analysis, as described in Sections 5.4.5 and 5.4.5.1:
  - CTC analysis: pre-dose.
- Tumor biopsy, if easily accessible, agreed to by the patient, and deemed safe for the patient, as described in Section 5.4.5.2.
  - Note: the blood sample for biomarker analysis should be obtained prior to tumor biopsy.
- AE monitoring, as described in Section 7.3.2.

5.2.10.2 ***Phase 2a***

Assessments must be performed in accordance with Table 6.

The following assessments and procedures are to be performed at the Cycle 2/Day 22 visit:

- Concomitant medications/treatments, as described in Section 5.4.1.
- Complete vital signs, as described in Section 5.4.2.4.
- BP measurements as described in Section 5.4.2.5.
- Laboratory safety tests (hematology and biochemistry), as described in Section 5.4.2.8.
- Blood sample collection for biomarker analysis, as described in Sections 5.4.5 and 5.4.5.1:
  - CTC analysis (excluding GBM patients).
- Tumor biopsy, if easily accessible, agreed to by the patient, and deemed safe for the patient, as described in Section 5.4.5.2 (excluding GBM patients).
  - Note: the blood sample for biomarker analysis should be obtained prior to tumor biopsy.
- AE monitoring, as described in Section 7.3.2.

5.2.11 Day 28 of Cycle 2

Day 28 assessments of a given cycle may be performed on Day 29 of that cycle, i.e., pre-dose on Day 1 of the subsequent cycle.

Assessments must be performed in accordance with Table 5 (Phase 1) and Table 6 (Phase 2a).

The following assessments and procedures are to be performed at the Cycle 2/Day 28 visit:

- Concomitant medications/treatments, as described in Section 5.4.1.
- Tumor assessment by radiological exam (CT/MRI scans) and CA-125 assessment:
  - May be performed at any time within the 7 days prior to completion of every even-numbered cycle, before administration of the next cycle of BAL101553.
- AE monitoring, as described in Section 7.3.2.

5.2.12 Day 1 of Cycle 3 onwards

Assessments must be performed in accordance with Table 5 (Phase 1) and Table 6 (Phase 2a).

The following assessments and procedures are to be performed at the Cycle 3 onwards/ Day 1 visit:

- Study-drug dispensing, administration and accountability.
- Concomitant medications/treatments, as described in Section 5.4.1.
- Physical examination, as described in Section 5.4.2.3.
- Complete vital signs, as described in Section 5.4.2.4:
  - Pre-dose, 1 hour after the start of study-drug infusion, and at the end of the 48-hour study-drug infusion.
- BP measurements as described in Section 5.4.2.5:
  - Pre-dose, 1 hour after the start of study-drug infusion, and at the end of the 48-hour study-drug infusion.
- Triplicate 12-lead ECGs, according to Section 5.4.2.6:
  - Prior to the start of study-drug infusion.
  - Triplicate 12-lead ECG should also be obtained when patients experience SBP > 200 mmHg or DBP > 110 mmHg, or whenever clinical cardiovascular signs or symptoms occur.
- Laboratory safety tests (hematology, biochemistry, coagulation, and urinalysis), as described in Section 5.4.2.8:
  - Analyses must be performed and reviewed within 1 day prior to BAL101553 administration.
- Women of child-bearing potential must have a negative pregnancy test (hCG), prior to dosing, as described in Section 5.4.2.8.6 (see also Section 7.3):
  - Analyses must be performed and reviewed within 1 day prior to BAL101553 administration.
- ECOG performance status, as described in 5.4.2.1.
- AE monitoring, as described in Section 7.3.2.

5.2.13 Day 8 of Cycle 3 onwards

Assessments must be performed in accordance with Table 5 (Phase 1) and Table 6 (Phase 2a).

The following assessments and procedures are to be performed at the Cycle 3 onwards/ Day 8 visit:

- Study-drug dispensing, administration and accountability.
- Concomitant medications/treatments, as described in Section 5.4.1.
- Complete vital signs, as described in Section 5.4.2.4:
  - Pre-dose, 1 hour after the start of study-drug infusion, and at the end of the 48-hour study-drug infusion.
- BP measurements as described in Section 5.4.2.5:
  - Pre-dose, 1 hour after the start of study-drug infusion, and at the end of the 48-hour study-drug infusion.
- Laboratory safety tests (hematology and biochemistry), as described in Section 5.4.2.8:
  - Analyses must be performed and reviewed within 1 day prior to BAL101553 administration.
- AE monitoring, as described in Section 7.3.2.

5.2.14 Day 15 of Cycle 3 onwards

Assessments must be performed in accordance with Table 5 (Phase 1) and Table 6 (Phase 2a).

The following assessments and procedures are to be performed at the Cycle 3 onwards/ Day 15 visit:

- Study-drug dispensing, administration and accountability.
- Concomitant medications/treatments, as described in Section 5.4.1.
- Complete vital signs, as described in Section 5.4.2.4:
  - Pre-dose, 1 hour after the start of study-drug infusion, and at the end of the 48-hour study-drug infusion.
- BP measurements as described in Section 5.4.2.5:
  - Pre-dose, 1 hour after the start of study-drug infusion, and at the end of the 48-hour study-drug infusion.
- Laboratory safety tests (hematology and biochemistry), as described in Section 5.4.2.8:
  - Analyses must be performed and reviewed within 1 day prior to BAL101553 administration.
- AE monitoring, as described in Section 7.3.2.

5.2.15 Day 22 of Cycle 3 onwards

Day 22 visits are optional from Cycle 3 onwards. However, if a Day 22 visit is scheduled, the following assessments should be performed:

- Concomitant medications/treatments, as described in Section 5.4.1.
- Complete vital signs, as described in Section 5.4.2.4.

- BP measurements as described in Section 5.4.2.5.
- Laboratory safety tests (hematology and biochemistry), as described in Section 5.4.2.8.
- Tumor biopsy, if easily accessible, agreed to by the patient, and deemed safe for the patient, as described in Section 5.4.5.2 (excluding GBM patients).
- AE monitoring, as described in Section 7.3.2.

5.2.16 Day 28 of Cycle 3 onwards

Day 28 assessments of a given cycle may be performed on Day 29 of that cycle, i.e., pre-dose on Day 1 of the subsequent cycle.

Assessments must be performed in accordance with Table 5 (Phase 1) and Table 6 (Phase 2a).

The following assessments and procedures are to be performed at the Cycle 3 onwards/Day 28 visit:

- Concomitant medications/treatments, as described in Section 5.4.1.
- Tumor assessment by radiological exam (CT/MRI scans) and CA-125 assessment:
  - Even-numbered cycles only.
  - May be performed at any time within the 7 days prior to completion of every even-numbered cycle, before administration of the next cycle of BAL101553.
  - In Phase 1, from Cycle 6 onwards, the interval between CT/MRI scans may be extended from 8 weeks to 12 weeks.
- AE monitoring, as described in Section 7.3.2.

5.2.17 End-of-Study visit

End-of-Study assessments are to be performed in patients who no longer receive BAL101553 treatment, and should take place within 7 days after the decision to discontinue treatment.

Assessments must be performed in accordance with Table 5 (Phase 1) and Table 6 (Phase 2a).

The following assessments and procedures are to be performed at the End-of-Study visit:

- Concomitant medications/treatments, as described in Section 5.4.1.
- Physical examination, as described in Section 5.4.2.3.
- Complete vital signs, as described in Section 5.4.2.4.
- BP measurements, as described in Section 5.4.2.5.
- Triplicate 12-lead ECGs, according to Section 5.4.2.6.
- Transthoracic echocardiography, as described in Section 5.4.2.7.
- Laboratory safety tests (hematology, biochemistry, coagulation, cardiac troponin and urinalysis), as described in Section 5.4.2.8.
- Women of child-bearing potential must have a negative serum pregnancy test (hCG), as described in Section 5.4.2.8.6 (see also Section 7.3).
- ECOG performance status, as described in 5.4.2.1.

- Tumor assessment by radiological exam (CT/MRI scans), and CA-125 assessment, if this has not been performed within the 28 days prior to this visit, as described in Section 5.4.3.1.
- Blood samples for PK analysis, as described in Section 5.4.4.
- AE monitoring, as described in Section 7.3.2.

5.2.18 Follow-up contact

All AEs must be followed up until they have returned to baseline status or have stabilized, until 28 days after the last study-drug administration, or as described in Sections 7.3.2.1.2 and 7.4.2. Patients must also be contacted to record antineoplastic therapies received after discontinuation of study drug. Any AEs that occur in, and all cancer medications/therapies given to, a patient up to 28 days after the last dose of study drug must be recorded in the CRF.

In addition, patients with GBM and patients with ovarian cancer (in the Phase 2a portion of the study) who did not have disease progression at the end of the 28-day safety follow-up period, and/or their treating physicians, will be contacted 4 months and 6 months after the date of first study-drug administration for the purpose of assessing progression-free survival (see Section 8.2.2.7).

Follow-up information can be obtained during an in-clinic visit, or by telephone if no physical assessments are required.

5.3 Study assessments for patients undergoing dose escalation or dose reduction

5.3.1 Phase 1

Intra-patient dose increases or reductions are permitted, in accordance with Section 3.2.3.

Dose increases, including multiple dose increases, may only occur after a patient has completed two full cycles without experiencing significant drug-related toxicities and only at the start of a subsequent cycle (i.e., Day 1 of the next treatment cycle).

For each patient, a maximum of two dose reductions by one dose level each will be allowed.

For the first cycle at each new dose level, assessments should be performed as described for Cycle 1 (see Table 5), all subsequent cycles should follow the Cycle 3 onwards schedule, with the following exceptions:

- Triplicate 12-lead ECGs, according to Section 5.4.2.6:
  - Day 1 and Day 8 of the first two cycles at each new dose level: pre-dose, 1 hour and 48 hours after the start of study-drug infusion.
- Blood sample collection for CTC analysis will follow the Cycle 1 and Cycle 2 schedules, as described in Section 5.4.5.1:
  - During the first cycle at each new dose level: pre-dose on Day 1, Day 15 and Day 22.
  - During the second cycle at each new dose level: pre-dose on Day 22.

5.3.2 Phase 2a

In addition to the assessments described in Table 6, the following will be performed for patients who dose reduce:

- PK sample collection:
  - Day 1 and Day 8 of the first cycle at each new dose level: pre-dose and at end of infusion (see Table 6).

5.4 Study assessments and procedures

5.4.1 Medical history, prior and concomitant medications

5.4.1.1 *Medical history*

A full medical history, including relevant abnormalities, surgeries, diseases, or disorders, must be obtained at Screening.

Medical history also includes any relevant change in, or worsening of, a patient's condition which occurs after consent, but prior to the start of first study-drug administration (see Section 7.3.1).

All non-antineoplastic medications taken within the 30 days up to and including the Screening visit must be documented for each patient in the CRF Any medications or significant non-drug therapies (including herbal medicines) that are taken by or administered to the patient during the course of the study (until the End-of-Study visit) must be recorded in the CRF including the dosage, frequency of administration, route of administration, therapeutic indication, and start/stop dates of use.

All prior anti-cancer treatments, including cancer surgeries, radiation therapy and chemotherapy/ medications since the diagnosis of cancer must be assessed during screening and documented for each patient in the CRF.

Available results of BRCA1/BRCA2 mutation status in patients with ovarian cancer and IDH mutation status in GBM patients will also be collected.

5.4.1.2 *Concomitant medications not permitted during the study*

In general, the use of concomitant medications or treatments considered necessary for appropriate patient care is permitted during the study with the following exceptions:

- Other investigational therapies must not be used while the patient is included in the study.
- Anticancer therapy (including cancer surgery, chemotherapy, biological [e.g. antibody-based], or radiation therapy) other than BAL101553 must not be given while the patient is included in the study. After completion of Cycle 1, single-fraction palliative radiotherapy is permitted if the respective tumor lesion is not the only index lesion, and if criteria of disease progression are not met.
- If other anticancer therapy is required for a patient then this patient must be discontinued from the study.
- Coumarin derivates (including warfarin potassium, phenprocoumon or acenocoumarol) are not permitted. Other anticoagulant treatments (including heparin,

low-molecular weight heparin, direct thrombin/factor Xa inhibitors, aspirin, or other oral platelet inhibitors such as clopidogrel) **are** allowed.

- New medications should be avoided on the days of full PK sampling, if medically feasible.

5.4.1.3 *Precautions for concomitant medications metabolized by CYP2C9*

In vitro studies suggested a potential for interactions in drug metabolism between BAL27862, the active component of BAL101553, and concomitant use of drugs metabolized by CYP2C9 (and to a lesser extent with CYP3A4 and CYP2C19).

Patients using concomitant medications known to interfere with CYP2C9 will not be excluded from the study. However, these patients must be carefully monitored for toxicity due to concomitant medications.

For phenytoin, due to its narrow therapeutic window, monitoring of plasma levels is recommended. Patients receiving warfarin potassium or other coumarin derivates are excluded from enrollment.

A list of known medications that are metabolized substrates, inhibitors, and inducers of CYP2C9 can be accessed at: http://medicine.iupui.edu/clinpharm/ddis/main-table/.

5.4.1.4 *Permitted use of prophylactic/supportive concomitant treatments*

5.4.1.4.1 Anti-emetic treatment

Prophylactic anti-emetic treatment is not primarily recommended. However, once a patient has experienced ≥ CTCAE grade 1 nausea or vomiting this patient may then receive prophylactic anti-emetic therapy at the discretion of the Investigator. Patients taking antiemetic treatment prior to the study may continue their treatment at the discretion of the Investigator.

5.4.1.4.2 Antidiarrheal treatment

The use of antidiarrheal treatment should be commenced at the first sign of abdominal cramping, loose stools or overt diarrhea. Diagnosis and appropriate management of diarrhea is mandatory.

5.4.1.4.3 Hematopoietic growth factors

Prophylactic treatment with granulocyte colony stimulating factor (G-CSF), or granulocyte-macrophage colony stimulating factor (GM-CSF), i.e., their use with the intention of supporting the dose density and/or intensity of BAL101553 treatment, is not recommended, and is not permitted during Cycle 1. However, patients who develop dose-limiting neutropenia (e.g., febrile neutropenia, prolonged grade 4 neutropenia) may be treated with G-CSF after Cycle 1 at the discretion of the Investigator, in accordance with applicable guidelines and the respective prescribing information.

5.4.1.4.4 Bisphosphonates

Bisphosphonates may be continued or initiated at the discretion of the Investigator. A dental examination and appropriate preventive dental care should be available or should be performed, and renal function should be carefully monitored.

5.4.1.4.5 Blood-pressure elevations

BAL101553 has been associated with asymptomatic BP elevations that appear to be transient. General recommendations on the clinical management of BP elevations are summarized below (see also 5.4.2.5).

The general applicable BP criteria to initiate treatment are as follows:

- Blood pressure should be recorded at Screening. Patients with resting BPs consistently above 140/90 mmHg should receive anti-hypertensive medication according to applicable guidelines. A patient should not be enrolled into the study until BP is consistently controlled to <140/90 mmHg.
- SBP ≥ 180 mmHg and/or DBP ≥ 110 mmHg (asymptomatic): treatment with antihypertensive medication should be administered ("mandatory") unless another treatment course is warranted by the clinical situation. The recommended treatment is oral labetalol 100 mg (50 mg in patients over 80 years of age or <50 kg). If this is contraindicated or the patient is already taking a beta-blocker, oral captopril 12.5 mg (6.25 mg in patients over 80 years of age or <50 kg) may be given. If this is contraindicated or the patient is already taking an ACE-inhibitor or adrenoreceptor blocker (ARB), oral clonidine 50 µg may be given. If this is contraindicated, specialist advice should be sought.
- Patients who experienced BP elevations of SBP ≥ 180 mmHg or DBP ≥ 110 mmHg during one or more previous BAL101553 administrations should be managed by pre-treatment with amlodipine 5 mg daily starting the night before BAL101553 infusion. Additional medication may be given as indicated above.
- Patients who experience BP elevations requiring additional medication despite pre-treatment with amlodipine 5 mg, should receive amlodipine 10 mg the night before BAL101553 infusion.

5.4.1.4.6 Implantable central venous access system

Patients who do not already have an implantable venous access system ('PORT') will undergo (ambulatory) surgery to have one inserted, according to the hospital's guidelines. Patients will receive subsequent training by a qualified nursing team on the use and proper handling of the PORT.

Implantation should be done at least 3 days prior to BAL101553 administration.

Study-approved devices include:

- Baxter pump model 2C4711K, or
- Baxter pump model 2C1009KP/2C4009K.

If a patient receives a PORT as part of the study, this will be recorded in the eCRF as part of the patient's medical history. Any insertion-related medications administered to the patient (e.g. anesthesia, analgesics, or antibiotics) will be captured in the concomitant medications page of the eCRF. Any serious adverse events (SAEs) that occur due to the insertion will be captured on the SAE form as a study procedure-related SAE.

Patients with an existing PORT will be eligible for the study if the PORT chamber is made of titanium and the cathether is either made of silicon or polyurethane. If a patient

has an exisiting PORT made of any other material, their eligibility may be approved by the Sponsor, based on the availability of compatibility data.

5.4.2 Safety assessments

The Investigator will evaluate patient safety by monitoring and recording all AEs and SAEs; regular monitoring of hematology, biochemistry, cardiac troponin, coagulation profile, urinalysis, pregnancy testing in women of childbearing potential, ECG, vital signs, ECOG performance status, physical examination, transthoracic echocardiography, chest X-ray/CT; and by evaluation of concomitant medications (see Table 5 [Phase 1] and Table 6 [Phase 2a]Table 5).

Safety assessments must be performed at intervals indicated in the schedule of assessments (see Table 5 [Phase 1] and Table 6 [Phase 2a]Table 5). More frequent assessments may be performed at the Investigator's discretion, if medically indicated.

5.4.2.1 *Eastern Cooperative Oncology Group performance status*

ECOG performance status will be assessed in accordance with Table 5 (Phase 1) and Table 6 (Phase 2a). Assessments must be performed within the 72 hours prior to dosing on Day 1 of each cycle. Table 7 provides the scale to be used for these assessments.

Table 7 ECOG performance status

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

5.4.2.2 *Adverse event monitoring*

Please refer to Section 7.3.2 for details regarding AE collection and management.

5.4.2.3 *Physical examination*

A complete physical examination must be performed in accordance with Table 5 (Phase 1) and Table 6 (Phase 2a).

Physical examination will include examination of general appearance, skin, neck (including thyroid), eyes, nose, throat, cardiovascular system, thorax/lungs, abdomen, lymph nodes, extremities, nervous system and mental status.

The exam must be performed within the 3 days prior to dosing on Day 1 of any cycle. If the Screening exam was performed within the 3 days prior to Day 1 of Cycle 1, it does not need to be repeated at this visit.

Any clinically-significant change in, or worsening of, a patient's condition that occurs after first study-drug administration must be reported as an AE (see Section 7.3.2).

5.4.2.4 *Vital signs*

Vital signs must be performed in accordance with Table 5 (Phase 1) and Table 6 (Phase 2a).

Vital signs include height, body weight, body temperature, respiratory rate and radial pulse rates. Pulse rates must be obtained in the same position throughout a given visit, i.e., either sitting or semi-supine. Recordings are to be made after the patient has been sitting or semi-supine for (at least) 5 min.

A patient's height must be assessed only during the Screening visit.

The body weight measured on Day 1 of each treatment cycle (or within the 3 days prior to Day 1), will be used to calculate the dose (in mg/m^2) to be administered throughout that cycle.

Any clinically-significant change in, or worsening of, a patient's condition that occurs after first study-drug administration must be reported as an AE (see Section 7.3.2).

5.4.2.5 *Blood pressure measurements*

Blood pressure measurements must be performed in accordance with Table 5 (Phase 1) and Table 6 (Phase 2a).

At Screening, pre-dose on every dosing day, at each in-clinic non-dosing Day 22 visit, and at the End-of-Study visit, (sitting or semi-supine) triple BP measurements (i.e., the average of three BP measurements taken at 1–2-min intervals) will be obtained for both arms. The average of the arm with the higher triple BP will be used as the Screening BP. Recordings are to be made after the patient has been sitting or semi-supine for (at least) 5 min.

If an average triple SBP of ≥ 140 mmHg or an average triple DBP of ≥ 90 mmHg is observed at the Screening visit, the patient must have an SBP of < 140 mmHg and a DBP of < 90 mmHg confirmed in two subsequent average triple BP measurements on the same day to continue in the study (see Section 5.4.1.4.5).

A patient's average triple SBP must be < 140 mmHg and DBP < 90 mmHg prior to dosing on Day 1 of Cycles 1 and 2. Pre-dose on Days 8 and 15 of Cycles 1 and 2, and on all dosing days from Cycle 3 onwards, a patient's average triple SBP must be < 160 mmHg and DBP < 100 mmHg to initiate dosing. If on any dosing day a patient's SBP exceeds 180 mmHg, or their DBP exceeds 110 mmHg, then their SBP must be < 140 mmHg and DBP < 90 mmHg prior to any subsequent dosing (see also Section 5.4.1.4.5).

After the start of study-drug infusion, or after oral study-drug intake, single BP measurements will be performed at the timepoints indicated in Table 5 (Phase 1) and Table 6 (Phase 2a) and must be obtained in the same position throughout a given visit, i.e., either sitting or supine. Recordings are to be made after the patient has been sitting or supine for (at least) 5 min.

If post-dose SBP ≥ 160 mmHg or DBP ≥100 mmHg occur, triple BP measurements will taken every 10–15 min until a return to SBP/DBP < 160/90 mmHg. Patients should only be discharged home once BP levels have stabilized to SBP levels < 160 mmHg and DBP levels < 100 mmHg.

5.4.2.6 *Electrocardiograms*

Triplicate 12-lead ECGs must be performed in accordance with Table 5 (Phase 1) and Table 6 (Phase 2a).

In addition to scheduled assessments, triplicate 12-lead ECGs should also be obtained when patients experience SBP > 200 mmHg or DBP > 110 mmHg, or whenever clinical cardiovascular signs or symptoms occur.

In Phase 1 only, patients undergoing intra-patient dose escalation or dose reduction must have triplicate 12-lead ECG performed on Day 1, Day 8 and Day 15 of the first two cycles at each new dose level; from all cycles onwards, ECG will only be obtained on Day 1.

Standard, triplicate, 12-lead ECG must be performed using the pre-programmed device provided by the Sponsor. Measurements should be separated by ~1 min and be taken within a 5 min time window. During PK assessments, ECG recordings must be obtained within 15 min before or after PK blood sampling. ECG must always be recorded after at least 5 min rest and while the patient is in a supine or semi-supine position.

Please refer to the ECG manual for more details.

The pre-programmed ECG device must provide automated QTcF intervals. For an individual patient, significant prolongation of QTcF will be defined as:

1. Increase in the QTcF to > 500 ms, or
2. Increase in the QTcF of > 60 ms compared to the respective baseline.

ECG must be assessed by the Investigator or his/her designee for any abnormalities, including prolongation of QTcF. The ECG printouts are to be signed and dated by the Investigator or his/her designee. Further instruction and training on handling the device and transmitting data will be provided to the study centers prior to study initiation.

Any abnormal on-study ECG must be transmitted to a central ECG laboratory for evaluation (including QTc assessment). Any clinically-significant ECG change from baseline that occurs after first study-drug administration must be reported as an AE (see Section 7.3.2).

5.4.2.6.1 Management of QTc prolongation or other significant ECG abnormalities

If significant QTc prolongation is observed, the patient must be monitored by the Investigator and hourly (triplicate) 12-lead ECG need to be obtained until the QTcF has returned to ≤ 470 ms and to ≤ 30 ms increase from baseline. The clinical context and possible factors contributing to QTc prolongations such as electrolyte abnormalities (potassium, calcium or magnesium), concomitant medications, or other clinical factors such as cardiac ischemia will be carefully assessed and any findings documented in the CRF. In addition, a blood sample for determination of BAL101553 concentration must be collected.

Once QTc prolongation has resolved, patients may continue treatment at a lower dose with ECG monitoring frequency as described for Cycle 1 (as in Day 1/Cycle 1 if patients continue treatment at a reduced dose within a treatment cycle). If the ECG obtained in the

first cycle after dose reduction are without any QTcF intervals > 500 ms, or increase from baseline > 60 ms, then ECG monitoring in subsequent cycles may follow the normal schedule.

Patients who experience absolute QTcF > 500 ms or QTcF increase from baseline > 60 ms after dose reduction must be discontinued from study.

The clinical management in case of other ECG abnormalities is to be performed at the discretion of the Investigator. Cardiac troponin must be assessed if ECG abnormalities suggestive of cardiac ischemia are observed.

All significant QTc prolongations or other relevant ECG abnormalities, must be transmitted to the central ECG reading laboratory for evaluation and confirmation.

5.4.2.7 *Transthoracic echocardiography*

A transthoracic echocardiograph must be performed at Screening and at the End-of-Study visit to assess the left ventricular ejection fraction and regional wall motion abnormalities. Additional echocardiography assessments may be repeated at the Investigator's discretion if clinically indicated. Left ventricular ejection fraction must be assessed using the same methodology (M-Mode, 2D [planimetry], 2D [visual] or 3D) at Screening and at the End-of-Study visit, and must be performed by the same person whenever feasible.

5.4.2.8 *Laboratory parameters*

The laboratory safety tests include hematology, biochemistry, cardiac troponin, coagulation and urinalysis as per schedule of assessments (see Table 5 [Phase 1] and Table 6 [Phase 2a]). Additional testing may be performed whenever clinically indicated at the discretion of the Investigator. All samples for a given study center must be analyzed by the same local laboratory throughout the study, as designated by the Investigator. The results are to be printed, signed and dated by the Investigator or his/her designee.

In the event of unexplained abnormal laboratory test values, the tests must be repeated immediately and followed-up until return to the normal range, stabilization, and/or until an adequate explanation of the abnormality has been determined. When a clear explanation is established this must be recorded in the CRF. Abnormal laboratory results should not be recorded as an AE unless the abnormality is associated with a clinically relevant condition (see Section 7.3.2.1 for further details).

Analyses must be performed and reviewed within the 3 days prior to administration of BAL101553 on Day 1 of Cycle 1, and within 1 day prior to study drug administration on any other dosing day.

5.4.2.8.1 Hematology

The schedules for hematology blood samples are described in Table 5 (Phase 1) and Table 6 (Phase 2a). Hematology analyses include hemoglobin, hematocrit, red blood cell count, platelet count, total and differential white blood cell count (neutrophil including bands, lymphocyte, monocyte, eosinophil, basophil counts).

Analyses must be performed and reviewed within the 3 days prior to administration of BAL101553 on Day 1 of Cycle 1, and within 1 day prior to study drug administration on any other dosing day.

General guidance regarding dose modifications for toxicities related to hematological laboratory assessments is provided in Table 4 (Section 3.2.3.2).

5.4.2.8.2 Biochemistry

The schedules for biochemistry blood samples are described in Table 5 (Phase 1) and Table 6 (Phase 2a). Biochemistry must be performed according to the same schedule as Hematology (see Section 5.4.2.8.1).

Biochemistry analyses include serum creatinine, blood urea nitrogen, uric acid, sodium, potassium, chloride, calcium, inorganic phosphorus, glucose, albumin, total protein, AST, ALT, total bilirubin, alkaline phosphatase, lipase, lactate dehydrogenase, and creatine phosphokinase.

Analyses must be performed and reviewed within the 3 days prior to administration of BAL101553 on Day 1 of Cycle 1, and within 1 day prior to study drug administration on any other dosing day.

General guidance regarding dose modifications for toxicities related to biochemical laboratory assessments is provided in Table 4 (Section 3.2.3.2).

5.4.2.8.3 Cardiac troponin

The schedules for cardiac troponin blood samples are described in Table 5 (Phase 1) and Table 6 (Phase 2a). The use of either cardiac troponin-I or troponin-T is permitted; however, the same troponin test must be used consistently for a given patient at Screening and throughout the study.

Analyses must be performed and reviewed within the 3 days prior to administration of BAL101553 on Day 1 of Cycle 1, and within 1 day prior to study drug administration on any other dosing day.

5.4.2.8.4 Coagulation

The schedules for coagulation blood samples are described in Table 5 (Phase 1) and Table 6 (Phase 2a). Coagulation analyses include International Normalized Ratio for reporting prothrombin time and Activated Partial Thromboplastin Time.

Analyses must be performed and reviewed within the 3 days prior to administration of BAL101553 on Day 1 of Cycle 1, and within 1 day prior to study drug administration on Day 1 of all subsequent cycles.

5.4.2.8.5 Urinalysis

The schedules for urinalyses are described in Table 5 (Phase 1) and Table 6 (Phase 2a). Urinalysis includes gross and microscopic exam. Dipstick analysis includes specific gravity, glucose, protein, and blood. Microscopic analysis includes white blood cells, red blood cells, and any additional findings (such as casts).

Analyses must be performed and reviewed within the 3 days prior to administration of BAL101553 on Day 1 of Cycle 1, and within 1 day prior to study drug administration on Day 1 of all subsequent cycles.

5.4.2.8.6 Pregnancy testing

Women of child-bearing potential (i.e., who are not surgically sterile or < 12 months of amenorrhea post-menopause) must have a negative serum pregnancy (hCG) test during Screening, and a negative serum or urine pregnancy (hCG) test prior to BAL101553 dosing on Day 1 of every cycle and at the End-of-Study visit.

Analyses must be performed and reviewed within the 3 days prior to administration of BAL101553 on Day 1 of Cycle 1, and within 1 day prior to study drug administration on any other dosing day.

5.4.2.8.7 Anticipated blood sample volumes

In addition to laboratory safety assessments of hematology, biochemistry, cardiac troponin, coagulation and pregnancy status, blood must also be obtained for PK measurements and for biomarker assessments.

Phase 1

The anticipated volume of blood for laboratory assessments will be ~20 mL for the Screening investigation (safety laboratory).

The maximum anticipated volume of blood for the 28-day treatment in Cycle 1 (including complete biomarker assessment and pregnancy testing) is ~124 mL (54 mL for safety laboratory, 36 mL for PK assessments, and 34 mL for biomarker assessments). For Cycle 2, the maximum anticipated volume of blood for the 28-day treatment cycle is 110 mL (54 mL for safety laboratory, 46 mL for PK assessments and 10 mL for biomarker assessments). For all subsequent 28-day cycles, the anticipated volume of blood for each treatment cycle is 48 mL (safety laboratory).

The anticipated volume of blood for laboratory assessments will be 22 mL for the End-of-Study visit (20 mL for safety laboratory and 2 mL for PK assessment).

Phase 2a

The anticipated volume of blood for laboratory assessments will be ~20 mL for the Screening investigation (safety laboratory).

The maximum anticipated volume of blood for the 28-day treatment in Cycle 1 (including complete biomarker assessment and pregnancy testing) for ovarian/GBM patients is ~108/78 mL (56 mL for safety laboratory, 18 mL for PK assessments, and 34/4 mL for biomarker assessments). For Cycle 2, the maximum anticipated volume of blood for the 28-day treatment cycle ovarian/GBM patients is 72/62 mL (54 mL for safety laboratory, 8 mL for PK assessments, and 10/0 mL for biomarker assessments). For all subsequent 28-day cycles, the anticipated volume of blood for each treatment cycle is 48 mL (safety laboratory).

The anticipated volume of blood for laboratory assessments will be 22 mL for the End-of-Study visit (20 mL for safety laboratory and 2 mL for PK assessment).

5.4.3 Efficacy assessments

5.4.3.1 *Assessment according to RECIST v1.1 or RANO criteria*

At Screening, patients (excluding those with GBM) must have measurable disease, evaluated using the methods and criteria according to RECIST guidelines, version 1.1 (Appendix 1). Patients with GBM must have measurable disease defined by contrast-enhancing MRI; evaluation of disease progression and response will be assessed based on the RANO criteria (Appendix 2).

All radiological tests that demonstrated tumor at baseline (i.e., at Screening, or within the 28 days [solid-tumor patients excluding GBM patients] or 21 days [GBM patients] prior to first study-drug administration), must be repeated within 7 days of completion of every even-numbered cycle (e.g., end of Cycle 2, 4, 6, etc.), prior to the next administration of BAL101553, in order to determine whether treatment should be continued. In Phase 1, from Cycle 6 onwards, the interval between CT/MRI scans may be extended from 8 weeks to 12 weeks. Each lesion measured at baseline is to be measured throughout the study by the same method of assessment and the same technique (e.g., consistent use of CT with same anatomic coverage, contrast administration [unless medically contraindicated], slice thickness, and reconstruction interval at all time points) in order to allow for consistent assessments and comparisons.

To determine complete response or partial response the required criteria must be present for at least 4 weeks.

Patients with objective response or stable disease will be permitted to continue to receive additional cycles of BAL101553 until disease progression or unacceptable toxicity. No patients are permitted to start subsequent cycles if progression is observed.

At study treatment completion (End-of-Study visit), radiology efficacy assessments must be repeated if these have not been performed within 28 days prior to this day.

5.4.3.2 *Clinical progression*

Patients who do not meet the criteria for progressive disease as described in Section 5.4.3.1, but who exhibit signs and symptoms of clinical progression of their cancer, will be considered for study purposes to have progressive disease.

5.4.3.3 *CA-125*

In Phase 2a, the CA-125 tumor marker will be monitored in ovarian cancer patients. The schedule for CA-125 blood samples is described in Table 6.

CA-125 will be used as supplementary information for efficacy assessments.

5.4.4 Pharmacokinetic assessments

The schedules for PK blood samples are described in Table 5 (Phase 1) and Table 6 (Phase 2a).

The following PK parameters will be determined for BAL101553 (if applicable), and for BAL27862: C_{max}, T_{max}, $AUC_{0-\tau}$, AUC_{0-last}, $AUC_{0-\infty}$, $t_{½}$, systemic clearance and volume of distribution. In addition, PK samples may be used to investigate, identify or quantify metabolites of BAL101553/BAL27862.

Detailed instructions and procedures for collecting and handling samples for PK analysis are provided in the 'BAL101553 Pharmacokinetics Manual' at the site. All samples for PK analysis will be shipped to and analyzed by [redacted]:

Contact Information:

[redacted]

If needed, the PK sampling schedule may be amended based on observed PK in humans, however, no more than 12 PK samples will be obtained in order to establish a plasma concentration-time profile at Day 1 of Cycles 1 and 2.

In the dose-escalation portion (Phase 1) of the study, concentration-over-time profiles will be obtained on Day 1 of Cycles 1 and 2 (48-hour continuous IV infusion) and on Day 21 of Cycle 2 (oral BAL101553 administration), according to Table 5. For patients undergoing intra-patient dose escalation or dose reduction, blood PK samples will be collected during one cycle at each new dose level for a given patient, according to the schedule for Cycle 1 in Table 5.

In the dose expansion portion (Phase 2a) of the study, a concentration-over-time profile will be obtained on Day 1 of Cycle 1, according to Table 6. For patients undergoing intra-patient dose reduction, blood PK samples will be collected pre-dose and at the end of infusion on Days 1 and 8 of the first cycle at each new dose level (see Section 5.3.2).

Based on the experience from the completed Phase 1 study CDI-CS-001, in which BAL101553 was administered as 2-hour infusions, urinary excretion of BAL101553/ BAL27862 is negligible. Therefore, no urinary excretion of BAL101553/BAL27862 will be measured in this study.

5.4.5 Biomarker assessments

The schedules for biomarker sample collection are described in Table 5 (Phase 1) and Table 6 (Phase 2a).

Samples for biomarker assessments will be analyzed by the Sponsor or in specialized laboratories. The collection, storage, and shipping of CTCs and of other biomarker blood or tumor samples will be performed as described in the 'BAL101553 Pharmacodynamics Manual' provided to the study centers prior to study initiation.

Exceptions to the schedule of Biomarker assessments can be made according to the Sponsor's discretion.

If available during the normal course of medical management, cells from malignant pleurocentesis or paracentesis fluid may also be analyzed for biomarkers.

5.4.5.1 *Collection of blood for the assessment of circulating cells and dried-blood-spot analysis*

5.4.5.1.1 CTCs

For each CTC analysis timepoint, one 10 mL blood sample should be obtained in EDTA tubes.

The assessment of CTCs will be performed at least two study centers, with the goal to obtain samples from at least 50% of patients in Phase 1 and 50% of ovarian-cancer patients in Phase 2a. Patients will have blood samples collected for the isolation, enumeration and biomarker staining of CTCs.

For patients undergoing intra-patient dose escalation or dose reduction in Phase 1, samples for CTCs will be obtained at each new dose level, using the same schedules as detailed in Table 5.

These samples will be shipped to and analyzed by [redacted]:

Contact Information:

[redacted]

5.4.5.1.2 Dried-blood-spot

Prior to first study-drug administration on Day 1 of Cycle 1, one blood sample (~4 mL) will be collected in an EDTA tube and distributed onto Centogene filtercards for dried-blood-spot analysis of single nucleotide polymorphisms, genes involved in drug transport or drug metabolism, and/or potential biomarkers.

Dried-blood-spot analyses will not be mandatory, and a separate Biomarker Consent will be obtained from each patient for dried-blood-spot analysis on Centogene Filtercards. Sample shipment and analysis organized by, the Sponsor:

Contact Information:

[redacted]

5.4.5.2 *Collection of tumor biopsies*

Tumor biopsies will be obtained from patients (excluding those with GBM) if easily accessible and deemed safe for the patient by the Investigator, and if patients are willing to undergo biopsy. These samples will be shipped to, and the analysis organized by, the Sponsor:

Contact Information:

Tumor biopsies will be performed during Screening. If a tumor biopsy is done on the same day, blood collection for blood biomarkers should be obtained prior to the tumor biopsy. If possible, additional biopsies can be obtained on Day 22 of Cycle 1 and/or Cycle 2; on Day 22 of one subsequent cycle after Cycle 2; or at progressive disease; to assess for example, the tissue characteristics of tumor lesions which display differential treatment response (such as shrinkage in one tumor lesion and growth in another tumor lesion).

Formalin-fixed paraffin-embedded samples must be prepared from the biopsies following standard protocols, as outlined in the 'BAL101553 Pharmacodynamics Manual'. Tissue obtained will be used for the analysis of PD biomarkers and biomarkers potentially predictive of tumor response (e.g., proliferation and cell death rates, vascularization and the expression of potential stratification biomarkers).

5.4.5.3 *Archival tumor blocks (collected from all patients when available)*

Archival tumor blocks which have been appropriately prepared and conserved, or unstained slides, will be used for the analysis of biomarkers potentially predictive of tumor response (e.g., baseline proliferation and cell death rates, vascularization and the expression of potential stratification biomarkers).

6. STUDY DRUG

6.1 Blinding and randomization

The Phase 1 and Phase 2a continuous dosing portions of this study are non-randomized and open-label.

6.2 Packaging and labeling

The study drug must be packed and labeled in accordance with local regulations and the Annex 13 Good Manufacturing Practice rules, including the identity of the Sponsor and Investigator, protocol number, drug identification, storage conditions, content of study drug, and expiry date. Information on drug shipment including temperature logger and acknowledgement of receipt form to be completed by the receiver must also be included.

The Sponsor must ensure that the study drug and certificates of release are available before the start of the study and at all times during the study.

6.3 Shipping and storage conditions

All vials of BAL101553 for IV administration must be shipped to the study centers and stored at temperatures of no more than -15 °C. All capsules of BAL101553 for oral administration must be shipped to the study centers and stored at temperatures between 2–8 °C.

All study drug must be kept under secure conditions, e.g., in the hospital pharmacy. Further information on the handling and stability of study drug will be provided in the 'BAL101553 Study Drug Administration Manual'.

6.4 Presentation of study drug

Any unused study drug will be kept at the study center for performance of drug accountability and for assessment of compliance (see Section 6.6).

6.4.1 BAL101553 for intravenous administration

BAL101553 for IV administration will be presented in vials containing 151.9 mg BAL101553 as powder for concentrate for solution for infusion. Complete and continuous daylight protection is mandatory during the handling, storage, transportation, and infusion of BAL101553 solutions. The following information applies to storage and handling of study-drug solutions prepared at room temperature:

- Each vial is to be reconstituted with 7 mL of sterile Ringer Lactate. The reconstituted solution, after careful visual inspection for any precipitations, must be used within 1 hour to prepare the infusion solution.
- The reconstituted solution will be further diluted in Ringer Lactate to obtain the scheduled dose. The solution for infusion must be transferred into the pump within 1 hour after dilution; thereafter, the infusion must start within 24 hours and will continue for up to an additional 72 hours.
- Solutions must not be frozen at any time.

Note: Glucose-containing solutions must not be used.

Two Baxter elastomeric pump models are approved for use:

1. 2C4711K (120 mL pump) – setup can be used for infusion solutions within the concentration range of 0.19–4.17 mg/mL (22.5 – 500 mg BAL101553)
2. 2C1009KP/2C4009K (250 mL pump) – setup can be used for infusion solutions within the concentration range of 0.15–2.00 mg/mL (37.5–500 mg BAL101553)

6.4.2 BAL101553 for oral administration

BAL101553 for oral administration will be presented as hard capsules, each containing 1 mg or 5 mg of study drug. The capsules also contain mannitol and magnesium stearate as excipients. The capsule shell is a white, opaque hydroxypropyl methylcellulose (HPMC) capsule, size 4.

6.5 Administration of study drug

Patients who do not have a PORT will undergo (ambulatory) surgery and will receive subsequent training by a qualified nursing team on the use and proper handling of the venous access system.

Intravenous administration

BAL101553 will be administered as a 48-hour IV infusion on Day 1, Day 8 and Day 15 of each cycle, with the exception of Days 15–21 of Cycle 2 in Phase 1 (see below), via the PORT using an elastomeric pump (Baxter pump models 2C4711K or

2C1009KP/2C4009K). Intravenous medication may only be administered by trained and qualified healthcare professionals in an appropriately supervised healthcare institution setting.

On Day 1 of Cycle 1, and on Day 1 of Cycle 2 (Phase 1 only), patients may be hospitalized for up to 72 hours for serial PK sampling and safety monitoring. Patients in Phase 1 can be discharged after the 30-hour PK sample. In Phase 2a, patients can be discharged after the 4-hour PK sample, but must return for the 24–30 hour PK sample. On all other intravenous BAL101553 dosing days, all patients must stay in the study center for at least 1 hour after the start of the BAL101553 infusion. Patients must always return to the study center at least 2 hours before the end of the 48-hour infusion.

Prolonged intravenous administration

If the infusion pump is not empty after 48 hours, the infusion may be prolonged by up to 24 hours, particularly if the patient would otherwise receive less than 80% of the assigned dose for the visit in Cycle 1. In this event, the patient must return to the study center at least 1 hour before the predicted end of the infusion based on the pump weight at the end of the 48 hours. All assessments planned to take place 48 hours after the start of the infusion should be performed at the time of the actual end of the prolonged infusion. Assessments planned thereafter should also be shifted accordingly.

Oral administration

Patients in Phase 1 will receive daily oral BAL101553 on Days 15–21 of Cycle 2 (i.e., for 1 week). During the oral administration portion of Cycle 2, BAL101553 capsules are to be taken in the fasted state before breakfast each morning, with 250 mL of still water, for 7 days. Patients must fast ≥ 4 h prior to and ≥ 1 h after dosing, but may eat normally outside of these times. Water is allowed at all times during all parts of the study. On Day 15 of Cycle 2, patients must stay in the study center for at least 6 hours after oral study-drug intake for safety monitoring. Starting on study Day 21, patients will be hospitalized for serial PK sampling for up to 48 hours post-study-drug administration.

Further details on dosage schedule and dose escalations/modifications are outlined in Section 3.2.1. Details on study drug administration are described in in the ‘BAL101553 Study Drug Administration Manual’ at the sites.

The Sponsor must be notified at least 24 hours before, and within the 24 hours after, administration of the first dose (Cycle 1 Day 1) to any patient, and within 24 hours after any dose of study drug associated with drug administration errors.

6.6 Compliance and drug supply accountability

6.6.1 Compliance

The Investigator or designee is responsible for drug accountability, reconciliation and record maintenance for used and unused study drug. The drug accountability records must be kept current and must be available for monitoring by the clinical research associate (CRA). The logs and all other forms or documents relating to overall drug accountability must be collected from study center by the CRA.

The Investigator or designee is responsible for maintaining the required infusion duration and intervals, to record start and stop times of the infusions, infusion interruption (if they occur), and the remaining volumes in the infusion pumps.

All oral dosing on PK sampling days must take place in the clinical study center. Compliance will be assessed by review of patient drug diaries and returned capsule counts.

Study drug must not be used after the retest date unless its release date has been extended based on updated information from ongoing stability studies.

Study drug must not be used for any purpose other than the study.

Further details on drug accountability will be provided to the study centers prior to study initiation.

6.6.1.1 *Phase 1*

Patients should receive the correct dose as described in Section 6.5.

Patients who received less than 80% of the assigned dose at any visit during Cycle 1, e.g. due to a protocol recommended dose reduction following an AE or due to an administration error, will only be considered as valid for the MTD-determining population if these patients experience a subsequent DLT during Cycle 1 (see Sections 4.5.1 and 8.2.1.4).

Patients who received more than 125% of the assigned dose at any visit during Cycle 1, e.g., due to an administration error, will only be included in the MTD-determining population if they did not experience subsequent DLTs during Cycle 1.

6.6.1.2 *Phase 2a*

Patients should receive the correct dose (70 mg/m^2) as described in Section 6.5 and in the 'BAL101553 Study Drug Administration Manual'.

6.6.2 Drug supply

A Drug Dispensing Log must be kept current and must contain the following information:

- Shipments received;
- Date(s), quantity and batch number of the drug administered/dispensed to the patient;
- Identification of the patient to whom the drug was administered/dispensed;
- Date(s), quantity and batch number of the drug returned to the site (oral capsules only);
- Principal Investigator name; and
- Quantity of the drug remaining.

6.6.3 Drug disposal

The Investigator (or designee) must maintain records of destruction. These records must show the identification and quantity of each study drug disposal, the method of

destruction (taking into account the requirements of local law), and the person who disposed of the study drug.

If study drug cannot be destroyed at the study center, off-site destruction will be organized by the CRA.

Study drug disposal is further addressed in the 'BAL101553 Study Drug Administration Manual (CDI-CS-003)'.

7. SAFETY

7.1 Definitions

7.1.1 Adverse occurrence

An adverse occurrence is any untoward medical occurrence taking place after informed consent and before first study-drug administration.

7.1.2 Adverse event

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

7.1.2.1 *Treatment-emergent adverse event*

A treatment-emergent adverse event is any AE which occurs from the start of first dosing up to and including the last scheduled follow-up (28 days after last study-drug administration).

7.1.3 Serious adverse event

A serious adverse event (SAE) is any AE that meets one or more of the following criteria:

- results in death
- is life-threatening
- requires inpatient hospitalization or prolongation of existing hospitalization
- results in persistent or significant disability/incapacity
- is a congenital anomaly/birth defect

Medical and scientific judgment should be exercised in deciding whether expedited reporting to the Sponsor is appropriate, 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 intervention to prevent one of the outcomes listed in the definitions above. These situations should also usually be considered serious.

Examples of such events include intensive treatment in an emergency room or at home for allergic bronchospasm, blood dyscrasias or convulsions that do not result in hospitalization, and development of drug dependency or drug abuse.

It should be noted that:

- Death is considered an outcome of an AE. Whenever possible the underlying cause of death must be reported as the AE.

- A life-threatening SAE is any adverse experience that places the patient at risk of death at the time of its occurrence, i.e., it does not include a reaction that, had it occurred in a more severe form, might have caused death.
- Inpatient hospitalization is defined as any inpatient admission, even if for less than 24 hours. For chronic or long-term inpatients, inpatient admission also includes transfer within the hospital to an acute/intensive care inpatient unit (e.g., from a medical floor to the coronary care unit, or from the neurological floor to the tuberculosis unit).

  The following hospitalizations, whether planned before or during the study, should not be considered SAEs:

  - Routine treatment or monitoring of the studied indication, not associated with any deterioration in condition (e.g., hospitalizations related to study procedures, such as study-drug administration, PK assessments, etc.).
  - Elective or pre-planned treatment for a pre-existing condition that is unrelated to the disease under study and has not worsened.
  - Admission to a hospital or other institution for general care, not associated with any deterioration in condition.
  - Treatment on an emergency outpatient basis for an event which does not meet any of the above definitions of 'serious', and does not result in hospital admission.

7.1.3.1 *Suspected unexpected serious adverse reaction*

A suspected unexpected serious adverse reaction (SUSAR) is any SAE considered to be related to the study treatment and for which the nature or severity is not consistent with the applicable reference safety information (i.e., regardless of whether the nature or severity of an SAE has been previously observed/documented).

Note: Expectedness of SAEs will be assessed by the Sponsor against the applicable reference safety information.

7.2 Evaluation of adverse events

7.2.1 Severity

The severity of AEs will be assessed according to the National Cancer Institute Common Terminology Criteria for Adverse Events version 4.03 (CTCAE).

Details of the CTCAE can be found at the following URL:

http://evs.nci.nih.gov/ftp1/CTCAE/CTCAE_4.03_2010-06-14_QuickReference_5x7.pdf

If CTCAE grading does not exist for an AE, one of the following severity grades will be assigned:

- mild: discomfort but no disruption of normal daily activity
- moderate: discomfort sufficient to reduce or affect daily activity
- severe: inability to work or to perform normal daily activities

7.2.2 Relationship

The relationship of AEs to the study treatment must be assessed by the Investigator as one of the following:

- not related
- unlikely
- possible
- probable

Appendix 3 provides criteria for relationship assessments.

According to the Sponsor's criteria for causality assessment, a causal relationship will be suspected for all AEs reported with a relationship of 'possible' or 'probable' and those with missing or unknown relationships.

7.3 Handling of safety information and collection periods

7.3.1 Handling of safety data during the pre-treatment period

Adverse occurrences (Section 7.1.1) will be recorded in the CRF as pre-dose medical history (see Section 5.4.1.1).

If a change in, or worsening of, a patient's condition is considered to be serious (i.e., meets one or more of the criteria for an SAE in Section 7.1.3), this information must also be reported to the Sponsor's safety representative, using the same forms and procedures as for an SAE (see Section 7.3.2.2).

7.3.2 Handling of safety data during the treatment period and up to the last scheduled follow-up

From the start of first dosing, up to and including the last scheduled follow-up (28 days after last study-drug administration), any change in, or worsening of, the patient's condition must be collected and reported in the CRF as an AE (see Section 7.3.2.1). In addition, SAEs must be recorded and reported using SAE report forms (see Section 7.3.2.2).

7.3.2.1 *Adverse event management*

The Investigator or the physician in attendance should administer therapy as clinically indicated for any AE/SAE that occurs.

7.3.2.1.1 Data collection

All AEs directly observed (physical examination, laboratory test or other assessments), mentioned by the patient, or reported by the patient upon non-directive questioning, must be recorded on the AE pages of the CRF.

All AEs must be recorded in the English language in the CRF and should include the following information:

1. Term. If possible, a diagnosis should be documented rather than signs and symptoms, using self-explanatory and concise medical terminology.

   Note: Use of the AE term 'disease progression', 'lack of efficacy', or equivalent terms, should be avoided. Instead, a diagnosis, signs, or symptoms should be used to describe the worsening of the disease under study.
2. Duration (start and end dates).
3. Toxicity grade (CTCAE grade 1–4), or severity grade (three-point scale, see Section 7.2.1).
4. Relationship to study treatment (see Section 7.2.2 and Appendix 3).
5. Action(s) taken with regards to the study treatment or additional treatments given for the event.
6. Whether the event is an SAE (see Section 7.1.3).
7. Outcome.

Abnormal laboratory results should not be recorded as an AE unless the abnormal result meets one or more of the following criteria:

- induces clinical signs or symptoms which require therapy or additional diagnostic evaluation
- requires changes in study-drug dosing or discontinuation of study participation
- is considered clinically significant

Signs, symptoms or diagnosis associated with these abnormal results must be recorded on the AEs page of the CRF.

Adverse events must also be reported in the source document with at least the nature of the event, the start and end date, the relationship to the study drug, and the treatment (if applicable).

7.3.2.1.2 Follow-up

Once an AE is detected, it must be proactively followed at each visit (or more frequently if necessary) for any changes in severity, relationship to the study drug, interventions required for treatment, and the event's outcome.

All AEs must be followed up until they have returned to baseline status or have stabilized, or until 28 days after the last study-drug administration.

In addition, an AE which remains unresolved after completion of the study (including the last scheduled follow-up contact) and meets one or more of the criteria listed below, requires detailed evaluation, follow-up and, if necessary, specific medical treatment until the AE is resolved or a reasonable explanation for its persistence is found:

- an AE evaluated as related to the study drug
- an AE that led to a patient withdrawal from the study
- an SAE

These cases will be followed-up on the CRF unless otherwise agreed with the Sponsor.

7.3.2.2 *Serious adverse event recording and reporting*

In addition to being recorded and followed-up as AEs (see Section 7.3.2.1), SAEs must be reported to the Sponsor's safety representative listed below, within 24 hours of awareness of the event.

The Investigator must complete the 'Serious Adverse Event Report Form' in English, and send the completed, signed form by fax or email to:

[redacted]

Such preliminary reports must be followed by detailed anonymized descriptions, which may include copies of hospital case reports, autopsy reports, and other documents if requested and applicable.

The original SAE Report Form and the correspondence to the Sponsor reporting the SAE (fax confirmation sheet/email) must be kept at the study center in the Investigator Site File (ISF).

7.3.3 Handling of post-study safety data

Any AE occurring after the last safety follow-up contact (28 days after last study drug administration), which is considered to be both:

- serious (i.e., meets one or more of the criteria listed for SAEs, see Section 7.1.3); and
- related to the study drug (see Section 7.2.2 and Appendix 3);

should be reported to the Sponsor's designated safety representative using the same forms and procedures as for an SAE (see Section 7.3.2.2).

Events occurring after the last follow-up contact should not be reported in the CRF.

7.3.4 Reporting of SAEs to regulatory authorities

7.3.4.1 *Sponsor's responsibilities*

The Sponsor's safety representative will ensure the reporting of SUSARs and any expeditable SAEs to regulatory Authorities, in accordance with applicable law.

In the event of a SUSAR, the Sponsor will ensure that all Investigators involved in all studies with BAL101553 are informed.

7.3.4.2 *Investigator's responsibilities*

It is the Investigator's responsibility to inform local IECs/IRBs of SUSARs and any other expeditable SAEs, in accordance with applicable law.

7.4 Pregnancy

7.4.1 Contraception for women of childbearing potential

As reproductive and fertility studies have not been performed with BAL101553 in animals, female patients of childbearing potential must not become pregnant while being treated with BAL101553.

The Investigator must make every effort to ensure that neither a clinical study patient, nor the partner of a male clinical study patient, becomes pregnant during the study, or within the 90 days after the last dose of study drug. This should be done and documented as part of the consent process, by explaining clearly to the patient the potential dangers of becoming pregnant/fathering a child, and also providing each patient with information about appropriate medically-approved effective contraception (see below).

Women of childbearing potential (i.e., who are not surgically sterile or < 12 months of amenorrhea post-menopause) must have a negative serum pregnancy test result during Screening. In addition, serum or urine pregnancy tests must be negative within the 3 days prior to Day 1 of each cycle. If the serum pregnancy test performed during Screening was conducted within the 3 days prior to first dosing (Day 1/Cycle1), additional testing is not required for Day 1/Cycle 1.

Women of childbearing potential must agree to use one of the following methods of contraception, to be strictly implemented during the study and for at least 90 days after the end of treatment:

- Male or female sterilization (bilateral tubal occlusion or vasectomy).
- Intrauterine device (IUD).
- Combined (estrogen and progesterone containing) hormonal contraception (oral, vaginal ring or transdermal patch) with an ethinylestradiol dose of at least 30 µg, plus use of male condoms (preferably with spermicides), female condoms, a female diaphragm or a cervical cap.

7.4.2 Reporting and handling of pregnancies

Female patients must inform the Investigator within 24 hours if they have experienced a ruptured condom, or any other concerns about possible reduction of contraceptive effectivity (i.e., forgotten pill or vomiting) during the study. In these cases the patients must return to the study center as soon as possible, but not later than 24 hours after the Investigator is informed.

Female patients must inform the Investigator if they become pregnant during the study or within the 90 days following the last study drug administration. The study drug must be discontinued immediately when a patient becomes pregnant. The patient must be monitored until conclusion of the pregnancy and infants must be followed-up at least for 8 weeks after delivery.

Pregnancy outcomes should be collected, if possible, for the female partners of any males who took the study drug. Consent to collect information regarding these pregnancies and their outcomes must be obtained from the mother.

The Investigator must immediately notify the Sponsor's safety representative about any pregnancy by submitting a Pregnancy Report Form, in accordance with the requirements (timelines and contact details) of an SAE (see Section 7.3.2.2). In addition, pregnancy-related adverse outcomes must also be reported as AEs or SAEs (see Sections 7.3.2.1 and 7.3.2.2). Note that an induced abortion which is not required by an AE does not constitute an SAE.

It is the Investigator's responsibility to notify the local IEC/IRB about any pregnancies resulting in an adverse outcome, in accordance with applicable laws and regulations.

8. STATISTICAL CONSIDERATIONS AND ANALYTICAL PLAN

PK parameters will be derived using Phoenix WinNonLin 6.3 software (Pharsight Corporation a CertaraTM Company, Saint Louis, MO, US). All analyses and data presentations will be generated using SAS® Version 9.3 or higher software (SAS Institute, Cary, North Carolina, USA).

8.1 Study variables

The primary study endpoint is the frequency and characteristics of DLT, or other toxicities which are relevant for determination of the MTD of BAL101553.

Secondary endpoints:

- Overall safety endpoints:
  - Type and frequency of AE, SAEs, laboratory, echocardiogram and ECG abnormalities; abnormalities in vital signs, physical examination results, chest X-ray/CT; frequency and causes of study withdrawals and dose modifications.
- Efficacy endpoints:
  - Best objective response according to RECIST v1.1 (patients with solid tumors, excluding GBM) or RANO criteria (GBM patients), based on the change from baseline in tumor measurements as measured in patients with measurable disease.
  - Progression-free survival.
- Pharmacokinetic assessments (BAL101553 and BAL27862):

  Phase 1
  - C_{max}, T_{max}, $AUC_{0-\tau}$, AUC_{0-last}, $AUC_{0-\infty}$, $t_{½}$, systemic clearance and volume of distribution.
  - Bioavailability of oral BAL101553 (relative bioavailability of BAL27862).

  Phase 2a
  - Tabulated listing of BAL101553 and BAL27862 plasma concentrations.
- Exploratory endpoints:
  - PK samples may be used to investigate and identify metabolites; known metabolites for which standards are available may also be quantified in these samples. These investigations will not be reported in the Clinical Study Report, but will be the subject of (a) separate report(s).
  - Change from baseline in biomarkers (including but not limited to number of CTCs).

8.2 Statistical and analytical methods

8.2.1 Analysis populations

8.2.1.1 *Full analysis population*

The full analysis population (FAP) includes all patients who received at least one partial or complete dose of study drug, based on the intent-to-treat principle. The FAP will be used for analyzing efficacy.

For efficacy analyses, patients will be primarily analyzed according to their originally-assigned dose level. In the case that intra-patient dose escalation or reduction occurs in a substantial number of patients, additional analyses may be produced.

8.2.1.2 *Safety population*

All patients who receive at least one full or partial dose of BAL101553 and had at least one post-baseline safety assessment must be included in the safety analysis population. In this context, documented information that a patient had no AEs constitutes a safety assessment. The safety analysis population must be used for all safety related analyses (AEs, vital signs, laboratory data, etc.).

For safety analyses, patients will be primarily analyzed according to their originally-assigned dose level. In the case that intra-patient dose escalation or reduction occurs in a substantial number of patients, additional analyses may be produced.

8.2.1.3 *Pharmacokinetic analysis population*

The PK analysis set includes all patients who received at least one partial or complete dose of study drug and had at least one post-baseline PK assessment.

8.2.1.4 *Maximum tolerated dose-determining population*

The MTD-determining population includes all Phase 1 patients from the safety set who meet the following minimum criteria during the first 28-day treatment cycle (Cycle 1):

- received at least one partial or complete dose of BAL101553 and has experienced a DLT;
- received all three doses of BAL101553 without experiencing a DLT (including the ability to initiate treatment Cycle 2), have been observed for ≥ 28 days following the first dose, and have been evaluated for safety.

Patients who do not meet these minimum evaluation requirements will be regarded as ineligible for the MTD-determining population. These patients will be included in the full analysis/safety population but will be excluded from the calculation of DLT incidence and will be replaced by recruitment of additional patients.

Patients who received less than 80% of the assigned dose at any visit during Cycle 1, e.g. due to a protocol recommended dose reduction following an AE or due to an administration error, will only be considered as valid for the MDT-determining population if these patients experience a subsequent DLT during Cycle 1. Patients who have received a lower-than-assigned dose and have tolerated BAL101553 without a DLT will be excluded from the MTD-determining population, as the toxicity assessment is not considered to be representative for the originally-assigned dose level.

Patients who received more than 125% of the assigned dose at any visit during Cycle 1, e.g., due to an administration error, will only be considered as valid for the MTD-determining population if these patients experience no subsequent DLT during Cycle 1.

8.2.1.5 *Efficacy-evaluable population*

Seperate EEPs will be defined for the Phase 2a ovarian cancer and GBM target populations.

The efficacy-evaluable populations (EEPs) include all Phase 2a patients:

- with progressive disease who completed at least Cycle 1 dosing (i.e., received study drug on Days 1, 8 and 15) and who underwent at least one on-study clinical tumor assessment, or radiological assessment by RECIST v1.1 guidelines (ovarian cancer patients) or RANO criteria (GBM patients).
- with stable disease, partial response, or complete response, based on a radiological assessment by RECIST v1.1 guidelines (ovarian cancer patients) or RANO criteria (GBM patients) at the end of Cycle 2, who received at least four doses of study drug in the first two cycles.

The EEPs will be the primary populations for analyzing efficacy in Phase 2a. Efficacy will also be analyzed in the FAP population.

Separate analyses will be performed for the ovarian cancer and GBM target populations.

8.2.2 Statistical analyses

Data from all participating study centers will be combined for analysis. The core study report will include patient data until the time point when the last patient has completed at least two cycles of treatment or discontinued the study.

In the case that patients continue to receive study drug past this time (in accordance with the protocol) an extension report will be prepared once these patients have completed the study, or have been discontinued.

8.2.2.1 *Patient demographics and other baseline characteristics*

Background and demographic characteristics of the FAP including age, gender, height, weight, BSA, tumor type, previous anticancer treatments, medical conditions, performance status etc. will be listed individually by patient, and summarized by dose level using descriptive statistics or contingency tables.

8.2.2.2 *Study treatment exposure and compliance*

The actual dose, duration in days and compliance of BAL101553 treatment will be listed by patient and summarized through descriptive statistics by dose level and treatment cycle in the safety population.

8.2.2.3 *Concomitant treatments*

Concomitant medications and significant non-drug therapies in the safety population prior to and after the start of the study drug will be listed by patient and summarized by Anatomical Therapeutic Chemical term and by dose level.

8.2.2.4 *Dose-limiting toxicity, MAD determination and MTD recommendation*

The dose-limiting toxicities in Phase 1 will be listed by patient for each dose level.

The MAD is defined as the dose level at which DLTs are observed during treatment Cycle 1 in ≥ two of [up to] three evaluable patients in the first three patients of a dose level, or ≥ two of [up to] six evaluable patients in a dose level that was expanded to two cohorts, and at which dose escalation is being stopped.

The MTD is defined as the highest dose level below the MAD with an acceptable tolerability profile.

8.2.2.5 *Objective response rate*

The objective response rate will be calculated using the EEPs and the FAP, as the proportion of patients responding (i.e., with a best observed objective response of complete or partial response), based on RECIST v1.1 guidelines for patients with solid tumors (excluding GBM) and RANO criteria for patients with GBM.

The proportion and its exact 95% confidence interval will be presented by dose level and by disease subgroup, if appropriate.

8.2.2.6 *Disease control rate*

The disease control rate will be calculated using the EEPs and the FAP, as the proportion of patients with disease controlled (i.e., complete response, partial response, or stable disease) after two treatment cycles, after four treatment cycles, and at the end of treatment.

The proportion and its exact 95% confidence interval will be presented by dose level and by disease subgroup, if appropriate.

8.2.2.7 *Progression-free survival*

Progression-free survival is defined as the interval between the date of first infusion and the earliest date of objective disease progression according to RECIST v1.1 criteria (excluding GBM patients), RANO criteria (GBM patients), or Investigator-confirmed clinical progression (see Section 5.4.3.2); or death due to any cause in the absence of progression. Surviving patients who have not progressed at the time of study closure will be censored at the timepoint of their latest objective tumor assessment.

Progression-free survival at 6 months is defined as the proportion of patients who have not progressed at the timepoint of 6 months, respectively, after first study-drug administration.

Progression-free survival will be listed for the EEPs and the FAP by patient and dose level and by disease subgroup if appropriate.

8.2.2.8 ***Safety data analysis***

The assessment of safety will be conducted in the safety population and will be primarily based on the frequency of AEs and laboratory abnormalities. Other safety data (e.g., ECG, vital signs, special testing) will be considered as appropriate. Safety data will be presented in individual listings and summary tables. Study-drug dose interruptions and study-drug dose reductions or increases will be presented in individual listings and summary tables.

8.2.2.8.1 Adverse events

AEs and SAEs will be described by body system in individual listings and frequency tables for each dose level and cycle as appropriate.

AEs leading to withdrawal or dose modifications will be presented in individual listings and summary tables.

8.2.2.8.2 Laboratory evaluations

Laboratory values will be converted into SI units and the severity grade determined based on CTCAE whenever applicable.

The frequency of laboratory abnormalities will be displayed by worst CTCAE grade and by dose level and cycle as appropriate. Newly occurring CTCAE laboratory abnormalities will be displayed in a separate listing. Shift tables will be provided for laboratory parameters classified according to CTCAE.

8.2.2.8.3 Other safety data

Data from other tests (e.g., ECGs) will be listed. Notable abnormalities will be discussed and shift tables provided as appropriate. Vital signs will be listed and summarized using descriptive summary statistics.

8.2.2.9 ***Pharmacokinetic analysis***

Plasma concentrations of BAL101553 and BAL27862 will be presented in tables for each patient and with descriptive statistics per dose group and per day.

PK parameters calculated by non-compartmental analysis will be presented as listings and descriptive summary statistics including arithmetic and geometric means, coefficient of variations, standard deviation, minimum, median and maximum. Bioavailability will be determined as the ratio of the AUCs after oral and IV administration.

8.2.2.10 ***Biomarker analysis***

All biomarker parameters will be presented in listings and descriptive summary statistics by dose level and scheduled time point and within disease subgroups, as appropriate.

Analyses of biomarkers and their association to clinical response or PK will be conducted as appropriate and will be exploratory.

8.2.3 Sample size calculation

Up to 56 evaluable patients will be enrolled in the study in total. Of the 20 patients dosed in the dose-escalation portion, 16 were MTD-evaluable; up to 20 evaluable ovarian tumor patients and up to 20 evaluable GBM patients will be included in the expansion portion.

Assuming an ~25% drop-out rate, up to 70 patients may be enrolled.

The 3+3 design does not require sample size specification; the escalation is continued until the MAD (i.e., a dose with an unacceptable number of DLT) is observed. The expansion portion is exploratory; therefore, no statistical sample size justification has been applied.

8.2.4 Handling of missing data and discontinuations

Patients whose clinical response is unknown or not reported will be treated as non-responders for summarizing the overall response rate.

Reasons for discontinuation and the Study Day of discontinuation from the study will be listed, and dates of first and last study drug provided as well as the duration of exposure to study drug and Study Day. Summary tables will be provided by dose group.

9. STUDY ADMINISTRATION AND REGULATORY ASPECTS

9.1 Study records

The Investigator must maintain adequate and accurate records to enable the conduct of the study to be fully documented and the study data to be subsequently verified.

9.1.1 Investigator site file

The ISF must contain all essential documents as required by International Conference on Harmonisation (ICH) E6 [1] and applicable regulations, including the protocol and any subsequent amendments, CRFs, Query Forms, documented IEC/IRB approvals, documented regulatory approvals, sample informed consent forms, drug records, staff *curriculum vitae*, and other appropriate documents/correspondence.

9.1.2 Case report forms

For each patient enrolled, a CRF must be completed and signed (manually or electronically) by the Investigator or authorized site staff. If a patient withdraws from the study, the reason must be noted on the eCRF. If a patient is withdrawn from the study because of an AE, thorough efforts should be made to clearly document the outcome.

The Investigator should ensure the accuracy, completeness, legibility, and timeliness of the data reported to the Sponsor in the CRFs and in all required reports.

If the CRF is to be the source document for certain data, this must be discussed and agreed with the Sponsor in advance, and clearly documented.

9.1.3 Patient source documents

Patient source documents used to record key efficacy/safety parameters, independent of the CRFs may include, but are not limited to, patient hospital/clinic records, physicians' and nurses' notes, appointment books, original laboratory reports, ECG read-outs, X-ray, pathology and special assessment reports, signed informed consent/assent forms, consultant letters, and patient screening and enrollment logs. Source documents are part of the study documents and must be maintained and made available upon request for clinical monitoring visits, audits or inspections.

9.1.4 Document retention and archiving

The Investigator must keep all study documents on file for at least 15 years after completion or discontinuation of the study. Subsequently, the Sponsor will inform the Investigator when the study documents can be destroyed, subject to applicable regulations.

These files must be made available for audits and inspection, upon reasonable request, to the authorized representative of the Sponsor, or to regulatory authorities.

Should the Investigator wish to assign the study records to another party, or move them to another location, the Sponsor must be notified in advance.

If the Investigator cannot guarantee the archiving requirement at the investigational site for any or all of the study documents, arrangements must be made between the Investigator and the Sponsor for appropriate storage.

9.1.5 Sample retention

Genetic filter cards, plasma samples collected for PK and tumor tissue material may be stored for up to 20 years for future medical and/or scientific research projects related to BAL101553. All patients will be asked to provide a separate informed consent for this purpose, authorizing the Sponsor to use their study information and samples for future research projects.

After a maximum of 20 years, all stored samples will be safely destroyed.

9.2 Clinical monitoring

Before study initiation, at a site initiation visit or at an Investigator's meeting, the Sponsor will review the protocol, CRFs and other study documentation with the Investigators and the site staff.

The Monitor must visit the Investigator and the study facilities on a regular basis throughout the study to verify adherence to Good Clinical Practice (GCP) and the protocol, and the completeness, consistency and accuracy of the data being entered into the CRFs. The Monitor must also ensure that the study drug is being stored, dispensed, and accounted for according to specifications.

The Investigator must ensure that the Monitor has direct access to all required study data (source documents) during the regular monitoring visits. This includes all patient records needed to verify the entries in the CRFs.

The Investigator must cooperate with the Monitor to ensure that any protocol deviations or other issues detected in the course of monitoring visits are resolved.

Monitoring reports must be written after each monitoring visit, per site and per visit. These monitoring reports must be reviewed and approved by the respective supervisors of the Monitors.

Monitoring instructions are provided in the Clinical Monitoring Plan.

9.3 Audits and inspections

The study may be audited at any time, with appropriate notification, by qualified personnel from the Sponsor or its designees, to assess compliance with the protocol, GCP, and regulatory requirements. These audits may also be conducted for quality assurance purposes, to ensure that complete and accurate data are submitted, and that all AEs are being identified and reported in compliance with the protocol and applicable regulations. The study may also be inspected by regulatory authority inspectors, after appropriate notification.

In the event of an audit or an inspection, the Investigator must ensure that direct access to all study documentation, including source documents, is granted to the auditors or inspectors.

9.4 Protocol amendments

Protocol amendments must be prepared by a representative of the Sponsor, and be reviewed and approved by the Project Physician and the Project Statistician.

All protocol amendments must be submitted to the appropriate IEC/IRB for information and approval in accordance with applicable laws and regulations, and to regulatory agencies if required.

Approval of a protocol amendment must be awaited before changes are implemented, with the exception of changes necessary to eliminate an immediate hazard to study participants, or changes involving only logistical or administrative aspects of the study (e.g., changes to Monitors, changes to telephone numbers).

9.5 Premature termination of the study

The Sponsor reserves the right to terminate the study at any time. An Investigator has the right to terminate his or her participation to the study at any time. Should either of these events occur, both parties will arrange the necessary procedures after review and consultation.

If the study is to be terminated early, the Sponsor and the Investigator must ensure that adequate consideration is given to the protection of the interests of all patients enrolled in the study.

9.6 Publication policy

The Sponsor is committed to registering all therapeutic studies in a publicly accessible clinical trial registry (e.g., www.clinicaltrials.gov), and will ensure that results of these studies will be made available to the medical community, consistent with applicable laws and regulations.

In accordance with standard editorial and ethical practice, the Sponsor will support publication of multicenter studies only in their entirety, and not as individual center data. Authorship is to be determined by mutual agreement.

The results of this study will be made available, e.g., submitted for publication and/or presentation at scientific meetings, in a timely manner. All manuscripts or abstracts must be submitted to the Sponsor prior to publication or presentation, allowing the Sponsor to protect proprietary information, and to provide comments based on information from other studies that may not yet be available to an Investigator.

10. ETHICS AND GOOD CLINICAL PRACTICE

10.1 Good Clinical Practice

The study must be conducted in compliance with this protocol, ICH Guideline E6 and any relevant supplementary guidance on GCP, and applicable laws and regulations.

10.2 Informed consent

Eligible patients may only be included in the study after providing written IEC/IRB-approved informed consent, or, if incapable of doing so, after such consent has been provided by a legally acceptable representative of the patient. Written informed consent must be obtained from each patient prior to initiation of any study procedures.

It is the responsibility of the Investigator, or a person designated by the Investigator if acceptable by local regulations, to obtain prior written informed consent from each individual participating in this study, after adequate explanation of the aims, methods, objectives and potential risks of the study. It must also be explained to patients that they are completely free to refuse to enter the study, or to withdraw from the study at any time for any reason. Appropriate forms for obtaining written informed consent will be provided to the Investigator by the Sponsor.

Written consent must be witnessed and countersigned by the Investigator or a qualified designee, as appropriate. In obtaining and documenting informed consent, the Investigator must comply with applicable regulatory requirements and GCP as outlined in ICH E6 and other relevant guidelines, and the ethical principles having their origin in the Declaration of Helsinki.

Copies of signed consent forms must be given to the patient, and the originals filed at the study center.

For patients not qualified to give legal consent, or incapable of doing so, written consent must be obtained from the patient's legally acceptable representative. In the event that both the patient and his or her legally acceptable representative are unable to read the consent document, an impartial witness must be present during the entire informed consent discussion. After the patient and representative have verbally consented to participation in the study, the witness' signature must be obtained on the form to attest that the information in the consent form was accurately explained and understood.

The CRFs for this study contain a section for documenting informed patient consent, and this must be completed appropriately. If new safety information results in significant changes in the benefit/risk assessment, the consent form must be reviewed and updated.

All patients currently enrolled in the study who have not yet completed the post-treatment phase must be given the new information and a copy of the revised form, and asked to give their consent to continuing in the study.

10.3 Patient confidentiality and data protection

The Investigator must ensure that patient anonymity is maintained and that patients' identities are protected from unauthorized parties. This includes any electronic data generated during the study. In the CRF, or other documents submitted to the Sponsor, patients must be identified only by an identification code and not by name. The Investigator must keep a confidential patient identification code list, as described in Section 8.3.21 of ICH E6.

The Sponsor is responsible for ensuring compliance with all applicable data protection laws.

10.4 Independent Ethics Committees/Institutional Review Boards

This protocol and any accompanying material provided to the patient, including patient information sheets or descriptions of the study used to obtain informed consent, as well as any advertising material and information about any compensation provided to the patient, must be submitted to an IEC/IRB operating in compliance with ICH Guideline E6 and any relevant supplementary guidance on GCP, and with applicable laws and regulations. Approval from the IEC/IRB must be obtained and documented before starting the study.

Amendments made to the protocol after receipt of IEC/IRB approval must also be submitted to the IEC/IRB in accordance with local procedures and applicable laws and regulations.

11. REFERENCES

1. Integrated Addendum to ICH E6(R1): Guideline For Good Clinical Practice E6(R2). ICH, 2016.
2. Prota, A.E., et al., *The novel microtubule-destabilizing drug BAL27862 binds to the colchicine site of tubulin with distinct effects on microtubule organization.* J Mol Biol, 2014. **426**(8): p. 1848-60.
3. Schmitt-Hoffmann, A., et al., *Poster abstract C233: BAL27862: A unique microtubule-targeted agent with a potential for the treatment of human brain tumors*, in *AACR*. 2009.
4. BasileaPharmaceutica. *An Open-Label Study of BAL101553 in Adult Patients With Solid Tumors*. 2014; Available from: http://clinicaltrials.gov/show/NCT01397929.
5. Molife, L.R., et al., *Phase I/IIa trial of the novel microtubule inhibitor BAL101553 in advanced solid tumors: Phase I completed.* Journal of Clinical Oncology, 2014. **35**(15s): p. suppl 2562.
6. Chen, Z., et al., *Range and trend of expected toxicity level (ETL) in standard A + B designs: a report from the Children's Oncology Group.* Contemp Clin Trials, 2009. **30**(2): p. 123-8.

7. Ivy, S.P., et al., *Approaches to phase 1 clinical trial design focused on safety, efficiency, and selected patient populations: a report from the clinical trial design task force of the national cancer institute investigational drug steering committee.* Clin Cancer Res, 2010. **16**(6): p. 1726-36.
8. Lopez, J., et al., *Poster absrtact 2525: Phase 1/2a trial of intravenous BAL101553, a novel tumor checkpoint controller (TCC), in advanced solid tumors*, in *ASCO*. 2016.

12. APPENDICES

Appendix 1 Response evaluation and criteria in solid tumors (RECIST) guidelines, version 1.1

Source:

Eisenhauer EA, Therasse P, Bogaerts J, Schwartz LH, Sargent D, Ford R, Dancey J, Arbuck S, Gwyther S, Mooney M, Rubinstein L, Shankar L, Dodd L, Kaplan R, Lacombe D, Verweij J. New response evaluation criteria in solid tumors: revised RECIST guideline (version 1.1). Eur J Cancer. 2009 ;45:228-47.

For specifics of RECIST v1.1 criteria and assessment, please refer to the following website: http://www.eortc.be/recist/documents/RECISTGuidelines.pdf.

Appendix 2 RANO criteria for glioblastoma and high-grade gliomas

Source: Wen PY, Macdonald DR, Reardon DA, Cloughesy TF, Sorensen AG, Galanis E, Degroot J, Wick W, Gilbert MR, Lassman AB, Tsien C, Mikkelsen T, Wong ET, Chamberlain MC, Stupp R, Lamborn KR, Vogelbaum MA, van den Bent MJ, Chang SM. Updated response assessment criteria for high-grade gliomas: response assessment in neuro-oncology working group. J Clin Oncol. 2010;28(11):1963-72. http://jco.ascopubs.org/content/28/11/1963.full

Criteria for Response Assessment Incorporating MRI and Clinical Factors

Response	Criteria
Complete response	Requires all of the following: complete disappearance of all enhancing measurable and nonmeasurable disease sustained for at least 4 weeks; no new lesions; stable or improved nonenhancing (T2/FLAIR) lesions; patients must be off corticosteroids (or on physiologic replacement doses only); and stable or improved clinically. Note: Patients with nonmeasurable disease only cannot have a complete response; the best response possible is stable disease.
Partial response	Requires all of the following: ≥ 50% decrease compared with baseline in the sum of products of perpendicular diameters of all measurable enhancing lesions sustained for at least 4 weeks; no progression of nonmeasurable disease; no new lesions; stable or improved nonenhancing (T2/FLAIR) lesions on same or lower dose of corticosteroids compared with baseline scan; the corticosteroid dose at the time of the scan evaluation should be no greater than the dose at time of baseline scan; and stable or improved clinically. Note: Patients with nonmeasurable disease only cannot have a partial response; the best response possible is stable disease.
Stable disease	Requires all of the following: does not qualify for complete response, partial response, or progression; stable nonenhancing (T2/FLAIR) lesions on same or lower dose of corticosteroids compared with baseline scan. In the event that the corticosteroid dose was increased for new symptoms and signs without confirmation of disease progression on neuroimaging, and subsequent follow-up imaging shows that this increase in corticosteroids was required because of disease progression, the last scan considered to show stable disease will be the scan obtained when the corticosteroid dose was equivalent to the baseline dose.
Progression	Defined by any of the following: ≥ 25% increase in sum of the products of perpendicular diameters of enhancing lesions compared with the smallest tumor measurement obtained either at baseline (if no decrease) or best response, on stable or increasing doses of corticosteroids*; significant increase in T2/FLAIR nonenhancing lesion on stable or increasing doses of corticosteroids compared with baseline scan or best response after initiation of therapy* not caused by comorbid events (eg, radiation therapy, demyelination, ischemic injury, infection, seizures, postoperative changes, or other treatment effects); any new lesion; clear clinical deterioration not attributable to other causes apart from the tumor (eg, seizures, medication adverse effects, complications of therapy, cerebrovascular events, infection, and so on) or changes in corticosteroid dose; failure to return for evaluation as a result of death or deteriorating condition; or clear progression of nonmeasurable disease.

NOTE. All measurable and nonmeasurable lesions must be assessed using the same techniques as at baseline.
MRI, magnetic resonance imaging; FLAIR, fluid-attenuated inversion recovery.
* Stable doses of corticosteroids include patients not on corticosteroids.

Appendix 3 Criteria for evaluating relationship between adverse events and study treatment

NOT RELATED

This category is applicable to an AE that meets the following three criteria:

1. It does not follow a reasonable temporal sequence from administration of the drug, i.e., the time between the administration of study drug and occurrence of the event is not plausible. If the drug was interrupted or stopped the event did not improve or disappear. (There are important exceptions when an AE does not disappear upon discontinuation of the drug, yet drug-relatedness clearly exists; e.g., [i] bone marrow depression, [ii] tardive dyskinesias.). If the drug was re-administered it did not reappear.
2. It does not follow a known pattern of the response to the suspected drug or drugs of the same substance class.
3. It is judged to be clearly and incontrovertibly due only to extraneous causes such as the patient's clinical state, environmental or toxic factors, or other modes of therapy administered to the patient.

UNLIKELY

This category is applicable to an AE that meets the following three criteria:

1. It does not follow a reasonable temporal sequence from administration of the drug, i.e., the time between the administration of study drug and occurrence of the event is not plausible. If the drug was interrupted or stopped the event did not improve or disappear. If the drug was re-administered it did not re-appear.
2. It does not follow a known pattern of the response to the suspected drug or drugs of the same substance class.
3. It may readily have been produced by the patient's clinical state, environmental or toxic factors, or other modes of therapy administered to the patient.

POSSIBLE

This category is applicable to an AE that does not meet the criteria for 'not related' or 'unlikely', nor the criteria for 'probable'. An AE would be considered possible if, or when e.g.:

1. It follows a reasonable temporal sequence from administration of the drug (see also additional explanations above) or it follows a known pattern of the response to the suspected drug or drugs of the same substance class.
2. It may or may not have been produced by the patient's clinical state, environmental or toxic factors, or other modes of therapy administered to the patient.

Note: If an event neither follows a plausible temporal relationship nor a known pattern of response but there is no alternative explanation for the event, this will usually be judged a possibly related event.

PROBABLE

This category is applicable to an AE that is considered, with a high degree of certainty, to be related to the test drug. An AE event may be considered probable if it meets the following three criteria:

1. It follows a reasonable temporal sequence from administration of the drug, i.e., the time between the administration of study drug and occurrence of the event is plausible. If the drug was interrupted or stopped the event did improve or disappear. (There are important exceptions when an AE does not disappear upon discontinuation of the drug, yet drug-relatedness clearly exists; e.g., [i] bone marrow depression, [ii] tardive dyskinesias.) If the drug was re-administered it did re-appear.
2. It follows a known pattern of the response to the suspected drug or drugs of the same substance class.
3. It cannot be reasonably explained by the known characteristics of the patient's clinical state, environmental or toxic factors, or other modes of therapy administered to the patient.

Regardless of the criteria mentioned above, reappearance of an event upon re-challenge must be regarded as strong evidence of probable relationship to test drug.

A causal relationship is suspected for all AEs/SAEs reported with a relationship of 'possible' or 'probable'.

Appendix 4 Investigator's protocol signature page

BASILEA

INVESTIGATOR'S PROTOCOL SIGNATURE PAGE

Protocol	CDI-CS-003 Version 7.0 (SAKK number: SAKK 67/15)	Basilea Product No:	BAL101553
Protocol Title:	**An open-label Phase 1/2a study of BAL101553 administered as intravenous 48-hour infusions in adult patients with advanced solid tumors or recurrent glioblastoma**		
Basilea Pharmaceutica International Ltd			
Approval Date:	8 October 2018	By (Project Physician):	[redacted]
Name of Principal Investigator:			
Study Center:			

I agree to the conditions relating to this study as set out in the above named Protocol and Study Procedures. I fully understand that any changes instituted by the Investigator(s) without previous discussion with the Sponsor's Project Clinician, Clinical Pharmacologist and Biostatistician (only if required) would constitute a violation of the protocol, including any ancillary studies or procedures performed on study patients (other than those procedures necessary for the well-being of the patients).

I agree to follow International Conference on Harmonisation (ICH) guidelines for Good Clinical Practice (GCP), including the EU Clinical Trial Directive 2001/20/EC and specifically, obtain approval from the Ethics Committee prior to study start, allow direct access to source documents and agree to inspection by auditors from Basilea and regulatory authorities, as required by ICH GCP. I will ensure that the investigational product(s) supplied by the Sponsor will be used only as described in the above named protocol; if *any* other use is desired, *written permission* must be obtained from the Sponsor.

I acknowledge that I have read the protocol for this study, and I agree to carry out all of its terms in accordance with applicable laws and regulations.

To be signed by Principal Investigator and Sub-Investigators (at minimum):

Please print names, qualifications, and dates next to the corresponding signatures

Signature	**Name**	**Date**
	Principal Investigator	
	Sub-Investigator	